Virologic Versus Cytologic Triage of Women With Equivocal Pap Smears: A Meta-analysis of the Accuracy To Detect High-Grade Intraepithelial Neoplasia

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Background: **The appropriate management of women with minor cytologic lesions in their cervix is unclear. We performed a meta-analysis to assess the accuracy of human papillomavirus (HPV) DNA testing as an alternative to repeat cytology in women who had equivocal results on a previous Pap smear.** ***Methods:*** **Data were extracted from articles published between 1992 and 2002 that contained results of virologic and cytologic testing followed by colposcopically directed biopsy in women with an index smear showing atypical cells of undetermined significance (ASCUS). Fifteen studies were identified in which HPV triage and the histologic outcome (presence or absence of a cervical intraepithelial neoplasia of grade II or worse [CIN2+]) was documented. Nine, seven, and two studies also documented the accuracy of repeat cytology when the cutoff for abnormal cytology was set at a threshold of ASCUS or worse, low-grade squamous intraepithelial lesion (LSIL) or worse, or high-grade squamous intraepithelial lesion (HSIL) or worse, respectively. Random-effects models were used for pooling of accuracy parameters in case of interstudy heterogeneity. Differences in accuracy were assessed by pooling the ratio of the sensitivity (or specificity) of HPV testing to that of repeat cytology.** ***Results:*** **The sensitivity and specificity were 84.4% (95% confidence interval [CI] = 77.6% to 91.1%) and 72.9% (95% CI = 62.5% to 83.3%), respectively, for HPV testing overall and 94.8% (95% CI = 92.7% to 96.9%) and 67.3% (95% CI = 58.2% to 76.4%), respectively, for HPV testing in the eight studies that used the Hybrid Capture II assay. Sensitivity and specificity of repeat cytology at a threshold for abnormal cytology of ASCUS or worse was 81.8% (95% CI = 73.5% to 84.3%) and 57.6% (95% CI = 49.5% to 65.7%), respectively. Repeat cytology that used higher cytologic thresholds yielded substantially lower sensitivity but higher specificity than triage with the Hybrid Capture II assay. The ratio of the sensitivity of the Hybrid Capture II assay to that of repeat cytology at a threshold of ASCUS or worse pooled from the four studies that used both triage tests was 1.16 (95% CI = 1.04 to 1.29). The specificity ratio was not statistically different from unity.** ***Conclusion:*** **The published literature indicates that the Hybrid Capture II assay has improved accuracy (higher sensitivity, similar specificity) than the repeat Pap smear using the threshold of ASCUS for an outcome of CIN2+ among women with equivocal cytologic results. The sensitivity of triage at higher cytologic cutoffs is poor. [J Natl Cancer Inst 2004;96:280–93]**

The main purpose of cytologic screening by Papanicolaou (Pap) smears is to identify women with cervical lesions that confer an increased risk of cervical cancer *(1).* Such women require further follow-up and/or treatment to prevent progression to invasive disease. Consensus exists that women with high-grade cytologic lesions should be referred immediately for further exploration *(2).* However, the management of women with minor cytologic lesions remains controversial *(3).* Follow-up recommendations for women with atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesions (LSILs) vary from conservative repeat cytology *(4–7)* to immediate referral for colposcopy and biopsy *(8–11).* Referral to the colposcopy clinic and the subsequent histologic examination result in substantial costs for the health care system *(12)* and often create feelings of anxiety and discomfort for women *(13).*

The natural history of minor cytologic lesions is difficult to predict on the basis of cytomorphologic grounds. These lesions often regress spontaneously and do not require treatment *(14–16).* Referring all women with minor cytologic lesions for further gynecologic exploration would, therefore, mean an increase in overdiagnosis and overtreatment *(12,17).* Lack of availability of colposcopic services at affordable prices often makes such an approach unrealistic. Nevertheless, although most women with an ASCUS smear result do not have clinically significant disease, a substantial proportion of them do have histopathologically confirmed high-grade cervical intraepithelial neoplasia or worse (CIN2+) *(18–20).* Indeed, from a population of screened U.S. women, it was estimated that one-third of CIN2+ lesions were discovered on follow-up of a previous smear with ASCUS *(20).*

Given the evidence concerning the etiologic role of oncogenic human papillomavirus (HPV) infections in the development of cervical cancer and CIN *(21–25),* HPV testing has been proposed as a triage method to identify women at increased risk of cervical cancer and thus requiring referral for colposcopic exploration *(18,19).* However, results concerning the utility of HPV triage for women with equivocal cytology are inconsistent *(26–28).* We therefore used meta-analytic tools to extract from

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the literature all available data concerning diagnostic accuracy parameters, studied the variation in a systematic way, and obtained overall synthetic measures.

METHODS

Research Question

In this meta-analysis, we addressed the following questions: 1) What is the accuracy (i.e., sensitivity, specificity, predictive values, and likelihood ratios) of HPV DNA testing to detect histologically confirmed CIN2+ disease in women with an index smear showing ASCUS? 2) In studies in which the Pap smear was repeated, what is the accuracy of repeat cytology at thresholds of ASCUS, LSIL, and HSIL (high-grade squamous intraepithelial lesion) to detect CIN2+? and 3) What are the differences in accuracy between both triage tests?

Retrieval Strategy

A systematic literature search identified articles published between 1992 and 2002 that contained quantitative data allowing assessment of one or more of the research questions. Articles were retrieved from the electronic bibliographic databases (MEDLINE, EMBASE, Cochrane Library) using the following search terms: (((cervix OR cervical) AND (cancer OR carcinoma OR neoplas* OR dysplas* OR CIN OR SIL)) OR (cervix neoplasm)) AND (HPV OR human papillomavirus) AND (triage OR management). The search was completed manually by searching the reference lists of relevant articles and by screening the tables of contents (for 1992–2002) of the following journals: *American Journal of Obstetrics and Gynecology*, *European Journal of Gynecological Oncology*, *Journal of Gynecological Oncology*, *Journal of Lower Genital Tract Disease*, *Journal of Reproductive Medicine*, and *Obstetrics and Gynecology*. References were selected if they fulfilled three inclusion criteria: 1) women in the study presented with an index Pap smear of the uterine cervix with atypical squamous/glandular cells of unspecified significance (ASCUS/AGUS); 2) an HPV DNA detection test was performed; and 3) women were subsequently subjected to colposcopy and colposcopy-directed biopsies, with or without endocervical curettage, for histologic verification. A fourth but non-obligatory criterion was the repetition of the Pap test.

For several studies, we considered limited information. From Ferris et al. *(29,30)*, we selected the HPV DNA data from the Hybrid Capture I assay because these data were contrasted with repeat cytology; from Morin et al. *(31)*, HPV data from the Hybrid Capture II assay were used; and from the ASCUS-LSIL Triage Study (ALTS) *(32,33)*, we used results from two of the three experimental arms: women randomly assigned to immediate colposcopic verification and women randomly assigned to the HPV DNA testing arm, in which colposcopy was restricted to women showing presence of high-risk HPV DNA or HSIL on the repeat smear *(32)*.

