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Human papillomavirus testing versus repeat cytology for triage of minor cytological cervical lesions (Review)

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[Diagnostic Test Accuracy Review]

Human papillomavirus testing versus repeat cytology for triage of minor cytological cervical lesions

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ABSTRACT

Background

Atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intra-epithelial lesions (LSIL) are minor lesions of the cervical epithelium, detectable by cytological examination of cells collected from the surface of the cervix of a woman.

Usually, women with ASCUS and LSIL do not have cervical (pre-) cancer, however a substantial proportion of them do have underlying high-grade cervical intra-epithelial neoplasia (CIN, grade 2 or 3) and so are at increased risk for developing cervical cancer. Therefore, accurate triage of women with ASCUS or LSIL is required to identify those who need further management.

This review evaluates two ways to triage women with ASCUS or LSIL: repeating the cytological test, and DNA testing for high-risk types of the human papillomavirus (hrHPV) - the main causal factor of cervical cancer.

Objectives

Main objective

To compare the accuracy of hrHPV testing with the Hybrid Capture 2 (HC2) assay against that of repeat cytology for detection of underlying cervical intraepithelial neoplasia of grade 2 or worse (CIN2+) or grade 3 or worse (CIN3+) in women with ASCUS or LSIL. For the HC2 assay, a positive result was defined as proposed by the manufacturer. For repeat cytology, different cut-offs were used to define positivity: Atypical squamous cells of undetermined significance or worse (ASCUS+), low-grade squamous intra-epithelial lesions or worse (LSIL+) or high-grade squamous intra-epithelial lesions or worse (HSIL+).

Secondary objective

To assess the accuracy of the HC2 assay to detect CIN2+ or CIN3+ in women with ASCUS or LSIL in a larger group of reports of studies that applied hrHPV testing and the reference standard (coloscopy and biopsy), irrespective whether or not repeat cytology was done.

Search methods

We made a comprehensive literature search that included the Cochrane Register of Diagnostic Test Accuracy Studies; the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), MEDLINE (through PubMed), and EMBASE (last search 6 January 2011). Selected journals likely to contain relevant papers were handsearched from 1992 to 2010 (December). We also searched CERVIX, the

bibliographic database of the Unit of Cancer Epidemiology at the Scientific Institute of Public Health (Brussels, Belgium) which contains more than 20,000 references on cervical cancer.

More recent searches, up to December 2012, targeted reports on the accuracy of triage of ASCUS or LSIL with other HPV DNA assays, or HPV RNA assays and other molecular markers. These searches will be used for new Cochrane reviews as well as for updates of the current review.

Selection criteria

Studies eligible for inclusion in the review had to include: women presenting with a cervical cytology result of ASCUS or LSIL, who had undergone both HC2 testing and repeat cytology, or HC2 testing alone, and were subsequently subjected to reference standard verification with colposcopy and colposcopy-directed biopsies for histologic verification.

Data collection and analysis

The review authors independently extracted data from the selected studies, and obtained additional data from report authors.

Two groups of meta-analyses were performed: group I concerned triage of women with ASCUS, group II concerned women with LSIL.

The bivariate model (METADAS-macro in SAS) was used to assess the absolute accuracy of the triage tests in both groups as well as the differences in accuracy between the triage tests.

Main results

The pooled sensitivity of HC2 was significantly higher than that of repeat cytology at cut-off ASCUS+ to detect CIN2+ in both triage of ASCUS and LSIL (relative sensitivity of 1.27 (95% CI 1.16 to 1.39; P value < 0.0001) and 1.23 (95% CI 1.06 to 1.4; P value 0.007), respectively. In ASCUS triage, the pooled specificity of the triage methods did not differ significantly from each other (relative specificity: 0.99 (95% CI 0.97 to 1.03; P value 0.98)). However, the specificity of HC2 was substantially, and significantly, lower than that of repeat cytology in the triage of LSIL (relative specificity: 0.66 (95% CI 0.58 to 0.75) P value < 0.0001).

Authors' conclusions

HPV-triage with HC2 can be recommended to triage women with ASCUS because it has higher accuracy (significantly higher sensitivity, and similar specificity) than repeat cytology.
When triaging women with LSIL, an HC2 test yields a significantly higher sensitivity, but a significantly lower specificity, compared to a repeat cytology. Therefore, practice recommendations for management of women with LSIL should be balanced, taking local circumstances into account.

SUMMARY OF FINDINGS

Summary of findings 1. Clinical impact of applying triage tests in a population of 1000 ASCUS patients with a given prevalence of disease

Test	Outcome	Sensitivity/ Specificity	Prevalence	Useful referrals	Missed cases	Unnecessary referrals	True reassurance	Post-test risk	
			Pre-test risk	TP	FN	FP	TN	if test+ (PPV)	if test- (1-NPV)
Repeat cytology (at ASCUS+)	CIN2+	71.5%/ 68.4%	5%	36	14	300	650	10.7%	2.1%
			10%	72	28	284	616	20.2%	4.4%
			15%	107	43	269	581	28.5%	6.9%
	CIN3+	77.9%/ 57.4%	2%	16	4	*	*	*	0.7%
			6%	47	15	*	*	*	2.7%
			10%	78	27	*	*	*	5.0%
HC2 (RLU > 1)	CIN2+	90.9%/ 60.7%	5%	45	5	307	643	12.8%	0.8%
			10%	91	9	291	609	23.8%	1.5%
			15%	136	14	274	576	33.1%	2.4%
	CIN3+	94.8%/ 56.6%	2%	19	1	*	*	*	0.2%
			6%	66	4	*	*	*	0.7%
			10%	114	6	*	*	*	1.2%

The clinical impact of applying HC2 in stead of repeat cytology at cut-off ASCUS+ is assessed for a population of 1000 ASCUS patients with low, intermediate and high prevalence of CIN2+ (5%, 10% or 15%) or CIN3+ (2%, 6% or 10%) accepting the sensitivity and specificity values derived from the meta-analyses.
*The number of unnecessarily referred and truly reassured cases was not computed for the outcome CIN3+, since CIN2 cannot be considered as an obvious false-positive case.
Abbreviations
ASCUS+ = ASCUS or worse

CIN2+ = cervical intraepithelial neoplasia of grade 2 or worse
CIN3+ = cervical intraepithelial neoplasia of grade 3 or worse
FN = false negatives
FP = false positives
HC2 = Hybrid Capture 2 assay
NPV = negative predictive value
PPV = positive predictive value
RLU = relative light units
TN = true negatives
TP = true positives

Summary of findings 2. Clinical impact of applying triage tests in a population of 1000 LSIL patients with a given prevalence of disease

Test	Outcome	Sensitivity/ Specificity	Prevalence	Useful referrals	Missed cases	Unnecessary referrals	True reassurance	Post-test risk	
			Pretest risk	TP	FN	FP	TN	+ (PPV)	- (1-NPV)
Repeat cytology (at ASCUS+)	CIN2+	77.1%/ 51.2%	10%	77	23	438	461	14.9%	4.8%
			20%	154	46	390	410	28.3%	10.1%
			25%	193	57	366	3844	34.5%	12.9%
	CIN3+	84.6%/ 44.4%	5%	42	8	*	*	*	1.9%
			10%	85	15	*	*	*	3.6%
			15%	127	23	*	*	*	5.7%
HC2 (RLU > 1)	CIN2+	96.2%/ 27.7%	10%	96	4	572	328	14.2%	1.2%
			20%	192	8	509	291	27.2%	2.7%
			25%	127	23	477	273	33.2%	3.2%
	CIN3+	97.5%/ 24.8%	5%	49	1	*	*	*	0.4%
			10%	98	2	*	*	*	0.9%

		15%	146	4	*	*	*	1.9%

The clinical impact of applying HC2 in stead of repeat cytology at cut-off ASCUS+ is computed for a population of 1000 LSIL patients with low, intermediate and high prevalence of CIN2+ (10%, 20% or 25%) or CIN3+ (5%, 10% or 15%) accepting the sensitivity and specificity values derived from the meta-analyses.
*The number of unnecessarily referred and truly reassured cases was not computed for the outcome CIN3+, since CIN2 cannot be considered as an obvious false-positive case.
Abbreviations
ASCUS+ = ASCUS or worse
CIN2+ = cervical intraepithelial neoplasia of grade 2 or worse
CIN3+ = cervical intraepithelial neoplasia of grade 3 or worse
FN = false negatives
FP = false positives
HC2 = Hybrid Capture 2 assay
NPV = negative predictive value
PPV = positive predictive value
RLU = relative light units
TN = true negatives
TP = true positives

Summary of findings 3. Summary of the main meta-analyses of the absolute and relative accuracy of HC2 and repeat cytology used to triage women with ASCUS

Studies where HC2 triage and repeat cytology were applied

Triage test	Test cut-off	Outcome	Studies	Accuracy parameter	Pooled estimate	(95% CI)	Analysis
HC2	**RLU > (1 pg/mL)**	**CIN2+**	10	Absolute sensitivity	90.9%	(85.7 to 94.4%)	29
			10	Absolute specificity	60.7%	(52.9 to 68.0%)	
		CIN3+	4	Absolute sensitivity*	94.8%	(89.6 to 97.5%)	30
			4	Absolute specificity*	56.6 %	(39.4 to 72.3%)	
Repeat cytology	**ASCUS+**	**CIN2+**	10	Absolute sensitivity	71.5%	(62.9 to 78.8%)	17
			10	Absolute specificity	68.4%	(59.9 to 75.8%)	
		CIN3+	4	Absolute sensitivity*	77.9%	(64.0 to 87.6%)	20

		4	Absolute specificity*	57.4%	(40.3 to 73.0%)	
HC2 (RLU > 1) vs repeat cytology (ASCUS+)	**CIN2+**	10	Relative sensitivity	1.27	(1.16 to 1.39)	1
		10	Relative specificity	0.99	(0.97 to 1.03)	
	CIN3+	4	Relative sensitivity*	1.14	(1.06 to 1.22)	4
		4	Relative specificity*	0.99	(0.89 to 1.09)	

*Univariate analyses using the bivariate model run separately for sensitivity and specificity.

Abbreviations

ASCUS+ = ASCUS or worse
CIN2+ = cervical intraepithelial neoplasia of grade 2 or worse
CIN3+ = cervical intraepithelial neoplasia of grade 3 or worse
HC2 = Hybrid Capture 2 assay
RLU = relative light units

Summary of findings 4. Summary of the main meta-analyses of the absolute and relative accuracy of HC2 and repeat cytology used to triage women with LSIL

Studies where HC2 triage and repeat cytology were applied

Triage test	Test cut-off	Outcome	Studies	Accuracy parameter	Pooled estimate	(95% CI)	Analysis
HC2	**RLU > 1 (1 pg/mL)**	**CIN2+**	6	Absolute sensitivity	96.2%	(91.4 to 98.3%)	31
			6	Absolute specificity	27.7%	(20.9 to 35.7%)	
		CIN3+	4	Absolute sensitivity*	97.5%	(69.6 to 99.8%)	32
			4	Absolute specificity*	24.8%	(7.3 to 58.1%)	
Repeat cytology	**ASCUS+**	**CIN2+**	6	Absolute sensitivity	77.1%	(59.5 to 88.5%)	23
			6	Absolute specificity	51.2%	(34.5 to 67.6%)	

	CIN3+	4	Absolute sensitivity*	84.6%	(48.6 to 97.0%)	26
		4	Absolute specificity*	44.4%	(16.0 to 76.9%)	
HC2 (RLU > 1) vs repeat cytology (ASCUS+)	**CIN2+**	10	Relative sensitivity	1.23	(1.06 to 1.43)	7
		10	Relative specificity	0.66	(0.58 to 0.75)	
	CIN3+	4	Relative sensitivity*	1.15	(0.89 to 1.48)	10
		4	Relative specificity*	0.56	(0.37 to 0.84)	

*Univariate analyses using the bivariate model run separately for sensitivity and specificity.

Abbreviations

ASCUS+ = ASCUS positive
CIN2+ = cervical intraepithelial neoplasia of grade 2 or worse
CIN3+ = cervical intraepithelial neoplasia of grade 3 or worse
HC2 = Hybrid Capture 2 assay
RLU = relative light units
> = less than

BACKGROUND

Target condition being diagnosed

Cervical cancer is the third most common cancer in women worldwide. It is estimated that, in 2008, approximately 530,000 women developed cervical cancer and that 275,000 died from the disease (Arbyn 2011). Cervical cancer primarily affects younger women, with the majority of cases becoming apparent between the ages of 30 and 50 years (Yang 2004). Nevertheless, of all malignant tumours cervical cancer is the one that is most easily preventable by screening. Cervical cancer screening is primarily performed using a Papanicolaou test, that is by taking a 'Pap smear'. Microscopical examination of these Pap smears may reveals cytological abnormalities, which may be classified as atypical, low- or high-grade. By application of a confirmation test, colposcopy and histological examination of colposcopy-targeted biopsies, cervical precancer can be identified. Cervical precancer is graded histologically as cervical intra-epithelial neoplasia (CIN), grade CIN1, CIN2 or CIN3. CIN2 and CIN3 are often joined together as high-grade CIN. The subsequent treatment of women with high-grade CIN prevents development of cancer (Miller 1993). Through well-organized screening and management of detected lesions, the incidence of cervical cancer can be reduced to a low level (IARC 2005; Arbyn 2009a).

Women with cytological lesions require further follow-up or treatment, or both, depending on the severity of the lesion. Women with high-grade cytological lesions should be referred immediately for further examination using the reference standard test that involves colposcopy (observation technique that can identify potential precancerous and cancerous lesions) and histological (tissue) examination of colposcopy-targeted biopsies (Wright 2002; Jordan 2009). However, management of women with minor cytologic lesions remains controversial (Cox 1998; Cox 2005; Sawaya 2005; Soutter 1994; Stoler 2001). Until recently, follow-up recommendations for women with atypical squamous cells of undetermined significance (ASCUS, or ASC-US) and low-grade squamous intra-epithelial lesions (LSIL) varied from conservative repeat cytology (Robertson 1988; Coleman 1993; Flannelly 1994), to immediate referral for colposcopy and biopsy (Richart 1987; Noumoff 1987; Richart 1993).

The natural history of minor cytological lesions is difficult to predict on the basis of cytomorphological (appearance of cells) grounds. These lesions often regress spontaneously without treatment (Narod 1991; Ostor 1993; Melnikow 1998). Therefore, referring all women with minor cytological lesions for further gynaecological examination would mean an increase in over-diagnosis and over-treatment (Murdoch 1992; Ferenczy 1995). Over-referral would also cause unnecessary anxiety in women (Wilkinson 1990), with substantial increases in costs to the healthcare system (Ferenczy 1995). Moreover, lack of availability of colposcopic services at affordable prices often makes such a policy unrealistic.

Although most women with an ASCUS or LSIL smear result do not have clinically significant disease, a substantial proportion of them do have histopathologically-confirmed high-grade cervical intra-epithelial neoplasia (CIN) (Cox 1995; Wright 1995; Kinney 1998). From a population of women screened in the USA, it was estimated that one third of CIN were discovered on follow-up of a previous smear with ASCUS (Kinney 1998). An appropriate triage (prioritising) method should identify those women that have, or will develop, a cervical cancer precursor. At the same time, an accurate triage would reduce the risk of over-diagnosis and over-treatment, and should limit adverse obstetric outcomes associated with excision of CIN lesions (Arbyn 2008b; Kyrgiou 2006).

Given the evidence concerning the etiological (causative) role of high-risk human papillomavirus (HPV) infections in the development of cervical cancer and its precursors (zur Hausen 1994; Walboomers 1999; Bosch 2002; IARC 2007), HPV testing has been proposed as an alternative triage method to distinguish between women with minor cytological lesions who need referral for colposcopy, and those who can be referred back to the normal screening schedule (Wright 1995; Cox 1998).

Index test(s)

The index test of interest is the B-probe of the Hybrid Capture 2 assay (HC2, Qiagen, Gaithersburg, MD, USA), which detects DNA of 13 high-risk HPV (hrHPV) types. HC2 contains a cocktail of 13 RNA probes that hybridise viral DNA of the following hrHPV types: HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, HPV59, and HPV68. The A-probe of HC2, which targets five low-risk HPV types (HPV6, HPV11, HPV42, HPV43, and HPV44) is not considered in the current systematic review.

HC2 is a sandwich hybridisation technique based on type-specific full genomic HPV RNA probes hybridising with DNA from human papillomaviruses in the test material (Lorincz 1997). DNA-RNA hybrids are captured by immobilised antibodies against RNA-DNA hybrids, coated on the surface of microplates. The antibody is conjugated to alkaline phosphatase to leave a chemiluminescent substrate, that yields a light signal measured with a luminometer. The intensity of light emission, expressed in relative light units (RLU), provides a semi-quantitative measure proportional to the amount of target HPV DNA present. The system is calibrated by positive and negative control samples provided by the manufacturer. The RLU corresponding to the average light intensity for the positive control sample is fixed at '1'. In standard conditions of the HC2 test, RLU = 1 corresponds to a detection threshold of 1 pg of HPV, 16 DNA/mL, or 5000 copies of HPV genome per sample.

HC2 is a standardised kit that can be easily used in a large range of laboratories. It is the only commercially available HPV test that is approved by the US Food and Drugs Administration for triage of women with ASCUS, or, in primary cervical cancer screening, for women older than 30.

Alternative test(s)

Repetition of cervical cytology is the conventional method of triage women with ASCUS or LSIL. When repeat cytology shows cervical abnormality again, three to six months after the first observation of ASCUS or LSIL, women are referred for further diagnostic investigations.

Rationale

Clinicians need an accurate triage method to decide whether a woman with minor cervical cytological abnormalities needs further investigation with colposcopy and biopsies. Testing for hrHPV DNA or repeating the cytological test are two possible triage methods.

In this Cochrane review the review authors will update previous meta-analyses, where accuracy estimates of triage tests were

pooled separately. Newer hierarchical or multilevel models, adapted by the Diagnostic Test Accuracy Working Group of The Cochrane Collaboration, will be applied (Macaskill 2010). These models account for the intrinsic negative correlation between sensitivity and specificity and for the usually considerable within- and inter-study heterogeneity in test accuracy meta-analyses.

OBJECTIVES

Main objective

For studies where both triage methods, i.e. repeat cytology and the HC2 assay, were assessed:

To assess the sensitivity and specificity of triage with HC2 and with repeat cytology to detect underlying cervical intraepithelial neoplasia of grade 2 or worse (CIN2+), or grade 3 or worse (CIN3+), in women with an index smear showing ASCUS (triage group I) or LSIL (triage group II), and to compare the accuracy of both triage methods.

Secondary objectives

To assess the accuracy of the HC2 assay to detect CIN2+ or CIN3+ in women with ASCUS or LSIL in a larger group of studies that investigated hrHPV testing, irrespective whether repeat cytology was done.

Investigation of sources of heterogeneity

The following sources of heterogeneity were investigated:

- Different cytological classification systems used to categorise equivocal and mild cytological abnormalities.
- Characteristics of the study population (study location, age distribution).
- Properties of the HPV testing (collection device, transport medium).
- Properties of repeat cytology (collection device, preparation method (conventional or liquid-based), cytological thresholds).
- Blinding of interpreters for other test results.
- Procedures of reference standard verification.

METHODS

Criteria for considering studies for this review

Types of studies

Two types of studies were considered:

- Studies with concomitant testing where all study participants were tested with the HC2 assay and repeat cytology, followed by verification with the reference standard; and studies where all study participants were tested only with HC2 followed by verification with the reference standard (coloscopy and biopsy).
- Randomised clinical trials (RCTs) where study participants were randomised to HPV-based triage or repeat cytology, and where, subsequently, all women were submitted to verification with the reference standard (coloscopy and biopsy).

Participants

Participants were women with a cervical cytology result of ASCUS (triage group I) or LSIL (triage group II) detected in the framework of cervical cancer screening. For a discussion on the cytological definitions of ASCUS and LSIL the reader is referred to Appendix 1.

Index tests

The index test was the B probe of the HC2 assay, which detects DNA of 13 hrHPV types (see Index test(s)).

For the main meta-analysis on the accuracy of triage with HC2, the review authors only considered the standard cut-off of test positivity as defined by the manufacturer. This standard cut-off of test positivity corresponds with a light signal of the test sample equivalent to that of a positive control containing 1 pg/mL of HPV DNA (RLU = 1).

Comparator tests

The conventional strategy to triage women with ASCUS or LSIL is to repeat the cytology test. Usually triage is done within six months after the first observation of ASCUS or LSIL. However, in practice this delay can vary between three to 12 months. When the result of the repeat cytology test is positive, women are referred for further diagnostic investigation with the reference standard. Three possible cut-offs to define a positive repeat cytology result will be distinguished: ASCUS+, LSIL+, and high-grade squamous intraepithelial lesion or worse (HSIL+). Cervical cytology testing can be performed with: (1) the Pap smear, where cellular material scraped from the transformation zone of the cervix is transferred to a glass slide and fixed, or (2) using liquid cytology, where scraped cervical cells are transferred into a vial with fixating fluid (Arbyn 2007; Arbyn 2008a).

Comparison of the accuracy of repeat cytology (comparator test) with HC2 (index test) was an optional selection criterion for inclusion in the review.

Target conditions

Presence of histologically-confirmed high-grade CIN was the target outcome of disease. Two separate outcomes were distinguished:

- CIN2 or worse disease (CIN2, CIN3, invasive squamous cervical cancer, and adenocarcinoma of the cervix (CIN2+));
- CIN3 or worse (CIN3, invasive squamous cervical cancer, and adenocarcinoma of the cervix (CIN3+)).

CIN3 is the most relevant clinical outcome, since it is considered to be an obvious precursor of cervical cancer, whereas CIN2 is a mixed condition that is less reproducible, with a lower probability of progression to cervical cancer. However, the outcome CIN2+ is reported more often than CIN3+. See Appendix 1 for a more detailed discussion on the natural history of the different degrees of CIN.

Reference standards

The following reference standards were considered as acceptable for judging on presence or absence of the target condition: colposcopy and colposcopy-directed punch biopsies or excision biopsies by large loop excision of the transformation zone or conization, with or without endocervical curettage, followed by histological verification of the biopsy specimen. Cases where no biopsy was taken, because colposcopy was negative and satisfactory, were considered as being free of CIN2+.

An overview of the key elements of the Cochrane review is summarised in Table 1.

Search methods for identification of studies

A systematic literature search identified articles published between 1992 and 2010 that contain data allowing assessment of the research questions. A previous meta-analysis revealed that in all retrieved triage studies published before 1992, only obsolete HPV testing systems were used; these systems are not used in current practice (Arbyn 2002; Arbyn 2004a).

No effort was made to identify studies where the only triage performed was by repeating Pap smears because:

1. Before the 1990s disparate cytological classification systems were used to categorise cervical abnormalities, impeding pooling of data (Lundberg 1989).
2. For reports published since the adaption of The Bethesda-System (TBS) (Lundberg 1989), recommendations for follow up of ASCUS involved repeat cytology with colposcopy if repeat cytology was abnormal, or direct referral for colposcopy and biopsy, which was considered as over-management (Kurman 1994).

In the context of the evaluation of HPV-based triage, studies had to be designed to include submission to verification by the reference standard for all participants.

Electronic searches

Studies were retrieved from the following electronic bibliographical databases: Cochrane Register of Diagnostic Test Accuracy Studies (up to published issue 12, 2011); the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library, up to published issue 12, 2011*), MEDLINE (through PubMed, from January 1992 to January 2011), and EMBASE (from January 1992 to January 2011). The search strategies for all the databases can be found in Appendix 2.

More recent searches, up to December 2012, targeted reports on the accuracy of triage of ASCUS or LSIL with other HPV DNA assays (Arbyn 2012), or HPV RNA assays (Arbyn 2013) and other molecular markers (Roelens 2012). These searches will be used for new Cochrane reviews as well as for updates of the current review. The recent references retrieved by these recent searches can be found in Studies awaiting classification.

The search string for PubMed-MEDLINE was saved into *My NCBI,* an electronic search tool developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine, which saves searches and automatically retrieves newer references not yet picked up at previous searches. An auto-alert was also set up in EMBASE.

The review authors acknowledge the possible limitations of the electronic database searches. The structure of the search strategy (index test AND target condition AND triage concept), in which the triage concept is also combined with the Boolean operator 'AND', may restrict the search. This option to increase specificity includes a risk of missing relevant studies. Therefore, other methods and resources were used to reduce this risk (see below).

Searching other resources

The 'related articles' feature in PubMed was used, from the original included studies; likewise for Scopus, to retrieve articles that cite the originally included studies.

Retrieval of reports was extended by manual searching of the reference lists of included papers, and by screening the tables of contents (for 1992 to December 2010) of the following journals: *American Journal of Obstetrics and Gynecology*; *Cancer Cytopathology*; *Diagnostic Cytopathology*; *Gynecologic Oncology*; and *Obstetrics and Gynecology*; which are journals that, according to previous meta-analysis, contributed multiple references.

We used the bibliographic database CERVIX of the Unit of Cancer Epidemiology at the Scientific Institute of Public Health (Brussels, Belgium) containing more than 20,000 references, mostly on cervical cancer, as an additional source.

The Trials Search Co-ordinator of the Cochrane Gynaecological Cancer Review Group requested a search from Mrs Ruth Mitchell, the Trials Search Co-ordinator of the Cochrane Renal Group, who is managing and developing the Cochrane Register of Diagnostic Test Accuracy Studies on behalf of The Cochrane Collaboration.

Data collection and analysis

Selection of studies

References were selected if they fulfilled the conditions for study selection, namely if they:

- Included women with ASCUS or LSIL.
- Used triage testing with HC2.
- Verified with the reference test.
- Used triage with repeat cytology (optional).

One selection criterion, triage by repeat cytology as the comparator test, was optional. See Criteria for considering studies for this review. For studies where no repeat cytology was done, only the accuracy of HC2 testing was assessed.

Three review authors (MA, CS and JR) verified inclusion and exclusion of eligible studies independently and discussed any discordance. If no consensus could be reached, other review authors (PMH or EP) were consulted.

Data extraction and management

After conversion of the cytological classification into the 1988 version of TBS, and separation of data by triage group (as explained in Participants), the numbers of true-positives, false-positives, false-negatives, and true-negatives defined at the considered thresholds were extracted from each study. The main review authors (MA, CS (until 2009) and JR (after 2009)) separately extracted data from the selected studies and subsequently discussed the extracted data where there were differences. Additional data on the absolute numbers of false and true positives and negatives were obtained from report authors in cases where accuracy parameters were reported but where the absolute number of false and true positives and negatives could not be derived or computed from the reported data.

Besides the quality issues (see Assessment of methodological quality), other trial properties were extracted from the included

studies and summarised in comprehensive tables (Characteristics of included studies and Appendix 3).

Assessment of methodological quality

Methodological quality

The methodological quality of selected studies were assessed using the QUADAS guidelines (Whiting 2003). For each study, a methodological quality table was completed. Table 2 contains an explanation of how the QUADAS items should be understood in terms of triage of women with minor cervical cytology lesions.

Other covariate information

All quality issues and other study characteristics were coded to allow subgroup meta-analysis and by including covariates in multivariate regressions (see Investigations of heterogeneity).

Where possible, age-stratified data were extracted to study the variation of test accuracy with age.

Statistical analysis and data synthesis

Separate analyses were performed for the two triage groups (ASCUS, LSIL) and the two disease thresholds (CIN2+, CIN3+).

Absolute accuracy

METADAS, an SAS macro for meta-analysis of diagnostic accuracy studies, was used to compute the pooled sensitivity and specificity and to plot the summary receiver operating curves (SROC) curve, with summary point and corresponding 95% confidence ellipse (Takwoingi 2009). METADAS can fit two statistical models: the hierarchical summary receiver operating curves (HSROC) and the bivariate model (Rutter 2002; Reitsma 2005; Chu 2006). For the computation of the pooled absolute sensitivity and specificity of the evaluated triage tests separately, we fitted the bivariate model.

In this case, all tests were considered as dichotomous variables (positive or negative result considering the standard cut-off of positivity).

Relative accuracy

Again, for computation of the relative sensitivity and specificity, we used the bivariate model in METADAS by adding a covariate for test, which estimates differences in logit sensitivity and logit specificity (Reitsma 2005; Takwoingi 2009).

Where no convergence was reached (in general when a small number of studies were included, in studies assessing both repeat cytology and HC2), accuracy parameters were estimated by omitting the correlation between the logit of true positivity rate (TPR) and the logit of the false positivity rate (FPR).

Investigations of heterogeneity

Multiple regressions were performed using the METADAS macro with each time point providing another covariate to verify the influence of study population and test characteristics on the accuracy estimates. If convergence failed for the bivariate model, the correlation between the logit TPR and logit FPR was removed to run separate univariate analyses, which should give consistent estimates of the means and variances of model parameters with some loss in efficiency (Riley 2007).

In the studies that provided data stratified by age group, particular attention was given to variation of test accuracy according to age.

To verify whether conclusions were robust over all subcategories of equivocal cervical cytology, as defined through different cytology classification systems, the review authors performed subgroup meta-analyses restricting selected studies by the classification system used for reporting cervical cytology results (see Assessment of methodological quality: other covariates).

Sensitivity analyses

The influence of outlying results was addressed by repeating the meta-analysis omitting the studies with extreme results. A sensitivity analysis was also performed by excluding randomised trials where not all cases were submitted to verification with the reference test. Finally, the absolute sensitivity and specificity estimates were pooled separately for the studies where only the HC2 assay was evaluated and where the comparator test (repeat cytology) was not applied.

Assessment of reporting bias

Publication bias

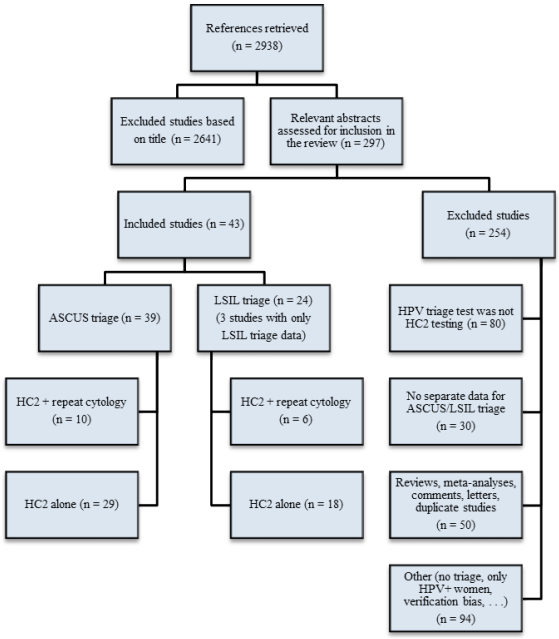
We used the effective sample size funnel plot and associated regression test of asymmetry to detect publication bias (Deeks 2005). These approaches are more appropriate in systematic reviews of diagnostic tests than the standard tests developed to detect publication bias in meta-analyses of randomised trials of healthcare interventions. It has been shown that the rank correlation test (Begg 1994), and the asymmetry regression test (Egger 1997), suffer from serious degrees of bias when applied to test accuracy studies (Deeks 2005).

RESULTS

Results of the search

We identified 2938 references from the electronic searches in the Cochrane Register of Diagnostic Test Accuracy Studies, the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), MEDLINE (through Pubmed) EMBASE and CERVIX databases. After initial evaluation of their titles, 2641 studies were excluded. We read the abstracts of the remaining 297 references, and the full papers of those that appeared to be potentially eligible. We excluded an additional 254 studies after reading the abstracts and/or full papers. A summary of the search results, with the main reasons for excluding publications, is shown in Figure 1.

Figure 1. Flowchart of retrieval, selection and exclusion of studies.



Included studies

We identified 39 different studies, allowing computation of the accuracy of HC2 triage in women with ASCUS: (Manos 1999; Bergeron 2000; Lytwyn 2000; Shlay 2000; Rebello 2001; Morin 2001; Zielinski 2001; Pretorius 2002; Kulasingam 2002; Solomon 2001/Sherman 2002; Wensveen 2003; Lonky 2003; Ordi 2003; Guyot 2003; Cuzick 2003; Andersson 2005; Davis-Devine 2005; Nieh 2005; Giovannelli 2005; Chen 2005b; Dalla Palma 2005; Kiatpongsan 2006; Bergeron 2006; Holladay 2006; Kelly 2006; Monsonego 2006; You 2007; Ronco 2007; Cuschieri 2007; De Francesco 2008; Szarewski 2008; Siddiqui 2008; Monsonego 2008; Lee 2009; Cattani 2009; Silverloo 2009; Huang 2009; Denton 2010; Del Mistro 2010).The accuracy of HC2 in triage of LSIL women could be evaluated in 24 studies (Bergeron 2000; Lytwyn 2000; Lee 2001; Rebello 2001; Zielinski 2001; Pretorius 2002; Kulasingam 2002; Sherman 2002; Guyot 2003; Andersson 2005; Chen 2005b; Holladay 2006; Monsonego 2006; You 2007; Ronco 2007; De Francesco 2008; Szarewski 2008; Monsonego 2008; Lee 2009; Cattani 2009; Huang 2009; Denton 2010; Voss 2010; Castle 2010a).

Only 10 of the 39 selected ASCUS studies presented data on triage by repetition of the Pap smear (Manos 1999; Bergeron 2000; Lytwyn 2000; Solomon 2001; Morin 2001; Kulasingam 2002; Andersson 2005; Monsonego 2008; Silverloo 2009; Del Mistro 2010), and only six of the 24 selected LSIL triage studies (Bergeron 2000; Lytwyn 2000; Kulasingam 2002; Sherman 2002; Andersson 2005; Monsonego 2008).

From the ALTS (ASCUS-LSIL Triage Study) study, we selected a first report for the extraction of accuracy data on ASCUS triage for the outcome of CIN2+ (Solomon 2001). For information on accuracy of ASCUS triage for outcome CIN3+ and LSIL triage (all outcomes), a second report of the ALTS study was used (Sherman 2002), which was completed by data sets received directly from the trial authors. More data sets were received from S Anderson, P Castle, A Lytwyn, J Monsonego, J Pretorius, G Ronco, M Schiffman and A Szarewski.

Description of the studies

Details of the study designs, the characteristics of the enrolled women and the applied tests (sampling devices, transport media, preparation methods of the repeat smear) are summarised in Characteristics of included studies and in Appendix 3.

Study design

Three studies were randomised controlled trials (Lytwyn 2000; Solomon 2001; Sherman 2002; Cuzick 2003). In all other studies, a concomitant testing design was used, where enrolled women received the HPV test, a repeat smear (if done) and the reference standard.

Study size

In total, 13,196 women with ASCUS, included in 39 studies, were triaged with HC2 at the standard test cut-off (1 pg/mL) and 5261 of them also received a repeat Pap smear. Twenty-one studies were small, each contributing fewer than 200 women; 11 studies were of intermediate size, each contributing between 200 and 500 women; and seven studies were large, each contributing more than 500 women. One of the large studies, the ASCUS-LSIL Triage Study (ALTS), enrolled more than 2300 women (Solomon 2001; Sherman 2002).

Nine-thousand nine-hundred and eighty-three women with LSIL, included in 24 studies were triaged with HC2 (at 1 pg/mLl) and 1591 of them also received a repeat smear. Fourteen studies were small with fewer than 200 women, seven studies were of intermediate size ranging 200 to 499 women, and three trials were large with more than 500 women.

Clinical setting and population characteristics

In all studies, women were recruited in colposcopy clinics or from gynaecologic services to which they had been referred because of cytologic abnormalities. In three studies, the referred women

with ASCUS cytology had repeated atypical cytology (Rebello 2001; Zielinski 2001; Guyot 2003). One study included only women with ASCUS occurring after two sequential normal smears (Morin 2001). Fifteen studies excluded women with a history of CIN, cervical surgery, or biopsy (Lytwyn 2000; Solomon 2001; Morin 2001; Zielinski 2001; Kulasingam 2002; Sherman 2002; Cuzick 2003; Davis-Devine 2005; Chen 2005b; Kiatpongsan 2006; Ronco 2007; De Francesco 2008; Szarewski 2008; Cattani 2009; Huang 2009).

Women with atypical squamous or atypical glandular endocervical cells were included in two studies (Shlay 2000; Wensveen 2003).

Enrolment of women with equivocal cytology was restricted to ASC-US cases, in fifteen studies where the 2001 Bethesda System (TBS 2001) was used (Pretorius 2002; Davis-Devine 2005; Giovannelli 2005; Dalla Palma 2005; Kiatpongsan 2006; Bergeron 2006; Holladay 2006; Kelly 2006; You 2007; Siddiqui 2008; Monsonego 2008; Huang 2009; Denton 2010; Del Mistro 2010; Castle 2010a).

Preparation of the repeat Pap test

A conventional Pap smear was used as cytologic triage method in six studies (Bergeron 2000; Lytwyn 2000; Morin 2001; Andersson 2005; Silverloo 2009; Del Mistro 2010). A liquid-based cytology specimen was prepared in four other studies (Manos 1999; Kulasingam 2002; Monsonego 2008; Solomon 2001/Sherman 2002).