Thresholds for Triage Tests

We considered a single threshold for HPV positivity: the presence of HPV DNA at a level greater than the cutoff for a positive test as stated by the test manufacturer. The variation in accuracy according to other thresholds of increasing viral load was studied by a summary receiver operating characteristic curve analysis and is reported elsewhere *(34)*. We retrieved information on the presence of oncogenic and high-risk HPV types only. We considered three threshold levels for abnormal cytology on the repeat Pap test: ASCUS or worse, LSIL or worse, and HSIL or worse. The 1991 version of the Bethesda Reporting System *(35)* was used for cytologic classification.

Outcome

The histologic result was used as the gold standard. We assumed that histologic examination of material obtained by colposcopy-directed biopsy, loop excision, or endocervical curettage provided complete ascertainment of the considered disease status. Throughout our systematic review, we used the CIN nomenclature to describe histologic outcomes *(36)*. We considered only the outcome of CIN2+.

Covariate Information

The following study properties were summarized in comprehensive tables: characteristics of the study population (place, inclusion and exclusion criteria, study size, and age distribution), properties of the HPV DNA testing systems (type of DNA detection method, collection device, transport medium), repeat cytology (conventional or liquid-based preparation, cytologic threshold, collection device), procedures for gold standard verification, and the blinding of interpreters for other test results.

Definition of Accuracy Measures and Statistical Analysis

The numbers of true-positives, false-negatives, false-positives, and true-negatives defined at the considered thresholds were extracted from each study, and the following accuracy parameters were calculated: sensitivity (true-positives/[true-positives plus false-negatives]); specificity (true-negatives/[true-negatives plus false-positives]); positive predictive value (true-positives/[true-positives plus false-positives]); negative predictive value (true-negatives/[true-negatives plus false-negatives]); test-positivity rate ([true-positives plus false-positives]/total number of patients), and prevalence of disease defined as presence of CIN2+ ([true-positives plus false-negatives]/total number of patients). The positive likelihood ratio (PLR = sensitivity/[1 – specificity]) and the negative likelihood ratio (NLR = [1 – sensitivity]/specificity) express the likelihood of the presence of CIN2+ versus the absence of CIN2+ when tests are positive or negative, respectively. The positive likelihood ratio should be greater than unity and as large as possible, whereas the negative likelihood ratio should be less than unity and tend toward zero. To assess differences in accuracy, we determined the ratio of the sensitivity (or specificity) of HPV testing to that of repeat cytology for those studies where both test systems were evaluated on the same women and then pooled the individual ratios. The variation in accuracy measures in the individual studies and in the pooled measures were displayed graphically using forest plots *(37–39)*. Random-effects models were used for pooling accuracy parameters in cases of statistically significant interstudy heterogeneity (i.e., when $P<.10$ for Cochran's Q test) *(40,41)*. In the absence of statistically significant heterogeneity, fixed models were used, with weighting of each individual study parameter according to the reciprocal of its variance *(39)*. Meta-analyses were performed using the Stata statistical package (version 7.0; Stata Corp., College Station, TX) *(42)*. Subgroup meta-analysis was used to assess the influ-

ence of study characteristics on the outcome. Age-stratified data on accuracy to detect CIN2+ were published in only one study *(43)*. We also obtained age-stratified data from the ALTS directly from Dr. M. Schiffman (National Cancer Institute, Bethesda, MD) *(33)*.

Publication Bias

Publication bias generally arises when smaller studies have a higher chance of being published if their results are positive. We assessed publication bias by using the asymmetry regression test and asymmetry plots, in which the normal deviate of the accuracy measure is plotted against its precision, which is related to the study size *(44,45)*.

RESULTS

Study Characteristics

Initially, we identified 29 potential articles for inclusion *(18,19,29–33,43,46–66)*. However, we excluded 12 articles concerning triage of patients with ASCUS or LSIL, because the group with an ASCUS index smear could not be separated out *(55–66)*. In total, 17 articles reporting results of 15 studies met the inclusion criteria *(18,19,29–33,43,46–54)*. Among the 15 studies, data allowing computation of the accuracy of repeat cytology at the thresholds ASCUS or worse, LSIL or worse, or HSIL or worse were obtained from nine, seven, and two studies, respectively. The characteristics of the included studies are summarized in Table 1 and Table 2.

Study Size

In total, 5454 women in the 15 included studies had ASCUS triage with HPV DNA testing. Nine studies were small, each contributing fewer than 200 women; four studies were of intermediate size, each contributing between 200 and 500 women; and two studies were large, each contributing more than 500 women. One of the large studies, the ALTS, contributed more than 2300 women *(32,33)*.

Clinical Setting and Population Characteristics

For each study, patients were recruited from colposcopy clinics or from gynecologic services to which women had been referred because of a cytologic result of ASCUS. In four studies *(48,51,53,54)*, the referred women had had repeated atypical cytology. Six studies *(18,29,32,49,52,54)* excluded women with a history of CIN, cervical surgery, or biopsy. One study *(19)* presented separate results for women with and without previous CIN. One study *(31)* included only women with ASCUS occurring after two sequential normal smears.

Blinding and Quality Review of Histologic Outcome

In six studies *(18,29,43,47,49,52)*, it was explicitly stated that the histologic interpretation was blinded to the triage test results. In three studies *(18,32,49)*, the histopathologic diagnosis was subjected to review by expert histologists.

Triage Tests

Several different HPV detection methods were used in the included studies. Two studies *(46,47)* used ViraPap and ViraType. These are two older commercial DNA dot blot test kits that use radioactive HPV RNA probes. The ViraPap contains a cocktail of seven probes that detect HPV types 6, 11, 16, 18, 31, 33, and 35. ViraType contains two distinct high-risk HPV cocktails that detect the high-risk HPV types 16, 18, 31, 33, and 35.

Hybrid Capture techniques were the most frequently used HPV DNA triage methods. The first generation Hybrid Capture I assay or Hybrid Capture Tube, which detects nine high-risk HPV types (i.e., 16, 18, 31, 33, 35, 45, 51, 52, and 56), was evaluated in five studies *(18,19,29,48,51)*. The Hybrid Capture II assay, which contains a cocktail of probes that detect the same nine high-risk HPV types and HPV types 39, 58, 59, and 68 *(67)*, was used in eight studies *(31,32,43,49,50,52–54)*. In one study *(49)*, a prototype Hybrid Capture II assay was used that did not contain probes for HPV types 59 and 68. For all Hybrid Capture techniques, the hybridization yields a chemiluminescent signal that is compared with positive controls containing a known amount of HPV16 DNA. The detection limit is 10 pg of HPV DNA/mL in the Hybrid Capture I assay and 1 pg/mL in the Hybrid Capture II assay.

Cytology and Hybrid Capture II accuracy data from the same subjects were available in four studies *(31,32,49,50)*. The conventional Pap smear was used as the cytologic triage method in most studies, although the ThinPREP liquid-based technique was used in two studies *(32,49)*.

Triage by HPV Testing

The sensitivity to detect CIN2+ varied from extremely low, 26.7% with the ViraPap test *(47)*, to 95.9% *(32)* and 100.0% *(52)* with the Hybrid Capture II assay (Table 3). The negative predictive values ranged from 88.7% *(47)* to 100.0% *(52)*. The specificity ranged from 48.4% *(32)* to 97.1% *(51)*. The positive predictive values ranged from 7.8% *(19)* to 90.6% *(51)*. The prevalence of HPV positivity varied between 16.4% *(46,48)* and 56.8% *(32)*.