Methodological quality of included studies

The overall methodological quality of all included studies is summarized in Figure 2. Overall, the quality of included studies was good with average negative scores for the 11 QUADAS items varying between 0% and 1à%; equivocal scores varying between 2% and 71% and positive scores varying between 29% and 95% of included studies (Figure 3). The clinical spectrum of participants was clearly representative in 74% of included studies and unclear in 21%. The reference standard was of acceptable quality in 95%, unclear in 5%, and never of unacceptable quality. The delay between triage testing and verification with the reference standard was short in 69%, unreported in 26% and long in 5%. Partial verification was avoided in 88%, unclear or not avoided in 12%, whereas differential verification was clearly absent in 86% and unclear in 5%. Incorporation bias was avoided in 93% and unclear in 5%. Blinding of the reference triage tests was reported in 52% of the studies and unreported in 45%. For the 8th QUADAS criterion (blinding of triage test), it was accepted that all HC2 interpretations were blinded, since results are generated automatically and, therefore, only studies including repeat cytology could be judged as potentially blinded, not-blinded or blinding unclear. Using this principle, 86% of the studies were considered as blinded, and for the other 14% it was unclear whether the comparator test (repeat cytology) was blinded towards the index test (HC2). Only 36% of studies reported on uninterpretable results, and 29% either explained any withdrawals or were clear that there were no withdrawals.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

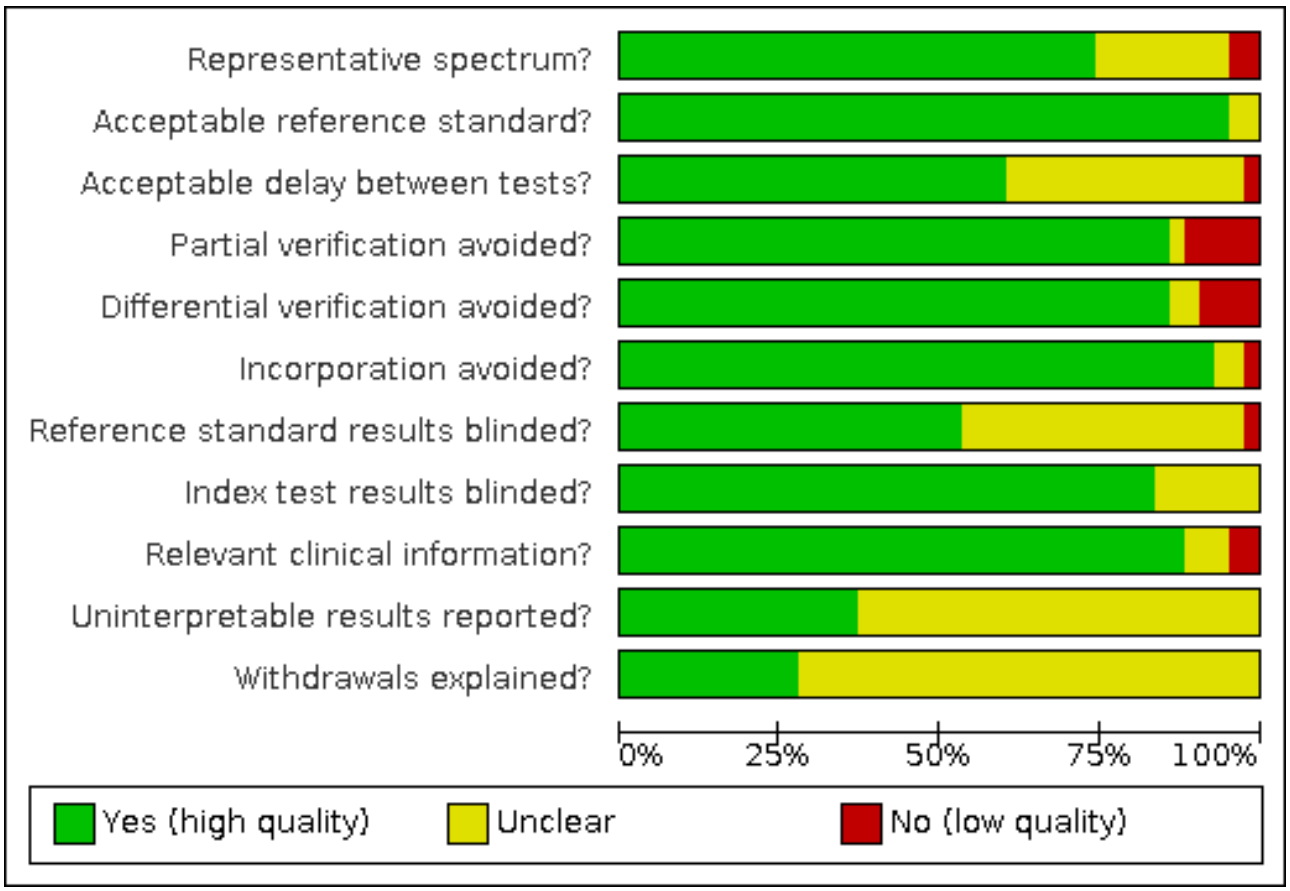
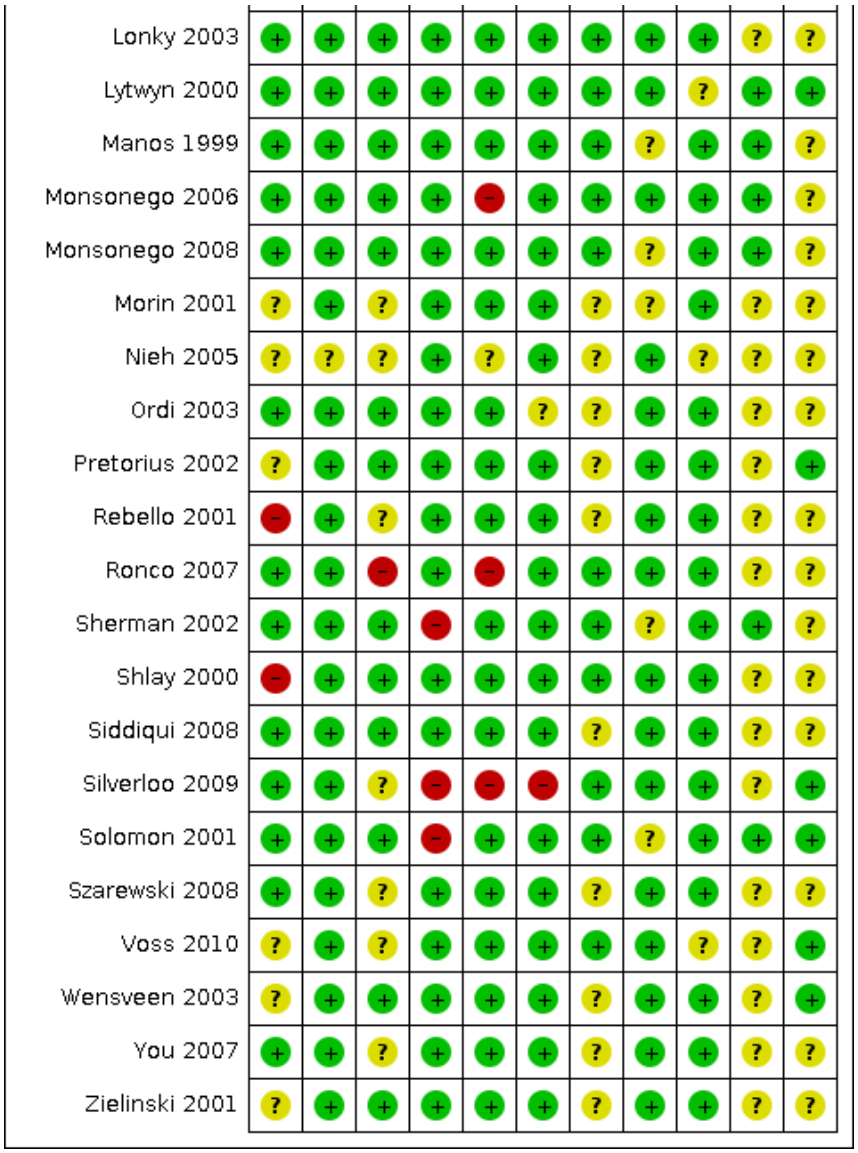


Figure 3. Methodological quality summary: review authors' judgements about each QUADAS item for each included study.

Figure 3. (Continued)



Findings

The main findings concerning the primary questions about the absolute and relative accuracy measures derived from studies where both triage methods (HC2 and repeat cytology) were used are presented first, and are summarised in the Summary of Results tables.

Subsequently, we assess the absolute accuracy of triage with HC2, derived from a larger group of studies that also included evaluations without repeat cytology (secondary objective). The results are summarised in tables included in the appendices.

1 Primary objective: accuracy of HC2 and repeat cytology in studies where both triage methods were applied

1.1 Triage of ASCUS

1.1.1 Absolute accuracy of HC2 triage of ASCUS cases

For the studies where both HC2 testing and repeat cytology were done, the absolute sensitivity of HC2, pooled from 10 studies, was 90.9% (95% CI 85.7 to 94.4%) for CIN2+. The pooled sensitivity from four studies where the outcome was CIN3+ was 94.8% (95% CI 89.6 to 97.5%) (Summary of findings 3). The pooled specificity was 60.7% (95% CI 52.9 to 68.0%) and 56.6% (95% CI 39.4 to 72.3%) for predicting absence of CIN2+ or CIN3+, respectively.

1.1.2 Absolute accuracy of cytology triage of ASCUS cases

The pooled sensitivity dropped substantially when the test threshold was increased: 71.5% (95% CI 62.9 to 78.8%) at ASCUS +, 44.1% (95% CI 33.3 to 55.5%) at LSIL+, and 15.8% (95% CI 6.5

to 33.6%) at HSIL+ for endpoint CIN2+; and 77.9% (95% CI 64.0 to 87.6%) at ASCUS+, 53.5% (95% CI 17.8 to 85.9%) at LSIL+, and 33.2% (95% CI 6.1 to 79.2%) at HSIL+ for endpoint CIN3+. The pooled specificity of repeat cytology rose with increasing test threshold: between 68.4% (95% CI 59.9 to 75.8%) at ASCUS+, and 98.3% (95% CI 96.7 to 99.1%) at HSIL+, for excluding CIN2+; and between 57.4% (95% CI 40.36 to 73.0%) at ASCUS+, and 95.6% (95% CI 93.6 to 97.1%) at HSIL+, for excluding CIN3+ (Summary of findings 3; Appendix 4).

1.1.3 Relative accuracy of HC2 compared to repeat cytology in triage of ASCUS cases

In order to compute the relative sensitivity and specificity of HC2 versus repeat cytology at different cut-offs, the triage test (HC2 or repeat cytology) was added as a covariate in the bivariate model.

Triage of ASCUS cases with HC2 was 27% more sensitive than repetition of the Pap smear at the lowest cytological cut-off (ASCUS +) for detecting CIN2+ (relative sensitivity: 1.27; 95% CI 1.16 to 1.39; P value < 0.0001) (Summary of findings 3; Figure 4). This contrast rose further when the cut-off of the repeated smear increased. The specificity of a repeat smear at the cut-off ASCUS+ was nearly identical (relative specificity: 0.99; 95% CI 0.97 to 1.03) to the specificity of HC2 for exclusion of CIN2+. At higher cytological cut-offs, HC2 became progressively less specific than repeat cytology (Figure 5).

Figure 4. Analysis 1: Summary ROC-plot (Bivariate model with test as covariate): Sensitivity and specificity of triage of ASCUS with HC2 (black) (at RLU>1) versus repeat cytology (red) at cut-off ASCUS+ for an outcome of underlying CIN2+ based on within study comparisons.

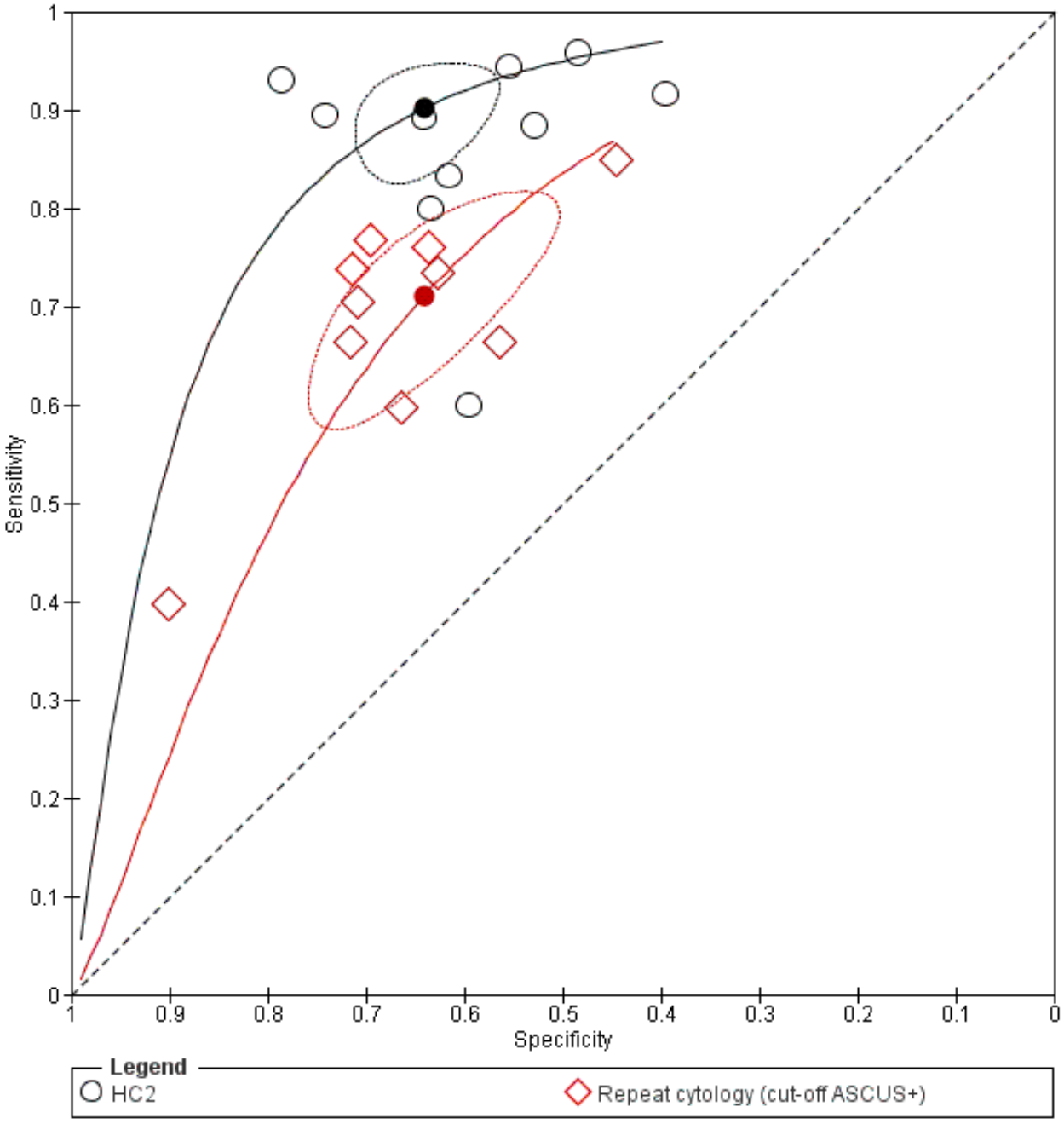
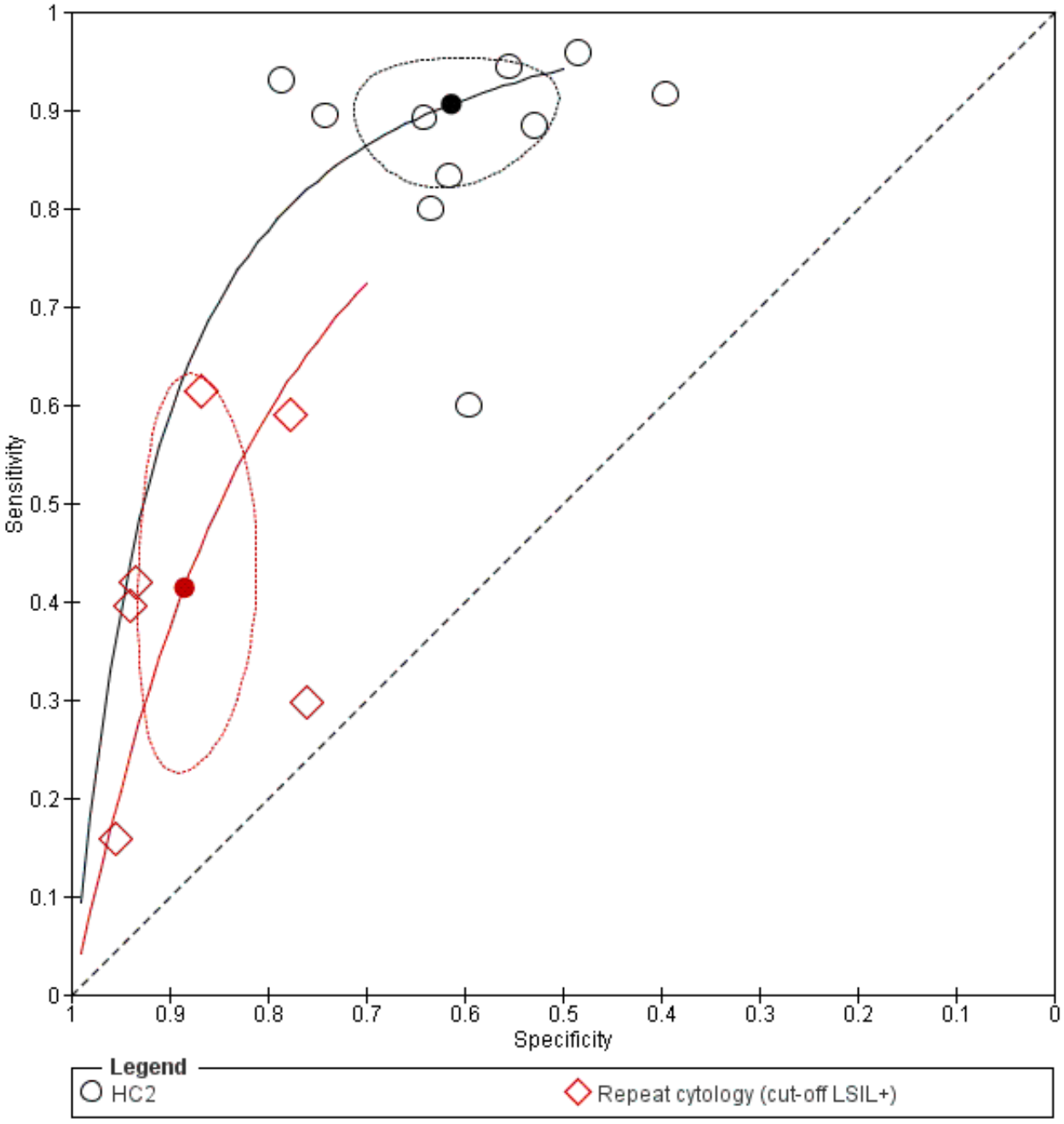


Figure 5. Analysis 2: Summary ROC-plot (Bivariate model with test as covariate): Sensitivity and specificity of triage of LSIL with HC2 (black) (at RLU>1) versus repeat cytology (red) at cut-off ASCUS+ for an outcome of underlying CIN2+ based on within study comparisons.



Due to failure of convergence, the relative accuracy measures for detection of CIN3+ had to be computed by removing the correlation parameter from the bivariate model. HC2 was more sensitive than repeat cytology for detection of CIN3+, and the difference rose with increasing cytological cut-off: ratios ranging from 1.13 (95% CI: 1.06 to 1.22) at cut-off ASCUS, to 2.82 (95% CI: 0.79 to 10) at cut-off HSIL. However, the specificity of HC2 for the outcome of CIN3+ was similar to repeat cytology at ASCUS, but became significantly lower at higher cytological cut-offs: ratios ranging from 1.13 (95% CI: 1.06 to 1.22) at cut-off ASCUS, to 2.82 (95% CI: 0.79 to 10) at cut-off HSIL (Table 3).

1.2 Triage of LSIL

1.2.1 Absolute accuracy of HC2 triage of LSIL cases

In the studies where both triage methods were applied, the sensitivity of HC2 was high: 96.2% (95% CI 91.4 to 98.3%) and 97.5%

(95% CI 69.6 to 99.8%) for CIN2+ and CIN3+, respectively (Summary of findings 4). HC2 triage in LSIL cases showed a low pooled specificity: 27.7% (95% CI 20.9 to 35.7%) and 24.8% (95% CI 7.32 to 58.1%) for predicting absence of CIN2+ and CIN3+, respectively.

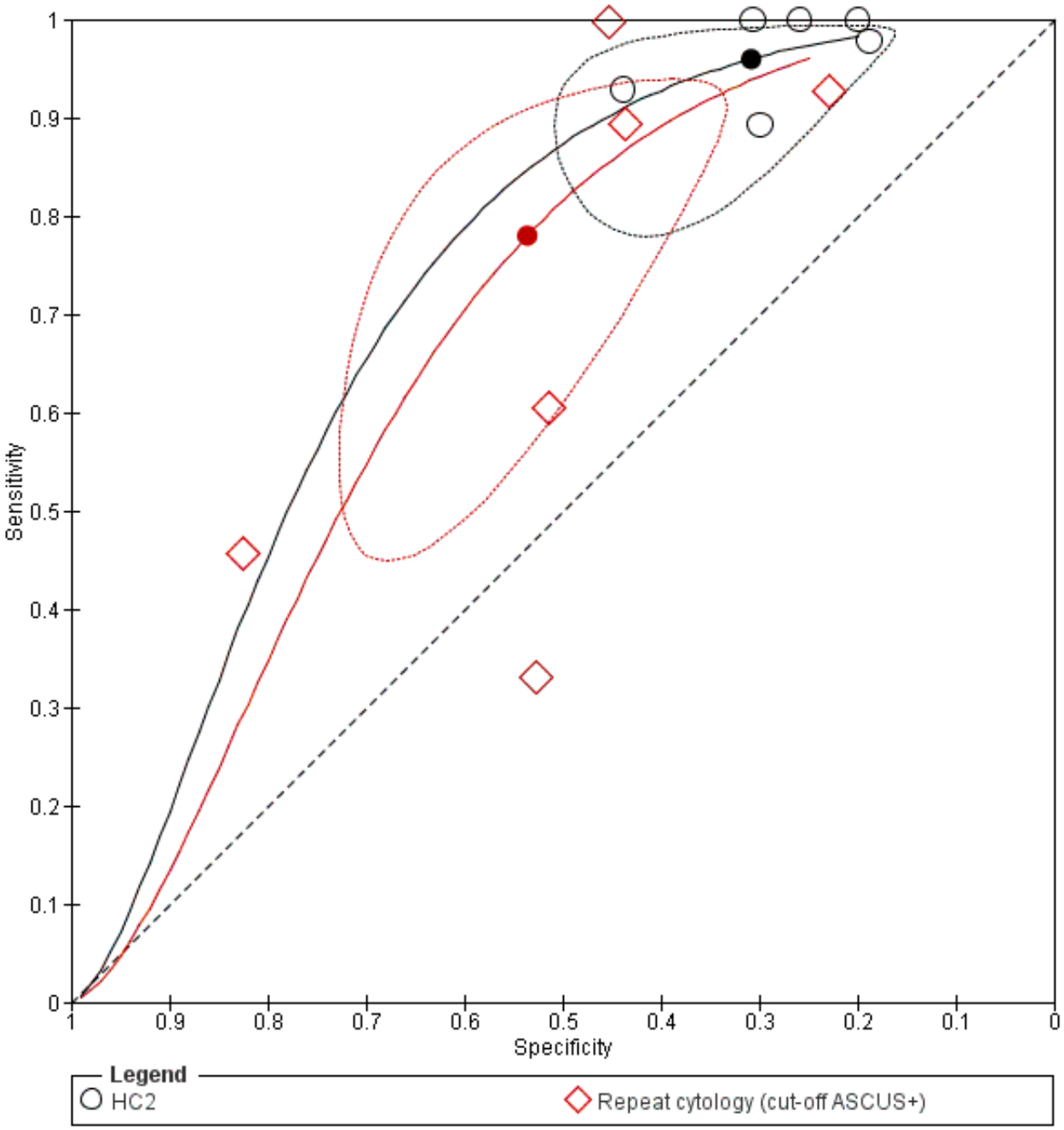
1.2.2 Absolute accuracy of cytology triage of LSIL cases

The pooled sensitivity for prediction of the presence of CIN2+ dropped with increasing cut-off: from 77.1% (95% CI 59.5 to 88.5%) at ASCUS+, to 31.6% (95% CI 18.2 to 49.0%) at HSIL+; and from 84.6% (95% CI 48.6 to 97.0%) at ASCUS+, to 41.9% (95% CI 24.8 to 61.2%) at HSIL+, for prediction of CIN3+ lesions. The specificity rose with increasing cytological cut-off (Summary of findings 4; Appendix 5).

1.2.3 Relative accuracy of HC2 compared to repeat cytology in triage of LSIL cases

The sensitivity of HC2 for CIN2+ was significantly higher than that of repeat cytology at cut-off ASCUS+ (P value 0.007) (relative sensitivity: 1.23 (95% CI 1.06 to 1.43)). The specificity of HC2, on the other hand, was substantially and significantly lower than that of repeat cytology at cut-off ASCUS+ (P value < 0.0001) (relative specificity: 0.66 (95% CI 0.58 to 0.75) (Figure 6; Summary of findings 4). At higher cytological thresholds, contrasts increased (progressively higher relative sensitivity and lower relative specificity). For the outcome CIN3+, the relative accuracy estimates were similar, but the differences between both triage tests were not always significant (Table 4).

Figure 6. Analysis 7: Summary ROC-plot (Bivariate model with test as covariate): Sensitivity and specificity of triage of ASCUS with HC2 (black) (at RLU>1) versus repeat cytology (red) at cut-off LSIL+ for an outcome of underlying CIN2+ based on within study comparisons.



2. Secondary objective: accuracy of HC2 irrespective of whether or not repeat cytology was done

2.1 Absolute accuracy in triage of ASCUS

In the 39 retrieved studies, the absolute sensitivity of triage with HC2 varied from 60% (Andersson 2005), to 100% for the detection of CIN2+ (Guyot 2003; Cuzick 2003; Davis-Devine 2005; Holladay 2006; Szarewski 2008),and from 75% (Andersson 2005; Cattani 2009), to 100% for detection of CIN3+ (Zielinski 2001; Wensveen 2003; Szarewski 2008; Siddiqui 2008). The pooled sensitivities were 90.4% (95% CI 88.1 to 92.3%) and 93.7% (95% CI 90.4 to 95.9%) for detecting CIN2+ and CIN3+, respectively (Appendix 4).

The specificity of HC2 varied from 31% (Nieh 2005), to 80% for the detection of CIN2+ (Giovannelli 2005), and from 25% (Lee 2009), to 70% for detection of CIN3+ (Pretorius 2002; Ronco 2007). The pooled specificities were 58.3% (95% CI 53.6 to 62.9%) and 52.3%

(95% CI 45.7 to 58.7%) for predicting absence of CIN2+ or CIN3+, respectively.

The pooled accuracy estimates of HC2 from the 29 studies where only HPV-based triage was done, were not significantly different from the 10 studies where both triage methods were assessed (P value 0.534, and P value 0.250 for CIN2+ and CIN3+, respectively).

2.2 Absolute accuracy in triage of LSIL

In the 24 retrieved studies, the absolute sensitivity of triage with HC2 varied from 80% (Cattani 2009), to 100% for the detection of CIN2+ (Lytwyn 2000; Zielinski 2001; Kulasingam 2002; Chen 2005b; Holladay 2006; Szarewski 2008; Monsonego 2008; Lee 2009; Voss 2010), and from 76% (De Francesco 2008) to 100% for detection of CIN3+ (Zielinski 2001; Kulasingam 2002; Andersson 2005; Chen 2005b; Holladay 2006; Ronco 2007; Szarewski 2008; Monsonego 2008; Lee 2009).

The pooled absolute sensitivities were 95.4% (95% CI 94.0.1 to 96.5%) and 96.4% (95% CI 90.5 to 98.7%) for detecting CIN2+ and CIN3+, respectively (Appendix 5).

The specificity varied between 16% (Chen 2005b) and 58% for confirming absence of CIN2+ (Lee 2009), and between 15% (Huang 2009) and 47% for confirming absence of CIN3+ (Lee 2009). The pooled specificities were 27.8% (95% CI 23.8 to 32.1%) and 23.7% (95% CI 19.4 to 28.7%) for CIN2+ and CIN3+, respectively.

There was no significant difference in pooled accuracy measures of HC2 between studies where both triage methods were applied and studies where only HC2 triage was applied (P value 0.715, and P value 0.450 for the outcomes CIN2+ and CIN3+, respectively).

3. Influence of study characteristics

When no convergence was reached using the bivariate model, including covariates, univariate analyses were run without the correlation parameter to investigate the influence of study and test characteristics on the sensitivity and specificity. Results of the heterogeneity analysis can be found in Appendix 6.

The heterogeneity analysis by covariate was performed only when the groups compared contained at least five studies in one group and at least three studies in the other group. Most often, the absolute accuracy of triage with HC2 or repeat cytology did not change significantly by covariate, except in the following cases:

- Triage of ASCUS with HC2 for outcome CIN2+, by sampling device and transport medium:
  - HC2 was less sensitive when the sample was collected with a brush than with a broom: relative sensitivity = 0.92 (95% CI: 0.88 to 0.97);
  - HC2 was less specific when the transport medium was Preservcyt compared to specimen transport medium (STM): relative sensitivity = 0.72 (95% CI: 0.55 to 0.95).
- Triage of ASCUS with repeat cytology for outcome CIN2+, by continent:
  - Repeat cytology was less sensitive (0.79; 95% CI: 0.63 to 0.99), but more specific (1.27; 95% CI: 1.02 to 1.58), in studies conducted in Europe compared to America.
- Triage of LSIL with HC2 for outcome CIN2+, by sampling device and continent:
  - HC2 was less sensitive (0.94; 95% CI: 0.91 to 0.98) when a brush was used compared to broom;
  - the specificity varied by continent (P value 0.04): 21.4% in America (95% CI: 16.7% to 27.0%), 24.7% in Asia (95% CI: 16.8% to 34.9%), and 33.1% in Europe (95% CI: 27.8% to 38.8%).
- Triage of LSIL with HC2 for the outcome CIN3+, by continent:
  - HC2 was more specific in Europe than in America (1.50; 95% CI: 1.01 to 2.21).

4. Influence of age

Age-stratified data on the accuracy of detection of high grade CIN were published in only three studies (Sherman 2002; Ronco 2007; Castle 2010a). However, no pooled analysis was possible from the published data because different cut-offs were used to define age strata. From the ASCUS-LSIL Triage Study (Solomon 2001), and the Italian NTCC study, we obtained non-published five-year age-stratified data for the outcomes of CIN2+ directly from Dr M Schiffman (National Cancer Institute, Bethesda, MD) and Dr G Ronco (Istituto Oncologica, Torino, Italy). Similarly stratified data could be extracted from the published paper of Castle 2010a for LSIL triage.

The HSROC analysis failed to calculate the age-specific absolute and relative accuracy measures for the triage of women with ASCUS, since only two studies provided data (Sherman 2002; Ronco 2007).

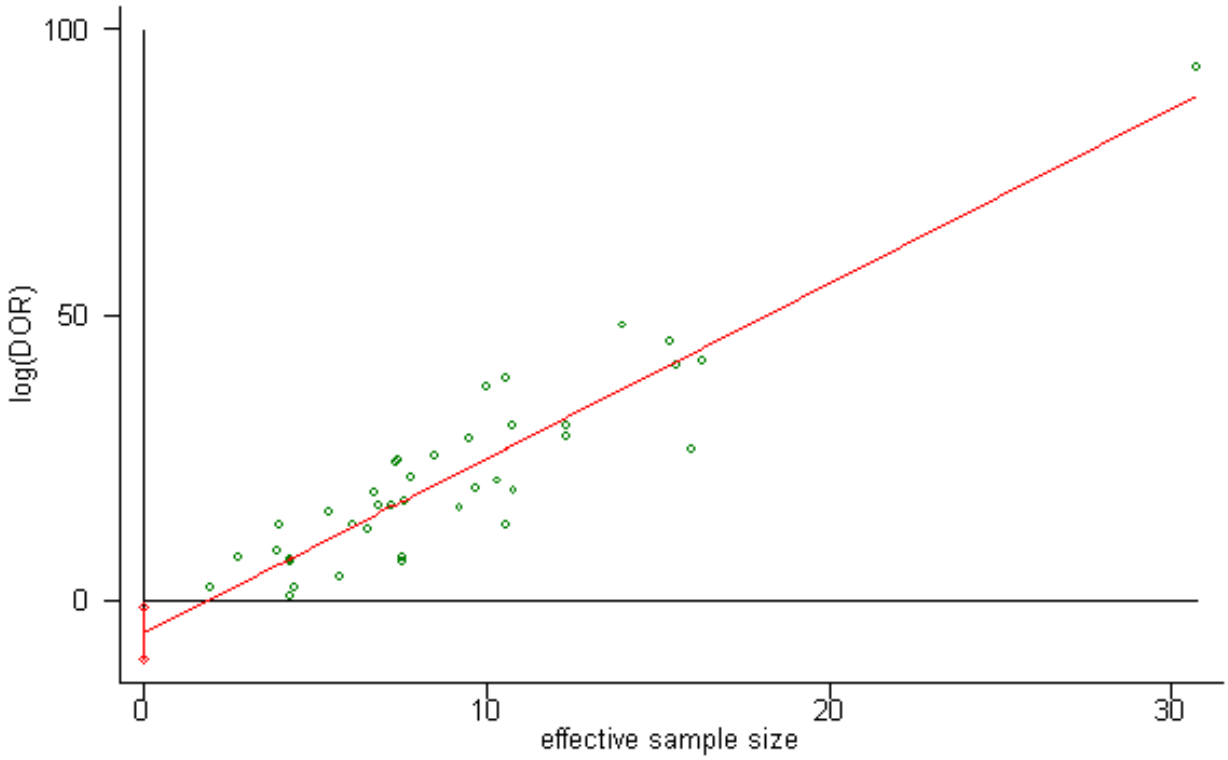
The age-specific absolute and relative sensitivity and specificity and confidence intervals for LSIL triage are shown in Appendix 7. The sensitivity did not vary significantly by age group. However the specificity of HC2 always increased by age. For instance, the pooled specificity of triaging LSIL women with HC2 for excluding CIN2+ was 18.0% (95% CI 15.6% to 20.6%) in women younger than 30, and 43.7% (95% CI 24.4% to 65.2%) in women aged 50 years or older.

5. Publication bias or sample size effects

Table 5 shows the intercept and its 95% CI of the asymmetry regression assessing the relationship between the effective sample size and the logarithm of the diagnostic odds ratio (DOR) for all triage groups (ASCUS, LSIL), triage tests (HC2, repeat cytology) and outcomes (CIN2+ and CIN3+). An intercept significantly different from zero suggests publication bias or sample size effects. A negative intercept significantly different from zero (-4.69 (95% CI -10.23 to -1.15), P value 0.015) was observed only in triage of ASCUS with HC2 for an outcome of CIN2+. This means that larger studies tended to show a larger overall accuracy (DOR). The asymmetry regression plot (Figure 7) indicates that the regression was influenced by one large study with high DOR (ALTS study of Solomon 2001). Omission of the ALTS study made the intercept statistically non significant from zero, but did not alter the intercept substantially: -4.00 (95% CI -9.59 to 1.60). These findings are suggestive of a positive relationship between diagnostic accuracy and sample size. The ALTS trial was one of the best designed triage studies with high-quality disease certification. The data show the opposite of the usual publication bias where excessive accuracy

in small published studies is unbalanced by non-published small studies with low accuracy.

Figure 7. Assymmetry regression plot showing the relation between the effective sample size and the logarithm of the diagnostic odds ratio of HC2 triage of ASCUS for the detection of CIN2+



A negative intercept was also observed In triage of ASCUS for CIN3+ with HC2, but this was not statistically significant (P value > 0.05). In LSIL triage with HC2, the intercepts were not significantly different from zero.

Triage with newer repeat cytology showed significant intercepts, but assessment was based on a small number of studies (10 or less), therefore, sample size effects cannot be excluded with certainty.

6. Sensitivity analyses

6.1 Triage of women with ASCUS

Rather low values of sensitivity for CIN2+ were reported in two studies (Andersson 2005; Giovannelli 2005): 60% and 75%, respectively. These two studies were small, and their omission resulted in a change in the pooled estimate of sensitivity of only 0.3%. The specificity of HC2 for CIN2+ was extremely low in one study, at 27% (Lee 2009). Exclusion of this study, yielded a small and non-significant increase of the pooled specificity: from 58.3% (95% CI 53.8% to 62.9%) to 58.8% (95% CI 54.1% to 63.4%).

Deletion of the ALTS trial from the meta-analysis yielded a minor insignificant decrease in the pooled absolute sensitivity of HC2 for CIN2+ from 90.4% (95% CI 88.2% to 92.3%) to 89.5% (95% CI 87.4% to 91.3%), whereas the specificity increased from 58.3% (95% CI 53.6% to 62.9%) to 58.6% (95%CI 53.7% to 63.3%).

The overall sensitivity and specificity pooled from the 29 studies where only HPV triage data were available were 89.9% (95%CI 86.9% to 92.2%) and 57.4% (95% CI 51.5% to 63.2%), respectively, and were not significantly different from the 10 studies where both triage tests were used (P values of 0.53 and 0.55, respectively).

6.2. Triage of women with LSIL

There were no studies that showed outlying results for sensitivity or specificity. Deletion of the ALTS trial yielded no changes in the pooled absolute sensitivity of HC2 for CIN2+ 95.4% to 95.2% (95%CI 93.7% to 96.4%) and an insignificant increase in pooled absolute specificity from 27.8% to 28.3% (95%CI 24.2% to 32.8%). The overall sensitivity and specificity pooled from the 18 studies where only HPV triage data were available were 95.2% (95%CI 93.6% to 96.4%) and 27.9% (95%CI 23.0% to 33.3%), respectively, and were not significantly different from the six studies for which both triage tests were available (P values of 0.97 and 0.45 respectively).

DISCUSSION

The current Cochrane review corroborates the conclusions from our previous meta-analyses which all indicated that HC2 triage of women with ASCUS predicts presence of underlying high-grade CIN with greater accuracy than a repeat Pap smear considering ASCUS+

as cut-off (significantly higher sensitivity, similar specificity) (Arbyn 2004a; Arbyn 2004b; Arbyn 2005).

However, the conclusions concerning the triage of LSIL differ from previous reviews, where HC2 triage showed no significant gain in sensitivity but a substantial and statistically significant loss in specificity compared to repeat cytology (Arbyn 2002; Arbyn 2006). In the current Cochrane review, with the inclusion of more studies, the lower specificity of HC2 triage of LSIL was confirmed, but a significant gain in sensitivity was revealed.

Below, we will discuss how robust and generalisable these findings are.

1. Consistency of the findings

1.1 Triage of women with ASCUS

The accuracy of cytological triage was described in a minority of studies: for instance, 39 studies assessed the sensitivity and specificity of HC2 for CIN2+, but only 10 of them evaluated repeat cytology (at cut-off ASCUS or worse) as well. However, no significant inter-study heterogeneity was found in the absolute sensitivities. Moreover, the fact that the sensitivity of HC2 did not differ between the 10 studies where both triage methods were evaluated and the 29 studies that only offered virological triage, provides considerable weight regarding the consistency and the generalisability of the study results. We included one randomised trial, the ALTS study (Sherman 2002; Solomon 2001), where not all women in the HPV-triage and cytology-arms were verified. However, in the HPV arm, the CIN2+ and CIN3+ detection rates were similar to those in the colposcopy arm where all women were submitted to the reference standard. Moreover, the pooled accuracy estimates of the meta-analyses did not change significantly after exclusion of the ALTS study.

1.2 Triage of women with LSIL

As for ASCUS above, the pooled accuracy estimates for LSIL triage did not change after omission of the ALTS study.

Only six studies reported data of virological and cytological triage of women with LSIL. However, there was no significant difference between the pooled accuracy of these six studies and the pooled accuracy of the 18 studies reporting only HC2 data.

LSIL is usually the manifestation of a productive HPV infection with low potential for neoplastic transformation (Zuna 2005). Therefore, HPV DNA testing nearly always yields positive results, limiting its capacity to distinguish between cases with, or without, severe underlying or developing lesions. The proportion of LSIL observed in women with a positive HC2 test reported in the included studies ranged from 55% to 89%. The test positivity rates were consistently higher than in ASCUS. Because of the high hrHPV positivity rate (83%), enrolment of LSIL women in the ALTS trial was interrupted (ALTS Group 2000). Moss found 89% positive HC2 results in women under 35 years of age with mild dyskaryosis on Pap smears, 69% in women between the ages of 35 and 49, and 51% in women aged 50 or over (Moss 2006). The specificity for the outcome CIN2+ in the ALTS study was 16% in women under 29 years of age, and 30% in women of 29 years or older (Sherman 2002).

2. Low specificity of all triage methods

The specificity of triage with HC2 or by repeat Pap smears at a low cytologic threshold ranged from moderate, in the case of ASCUS, to poor, in the case of LSIL. Colposcopy of all triage positive women generates considerable costs. Therefore, there is a need for specific triage tests for women with LSIL, with high predictive values, that allow for the identification of women at increased risk for cervical cancer.

Virological triage could be made more specific by increasing the viral load cut-off, by adding a second triage test, by choosing an alternative triage test, or by excluding young women.

Viral load cut-off

Very few published data are available concerning HC2 triage at higher test thresholds. Increasing the cut-off from 1 pg/mL to 10 pg/mL, in the ALTS, yielded a gain in specificity for exclusion of CIN2+ of 12% in triage of ASCUS, and 11% in triage of LSIL. This gain in specificity was accompanied by a loss in sensitivity of 9% for women with ASCUS or 10% for women with LSIL (Sherman 2002). Guyot observed an increase in specificity (13.6%, 95% CI to -15.4 to 42.6%), without loss in sensitivity, by raising the HC2 cut-off to 3 pg/mL in a small-sized triage study where the included women had persistent borderline smears (Guyot 2003). Rebello triaged women with two smears showing borderline or mild dyskaryosis with HC2 at 1 pg/mL, 2 pg/mLand 4 pg/mL and found sensitivities for CIN2+ of 108/116 (93%), 106/116 (91%), and 99/116 (85%) respectively, and specificities of 119/217 (55%), 124/217 (57%), and 134/217 (62%) (Rebello 2001). Ronco made the same conclusions after observing an increase of specificities of HC2 for CIN2+ among women with ASCUS at 1 pg/mL, 2 pg/mL, 4 pg/mL, 10 pg/mL and 20 pg/mL, of 70.9%, 75.5%, 78.0%, 81.1% and 83.6%, respectively. In contrast, sensitivities decreased with higher positivity threshold of HC2 (96.2%, 96.2%, 88.5%, 84.6%, and 73.1%, respectively) (Ronco 2007). In women with LSIL, the specificities of HC2 for outcome CIN2+ increased from 48.3% to 55.6%, whereas the sensitivity dropped from 96.9% to 90.6% when raising the HC2 cut-off from 1 pg/mL to 20 pg/mL (Ronco 2007).

Targeted HPV types

The composition of the cocktail of HPV type-specific probes, the analytical capacity to pick up DNA from target types, and cross-reactivity with non-target types influence the specificity of HPV triage. *A posteriori* HPV typing of the ALTS samples, taken at enrolment, indicated that genotyping for more than 10 HPV genotypes resulted in serious loss in the specificity, with almost no additional gain in sensitivity (Schiffman 2005a). Schiffman compared HC2 accuracy for CIN3+ with that of polymerase chain reaction (PCR) amplification with L1 consensus primer PGMY09/11 followed by reverse-line blot hybridisation for 13 high-risk types in triage of women with ASCUS (Schiffman 2005b). Sensitivity and specificity of HC2 for CIN3+, corrected for the insensitivity of colposcopy, was 92% and 53%, whereas the PCR showed - surprisingly - a lower sensitivity (87%) and a higher specificity (56%) (P value for differences in sensitivity and specificity < 0.001). The specificity for a cumulative diagnosis (defined over 0 to two years after enrolment) could be increased substantially by identifying HPV 16 (see below) (Castle 2005).

Triage with other molecular markers

Testing of ASCUS women for E6/E7 transcripts of HPV types 16, 18, 31, 33, and 45 using real-time multiplex Nucleic acid sequence based amplification (NASBA) (Pretect HPV Proofer, Norchip, AS, Klokkarstua, Norway) yielded an equal sensitivity (100% (2/2)) but a higher specificity (83%; 95% CI 70.7% to 91.8%) for subsequent CIN2+ than triaging with GP5+/GP6+ consensus PCR (specificity of 56%; 95% CI 41.3% to 69.5%) (P value for difference in specificity: 0.003) (Molden 2005).

Carozzi could reduce the false positivity rate of HPV triage by a factor of approximately 2.5 by p16-immunostaining slides from women with minor cytological lesions testing HPV-positive. This policy was accompanied with loss in sensitivity for CIN2+ of 12% (Carozzi 2006).

Nieh tested ASCUS cases for p16-overexpression, and with HC2 and found an insignificantly higher sensitivity and a significantly higher specificity for p16 (sensitivity of p16 was 20/21, sensitivity of HC2 was 18/21 (P value for McNemar's Chi^2 = 0.157); specificity of p16 was 14/45, specificity of HC2 was 25/45 (P value for McNemar's Chi^2 = 0.012) (Nieh 2005). However, Longatto-Filho found equal sensitivity for CIN2+ (3/3), but lower specificity for p16 staining (19/40) compared to HPV testing (27/40) in a small series of ASCUS cases (P value for Pearson's Chi^2 = 0.070) (Longatto-Filho 2005). Triage of ASCUS or LSIL with new molecular markers is the target of ongoing research and systematic reviews should be performed as soon as more studies become available.

Influence of age

The influence of age on the accuracy could be assessed in only two studies for triage of ASCUS, and in three studies for triage of LSIL. Multivariate analyses identified a significant increase in specificity by age in triage of LSIL when the outcome was CIN3+. The increase in specificity reflects the drop in HPV test positivity rate with increasing age. However, in LSIL triage, the drop in test positivity, and consequent increase in specificity in older women, varied in size between the studies. In one study, the test positivity rates were 57% and 38%, and the specificity rates were 45% and 66%, in the 30 to 39 years and over 50 years age groups, respectively (Ronco 2007). In another study, the age variation in the test positivity and specificity was limited, with a test positivity rate of 76% and a specificity of 25% in women aged 50 or older (Castle 2010a).

3. Verification bias

According to the study selection criteria, colposcopy was performed on all subjects, and, therefore, in principle, no verification bias could occur. In the ALTS, results from women in the HPV arm were not verified when the HC2 test was negative, if results from repeat cytology ranged from normal to LSIL, and if no suspect macroscopic lesions were observed. However, colposcopy was performed on all women in a second arm of the ALTS. We can conclude that it is probable that no - or very few cases - of CIN2+ were missed in the HPV arm, and that there is no evidence of verification bias in the ALTS because the cross-sectional detection rates of histologically confirmed CIN2+ were 11.3% (95% CI 9.5% to 13.2%) for women in the colposcopy arm, and 11.7% (95% CI 9.9% to 13.7%) for women in the HPV arm (Sherman 2002; Solomon 2001). Three other studies could be considered as potentially suffering from verification bias because of incomplete verification with the reference test (Dalla Palma 2005; Holladay 2006; Silverloo 2009). Indeed, the low specificity (37%) and the rather high sensitivity (94%) reported in triage of ASCUS participants by Dalla Palma 2005 could be explained by some degree of verification bias. The other two studies did not show an outlying low specificity (Holladay 2006, Silverloo 2009). Moreover, the multivariate regression analysis did not reveal "partial verification" as a significant factor that explained the inter-study heterogeneity of the accuracy.

It should be recognised that certain studies described accuracy in series of women with ASCUS and LSIL who all were submitted to verification without providing details about non-verified women, giving the impression that partial verification was completely avoided.

4. Validity of the reference standard

We used histology as the reference standard and accepted negative satisfactory colposcopy as evidence for absence of high-grade CIN when no biopsies were taken. This definition of the reference standard might be imperfect. Recent data have shown that the sensitivity of colposcopy for high-grade CIN might be considerably lower than usually believed. Mitchell estimated, from a meta-analysis including nine studies, that the average sensitivity and specificity of colposcopy in detecting CIN2+ was 96% and 48% respectively (Mitchell 1998). However, in most studies included in this meta-analysis, biopsy taking was triggered by a positive colposcopic interpretation. Since biopsy taking was correlated to a positive colposcopic impression, the sensitivity estimation of colposcopy for detection of CIN2+ is inflated artificially (Arbyn 2009b). In one particular study, conducted in China, a more unbiased assessment of colposcopic accuracy was revealed. Biopsies were taken not only from colposcopically-suspect areas but also from the four quadrants of the transformation zone in colposcopically negative cases (Pretorius 2004). Moreover, endocervical curettage was performed in every woman. In this study the sensitivity of colposcopy-directed biopsy for CIN2+ in women with satisfactory colposcopy was 57% (95% CI 52% to 62%). In the ALTS, immediate colposcopy at enrolment detected 64% (95% CI 57% to 71%) of the two-year clinical cumulative diagnoses of CIN2+ (ALTS Group 2003a).

The fact that histological interpretation of biopsy material is also prone to error has been widely documented in the literature (Ismail 1989; Robertson 1989; O'Sullivan 1998; Stoler 2001).

Misclassifications in colposcopy and histology may yield biased estimates of the accuracy of triage tests, if the correlation of test and reference standard ratings are dependent on disease status (Pepe 2004). However, if reference standard classification errors are independent, test accuracy estimates will not be affected. In the Chinese study, Pretorius showed that the sensitivity of HPV testing was similar when either the usual or the improved reference standard was used (Pretorius 2006).

5. Choice of the endpoints: CIN2+ or CIN3+

All included studies described accuracy for CIN2+ but only half of them also provided data for the outcome of CIN3+. Nevertheless, CIN3+ might be a more relevant endpoint, since its potential to regress spontaneously is more limited than CIN2 (Morrison 1992; Ostor 1993; Schiffman 2003). Moreover, CIN2, is less reproducible and comprises over-classified CIN1 (Ismail 1989; Robertson 1989). It is possible that HPV triage leads to detection of additional CIN

lesions which may, predominantly, be at lower risk of progression than those usually detected after an HSIL smear (Sherman 2003). The fact that the pooled relative sensitivities (HC2/repeat cytology) were 1.33 (for CIN2+) and 1.21 (for CIN3+), in the four studies where both outcomes were documented (Kulasingam 2002; Sherman 2002; Andersson 2005; Monsonego 2008) provides some evidence for the hypothesis that HPV triage results in a small amount of over-diagnosis. Sherman noted that CIN3 lesions, found after enrolment in the ALTS study as a consequence of HC2 testing, were overwhelmingly small and showed less gland involvement than those found after a HSIL repeat smear (Sherman 2003).

6. Previous reviews and meta-analyses

Conclusions from the current Cochrane review on triage of women with ASCUS are in agreement with findings from previous meta-analyses conducted by the review authors and by others (Cuzick 1999; ANAES 2002; Arbyn 2004b; Arbyn 2006), which were already accepted as evidence for recent European and American guidelines for management of women with ASCUS or borderline cervical cytology (ASCCP 2006; Wright 2007; European Commission 2008; Jordan 2008b; Solomon 2009; ACOG 2009; Partridge 2010; Stampler 2010).

The findings on triage of women of LSIL are different from previous meta-analyses, where it was concluded that triage with HC2 was not more sensitive, but substantially less specific than repeat cytology (Arbyn 2005; Arbyn 2006). Therefore HC2 was not recommended in guiding management of women with low-grade cytological lesions (Wright 2007; Jordan 2008b). The current Cochrane Review demonstrated significantly higher sensitivity of HC2 for CIN2+ and CIN3+. This new finding could justify recommending the use of HC2 to decide whether women need referral to colposcopy. However, the practice recommendations for management of LSIL should be based on local cost-effectiveness analyses, the local prevalence of HPV in LSIL, and compliance of women with follow-up recommendations, and should be restricted in situations where access to colposcopy referral is limited and/or expensive. Where sufficient colposcopy capacity exists, and where colposcopy is not excessively expensive, direct referral of LSIL women to colposcopy is a defendable option. The American Society for Colposcopy and Cervical Pathology (ASCCP) does not recommend reflex HPV triage, but proposes to refer to colposcopy (Wright 2002). If colposcopy and/or biopsy are normal, or only reveal CIN1, an HPV test at 12 months or two repeat smears after the initial LSIL smear is recommended. Postponing triage, is another option, allowing viral clearance - over a period of six to 12 months this can vary from 18% to 45% (Bais 2005) - and reducing the need for colposcopy. This latter recommendation is conditioned by good compliance with follow-up recommendations. HPV DNA testing certainly is not useful in young women with LSIL, given the very high prevalence of HPV infection and the very high probability of regression unrelated to initial HPV status (Woodman 2001; Moscicki 2004). HPV triage in older women, using higher viral load cut-off, might be an acceptable management option, but more age-specific accuracy data are needed to define the age cut-off. In the USA, LSIL triage with hrHPV testing is only recommended for postmenopausal women (Solomon 2009).

Summary of main results

Triage of women with a cytological test result of ASCUS (or ASC-US) by means of the HC-2 assay is more accurate (i.e. more sensitive, and equally specific) than repetition of the cytological test to detect underlying CIN2, or worse, and CIN3, or worse.

Triage of women with a cytological test result of LSIL by means of the HC-2 assay is more sensitive, but substantially less specific, than repetition of the cytological test to detect CIN2+ or CIN3+. The specificity of HC2 improves for older women, but a clear universal age cut-off (older than 35, 40 or 45 years) cannot be defined because of the low number of studies with age-specific data, and the heterogeneity amongst them.

Strengths and weaknesses of the review

The following strong and weak elements of the current review are recognised:

Strengths

- We retrieved a large number of studies that evaluated the accuracy of HC2-based triage of women with ASCUS, allowing us to run models with covariates.
- We took different cytological classifications into consideration (BSCC, TBS89 and TBS01).
- The quality of reporting in retrieved studies was good, with negative scores for the diverse QUADAS items varying between zero and 10%.
- All trial authors who were contacted and asked to provide additional data responded positively.
- We used robust modern statistical procedures recommended by the DTA-group of the Cochrane Collaboration.

Weaknesses

- A low number of studies contained accuracy data on HC2 and repeat cytology (only 10 in ASCUS triage for outcome CIN2+, and even fewer for the other situations).
- Different classification systems were used to categorise cervical lesions throughout the literature. However, this potential weakness did not influence accuracy estimates, as shown in multivariate analyses.
- The reference standard was not always uniformly defined - and varied between studies - from systematic biopsies taken from all eligible women; to colposcopy in all women, and biopsy only in case of colposcopic suspicion, completed with endocervical brushing or curettage in case of unsatisfactory colposcopy; accepting negative satisfactory colposcopy as sufficient ascertainment of absence of CIN2+. Moreover, techniques for taking biopsies varied between conization, large loop excision and multiple or single targeted biopsies. Verification of the outcome was not always performed within a short time (six months) after triage testing, and sometimes follow-up cytology was also used to verify outcomes. We addressed all these potentially influencing issues in subgroup meta-analyses, or multivariate regression, but they did not influence outcomes significantly.
- The inter-study variation in accuracy was large, particularly for specificity. In most situations, no significant explanatory factors could be identified.
- The evaluation of the variation of the test accuracy by age could not be assessed from the published data, however, accuracy data, requested from trial authors, and equally stratified by age group, allowed an increase of the specificity of HC2 by age to

be identified. This could offer the possibility of using HC2 in older women with LSIL, however, due to the large inter-study variability no universal age cut-off could be identified to justify precise recommendations.

- We did not evaluate the accuracy of repeat cytology or HC2 in women with other equivocal cytology categories such as ASC-H (atypical squamous cells of undetermined significance, where HSIL cannot be excluded) and AGC (atypical glandular cells), as hoped in the original protocol, since this would have contributed additional complexity.

Applicability of findings to the review question

The clinical impact of our findings is simulated in Summary of findings 1 for ASCUS triage, and in Summary of findings 2 for LSIL triage using a population of 1000 women. We assumed a low, moderate or high prevalence of disease, and accepted the pooled sensitivity and specificity values estimated from the current meta-analyses (Summary of findings 3 and Summary of findings 4). To assess the clinical utility of triaging, we computed the risk of disease in women testing positive (PPV) or negative (cNPV = complement of NPV = 1-NPV). The PPV should be sufficiently high to justify referral to colposcopy with biopsy-taking, possibly followed by treatment, whereas the cNPV should be sufficiently low to justify safe referral of triage-negative women to the normal screening schedule.

Triage of ASCUS

In triage of women with ASCUS (Summary of findings 1), a negative HC2 test always corresponds with a risk (1-NPV) for CIN2+ which is lower than 2.5% (and lower than 1.5% for CIN3+). A negative repeat Pap smear still is associated with a risk of CIN2+ of more than 4%, and possibly as high as 7% in moderate and high prevalence situations. Depending on the local prevalence, repeat cytology misses between 14 and 43 CIN2+ cases/1000 ASCUS women, whereas the HC2 misses only five to 14 CIN2+/1000 ASCUS women. Corresponding figures for the outcome of CIN3+ show repeat cytology misses four to 27 cases, and HC2 misses only one to six cases in a population of 1000 ASCUS women.

A positive HC2 test corresponds with a risk (PPV) of CIN2+ that is similar to, or even slightly higher than, a positive repeat cytology result. However, both tests result in a considerable number of unnecessary referrals (around 300 per 1000 women with ASCUS).

More than 576 women (range of 576 to 650) per 1000 ASCUS women, with a negative test result can be reassured that they are free of disease (CIN2+).

Triage of LSIL

In triage of women with LSIL (Summary of findings 2), a negative HC2 test corresponds with a risk (1-NPV) for CIN2+ that ranges between 1.2% and 3.2% (and for CIN3+ between 0.4% and 1.9%). A negative repeat Pap smear still is associated with a risk of CIN2+ in the range of 5% to 13% (and for CIN3+ the range is 2% to 6%). Depending on the local prevalence, repeat cytology misses between 23 and 57 per 1000 LSIL women, whereas the HC2 misses only four CIN2 cases, in a low-prevalence situation, and 23 CIN2+ cases in a high-prevalence situation per 1000 LSIL women. Corresponding figures for the outcome of CIN3+ show that repeat cytology misses eight to 23 cases and HC2 misses one to four per 1000 LSIL women.

A positive HC2 test corresponds with a risk (PPV) of CIN2+ that is lower than a positive repeat cytology result: the difference is about 1%. In spite of the low specificity of both tests in triage of LSIL, the PPV is slightly higher than in triage of ASCUS, which is due to the higher prevalence of underlying CIN2+. However, given the high HPV positivity rate in LSIL women, a positive HC2 test results in approximately 500 or more unnecessary referrals per 1000 LSIL women. A positive repeat Pap smear results in about 100 fewer unnecessary referrals than a positive HC2 test (still about 300 to 400). HC2 triage in LSIL yields substantially more false positive and fewer true negative cases compared to repeat cytology.

The finding of higher sensitivity, but lower specificity, makes it difficult to recommend whether or not to use HC2 in LSIL triage The decision should be based on the local costs of HPV tests and colposcopy, the local prevalence of HPV in LSIL, and the compliance of women with follow-up recommendations, and should be restricted to situations where access to colposcopy referral is limited and/or expensive. Where sufficient colposcopy capacity exists, and where colposcopy is not excessively expensive, direct referral of LSIL women to colposcopy is a defendable option.

Tests as sensitive - but more specific - than HC2, or more sensitive and more specific than repeat cytology, would be very welcome to triage women with LSIL.

AUTHORS' CONCLUSIONS

Implications for practice

We conclude that virological testing using HC2 is a more accurate method than repeat cytology to triage women with ASCUS (atypical squamous cells of undetermined significance). Moreover, when the collected cervical specimen is a liquid sample, HC2 can be applied on the same sample using remnant material, avoiding an additional visit to take a new cytological specimen.

LSIL (low-grade squamous intra-epithelial lesions) triage with HC2 is more sensitive than triage with repeat cytology, but its specificity is substantially lower than that of repeat cytology. HC2 could be considered for triage of older women with LSIL, but no precise universal evidence-based guidelines can be formulated at present.

Implications for research

Since no good reflex method is currently available to triage women with LSIL, research aiming to find specific markers that allow identification of women with LSIL who are at risk of having, or developing, high-grade intraepithelial neoplasia, should be considered as a priority.

A substantial number of research reports are available that illustrate the strong correlation between severity of cervical lesions, infection with high-risk human papillomavirus types (in particular HPV types 16 and 18), presence of viral mRNA and over-expression of certain cell-cycle regulating proteins, such as p16 or Ki-67.

Nevertheless, there is a need for studies in which the central research question concerns the diagnostic and prognostic roles of these markers. Systematic reviews on triage of ASCUS and low-grade cytological lesions using these markers need to be performed as soon as new studies become available.

Authors of papers and editors of journals should be encouraged to produce age-stratified results for the histological outcomes of CIN2+ and CIN3+.

The current review was restricted to triage of ASCUS and LSIL. An additional new review to address the accuracy of HPV-based triage in more rare cytological abnormalities, such as AGC (atypical glandular cells) and ASC-H (atypical squamous cells of undetermined significance, where HSIL cannot be excluded), is warranted.

Individual patient-data meta-analyses of the larger triage reports could already provide better insight into optimising viral-load cut-offs and age-delimitations of triage strategies. Current ongoing primary screening trials, comparing cytology-based screening with HPV-based screening or combined HPV and cytology screening, will provide high-quality information on the performance of different triage strategies for women with minor cytological lesions (Davies 2006).

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Andersson 2005

Study characteristics	
Clinical features and settings	Women with low-grade atypia in the Stockholm area. Population-based cytology screening.
Participants	Women with ASCUS or LSIL.
Study design	177 women (52 ASCUS, 125 LSIL) tested with HC2 and repeat cytology. All women underwent colposcopy and punch biopsies were taken in all cases.
Target condition and reference standard(s)	**Outcome condition**: CIN2+ and CIN3+. **Reference standard**: colposcopy and biopsy from all women.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: repeat cytology (conventional Pap test).
Follow-up	Colposcopy verification and triage tests were performed 4–6 months after observation of ASCUS or LSIL
Notes	

Methodological quality		
Item	**Authors' judgement**	**Support for judgement**
Representative spectrum? All tests	Yes	Consecutive enrolment of women with low-grade atypia, detected at a population-based screening.
Acceptable reference standard? All tests	Yes	Colposcopy and histological examination of colposcopically directed biopsies.
Acceptable delay between tests? All tests	Yes	Reference standard verification performed by enrolment, together with the index and comparator test.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy and biopsies, independent of the HC2 result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy.
Reference standard results blinded? All tests	Unclear	Not reported.

Andersson 2005 *(Continued)*

Index test results blinded? All tests	Unclear	Not reported.
Relevant clinical information? All tests	Yes	Women with known low-grade atypia.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Bergeron 2000

Study characteristics	
Clinical features and settings	Opportunistic screening. 41 gynaecological practices collaborating with a private cytological laboratory in Paris (France).
Participants	Women with ASCUS or LSIL.
Study design	378 women (111 ASCUS, 267 LSIL) tested with HC2 and repeat cytology. All women underwent colposcopy and biopsies were taken in all cases (type of biopsies not reported).
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: colposcopy and biopsy from all women.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: repeat cytology (conventional Pap test). PCR and Southern blot hybridisation (not evaluated in the current review).
Follow-up	Two months between referral cytological test and enrolment. Colposcopy verification and triage tests were performed simultaneously.
Notes	

Methodological quality		
Item	**Authors' judgement**	**Support for judgement**
Representative spectrum? All tests	Yes	Women referred to colposcopy because of ASCUS or LSIL cytology result.
Acceptable reference standard? All tests	Yes	Colposcopy and histological examination of biopsies.
Acceptable delay between tests? All tests	Yes	Less than 2 months between first test and enrolment tests. Reference standard verification performed concurrently with index and comparator tests.

Bergeron 2000 *(Continued)*

Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy and biopsies (reference standard), independent of the index test result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy.
Reference standard results blinded? All tests	Yes	Colposcopy and histology were blinded to HC2 and repeat cytology results.
Index test results blinded? All tests	Yes	HC2 and repeat cytology were assessed independently.
Relevant clinical information? All tests	Yes	Women with known low-grade atypia (ASCUS and LSIL) referred to colposcopy.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Bergeron 2006

Study characteristics	
Clinical features and settings	Opportunistic screening.
Participants	Women with ASCUS cytology.
Study design	1880 women (ASCUS) were tested with HC2 and repeat cytology. All women underwent colposcopy and if a colposcopic suspicious lesion was found, biopsies were taken.
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: colposcopy and/or biopsy from all women.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test:** no repeat cytology data available.
Follow-up	6-18 months.
Notes	
Methodological quality	

Bergeron 2006 *(Continued)*

Item	Authors' judgement	Support for judgement
Representative spectrum? All tests	Yes	Women diagnosed with ASCUS cytology.
Acceptable reference standard? All tests	Yes	Colposcopy and histological examination of biopsies.
Acceptable delay between tests? All tests	Yes	6-18 months between first test and enrolment tests.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy and/or the same type of biopsies, independent of the index test result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy.
Reference standard results blinded? All tests	Unclear	Not reported.
Index test results blinded? All tests	Yes	The HC2 test interpretation is machine-based.
Relevant clinical information? All tests	Yes	Women with known ASCUS.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Castle 2010a

Study characteristics	
Clinical features and settings	CC screening from 2003-2008 at Kaiser Permanente, USA.
Participants	Women aged ≥ 30 years who underwent CC screening between 2003-2008 at Kaiser Permanente hospital.

Castle 2010a *(Continued)*

Study design	Women were screened using conventional Pap tests and an HC2 test. Women with HPV+ and abnormal cervical cytology (ASC-H, ASCUS, LSIL, HSIL, AGC) routinely underwent colposcopy. If colposcopy showed a CIN2+ lesion, Loop Electrical Excision Procedure (LEEP) was performed.
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: colposcopy and histology. HPV+ women with abnormal cytology and HPV- women with abnormal cytology (ASC-H, LSIL, HSIL, AGC) underwent colposcopy. HPV- women with ASCUS cytology were re-screened after 6-12 months.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test:** no repeat cytology data available.
Follow-up	HPV-negative women with ASCUS were followed-up by retesting after 6-12 months and did not receive verification if retesting was negative. Therefor data on ASCUS triage was not included in the review.
Notes	We only included the data for LSIL triage, because women with ASCUS cytology and HPV- results did not undergo colposcopy. Age-stratified data available.

Methodological quality

Item	Authors' judgement	Support for judgement
Representative spectrum? All tests	Yes	Women attending cervical cancer screening. (**Note**: only women > 30 years included.)
Acceptable reference standard? All tests	Yes	Colposcopy and LEEP, if a colposcopic suspicious lesion was found.
Acceptable delay between tests? All tests	Unclear	Delay not reported.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	No	Women with LSIL, AGC, ASC-H or HSIL cytology were referred to colposcopy irrespective of the HPV testing results. In contrast, women with ASCUS cytology and HPV+ results underwent colposcopy while women with ASCUS and HPV- test results, did not undergo colposcopy. For this meta-analysis we did not include the ASCUS data.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy.
Reference standard results blinded? All tests	Yes	Colposcopy was blinded to HPV test results.
Index test results blinded? All tests	Yes	The HC2 test interpretation is machine-based.

Castle 2010a *(Continued)*

Relevant clinical information? All tests	Yes	Women with abnormal cytology were referred to colposcopy.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Cattani 2009

Study characteristics	
Clinical features and settings	Secondary screening in Italy.
Participants	Women with ASCUS or LSIL.
Study design	Cross-sectional study enrolling women referred to colposcopy with HC2 and mRNA testing for viral genes E6 and E7 using the NucliSens EasyQ HPV assay.
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: all women underwent colposcopy. If a suspicious lesion was found, a biopsy was taken.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: NucliSens EasyQ HPV mRNA test (not evaluated in the current review). No repeat cytology data available.
Follow-up	No information provided.
Notes	Separated ASCUS and LSIL data were obtained from the author.

Methodological quality		
Item	**Authors' judgement**	**Support for judgement**
Representative spectrum? All tests	Yes	Women diagnosed with ASCUS or LSIL cytology.
Acceptable reference standard? All tests	Yes	Colposcopy, colposcopy-directed biopsy (punch biopsies), cone specimens by LLETZ or cytological surveillance.
Acceptable delay between tests? All tests	Unclear	Delay not reported.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.

Cattani 2009 *(Continued)*

Differential verification avoided? All tests	Yes	All women received the same type of reference standard, independent of the index test result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy.
Reference standard results blinded? All tests	Yes	Pathologists involved in cytological and histological assessments were not involved in testing for HPV.
Index test results blinded? All tests	Yes	The HC2 test interpretation is machine-based.
Relevant clinical information? All tests	Yes	Women who underwent a secondary screening.
Uninterpretable results reported? All tests	Yes	All except 2 Pap smears were of satisfactory quality.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Chen 2005b

Study characteristics	
Clinical features and settings	Women with mildly abnormal Pap results, either ASCUS or LSIL, who were referred to a colposcopy clinic, in Taiwan.
Participants	Women with ASCUS or LSIL cytology.
Study design	266 women with abnormal cytology (160 ASCUS and 106 LSIL) underwent colposcopy-directed biopsy. The women were tested for the presence of HPV DNA with the HC2 test.
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: colposcopy-directed biopsy.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test:** no repeat cytology data available.
Follow-up	There was no follow-up. All triage tests and verification were performed simultaneously.
Notes	

Methodological quality		
Item	**Authors' judgement**	**Support for judgement**

Chen 2005b *(Continued)*

Representative spectrum? All tests	Yes	Women with mildly abnormal Pap results, either ASCUS or LSIL, who were referred to the colposcopy clinic.
Acceptable reference standard? All tests	Yes	Colposcopy-directed biopsy.
Acceptable delay between tests? All tests	Yes	HPV test, Pap smear and colposcopy-directed biopsy were performed at the same time.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy and biopsies, independent of the index test result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy.
Reference standard results blinded? All tests	Unclear	Not reported.
Index test results blinded? All tests	Yes	The HC2 test interpretation is machine-based.
Relevant clinical information? All tests	Yes	Women with ASCUS or LSIL cytology, referred to a colposcopy clinic.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Cuschieri 2007

Study characteristics	
Clinical features and settings	Prospective study in multiple General Practitioners' practices in the UK.
Participants	Women with ASCUS cytology diagnosis.
Study design	190 women diagnosed with ASCUS were tested with HC2 and AMPLICOR. Biopsies were taken from all women.
Target condition and reference standard(s)	**Outcome condition**: CIN2+.

Cuschieri 2007 *(Continued)*

	Reference standard: colposcopy and biopsy from all women.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: AMPLICOR (not evaluated in the current review). No repeat cytology data available.
Follow-up	Average time of follow-up: 3.5 years.
Notes	

Methodological quality

Item	Authors' judgement	Support for judgement
Representative spectrum? All tests	Yes	Women with borderline changes attending routine screening.
Acceptable reference standard? All tests	Yes	Colposcopy and biopsy performed on all borderline (ASCUS) cases.
Acceptable delay between tests? All tests	Unclear	Followed up for 3-3.5 years.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy and biopsies, independent of the HC2 result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy.
Reference standard results blinded? All tests	Unclear	Not reported.
Index test results blinded? All tests	Yes	The HC2 test interpretation is machine-based.
Relevant clinical information? All tests	Yes	Women referred to colposcopy because of abnormal cytology.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Cuzick 2003

Study characteristics	
Clinical features and settings	Multicenter screening study: 161 family practices in the UK associated with 5 referral centres.
Participants	Women with ASCUS cytology diagnosis (restricted to immediate colposcopy arm).
Study design	11,085 women (aged 30-60 years) were screened with cytology and HC2 testing. Women with borderline cytology or positive for high-risk HPV with negative cytology were randomised to immediate colposcopy or to surveillance by repeat HPV testing, cytology, and colposcopy at 12 months.
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: colposcopy.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: no repeat cytology data available.
Follow-up	For this review, data were selected for women with borderline cytology and included in the immediate colposcopy arm. Women in the surveillance arm (including follow-up over 12 months) were ignored.
Notes	

Methodological quality		
Item	**Authors' judgement**	**Support for judgement**
Representative spectrum? All tests	Yes	Women attending for routine cervical screening, without abnormal smear in the past 3 years or treatment for CIN.
Acceptable reference standard? All tests	Yes	Colposcopy.
Acceptable delay between tests? All tests	Unclear	Delay was not reported.
Partial verification avoided? All tests	Yes	A random sample of women with negative cytology and HPV test in the surveillance arm was selected for colposcopy. However, for this review, verification bias was avoided by restriction to the direct colposcopy arm.
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy (reference standard), independent of the index test result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the colposcopy.
Reference standard results blinded? All tests	Yes	Histology was read locally, but was reviewed centrally in a blinded fashion by one pathologist.
Index test results blinded? All tests	Yes	Interpretation of the HC2 test is machine-based.

Cuzick 2003 *(Continued)*

Relevant clinical information? All tests	Yes	Women with abnormal cytology, referred to colposcopy.
Uninterpretable results reported? All tests	Yes	Inadequate smears or colposcopy, lost or damaged HPV sample/cytology slides.
Withdrawals explained? All tests	Yes	Women who did not return for repeat test, of whom the sample was lost or damaged. Participants who withdrew consent, did not attend colposcopy/cytology/HPV test or who had inadequate testing.

Dalla Palma 2005

Study characteristics	
Clinical features and settings	Screening population, of whom > 2% had ASCUS.
Participants	Women with ASCUS cytology.
Study design	909 women (aged 25-65 years) with equivocal cytological findings were tested for HPV DNA testing (HC2). All women with positive cytology and/or positive HC2 result, underwent colposcopy and biopsy.
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: colposcopy and biopsy.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test:** no repeat cytology data available.
Follow-up	No information provided.
Notes	

Methodological quality

Item	**Authors' judgement**	**Support for judgement**
Representative spectrum? All tests	Yes	Women attending an organised cervical screening.
Acceptable reference standard? All tests	Yes	Colposcopy and biopsy (only cases with positive cytology or positive HC2 result, or both).
Acceptable delay between tests? All tests	Unclear	Delay was not reported.
Partial verification avoided? All tests	No	Only cases with positive cytology or positive HC2 result, or both, underwent colposcopy and biopsy.

Dalla Palma 2005 *(Continued)*

Differential verification avoided? All tests	Yes	The same type of colposcopy and biopsy was performed on all women who were referred to colposcopy.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy.
Reference standard results blinded? All tests	Unclear	Probably not, as only cases with positive cytology or HC2, or both, had colposcopy and biopsy.
Index test results blinded? All tests	Yes	Interpretation of the HC2 test is machine-based.
Relevant clinical information? All tests	Yes	Women with known ASCUS/ASCUS and ASC-H.
Uninterpretable results reported? All tests	Yes	HPV test invalid because the quantity of residual PreservCyt < 4 mL.
Withdrawals explained? All tests	Yes	Not all the women who were asked to undergo colposcopy participated.

Davis-Devine 2005

Study characteristics	
Clinical features and settings	Women with an abnormal SurePath result within the preceding year attending a gynaecology department in the USA.
Participants	Women with abnormal SurePath results (ASCUS, ASC-H, AGUS).
Study design	45 women with ASCUS cytology diagnosis underwent colposcopy and cervical biopsy. The presence of HPV DNA was tested with HC2 testing and the Inform HPV assay (=in situ hybridisation assay).
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: colposcopy and cervical biopsy.
Index and comparator tests	**Index test**: HC2. **Comparator test**: inform HPV assay (not evaluated in the current review). No repeat cytology data available.
Follow-up	HPV testing and colposcopy verification performed at enrolment. No further follow-up.
Notes	

Methodological quality		
Item	**Authors' judgement**	**Support for judgement**

Davis-Devine 2005 *(Continued)*

Representative spectrum? All tests	Yes	Women 18-60 years old with an intact cervix, and abnormal SurePath result within the preceding year.
Acceptable reference standard? All tests	Yes	Colposcopy and cervical biopsy.
Acceptable delay between tests? All tests	Yes	Colposcopy and biopsy within 10 minutes of the Pap sample, used for both cytologic examination as HPV testing.
Partial verification avoided? All tests	Yes	All women were verified with the reference standard.
Differential verification avoided? All tests	Yes	Each woman received the same type of colposcopy and biopsies, independent of the index test result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy.
Reference standard results blinded? All tests	Yes	All cytologic and histologic materials were reviewed without knowledge of the study design.
Index test results blinded? All tests	Yes	Interpretation of the HC2 test is machine-based.
Relevant clinical information? All tests	Yes	Women with ASC (atypical squamous cells (comprises ASC-US and ASC-H)) or worse.
Uninterpretable results reported? All tests	Yes	1 x unsatisfactory (Pap), 8 x < 5000 squamous cells (Inform HPV), 1 x insufficient tissue (PCR).
Withdrawals explained? All tests	Yes	Women excluded from the study because of insufficient residual material for HC2 testing.

De Francesco 2008

Study characteristics	
Clinical features and settings	Routine cervical screening in a hospital in Italy.
Participants	Women with abnormal Pap smear results (ASCUS or LSIL).
Study design	Women with abnormal Pap smear results were tested for HPV DNA with HC2 and AMPLICOR test. All women underwent colposcopy and directed punch biopsies were taken.
Target condition and reference standard(s)	**Outcome condition**: CIN2+ and CIN3+.

De Francesco 2008 *(Continued)*

	Reference standard: colposcopy and directed punch biopsies.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: AMPLICOR (not evaluated in the current review). No repeat cytology data available.
Follow-up	No information provided.
Notes	

Methodological quality

Item	Authors' judgement	Support for judgement
Representative spectrum? All tests	Yes	213 women with abnormal cytology out of 3900 who came for routine cervical screening.
Acceptable reference standard? All tests	Yes	Colposcopy and directed punch biopsies.
Acceptable delay between tests? All tests	Unclear	Specimens for HC2 were collected during Pap visit, timing of colposcopy and biopsy not reported.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy and biopsies, independent of the index test result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy.
Reference standard results blinded? All tests	Unclear	Not reported.
Index test results blinded? All tests	Yes	Interpretation of the HC2 test is machine-based.
Relevant clinical information? All tests	Yes	Women with abnormal cytology referred to colposcopy.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Del Mistro 2010

Study characteristics	
Clinical features and settings	Organised cytological screening in 5 Italian screening centres.
Participants	Women with ASCUS cytology diagnosis.
Study design	749 women with ASCUS cytology tested for HPV DNA with HC2 test and repeat cytology samples (conventional cytology). All women underwent colposcopy. If a suspicious colposcopic lesion was found, punch biopsies were taken.
Target condition and reference standard(s)	**Outcome condition**: CIN2+ and CIN3+. **Reference standard**: colposcopy (n = 749) with punch biopsy when indicated (n = 338).
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: repeat cytology (conventional cytology).
Follow-up	Re-examination after 12 months (colposcopy, Pap and HC2). Re-examination after 6 months (Pap and HC2) if any positive finding at enrolment tests.
Notes	Data available for 2 age groups (< 35 years and ≥35 years).

Methodological quality		
Item	**Authors' judgement**	**Support for judgement**
Representative spectrum? All tests	Yes	Women with ASCUS selected from organized cytological screening.
Acceptable reference standard? All tests	Yes	Colposcopy (n = 742) (with punch biopsy when indicated, n = 338).
Acceptable delay between tests? All tests	Yes	About 3 months (median 72.2 days) between initial Pap test and enrolment tests.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy and biopsy, independent of the index test result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based on the histological interpretation of the biopsy. A colposcopic negative result was diagnosed as negative for high-grade CIN lesions.
Reference standard results blinded? All tests	Unclear	Not reported.
Index test results blinded?	Yes	Pap smears at enrolment were blinded to the results of HPV test.

Del Mistro 2010 *(Continued)*

All tests		
Relevant clinical information? All tests	Yes	Women with ASCUS cytology diagnosis referred to colposcopy.
Uninterpretable results reported? All tests	Yes	2.2% inadequate Pap smears (at enrolment), 2.4% inadequate biopsies.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Denton 2010

Study characteristics	
Clinical features and settings	Cervical ASCUS or LSIL samples retrospectively collected from 5 anatomy pathology laboratories in Switzerland and Italy.
Participants	Women with ASCUS or LSIL cytology.
Study design	Retrospective diagnostic case-control study. p16 immunostaining and HC2 test performed on 810 ASCUS/LSIL samples. Histological data for all 810 cases was available.
Target condition and reference standard(s)	**Outcome condition**: CIN2+ and CIN3+. **Reference standard**: histology of colposcopic-directed biopsies (punch/cone biopsies or ECC).
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: p16 immunostaining (not evaluated in the current review). No repeat cytology data available.
Follow-up	The follow-up period between index cytology of ASCUS or LSIL and triage/verification tests was less than six months.
Notes	

Methodological quality

Item	Authors' judgement	Support for judgement
Representative spectrum? All tests	Yes	Study contains separate results for ASCUS and LSIL cases.
Acceptable reference standard? All tests	Yes	Histologic diagnosis on re-cut tissue block specimens (coming from colposcopic directed biopsies (punch/cone biopsies or ECC)).
Acceptable delay between tests? All tests	Yes	All tests and reference verification were simultaneous; < 6 months between initial cytology and enrolment tests.