Triage by Repeat Cytology at Cutoff ASCUS or Worse

The numbers of true- and false-positive and true- and false-negative results for repeat cytology, defined at the cutoff ASCUS or worse, and derived parameters are shown in Table 4. Sensitivity ranged from 60.0% *(46)* to 85.0% *(32)*, and specificity ranged from 44.7% *(29,32)* to 71.7% *(50)*. Positive predictive values ranged from 3.8% *(46)* to 22.2% *(47,50)*, and negative predictive values ranged from 93.4% *(47)* to 97.8% *(46)*. The test positivity rate ranged from 32.4% *(50)* to 58.8% *(32)*.

Triage by Repeat Cytology at Cutoff LSIL or Worse

The numbers of true- and false-positive and true- and false-negative results for repeat cytology, defined at the cutoff LSIL or worse, and derived parameters are shown in Table 4. Sensitivity ranged from 20.0% *(29)* to 59.2% *(32)*, and specificity ranged from 77.9% *(32)* to 96.4% *(46)*. Because of higher specificity in triaging at cutoff LSIL, the positive predictive value increased and ranged from 8.0% *(29)* to 32.5% *(49)*. The negative predictive value ranged from 93.6% *(32)* to 98.2% *(46)*. Test positivity was considerably lower than triage at cutoff ASCUS and varied between 4.7% *(46)* and 26.4% *(32)*.

Triage by Repeat Cytology at Cutoff HSIL or Worse

Both studies *(32,49)* in which the accuracy of the repeat cytology was defined at the cutoff HSIL or worse had very low

Table 1. Characteristics of the study populations recruited for included triage studies*

Author, reference	Country	Study location	Study population and inclusion criteria	Exclusion criteria	Study size	Age distribution, y
Goff et al., 1993 *(46)*	United States	Colposcopy clinic in Boston, MA	Selected from 360 consecutive patients consulting at a colposcopy clinic, with an ASCUS index smear	No information provided	171	Mean = 35; no further details
Slawson et al., 1994 *(47)*	United States	General practitioners in Harrisburg, PA	Selected from a GP screening population, with an ASCUS index smear	Incomplete data, refusal of colposcopy, women claiming immediate colposcopy	121	Mean = 25; range = 15–45
Cox et al., 1995 *(18)*	United States	University of California clinic in Santa Barbara	Young women referred because of ASCUS	Preference for follow-up with cytology, refusal of colposcopy, history of treatment for CIN	217	Mean = 21; >90% in 18–22 range
Wright et al., 1995 *(19)*	United States, Canada	Colposcopy clinics in New York and Quebec	Women referred to a colposcopy clinic (19% were previously treated for CIN), with index smear showing ASCUS/AGUS	Results are presented for all women (n = 181) and for the subgroup of women without history of treatment (n = 136)	181	Median = 36
Fait et al., 1998 *(48)*	Israel	Colposcopy clinic in Tel Aviv	Women with repeated ASCUS and normal previous colposcopy	No information provided	67	Mean = 28; range = 17–49
Ferris et al., 1998 *(29,30)*	United States	Six colposcopy clinics	Women referred to colposcopy clinic with a previous ASCUS <4 mo earlier	Pregnancy, HSIL, or cervical cancer <12 mo earlier, immunosuppression, prior colposcopy or CIN in last 12 mo; cervical evaluation impossible	169	Mean = 27; SD = 2.4; range = >18
Manos et al., 1999 *(49)*	United States	12 gynecology clinics belonging to the Kaiser Permanente Medical Care Programme (Northern California)	Screened women recalled for a smear showing ASCUS, consenting with participation for triage, and gold standard results were available	Pregnancy, treatment for cervical neoplasia <6 mo earlier, recalling impossible	973	Mean = 40; range = 14–92
Bergeron et al., 2000 *(50)*	France	41 private gynecologists in Paris	Screened women with index smear showing ASCUS	Biopsy containing only endocervical cylindrical cells	111	Mean = 35; SD = 10; range = 15–75
Fait et al., 2000 *(51)*	Israel	Colposcopy clinic in Tel Aviv	Women with two consecutive smears showing ASCUS	Patients with colposcopically visible HPV-related disease in the anogenital area	226	Mean = 28; range = 17–48
Lin et al., 2000 *(52)*	Taiwan	Colposcopy clinic in Chang Gung	Women with ASCUS <3 mo earlier	Menopausal bleeding <6 mo earlier, previous diagnosis or treatment of CIN or cancer, immunosuppression, gynecologic evaluation impossible	74	Median = 62; range = 50–78
Shlay et al., 2000 *(43)*	United States	Women's clinic in Denver, CO	Indigent women referred for ASCUS or AGUS	Menstruation, pregnancy, refusal of consent	195	≤20 (6.2%), 20–29 (32.8%), 30–39 (29.7%), ≥40 (31.3%)
Morin et al., 2001 *(31)*	Canada	Gynecology services, University of Quebec	Women with diagnosis of ASCUS after two consecutive normal smears; informed consent	Pregnancy, previous biopsy or treatment of the cervix	360	Range = 18–50
Rebello et al., 2001 *(53)*	United Kingdom	Colposcopy clinic in Edinburgh	Women with persistent borderline smears	No information provided	75	Median = 30; range = 17–61
Solomon, 2001 *(32)*; Sherman et al., 2002 *(33)*	United States	Gynecology clinics in Birmingham, AL; Oklahoma City, OK; Pittsburgh, PA; Seattle, WA	3600 women enrolled on average 2 mo after an index smear showing ASCUS enrolled in ALTS in the immediate colposcopy arm or in the HPV arm	Pregnancy, ablative surgery, or excisional therapy on the cervix	2336	Mean = 29
Zielinski et al., 2001 *(54)*	The Netherlands	General practitioners and outpatient clinic in Walcheren	278 women consulting at general practitioners or outpatient clinic with two previous smears showing borderline or mild dysplasia; 213 had a last smear showing borderline dysplasia	Known history of cervical pathology, glandular lesion, lost to follow-up	213	Mean = 41; range = 20–76

*ASCUS = atypical squamous cells of undetermined significance; AGUS = atypical glandular cells of undetermined significance; CIN = cervical intraepithelial neoplasia; HSIL = high-grade squamous intraepithelial lesion; HPV = human papillomavirus; ALTS = ASCUS-LSIL Triage Study.