Denton 2010 *(Continued)*

Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women underwent the same reference standard, independent of the index test results.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on histologic interpretation of biopsies.
Reference standard results blinded? All tests	Yes	Colposcopy and histological diagnoses were blinded to HPV and p16 status.
Index test results blinded? All tests	Yes	Interpretation of the HC2 test is machine-based.
Relevant clinical information? All tests	Yes	Women referred to colposcopy because of abnormal cytology.
Uninterpretable results reported? All tests	Yes	135 samples (out of 945 initial samples) excluded because of sample age. Total number of samples included was 810.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Giovannelli 2005

Study characteristics	
Clinical features and settings	Consecutive enrolment of women with ASCUS cytological abnormalities presenting to the Pathology Service (Palermo). .
Participants	Women with ASCUS cytology diagnosis.
Study design	100 women with ASCUS were consecutively included in the study. All participants underwent colposcopy, followed by biopsy when suspicious colposcopic lesion(s) found, and screened for HPV infection by the combined use of HC2 and PCR with MY09/11 primers.
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: colposcopy and colposcopically-directed biopsy.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: PCR with MY09/11 primers (not evaluated in the current review). No repeat cytology data available.
Follow-up	Colposcopy and HPV testing took place 4-5 weeks after finding the ASCUS cases. No further follow-up.
Notes	
Methodological quality	

Giovannelli 2005 *(Continued)*

Item	Authors' judgement	Support for judgement
Representative spectrum? All tests	Yes	Women with ASCUS cytology.
Acceptable reference standard? All tests	Yes	Colposcopy and colposcopically directed biopsy (when necessary).
Acceptable delay between tests? All tests	Yes	Participants underwent HPV typing, gynaecological examination, colposcopy (within 4-5 weeks of the initial diagnosis) and, when necessary, colposcopically-directed biopsy. Samples for HPV test and Pap smear were co-collected.
Partial verification avoided? All tests	Yes	All subjects received the reference standard.
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy or biopsy, independent of the index test result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on histologic interpretation of the biopsy. If colposcopy was negative, women were diagnosed as negative for high-grade CIN lesions.
Reference standard results blinded? All tests	Unclear	Not reported.
Index test results blinded? All tests	Yes	Interpretation of the HC2 test is machine-based.
Relevant clinical information? All tests	Yes	Women with ASCUS cytology referred to colposcopy.
Uninterpretable results reported? All tests	Yes	4 samples from the ASCUS group were unsuitable for PCR assay, and were excluded.
Withdrawals explained? All tests	Yes	4 women with ASCUS did not undergo colposcopy and were excluded from the analysis.

Guyot 2003

Study characteristics	
Clinical features and settings	Women referred to the colposcopy clinic of West Middlesex University Hospital for minor cytological abnormalities in their cervical smears.
Participants	Women with ASCUS or LSIL cytology diagnosis.
Study design	146 women (110 with mild dyskaryosis and 23 with persistent borderline changes) evaluated with HC2, all were referred for colposcopy. Punch biopsies taken from suspicious areas of the cervix.

Guyot 2003 *(Continued)*

Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: colposcopy and punch biopsy from suspicious areas of the cervix.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: no repeat cytology data available.
Follow-up	Collection for HC2 testing and colposcopy verification were performed simultaneously. No further follow-up.
Notes	

Methodological quality

Item	Authors' judgement	Support for judgement
Representative spectrum? All tests	Yes	Women with ASCUS or LSIL cytology referred to colposcopy.
Acceptable reference standard? All tests	Yes	Colposcopy and punch biopsy from suspicious areas of the cervix.
Acceptable delay between tests? All tests	Yes	Less than three months between abnormal Pap smear and colposcopy (median = 4 weeks). Pap smear and HPV test were performed simultaneously.
Partial verification avoided? All tests	Yes	All subjects received the reference standard.
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy and (if necessary) biopsy, independent of the index test result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy. Women with a negative colposcopy were diagnosed as negative for high-grade CIN lesions.
Reference standard results blinded? All tests	Yes	The histopathologists were blinded to HPV results.
Index test results blinded? All tests	Yes	Interpretation of the HC2 test is machine-based.
Relevant clinical information? All tests	Yes	Women were referred to the colposcopy clinic for minor cytological abnormalities in their cervical smear.
Uninterpretable results reported? All tests	Yes	2 women had an inadequate biopsy, 5 had low cell count in the liquid-based cytology, which did not allow an additional HPV test, and were excluded.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Holladay 2006

Study characteristics	
Clinical features and settings	Randomly selected ThinPrep cytological specimens, setting not reported.
Participants	Women with normal cytology (NILM), ASCUS, LSIL or HSIL cytology diagnosis.
Study design	400 ThinPrep cytological specimens randomly selected (100 normal (NILM), 100 ASCUS, 100 LSIL, 100 HSIL). p16 immunostaining and HC2 test performed on these specimens.
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: we can assume that verification was done as usually recommended with colposcopy and biopsies, but no information was provided.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: p16 immunostaining (not evaluated in the current review). No repeat cytology data available.
Follow-up	Follow-up interval between finding ASCUS and HC2 triage and between ASCUS finding and colposcopy verification was <8 months.
Notes	

Methodological quality		
Item	**Authors' judgement**	**Support for judgement**
Representative spectrum? All tests	Yes	Randomly selected ThinPrep specimens.
Acceptable reference standard? All tests	Unclear	We can assume that verification was done as usually recommended with colposcopy and biopsies, but no information was provided.
Acceptable delay between tests? All tests	Yes	Delay between specimen collection and index test-comparator test was < 2-8 months. Delay between initial cytology diagnosis and colposcopy-biopsy outcome: ≤ 6 months.
Partial verification avoided? All tests	No	Only a part of the ASCUS (48/100) and LSIL (76/100) cases had a histologic interpretation available. The accuracy was computed on these histologically-verified cases.
Differential verification avoided? All tests	Unclear	Not reported.
Incorporation avoided? All tests	Unclear	Not reported.
Reference standard results blinded? All tests	Yes	Histologic confirmation was determined by board-certified pathologists without knowledge of the p16 or HC2 results.

Holladay 2006 *(Continued)*

Index test results blinded? All tests	Yes	Interpretation of p16 was blinded. Interpretation of the HC2 test is machine-based.
Relevant clinical information? All tests	No	Apparently 400 study slides were selected from recently stored ThinPrep cytological specimen.
Uninterpretable results reported? All tests	Yes	Specimens with inadequate cellularity or cellular preservation inadequacies on the immuno-stained slide were deemed inconclusive and were excluded from accuracy calculations.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Huang 2009

Study characteristics	
Clinical features and settings	Women attending 5 colposcopy clinics in Canada.
Participants	Women with abnormal cervical cytology referred to colposcopy.
Study design	193 women with ASCUS and 170 with LSIL cytology referred to colposcopy. Biopsies were taken. HC2 HPV test and Abbott RT PCR performed on all women
Target condition and reference standard(s)	**Outcome condition**: CIN2+ and CIN3+. **Reference standard**: colposcopy and biopsy (type of biopsies not reported).
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: Abbott RT PCR and Linear Array (not evaluated in the current review). No repeat cytology data available.
Follow-up	Longitudinal component of study not reported yet.
Notes	

Methodological quality

Item	Authors' judgement	Support for judgement
Representative spectrum? All tests	Yes	Women attending a colposcopy clinic, with abnormal cytology results (ASCUS or LSIL).
Acceptable reference standard? All tests	Yes	Colposcopy on all participants, followed by biopsies on all (type of biopsy not reported).
Acceptable delay between tests? All tests	Yes	All tests and reference verification were simultaneous.1-3 months between initial cytology and enrolment tests. All cases expected to be followed for a further 2 years. Longitudinal follow-up not included in current paper.
Partial verification avoided?	Yes	All subjects were verified with the reference standard.

Huang 2009 *(Continued)*

All tests		
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy and biopsy, independent of the index test results.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy.
Reference standard results blinded? All tests	Yes	Colposcopy and histology of biopsies were blinded to HPV status.
Index test results blinded? All tests	Yes	Interpretation of the HC2 test is machine-based.
Relevant clinical information? All tests	Yes	Women referred to colposcopy because of abnormal cytology.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Kelly 2006

Study characteristics	
Clinical features and settings	Residual cytology samples from women with abnormal cytology, collected in a cytopathology laboratory.
Participants	Women with abnormal cytology and follow-up biopsy within 6 months of cytologic enrolment.
Study design	317 residual cytology samples (156 NLIM, 55 ASCUS, 1 AGUS, 24 ASC-H, 53 LSIL, 28 HSIL) were selected in a cytopathology laboratory. Priority given to those with available follow-up biopsy results. ProExC immunostaining and HC2 test performed on these samples.
Target condition and reference standard(s)	**Outcome condition**: CIN2+ **Reference standard**: colposcopy, histological assessment of biopsies on women with abnormal cytology.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: ProExC immunostaining (not evaluated in the current review). No repeat cytology data available.
Follow-up	Follow-up period between index cytology and verification: < 6 months.
Notes	
Methodological quality	

Kelly 2006 *(Continued)*

Item	Authors' judgement	Support for judgement
Representative spectrum? All tests	Unclear	Residual cytology specimens (priority was given to those with abnormal cytology).
Acceptable reference standard? All tests	Yes	Colposcopy and biopsy on all ASCUS cases. Type of biopsy not reported.
Acceptable delay between tests? All tests	Yes	Delay between LBC and biopsy was < 6 months. All tests (index and comparator) were performed within 1 year after cytology specimen collection.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women were verified with the same reference standard, independent of the index test result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy.
Reference standard results blinded? All tests	Yes	Colposcopy and histology of biopsies blinded to HPV status and immunostaining results.
Index test results blinded? All tests	Yes	Interpretation of the HC2 test is machine-based.
Relevant clinical information? All tests	Yes	Women referred to colposcopy because of abnormal cytology.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Kiatpongsan 2006

Study characteristics	
Clinical features and settings	Enrolment of ASCUS cases (diagnosis within the 2 months previous to enrolment) at outpatient gynaecological and family planning clinics of King Chulalongkorn Memorial Hospital.
Participants	Women with ASCUS cytology diagnosis.
Study design	Enrolled all new cases with cytologic smears showing ASCUS that presented in King Chulalongkorn Memorial Hospital, excluding known cases of HSILs and pregnancies. All women underwent colposcopy and had colposcopic-directed cervical biopsies taken.

Kiatpongsan 2006 *(Continued)*

Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: colposcopic-directed cervical biopsy.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test:** no repeat cytology data available.
Follow-up	No data provided.
Notes	

Methodological quality

Item	Authors' judgement	Support for judgement
Representative spectrum? All tests	Unclear	Very little information provided about background, or reasons for inclusion of participants. Women with ASCUS cytology.
Acceptable reference standard? All tests	Yes	Colposcopic-directed cervical biopsy or ECC.
Acceptable delay between tests? All tests	Unclear	Delay was not reported.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women received the same type of colposcopic-directed cervical biopsy, independent of the index test result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy or the ECC.
Reference standard results blinded? All tests	Yes	The gynaecologic pathologists examined and reviewed the pathologic slides without knowing the HC2 test results.
Index test results blinded? All tests	Yes	Interpretation of the HC2 test is machine-based.
Relevant clinical information? All tests	Yes	All women with known ASCUS referred to colposcopy.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Kulasingam 2002

Study characteristics	
Clinical features and settings	Women attending the Planned Parenthood clinics in Washington State.
Participants	Women with ASCUS or LSIL cytology diagnosis.
Study design	4075 women were screened simultaneously using thin-layer Pap and HPV DNA testing by a PCR-based method and HC2. Women with a positive screening test, and a random sample of women with negative screening results, were referred for colposcopy and biopsy.
Target condition and reference standard(s)	**Outcome condition**: CIN3+. **Reference standard**: colposcopy or biopsy.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: repeat cytology (liquid-based cytology) and HPV PCR (not evaluated in the current review).
Follow-up	The average time between enrolment tests and colposcopy verification was 3 months.
Notes	

Methodological quality		
Item	**Authors' judgement**	**Support for judgement**
Representative spectrum? All tests	Yes	Consecutive enrolment of women presenting for annual examinations at 1 of 3 Planned Parenthood clinics in Washington State.
Acceptable reference standard? All tests	Yes	Colposcopy and biopsy.
Acceptable delay between tests? All tests	Yes	The average time between the screening visit (gynaecologic examination, cervical cytology, HPV DNA testing) and the colposcopy visit was 3 months.
Partial verification avoided? All tests	Yes	Women were referred for colposcopy and biopsy if they had ASCUS, AGUS, LSIL or HSIL; or a positive PCR test result. A 45% random sample of the first 1000 women with negative Pap and HPV DNA test results was invited to have colposcopy performed.
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy and cervical biopsy, independent of the index test result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy or the ECC.
Reference standard results blinded? All tests	No	Reference standard not blinded to cytology or HPV testing.
Index test results blinded?	Unclear	Not reported.

Kulasingam 2002 *(Continued)*

All tests		
Relevant clinical information? All tests	No	The pathologists had no knowledge of other laboratory or clinical data.
Uninterpretable results reported? All tests	Yes	Inadequate Pap samples, insufficient HPV DNA samples, missing HPV DNA test results, women who did not undergo biopsy.
Withdrawals explained? All tests	Yes	283 eligible women refused to participate.

Lee 2001

Study characteristics	
Clinical features and settings	Women screened for cervical carcinoma and precancerous cervical lesions at Korea University Ansan Hospital.
Participants	Women with ASCUS and LSIL.
Study design	66 women with a cervical cytology result of LSIL who received a Pap test and HC2 test. Colposcopy and colposcopy-directed biopsy of hysterectomy was performed on all women.
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: colposcopy and colposcopy-directed biopsy or hysterectomy (for women with normal cytology, performed to treat other benign diseases).
Index and comparator tests	**Index test**: HC2 assay. **Comparator test:** no repeat cytology data available.
Follow-up	No information provided.
Notes	

Methodological quality

Item	**Authors' judgement**	**Support for judgement**
Representative spectrum? All tests	Unclear	A subset of 457 women out of the 2967 screened for cervical carcinoma and precancerous cervical lesions during 1 year.
Acceptable reference standard? All tests	Yes	Colposcopy and colposcopy-directed biopsy (in participants with LSIL or HSIL, or with ASCUS and high-risk HPV) or hysterectomy (for WNL and BCC women, performed to treat other benign diseases).
Acceptable delay between tests? All tests	Unclear	Delay was not reported.
Partial verification avoided? All tests	Unclear	Histological results only available for 206 participants out of the cohort of 457 women.

Lee 2001 *(Continued)*

Differential verification avoided? All tests	Yes	All women received the same type of colposcopy and cervical biopsy, independent of the index test result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy or the hysterectomy.
Reference standard results blinded? All tests	Yes	Two pathologists confirmed all histologic diagnoses without any knowledge of the HPV status.
Index test results blinded? All tests	Yes	Interpretation of the HC2 test is machine-based.
Relevant clinical information? All tests	Yes	Clinical data were recorded from the participants' medical records.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Lee 2009

Study characteristics	
Clinical features and settings	Consecutive women who visited a colposcopy clinic in Korea.
Participants	Women with abnormal cytology.
Study design	74 women consecutively visited the clinic and underwent LBC. They also were tested for HPV DNA with HC2, Linear Array, HPV DNA Chip test, cycle sequencing. All women also underwent colposcopy and colposcopy-directed biopsy.
Target condition and reference standard(s)	**Outcome condition**: CIN2+ and CIN3+. **Reference standard**: colposcopy and colposcopy-directed biopsies.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: HPV DNA Chip test, Linear Array, cycle sequencing (not evaluated in the current review). No repeat cytology data available.
Follow-up	Enrollment tests and verification were performed simultaneously. No further follow-up.
Notes	Additional data obtained from author. Women had LSIL lesions.
Methodological quality	

Item	Authors' judgement	Support for judgement

Lee 2009 *(Continued)*

Representative spectrum? All tests	Yes	Consecutive women who visited the colposcopy clinic.
Acceptable reference standard? All tests	Yes	Colposcopy, colposcopy-directed biopsy.
Acceptable delay between tests? All tests	Unclear	Delay was not reported.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy and biopsies, independent of the index test result.
Incorporation avoided? All tests	Yes	Index/comparator test does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy.
Reference standard results blinded? All tests	Unclear	Not reported.
Index test results blinded? All tests	Yes	Interpretation of the HC2 test is machine-based.
Relevant clinical information? All tests	Yes	Women visiting a colposcopy clinic.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Yes	3 cases of nonsquamous lesion, adenocarcinoma in situ, endometrial cancer, and malignant mixed mullerian tumour were excluded from the analysis of HPV DNA test of squamous cervical lesions.

Lonky 2003

Study characteristics	
Clinical features and settings	Women with abnormal cytology diagnosis, setting not defined.
Participants	Women with ASCUS or LSIL.
Study design	8170 women screened with Pap smears; all ASCUS cases (278) underwent colposcopy and/or colposcopically directed punch biopsies. HC2 testing was performed on all of them.
Target condition and reference standard(s)	**Outcome condition**: CIN2+.

Lonky 2003 *(Continued)*

	Reference standard: colposcopy or colposcopically directed punch biopsy.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test:** no repeat cytology data available.
Follow-up	Sample collection for HC2 testing and colposcopy verification were performed simultaneously. No further follow-up.
Notes	

Methodological quality

Item	Authors' judgement	Support for judgement
Representative spectrum? All tests	Yes	278 women with ASCUS out of 8170 women screened.
Acceptable reference standard? All tests	Yes	Colposcopy and biopsy.
Acceptable delay between tests? All tests	Yes	All participants were referred for colposcopy within 3-4 weeks of their initial ASCUS result.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy and biopsy (if necessary), independent of the index test result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy. If no suspicious colposcopic lesion was found, women were diagnosed as negative for high-grade CIN lesions.
Reference standard results blinded? All tests	Yes	The investigators of the Department of Pathology, Women's and Children's Hospital of the University of Southern California were blinded to the antecedent referral Pap smear result, the result of HC2 testing, and the histologic diagnosis rendered at Keiser Permanente Medical Center.
Index test results blinded? All tests	Yes	Interpretation of the HC2 test is machine-based.
Relevant clinical information? All tests	Yes	Women with ASCUS cytology referred to colposcopy.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Lytwyn 2000

Study characteristics	
Clinical features and settings	Community-based randomised trial (52 community-based family practices and 1 university student health clinic in Ontario). Randomly assignment of women with ASCUS or LSIL.
Participants	Women with ASCUS or LSIL.
Study design	Random assignment of 212 women (16-50 years) with diagnosis of ASCUS or LSIL on cervical cytology screening to undergo either immediate HPV DNA testing or a repeat Pap test in 6 months. Colposcopy was performed on all women, and directed biopsy or ECC was also performed.
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: colposcopy, regardless of the cytology results, or directed biopsy or ECC.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: repeat cytology (conventional cytology).
Follow-up	Repeat cytology after 6 months; HPV testing was done soon after the index smear.
Notes	

Methodological quality		
Item	**Authors' judgement**	**Support for judgement**
Representative spectrum? All tests	Yes	By recruiting women from primary care practices, the results of this trial are more generalized to a primary care setting than those obtained in a colposcopy referral population.
Acceptable reference standard? All tests	Yes	Colposcopy and/or directed biopsy or ECC.
Acceptable delay between tests? All tests	Yes	Immediately after randomisation, the family physician obtained material for the HPV DNA testing; repeat Pap smears were taken after 6 months.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy, independent of the index test result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the results of the colposcopic examination and/or the histological interpretation of the biopsy.
Reference standard results blinded? All tests	Yes	Two expert gynaecologic pathologists, blinded to the HPV or repeat Pap test result, independently reviewed all specimens.

Lytwyn 2000 *(Continued)*

Index test results blinded? All tests	Yes	The colposcopists, physicians and the participants were blinded to the HPV test results.
Relevant clinical information? All tests	Unclear	Women with known low-grade abnormality on screening Pap test.
Uninterpretable results reported? All tests	Yes	A swab from 1 woman did not have sufficient material for testing; 14 women did not return for repeat cytology, the specimen from 1 woman was not received by the laboratory and could not be traced, 2 women presented after the 6 months and were referred immediately for colposcopy.
Withdrawals explained? All tests	Yes	Some women withdrew from the trial, for instance those women who did not present for colposcopy or the repeat Pap test.

Manos 1999

Study characteristics	
Clinical features and settings	A cohort of 995 ASCUS women out of 46,009 women from the Kaiser Permanente Medical Care Program (12 gynaecology clinics at 4 medical centres), who had a routine cervical Pap examination.
Participants	Women with ASCUS.
Study design	Women with ASCUS Pap smear results (995) at routine screening, all had LBC, HPV testing, and subsequent repeat Pap tests and colposcopy with histologic evaluation.
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: colposcopy with biopsy and/or ECC.
Index and comparator tests	**Index test**: HC2. **Comparator test**: repeat cytology (liquid-based cytology).
Follow-up	Mean interval of 67 days between index smear and repeat cytology/colposcopy.
Notes	

Methodological quality		
Item	**Authors' judgement**	**Support for judgement**
Representative spectrum? All tests	Yes	Kaiser Permanente membership is demographically similar to the US census-enumerated population in the Bay Area Metropolitan Statistical Area, so population is representative for Northern California, with the exception that extremes are not represented.
Acceptable reference standard? All tests	Yes	Colposcopy and biopsy and/or ECC performed on all participants. The reported results of the HPV tests are those taken at the same time as the initial index smear.
Acceptable delay between tests? All tests	Yes	Colposcopy examinations with repeat Pap specimen collection was conducted after a median of 67 days (range, 12-240 days) after the initial Pap examination.

Manos 1999 *(Continued)*

		HPV DNA testing was performed independently on PreservCyt and the specimen transport medium (STM) specimens that were collected at the initial Pap examination.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy and biopsy/ECC, independent of the index test result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological examination of the biopsy.
Reference standard results blinded? All tests	Yes	Examinations were conducted without knowledge of the women's HPV or ThinPrep Pap results. Histopathologic diagnoses were made without knowledge of HPV results.
Index test results blinded? All tests	Unclear	Not reported.
Relevant clinical information? All tests	Yes	Women who underwent routine cervical cytology screening.
Uninterpretable results reported? All tests	Yes	Histology specimens from 17 participants were considered insufficient. 5 of the PreservCyt specimens had insufficient material for HPV testing after slide preparation. For 16 women a repeat Pap result was not available.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Monsonego 2006

Study characteristics	
Clinical features and settings	Women with abnormal Pap smear or previous/current HPV-related disease who attended a colposcopy centre in France.
Participants	Women with abnormal Pap smear results, women with ASCUS or LSIL.
Study design	Women with abnormal Pap smear results were selected and underwent colposcopy and biopsy. HPV DNA was tested with HC2 testing.
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: colposcopy (n = 389), LEEP cone biopsy (n = 344) or directed punch biopsy (n = 43), repeat Pap/colposcopy after 4 months (n = 2).
Index and comparator tests	**Index test**: HC2 assay.

Monsonego 2006 *(Continued)*

	comparator test: no repeat cytology data available.
Follow-up	Sample collection for HC2 testing and colposcopy verification were performed simultaneously. No further follow-up.
Notes	

Methodological quality

Item	Authors' judgement	Support for judgement
Representative spectrum? All tests	Yes	389 women with abnormal Pap smear, or previous/current HPV-related disease.
Acceptable reference standard? All tests	Yes	Colposcopy and LEEP cone biopsy (if indicated).
Acceptable delay between tests? All tests	Yes	HC2 within 3 months after enrolment (referral) Pap test. HC2 sample taken just before colposcopy/cone biopsy.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	No	- Leep if: a) Pap showed HSIL, b) atypical transformation zone, c) endocervical lesion + unsatisfactory colposcopy, d) squamocolumnar junction > 3 mm within endocervix. - Directed punch biopsy if: a) normal Pap + external genital warts, b) follow-up after CIN + abnormal colposcopy. - Repeat Pap + colposcopy if: a) abnormal Pap + satisfactory normal colposcopy.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological examination of the biopsy.
Reference standard results blinded? All tests	Yes	Pathologists were unaware of the HPV DNA status.
Index test results blinded? All tests	Yes	Interpretation of the HC2 test is machine-based.
Relevant clinical information? All tests	Yes	Women with abnormal cytology referred to colposcopy.
Uninterpretable results reported? All tests	Yes	If Pap smear, colposcopy or biopsy could not be evaluated for technical reasons, the woman was excluded from the study.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Monsonego 2008

Study characteristics	
Clinical features and settings	Women with abnormal cytology who attended a colposcopy clinic in France.
Participants	Women with ASCUS, LSIL, HSIL, AGC or ASC-H cytology diagnosis.
Study design	575 women had abnormal cytology and underwent colposcopy. Biopsies taken from the women with abnormal colposcopies (n = 520). The presence of HPV DNA was tested through HC2 testing and Linear Array. Also repeat ThinPrep smears were taken.
Target condition and reference standard(s)	**Outcome condition**: CIN2+ and CIN3+. **Reference standard**: colposcopy, and biopsy if colposcopic abnormal results.
Index and comparator tests	**Index test**: HC2 assay **Comparator test**: repeat cytology (liquid-based cytology), Linear Array (not evaluated in the current review).
Follow-up	Sample collection for HC2 testing and colposcopy verification were performed simultaneously. No further follow-up.
Notes	Data for different triage-groups received from trial authors.

Methodological quality		
Item	**Authors' judgement**	**Support for judgement**
Representative spectrum? All tests	Yes	Study contains separate results for ASCUS and LSIL cases (also for ASC-H cases). Women attended a colposcopy clinic.
Acceptable reference standard? All tests	Yes	Colposcopy on all followed by biopsies on 520 subjects. Type of biopsy: LEEP or punch biopsy.
Acceptable delay between tests? All tests	Yes	All tests and reference verification were simultaneous (2-3 months after initial Pap-smear).
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women underwent the same type of colposcopy (and punch biopsy if indicated), independent of the index test result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy. Women with no suspicious colposcopic lesions were diagnosed as negative for high-grade CIN lesions.
Reference standard results blinded? All tests	Yes	Colposcopy and histology of biopsies were blinded to HPV status.

Monsonego 2008 *(Continued)*

Index test results blinded? All tests	Unclear	Not reported.
Relevant clinical information? All tests	Yes	Women referred to colposcopy because of abnormal cytology.
Uninterpretable results reported? All tests	Yes	See Table I of the paper: 30 equivocal results for colposcopy were registered, as well as 1 unsatisfactory result.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Morin 2001

Study characteristics	
Clinical features and settings	Part of a case-control study (university clinic of Quebec) evaluating determinants of concomitant CIN in women with a cytologic diagnosis of ASCUS in conventional Pap smears.
Participants	Women with ASCUS.
Study design	360 women cytologically diagnosed with ASCUS referred for colposcopy who had a repeat Pap smear, a biopsy, when necessary, and HPV testing.
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: colposcopy with directed biopsy or ECC.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: repeat cytology (conventional cytology).
Follow-up	No information provided.
Notes	

Methodological quality		
Item	**Authors' judgement**	**Support for judgement**
Representative spectrum? All tests	Unclear	Women with ASCUS selected out of a case-control study.
Acceptable reference standard? All tests	Yes	Colposcopy and biopsy or ECC.
Acceptable delay between tests? All tests	Unclear	Delay was not reported.
Partial verification avoided?	Yes	All subjects were verified with the reference standard.

Morin 2001 *(Continued)*

All tests		
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy and biopsy/ECC, independent of the index test result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy.
Reference standard results blinded? All tests	Unclear	Not reported.
Index test results blinded? All tests	Unclear	Not reported.
Relevant clinical information? All tests	Yes	Women with known ASCUS on initial Pap smear.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Nieh 2005

Study characteristics	
Clinical features and settings	Women who had a routine Pap smear diagnosis of ASCUS in Taiwan.
Participants	Women with ASCUS cytology diagnosis.
Study design	66 women with ASCUS Pap smear were tested for the presence of HPV DNA through HC2 testing and p16 immunostaining.
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: histological diagnosis (unclear: done through follow-up biopsy?).
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: p16 immunostaining (not evaluated in the current review). No repeat cytology data available.
Follow-up	No information provided.
Notes	

Methodological quality		
Item	**Authors' judgement**	**Support for judgement**

Nieh 2005 *(Continued)*

Representative spectrum? All tests	Unclear	66 routine selected ASCUS smears, but source/setting not documented.
Acceptable reference standard? All tests	Unclear	Histological diagnosis through follow-up biopsy.
Acceptable delay between tests? All tests	Unclear	Delay was not reported.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Unclear	Not reported.
Incorporation avoided? All tests	Yes	Outcome was based only on histology results for all cases.
Reference standard results blinded? All tests	Unclear	Not reported.
Index test results blinded? All tests	Yes	Interpretation of the HC2 test is machine-based.
Relevant clinical information? All tests	Unclear	Women with abnormal cytology.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained, but this is not applicable since this was a selected series of Pap smears.

Ordi 2003

Study characteristics	
Clinical features and settings	1005 women referred to colposcopy, in a cervical pathology unit, as a result of ASCUS or LSIL cytology.
Participants	Women with cytological diagnosis of ASCUS or LSIL.
Study design	Women with ASCUS or LSIL cytology were referred to colposcopy. HC2 HPV testing was performed on all participants and a biopsy was taken if colposcopy was abnormal. If colposcopy was negative, diagnosis was based on cytology.
Target condition and reference standard(s)	**Outcome condition**: CIN2+.

Ordi 2003 *(Continued)*

	Reference standard: colposcopy and biopsy if suspicious colposcopic lesions.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test:** no repeat cytology data available.
Follow-up	Follow-up period of 6 months on average between index cytology result of ASCUS or LSIL and HC2 testing and colposcopy verification.
Notes	

Methodological quality

Item	Authors' judgement	Support for judgement
Representative spectrum? All tests	Yes	Women referred to cervical pathology institute between 1999-2002 because of an abnormal (ASCUS, LSIL) cytology result.
Acceptable reference standard? All tests	Yes	Colposcopy on all. Biopsy if colposcopy was abnormal.
Acceptable delay between tests? All tests	Yes	6 months.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy (and biopsy if necessary), independent of the index test result.
Incorporation avoided? All tests	Unclear	For women with a negative colposcopy, final diagnosis was based on cytology results.
Reference standard results blinded? All tests	Unclear	Not reported.
Index test results blinded? All tests	Yes	Interpretation of the HC2 test is machine-based.
Relevant clinical information? All tests	Yes	Women referred to colposcopy because of an abnormal cytology result.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Pretorius 2002

Study characteristics	
Clinical features and settings	Women who had colposcopy performed by 1 of 21 physicians at the Southern California Permanente clinics in Fontana (California).
Participants	Women with ASCUS or LSIL.
Study design	Colposcopy and HPV testing (HC2) performed on 1309 women for evaluation of abnormal Pap smears.
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: colposcopy and/or biopsy or ECC.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: first generation Hybrid Capture test (not evaluated in the current review). No repeat cytology data available.
Follow-up	Colposcopy verification and HPV testing were performed simultaneously. No further follow-up.
Notes	

Methodological quality

Item	Authors' judgement	Support for judgement
Representative spectrum? All tests	Unclear	Women selected out of a cohort of women who underwent colposcopy. All women had abnormal cytology (ASCUS or LSIL).
Acceptable reference standard? All tests	Yes	Colposcopy and/or biopsy or ECC.
Acceptable delay between tests? All tests	Yes	Delay was not reported.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy and biopsy/ECC, independent of the index test result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy.
Reference standard results blinded? All tests	Unclear	Not reported.
Index test results blinded? All tests	Yes	Interpretation of the HC2 test is machine-based.
Relevant clinical information?	Yes	Women with abnormal Pap smears (ASCUS, LSIL, HSIL or AGUS).

Pretorius 2002 *(Continued)*

All tests		
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Yes	153 women with colposcopy for reasons other than for evaluation of an abnormal Pap smear were excluded, 80 refused to participate, 83 women without a specimen for the HPV test were excluded from the study.

Rebello 2001

Study characteristics	
Clinical features and settings	333 consecutive women referred for colposcopy with persistent borderline, or mildly dyskaryotic, smears were tested for HPV with HC2.
Participants	Women with ASCUS or LSIL.
Study design	75 ASCUS and 117 LSIL cases with persistent borderline smears and mild dyskaryosis referred for colposcopy were tested for hrHPV (HC2).
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: large loop excisions of the transformation zone.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test:** no repeat cytology data available.
Follow-up	No information provided.
Notes	

Methodological quality

Item	**Authors' judgement**	**Support for judgement**
Representative spectrum? All tests	No	Study population with repeated abnormal smears. If the study had been a triage of women with only 1 abnormal smear, the prevalence of high grade disease would probably be lower.
Acceptable reference standard? All tests	Yes	Large loop excisions were performed on all participants.
Acceptable delay between tests? All tests	Unclear	Delay was not reported.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided?	Yes	All women underwent the same type of large loop excisions, independent of the index test result.

Rebello 2001 *(Continued)*

All tests		
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the large loop excision.
Reference standard results blinded? All tests	Unclear	Not reported.
Index test results blinded? All tests	Yes	Interpretation of the HC2 test is machine-based.
Relevant clinical information? All tests	Yes	Women with persistent borderline or mild dyskaryosis.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Ronco 2007

Study characteristics	
Clinical features and settings	Women with ASCUS, AGUS or LSIL cytology diagnosis, selected out of a large randomised controlled trial of 9 screening programmes in Italy.
Participants	Women with ASCUS, AGUS or LSIL cytology.
Study design	757 women with ASCUS/AGUS and 485 with LSIL cytology, underwent colposcopy and biopsy. All these women were tested for the presence of HPV DNA through HC2 testing.
Target condition and reference standard(s)	**Outcome condition**: CIN2+ and CIN3+. **Reference standard**: colposcopy and eventually biopsy (type of biopsies not reported).
Index and comparator tests	**Index test**: HC2 assay. **Comparator test:** no repeat cytology data available.
Follow-up	Follow-up up to one year after triage testing.
Notes	Age-specific data reported.

Methodological quality		
Item	**Authors' judgement**	**Support for judgement**
Representative spectrum? All tests	Yes	Selected samples (with valid HPV test and colposcopy) out of a large randomised controlled trial.

Ronco 2007 *(Continued)*

Acceptable reference standard? All tests	Yes	Colposcopy, followed by biopsy when indicated. Type of biopsy not reported.
Acceptable delay between tests? All tests	No	Same cervical cell sample for LBC and HPV testing. Included histologically-confirmed lesions detected within 1 year from referral to colposcopy.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	No	Did not report who just had colposcopy and who also had a biopsy (suspicious areas were biopsied).
Incorporation avoided? All tests	Yes	Index test does not form part of the reference standard.
Reference standard results blinded? All tests	Yes	Histology was independently reviewed, blinded to HPV test and cytology results. (But colposcopists had access to participants' notes, both for cytology and HPV).
Index test results blinded? All tests	Yes	Slides were read without knowledge of HPV results, HPV testing was blind to cytology.
Relevant clinical information? All tests	Yes	Women with ASCUS/AGUS and LSIL referred to colposcopy.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Sherman 2002

Study characteristics	
Clinical features and settings	Enrolled 3488 women with ASCUS and 1572 women with LSIL reported by community laboratories.
Participants	Women with ASCUS or LSIL.
Study design	2198 ASCUS and 848 LSIL cases, referred to colposcopy, were subjected to HPV testing and repeat thin layer cytopathology.
Target condition and reference standard(s)	**Outcome condition**: CIN3+. **Reference standard**: colposcopy and biopsy or ECC.
Index and comparator tests	**Index test**: HC2 assay.

Sherman 2002 *(Continued)*

	Comparator test: repeat cytology (liquid-based cytology).
Follow-up	Women are enrolled an average of 2 months after the index smear was obtained. Colposcopy in arm 2 (for HPV-positive women) took place on average 8 weeks after enrolment while less than 1 day in arm 1 (where all women received colposcopy).
Notes	Reported age-specific data.

Methodological quality

Item	Authors' judgement	Support for judgement
Representative spectrum? All tests	Yes	The findings in this study should apply to most US screening populations in which cytopathology is performed with standard diagnostic criteria, because the study was large, with a broad representation of the US population and quality-control components, .
Acceptable reference standard? All tests	Yes	Colposcopy and biopsy or ECC.
Acceptable delay between tests? All tests	Yes	The cervical sample collected at the pelvic examination was used to prepare a thin-layer slide and for HPV DNA testing. The time interval between referral smear to collection of cells for HPV testing could exceed 65 days. No information was available about the colposcopy.
Partial verification avoided? All tests	No	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy and biopsy/ECC, independent of the index test result.
Incorporation avoided? All tests	Yes	Index test does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy or ECC.
Reference standard results blinded? All tests	Yes	Not reported.
Index test results blinded? All tests	Unclear	Not reported.
Relevant clinical information? All tests	Yes	Women with known ASCUS or LSIL.
Uninterpretable results reported? All tests	Yes	153 women with missing HPV results, 18 with missing cytopathology results, and 4 with both results missing, were excluded from the analysis.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Shlay 2000

Study characteristics	
Clinical features and settings	Women from a local clinic within the Denver Health system (the major provider of health care for the indigent population in Denver, Colorado), with a single atypical Pap smear diagnosis.
Participants	Women with ASCUS/AGUS.
Study design	195 consenting women referred for colposcopy because of atypia on Pap smears. Before colposcopy, a cervical swab was collected for HPV testing (HC2).
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: colposcopy and/or biopsy and ECC.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test:** no repeat cytology data available.
Follow-up	Enrolment smears were collected 64 days (median; range: 12-430 days) after the index smear.
Notes	

Methodological quality

Item	Authors' judgement	Support for judgement
Representative spectrum? All tests	No	Study at the Women's Care Clinic at Denver Health, the major provider of health care for the indigent population in Denver, Colorado.
Acceptable reference standard? All tests	Yes	Colposcopy and/or biopsy and ECC.
Acceptable delay between tests? All tests	Yes	Study visits (colposcopy and collection of specimens for HPV testing) performed a median of 64 days (range 12-430 days) after atypical Pap smear results.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy and biopsy/ECC, independent of the index test result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy or ECC.
Reference standard results blinded? All tests	Yes	Laboratory personnel were unaware whether women participated in the study and were blinded to the HPV test results.
Index test results blinded? All tests	Yes	Laboratory personnel were blinded to the biopsy results.
Relevant clinical information?	Yes	Women with known atypia on the initial Pap smear.

Shlay 2000 *(Continued)*
All tests

Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Siddiqui 2008

Study characteristics	
Clinical features and settings	Cervical cytology samples of women with ASCUS were selected out of all the samples collected in a cytopathology laboratory in the USA between 2006-2007.
Participants	Women with ASCUS cytology.
Study design	200 samples of women with ASCUS were selected. All these women underwent colposcopy and biopsy. All samples tested for the presence of HPV DNA with ProExC immunostaining and HC2 test.
Target condition and reference standard(s)	**Outcome condition**: CIN2+ and CIN3+. **Reference standard**: colposcopy and biopsy (type of biopsies not reported).
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: ProExC immunostaining (not evaluated in the current review). No repeat cytology data available.
Follow-up	Triage tests and colposcopy verification were performed simultaneously.
Notes	

Methodological quality

Item	**Authors' judgement**	**Support for judgement**
Representative spectrum? All tests	Yes	200 women with ASCUS cervical cytology selected out of samples collected between 2006-2007.
Acceptable reference standard? All tests	Yes	Colposcopy on all, followed by biopsies on all subjects. Type of biopsy not reported.
Acceptable delay between tests? All tests	Yes	All tests and reference verification were simultaneous. < 1 month between initial cytology and enrolment tests.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women underwent the same colposcopy, independent of the index test results.