Table 2. Characteristics of test procedures applied in retrieved triage studies*

Author	HPV triage test	Collection device for HPV	Transport medium for HPV	Cytologic triage test	Cutoff for cytologic triage	Collection device for cytology	Gold standard	Blinding of testing
Goff et al., 1993 *(46)*	ViraType	No information provided	No information provided	Pap smear	≥ASCUS ≥LSIL	No information provided	Colposycopy, ECC, colposcopically oriented biopsies when indicated	No information provided
Slawson et al., 1994 *(47)*	ViraPap	Dacron swab	ViraPap	Pap smear	≥ASCUS	No information provided	Colposcopy and directed biopsies. ECC for all cases. All histological results were reviewed	Histological review was blinded
Cox et al., 1995 *(18)*	HC1	Cone brush	ViraPap	Pap smear	≥ASCUS ≥LSIL	Ayre spatula and Cytobrush	Colposcopy and directed biopsies from abnormal zones. ECC if index smear showed glandular atypia or if atypical transformation zone	Histological review was blinded
Wright et al., 1995 *(19)*	HCT	Dacron swab	ViraPap	Pap smear	≥ASCUS ≥LSIL	Ayre spatula and Cytobrush	Colposcopy and biopsy of visible abnormalities ECC for most cases, also when no visible lesion was observed	No information provided
Fait et al., 1998 *(48)*	HC1	Cotton tip applicator	STM	None	Not applicable	Not applicable	Colposcopy and cone biopsies	No information provided
Ferris et al., 1998 *(29,30)*	HCT	Dacron swab	ViraPap	Pap smear	≥ASCUS ≥LSIL	Ayre spatula and Cytobrush or Ancellon sampler	Biopsies from lesions under colposcopic control. ECC when indicated	Histology was blinded from HPV
Manos et al., 1999 *(49)*	HC2	Papette brush	ThinPrep	Pap smear (and LBC)	≥ASCUS ≥LSIL ≥HSIL	Papette brush; Cytobrush if cervical stenosis	Colposcopy with biopsy and/or ECC for all cases. ECC for cases in which no lesion requiring biopsy was seen. Double (and if discordance, triple) reading of histology	Colposcopy/histology was blinded from triage test results
Bergeron et al., 2000 *(50)*	HC2, PCR, SB	Cone brush	STM	Pap smear	≥ASCUS	Ayre spatula and Cytobrush	Colposcopy and biopsies taken from the transformation zone	Pathologist was masked to the other test results
Fait et al., 2000 *(51)*	HCl	Dacron swab	STM	None	Not applicable	Not applicable	Punch biopsy from the most severe lesion, diagnostic cone biopsy if colposcopy was normal and adequate	Colposcopy not blinded; histology blinded
Lin et al., 2000 *(52)*	HC2	Cone brush	STM	None	Not applicable	Not applicable	Punch biopsies from most affected area, random biopsies and/or ECC when no visible lesion was identified. Treatment of CIN2+ with cervical cone or LEEP	Histology blinded to HPV test results
Shlay et al., 2000 *(43)*	HC2	Cone brush	STM	None	Not applicable	Not applicable	Biopsy from colposcopically abnormal areas. ECC and endocervical brush sample from all subjects	Histology blinded to clinic and HPV results
Morin et al., 2001 *(31)*	HC1/2 PCR	Dacron swab	STM	Pap smear	≥ASCUS ≥LSIL	No information provided	Colposcopy and directed biopsies or ECC for all lesions of the cervix	No information provided
Rebello et al., 2001 *(53)*	HC2	Cone brush	STM	None	Not applicable	Not applicable	Large loop excision on all patients	No information provided
Solomon et al., 2001 *(32)*; Sherman et al., 2002 *(33)*	HC2	Papette brush	ThinPrep	LBC	≥ASCUS ≥LSIL ≥HSIL	Papette brush	Biopsy from colposcopically suspected CIN, ECC if indicated (transformation zone or extent of lesion not completely visible). CIN2+ lesions treated with LEEP. Quality review of histology.	Histology not blinded from cytology. Colposcopy repeated when histology was less severe than cytology. No statement on independence of histology and/or virology. In arm 2, almost all referred cases were HPV-positive
Zielinski et al., 2001 *(54)*	HC2	No information provided	No information provided	None	Not applicable	Not applicable	Colposcopically directed biopsies when a lesion was visible	No information provided

*HC = Hybrid Capture; HCT = Hybrid Capture Tube; SB = Southern blot; PCR = polymerase chain reaction; ECC = endocervical curettage; LEEP = loop electrosurgical excision procedure; STM = specimen transport medium; LBC = liquid-based cytology; ASCUS = atypical squamous cells of undetermined significance; LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion; CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; ≥ = cutoff level or worse.

Table 3. Triage of atypical squamous cells of undetermined significance (ASCUS) by human papillomavirus (HPV) DNA testing for the detection of histologically confirmed cervical intraepithelial neoplasia grade II or worse (CIN2+): number of true- and false-positives and true- and false-negatives, accuracy parameters, test positivity rate, and prevalence of disease derived from different published studies*

Study	Type	True-positive	False-negative	False-positive	True-negative	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Test positivity rate	Prevalence of disease
Goff et al., 1993 *(46)*	VT	3	2	25	141	0.600	0.849	0.107	0.986	0.164	0.029
Slawson et al., 1994 *(47)*	VP	4	11	20	86	0.267	0.811	0.167	0.887	0.198	0.124
Cox et al., 1995 *(18)*	HC1	14	1	67	135	0.933	0.668	0.173	0.993	0.373	0.069
Wright et al., 1995 *(19)*	HC1	6	5	71	99	0.545	0.582	0.078	0.952	0.425	0.061
Fait et al., 1998 *(48)*	HC1	9	1	2	55	0.900	0.965	0.818	0.982	0.164	0.149
Ferris et al., 1998 *(29)*	HC1	5	5	53	106	0.500	0.667	0.086	0.955	0.343	0.059
Manos et al., 1999 *(49)*	HC2	58	7	326	582	0.892	0.641	0.151	0.988	0.395	0.067
Bergeron et al., 2000 *(50)*	HC2	10	2	38	61	0.833	0.616	0.208	0.968	0.432	0.108
Fait et al., 2000 *(51)*	HC1	48	8	5	165	0.857	0.971	0.906	0.954	0.235	0.248
Lin et al., 2000 *(52)*	HC2	27	0	12	35	1.000	0.745	0.692	1.000	0.527	0.365
Shlay et al., 2000 *(43)*	HC2	14	1	47	133	0.933	0.739	0.230	0.993	0.313	0.077
Morin et al., 2001 *(31)*	HC2	17	2	88	253	0.895	0.742	0.162	0.992	0.292	0.053
Rebello et al., 2001 *(53)*	HC2	18	3	13	41	0.857	0.759	0.581	0.932	0.413	0.280
Solomon et al., 2001 *(32)*	HC2	256	11	1050	984	0.959	0.484	0.196	0.989	0.568	0.116
Zielinski et al., 2001 *(54)*	HC2	11	1	63	138	0.917	0.687	0.149	0.993	0.347	0.056

*VT = ViraType; VP = ViraPap; HC = Hybrid Capture.

sensitivities (34.8% and 25.4%, respectively) and high specificities (96.8% and 99.2%, respectively).

Forest Plots

We created forest plots for the accuracy of all HPV tests combined (Fig. 1, upper panel) and for the Hybrid Capture II assay alone (Fig. 1, lower panel). Interstudy variation in sensitivity and specificity among all the HPV testing methods combined was large. The heterogeneity associated with the sensitivity of the Hybrid Capture II assay was much less than that for all HPV testing methods combined. Variation in the specificity of the Hybrid Capture II assay was reduced but was still substantial due to the low value observed in the ALTS study *(32)*.

The heterogeneity associated with sensitivity of repeat cytology at the cutoffs ASCUS or worse and LSIL or worse and with specificity at cutoff ASCUS was large, whereas the interstudy variation in specificity at the cutoff LSIL or worse was substantially smaller. Fig. 2 clearly shows that changing the threshold from ASCUS or worse to LSIL or worse increased the sensitivity values and decreased the specificity values.