Siddiqui 2008 *(Continued)*

Incorporation avoided? All tests	Yes	Index/comparator tests did not form part of the reference standard. The reference standard outcome was based only on the histological verification of the biopsies.
Reference standard results blinded? All tests	Unclear	Not reported; separate clinical protocol for colposcopy-biopsy.
Index test results blinded? All tests	Yes	Interpretation of the HC2 test is machine-based.
Relevant clinical information? All tests	Yes	Women referred to colposcopy because of abnormal cytology.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Silverloo 2009

Study characteristics	
Clinical features and settings	Women with ASCUS diagnosis on primary organised cytological screening in Sweden.
Participants	Women with ASCUS cytology.
Study design	197 women with ASCUS tested with the HC2 assay and a new Pap smear taken.
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: 1) If cyto+ and/or HPV+, then colposcopy, new Pap-smear, cervical biopsy and ECC. 2) If cyto-/HPV-, then 3-yearly organised screenings via Pap-smear.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: repeat cytology (conventional cytology).
Follow-up	Re-examination after 3 months, 2 cervical smears: primary assessment via cytology, secondary assessment via hrHPV test.
Notes	

Methodological quality		
Item	**Authors' judgement**	**Support for judgement**
Representative spectrum? All tests	Yes	Consecutive ASCUS women from an organized screening program.
Acceptable reference standard?	Yes	Colposcopy, biopsy and ECC for women who were cytology+ and/or HPV+, repeated cytology after 3 years for women who were cytology- and HPV-.

Silverloo 2009 *(Continued)*

All tests		
Acceptable delay between tests? All tests	Unclear	Not documented.
Partial verification avoided? All tests	No	Cyto/HPV- women did not undergo colposcopy/biopsy, but repeat cytology was performed.
Differential verification avoided? All tests	No	According to the result of the index and comparator test, women received colposcopy/biopsy or repeat cytology after 3 years.
Incorporation avoided? All tests	No	Repeat cytology as reference test for 1 group, equal to the primary screenings test.
Reference standard results blinded? All tests	Yes	Colposcopy blinded to triage results (whether cytology+ or HPV+).
Index test results blinded? All tests	Yes	Index/comparator test performed and interpreted before reference test.
Relevant clinical information? All tests	Yes	ASCUS information was available.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Yes	15 women could not be re-examined 3 years later in the organized screening.

Solomon 2001

Study characteristics	
Clinical features and settings	Multicenter, randomised trial. Woman with ASCUS or LSIL referred to one of 4 clinics throughout the US.
Participants	Women with ASCUS cytology.
Study design	3488 women with a referral diagnosis of ASCUS either underwent 1) immediate colposcopy, 2) triage to colposcopy based on HPV (HC2) and thin-layer cytology results, or 3) triage based on cytology results alone.
Target condition and reference standard(s)	**Outcome condition**: CIN2+ and CIN3+. **Reference standard**: colposcopy and biopsy for any colposcopically-suspected CIN.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: repeat cytology (liquid-based cytology).

Solomon 2001 *(Continued)*

Follow-up	Women are enrolled an average of 2 months after the index smear was obtained. Colposcopy in arm 2 (for HPV-positive women) took place on average 8 weeks after enrolment while less than 1 day in arm 1 (where all women received colposcopy).
Notes	

Methodological quality

Item	Authors' judgement	Support for judgement
Representative spectrum? All tests	Yes	A large study of 3488 women referred to one of 4 clinics throughout the US.
Acceptable reference standard? All tests	Yes	Colposcopy and biopsy for any colposcopically-suspected CIN.
Acceptable delay between tests? All tests	Yes	Women were enrolled an average of 2 months after the index smear was obtained. Colposcopy in arm 1 after < 1 day, and in arm 2 after 8 weeks (median).
Partial verification avoided? All tests	No	All women assigned to arm 1 referred for colposcopy and/or biopsy or ECC, regardless of the cytology results. In arm 2 (HPV triage), colposcopy was performed only if the enrolment HPV test was positive, or missing, or any cytology was HSIL+.
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy and biopsy/ECC, independent of the index test result.
Incorporation avoided? All tests	Yes	Index test does not form part of the reference standard. The reference standard outcome was based only on the histological result.
Reference standard results blinded? All tests	Yes	For histology slides, the Pathology Quality Control Group review protocol included review by a quality control pathologist who was masked to the original diagnosis. (In contrast to the immediate colposcopy arm (arm 1), in arm 2 and 3, colposcopists were aware of the triage test results at the time of colposcopy, which may have influenced clinical assessment of the cervix.)
Index test results blinded? All tests	Unclear	Not reported.
Relevant clinical information? All tests	Yes	Previous histological diagnoses were given.
Uninterpretable results reported? All tests	Yes	164 HPV tests not done (missing), most often because of an insufficient amount of residual specimen in the PreservCyt vial.
Withdrawals explained? All tests	Yes	Some women triaged to colposcopy refused the procedure or were lost to follow-up (1.2% in arm 1, 6.1% in arm 2, and 6.9% in arm 3).

Szarewski 2008

Study characteristics	
Clinical features and settings	Women referred for colposcopy to 2 colposcopic clinics in the UK, as the result of an abnormal Pap smear.
Participants	Women with abnormal Pap smear results.
Study design	953 women with abnormal Pap smear results (104 ASCUS, 617 LSIL) had colposcopy and were tested for the presence of HPV via the following tests: HC2, AMPLICOR, Linear Array, clinical array, PreTect Proofer, P16 immunostaining and APTIMA. Histological data were available for the women.
Target condition and reference standard(s)	**Outcome condition:** CIN2+ and CIN3+. **Reference standard**: colposcopy and histology.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: AMPLICOR, APTIMA, Linear Array, clinical array, PreTect Proofer, p16 immunostaining (not evaluated in the current review). No repeat cytology data available.
Follow-up	Collection for triage tests and colposcopy verification were performed simultaneously. Varabiable follow-up period between index cytology and referral.
Notes	Separate data for ASCUS and LSIL triage groups were received from the authors.

Methodological quality

Item	Authors' judgement	Support for judgement
Representative spectrum? All tests	Yes	Study contained results for 953 women referred for colposcopy and histology as a result of abnormal cervical smears. Separate data for different triage groups were received from trial authors.
Acceptable reference standard? All tests	Yes	Colposcopy and histology.
Acceptable delay between tests? All tests	Unclear	Median delay between cytological screening and reference test was 2.4 months, the range of delays was 0.6-50 months.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women underwent the same type of colposcopy, independent of the index test results.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological data available for all cases.
Reference standard results blinded? All tests	Unclear	Histopathology was blinded to test results, but the pathologist had access to cytology results.

Szarewski 2008 *(Continued)*

Index test results blinded? All tests	Yes	All molecular tests were blinded to the cytology and histopathology results. Not mentioned if the tests were blinded to each other.
Relevant clinical information? All tests	Yes	Women referred to colposcopy because of abnormal cytology.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Voss 2010

Study characteristics	
Clinical features and settings	Women with LSIL diagnosis who had biopsy within 1 year after cytological enrolment in a clinic (USA).
Participants	Women with LSIL diagnosis.
Study design	Out of the total number of women who had biopsy within 1 year after cytological enrolment (n = 204), 115 women with LSIL diagnosis were chosen. The presence of HPV DNA in these women was tested through Multiprobe FISH and HC2 testing.
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: colposcopy and biopsy (type of biopsies not reported).
Index and comparator tests	**Index test**: HC2 assay. **Comparator test**: Multiprobe FISH (not evaluated in the current review). No repeat cytology data available.
Follow-up	Follow-up period between HC2 tests and colposcopy verification was less than one year..
Notes	

Methodological quality

Item	Authors' judgement	Support for judgement
Representative spectrum? All tests	Unclear	115 women with LSIL cytology selected from group of 204 women who had biopsy within 1 year after cytological enrolment.
Acceptable reference standard? All tests	Yes	Colposcopy on all, followed by biopsies on all 115 subjects. Type of biopsy not reported.
Acceptable delay between tests? All tests	Unclear	Delay between all tests and reference verification was not specifically reported. Follow-up biopsies done within 1 year after enrolment.

Voss 2010 *(Continued)*

Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women underwent the same type of colposcopy, independent of the index test result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on histologic interpretation of the biopsies.
Reference standard results blinded? All tests	Yes	Colposcopy and histology of biopsies were blinded to HPV status.
Index test results blinded? All tests	Yes	Interpretation of the HC2 test is machine-based.
Relevant clinical information? All tests	Unclear	Not reported.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Yes	3 withdrawals reported during follow-up.

Wensveen 2003

Study characteristics	
Clinical features and settings	Prospective cohort study at the gynaecologic outpatients clinic of the Medical Center Haaglanden (the Netherlands).
Participants	Women with ASCUS/AGUS.
Study design	148 women with ASCUS or AGUS on cervical smears evaluated by colposcopy, histological sampling, and HPV testing (HC2).
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: colposcopy and biopsy or ECC.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test:** no repeat cytology data available.
Follow-up	Colposcopy verification and triage tests were performed simultaneously.
Notes	
Methodological quality	

Wensveen 2003 *(Continued)*

Item	Authors' judgement	Support for judgement
Representative spectrum? All tests	Unclear	85% of the population was immigrant, so the cohort may not really representative for the Dutch population.
Acceptable reference standard? All tests	Yes	Colposcopy and biopsy or ECC.
Acceptable delay between tests? All tests	Yes	No more then 12 weeks between the Pap smear and intake tests.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy and biopsy/ECC, independent of the index test result.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy.
Reference standard results blinded? All tests	Unclear	Not reported.
Index test results blinded? All tests	Yes	Interpretation of the HC2 test is machine-based.
Relevant clinical information? All tests	Yes	Women with known ASCUS/AGUS.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Yes	3 women were pregnant, 1 was HIV positive, in 11 cases there was a delay of more than 12 weeks between the Pap smear and the intake, 8 because of a normal or dysplastic smear after review, 36 did not arrive for intake or colposcopy, 2 because of a missed HPV test, 1 because of a carcinoma of the corpus uteri.

You 2007

Study characteristics	
Clinical features and settings	Women with abnormal cytology and who received HPV test and biopsy were selected out of the women who visited the gynaecology or maternal health department of a Chinese hospital.
Participants	Women with abnormal cytology.

You 2007 *(Continued)*

Study design	2152 women (selected from 20,000 women) with abnormal cytology (1171 ASCUS, 109 ASC-H, 656 LSIL), were tested for the presence of HPV DNA via HC2 testing and taking of biopsies.
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: colposcopy-directed biopsy.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test:** no repeat cytology data available.
Follow-up	No information provided.
Notes	

Methodological quality

Item	Authors' judgement	Support for judgement
Representative spectrum? All tests	Yes	Study contained separate results for ASCUS, ASC-H and LSIL cases. Selected samples of 2152 women with abnormal cytology + biopsy + HPV test.
Acceptable reference standard? All tests	Yes	Colposcopy-directed biopsy.
Acceptable delay between tests? All tests	Unclear	Not reported.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women underwent the same type of colposcopy and biopsy, independent of the index test results.
Incorporation avoided? All tests	Yes	Index test (HC2) does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsies.
Reference standard results blinded? All tests	Unclear	Not reported.
Index test results blinded? All tests	Yes	Interpretation of the HC2 test is machine-based.
Relevant clinical information? All tests	Yes	Women with abnormal cytology (ASCUS, ASC-H, LSIL).
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained?	Unclear	No withdrawals reported, not applicable (selected sample).

You 2007 *(Continued)*

All tests

Zielinski 2001

Study characteristics	
Clinical features and settings	Participants recruited from general practitioners or from a gynaecological outpatient clinic (The Netherlands), with a borderline or mild dyskaryosis result of their Pap smear.
Participants	Women with ASCUS or LSIL.
Study design	278 women with smears read as borderline, or mild dyskaryosis, referred for colposcopy. HC2 performed on a cervical scrape taken at the first visit before colposcopy and follow-up. Biopsies were taken if a lesion was observed.
Target condition and reference standard(s)	**Outcome condition**: CIN2+. **Reference standard**: colposcopy and colposcopically-directed biopsy.
Index and comparator tests	**Index test**: HC2 assay. **Comparator test:** no repeat cytology data available.
Follow-up	Median follow-up time of 1.4 years (range 0-4.5 years). All cytologically positive and HPV+ women followed-up at 6-monthly intervals.
Notes	

Methodological quality

Item	Authors' judgement	Support for judgement
Representative spectrum? All tests	Unclear	Participants recruited from general practitioners or from a gynaecological outpatient clinic in Walcheren (The Netherlands).
Acceptable reference standard? All tests	Yes	Colposcopy.
Acceptable delay between tests? All tests	Yes	All participants were referred to the gynaecologist for a colposcopy within 3 months.
Partial verification avoided? All tests	Yes	All subjects were verified with the reference standard.
Differential verification avoided? All tests	Yes	All women received the same type of colposcopy and biopsy, independent of the index test result.
Incorporation avoided? All tests	Yes	Index test does not form part of the reference standard. The reference standard outcome was based only on the histological interpretation of the biopsy.
Reference standard results blinded?	Unclear	Not reported.

Zielinski 2001 *(Continued)*

All tests		
Index test results blinded? All tests	Yes	Interpretation of the HC2 test is machine-based.
Relevant clinical information? All tests	Yes	Women with known borderline or mild dyskaryosis smears.
Uninterpretable results reported? All tests	Unclear	There were no cases of uninterpretable results reported.
Withdrawals explained? All tests	Unclear	No withdrawals were reported, or explained.

Abbreviations

< = less than
≥ = greater than or equal to
AGC = atypical glandular cells
AGUS = atypical glandular cells of undermined significance
AIS: adenocarcinoma in situ
ASC-H = atypical squamous cells of undetermined significance, where HSIL cannot be excluded
ASCUS = atypical squamous cells of undetermined significance
CC = cervical cancer
CIN2+ = cervical intraepithelial neoplasia of grade 2 or worse
CIN3+ = cervical intraepithelial neoplasia of grade 3 or worse
CIS: carcinoma in situ
ECC = endocervical curettage
HC2 = Hybrid Capture 2 assay
HPV = human papillomavirus
HPV+ = human papillomavirus positive
HPV- = human papillomavirus negative
HSIL = high-grade squamous intraepithelial lesion
LBC = liquid-based cytology
LEEP = loop electrical excision procedure
LSIL = low-grade squamous intra-epithelial lesions
Pap = Papanicolaou test
PCR = polymerase chain reaction

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adam 1998	Triage concerns women with ASCUS or LSIL. No distinct data provided to separate the 2 triage groups. HPV triage test was not HC2, but HPV Profile.
Aerssens 2009	Follow-up study, no triage of women with minor cytological lesions.
Ahmed 2008	No HPV testing done, only follow-up over time with follow-up cytology and colposcopy/biopsy provided according to follow-up cytology.
Alameda 2010	Discrepancy between reported and computed numbers of false positives and true negatives .
Allen 2009	No verification was done. Compared hrHPV (HC2) rates in ASCUS women from a private clinic (low-risk) with women from a public clinic (high-risk).

Study	Reason for exclusion
Antonishyn 2009	No HC2 testing was done. HPV triage done with several other HPV markers (genotyping, mRNA).
Arbyn 2010	Comments on TOMBOLA trial.
Armah 2009	Only HPV-positive cases included.
Atkins 2006	Contained only the outcome of cancer from the ALTS study, already included in Solomon 2001.
Bais 2005	Triage concerned women with ASCUS or LSIL. No distinct data available to separate the 2 triage groups. HPV triage test was not HC2 but GP5+6+ PCR followed by identification of 14 high-risk types using EIA. Longitudinal outcome at 6 months (only for women with CIN2+ at baseline) and at 12 months for all women was provided.
Baseman 2008	Primary screening, not a triage study.
Bavin 1993	HPV triage test was not HC2 but PCR.
Beccati 2008	Study sample too small, contained marker data for Ki67 and ProExcy for women with ASCUS, ASC-H or LSIL.
Bellinson 2009	No triage of ASCUS, LSIL. Primary screening with HPV testing on self samples using visual inspection after application of acetic acid (VIA) as a triage method.
Bello 2009	No triage of ASCUS, LSIL. Colposcopy setting without cytological subgroups distinguished. HPV genotyping, but no HC2.
Bentley 2006	No primary data, ongoing study from the TOMBOLA group.
Berkhof 2006a	Triage test was PCR (GP5+/6+) and not HC2.
Berkhof 2006b	Model to evaluate cervical screening strategies, with no primary data.
Bewtra 2005	The HPV test evaluated was an in situ hybridization (ISH) method (Ventana Inform HPV Test, Tucson, Arizona, US A). Included women with ASCUS and histologically-confirmed CIN in follow-up biopsies. No histological gold standard information available for all cases.
Biu 2009	Evaluated HPV in women with ASCUS or ASC-H with colpo/biopsy data. Test was a genotyping assay, not HC2.
Bjerre 2008	HPV and cytology results grouped together. Triage group not defined. No histopathology results available for all women. Only relative sensitivity could be calculated.
Boardman 2005	Only age-specific (high-risk) HC2 positivity rates were presented. No gold standard-verified accuracy data were presented.
Boardman 2006	Only age-specific (high-risk) HC2 positivity rates were presented. No gold standard-verified accuracy data were presented. Only risk factors for CIN2+ were provided.
Bohmer 2002	Triage concerned women with ASCUS, LSIL or other lesions. No separate data for the ASCUS or LSIL triage groups could be extracted since the used Munich cytological classification system did not allow translation into equivalent categories of The Bethesda System.

Study	Reason for exclusion
Bollen 1997	Triage concerned women with ASCUS, LSIL or other lesions. No separate data for the ASCUS or LSIL triage groups were provided.
Botezatu 2009	Measurement of HPV16/18 viral load. ASCUS/LSIL grouped together, no separate data available. HPV test was not HC2. No colposcopy or biopsy was performed.
Boulanger 2006	Review article, no primary data available. Article provides guidelines to manage ASCUS.
Brismar 2009	No HC2 performed. HPV triage with linear array testing.
Brown 2009	No HC2 testing, but PCR for HPV triage.
Bruner 2004	Only age-specific (high-risk) HC2 positivity rates presented. No gold standard-verified accuracy data presented.
Burgis 2009	Paper discussed guidelines for adolescents. No triage data.
Carozzi 2005	HPV triage test was not HC2, but a type-specific PCR, based on E6/E7 amplification of 8 high-risk HPV types.
Carozzi 2006	Triage concerned women with ASCUS, LSIL or other lesions. No distinct data provided to separate the two triage groups. HPV triage test was not HC2, but a PCR based on E6/E7 amplification of 8 high-risk HPV types and p16 immunostaining of residual material remnant after preparation of a liquid-based smear.
Carozzi 2008	HPV testing with triage by p16. Data available only for HPV+ women.
Carvalho 2010	Type-specific PCR and sequencing. No HC2 testing.
Castle 2008	More relevant data published in other papers (Solomon 2001), already included in the meta-analysis.
Castle 2009a	Concerned negative predictive values of primary screening tests (Hybrid Capture tube test, VIA, cervicography). No triage data.
Castle 2009b	No triage of ASCUS, LSIL. Focus on primary screening in the US with HPV and cytology for women over 30 years of age.
Castle 2010b	ALTS study with focus on the odds ratio between hrHPV infection and subsequent CIN3+ according to the quality of histological ascertainment.
Castle 2010c	Included only patients with CIN3+ diagnosis from the clinical laboratories in the ALTS study. The quality-centre (QC) diagnosis was analysed versus HPV typing and other variables.
Chaiwongkot 2007	Different PCRs compared for hrHPV positivity. No histological outcomes reported.
Chen 2005a	Triage concerned women with AGC. This study was included in the sub-group meta-analysis for specific categories of equivocal cytology.
Chesebro 1997	HPV triage test was not HC2, but HC1.
Cheung 2010	p63 and p73 expression in different categories of cytological lesions. Progression and regression in women with ASCUS or LSIL evaluated according to the p63:73 status. No accuracy data presented.
Chivukula 2006	Triage concerns women with atypical squamous cells where HSIL cannot be ruled out (ASC-H).

Study	Reason for exclusion
Conesa-Zamora 2010	No HC2 testing. Polymorphism of FcGR3A gene compared in LSIL versus HSIL cytology cases. No histological outcome reported. Association between polymorphism and HPV genotypes also evaluated.
Constandinou-Williams2010	No data for ASCUS or LSIL women. Evaluated risk of developing cytological cervical abnormalities as a function of type-specific viral load of HPV (quantitative PCR GP5+/6+).
Coste 2003	No separate accuracy data for the criterion HC2 or repeat cytology were presented in the colposcopy group.
Cotton 2006	Described only the design of an RCT regarding different management options for women with borderline or low-grade abnormal cytology.
Cotton 2010	HPV testingwas not performed with HC2 but with GP5+/6+ PCR. HPV testing performed on archived residual material and the result was blinded (no diagnostic process was initiated on HPV+ women).
Cox 1992	Triage concerned women with ASCUS, LSIL or other lesions. No separate data for the ASCUS or LSIL triage groups were provided.
Cox 1995	HPV triage test was not HC2, but HC1.
Crabtree 2002	Only HC2+ positive cases with ASCUS and ASC-H were verified. Only the PPVs for different degrees of CIN were evaluated.
Cricca 2009	No HC2 but mRNA testing and no HPV negative cases included.
Del Mistro 2007	Conference report, no primary data.
Del Pino 2009	No ASCUS/LSIL triage, but triage of histologically confirmed CIN cases with p16 immunostaining.
Derchain 2004	Triage concerned women with atypical glandular cells (AGC).
Diaz-Montes 2007	Compares histological outcomes of AGC in conventional Pap smears and LBC. For a subset of women, HPV testing was done, but the histological outcome for HPV triage was insufficiently detailed (no CIN category given).
Difurio 2010	No HPV testing, only Pap test.
Dockter 2009	Women with abnormal cytology were grouped together, no separate data for ASCUS, LSIL.
Duerr 2006	Study compared women with and without human immunodeficiency virus (HIV) infection: prevalence of ASCUS, HC2+ positivity rate and cumulative incidence of cervical lesions among ASCUS cases. No gold standard-verified accuracy data were provided.
Duncan 2005	HPV testing done in only a small fraction of the women. Outcomes were not differentiated by HPV test result.
Einstein 2010	No HC2 data available.
Ekalaksananan 2006	No separate accuracy data available for ASCUS and LSIL group.
Eleuterio 2007	No index cytology, apart from biopsies, no HC2 results were shown.
Eltoum 2005	Study contained information of HC2 positivity rate in ASCUS cases, but, due to incomplete verification, no accuracy parameters could be presented. The presentation of other rates and ratios was unclear.

Study	Reason for exclusion
Evans 2006	HPV triage test was not HC2, but PCR. Outcome was restricted to biopsy-confirmed cases yielding accuracy estimates suffering from verification bias.
Fadare 2009	No triage of ASCUS or LSIL, but follow-up of women with CIN1 biopsies.
Fait 1998	HPV triage test was not HC2, but HC1.
Fait 2000	HPV triage test was not HC2, but HC1.
Farag 2008	Follow-up with HPV testing, no triage.
Feng 2005	This study evaluated the influence of pretreatment of bloody liquid-based specimens with acetic acid on HC2 positivity in ASCUS cases. No gold standard-verified accuracy data were presented.
Feng 2007a	Outcome only available for HPV+ women.
Feng 2007b	No data for ASCUS or LSIL. Evaluated association between HPV infection, epidermal growth factor receptor (EGFR) status in normal, CIN and cervical cancer biopsies.
Feng 2008	Only data about HPV+ women, no data about HPV negative women. Risk for verification bias.
Ferenczy 1996	Triage concerned women with ASCUS, LSIL or other lesions. No separate data for the ASCUS or LSIL triage groups were provided.
Ferris 1998a	HPV triage test was not HC2, but HC1.
Ferris 1998b	HC2 was not defined at the standard cut-off but at 0.3 pg/mL.
Fletcher 2009	Adolescent population. Almost no colposcopy verification in HPV subjects.
Fröberg 2008	Triage test was a linear array, no HC2 results.
Ge 2009	Only follow-up of HPV+ women.
Getman 2009	In vitro experience to derive analytical sensitivity of APTIMA vs HC2. Test positivity in clinical ASCUS samples without verification.
Goff 1993	HPV triage test was not HC2, but ViraType.
Griesser 2009	Only HPV+ mild and modarate dyskaryosis cases followed with L1 immunostaining.
Guarisi 2009	Cohort study on incidence of CIN in ASCUS/LSIL cases smokers vs non smokers. No triage data.
Guimaraes 2005	Study patients had CIN1 biopsy confirmed at baseline instead of an LSIL smear. HPV triage test was not HC2, but PCR. The study addressed correlation between protein markers p16 and bcl-2 with HPV16 and HPV18 in CIN1 progressors and CIN1-non progressors.
Guo 2004	Compareed positivity-rates and PPV for CIN2+ of p16 and HC2 in a LSIL group and a HSIL group.
Guo 2007	Triage test was Inform HPV (Ventana), no HC2 results.
Guo 2008	Triage test was PCR (GP5+/GP6+), no HC2 results.

Study	Reason for exclusion
Gupta 2007	No HPV DNA results included.
Gupta 2010	No HPV testing.
Gustavsson 2009	No verification with gold standard; HC2 and hpVIR real time PCR compared for virological concordance and by cytological categories.
Halfon 2007	No gold standard verification. Addressed HPV test concordance (HC2 and AMPLICOR).
Halfon 2010a	Data not separated into ASCUS or LSIL triage groups.
Halfon 2010b	Data not separated into ASCUS or LSIL triage groups.
Hall 1996	Triage concerned women with ASCUS or LSIL. No separate data for the two triage groups were provided. HPV triage test was not HC2, but HCT.
Harvey 2009	No separate data available for ASCUS or LSIL triage groups.
Hatch 1995	Triage concerned women with ASCUS, LSIL or other lesions. No separate data provided for the ASCUS or LSIL triage groups.
Herrington 1995	Triage concerned women with ASCUS or LSIL. No separate data provided for the 2 triage groups. HPV triage test was not HC2, but PCR and in situ hybridisation.
Ho 2003	Triage concerned women with ASCUS or LSIL. No separate data provided for the 2 triage groups. HPV triage test was not HC2, but PCR and HPV typing
Howard 2008	Economic evaluation.
Howell 2010	Review concerning the evolution of atypical squamous cells (ASC) terminology
Hughes 2002	HPV triage test was not HC2, but PCR.
Irvin 2005	Triage concerned women with AGC. This study was included in the sub-group meta-analysis for specific categories of equivocal cytology.
Jamison 2009	No HC2 testing was done. Linear array results correlated with cytology. No verification with gold standard.
Jarboe 2010	No HPV negative cases included. Only comparison of women with ASCUS with low or high viral load.
Jeantet 2009	Focus on analytical accuracy of NucliSENS EasyQ HPV v1 test and concordance with PreTect HPV-Proofer. No triage data. No HC2 testing.
Jeronimo 2007	Triage test was PGMY 09/11 instead of HC2, contained cervicography and HPV16 data, other results from the ALTS study already included in the Solomon 2001 and Sherman 2002 papers.
Julian 2006	No primary data available.
Kapeu 2009	Case-control study addressing smoking as risk factor for CC. No triage data available.
Kaufman 1997a	Triage concerned women with ASCUS or LSIL. No separate data provided for the 2triage groups. HPV triage test was not HC2, but HPV Profile.

Study	Reason for exclusion
Kaufman 1997b	Triage concerned women with ASCUS or LSIL. No separate data provided for the 2 triage groups. HPV triage test was not HC2, but HPV Profile.
Kavoussi 2009	No triage was done; CC screening with liquid cytology in women with developmental disabilities.
Keegan 2009	No gold standard verification, compared positivity rates in different cytological categories for HC2 and PreTect HPV-Proofer.
Kendall 2005	Presented only age-specific (high-risk) HC2 positivity rates. No gold standard-verified accuracy data presented.
Kitchener 2008	Follow-up of women, no triage.
Knoepp 2007	Examined histological outcomes in a group with mixed cytology index diagnoses and with an equivocal HC2 result. No HPV- cases were included. All were a priori borderline cytology and HPV+.
Knoepp 2010	Only histological follow-up data available for HPV+ cases. Cases with equivocal hrHPV results (low load) compared with higher load.
Kong 2007	Material of atypical squamous metaplasia was histological and not cytological.
Kovacs 2009	No ASCUSLSIL triage data. The paper describes the natural history of HPV infection by type of HPV infection
Krambeck 2008	Triage test was PCR, no HC2 results.
Krane 2004	Triage concerned women with AGC.
Kulasingam 2006	No primary data (ALTS data and medical care costs).
Kumar 2007	Study sample too small.
Kuperman 2000	HPV triage test was not HC2, but HC1.
Layfield 2005	Comparison of costs of HC2 versus INFORM HPV test (in situ hybridisation).
Lee 2006	Compared outcomes of triage: repeat smear vs HPV vs immediate colposcopy or combinations in 50 -/+ year old women with ASCUS. Incomplete verification. Colposcopy or biopsy in ASC-H (incomplete verification and no HPV data).
Lee 2007	No HPV test results. Discussed impact of LBC and TBS2001 on PPV of atypical smears.
Legood 2006	No primary data, modelling study, no outcome results for all subjects.
Leo 2009	No HC2, Locked Nucleic Acid real time PCR genotyping compared with InnoLiPA. No triage data available.
Liang 2010	Papillary SIL: distribution of markers in hrHPV+ cases and lrHPV+ cases.
Lim 2010	No HC2 testing. Selected population where all LSIL patients had histologically-confirmed CIN1.
Liman 2005	Triage concerned women with ASC-H.
Lin 2000	HC2 not defined at the standard cut-off but at 0.3 pg/mL.

Study	Reason for exclusion
Lin 2010	HC2, PCR-reverse line blot hybridization, methylation-specific PCR. Markers correlated to cytology and to histology, but histology not stratified separately for ASCUS or LSIL triage groups.
Longatto-Filho 2005	Limited to ASCUS/HPV+ cases. Outcome poorly documented, 2 tests used; HC2 or PCR, no separate data for HC2. Described KI67/p16 correlations.
Martin 2009	No clinical samples. Gene expression profiles (RNA, proteins) in cell cultures.
Massad 2004	HPV triage test was not HC2, but PCR, and concerned triage of HIV positive women with ASCUS.
Massad 2009	No HC2 testing, focus on colposcopy grading. No triage data (ALTS).
Maucort-Boulch 2010	ALTS study: focussed on the persistence of HPV as a function of age and incidence/prevalence status. No ASCUS triage data presented.
McHale 2007	Descibed outcome of ASC-H without relating to HPV status.
Melnikow 2006	Editorial, no primary data.
Mesher 2010	Primary screening (HART study), no triage.
Mirasoli 2009	Histological distinction between CIN categories using p16. No ASCUS triage data. No HC2 testing.
Mo 2008	No histological outcomes.
Mokhtar 2008	No HPV testing, ASC-H cases followed-up by cytology and by biopsy for some of the cases.
Molden 2005	HPV triage test was not HC2, but PreTect HPV-Proofer (test for mRNA coding for E6/7 from 5 high-risk types).
Monsonego 2005	No HC2 testing, but AMPLICOR and LBC.
Monsonego 2008a	Contained complete verification data for a series of women with WNL, ASCUS, LSIL, and HSIL tested with p16,HC2 and linear array. No separate accuracy data available for ASCUS or LSIL triage groups.
Moore 2010	No accuracy data, provided risk CIN3+ in 21-24 year old women with ASCUS, HPV+ and LSIL from ALTS study.
Moscicki 2008	Study about the management and treatment of women with minor cytological abnormalities, no HC2 testing results.
Mould 2000	Triage concerns women with ASCUS or LSIL. No separate data proivided for the 2 triage groups. HPV triage test was not HC2 but HC1.
Nassar 2008	Outcome threshold was not defined. Where it was defined, data not stratified by cytological category.
Noel 2006	Review article, no primary data available.
Nomelini 2007	Results for ASCUS and LSIL triage groups could not be separated.
Nuovo 2008	No outcome available with CIN2+ details, only CIN+ outcomes were reported.
Nyirjesy 1998	Triage concerned women with ASCUS or LSIL. No separate data provided for the 2 triage groups. HPV triage test was not HC2 but HC1.

Study	Reason for exclusion
Ogilvie 2010	Preliminary results, might give data in the future.
Oliveira 2004	Triage concerned only women with AGC. The outcome was the cytological result of a repeat smear. No gold standard-verified data provided.
Oliveira 2010	HPV prevalence (and typing) and cyto-virological correlation in Brazilian students. No histological outcome reported.
Onuma 2006	Only pregnant women with ASC-H cytology included. Incomplete verification.
Ou 2007	Only abstract available, article in Chinese. Insufficient data were given.
Ozsaran 2003	HPV triage test was not HC2, but HC1.
Pajtler 2010	No separate accuracy data for ASCUS group. No point in requesting separate data, since only 11 ASCUS women included.
Pambuccian 2002	HPV triage test was not HC2, but PCR.
Paternoster 2008	No HC2 triage test; no gold standard-verification.
Patton 2008	No general screening population. Addressed outcome in ASC-H according to hormonal status.
Peng 2006	Compared outcomes in triage versus no triage situation vs situation where HPV testing always used; incomplete verification in triage situation.
Perrons 2005	Follow-up and post treatment data; no accuracy parameters could be derived.
Philips 2006	No primary data, questionnaire about consequences of introduction of HPV triage into screening.
Pisal 2003	Triage concerned women with ASCUS or LSIL. No separate data provided for the 2 triage groups.
Poljak 2009	No ASCUS or LSIL triage; concordance between Abbott RealTime PCR and HC2 testing.
Pretet 2008	Triage test was INNO-LiPA, no HC2 results.
Quddus 2002	Only CIN1+ outcome documented (cervical intraepithelial neoplasia of grade 1 or worse), triage of atypical squamous metaplasia (ASM), was not ASCUS.
Quddus 2009	Addressed ASCUS and AGUS rates, %hrHPV among these and the detection rate of histological outcomes before and after introduction of ThinPrep Imager.
Qureshi 2003	Triage concerned women with ASCUS or LSIL. No separate data provided for the 2 triage groups.
Rabelo-Santos 2009	Not HC2 testing, but Roche reverse line blot assay.
Rana 2004	Longitutidinal cytological or histological outcomes of borderline or mild dyskaryosis. No HPV testing done.
Raskin 2009	No HC2 testing.
Rauber 2008	No HPV testing. L1 immunostaining correlated with regression/progression.
Recio 1998	HPV triage test was not HC2, but HC1.

Study	Reason for exclusion
Reesink-Peters 2003	Triage concerned women with ASCUS, LSIL or other lesions. No separate data provided for the ASCUS or LSIL triage groups. HPV triage test not HC2, but PCR and detection of telomerase.
Riethmuller 2008	Follow-up, no triage.
Rijkaart 2009	No complete accuracy data. Only cumulative detection of CIN2/3+ in cytology versus HPV-based follow-up; PPV and colposcopy referral.
Robova 2007	hrHPV test was not specified.
Rodriguez 2008	Data restricted to HPV triage negative patients and no colposcopy data (gold standard-verification) available, only follow-up Pap tests.
Ronnett 1999	Triage concerned women with AGC.
Rosini 2007	3 groups were not separated. Outcome was based on colposcopy. Only DNA/RNA test and cytology were documented with crude data.
Rowe 2004	Study evaluatesd only the HC2-positivity rate in women with different categories of equivocal squamous or glandular abnormalities or LSIL. No gold standard-verified accuracy data were presented.
Saad 2006	Only women of peri and post menopausal age included.
Safaeian 2007	Documented accuracy of HPV/cytology testing at 12 months among HPV-ASCUS women; also gave accuracy of HPV testing for cumulative CIN2/3+ according to age group.
Samarawardana 2010	No HC2, but type-specific PCR and p16.
Santos 2003	Triage concerned women with ASCUS or LSIL. No separate data provided for the 2 triage groups.
Santos 2006	Patients had histologically confirmed CIN1, not LSIL.
Saqi 2006	Triage concerned women with AGC.
Sargent 2010	Accuracy data for triage of borderline/mild dyskaryosis (nested in ARTISTIC trial) were not presented separately.
Sarian 2009	Natural history study: risk of HPV infection and lesions related to smoking. No triage data.
Sarode 2003	In the ASCUS group (including women with ASC-H, ASC-R (atypical squamous cells which are probably reactive) or ASCUS), verification was done only if HC2+. In the LSIL group, all women were verified but the data were not separated from the ASCUS groups..
Schiffman 2006	No primary data, comment on Legood and Moss paper.
Schledermann 2008	No HC2 testing.
Schmitz 2009	No triage data. No HC2. Compared analytical accuracy genotyping realtime PCR (and concordance with GP5/6+ PCR).
Schnatz 2006	Systematic review of outcomes of AGC. No HPV testing.

Study	Reason for exclusion
Seme 2006	Repeated borderline virological HC2 results. No gold standard outcome; objective was to determine concordance between HC2/PCR and typing.
Sharpless 2005a	Adherence of guidelines for management of AGC.
Sharpless 2005b	Outcomes of AGC. No HPV testing.
Sharpless 2009	Systematic review on HPV triage in AGC.
Sheriff 2007	Economic analysis, no primary data.
Shi 2009	No ASCUS or LSIL triage. Longitudinal absolute risk of CIN2+ after 1st screening round.
Shidham 2007	Did not contain ASCUS or LSIL data, only LSIL-H (LSIL lesions which might be high-grade). Contained HPV and histological data, only PPV could be calculated, verification bias.
Shin 2008	Index result for ASCUS and LSIL were grouped together and could not be separated.
Siddiqi 2009	Extremely low sensitivity of HC2 and nearly perfect sensitivity of ProExC.
Siddiqui 2008a	No complete gold standard-verification.
Sideri 1998	HPV triage test was not HC2, but HC1.
Singh 2009	No HC2; PCR test and 2 protein markers (p53,Bcl-2) evaluated for prediction of progression.
Six 2008	PCR, serology - vaccination.
Slawson 1994	HPV triage test was not HC2, but ViraPap.
Sorbye 2010	Only histological follow-up data available for mrRNA+ cases: only PPV could be evaluated.
Srodon 2005	Triage concerned women with ASC-H.
Steinman 2008	No gold standard verification.
Stemberger-Papic 2010	All samples were HC2 positive. The natural history was evaluated according to L1 immunochemistry. No separate data presented for LSIL.
Stevens 2007	Complete accuracy data for HC2, linear array HPV genotyping, AMPLICOR PCR, but not presented separately for ASCUS or LSIL triage groups.
Stoler 2001	Documented only high HC2 rate in LSIL.
Stoler 2007	No primary data.
Suba 2009	Comment;. no primary data.
Sun 2006	Triage test was DNA image cytometry, no HC2 testing; article in Chinese.
Sung 2010	Addressed p16 in ASCUS and ASC-H for subsequent CIN. Incomplete HPV test data, HPV data not linked to follow-up outcome.
Tambouret 2008	Histological outcome for some subjects and follow-up cytology for others. No separate data for ASCUS/LSIL. Triage test was HC2 and ProEx C.

Study	Reason for exclusion
Tang 2009	The test used was: Abbot rtPCR in CIN3, cancer and cyto-negative subjects. No triage data.
Tarkkanen 2007	ASCUS-LSIL could not be separated in the index smear.
Thrall 2008	HPV triage was HC2, but histological verification was overwhelmingly based on a positive HC2 result resulting in extremely low specificity estimates due to verification bias.
Thrall 2010	No gold standard verification of HPV testing on all participants; triage in women > 30 years of age.
TOMBOLA 2009a	No HPV testing accuracy data presented in this paper.
TOMBOLA 2009b	No HPV testing accuracy data presented in this paper.
TOMBOLA 2009c	No HPV testing accuracy data presented in this paper.
Torres 2009	Study of prevalence of HPV (HC2) in a CC screening population, with correlation with cytology. No verification data.
Tu 2009	No HC2 testing. Telomerase presence documented separately in different categories of cytology and histology.
Vijayaraghavan 2010	0nly cost-effectiveness results of HPV16/18 triage of HPV+ women.
Vince 2001	HC2 test positivity rate was documented for women with LSIL, but no gold standard-verified outcome data were provided.
Walker 2006	Contained data only on the risk of CIN3 by follow up (ALTS), other data from this study already included in Solomon 2001 and Sherman 2002.
Wang 2007	Article in Chinese, only abstract available, HPV test not specified.
Wensveen 2006	ASCUS and AGUS were grouped together. The accuracy data for triage separated for ASCUS and LSIL were reported in Wensveen 2003.
Wheeler 2006	Triage test was PCR instead of HC2, results of ALTS study already included in Solomon 2001 and Sherman 2002.
Wong 2008	No gold standard-verification. Addressesses HPV test concordance (HC2 and Inv2).
Wong 2008a	No colposcopy/biopsy results. Study focusses on morphological correlates for lr & hrHPV infection. No triage data.
Wright 1995	HPV triage test was not HC2, but HC1.
Wright 1998	Triage test was HC1, secondary publication of Wright 1995.
Wright 2006	HPV triage was HC2, but histological verification was overwhelmingly based on a positive HC2 result resulting in extremely low specificity estimates due to verification bias.
Wu 2006	Gold standard-verification was incomplete.
Xi 2009	This report of the ALTS study does not describe the perforamce of HC2 but focuses on the viral load of HPV18.
Yarandi 2009	No HC2 testing, but PCR.

Study	Reason for exclusion
Yu 2010	No HPV testing. P16, Ki67 and L1 immunostaining in LBC and cell block were correlated with histological outcomes.
Zhao 2009a	No HPV triage investigated.
Zhao 2009b	No ASCUS/LSIL smears, but unsatisfactory Pap smears.
Zivadinovic 2009	Incomplete HPV testing and histological outcomes.

Abbreviations
AGC = atypical glandular cells
AGUS = atypical glandular cells of undermined significance
AMPLICOR = PCR-based test for detection of 13 high-risk HPVgenotypes
ASC-H = atypical squamous cells of undetermined significance, where HSIL cannot be excluded
ASCUS = atypical squamous cells of undetermined significance
ASM = atypical squamous metaplasia
CC = cervical cancer
CIN2+ = cervical intraepithelial neoplasia of grade 2 or worse
CIN3+ = cervical intraepithelial neoplasia of grade 3 or worse
HC2 = Hybrid Capture 2 assay
HPV = human papillomavirus
HPV+ = human papillomavirus positive
HSIL = high-grade squamous intraepithelial lesion
LBC = liquid-based cytology
LSIL = low-grade squamous intra-epithelial lesions
Pap = Papanicolaou test
PCR = polymerase chain reaction
PPV = positive predictive value
VIA =

Characteristics of studies awaiting classification *[ordered by study ID]*

Alameda 2011

Clinical features and settings	
Participants	Women with ASCUS.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2. Comparator test: p16 immunocytochemistry.
Follow-up	
Notes	

Barcelos 2011

Clinical features and settings	

Barcelos 2011 *(Continued)*

Participants	Women with ASC-US and ASC-H.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2 Comparator test: review of cytological specimen.
Follow-up	
Notes	

Belinson 2011

Clinical features and settings	
Participants	Women participating in a primary screening trial, involving self-sampling and sampling by a clinician.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	
Follow-up	Index test: HC2. Comparator tests: Cervista and MALDI-TOF [PCR-based mass array matrix-assisted laser desorption/ionization time-offlight mass spectrometry system]).
Notes	Data requested from authors separately for women with ASC-US and for women with LSIL.

Chao 2013

Clinical features and settings	
Participants	Women with ASC-US or ASC-H.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2. Comparator test: methylation markers.
Follow-up	
Notes	

Clad 2011

Clinical features and settings	
Participants	Women with ASCUS or LSIL.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2. Comparator test: APTIMA hrHPV RNA assay.
Follow-up	
Notes	Data requested from authors separately for women with ASC-US and for women with LSIL.

Cuzick 2013

Clinical features and settings	
Participants	Women with LSIL.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2. Comparator test: COBAS-4800 assay.
Follow-up	
Notes	

Dona 2012

Clinical features and settings	
Participants	Women referred to colposcopy.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: Linear Array. Comparator test: p16/Ki67 cytoimmunochemistry.
Follow-up	

Dona 2012 *(Continued)*

Notes	Data requested from authors separately for women with ASC-US and for women with LSIL.

Dufresne 2011

Clinical features and settings	
Participants	Women with ASC-US
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2 Comparator tests: AMPLICOR, Linear Array and COBAS-4800
Follow-up	
Notes	

Edgerton 2011

Clinical features and settings	
Participants	Women with ASCUS.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2. Comparator test: p16 immunocytochemistry.
Follow-up	
Notes	

Gustinucci 2012

Clinical features and settings	
Participants	
Study design	Women with ASC-US, ASC-H or LSIL.
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2.

Gustinucci 2012 *(Continued)*

	Comparator test: p16 cyto-immunochemistry.
Follow-up	
Notes	

Heider 2011

Clinical features and settings	
Participants	Women with LSIL.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2. No comparator tests.
Follow-up	
Notes	

Huang 2012

Clinical features and settings	
Participants	Women with mildly cytologic abnormalities
Study design	
Target condition and reference standard(s)	
Index and comparator tests	
Follow-up	Index test: EasyChip HPV Blot
Notes	Data requested from authors separately for women with ASC-US and for women with LSIL.

Ibanez 2012

Clinical features and settings	
Participants	Women with ASCUS.
Study design	
Target condition and reference standard(s)	

Ibanez 2012 *(Continued)*

Index and comparator tests	Index test: HC2.
Follow-up	
Notes	

Jakobsson 2012

Clinical features and settings	
Participants	Women with ASC-US.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: AMPLICOR;
Follow-up	
Notes	

Jiang 2011

Clinical features and settings	
Participants	Women with ASC-US and LSIL.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: PCR (ABI 7500 PCR system, Applied Biosystems, USA) detecting nine hrHPV types.
Follow-up	
Notes	

Koliopoulos 2012

Clinical features and settings	
Participants	Women with ASC-US or LSIL.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test:PreTect HPV-Proofer.

Koliopoulos 2012 *(Continued)*

	Comparator test: flow cytometry for E6&E7 mRNA (Onco-Tect)
Follow-up	
Notes	

Lapierre 2012

Clinical features and settings	
Participants	Women with ASC-US
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2. Comparator test: Linear Array, COBAS-4800 assay.
Follow-up	
Notes	

Levi 2011

Clinical features and settings	
Participants	Women with LSIL.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2. No comparator test.
Follow-up	
Notes	

Loghavi 2012

Clinical features and settings	
Participants	Women with ASC-US or LSIL.
Study design	

Loghavi 2012 *(Continued)*

Target condition and reference standard(s)	
Index and comparator tests	Index test: Cervista/Invader test. Comparator test: p16/Ki69 cytoimmunochemistry.
Follow-up	
Notes	

Ma 2011

Clinical features and settings	
Participants	Women with ASC-US or LSIL.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2. Comparator test; p16 immunocytochemistry.
Follow-up	
Notes	

Monsonego 2011

Clinical features and settings	
Participants	Women with diverse cytology results participating in a screening trial.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2. Comparator test:APTIMA hrHPV RNA assay, Linear Array.
Follow-up	
Notes	Data requested from authors separately for women with ASC-US and for women with LSIL.

Nasioutziki 2011

Clinical features and settings	

Nasioutziki 2011 *(Continued)*

Participants	Women with ASC-US or LSIL.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2. Comparator test: p16 immunocytochemistry.
Follow-up	
Notes	

Origoni 2012

Clinical features and settings	
Participants	Women with ASC-US.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2.
Follow-up	
Notes	

Ovestad 2011

Clinical features and settings	
Participants	Women with ASC-US or LSIL.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test; AMPLICOR; Comparator test;APTIMA hrHPV RNA assay, COBAS-4800 assay and Pretect HPV Proofer.
Follow-up	
Notes	

Pista 2011

Clinical features and settings	
Participants	Women with ASC-US and LSIL.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2. No comparator test.
Follow-up	
Notes	Data requested from authors.

Ratnam 2011

Clinical features and settings	
Participants	Women with diverse cytology results participating in a screening trial. and women referred to colposcopy.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2. Comparator test:APTIMA hrHPV RNA assay, Linear Array and PreTect HPV Proofer.
Follow-up	
Notes	Data requested from authors separately for women with ASC-US and for women with LSIL.

Rodriguez 2012

Clinical features and settings	
Participants	Women with ASC-US being HC2+.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2.
Follow-up	
Notes	

Schmidt 2011

Clinical features and settings	
Participants	Women with ASC-US or LSIL.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2. Comparator test: p16 immunocytochemistry.
Follow-up	
Notes	

Soderlund-Strand 2011

Clinical features and settings	
Participants	Women low-grade cervical lesions
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: PCR amplification using 5/bioGP 6 primers followed by luminex-based identification of multiple high- and low-risk HPV types.
Follow-up	
Notes	

Stoler 2011

Clinical features and settings	
Participants	Women with ASC-US
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2. Comparator test: COBAS-4800.
Follow-up	
Notes	

Stoler 2013

Clinical features and settings	
Participants	Women with ASC-US.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2. Comparator test:APTIMA HPV mRNA assay..
Follow-up	
Notes	

Szarewski 2012

Clinical features and settings	
Participants	Women with diverse abnormal cytology referred to colposcopy.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2. Comparator tests: p16 cytoimmunochemistry,Abbott RealTime hrHPV PCR, Cobas-4800, APTIMA hrHPV RNA assay,BD HPV tests, APTIMA hrHPV RNA test and,PreTect HPV-Proofer.
Follow-up	
Notes	Data requested from authors separated for women with ASC-US and for women with LSIL.

Tsoumpou 2010

Clinical features and settings	
Participants	Women with LSIL.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: PCR test (CLART [(Clinical Array Technology] including identification for 35 HPV types). Comparator test: p16 immunocytochemistry.

Tsoumpou 2010 *(Continued)*

Follow-up	
Notes	

Valasoulis 2011

Clinical features and settings	
Participants	Women with LSIL.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: p16 cytoimmunochemistry.
Follow-up	
Notes	

Waldstrom 2011

Clinical features and settings	
Participants	Women with ASC-US or LSIL
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: Linear Array. Comparator test: APTIMA hrHPV RNA assay and p16/Ki67 immunocytochemistry.
Follow-up	
Notes	

Wentzensen 2012

Clinical features and settings	
Participants	Women referred to colposcopy.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index: Linear Array.

Wentzensen 2012 *(Continued)*

	Comparator test: p16/Ki67 immunocytochemistry.
Follow-up	
Notes	Data requested from authors separately for women with ASC-US and for women with LSIL.

Wong 2011

Clinical features and settings	
Participants	Women with ASC-US.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2. Comparator test: Abott real time PCR for hrHPV.
Follow-up	
Notes	

Wong 2012

Clinical features and settings	
Participants	Women with ASC-US.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2. Comparator test: Linear Array and GenoFlow human papillomavirus assay.
Follow-up	
Notes	

Wu 2010

Clinical features and settings	
Participants	Women participating in a primary screening trial.
Study design	

Wu 2010 *(Continued)*

Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2. Comparator test: APTIMA hrHPV RNA assay.
Follow-up	
Notes	Data requested from authors separately for women with ASC-US and for women with LSIL.

Ziemke 2012

Clinical features and settings	
Participants	Women with LSIL.
Study design	
Target condition and reference standard(s)	
Index and comparator tests	Index test: HC2. Comparator test: p16/Ki67 cytoimmunocyto-chemistry.
Follow-up	
Notes	

DATA

Presented below are all the data for all of the tests entered into the review.

Table Tests. Data tables by test

Test	No. of studies	No. of participants
1 Triage ASCUS with HC2, CIN2+ (all studies)	39	13196
2 Triage of ASCUS with HC2, CIN2+ (studies with both tests)	10	5261
3 Triage of ASCUS with HC2, CIN3+ (all studies)	17	6144
4 Triage of ASCUS with HC2, CIN3+ (studies with both tests)	4	2726
5 Triage of ASCUS with repeat cytology (cut-off ASCUS+), CIN2+	10	5208
6 Triage of ASCUS with repeat cytology (cut-off LSIL+), CIN2+	6	4161
7 Triage of ASCUS with repeat cytology (cut-off HSIL+), CIN2+	5	3744

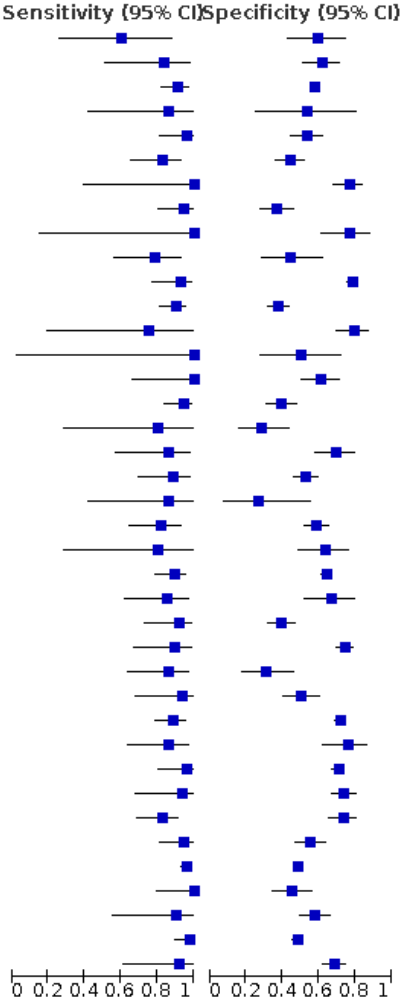
Test	No. of studies	No. of participants
8 Triage of ASCUS with repeat cytology (cut-off ASCUS+), CIN3+	4	2731
9 Triage of ASCUS with repeat cytology (cut-off LSIL+), CIN3+	4	2731
10 Triage of ASCUS with repeat cytology (cut-off HSIL+), CIN3+	4	2731
11 Triage LSIL with HC2, CIN2+ (all studies)	24	9983
12 Triage of LSIL with HC2, CIN2+ (studies with both tests)	6	1591
13 Triage of LSIL with HC2, CIN3+ (all studies)	14	8253
14 Triage of LSIL with HC2, CIN3+ (studies with both tests)	4	1295
15 Triage of LISL with repeat cytology (cut-off ASCUS+), CIN2+	6	1587
16 Triage of LSIL with repeat cytology (cut-off LSIL+), CIN2+	4	1300
17 Triage of LSIL with repeat cytology (cut-off HSIL+), CIN2+	4	1300
18 Triage of LSIL with repeat cytology (cut-off ASCUS+), CIN3+	4	1300
19 Triage of LSIL with repeat cytology (cut-off LSIL+), CIN3+	4	1300
20 Triage of LSIL with repeat cytology (cut-off HSIL+), CIN3+	4	1300
25 Triage of ASCUS with HC2, CIN2+ (according to collection device)	24	9218
26 Triage of ASCUS with HC2, CIN2+ (according to transport medium)	23	4367
27 Triage of ASCUS with HC2, CIN2+ (<30y)	2	2259
28 Triage of ASCUS with HC2, CIN2+ (30-39y)	2	974
29 Triage of ASCUS with HC2, CIN2+ (40-49y)	2	569
30 Triage of ASCUS with HC2, CIN2+ (50y or older)	2	281
31 Triage of ASCUS with HC2, CIN3+ (<30y)	2	2259
32 Triage of ASCUS with HC2, CIN3+ (30-39y)	2	974
33 Triage of ASCUS with HC2, CIN3+ (40-49y)	2	569
34 Triage of ASCUS with HC2, CIN3+ (50y or older)	2	281
35 Triage of LSIL with HC2, CIN2+ (<30y)	2	1363
36 Triage of LSIL with HC2, CIN2+ (30-39y)	3	2915
37 Triage of LSIL with HC2, CIN2+ (40-49y)	3	1666
38 Triage of LSIL with HC2, CIN2+ (50y or older)	3	801
39 Triage of LSIL with HC2, CIN3+ (<30y)	2	1363

Test	No. of studies	No. of participants
40 Triage of LSIL with HC2, CIN3+ (30-39y)	3	2915
41 Triage of LSIL with HC2, CIN3+ (30-49y)	3	1666
42 Triage of LSIL with HC2, CIN3+ (50y or older)	3	801

Test 1. Triage ASCUS with HC2, CIN2+ (all studies)

Triage ASCUS with HC2, CIN2+ (all studies)

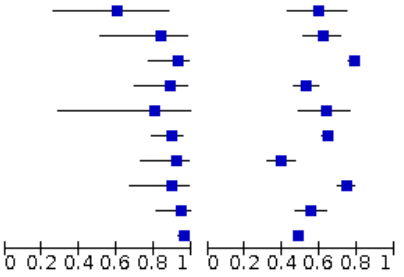
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Andersson 2005	6	17	4	25	0.60 [0.26, 0.88]	0.60 [0.43, 0.74]
Bergeron 2000	10	38	2	61	0.83 [0.52, 0.98]	0.62 [0.51, 0.71]
Bergeron 2006	63	772	6	1039	0.91 [0.82, 0.97]	0.57 [0.55, 0.60]
Cattani 2009	6	6	1	7	0.86 [0.42, 1.00]	0.54 [0.25, 0.81]
Chen 2005b	26	62	1	71	0.96 [0.81, 1.00]	0.53 [0.45, 0.62]
Cuschieri 2007	28	87	6	69	0.82 [0.65, 0.93]	0.44 [0.36, 0.52]
Cuzick 2003	4	28	0	91	1.00 [0.40, 1.00]	0.76 [0.68, 0.84]
Dalla Palma 2005	32	77	2	45	0.94 [0.80, 0.99]	0.37 [0.28, 0.46]
Davis-Devine 2005	2	10	0	33	1.00 [0.16, 1.00]	0.77 [0.61, 0.88]
De Francesco 2008	18	21	5	17	0.78 [0.56, 0.93]	0.45 [0.29, 0.62]
Del Mistro 2010	27	154	2	566	0.93 [0.77, 0.99]	0.79 [0.75, 0.82]
Denton 2010	73	189	8	115	0.90 [0.81, 0.96]	0.38 [0.32, 0.44]
Giovannelli 2005	3	18	1	70	0.75 [0.19, 0.99]	0.80 [0.70, 0.87]
Guyot 2003	1	11	0	11	1.00 [0.03, 1.00]	0.50 [0.28, 0.72]
Holladay 2006	9	35	0	55	1.00 [0.66, 1.00]	0.61 [0.50, 0.71]
Huang 2009	49	86	3	55	0.94 [0.84, 0.99]	0.39 [0.31, 0.48]
Kelly 2006	4	33	1	13	0.80 [0.28, 0.99]	0.28 [0.16, 0.43]
Kiatpongsan 2006	12	23	2	53	0.86 [0.57, 0.98]	0.70 [0.58, 0.80]
Kulasingam 2002	23	115	3	129	0.88 [0.70, 0.98]	0.53 [0.46, 0.59]
Lee 2009	6	11	1	4	0.86 [0.42, 1.00]	0.27 [0.08, 0.55]
Lonky 2003	27	101	6	144	0.82 [0.65, 0.93]	0.59 [0.52, 0.65]
Lytwyn 2000	4	19	1	33	0.80 [0.28, 0.99]	0.63 [0.49, 0.76]
Manos 1999	58	326	7	582	0.89 [0.79, 0.96]	0.64 [0.61, 0.67]
Monsonego 2006	17	17	3	34	0.85 [0.62, 0.97]	0.67 [0.52, 0.79]
Monsonego 2008	22	110	2	72	0.92 [0.73, 0.99]	0.40 [0.32, 0.47]
Morin 2001	17	88	2	253	0.89 [0.67, 0.99]	0.74 [0.69, 0.79]
Nieh 2005	18	31	3	14	0.86 [0.64, 0.97]	0.31 [0.18, 0.47]
Ordi 2003	14	52	1	53	0.93 [0.68, 1.00]	0.50 [0.41, 0.60]
Pretorius 2002	56	250	7	636	0.89 [0.78, 0.95]	0.72 [0.69, 0.75]
Rebello 2001	18	13	3	41	0.86 [0.64, 0.97]	0.76 [0.62, 0.87]
Ronco 2007	25	213	1	518	0.96 [0.80, 1.00]	0.71 [0.67, 0.74]
Shlay 2000	14	47	1	133	0.93 [0.68, 1.00]	0.74 [0.67, 0.80]
Siddiqui 2008	42	40	9	109	0.82 [0.69, 0.92]	0.73 [0.65, 0.80]
Silverloo 2009	34	65	2	81	0.94 [0.81, 0.99]	0.55 [0.47, 0.64]
Solomon 2001	256	1050	11	984	0.96 [0.93, 0.98]	0.48 [0.46, 0.51]
Szarewski 2008	16	47	0	39	1.00 [0.79, 1.00]	0.45 [0.35, 0.56]
Wensveen 2003	9	58	1	80	0.90 [0.55, 1.00]	0.58 [0.49, 0.66]
You 2007	50	579	1	541	0.98 [0.90, 1.00]	0.48 [0.45, 0.51]
Zielinski 2001	11	63	1	138	0.92 [0.62, 1.00]	0.69 [0.62, 0.75]



Test 2. Triage of ASCUS with HC2, CIN2+ (studies with both tests)

Triage of ASCUS with HC2, CIN2+ (studies with both tests)

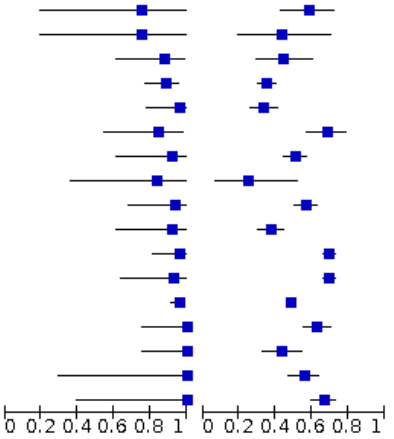
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Andersson 2005	6	17	4	25	0.60 [0.26, 0.88]	0.60 [0.43, 0.74]		
Bergeron 2000	10	38	2	61	0.83 [0.52, 0.98]	0.62 [0.51, 0.71]		
Del Mistro 2010	27	154	2	566	0.93 [0.77, 0.99]	0.79 [0.75, 0.82]		
Kulasingam 2002	23	115	3	129	0.88 [0.70, 0.98]	0.53 [0.46, 0.59]		
Lytwyn 2000	4	19	1	33	0.80 [0.28, 0.99]	0.63 [0.49, 0.76]		
Manos 1999	58	326	7	582	0.89 [0.79, 0.96]	0.64 [0.61, 0.67]		
Monsonego 2008	22	110	2	72	0.92 [0.73, 0.99]	0.40 [0.32, 0.47]		
Morin 2001	17	88	2	253	0.89 [0.67, 0.99]	0.74 [0.69, 0.79]		
Silverloo 2009	34	65	2	81	0.94 [0.81, 0.99]	0.55 [0.47, 0.64]		
Solomon 2001	256	1050	11	984	0.96 [0.93, 0.98]	0.48 [0.46, 0.51]		



Test 3. Triage of ASCUS with HC2, CIN3+ (all studies)

Triage of ASCUS with HC2, CIN3+ (all studies)

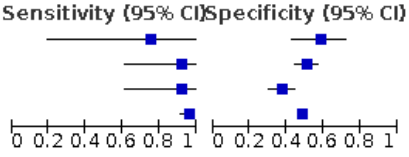
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Andersson 2005	3	20	1	28	0.75 [0.19, 0.99]	0.58 [0.43, 0.72]		
Cattani 2009	3	9	1	7	0.75 [0.19, 0.99]	0.44 [0.20, 0.70]		
De Francesco 2008	14	25	2	20	0.88 [0.62, 0.98]	0.44 [0.30, 0.60]		
Denton 2010	48	214	6	117	0.89 [0.77, 0.96]	0.35 [0.30, 0.41]		
Huang 2009	22	113	1	57	0.96 [0.78, 1.00]	0.34 [0.26, 0.41]		
Kiatpongsan 2006	11	24	2	53	0.85 [0.55, 0.98]	0.69 [0.57, 0.79]		
Kulasingam 2002	11	127	1	131	0.92 [0.62, 1.00]	0.51 [0.45, 0.57]		
Lee 2009	5	12	1	4	0.83 [0.36, 1.00]	0.25 [0.07, 0.52]		
Lonky 2003	14	114	1	149	0.93 [0.68, 1.00]	0.57 [0.50, 0.63]		
Monsonego 2008	11	121	1	73	0.92 [0.62, 1.00]	0.38 [0.31, 0.45]		
Pretorius 2002	27	279	1	642	0.96 [0.82, 1.00]	0.70 [0.67, 0.73]		
Ronco 2007	12	226	1	518	0.92 [0.64, 1.00]	0.70 [0.66, 0.73]		
Sherman 2002	124	1063	5	1006	0.96 [0.91, 0.99]	0.49 [0.46, 0.51]		
Siddiqui 2008	13	69	0	118	1.00 [0.75, 1.00]	0.63 [0.56, 0.70]		
Szarewski 2008	13	50	0	39	1.00 [0.75, 1.00]	0.44 [0.33, 0.55]		
Wensveen 2003	3	64	0	81	1.00 [0.29, 1.00]	0.56 [0.47, 0.64]		
Zielinski 2001	4	70	0	139	1.00 [0.40, 1.00]	0.67 [0.60, 0.73]		



Test 4. Triage of ASCUS with HC2, CIN3+ (studies with both tests)

Triage of ASCUS with HC2, CIN3+ (studies with both tests)

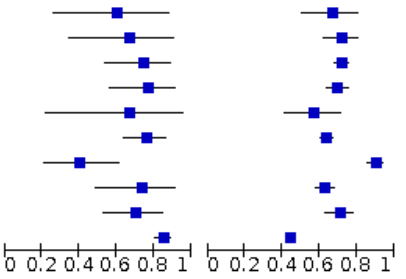
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Andersson 2005	3	20	1	28	0.75 [0.19, 0.99]	0.58 [0.43, 0.72]		
Kulasingam 2002	11	127	1	131	0.92 [0.62, 1.00]	0.51 [0.45, 0.57]		
Monsonego 2008	11	121	1	73	0.92 [0.62, 1.00]	0.38 [0.31, 0.45]		
Sherman 2002	124	1063	5	1006	0.96 [0.91, 0.99]	0.49 [0.46, 0.51]		



Test 5. Triage of ASCUS with repeat cytology (cut-off ASCUS+), CIN2+

Triage of ASCUS with repeat cytology (cut-off ASCUS+), CIN2+

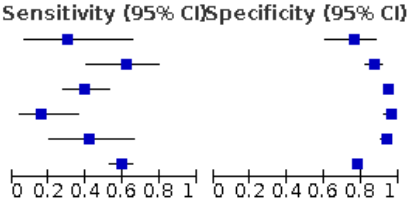
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Andersson 2005	6	14	4	28	0.60 [0.26, 0.88]	0.67 [0.50, 0.80]		
Bergeron 2000	8	28	4	71	0.67 [0.35, 0.90]	0.72 [0.62, 0.80]		
Del Mistro 2010	20	191	7	483	0.74 [0.54, 0.89]	0.72 [0.68, 0.75]		
Kulasingam 2002	20	74	6	170	0.77 [0.56, 0.91]	0.70 [0.63, 0.75]		
Lytwyn 2000	4	20	2	26	0.67 [0.22, 0.96]	0.57 [0.41, 0.71]		
Manos 1999	48	324	15	570	0.76 [0.64, 0.86]	0.64 [0.61, 0.67]		
Monsonego 2008	10	18	15	168	0.40 [0.21, 0.61]	0.90 [0.85, 0.94]		
Morin 2001	14	126	5	214	0.74 [0.49, 0.91]	0.63 [0.58, 0.68]		
Silverloo 2009	24	43	10	105	0.71 [0.53, 0.85]	0.71 [0.63, 0.78]		
Solomon 2001	227	1132	40	914	0.85 [0.80, 0.89]	0.45 [0.43, 0.47]		



Test 6. Triage of ASCUS with repeat cytology (cut-off LSIL+), CIN2+

Triage of ASCUS with repeat cytology (cut-off LSIL+), CIN2+

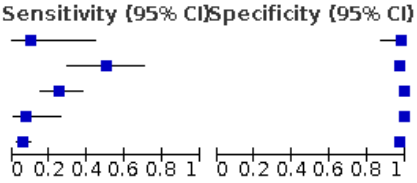
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Andersson 2005	3	10	7	32	0.30 [0.07, 0.65]	0.76 [0.61, 0.88]		
Kulasingam 2002	16	32	10	212	0.62 [0.41, 0.80]	0.87 [0.82, 0.91]		
Manos 1999	25	52	38	842	0.40 [0.28, 0.53]	0.94 [0.92, 0.96]		
Monsonego 2008	4	8	21	178	0.16 [0.05, 0.36]	0.96 [0.92, 0.98]		
Morin 2001	8	22	11	318	0.42 [0.20, 0.67]	0.94 [0.90, 0.96]		
Solomon 2001	158	452	109	1593	0.59 [0.53, 0.65]	0.78 [0.76, 0.80]		



Test 7. Triage of ASCUS with repeat cytology (cut-off HSIL+), CIN2+

Triage of ASCUS with repeat cytology (cut-off HSIL+), CIN2+

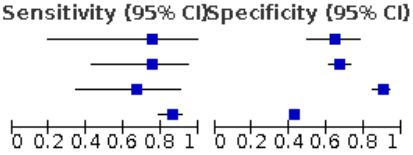
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Andersson 2005	1	1	9	41	0.10 [0.00, 0.45]	0.98 [0.87, 1.00]		
Kulasingam 2002	13	7	13	237	0.50 [0.30, 0.70]	0.97 [0.94, 0.99]		
Manos 1999	16	7	47	887	0.25 [0.15, 0.38]	0.99 [0.98, 1.00]		
Monsonego 2008	2	1	23	185	0.08 [0.01, 0.26]	0.99 [0.97, 1.00]		
Solomon 2001	11	67	174	2002	0.06 [0.03, 0.10]	0.97 [0.96, 0.97]		



Test 8. Triage of ASCUS with repeat cytology (cut-off ASCUS+), CIN3+

Triage of ASCUS with repeat cytology (cut-off ASCUS+), CIN3+

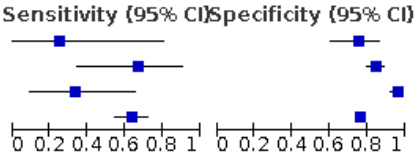
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Andersson 2005	3	17	1	31	0.75 [0.19, 0.99]	0.65 [0.49, 0.78]		
Kulasingam 2002	9	85	3	173	0.75 [0.43, 0.95]	0.67 [0.61, 0.73]		
Monsonego 2008	8	20	4	179	0.67 [0.35, 0.90]	0.90 [0.85, 0.94]		
Sherman 2002	111	1189	18	880	0.86 [0.79, 0.92]	0.43 [0.40, 0.45]		



Test 9. Triage of ASCUS with repeat cytology (cut-off LSIL+), CIN3+

Triage of ASCUS with repeat cytology (cut-off LSIL+), CIN3+

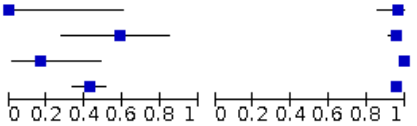
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Andersson 2005	1	12	3	36	0.25 [0.01, 0.81]	0.75 [0.60, 0.86]		
Kulasingam 2002	8	40	4	218	0.67 [0.35, 0.90]	0.84 [0.79, 0.89]		
Monsonego 2008	4	8	8	191	0.33 [0.10, 0.65]	0.96 [0.92, 0.98]		
Sherman 2002	82	494	47	1575	0.64 [0.55, 0.72]	0.76 [0.74, 0.78]		



Test 10. Triage of ASCUS with repeat cytology (cut-off HSIL+), CIN3+

Triage of ASCUS with repeat cytology (cut-off HSIL+), CIN3+

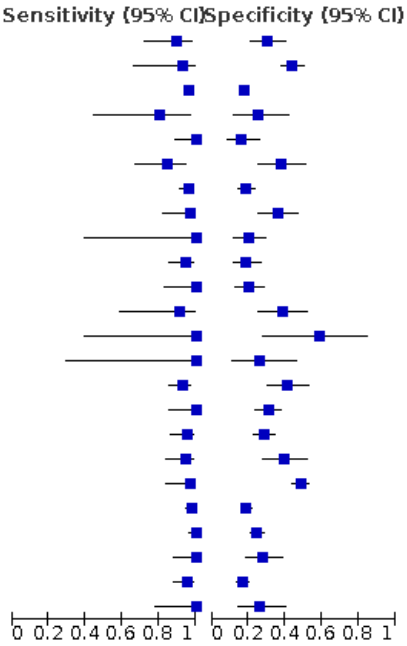
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Andersson 2005	0	2	4	46	0.00 [0.00, 0.60]	0.96 [0.86, 0.99]		
Kulasingam 2002	7	13	5	245	0.58 [0.28, 0.85]	0.95 [0.92, 0.97]		
Monsonego 2008	2	1	10	198	0.17 [0.02, 0.48]	0.99 [0.97, 1.00]		
Sherman 2002	55	96	74	1973	0.43 [0.34, 0.52]	0.95 [0.94, 0.96]		



Test 11. Triage LSIL with HC2, CIN2+ (all studies)

Triage LSIL with HC2, CIN2+ (all studies)

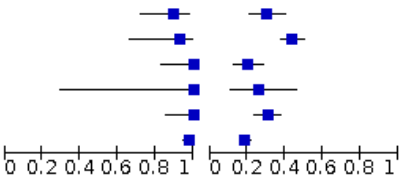
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Andersson 2005	25	68	3	29	0.89 [0.72, 0.98]	0.30 [0.21, 0.40]		
Bergeron 2000	13	142	1	111	0.93 [0.66, 1.00]	0.44 [0.38, 0.50]		
Castle 2010a	730	3303	29	705	0.96 [0.95, 0.97]	0.18 [0.16, 0.19]		
Cattani 2009	8	27	2	9	0.80 [0.44, 0.97]	0.25 [0.12, 0.42]		
Chen 2005b	31	63	0	12	1.00 [0.89, 1.00]	0.16 [0.09, 0.26]		
De Francesco 2008	27	38	5	23	0.84 [0.67, 0.95]	0.38 [0.26, 0.51]		
Denton 2010	135	231	6	53	0.96 [0.91, 0.98]	0.19 [0.14, 0.24]		
Guyot 2003	28	52	1	29	0.97 [0.82, 1.00]	0.36 [0.25, 0.47]		
Holladay 2006	4	76	0	19	1.00 [0.40, 1.00]	0.20 [0.12, 0.29]		
Huang 2009	54	92	3	21	0.95 [0.85, 0.99]	0.19 [0.12, 0.27]		
Kulasingam 2002	20	84	0	21	1.00 [0.83, 1.00]	0.20 [0.13, 0.29]		
Lee 2001	10	34	1	21	0.91 [0.59, 1.00]	0.38 [0.25, 0.52]		
Lee 2009	4	5	0	7	1.00 [0.40, 1.00]	0.58 [0.28, 0.85]		
Lytwyn 2000	3	20	0	7	1.00 [0.29, 1.00]	0.26 [0.11, 0.46]		
Monsonego 2006	79	47	6	33	0.93 [0.85, 0.97]	0.41 [0.30, 0.53]		
Monsonego 2008	23	120	0	53	1.00 [0.85, 1.00]	0.31 [0.24, 0.38]		
Pretorius 2002	56	160	3	64	0.95 [0.86, 0.99]	0.29 [0.23, 0.35]		
Rebello 2001	48	40	3	26	0.94 [0.84, 0.99]	0.39 [0.28, 0.52]		
Ronco 2007	31	234	1	219	0.97 [0.84, 1.00]	0.48 [0.44, 0.53]		
Sherman 2002	178	541	4	125	0.98 [0.94, 0.99]	0.19 [0.16, 0.22]		
Szarewski 2008	103	380	0	125	1.00 [0.96, 1.00]	0.25 [0.21, 0.29]		
Voss 2010	29	62	0	24	1.00 [0.88, 1.00]	0.28 [0.19, 0.39]		
You 2007	77	478	4	97	0.95 [0.88, 0.99]	0.17 [0.14, 0.20]		
Zielinski 2001	15	37	0	13	1.00 [0.78, 1.00]	0.26 [0.15, 0.40]		



Test 12. Triage of LSIL with HC2, CIN2+ (studies with both tests)

Triage of LSIL with HC2, CIN2+ (studies with both tests)

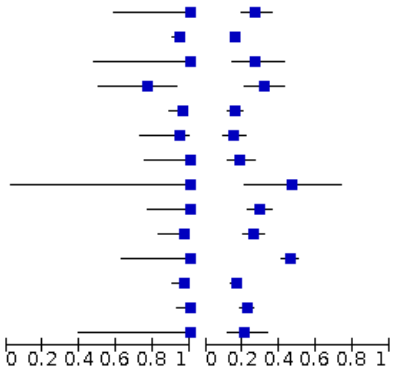
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Andersson 2005	25	68	3	29	0.89 [0.72, 0.98]	0.30 [0.21, 0.40]		
Bergeron 2000	13	142	1	111	0.93 [0.66, 1.00]	0.44 [0.38, 0.50]		
Kulasingam 2002	20	84	0	21	1.00 [0.83, 1.00]	0.20 [0.13, 0.29]		
Lytwyn 2000	3	20	0	7	1.00 [0.29, 1.00]	0.26 [0.11, 0.46]		
Monsonego 2008	23	120	0	53	1.00 [0.85, 1.00]	0.31 [0.24, 0.38]		
Sherman 2002	178	541	4	125	0.98 [0.94, 0.99]	0.19 [0.16, 0.22]		



Test 13. Triage of LSIL with HC2, CIN3+ (all studies)

Triage of LSIL with HC2, CIN3+ (all studies)

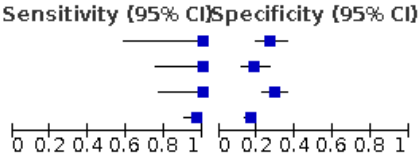
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Andersson 2005	7	86	0	32	1.00 [0.59, 1.00]	0.27 [0.19, 0.36]		
Castle 2010a	222	3811	13	721	0.94 [0.91, 0.97]	0.16 [0.15, 0.17]		
Cattani 2009	5	30	0	11	1.00 [0.48, 1.00]	0.27 [0.14, 0.43]		
De Francesco 2008	13	52	4	24	0.76 [0.50, 0.93]	0.32 [0.21, 0.43]		
Denton 2010	71	295	3	56	0.96 [0.89, 0.99]	0.16 [0.12, 0.20]		
Huang 2009	17	129	1	23	0.94 [0.73, 1.00]	0.15 [0.10, 0.22]		
Kulasingam 2002	13	91	0	21	1.00 [0.75, 1.00]	0.19 [0.12, 0.27]		
Lee 2009	1	8	0	7	1.00 [0.03, 1.00]	0.47 [0.21, 0.73]		
Monsonego 2008	14	129	0	53	1.00 [0.77, 1.00]	0.29 [0.23, 0.36]		
Pretorius 2002	29	187	1	66	0.97 [0.83, 1.00]	0.26 [0.21, 0.32]		
Ronco 2007	8	257	0	220	1.00 [0.63, 1.00]	0.46 [0.42, 0.51]		
Sherman 2002	88	632	3	126	0.97 [0.91, 0.99]	0.17 [0.14, 0.19]		
Szarewski 2008	53	430	0	125	1.00 [0.93, 1.00]	0.23 [0.19, 0.26]		
Zielinski 2001	4	48	0	13	1.00 [0.40, 1.00]	0.21 [0.12, 0.34]		