Table 4. Triage of atypical squamous cells of undetermined significance (ASCUS) by repeat cytology at cutoffs of ASCUS or worse, low-grade squamous intraepithelial lesion (LSIL) or worse, and high-grade squamous intraepithelial lesion (HSIL) or worse for the detection of histologically confirmed cervical intraepithelial neoplasia grade II or worse (CIN2+): number of true- and false-positives and true- and false-negatives, accuracy parameters, and test positivity rate derived from different published studies*

Study	Type	True-positive	False-negative	False-positive	True-negative	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Test positivity rate
					Cutoff of ASCUS or worse					
Goff et al., 1993 *(46)*	CP	3	2	75	91	0.600	0.548	0.038	0.978	0.456
Slawson et al., 1994 *(47)*	CP	10	5	35	71	0.667	0.670	0.222	0.934	0.372
Cox et al., 1995† *(18)*	CP	11	4	NA	NA	0.733	NA	NA	NA	NA
Wright et al., 1995 *(19)*	CP	8	3	81	89	0.727	0.524	0.090	0.967	0.492
Ferris et al., 1998 *(29)*	CP	7	3	88	71	0.700	0.447	0.074	0.959	0.562
Manos et al., 1999 *(49)*	ThinPr	48	15	324	570	0.762	0.638	0.129	0.974	0.389
Bergeron et al., 2000 *(50)*	CP	8	4	28	71	0.667	0.717	0.222	0.947	0.324
Morin et al., 2001 *(31)*	CP	14	5	126	214	0.737	0.629	0.100	0.977	0.390
Solomon et al., 2001 *(32)*	ThinPr	227	40	1132	914	0.850	0.447	0.167	0.958	0.588
					Cutoff of LSIL or worse					
Goff et al., 1993 *(46)*	CP	2	3	6	160	0.400	0.964	0.250	0.982	0.047
Cox et al., 1995† *(18)*	CP	8	7	NA	NA	0.533	NA	NA	NA	NA
Wright et al., 1995 *(19)*	CP	6	5	22	148	0.545	0.871	0.214	0.967	0.155
Ferris et al., 1998 *(29)*	CP	2	8	23	136	0.200	0.855	0.080	0.944	0.148
Manos et al., 1999 *(49)*	ThinPr	25	38	52	842	0.397	0.942	0.325	0.957	0.080
Morin et al., 2001 *(31)*	CP	8	11	22	318	0.421	0.935	0.267	0.967	0.084
Solomon et al., 2001 *(32)*	ThinPr	158	109	452	1593	0.592	0.779	0.259	0.936	0.264
					Cutoff of HSIL or worse					
Manos et al., 1999 *(49)*	ThinPr	16	47	7	887	0.254	0.992	0.696	0.950	0.024
Solomon et al., 2001 *(32)*	ThinPr	93	174	67	2002	0.348	0.968	0.581	0.920	0.068

*CP = conventional Pap smear; ThinPr = smear prepared using ThinPrep liquid-based technology. NA = data not available.

†Cox *(18)* was not included for computation of specificity of repeat cytology because of unavailability of data.

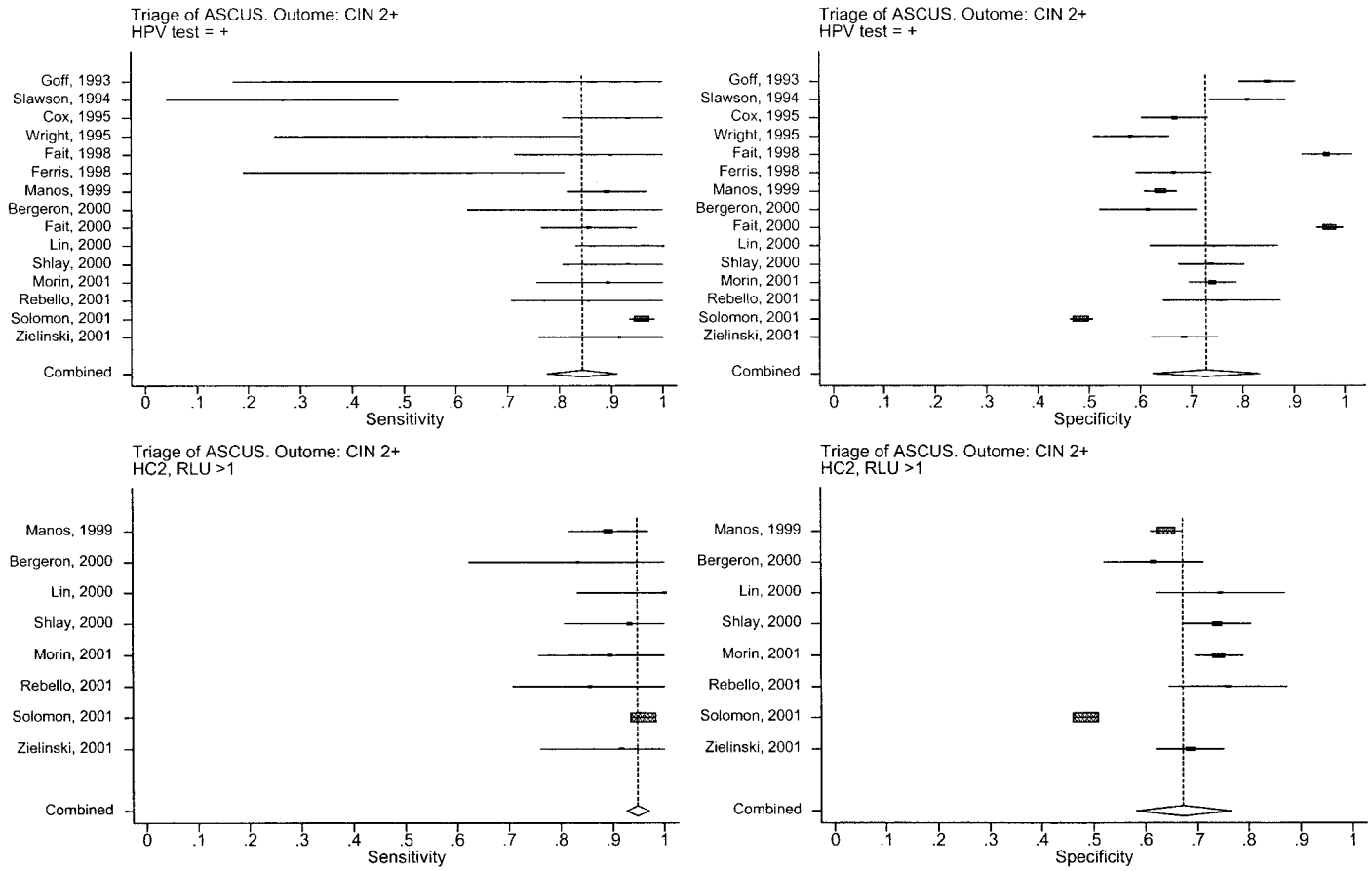

Fig. 1. Forest plots of the sensitivity and the specificity of human papillomavirus (HPV) DNA detection methods defined at the base level threshold for all 15 studies (**upper panel**) and for the eight studies in which the Hybrid Capture II assay was used (**lower panel**). The value of the plotted parameter is represented by a **rectangle**, the surface of which is proportional to the weight that the study contributes to the meta-analysis. The width of the horizontal line depicts the 95% confidence interval. The 95% confidence interval of the pooled estimate is displayed at the bottom as a **diamond**.

Meta-analysis

We computed pooled estimates of the sensitivity and specificity (diamonds in Figs. 1 and 2) and of predictive values and likelihood ratios (Table 5). Meta-analysis including all HPV tests yielded a pooled sensitivity of 84.4% (95% CI = 77.6% to 91.1%) and a specificity of 72.9% (95% CI = 62.5% to 83.3%). Consideration of just the eight studies *(31,32,43,49,50,52–54)* in which the Hybrid Capture II assay was used for the detection of high-risk HPV types yielded a sensitivity of 94.8% (95% CI = 92.7% to 96.9%) and a specificity of 67.3% (95% CI = 58.2% to 76.4%).

The sensitivity and specificity of repeat cytology at cutoff ASCUS or worse was 81.8% (95% CI = 73.5% to 84.3%) and 57.6% (95% CI = 49.5% to 65.7%), respectively. The sensitivity and specificity of repeat cytology at cutoff LSIL or worse were 45.7% (95% CI = 34.0% to 57.4%) and 89.1% (95% CI = 82.1% to 96.2%), respectively—substantially lower and higher than at a cutoff of ASCUS or worse.

The pooled ratio of the sensitivity of the Hybrid Capture II assay to the sensitivity of repeat cytology at cutoff ASCUS or worse, determined from four studies that evaluated both triage methods, was 1.16 (95% CI = 1.04 to 1.29), suggesting that the pooled sensitivity of the Hybrid Capture II assay was statistically significantly higher than that of repeat cytology at cutoff ASCUS or worse. The pooled specificity of the Hybrid Capture II assay was also higher, but the difference was not statistically significant (1.05, 95% CI = 0.96 to 1.15). Comparison of the Hybrid Capture II assay with repeat cytology at the respective cutoffs LSIL or worse and HSIL or worse yielded sensitivity ratios of 1.69 (95% CI = 1.54 to 1.85) and 2.80 (95% CI = 2.43 to 3.31), respectively, and specificity ratios of 0.71 (95% CI = 0.64 to 0.80) and 0.57 (95% CI = 0.44 to 0.74), respectively.

The negative likelihood ratio for the Hybrid Capture II assay was substantially lower than that for repeat cytology. The positive likelihood ratio for cytologic triage at cutoff LSIL or worse was substantially higher than that at cutoff ASCUS or worse because of its high specificity despite a low sensitivity. Both primary studies that provided data for cytologic triage at cutoff HSIL or worse *(32,49)* had extremely low sensitivity (meta-analysis data not shown).

The prevalence of CIN2+ ranged from 3% *(46)* to 36% *(52)*, with a pooled mean of 10.5% (95% CI = 7.9% to 13.1%). Studies in which women with repeated atypia were evaluated had the highest prevalence of CIN2+ *(52,53)*.

Influence of Study Characteristics

We determined the change in pooled sensitivity and specificity over technical and design variables for HPV DNA detection methods and repeat cytology at cutoff ASCUS or worse (Table 6). The sensitivity varied by viral test technique: it was low for

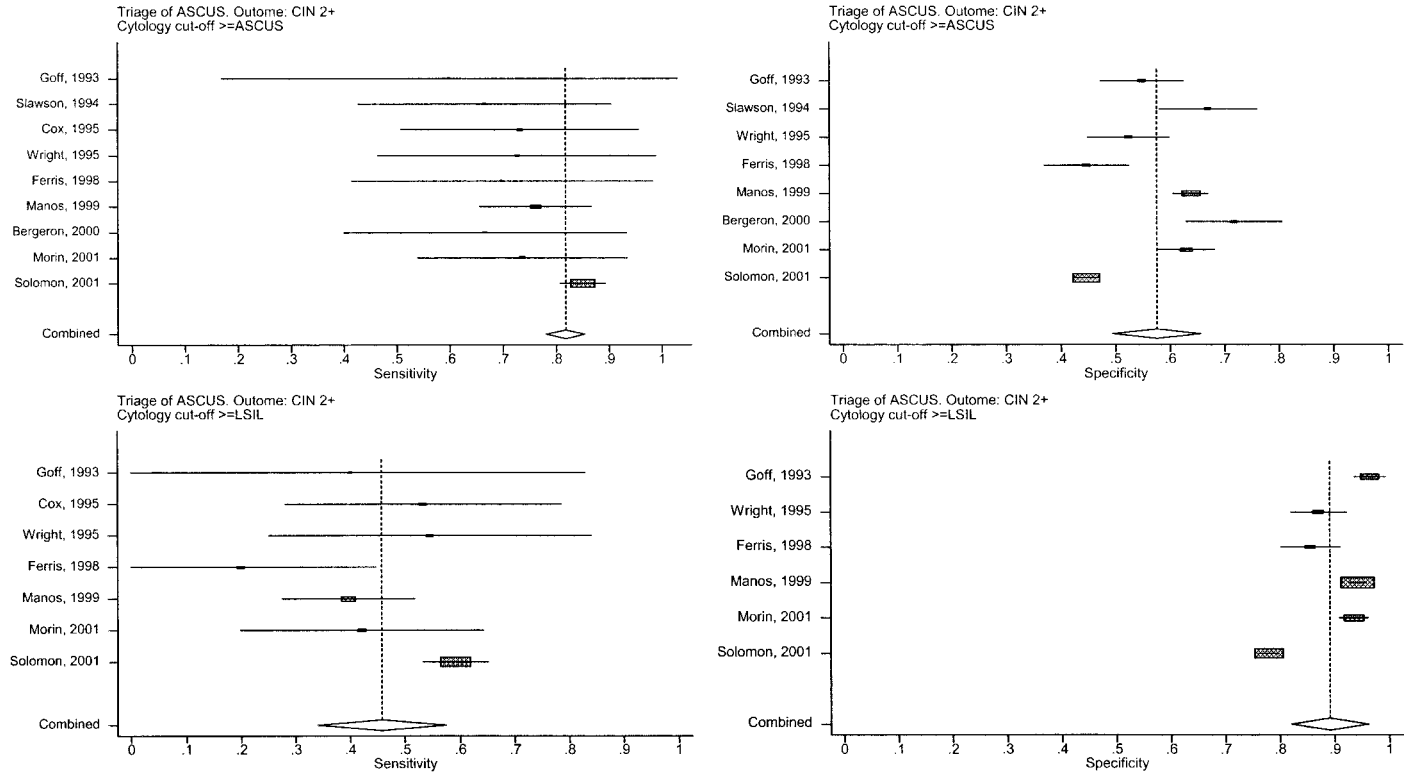

Fig. 2. Forest plots of the sensitivity and the specificity of repeat cytology defined at thresholds greater than or equal to atypical squamous cells of undetermined significance (≥ASCUS, **upper panel**) and greater than or equal to low-grade squamous intraepithelial lesion (≥LSIL, **lower panel**) for the presence of histologically confirmed cervical intraepithelial neoplasia grade II or worse (CIN2+).