Test 14. Triage of LSIL with HC2, CIN3+ (studies with both tests)

Triage of LSIL with HC2, CIN3+ (studies with both tests)

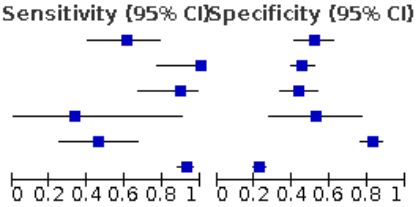
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Andersson 2005	7	86	0	32	1.00 [0.59, 1.00]	0.27 [0.19, 0.36]		
Kulasingam 2002	13	91	0	21	1.00 [0.75, 1.00]	0.19 [0.12, 0.27]		
Monsonego 2008	14	129	0	53	1.00 [0.77, 1.00]	0.29 [0.23, 0.36]		
Sherman 2002	88	632	3	126	0.97 [0.91, 0.99]	0.17 [0.14, 0.19]		



Test 15. Triage of LISL with repeat cytology (cut-off ASCUS+), CIN2+

Triage of LISL with repeat cytology (cut-off ASCUS+), CIN2+

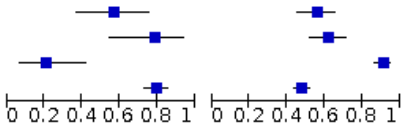
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Andersson 2005	17	47	11	50	0.61 [0.41, 0.78]	0.52 [0.41, 0.62]		
Bergeron 2000	14	138	0	115	1.00 [0.77, 1.00]	0.45 [0.39, 0.52]		
Kulasingam 2002	17	59	2	46	0.89 [0.67, 0.99]	0.44 [0.34, 0.54]		
Lytwyn 2000	1	8	2	9	0.33 [0.01, 0.91]	0.53 [0.28, 0.77]		
Monsonego 2008	11	31	13	148	0.46 [0.26, 0.67]	0.83 [0.76, 0.88]		
Sherman 2002	169	513	13	153	0.93 [0.88, 0.96]	0.23 [0.20, 0.26]		



Test 16. Triage of LSIL with repeat cytology (cut-off LSIL+), CIN2+

Triage of LSIL with repeat cytology (cut-off LSIL+), CIN2+

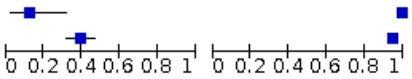
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Andersson 2005	16	43	12	54	0.57 [0.37, 0.76]	0.56 [0.45, 0.66]		
Kulasingam 2002	15	40	4	65	0.79 [0.54, 0.94]	0.62 [0.52, 0.71]		
Monsonego 2008	5	16	19	163	0.21 [0.07, 0.42]	0.91 [0.86, 0.95]		
Sherman 2002	145	347	37	319	0.80 [0.73, 0.85]	0.48 [0.44, 0.52]		



Test 17. Triage of LSIL with repeat cytology (cut-off HSIL+), CIN2+

Triage of LSIL with repeat cytology (cut-off HSIL+), CIN2+

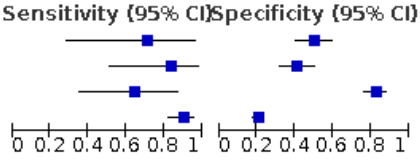
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Andersson 2005	8	4	20	93	0.29 [0.13, 0.49]	0.96 [0.90, 0.99]		
Kulasingam 2002	8	7	11	98	0.42 [0.20, 0.67]	0.93 [0.87, 0.97]		
Monsonego 2008	3	1	21	178	0.13 [0.03, 0.32]	0.99 [0.97, 1.00]		
Sherman 2002	72	37	110	629	0.40 [0.32, 0.47]	0.94 [0.92, 0.96]		



Test 18. Triage of LSIL with repeat cytology (cut-off ASCUS+), CIN3+

Triage of LSIL with repeat cytology (cut-off ASCUS+), CIN3+

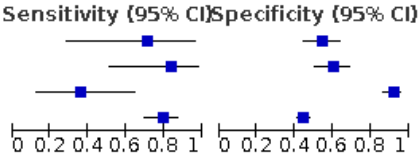
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Andersson 2005	5	59	2	59	0.71 [0.29, 0.96]	0.50 [0.41, 0.59]		
Kulasingam 2002	10	66	2	46	0.83 [0.52, 0.98]	0.41 [0.32, 0.51]		
Monsonego 2008	9	33	5	156	0.64 [0.35, 0.87]	0.83 [0.76, 0.88]		
Sherman 2002	82	600	9	157	0.90 [0.82, 0.95]	0.21 [0.18, 0.24]		



Test 19. Triage of LSIL with repeat cytology (cut-off LSIL+), CIN3+

Triage of LSIL with repeat cytology (cut-off LSIL+), CIN3+

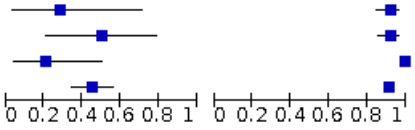
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Andersson 2005	5	54	2	64	0.71 [0.29, 0.96]	0.54 [0.45, 0.63]		
Kulasingam 2002	10	45	2	67	0.83 [0.52, 0.98]	0.60 [0.50, 0.69]		
Monsonego 2008	5	16	9	173	0.36 [0.13, 0.65]	0.92 [0.87, 0.95]		
Sherman 2002	72	420	19	337	0.79 [0.69, 0.87]	0.45 [0.41, 0.48]		



Test 20. Triage of LSIL with repeat cytology (cut-off HSIL+), CIN3+

Triage of LSIL with repeat cytology (cut-off HSIL+), CIN3+

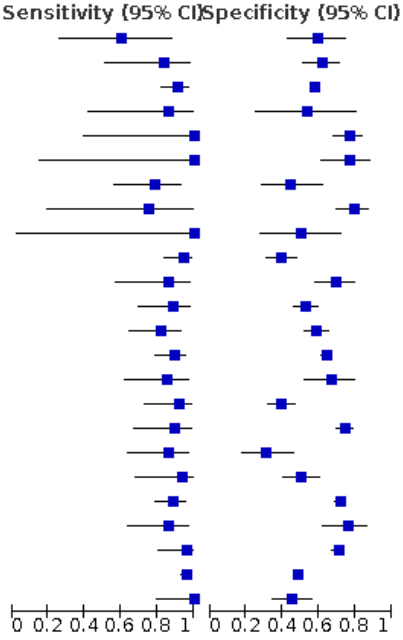
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Andersson 2005	2	10	5	108	0.29 [0.04, 0.71]	0.92 [0.85, 0.96]		
Kulasingam 2002	6	9	6	103	0.50 [0.21, 0.79]	0.92 [0.85, 0.96]		
Monsonego 2008	3	1	11	188	0.21 [0.05, 0.51]	0.99 [0.97, 1.00]		
Sherman 2002	41	68	50	689	0.45 [0.35, 0.56]	0.91 [0.89, 0.93]		



Test 25. Triage of ASCUS with HC2, CIN2+ (according to collection device)

Triage of ASCUS with HC2, CIN2+ (according to collection device)

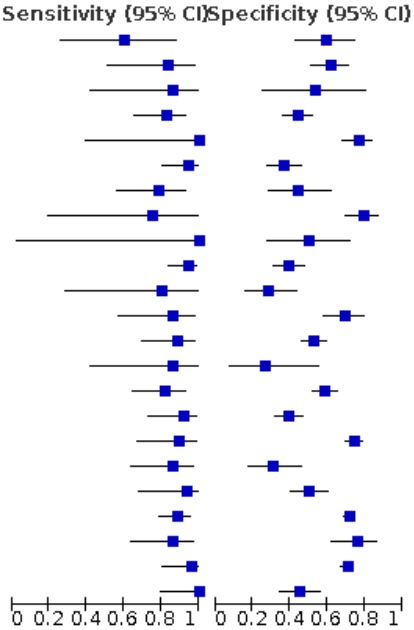
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Andersson 2005	6	17	4	25	0.60 [0.26, 0.88]	0.60 [0.43, 0.74]
Bergeron 2000	10	38	2	61	0.83 [0.52, 0.98]	0.62 [0.51, 0.71]
Bergeron 2006	63	772	6	1039	0.91 [0.82, 0.97]	0.57 [0.55, 0.60]
Cattani 2009	6	6	1	7	0.86 [0.42, 1.00]	0.54 [0.25, 0.81]
Cuzick 2003	4	28	0	91	1.00 [0.40, 1.00]	0.76 [0.68, 0.84]
Davis-Devine 2005	2	10	0	33	1.00 [0.16, 1.00]	0.77 [0.61, 0.88]
De Francesco 2008	18	21	5	17	0.78 [0.56, 0.93]	0.45 [0.29, 0.62]
Giovannelli 2005	3	18	1	70	0.75 [0.19, 0.99]	0.80 [0.70, 0.87]
Guyot 2003	1	11	0	11	1.00 [0.03, 1.00]	0.50 [0.28, 0.72]
Huang 2009	49	86	3	55	0.94 [0.84, 0.99]	0.39 [0.31, 0.48]
Kiatpongsan 2006	12	23	2	53	0.86 [0.57, 0.98]	0.70 [0.58, 0.80]
Kulasingam 2002	23	115	3	129	0.88 [0.70, 0.98]	0.53 [0.46, 0.59]
Lonky 2003	27	101	6	144	0.82 [0.65, 0.93]	0.59 [0.52, 0.65]
Manos 1999	58	326	7	582	0.89 [0.79, 0.96]	0.64 [0.61, 0.67]
Monsonego 2006	17	17	3	34	0.85 [0.62, 0.97]	0.67 [0.52, 0.79]
Monsonego 2008	22	110	2	72	0.92 [0.73, 0.99]	0.40 [0.32, 0.47]
Morin 2001	17	88	2	253	0.89 [0.67, 0.99]	0.74 [0.69, 0.79]
Nieh 2005	18	31	3	14	0.86 [0.64, 0.97]	0.31 [0.18, 0.47]
Ordi 2003	14	52	1	53	0.93 [0.68, 1.00]	0.50 [0.41, 0.60]
Pretorius 2002	56	250	7	636	0.89 [0.78, 0.95]	0.72 [0.69, 0.75]
Rebello 2001	18	13	3	41	0.86 [0.64, 0.97]	0.76 [0.62, 0.87]
Ronco 2007	25	213	1	518	0.96 [0.80, 1.00]	0.71 [0.67, 0.74]
Solomon 2001	256	1050	11	984	0.96 [0.93, 0.98]	0.48 [0.46, 0.51]
Szarewski 2008	16	47	0	39	1.00 [0.79, 1.00]	0.45 [0.35, 0.56]



Test 26. Triage of ASCUS with HC2, CIN2+ (according to transport medium)

Triage of ASCUS with HC2, CIN2+ (according to transport medium)

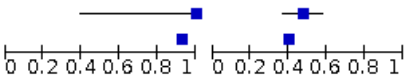
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Andersson 2005	6	17	4	25	0.60 [0.26, 0.88]	0.60 [0.43, 0.74]
Bergeron 2000	10	38	2	61	0.83 [0.52, 0.98]	0.62 [0.51, 0.71]
Cattani 2009	6	6	1	7	0.86 [0.42, 1.00]	0.54 [0.25, 0.81]
Cuschieri 2007	28	87	6	69	0.82 [0.65, 0.93]	0.44 [0.36, 0.52]
Cuzick 2003	4	28	0	91	1.00 [0.40, 1.00]	0.76 [0.68, 0.84]
Dalla Palma 2005	32	77	2	45	0.94 [0.80, 0.99]	0.37 [0.28, 0.46]
De Francesco 2008	18	21	5	17	0.78 [0.56, 0.93]	0.45 [0.29, 0.62]
Giovannelli 2005	3	18	1	70	0.75 [0.19, 0.99]	0.80 [0.70, 0.87]
Guyot 2003	1	11	0	11	1.00 [0.03, 1.00]	0.50 [0.28, 0.72]
Huang 2009	49	86	3	55	0.94 [0.84, 0.99]	0.39 [0.31, 0.48]
Kelly 2006	4	33	1	13	0.80 [0.28, 0.99]	0.28 [0.16, 0.43]
Kiatpongsan 2006	12	23	2	53	0.86 [0.57, 0.98]	0.70 [0.58, 0.80]
Kulasingam 2002	23	115	3	129	0.88 [0.70, 0.98]	0.53 [0.46, 0.59]
Lee 2009	6	11	1	4	0.86 [0.42, 1.00]	0.27 [0.08, 0.55]
Lonky 2003	27	101	6	144	0.82 [0.65, 0.93]	0.59 [0.52, 0.65]
Monsonego 2008	22	110	2	72	0.92 [0.73, 0.99]	0.40 [0.32, 0.47]
Morin 2001	17	88	2	253	0.89 [0.67, 0.99]	0.74 [0.69, 0.79]
Nieh 2005	18	31	3	14	0.86 [0.64, 0.97]	0.31 [0.18, 0.47]
Ordi 2003	14	52	1	53	0.93 [0.68, 1.00]	0.50 [0.41, 0.60]
Pretorius 2002	56	250	7	636	0.89 [0.78, 0.95]	0.72 [0.69, 0.75]
Rebello 2001	18	13	3	41	0.86 [0.64, 0.97]	0.76 [0.62, 0.87]
Ronco 2007	25	213	1	518	0.96 [0.80, 1.00]	0.71 [0.67, 0.74]
Szarewski 2008	16	47	0	39	1.00 [0.79, 1.00]	0.45 [0.35, 0.56]



Test 27. Triage of ASCUS with HC2, CIN2+ (<30y)

Triage of ASCUS with HC2, CIN2+ (<30y)

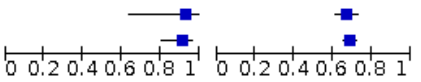
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Ronco 2007	4	53	0	48	1.00 [0.40, 1.00]	0.48 [0.37, 0.58]		
Sherman 2002	393	1030	30	701	0.93 [0.90, 0.95]	0.40 [0.38, 0.43]		



Test 28. Triage of ASCUS with HC2, CIN2+ (30-39y)

Triage of ASCUS with HC2, CIN2+ (30-39y)

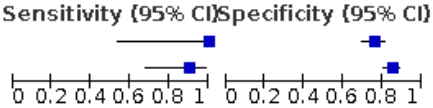
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Ronco 2007	12	88	1	180	0.92 [0.64, 1.00]	0.67 [0.61, 0.73]		
Sherman 2002	58	196	6	433	0.91 [0.81, 0.96]	0.69 [0.65, 0.72]		



Test 29. Triage of ASCUS with HC2, CIN2+ (40-49y)

Triage of ASCUS with HC2, CIN2+ (40-49y)

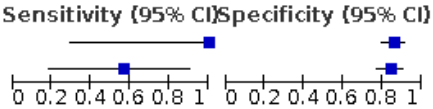
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Ronco 2007	6	53	0	169	1.00 [0.54, 1.00]	0.76 [0.70, 0.82]		
Sherman 2002	18	48	2	273	0.90 [0.68, 0.99]	0.85 [0.81, 0.89]		



Test 30. Triage of ASCUS with HC2, CIN2+ (50y or older)

Triage of ASCUS with HC2, CIN2+ (50y or older)

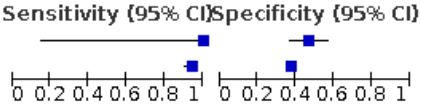
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Ronco 2007	3	19	0	121	1.00 [0.29, 1.00]	0.86 [0.80, 0.92]		
Sherman 2002	4	20	3	111	0.57 [0.18, 0.90]	0.85 [0.77, 0.90]		



Test 31. Triage of ASCUS with HC2, CIN3+ (<30y)

Triage of ASCUS with HC2, CIN3+ (<30y)

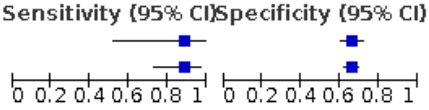
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Ronco 2007	2	55	0	48	1.00 [0.16, 1.00]	0.47 [0.37, 0.57]		
Sherman 2002	226	1197	14	717	0.94 [0.90, 0.97]	0.37 [0.35, 0.40]		



Test 32. Triage of ASCUS with HC2, CIN3+ (30-39y)

Triage of ASCUS with HC2, CIN3+ (30-39y)

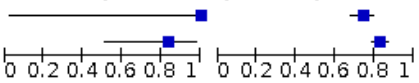
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Ronco 2007	8	92	1	180	0.89 [0.52, 1.00]	0.66 [0.60, 0.72]		
Sherman 2002	31	223	4	435	0.89 [0.73, 0.97]	0.66 [0.62, 0.70]		



Test 33. Triage of ASCUS with HC2, CIN3+ (40-49y)

Triage of ASCUS with HC2, CIN3+ (40-49y)

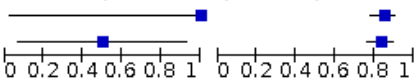
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Ronco 2007	1	58	0	169	1.00 [0.03, 1.00]	0.74 [0.68, 0.80]		
Sherman 2002	10	56	2	273	0.83 [0.52, 0.98]	0.83 [0.78, 0.87]		



Test 34. Triage of ASCUS with HC2, CIN3+ (50y or older)

Triage of ASCUS with HC2, CIN3+ (50y or older)

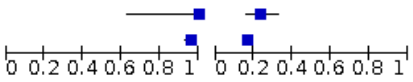
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Ronco 2007	1	21	0	121	1.00 [0.03, 1.00]	0.85 [0.78, 0.91]		
Sherman 2002	2	22	2	112	0.50 [0.07, 0.93]	0.84 [0.76, 0.89]		



Test 35. Triage of LSIL with HC2, CIN2+ (<30y)

Triage of LSIL with HC2, CIN2+ (<30y)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Ronco 2007	8	87	0	27	1.00 [0.63, 1.00]	0.24 [0.16, 0.33]		
Sherman 2002	313	758	13	157	0.96 [0.93, 0.98]	0.17 [0.15, 0.20]		



Test 36. Triage of LSIL with HC2, CIN2+ (30-39y)

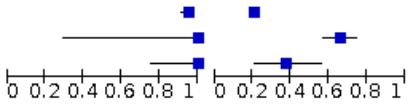
Triage of LSIL with HC2, CIN2+ (30-39y)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Castle 2010a	463	1795	16	254	0.97 [0.95, 0.98]	0.12 [0.11, 0.14]		
Ronco 2007	17	91	0	84	1.00 [0.80, 1.00]	0.48 [0.40, 0.56]		
Sherman 2002	43	102	3	47	0.93 [0.82, 0.99]	0.32 [0.24, 0.40]		

Test 37. Triage of LSIL with HC2, CIN2+ (40-49y)

Triage of LSIL with HC2, CIN2+ (40-49y)

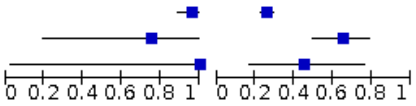
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Castle 2010a	195	1019	10	276	0.95 [0.91, 0.98]	0.21 [0.19, 0.24]		
Ronco 2007	3	40	0	78	1.00 [0.29, 1.00]	0.66 [0.57, 0.75]		
Sherman 2002	13	20	0	12	1.00 [0.75, 1.00]	0.38 [0.21, 0.56]		



Test 38. Triage of LSIL with HC2, CIN2+ (50y or older)

Triage of LSIL with HC2, CIN2+ (50y or older)

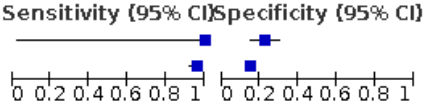
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Castle 2010a	72	489	3	175	0.96 [0.89, 0.99]	0.26 [0.23, 0.30]		
Ronco 2007	3	16	1	30	0.75 [0.19, 0.99]	0.65 [0.50, 0.79]		
Sherman 2002	1	6	0	5	1.00 [0.03, 1.00]	0.45 [0.17, 0.77]		



Test 39. Triage of LSIL with HC2, CIN3+ (<30y)

Triage of LSIL with HC2, CIN3+ (<30y)

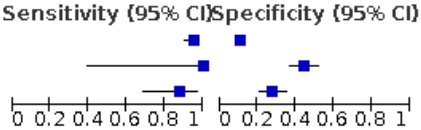
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Ronco 2007	1	94	0	27	1.00 [0.03, 1.00]	0.22 [0.15, 0.31]		
Sherman 2002	186	885	8	162	0.96 [0.92, 0.98]	0.15 [0.13, 0.18]		



Test 40. Triage of LSIL with HC2, CIN3+ (30-39y)

Triage of LSIL with HC2, CIN3+ (30-39y)

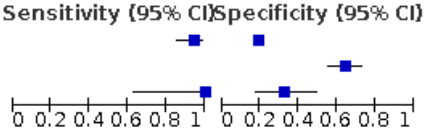
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Castle 2010a	147	2111	8	262	0.95 [0.90, 0.98]	0.11 [0.10, 0.12]		
Ronco 2007	4	104	0	84	1.00 [0.40, 1.00]	0.45 [0.37, 0.52]		
Sherman 2002	22	123	3	47	0.88 [0.69, 0.97]	0.28 [0.21, 0.35]		



Test 41. Triage of LSIL with HC2, CIN3+ (30-49y)

Triage of LSIL with HC2, CIN3+ (30-49y)

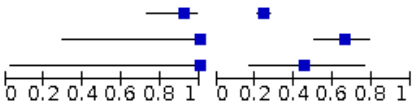
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Castle 2010a	53	1161	3	283	0.95 [0.85, 0.99]	0.20 [0.18, 0.22]		
Ronco 2007	0	43	0	78	Not estimable	0.64 [0.55, 0.73]		
Sherman 2002	8	25	0	12	1.00 [0.63, 1.00]	0.32 [0.18, 0.50]		



Test 42. Triage of LSIL with HC2, CIN3+ (50y or older)

Triage of LSIL with HC2, CIN3+ (50y or older)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Castle 2010a	22	539	2	176	0.92 [0.73, 0.99]	0.25 [0.21, 0.28]		
Ronco 2007	3	16	0	31	1.00 [0.29, 1.00]	0.66 [0.51, 0.79]		
Sherman 2002	1	6	0	5	1.00 [0.03, 1.00]	0.45 [0.17, 0.77]		



ADDITIONAL TABLES

Table 1. Key elements of the systematic review

Study questions	What is the accuracy of HPV DNA testing and repeat cytology to detect CIN2, or worse (CIN2+), disease in women with ASCUS or LSIL?
Patient population	Women with a cervical cytology result showing ASCUS or LSIL.
Prior testing	Prior screening, screening for first time, or not documented.
Setting	Cervical cancer screening using cytology and follow-up of women with minor cytological lesions.
Index test	Triage with HPV DNA testing using HC2 (test positivity defined as RLU > 1).
Comparator test	Triage with repeat cytology considered at 3 cut-offs (ASCUS+, LSIL+, HSIL+).
Target disease	Cervical cancer precursors: CIN2+ or CIN3+.
Reference standard	Colposcopy with colposcopy-targeted biopsies or biopsies from all cases, considering the histological result as the outcome, where available, but accepting negative colposcopy as sufficient ascertainment for absence of CIN2+ or CIN3+ when no biopsies were taken.
Importance	ASCUS and LSIL indicate an increased risk for having or developing cervical precancer. Nevertheless, frequently no underlying or incipient precursors CIN2+ can be identified. Therefore, accurate triage methods are needed that identify women with cervical precancer who are at increased risk for developing cancer, but that also avoid over-diagnosis and over-treatment.
Studies	*1) Triage of ASCUS* Outcome CIN2+: 39 studies (including 13,196 women) allowing evaluation of the accuracy of HC2; 10 of these studies (including 5261 women) permitted investigation of the accuracy of repeat cytology. Outcome CIN3+: 17 studies (6144 women) with accuracy of HC2; 4 of these studies (2726 women) allowed assessment of accuracy of both HC2 and repeat cytology. *2) Triage of LSIL* Outcome CIN2+: 24 studies (including 9983 women) allowed evaluation of the accuracy of HC2; 6 of these studies (including 1591 women) also allowed assessment of the accuracy of repeat cytology. Outcome CIN3+: 14 studies (8253 women) with accuracy of HC2; 4 of these studies (1295 women) permitted assessment of accuracy of both HC2 and repeat cytology.

Abbreviations
ASCUS = atypical squamous cells of undetermined significance
ASCUS+ = ASCUS or worse
CIN2 = cervical intraepithelial neoplasia of grade 2
CIN2+ = cervical intraepithelial neoplasia of grade 2 or worse
CIN3+ = cervical intraepithelial neoplasia of grade 3 or worse
HC2 = Hybrid Capture 2 assay
HPV = human papillomavirus
HSIL+ = high-grade squamous intraepithelial lesion or worse
LSIL = low-grade squamous intra-epithelial lesions
LSIL+ = LSIL or worse
RLU = relative light units

Table 2. QUADAS quality assessment table

Quality item	Definition	Comment
Representative spectrum	Was the spectrum of participants representative of the women who will receive the test in practice?	By restricting the study participants to the two triage groups, the spectrum necessarily coincides with the clinical indication of HPV testing: women with a cervical cytology result showing squamous atypia (ASCUS = triage group I) or mild dysplasia (LSIL = triage group II). However within the spectrum of clinical groups we can distinguish: • different cytological classification systems (Bethesda 1989 or Bethesda 2001; BSCC); • glandular atypia included with squamous atypia or only squamous atypia; • first or subsequent observation of equivocal or low-grade cytology; • continuous series of included participants versus inclusion of arbitrarily selected subjects.
Acceptable reference test	Is the reference standard likely to classify the target condition correctly?	The following possible reference standards were distinguished: • colposcopy followed by colposcopy-targeted biopsies where a cervical intraepithelial neoplasia is suspected colposcopically; result of the histological interpretation is considered as the outcome and negative colposcopy was accepted as evidence for absence of high-grade CIN; • biopsies taken from all cases. The type of biopsy (punch biopsy or excision biopsy) was recorded.
Acceptable delay between tests	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	The delay between the index triage with HC2 (and repeat cytology if done) and colposcopy and biopsy will be assessed. The delay should be no more than 6 months. Also the delay between the finding of a case with ASCUS or LSIL and the triage test was noted.
Partial verification avoided	Did the whole sample, or a random selection of the sample, receive verification using a reference standard of diagnosis?	By imposing complete verification for all participants, verification bias should be avoided. In randomised trials, verification is restricted to all women with positive results in the triage test, but this will not involve bias of relative sensitivity or relative PPV.
Differential verification avoided	Did participants receive the same reference standard regardless of the index test result?	For studies where the index triage test (HC2 assay) and the comparator triage test (repeat cytology) were used, all subjects should be submitted to the same type of verification with reference standard used to verify presence or absence of CIN2+ or CIN3+.
Incorporation avoided	Was the reference standard independent of the index test? (i.e. the index test did not form part of the reference standard.)	By imposing complete verification by colposcopy and histological interpretation for all participants, we avoided incorporation of the triage test in the outcome assessment.
Reference standard results blinded	Were the reference standard results interpreted without knowledge of the results of the index or comparator tests?	It was noted whether or not colposcopists and histologists were aware of the HC2 or repeat cytology result.
Index test results blinded	Were the index test or comparator test results interpreted without knowledge of the	Since the HC2-result is generated by the assay, based on light emission measured by a luminometer (expressed as a relative light unit, a quantified computer-generated measure), objective assessment of the index

Table 2. QUADAS quality assessment table *(Continued)*

	results of the reference standard or the other test?	triage test is assured. Independence of repeat cytology interpretation towards the HC2 result was noted.
Relevant clinical information	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	The most essential clinical information is the triage group (ASCUS or LSIL), which, in principle, always is available in clinical practice.
Uninterpretable results reported	Were non-interpretable or intermediate test results reported?	Given the definition of the quantitatively defined cut-off for a positive HC2 test, no problems are expected regarding interpretation. Occurrence of unsatisfactory HC2 (insufficient material, for instance) was notified. For repeat cytology, presence of inadequate preparations will be recorded.
Withdrawals explained	Were withdrawals from the study explained?	Loss of participants for whom no outcome could be obtained was recorded.

Abbreviations
ASCUS = atypical squamous cells of undetermined significance
BSCC = British Society of Clinical Cytology
CIN = cervical intraepithelial neoplasia
CIN2+ = cervical intraepithelial neoplasia of grade 2 or worse
CIN3+ = cervical intraepithelial neoplasia of grade 3 or worse
HC2 = Hybrid Capture 2 assay
HPV = human papillomavirus
HPV+ = human papillomavirus positive
LSIL = low-grade squamous intra-epithelial lesions
PPV = positive predictive value

Table 3. Triage of ASCUS: relative sensitivity and specificity of HC2 versus repeat cytology

Cut-off repeat cytology	Studies	Relative sensitivity (95% CI)	Relative specificity (95% CI)	P value	
				Effect on sensitivity**	Effect on specificity**
Outcome CIN2+					
ASCUS+	10	1.27 (1.16 to 1.39)	0.99 (0.97 to 1.03)	< 0.001	1.000
LSIL+	6	2.19 (1.71 to 2.81)	0.69 (0.64 to 0.75)	< 0.001	< 0.001
HSIL+	5	8.06 (4.46 to 14.58)	0.62 (0.55 to 0.69)	< 0.001	< 0.001
Oucome CIN3+					
ASCUS+	4*	1.14 (1.06 to 1.22)	0.99 (0.89 to 1.09)	0.01	0.6
LSIL+	4*	1.74 (0.86 to 3.54)	0.62 (0.55 to 0.72)	0.08	0.004
HSIL+	4*	2.82 (0.79 to 10)	0.50 (0.46, 0.55)	0.07	< 0.001

* Univariate analyses using the bivariate model run separately for sensitivity and specificity with test as covariate.
** Likelihood ratio test for the bivariate model with versus without the covariate 'test'.
Abbreviations
ASCUS = atypical squamous cells of undetermined significance

ASCUS+ = ASCUS or worse
CIN2+ = cervical intraepithelial neoplasia of grade 2 or worse
CIN3+ = cervical intraepithelial neoplasia of grade 3 or worse
HC2 = Hybrid Capture 2 assay
HSIL+ = positive for high-grade squamous intraepithelial lesion or worse
LSIL+ = low-grade squamous intra-epithelial lesions or worse

Table 4. Triage of LSIL: relative sensitivity and specificity of HC2 versus repeat cytology

Cut-off repeat cytology	Studies	Relative sensitivity (95% CI)	Relative specificity (95% CI)	P value	
				Effect on sensitivity**	Effect on specificity**
Outcome CIN2+					
ASCUS+	6	1.23 (1.06 to 1.43)	0.66 (0.58 to 0.75)	< 0.001	< 0.001
LSIL+	4*	1.55 (1.02 to 2.36)	0.42 (0.32 to 0.55)	0.04	0.001
HSIL+	4*	3.06 (1.88 to 4.99)	0.42 (0.32 to 0.55)	0.003	< 0.001
Outcome CIN3+					
ASCUS+	4*	1.15 (0.89 to 1.38)	0.56 (0.37 to 0.84)	0.14	0.02
LSIL+	4*	1.36 (0.88 to 2.11)	0.38 (0.22 to 0.63)	0.09	0.01
HSIL+	4*	2.33 (1.47 to 3.68)	0.24 (0.13 to 0.42)	0.02	0.009

* Univariate analyses using the bivariate model run separately for sensitivity and specificity with test as covariate.
** Likelihood ratio test for the bivariate model with versus without the covariate 'test'.
Abbreviations
ASCUS+ = atypical squamous cells of undetermined significance or worse
CIN2+ = cervical intraepithelial neoplasia of grade 2 or worse
CIN3+ = cervical intraepithelial neoplasia of grade 3 or worse
HC2 = Hybrid Capture 2 assay
HSIL+ = positive for high-grade squamous intraepithelial lesion or worse
LSIL+ = low-grade squamous intra-epithelial lesions or worse

Table 5. Publication bias and sample size effects

Triage group	Triage test	Outcome	No studies	Regression test asymmetry		
				Intercept	CI	P value
ASCUS	**HC2**	**CIN2+**	39	-5.69	(-10.23, -1.15)	0.015
		CIN3+	17	-4.98	(-12.29, 2.33)	0.167
	Repeat cytology	**CIN2+**	10	0.50	(-3.29, 4.29)	0.769
		CIN3+	4	6.20	(-8.07, 20.47)	0.202
LSIL	**HC2**	**CIN2+**	24	3.06	(-4.73, 10.84)	0.424

Table 5. Publication bias and sample size effects *(Continued)*

		CIN3+	14	5.21	(-3.26, 13.68)	0.205
	Repeat cytology	**CIN2+**	6	10.84	(-69.05, 90.72)	0.726
		CIN3+	4	10.59	(-138.10, 159.27)	0.310

Abbreviations
ASCUS = atypical squamous cells of undetermined significance
CIN2+ = cervical intraepithelial neoplasia of grade 2 or worse
CIN3+ = cervical intraepithelial neoplasia of grade 3 or worse
HC2 = Hybrid Capture 2 assay
LSIL = low-grade squamous intra-epithelial lesions

APPENDICES

Appendix 1. Classifications used for reporting cervical epithelial lesions

Cytological classification

In the current review two groups of participants are considered: triage group I (women with equivocal cervical lesions or ASCUS) and triage group II (women with low-grade cytological grade cytological lesions or LSIL).

In triage group I, participants are women with atypical squamous cells of undetermined significance (ASCUS), as defined in the 1988 version of The Bethesda System (TBS) (Lundberg 1989). In the 1991 version of TBS (Luff 1992), subclassification of the equivocal category of ASCUS was proposed: (a) atypical squamous cells favouring a benign reactive process squamous cells of undetermined significance (ASC-R); (b) undetermined significance and (c) neoplasia cannot be excluded. In TBS-2001, the first subcategory (ASC-R) was included with "negative for neoplasia or malignancy", whereas the second and third subcategories were identified as ASC-US (with hyphen; atypical squamous cells of undetermined significance) and ASC-H (atypical squamous cells where a high grade lesion cannot be excluded), respectively. For the current meta-analysis, if possible the number of ASCUS cases will be computed from the respective subcategories. In publications using TBS-2001, where this was not possible, only data on ASC-US cases will be extracted. Studies reporting data exclusively on ASC-R or ASC-H will be excluded from the main meta-analysis, but will be included in subgroup meta-analyses.

Glandular cytological lesions (AGUS (atypical glandular cells of undermined significance), and AGC (atypical glandular cells)) are rare findings that are not the focus of the current review. However, when triage data concern women with squamous or glandular atypia and the outcome of glandular lesions is not documented separately, the whole triage group will be considered as ASCUS. Studies reporting data exclusively on glandular atypia will be excluded from the main meta-analysis but will be included in subgroup meta-analyses.

In triage group II, participants will be women with low-grade squamous intraepithelial lesions (LSIL). The definition of low-grade squamous intraepithelial lesions remained unchanged in the successive versions of TBS.

The terminology of the British Society of Clinical Cytology (BSCC), used by NHSCSP (Evans 1986), will be translated into TBS-1988. The BSCC terms borderline cytology and mild dyskaryosis will be considered as similar to ASCUS and LSIL, respectively (Dudding 2002).

Table 3 contains all the categories of cervical neoplastic changes (from normal to cancer), used in different classification systems. It formed the basis for translation of different terminologies into TBS 1988, used in the current systematic review.

Histological classification

Throughout the current review, the CIN nomenclature is used to describe histologically-confirmed dysplasia of the cervical squamous epithelium (Richart 1973), whereas TBS is used to describe cytological cervical lesions (see Table 3 and Appendix 1). CIN1 (mild dysplasia) has a low potential of progression to cancer (Holowaty 1999; Ostor 1993). Moreover, cytological, virological and molecular profiles of CIN1 appear to be similar to that of epithelium without CIN (Wentzensen 2008). On the other hand, CIN2 (moderate dysplasia), and in particular CIN3 (severe dysplasia and carcinoma in situ), indicate a considerable risk of developing cancer (Holowaty 1999; Ostor 1993). Consensus exists to recommend treatment of CIN2 and CIN3 (Jordan 2008a), and, therefore, they are often included within the term high-grade CIN. However, it is clinically relevant to distinguish CIN2 from CIN3 (Herbert 2008). CIN2 is an intermediate condition, which contains over-called CIN1 and under-called CIN3 (Sherman 2002). CIN3 (encompassing severe dysplasia and carcinoma in situ) is a more progressive and reproducible histological diagnosis than CIN2 (Ismail 1989; Ostor 1993). Therefore, in the current review, the authors will assess the accuracy separately for both outcomes:

- CIN2 or worse disease (CIN2, CIN3, invasive squamous cervical cancer and adenocarcinoma of the cervix) (CIN2+));
- CIN3 or worse (CIN3, invasive squamous cervical cancer and adenocarcinoma of the cervix (CIN3+)).

WHO (WHO 2003)	CIN (Richart 1973)	BSCC 1986 (NHSCSP 1995)	TBS 1988 (Lundberg 1989)	TBS 2001 (Solomon 2002)
Normal	Absence of CIN	No dyskaryotic cells	Within normal limits	Negative for epithelial abnormality,
Atypia	Atypia	Borderline nuclear change	ASCUS	encompassing ASC-R
				ASC-US
				ASC-H
Atypical glandular cells	Cervical glandular intraepithelial neoplasia (CGIN)	Borderline nuclear change, glandular	AGUS	Atypical glandular cells
Koylocytosis	Condyloma	Borderline nuclear change with koylocytes	LSIL	LSIL
Mild dysplasia	CIN1	Mild dyskaryosis		
Moderate dysplasia	CIN2	Moderate dyskaryosis	HSIL	HSIL
Severe dysplasia	CIN3	Severe dyskaryosis		
Carcinoma in situ (CIS)				
Adenocarcinoma in situ (AIS)	CGIN	Glandular neoplasia	AGUS	AIS
Invasive carcinoma	Invasive carcinoma	Invasive carcinoma	Invasive carcinoma	Invasive carcinoma

Footnote

is adapted from Herbert 2007 and NHSCSP 1995. In the current review, we used the CIN classification to identify histological outcomes and the Bethesda system to describe cytological cervical abnormalities.

Appendix 2. Search strategies used in PubMed MEDLINE, CENTRAL, EMBASE AND CERVIX

- Search string in CENTRAL:(http://onlinelibrary.wiley.com/o/cochrane/) and PubMed MEDLINE (http://www.ncbi.nlm.nih.gov/sites/entrez):

((cervix OR cervical OR cervico*) AND (cancer OR carcinoma OR neoplas* OR dysplas* OR squamous OR CIN[tw] OR CINII*[tw] OR CIN2*[tw] OR CINIII*[tw] OR CIN3[tw] OR SIL[tw] OR HSIL[tw] OR H-SIL[tw] OR LSIL[tw] OR L-SIL OR ASCUS[tw] OR “ASC R”[tw] OR “ASC US”[tw] OR “ASC H”[tw])) AND (HPV OR “human papillomavirus” OR papillomaviridae OR papillomavirus infections[MeSH Terms] OR “hybrid capture” OR HC2 OR “HC 2” OR HCII OR “HC II” OR DNA OR viral OR virolog*) AND (triage OR management OR followup OR “follow up”)

- Search string in EMBASE (http://www.embase.com):

'cervix'/exp OR cervic* AND ('cancer'/exp OR cancer OR 'carcinoma'/exp OR carcinoma OR 'neoplasia'/exp OR neoplasia OR 'dysplasia'/exp OR dysplasia OR cin OR sil) OR ('cervix'/exp OR cervix AND ('neoplasm'/exp OR neoplasm)) AND ('hpv'/exp OR hpv OR 'wart virus'/exp OR 'wart virus' OR ('hpv'/exp OR hpv AND ('dna'/exp OR dna)) OR ('hpv'/exp OR hpv AND viral) OR 'human papillomavirus'/exp OR 'human

papillomavirus' OR 'hybrid'/exp OR hybrid AND capture OR 'hc2 assay' OR hc2 OR 'hc 2' OR hcii OR 'hc ii') AND ('triage'/exp OR triage OR 'management'/exp OR management OR 'follow up'/exp OR 'follow up')

The EMBASE string was saved using the name "ascuslsiltriage" by setting a weekly email alert.