Table 5. Summary of the meta-analyses of the accuracy of atypical squamous cells of undetermined significance (ASCUS) triage to predict the presence of cervical intraepithelial neoplasia grade II or worse (CIN2+): pooled estimates and confidence intervals, model of pooling, range (lowest to highest accuracy), and number of included studies*

Triage test	Test cutoff	Accuracy parameter	Model	Pooled estimate (95% CI)	Range	No. of studies
HPV DNA testing (all)	Positive signal	Sensitivity	R	0.844 (0.776 to 0.911)	0.267–1.000	15
		Specificity	R	0.729 (0.625 to 0.833)	0.484–0.971	15
		PPV	R	0.301 (0.203 to 0.398)	0.068–0.906	15
		NPV	R	0.985 (0.979 to 0.992)	0.887–1.000	15
		PLR	R	2.970 (2.380 to 3.690)	1.310–29.140	15
		NLR	R	0.240 (0.130 to 0.430)	0.010–0.660	14
HC2	RLU >1	Sensitivity	F	0.948 (0.927 to 0.969)	0.833–1.000	8
		Specificity	R	0.673 (0.582 to 0.764)	0.484–0.759	8
		PPV	R	0.264 (0.192 to 0.336)	0.149–0.906	8
		NPV	F	0.990 (0.985 to 0.994)	0.932–1.000	8
		PLR	R	2.820 (2.240 to 3.540)	1.860–3.920	8
		NLR	F	0.130 (0.090 to 0.190)	0.080–0.270	7
Repeat cytology	ASCUS	Sensitivity	F	0.818 (0.735 to 0.843)	0.600–0.850	9
		Specificity	R	0.576 (0.495 to 0.657)	0.447–0.717	8
		PPV	R	0.118 (0.076 to 0.159)	0.038–0.222	8
		NPV	F	0.967 (0.960 to 0.975)	0.934–0.987	8
		PLR	R	1.750 (1.490 to 2.060)	1.260–2.360	8
		NLR	F	0.390 (0.320 to 0.480)	0.340–0.730	8
	LSIL	Sensitivity	R	0.457 (0.340 to 0.574)	0.200–0.592	7
		Specificity	R	0.891 (0.821 to 0.962)	0.779–0.964	6
		PPV	R	0.232 (0.160 to 0.304)	0.080–0.325	6
		NPV	R	0.958 (0.943 to 0.974)	0.936–0.982	6
		PLR	R	4.440 (2.600 to 7.610)	1.380–11.070	6
		NLR	R	0.630 (0.520 to 0.770)	0.520–0.940	6

*CI = confidence interval; F = fixed model of pooling; HC = Hybrid Capture; HPV = human papillomavirus; LSIL = low-grade squamous intraepithelial lesion; NLR = negative likelihood ratio; NPV = negative predictive value; PLR = positive likelihood ratio; PPV = positive predictive value; R = random-effects model of pooling; RLU = relative light units.

Table 6. Variation of the sensitivity and specificity of human papillomavirus (HPV) DNA detection methods and repeat cytology by study characteristics*

Covariate	Sensitivity (95% CI)	Method†	Specificity (95% CI)	Method†
	HPV testing for an outcome of CIN2+			
HPV DNA detection method				
ViraPap, ViraType	0.381 (0.071 to 0.691)	R	0.836 (0.792 to 0.880)	F
HC1, HCT	0.788 (0.670 to 0.905)	R	0.789 (0.669 to 0.908)	R
HC2	0.948 (0.927 to 0.969)	F	0.673 (0.582 to 0.764)	R
Sampling device				
Dacron swab	0.635 (0.409 to 0.860)	R	0.756 (0.601 to 0.911)	R
Cone brush	0.919 (0.853 to 0.985)	F	0.701 (0.650 to 0.752)	R
Cotton applicator	0.900 (0.714 to 1.000)	B	0.965 (0.917 to 1.000)	B
Broom	0.936 (0.873 to 0.998)	R	0.562 (0.408 to 0.716)	R
Not documented	0.824 (0.542 to 1.000)	R	0.759 (0.609 to 0.928)	R
Transport medium				
ViraPap	0.570 (0.215 to 0.925)	R	0.682 (0.592 to 0.772)	R
STM	0.891 (0.839 to 0.944)	F	0.796 (0.689 to 0.902)	R
ThinPrep	0.936 (0.873 to 0.998)	R	0.562 (0.408 to 0.716)	R
Not documented	0.824 (0.542 to 1.000)	R	0.769 (0.609 to 0.928)	R
Year of publication				
≤1998	0.638 (0.395 to 0.881)	R	0.759 (0.638 to 0.880)	R
>1998	0.943 (0.923 to 0.964)	F	0.709 (0.564 to 0.854)	R
Quality review of histological outcome				
No	0.796 (0.696 to 0.896)	R	0.763 (0.680 to 0.847)	R
Yes	0.952 (0.930 to 0.975)	F	0.596 (0.470 to 0.721)	R
Blinding of outcome verification				
No	0.878 (0.811 to 0.944)	R	0.740 (0.578 to 0.902)	R
Yes	0.786 (0.624 to 0.949)	R	0.706 (0.650 to 0.762)	R
Clinical history: old CIN cases included				
No	0.920 (0.863 to 0.976)	R	0.658 (0.567 to 0.750)	R
Yes	0.754 (0.619 to 0.890)	R	0.790 (0.688 to 0.892)	R
Prevalence of CIN2+, %				
<10	0.859 (0.779 to 0.939)	R	0.698 (0.642 to 0.754)	R
≥10–<20	0.752 (0.487 to 1.000)	R	0.719 (0.442 to 0.996)	R
≥20	0.883 (0.812 to 0.953)	F	0.833 (0.658 to 1.000)	R
	Repeat cytology at cutoff ASCUS or worse for an outcome of CIN2+			
Sampling device				
Ayre and Cytobrush	0.712 (0.569 to 0.856)	F	0.619 (0.429 to 0.809)	R
Broom	0.820 (0.737 to 0.902)	R	0.542 (0.355 to 0.729)	R
Unknown	0.697 (0.569 to 0.825)	F	0.574 (0.482 to 0.665)	R
Year of publication				
≤1998	0.699 (0.579 to 0.819)	F	0.545 (0.460 to 0.630)	R
>1998	0.801 (0.728 to 0.873)	R	0.604 (0.476 to 0.733)	R
Preparation of smear				
Conventional	0.704 (0.608 to 0.799)	F	0.588 (0.513 to 0.663)	R
LBC	0.820 (0.737 to 0.902)	R	0.542 (0.355 to 0.729)	R
Quality review of histological outcome				
No	0.697 (0.591 to 0.803)	F	0.588 (0.513 to 0.660)	R
Yes	0.834 (0.795 to 0.873)	F	0.542 (0.355 to 0.729)	R
Blinding of outcome verification				
No	0.836 (0.795 to 0.876)	F	0.570 (0.467 to 0.673)	R
Yes	0.740 (0.656 to 0.825)	F	0.586 (0.463 to 0.708)	R
Clinical history, old CIN cases included				
No	0.828 (0.790 to 0.866)	F	0.541 (0.422 to 0.660)	R
Yes	0.677 (0.537 to 0.816)	F	0.612 (0.521 to 0.703)	R
Prevalence of CIN2+, %				
<10	0.742 (0.665 to 0.819)	F	0.563 (0.495 to 0.630)	R
≥10–<20	0.775 (0.636 to 0.914)	R	0.608 (0.411 to 0.804)	R

*CIN2+ = cervical intraepithelial neoplasia grade II or worse; ASCUS = atypical squamous cells of undetermined significance; HC1 = Hybrid Capture I assay; HCT = Hybrid Capture Tube test; HC2 = Hybrid Capture II assay; CI = confidence interval; STM = specimen transport medium; LBC = liquid-based cytology.