- In the CERVIX database, the following keywords were used: ((cervix AND cancer) OR (cervical cancer)) AND (ASC-US OR ASCUS OR LSIL) AND HPV AND triage

Appendix 3. Characteristics of included studies (additional tables)

Additional characteristics of included studies

Author, Year	Study location	Study population	Exclusion criteria	Details of diagnosis of ASCUS/ LSIL cases	Positivity criterion HPV test	Reference standard
Manos, 1999	12 gynaecology clinics belonging to the Kaiser Permanente Medical Care Programme (N-California, USA)	Screened women recalled for a smear showing ASCUS	Pregnancy, treatment cervical neoplasia < 6 months before, recalling impossible	Papette brush + cytobrush if stenosis	1 pg/mL HPV DNA	Colposcopy with biopsy and/or ECC on all cases. ECC on cases in which no lesion requiring biopsy was seen
Bergeron, 2000	41 private gynaecologists working with 1 laboratory in Paris (France)	Screened women with index smear showing ASCUS or LSIL	Biopsy containing only endocervical cylindrical cells	No information	1 pg/mL HPV DNA	Colposocpy and biopsies taken from the TZ
Lytwyn, 2000	Family practices & 1 university health clinic in Ontario (Canada)	Women having a screen test result of ASCUS or LSIL	Expected low compliance, absence of cervix, previous diagnosis HSIL/AGUS/ GIN/ cancer, previous surgery on cervix, current vaginal/vulvar neoplasia, immunosuppression, current indication for gynaecologic surgery	No information	1 pg/mL HPV DNA	Directed biopsies of abnormal looking areas, ECC if abnormality extending into the endocervical canal or if repeat cytology = HSIL with normal colposcopy. No biopsy if colposcopy normal & ECC not indicated
Shlay, 2000	Women's clinic in Denver (USA)	Indigent women referred for ASCUS or AGUS	Menstruation, pregnancy, refusal of consent	No information	1 pg/mL HPV DNA	Biopsy from colposcopically abnormal areas. ECC and endocervical brush from all subjects
Lee, 2001	University hospital Seoul (South-Korea)	Women screened for cervical carcinoma and precancerous cervical lesions	Women without subsequent HC2 testing	Cervico-vaginal cytology, Cervex brush	1 pg/mL HPV DNA	Colposcopy and colposcopy-directed biopsy

(Continued)

Morin, 2001	Service of gynaecology University of Quebec (Canada)	Women with diagnosis of ASCUS after 2 consecutive normal smears	Pregnancy, previous biopsy or treatment on the cervix	No information	1pg/mL HPV DNA	Colposcopy and directed biopsies or ECC on all lesions of the cervix
Rebello, 2001	Colposcopy clinic in Edinburgh (Scotland)	Women with persistent borderline of mildly dyskaryotic smears	No information	No information	1, 2 and 4 pg/mL HPV DNA	Large loop excision on all patients
Solomon, 2001	Gynaecology clinics at Birmingham, Oklahoma, Pittsburgh, Seattle (USA)	Women enrolled on average 2 months after an index smear showing ASCUS enrolled in ALTS study	Pregnancy, ablative surgery or excisional therapy on the cervix	No information	1 pg/mL HPV DNA	Biopsy from colposcopically suspected CIN, ECC if indicated (TZ or extent of lesion not completely visible). CIN2+ lesions treated with LEEP. Quality review of histology
Zielinski, 2001	General practitioners (GPs) and outpatient clinic in Walcheren (the Netherlands)	Women consulting at GPs or outpatient clinic	Known history of cervical pathology, glandular lesion, lost to follow-up	No information	1 pg/mL HPV DNA	Colposcopically-directed biopsies when a lesion was visible
Kulasingam, 2002	Planned Parenthood clinics in Washington (USA)	Consecutive enrolment of women presenting for annual examinations at 1 of 3 Planned Parenthood clinics	No history of hysterectomy, chronic immune suppression, treatment of CIN, women younger than 18 or older than 50 years	LBC	1 pg/mL HPV DNA	Colposcopy, biopsy from visible lesions, 12 o'clock biopsies if no visible lesions
Pretorius, 2002	Southern California Permanente clinics (USA)	Women selected out of a cohort of women who underwent colposcopy. All women had abnormal cytology (ASCUS or LSIL)	Colposcopy performed for reasons other than evaluation of abnormal Pap smear (e.g. follow-up treatment of CIN) No specimens for HPV testing	No information	1 pg/mL HPV DNA	Colposcopy, biopsy of all abnormalities, endocervical curettage if not pregnant
Sherman, 2002	Gynaecology clinics at Birmingham, Oklahoma, Pittsburgh, Seattle (USA)	2198 women with previous ASCUS 848 women with previous LSIL enrolled in ALTS study	Pregnancy, ablative surgery or excisional therapy on the cervix	No information	1 pg/mL and 10 pg/mL HPV DNA	See Solomon, 2001
Cuzick, 2003	161 family practices associated with 5 referral	Women with a screening result of borderline cytology/positive for	Previous CIN treatment, previous (< 3 years before enrol-	Conventional cytology (ex-	1 pg/mL HPV DNA	Colposcopy and target biopsies.

(Continued)

	centres (Birmingham, Edinburgh, London, Manchester, Mansfield (UK)	hrHPV, randomised to immediate colposcopy or surveillance by repeat HPV testing, cytology, colposcopy at 12 months	ment) abnormal cytology result	tended tip spatula)		Negative colposcopy without biopsy accepted as negative outcome
Guyot, 2003	Colposcopy clinic in West- Middlesex (UK)	Women referred to colposcopy clinic for minor cytological abnormalities in their cervical smear	Previous LLETZ, inadequate biopsy specimen, low cell count in LBC	No information	1 and 3 pg/mL HPV DNA	Colposcopy on all and punch biopsies if colposcopically-abnormal result
Lonky, 2003	No information (USA)	Women who underwent pelvic examination and conventional Pap smear	No information	Conventional Pap smear obtained with wooden spatula and endocervical brush	1 pg/mL HPV DNA	Colposcopy on all, biopsy if suspicious lesion, ECC if colposcopy was unsatisfactory
Ordi, 2003	No information (Spain)	Women referred to colposcopy because of ASCUS or SIL or AIS diagnosis in the previous 6 months	No information	Ayre spatula	1 pg/mL HPV DNA	Colposcopy on all, biopsy if suspicious lesion
Wensveen, 2003	Gynaecologic outpatients clinic in The Hague (the Netherlands)	Women with ASCUS/AGUS on cervical smears	Pregnant women, women with HIV	Cervical smear	1 pg/mL HPV DNA	Colposcopy and biopsy or ECC
Andersson, 2005	Gynaecologic departments of 3 university hospitals in Stockholm (Sweden)	Women with atypia or low-grade lesions detected at a population based screening	None reported	No information	1 pg/mL HPV DNA	Colposcopy, biopsy from visible lesions, 12 o'clock biopsies if no visible lesions
Chen, 2005	Colposcopy hospital in Mackay (Taiwan)	Women with mildly abnormal Pap results, either ASCUS or LSIL, who were referred to a Taiwanese colposcopy clinic	Subjects were excluded if they had a prior cytologic diagnosis of HSIL or had been treated for (CIN)	No information	1 pg/mL HPV DNA	Colposcopy-directed biopsies
Dalla Palma, 2005	Pathology institute in Trentino (Italy)	Women attending a population-based free organised screening, with equivocal cytological findings	No information	No information	1.0 pg/mL HPV DNA	Colposcopy and biopsy
Davis-Devine, 2005	Gynaecology department of the Carle Clinic, Illinois (USA)	Women with an abnormal SurePath result within the preceding year	CIN treatment. Women with no intact cervix	SurePath (Rovers cervexbrush)	1 pg/mL HPV DNA	Colposcopy and biopsy

(Continued)

Giovanelli, 2005	Pathology Service of Palermo (Italy)	Women presenting to the Pathology Service consecutively enrolled when ASC-US or AFR cytological abnormalities were found	No colposcopy	No information	1 pg/mL HPV DNA	Colposcopy and colposcopy-directed biopsy when necessary
Nieh, 2005	No information (Taiwan)	Women who had a routine Pap smear diagnosis of ASCUS	No information	Pap smear, cervical cytobrush	1 pg/mL HPV DNA	Histological diagnosis through follow-up biopsies
Bergeron, 2006	Laboratory in Paris (France)	Screened women with index smear showing ASCUS	Women with no histology follow-up data available	No information	1 pg/mL HPV DNA	Colposcopy and biopsy if colposcopically-suspicious
Holladay, 2006	Center for cytopathology research and molecular diagnostics (USA)	400 randomly selected ThinPrep specimens	Specimens not stored at room temperature or volume of the specimen < 12 mL	No information	1 pg/mL HPV DNA	Histological diagnosis if available
Kelly, 2006	Johns Hopkins Cytopathology laboratory, Baltimore (USA)	Residual cervical cytology samples	Specimens with no follow-up biopsy data available after 6 months of cytology specimen procurement. Samples stored for more than 1 year	No information	1 pg/mL HPV DNA	Colposcopy and biopsy
Kiatpongsan, 2006	King Chulalongkorn Memorial Hospital in Bangkok (Thailand)	Women with cytological smears showing ASCUS cytologic within the past 2 months	Pregnant women and known cases of high-grade precancerous cervical lesions (CIN2 or worse (CIN2+))	No information	1 pg/mL HPV DNA	Colposcopy-directed cervical biopsy
Monsonego, 2006	Colposcopy center Institute Alfred Fournier in Paris (France)	Women with abnormal Pap smear or previous/current HPV-related disease referred to colposcopy	All patients in whom Pap smear, colposcopy or biopsy could not be evaluated for technical reasons Immunosuppressed/pregnant women	No information	1 pg/mL HPV DNA	Colposcopy and biopsy (LEEP, punch biopsy) when indicated
Cushieri, 2007	15 GP practices in Edinburgh area (Scotland)	Women attending for routine cytology screening	Women with no follow-up pathology records available for a minimum of 3 years subsequent	LBC	1 pg/mL HPV DNA	Colposcopy and biopsy

(Continued)

			to the borderline cytology diagnosis			
Ronco, 2007	9 cervical cancer screening centers in Italy	Women with ASCUS, AGUS or LSIL diagnosis selected out of a large randomised controlled trial of 9 screening programmes	Women who were pregnant, underwent hysterectomy or had been treated for CIN within 5 years Women younger than 25 or older than 60 years	Conventional cytology and LBC	1, 2, 4, 10 and 20 pg/mL HPV DNA	Colposcopy, and biopsy when indicated
You, 2007	Department of Gynecology, the Third Hospital of Peking University and the Maternal and Child Health Hospital of Haidian District of Beijing (China)	Selected women with abnormal cytology who had received HPV-test and biopsy	No information	LBC	1 pg/mL HPV DNA	Colposcopy-directed biopsy
De Francesco, 2008	Main hospital of Brescia (Italy)	Women attending routine cervical screening, with abnormal Pap smear results	Pregnant women, women with no intact uterus, a treatment for SILs or a history of chronic illness	Cytobrush, STM	1 pg/mL HPV DNA	Colposcopy and colposcopy-directed punch biopsy
Monsonego, 2008	Colposcopy clinic in Paris (France)	Women with abnormal Pap smear referred to colposcopy	No information	No information	1 pg/mL HPV DNA	Colposcopy on all, biopsies if abnormal colposcopy (LEEP or punch biopsy)
Siddiqui, 2008	Cytopathology laboratory Emory University Hospital, Atlanta (USA)	Cervical cytology samples of consecutive women with ASCUS cytology, selected out of all the samples collected between 2006-2007	No information	Residual cervical/vaginal cytology specimens in SurePath preservative	Threshold at RLU 1 (RLU between 1-2.5 = equivocal, RLU > 2.5 = positive)	Histological diagnosis of cervical/vaginal biopsy

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Szarewski, 2008	Colposcopy clinics at the Hammersmith and St Mary's Hospitals in London (UK)	Women referred to colposcopy because of an abnormal Pap smear	Pregnant women, women treated for CIN, hysterectomy	No information	1 pg/mL HPV DNA	Colposcopy and histology
Cattani, 2009	Colposcopy hospital and gynaecological oncology unit, Rome & Campobasso (Italy)	Women who attended secondary screening	Pregnant women or women under treatment for invasive cervical cancer Women who didn't underwent colposcopy and HPV testing	Cytology, conventional Pap smear	1 pg/mL HPV DNA	Colposcopy, colposcopy-directed biopsy (punch biopsies), cone specimens by LLETZ or cytological surveillance
Huang, 2009	5 colposcopy clinics across Canada	Women with abnormal cytology of any grade referred for colposcopy, or had a history of abnormal cytology, who were being followed-up in colposcopy clinics per the routine standard of care	Women younger than 16 years or women who had a CIN-treatment	No information	1 pg/mL HPV DNA	Colposcopy and biopsy
Lee, 2009	Colposcopy clinic (South-Korea)	Consecutive women who visited a colposcopy clinic	No information	No information	1 pg/mL HPV DNA	Colposcopy, colposcopy-directed biopsy
Silverloo, 2009	No information (Sweden)	Consecutive women with ASCUS diagnosis on a primary organised cytological screening	No information	No information	1 pg/mL HPV DNA	Colposcopy, Pap-smear, cervical biopsy, ECC
Castle, 2010	Health maintenance organization (Kaiser Permanente, Northern California (USA)	Women with abnormal cytology, aged 30 years or older, who attended cervical cancer screening between 2003-2008	Women older than 65 years, women with HPV + results and negative cytology	Conventional Pap smear	1 pg/mL HPV DNA	Colposcopy and LEEP if colposcopically suspicious
Del Mistro, 2010	5 screening centres in Veneto region (Italy)	Women with ASCUS diagnosis on organised cytological screening	No information	Pap smear	1 pg/mL HPV DNA	Colposcopy with punch biopsy when indicated
Denton, 2010	5 anatomic pathology laboratories (Switzerland & Italy)	Retrospectively collected, consecutive specimens from women with ASCUS or LSIL cytology	Damaged samples, contamination of slides with blood/mucus/inflammatory cells, age sample > 36 months, women with no follow-up biopsy data available	LBC (ThinPrep)	1 pg/mL HPV DNA	Histological diagnosis on re-cut tissue block specimens

(Continued)

Voss, 2010	Mayo Clinic, Rochester (USA)	Previously collected, residual cervical cytology ThinPrep vials randomly selected for research testing from women who underwent same-day colpo-biopsy or had follow-up biopsy data available	No information	LBC	1 pg/mL HPV DNA	Colposcopy-directed biopsy

Footnotes

See Appendix 3 for explanation of acronyms and abbreviations

Technical details of the triage tests

Author, year	Blinding of testing	Potential verification bias	Interval index-enrolment tests	Collection device for repeat cytology	Device for collection of material for HPV testing	Transport medium for HPV test
Manos, 1999	Colposcopy/histology was blinded to triage test results	No	67 days	Papette brush	Papette brush	Thinprep
Bergeron, 2000	Pathologist was masked to the other test results	No	2 months	Ayre spatula + cytobrush	Cone brush	STM
Lytwyn, 2000	Histology blinded from HPV and repeat cytology	No	6 months for cytology	Extended tip spatula (sometimes + cytobrush)	-	-
Shlay, 2000	Histology blinded to clinic and HPV results	No	-	-	-	-
Lee, 2001	All histologic diagnoses blinded to HPV status	Unclear	-	Cervex brush	Dacron swab	STM
Morin, 2001	Not documented	No	-	-	Dacron brush	STM
Rebello, 2001	Not documented	No	-	-	Cone brush	STM
Solomon, 2001	Histology not blinded to cytology. Colposcopy repeated when histology < cytology. No statement on independence of histo/viro. In arm 2 almost all cases were HPV+	Yes	2 months	Papette brush	Papette	Thinprep
Zielinski, 2001	Not documented	No	-	-	-	-

(Continued)

Kulasingam, 2002	Gold standard not blinded to cytological or HPV testing	No	-	Ayre spatula + cytobrush	Dacron swab	STM
Pretorius, 2002	Not documented	No	-	-	Cone brush or Dacron swab (if pregnant)	STM
Sherman, 2002	See Solomon, 2001	Yes	2 months	Papette brush	Papette	Thinprep
Cuzick, 2003	Histology read locally, but reviewed centrally in a blinded fashion by one pathologist	Yes. Only women with negative cytology and HPV test were randomly selected for colposcopy	-	-	Cone brush	STM
Guyot, 2003	HPV testing, colposcopy and histology interpretation were blinded	No	< 3 months	Papette brush	Papette brush	PreservCyt
Lonky, 2003	Pathology blinded to HPV test and cytology results	No	3-4 weeks	-	Cone brush	STM
Ordi, 2003	Not documented	No	6 months	-	Cervical brush (Digene cervical sampler)	STM
Wensveen, 2003	Not documented	No	< 12 weeks	-	-	-
Andersson, 2005	Not documented	No	4-6 months	Cervical brush	Cervical brush	STM
Chen, 2005	Not documented	No	-	-	-	-
Dalla Palma, 2005	Probably not, as only cases with positive cytology and/or HC2 had colposcopy and biopsy	Yes. Only cases with positive cytology and/or HC2 had colposcopy and biopsy	-	-	-	PreservCyt
Davis-Devine, 2005	All cytologic and histologic materials were reviewed without knowledge of the study design	No	7 days	Broom device (Rovers cervex brush)	Broom device (Rovers cervex brush)	SurePath

(Continued)

Giovanelli, 2005	Not documented	No	Co-collection	-	Ecto-cervical wooden spatula and endo-cervical cytobrush	STM
Nieh, 2005	Not documented	No	-	-	Cytobrush	STM
Bergeron, 2006	Not documented	No	6-18 months	Cervical brush	Cervical brush	Cyto-screen liquid
Holladay, 2006	Histo-confirmation was blinded to p16 and HC2 results	Yes. Only a part of the cases had histologic outcome available. The accuracy data were computed on these histologically-verified cases	< 2 months? 8 months	-	-	ThinPrep
Kelly, 2006	Colposcopy and histology of biopsies blinded to HPV status and immunostaining results	No	-	-	-	PreservCyt
Kiatpongsan, 2006	HC2 test blinded to histopathology and *vice versa*.	No	2 months	-	Cytobrush	STM
Monsonego, 2006	Yes	Possible differential verification	3 months	-	Cone brush	-
Cushieri, 2007	Not documented	No	Unclear, 3-3.5 year follow-up	-	-	PreservCyt
Ronco, 2007	Yes	No	Co-testing	Ayre spatula	Ayre spatula	PreservCyt
You, 2007	Not documented	No	-	-	-	-
De Francesco, 2008	Not documented	No	-	Cytobrush	Cytobrush	STM
Monsonego, 2008	Yes	No	2-3 months	Broom-like collection device	HC2 collection device	Universal Collecting Medium

(Continued)

Siddiqui, 2008	Not mentioned	No	< 2 weeks	-	-	SurePath
Szarewski, 2008	Unclear	No	Median: 2.4 months	-	Cervex broom	PreservCyt
Cattani, 2009	Pathologists involved in cytological and histological assessments were not involved in testing for HPV. HPV tests were blinded to results of cytology and histology	No	-	-	Cervical brush	PreservCyt/ThinPrep
Huang, 2009	Colposcopy and histology were blinded to HPV status. HPV tests were carried out independent of each other	No	1-3 months	Cervexbrush	Cervexbrush	PreservCyt
Lee, 2009	Not documented	No		Cervex brush	-	PreservCyt
Silverloo, 2009	Yes	Yes. Cytology/HPV negative women did not undergo colposcopy/biopsy, but had a repeat Pap smear	< 3 months	-	-	-
Castle, 2010	Yes, results of tests were blinded	No	-	-	-	-
Del Mistro, 2010	Pap smears at enrolment were blinded to the results of HPV tests	No	3 months	-	-	-
Denton, 2010	Histology diagnoses were blinded to HPV and p16 status	No	6 months	-	-	-
Voss, 2010	Not documented	No	-	-	-	PreservCyt

Appendix 4. Summary of all the meta-analyses of the absolute accuracy in ASCUS triage

Studies where HC2 triage and repeat cytology were applied							
Triage test	**Test cut-off**	**Outcome**	**Studies**	**Accuracy parameter**	**Pooled estimate**	**(95% CI)**	**Range**
HC2	**RLU > 1 (1 pg/mL)**	**CIN2+**	10	Sensitivity	90.9%	(85.7% to 94.4%)	60%-96%
			10	Specificity	60.7%	(52.9% to 68.0%)	39%-79%
		CIN3+	4*	Sensitivity	94.8%	(89.6% to 97.5%)	75%-96%
			4*	Specificity	56.6%	(39.4% to 72.3%)	38%-58%
Repeat cytology	**ASCUS+**	**CIN2+**	10	Sensitivity	71.5%	(62.9% to 78.8%)	40%-94%
			10	Specificity	68.4%	(59.9% to 75.8%)	45%-90%
		CIN3+	4*	Sensitivity	77.9%	(64.0% to 87.6%)	67%-86%
			4*	Specificity	57.4%	(40.3% to 73.0%)	42%-90%
	LSIL+	**CIN2+**	6	Sensitivity	44.1%	(33.3% to 55.5%)	16%-61%
			6	Specificity	90.1%	(83.3% to 94.4%)	76%-96%
		CIN3+	4*	Sensitivity	53.5%	(17.8% to 85.9%)	25%-67%
			4	Specificity	79.9%	(73.4% to 85.2)%)	75%-96%
	HSIL+	**CIN2+**	5	Sensitivity	15.8%	(6.5% to 33.6%)	8%-50%
			5	Specificity	98.3%	(96.7% to 99.1%)	97%-99%
		CIN3+	4*	Sensitivity	33.2%	(6.1% to 79.2%)	0-58%
			4*	Specificity	95.6%	(93.6% to 97.1%)	95%-99%
Studies where HC2 triage was applied with or without repeat cytology							

(Continued)

HC2	**RLU > 1 (1 pg/mL)**	**CIN2+**	39	Sensitivity	90.4%	(88.1% to 92.3%)	60%-100%
			39	Specificity	58.3%	(53.6% to 62.9%)	27%-79%
		CIN3+	17	Sensitivity	93.7%	(90.4% to 95.9%)	75%-100%
			17	Specificity	52.3%	(45.7% to 58.7%)	33%-70%

Footnotes

*Univariate analyses using the bivariate model run separately for sensitivity and specificity.

Appendix 5. Summary of all the meta-analyses of the absolute accuracy in LSIL triage

Triage test	Triage cut-off	Outcome	Studies	Accuracy parameter	Pooled estimate	(95% CI)	Range
Studies where HC2 triage and repeat cytology were applied							
HC2	**RLU > 1 (1 pg/mL)**	**CIN2+**	6	Sensitivity	96.2%	(91.4 to 98.3%)	89%-100%
			6	Specificity	27.7%	(20.9 to 35.7%)	19%-44%
		CIN3+	4*	Sensitivity	97.5%	(69.6 to 99.8%)	97%-100%
			4*	Specificity	24.8%	(7.3 to 58.1%)	17%-29%
Repeat cytology	**ASCUS+**	**CIN2+**	6	Sensitivity	77.1%	(59.5 to 88.5%)	33%-100%
			6	Specificity	51.2%	(34.5% to 67.6%)	23%-83%
		CIN3+	4*	Sensitivity	84.6%	(48.6% to 97.0%)	64%-90%
			4*	Specificity	44.4%	(16.0% to 76.9%)	21%-82%
	LSIL+	**CIN2+**	4*	Sensitivity	62.1%	(33.4% to 84.3%)	21%-80%
			4*	Specificity	66.9%	(51.5% to 79.4%)	48%-91%
		CIN3+	4*	Sensitivity	71.6%	(33.4% to 92.7%)	36%-83%
			4*	Specificity	61.8%	(33.1% to 84.1%)	44%-91%
	HSIL+	**CIN2+**	4*	Sensitivity	31.6%	(18.2% to 49.0%)	12%-42%
			4*	Specificity	96.6%	(93.6% to 98.3%)	93%-99%
		CIN3+	4*	Sensitivity	41.9%	(24.8% to 61.2%)	21%-50%
			4*	Specificity	93.8%	(86.1% to 97.4%)	91%-99%
Studies where HC2 triage was applied with or without repeat cytology							

(Continued)

HC2	**RLU > 1 (1 pg/mL)**	**CIN2+**	24	Sensitivity	95.4%	(94.0% to 96.5%)	80%-100%
			24	Specificity	27.8%	(23.8% to 32.1%)	16%-58%
		CIN3+	14	Sensitivity	96.4%	(90.5% to 98.7%)	76%-100%
			14	Specificity	23.7%	(19.4% to 28.7%)	15%-47%

Appendix 6. Heterogeneity analysis

The heterogeneity analysis of the accuracy of the triage tests by covariate was performed when the compared groups contained at least three studies in one group and at least five studies in another group. The influence of the following covariates on the accuracy could be addressed: use of the cytological classification system (Bethesda versions 1989 or 2001 and BSCC); collection device used to collect cellular material for the HPV test (brush or broom); blinding of tests (yes or unclear); transport medium to store the sample for virological testing (Preservcyt, STM),

7.1 Influence of covariates on the accuracy of ASCUS triage by HC2, outcome CIN2+ or CIN3+

Analysis	Number of studies	Summary sensitivity (95% CI)	Summary specificity (95% CI)	P value LR test**
ASCUS triage with HC2 for CIN2+: Classification system for reporting of cervical cytology				
BSCC	5	86.5 (74.3-93.4)	64.4 (50.7-76.1)	0.8
Bethesda 1989	23	91.0 (88.0-93.3)	56.8 (50.4-63.0)	
Bethesda 2001	11	90.3 (85.6-93.6)	58.8 (49.7-67.4)	
ASCUS triage with HC2 for CIN2+: device to collect sample for HPV testing*				
Broom	5	94.9 (91.3-97.0)	57.2 (43.4-69.9)	0.03
Brush	16	87.5 (83.4-90.7)	59.4 (51.8-66.6)	
Ratio brush vs broom		0.92 (0.88-0.97), P = 0.002	1.04 (0.80-1.36), P = 0.8	
ASCUS triage with HC2 for CIN2+: blinding				
Yes	21	91.4 (88.4 93.8)	60.4 (53.7-66.7)	0.3
Unclear	17	89.0 (84.9-92.1)	56.1 (48.6-63.4)	
Ratio unclear vs blinded		0.97 (0.93-1.02), P = 0.3	0.93 (0.78-1.10), P = 0.4	
ASCUS triage with HC2 for CIN2+: transport medium				
STM	14	85.9 (81.0-89.7)	61.5 (53.4-69.0)	0.006
Preservcyt	9	91.7 (86.4-95.1)	44.4 (34.0-55.3)	
Ratio Preservcyt vs STM		1.07 (1.00-1.14), P = 0.06	0.72 (0.55-0.95), P = 0.02	
ASCUS triage with HC2 for CIN3+: Classification system for reporting of cervical cytology				
Bethesda 1989	13	92.9 (88.0-95.9)	51.3 (43.1-59.4)	0.6
Bethesda 2001	3	96.3 (84.2-99.2)	51.1 (35.4-66.6)	
Ratio Bethesda 2001 vs 1989		1.04 (0.96-1.11), P = 0.3	1.00 (0.70-1.42), P = 1.0	

(Continued)

ASCUS triage with HC2 for CIN3+: continent *				
America	6	95.9 (91.8-98.0)	54.0 (43.3-64.5)	0.1
Europe	9	90.2 (82.8-94.7)	51.3 (41.8-60.6)	
Ratio Europe vs America		0.94 (0.88-1.01), P = 0.09	0.95 (0.72-1.24), P = 0.7	
ASCUS triage with HC2 for CIN3+: blinding*				
Yes	8	91.4 (85.3-95.1)	52.6 (42.1-62.9)	0.3
Unclear	8	95.2 (90.5-97.6)	52.4 (41.5-63.0)	
Ratio unclear vs blinded		1.04 (0.98-1.11), P = 0.2	1.0 (0.75-1.33), P = 1.0	
ASCUS triage with HC2 for CIN3+: transport medium*				
STM	7	91.0 (82.3-95.7)	55.6 (44.1-66.5)	0.4
Preservcyt	5	93.2 (81.3-97.8)	45.4 (31.4-60.2)	
Ratio Preservcyt vs STM		1.02 (0.92-1.14), P = 0.6	0.82 (0.56-1.20), P = 0.3	

*Univariate analyses using the bivariate model run separately for sensitivity and specificity.

**Likelihood ratio test for model with and without the covariate.

7.2 Influence of covariates on the accuracy of ASCUS triage by repeat cytology, outcome CIN2+

Analysis	Number of studies	Summary sensitivity (95% CI)	Summary specificity (95% CI)	P value LR test**
ASCUS with repeat cytology at cut-off ASCUS+ for CIN2+: continent*				
America	5	80.1 (70.5-87.1)	59.8 (48.5-70.1)	0.007
Europe	5	62.9 (49.6-74.5)	75.8 (65.9-83.6)	
Ratio Europe vs America		0.79 (0.63-0.99), P = 0.04	1.27 (1.02-1.58), P = 0.04	

*Univariate analyses using the bivariate model run separately for sensitivity and specificity.

**Likelihood ratio test for model with and without the covariate.

7.3 Influence of covariates on the accuracy of LSIL triage by HC2, outcome CIN2+ or CIN3+

Analysis	Number of studies	Summary sensitivity (95% CI)	Summary specificity (95% CI)	P value LR test**
LSIL triage with HC2 for CIN2+: Classification system for reporting of cervical cytology*				
BSCC	3	96.1 (88.1-98.8)	33.8 (22.6-47.1)	0.2
Bethesda 1989	16	95.8 (93.6-97.3)	29.8 (25.2-34.8)	
Bethesda 2001	5	96.2 (93.0-98.0)	19.5 (14.0-26.4)	
LSIL triage with HC2 for CIN2+: device to collect sample for HPV testing*				
Broom	3	98.4 (95.8-99.4)	24.8 (17.5-33.8)	0.003
Brush	9	92.8 (89.1-95.3)	32.6 (26.8-38.9)	
Ratio brush vs broom		0.94 (0.91-0.98), P = 0.005	1.32 (0.90-1.92), P = 0.1	
LSIL triage with HC2 for CIN2+: continent*				
America	8	96.5 (95.2-97.5)	21.4 (16.7-27.0)	0.04
Asia	4	96.1 (90.5-98.4)	24.7 (16.8-34.9)	
Europe	12	95.0 (92.7-96.6)	33.1 (27.8-38.8)	
LSIL triage with HC2 for CIN2+: Classification system for reporting of cervical cytology*				
BSCC	3	96.1 (88.1-98.8)	33.8 (22.6-47.1)	0.2
Bethesda 1989	16	95.8 (93.6-97.3)	29.8 (25.2-34.8)	
Bethesda 2001	5	96.2 (93.0-98.0)	19.5 (14.0-26.4)	
LSIL HC2 CIN2+: device to collect sample for HPV testing*				
Broom	3	98.4 (95.8-99.4)	24.8 (17.5-33.8)	0.003
Brush	9	92.8 (89.1-95.3)	32.6 (26.8-38.9)	
Ratio brush vs broom		0.94 (0.91-0.98), P = 0.005	1.32 (0.90-1.92), P = 0.1	
LSIL HC2 CIN2+: continent*				
America	8	96.5 (95.2-97.5)	21.4 (16.7-27.0)	0.04
Asia	4	96.1 (90.5-98.4)	24.7 (16.8-34.9)	
Europe	12	95.0 (92.7-96.6)	33.1 (27.8-38.8)	
LSIL triage with HC2 for CIN3+: blinding*				

(Continued)

Yes	13	95.4 (93.1-97.0)	29.3 (23.7-35.6)	0.5
Unclear	10	96.5 (94.2-98.0)	26.4 (20.3-33.5)	
Ratio unclear vs blinded		1.01 (0.98-1.04), P = 0.4	0.90 (0.65-1.25), P = 0.5	
LSIL triage with HC2 for CIN2+: transport medium				
STM	8	93.6 (87.6-96.9)	33.1 (26.3-40.6)	0.4
Preservcyt	7	97.2 (93.0-98.9)	31.9 (24.5-40.3)	
Ratio Preservcyt vs STM		1.04 (0.98-1.09), P = 0.2	0.96 (0.69-1.34) P = 0.8	
LSIL triage with HC2 for CIN3+: continent				
America	5	96.0 (88.5-98.7)	18.1 (13.1-24.5)	0.1
Europe	8	96.3 (86.4-99.1)	27.1 (21.2-33.8)	
Ratio Europe vs America		1.00 (0.95-1.06), P = 0.9	1.50 (1.01-2.21), P = 0.04	
LSIL triage with HC2 for CIN3+: blinding				
Yes	7	96.1 (84.2-99.1)	23.7 (17.2-31.8)	1.0
Unclear	6	95.9 (87.8-98.7)	24.8 (17.1-34.5)	
Ratio Unclear vs Blinded		1.00 (0.94-1.06), P = 0.9	1.04 (0.65-1.67), P = 0.8	
LSIL triage with HC2 for CIN3+: transport medium				
STM	5	96.5 (74.2-99.6)	26.2 (18.2-36.2)	0.5
Preservcyt	5	99.2 (71.9-100)	28.6 (19.7-39.7)	
Ratio Presercyt vs STM		1.03 (0.95-1.11), P = 0.4	1.09 (0.67-1.79), P = 0.7	

*Univariate analyses using the bivariate model run separately for sensitivity and specificity.

**Likelihood ratio test for model with and without the covariate.

7.4. Influence of covariates on the accuracy of LSIL triage by repeat cytology

No analyses performed because of the small number of studies.

Appendix 7. Influence of age on the accuracy of HC2

Triage group	Outcome	Age group	Estimate of pooled sensitivity (95% CI)	Estimate of pooled specificity (95% CI)	Relative sensitivity (95% CI)	P value (relative sensitivity)	Relative specificity (95% CI)	P value (relative specificity)
ASCUS	**CIN2+**	< 30	-	-	-	-	-	-
		30-39	-	-	-	-	-	-
		40-49	-	-	-	-	-	-
		50+	-	-	-	-	-	-
	CIN3+	< 30	-	-	-	-	-	-
		30-39	-	-	-	-	-	-
		40-49	-	-	-	-	-	-
		50+	-	-	-	-	-	-
LSIL	**CIN2+**	< 30	96.2% (93.4% to 97.8%)	18.0% (15.6% to 20.6%)	0.99 (0.97 to 1.02)	0.81	0.64 (0.32 to 1.31)	0.222
		30-39	96.5% (94.6% to 97.7%)	27.9% (12.9% to 50.5%)	reference	reference	reference	reference
		40-49	95.4% (91.6% to 97.5%)	40.3% (21.4% to 62.5%)	0.99 (0.96 to 1.02)	0.416	1.44 (0.60 to 3.48)	0.416
		50+	95.0% (85.9% to 98.3%)	43.7% (24.4% to 65.2%)	0.98 (0.93 to 1.04)	0.592	1.56 (0.66 to 3.68)	0.304
	CIN3+	< 30	95.8% (91.7% to 97.9%)	16.3% (14.0% to 18.9%)	1.02 (0.97 to 1.07)	0.410	0.71 (0.41 to 1.22)	0.214
		30-39	93.9% (89.6% to 96.5%)	22.9% (13.2% to 36.7%)	reference	reference	reference	reference
		40-49	95.2% (87.7% to 98.2%)	28.5% (13.2% to 51.0%)	1.01 (0.96 to 1.07)	0.653	1.24 (1.11 to 1.39)	0.0002
		50+	93.0% (78.2% to 98.0%)	43.4% (22.5% to 67.0%)	0.99 (0.90 to 1.09)	0.832	1.90 (0.89 to 4.02)	0.095

Appendix 8. List of abbreviations

AGC: atypical glandular cells
AGUS: atypical glandular cells of undetermined significance
AIS: adenocarcinoma in situ
ALTS: ASCUS-LSIL Triage Study
ASC: atypical squamous cells (comprises ASC-US and ASC-H)
ASC-H: atypical squamous cells, HSIL cannot be ruled out
ASC-R: atypical squamous cells favouring a benign reactive process squamous cells of undetermined significance
ASC-US: atypical squamous cells of undetermined significance
ASCUS: atypical squamous cells of undetermined significance (comprises ASC-R, ASC-US and ASC-H)
BSCC: Brittish Society of Clinical Cytology
CGIN: cervical glandular intraepithelial neoplasia
CI (95%) confidence interval
CIN: cervical intra-epithelial neoplasia
CIS: carcinoma in situ
DNA: deoxyribo-nucleic acid
DOR: diagnostic odds ratio
ECC: endocervical curettage
FN: false negative
FP: false positive
HC: Hybrid Capture
HC2: Hybrid Capture-II (2nd generation assay)
HCT: Hybrid Capture tube-based assay
HPV: human papillomavirus
hrHPV: high-risk HPV
HSIL: high-grade squamous intraepithelial lesion
HSROC: hierarchical summary receiver operating characteristic
LBC: liquid-based cytology
LEEP: loop electrosurgical excision procedure
LLETZ: large loop excision of the transformation zone
LSIL: low-grade squamous intraepithelial lesion
NASBA: nucleic acid sequence-based amplification
NHSCSP: National Health Service Cervical Screening Programme

NILM: negative for intraepithelial lesion or malignancy (=normal cytology)
NPV: negative predictive value
PCR: polymerase chain reaction
PPV: positive predictive value
RLU: relative light units
RNA: ribo-nucleic acid
ROC: receiver operating characteristic
SROC-curve: summary receiver operating characteristic curve
STM: specimen transport medium
TBS: The Bethesda System
TN: true negative
TP: true positive
TZ: transformation zone
VIA: visual inspection after application of acetic acid

WHAT'S NEW

Date	Event	Description
25 March 2021	Review declared as stable	This review has been superseded by Cytology versus HPV testing for cervical cancer screening in the general population (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008587.pub2/full).

HISTORY

Protocol first published: Issue 4, 2009
Review first published: Issue 3, 2013

CONTRIBUTIONS OF AUTHORS

Conception of the systematic review: M Arbyn, F Buntinx, P Martin-Hirsch, E Paraskevaidis and W Prendiville.
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Critical review of the protocol: P Martin-Hirsch, E Paraskevaidis and W Prendiville.

DECLARATIONS OF INTEREST

All review authors declare that they do not have any conflicts of interest regarding the test assays discussed in the systematic review.

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- Belgian Foundation Against Cancer, Belgium

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- IARC (International Agency for Research on Cancer), Lyon, France

  Financial support to update recommendations on cancer screening in the European Code Against Cancer and to develop criteria for evaluating the diagnostic accuracy of new cancer screening tests

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original review protocol also proposed to evaluate the accuracy of HC2 triage of women with ASC-H cytology (atypical squamous cells where HSIL cannot be excluded) and AGC cytology (atypical glandular cells). Given the large quantity and complexity of studies addressing triage of ASCUS and LSIL, we preferred to focus on the main triage groups in this review. Triage of ASC-H and AGC, and also triage of ASCUS and LSIL, with other HPV assays and molecular markers will be the target of a future, separate meta-analysis.

INDEX TERMS

Medical Subject Headings (MeSH)

DNA, Viral [*isolation & purification]; Papillomaviridae [*genetics]; Papillomavirus Infections [*diagnosis]; Sensitivity and Specificity; Triage [*methods]; Uterine Cervical Dysplasia [*diagnosis] [virology]; Uterine Cervical Neoplasms [*diagnosis] [virology]; Vaginal Smears [*methods]

MeSH check words

Female; Humans