†A fixed (F) model was used for pooling. However, a random-effects pooling method (R) was chosen if the *P* value for the heterogeneity test >0.2, because the number of studies in the subgroups was often small. B = when only one study was concerned, confidence intervals were computed according to the binomial distribution.

ViraPap and ViraType (38.1%, 95% CI = 7.1% to 69.1%), higher for the Hybrid Capture I/Hybrid Capture Tube (78.8%, 95% CI = 67.0% to 90.5%), and even higher for the Hybrid Capture II assay (94.8%, 95% CI = 92.7% to 96.9%). The use of different HPV detection methods over time yielded a period effect for test sensitivity. The sensitivity of HPV DNA detection was also higher in studies in which a cervical broom or a conical brush was used for sample collection and in which the histologic

outcome was submitted to quality review. There was no difference in sensitivity or specificity among cytologic triage subgroups.

Differences in accuracy by age group could be assessed from only two studies *(33,43)* (data not shown). A statistically significant increase in specificity for triage with Hybrid Capture II and cytologic triage at a cutoff of ASCUS or worse and a statistically nonsignificant decrease in sensitivity for the Hybrid Capture II assay were observed with increasing age.

Publication Bias

We found a lower sensitivity for cytologic triage and a higher specificity for cytologic and virologic triage in smaller studies than in larger studies. This relation was, to a large extent, driven by the ALTS results *(32,33)*, which include younger women. However, no asymmetry was found when odds ratios of accuracy for HPV triage and repeat cytology were considered. We conclude that the selective publication of smaller studies did not affect our main conclusions.

Discussion

In this meta-analysis, we evaluated the accuracy of two triage tests used for women who had a previous equivocal Pap smear, focusing on the internal test validity parameters of sensitivity and specificity because of their more universal properties. We identified several sources of interstudy variability from the retrieved literature and identified potential biases that can affect the quality of the evaluation of test accuracy. Predictive values are dependent on local disease prevalence and therefore have limited generalizability. Likelihood ratios only have a relative value—for pooling data dependent on local prevalence—they are clinically less useful parameters than sensitivity and specificity parameters. For example, a high positive likelihood was found for triage at LSIL or worse due to a relatively high specificity (89%) despite a low sensitivity (46%).

Extent of Interstudy Heterogeneity

There was a wide range of sensitivities and specificities for cytologic triage. This was expected because the reproducibility of the cytologic interpretation of Pap smears is often reported as moderate to poor, especially for women with atypia or borderline disease *(68–70)*.

In the ALTS, only 32.4% of women with an original interpretation of ASCUS had a subsequent ASCUS result at enrollment, on average 2 months later *(71)*. In the other studies, the proportion of women with ASCUS at index and enrollment smears varied from 17% *(47)* to 41% *(29)*. The low reproducibility of cytology decreases the capacity to detect or to exclude intraepithelial disease and is likely to result in the variability in accuracy observed in the forest plots (Fig. 2). Accuracy varied even more for HPV triage methods than for cytology (Fig. 1), largely because of the use of different HPV DNA detection systems. It was therefore not recommended that they be combined into one pooled measure of HPV DNA testing. Nevertheless, it was useful to describe this variability among historical test systems, because we could clearly show that not all HPV DNA detection systems have the same accuracy. The sensitivity of the Hybrid Capture II assay showed low variability, reflecting the improved reliability of HPV DNA detection with the Hybrid Capture assay. Indeed, both the Hybrid Capture I and Hybrid Capture II assays have excellent reproducibility (unweighted kappa = 0.85 and 0.72, respectively) *(19,72)*.

Specificity for the Hybrid Capture II assay was consistent across studies, with the only exception being that it was considerably lower in the ALTS. A possible explanation is that the majority of women in the ALTS belong to younger age groups in whom HPV infection may be common in the absence of cervical lesions *(33,73)*.

Other HPV DNA Detection Methods

Certain authors applied additional HPV detection methods other than the Hybrid Capture assays. Morin et al. *(31)* used a polymerase chain reaction (PCR) amplifying a 450-base-pair sequence from the L1 region of the HPV genome, followed by a probe targeting 11 high-risk types. Compared with that of the Hybrid Capture II assay, the sensitivity of the PCR test to detect women with CIN2+ was equal (89.5% [95% CI = 66.9% to 98.7%]), but the specificity was substantially lower (59.0% [95% CI = 53.6% to 64.1%] for PCR versus 74.2% [95% CI = 69.2% to 78.8%] for the Hybrid Capture II assay). In a population of women with ASCUS or LSIL, Bergeron et al. *(50)* found a statistically nonsignificantly higher sensitivity for a PCR test that used MY9/11 HPV consensus primers (96%, 95% CI = 77% to 99%) than for the combined low- and high-risk probe of the Hybrid Capture II assay (86%, 95% CI = 65% to 97%), although the specificity for each test was similar (40% versus 41%). Bergeron et al. also used Southern blot hybridization to detect HPV, which was considerably more specific (65%, 95% CI = 60% to 71%) but also much less sensitive (46%, 95% CI = 24% to 68%) than PCR and the Hybrid Capture II assay. From Table 6, we conclude that certain HPV tests (ViraPap, ViraType, and Hybrid Capture I) cannot be recommended for triage of women with ASCUS. The performance of PCR-based systems is insufficiently documented in the ASCUS triage setting and needs further study.

Robustness of the Meta-analysis Results

This meta-analysis appears to corroborate the conclusions of the ALTS *(32,33,74)*. However, from the forest plots (Figs. 1 and 2), the results from the ALTS are rather extreme. Sensitivity values were 85.0% and 59.2% for triage at cutoffs ASCUS or worse and LSIL or worse, respectively, in the ALTS, but 81.8% (95% CI = 73.5% to 84.3%) and 45.7% (95% CI = 34.0% to 57.4%), respectively, in our meta-analysis. The specificity was 44.7% for repeat cytology at the threshold of ASCUS or worse in the ALTS and 57.6% (95% CI = 49.5% to 65.7%) in our meta-analysis. The sensitivity of the Hybrid Capture II assay was 95.9% in the ALTS and 94.8% (95% CI = 92.7% to 96.9%) in our pooled data, and its specificity was 48.4% in the ALTS and 67.3% (95% CI = 58.2% to 76.4%) in our pooled data.

To investigate whether the difference in sensitivity between repeat cytology and Hybrid Capture II assay was influenced by the ALTS results, we repeated the meta-analysis excluding the ALTS results. A meta-analysis considering only three studies *(31,49,50)* resulted in a pooled sensitivity ratio of 1.18 (95% CI = 1.03 to 1.36) and a pooled specificity ratio of 1.03 (95% CI = 0.89 to 1.19). Thus, inclusion of the ALTS data did not influence the pooled relative accuracy values.

Verification Bias

Because colposcopy was performed on every woman, with the exception of those in the ALTS, there was no verification bias in our analysis. In the ALTS, results from women in the HPV arm were not verified if the Hybrid Capture II assay was negative, if results from repeat cytology ranged from normal to LSIL, or if no suspect macroscopic lesions were observed. However, colposcopy was performed on all women in a second arm of the ALTS. Because the 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, we conclude that there is no evidence of verification bias in the ALTS that could have potentially influenced our results.

Validity of the Gold Standard

We used colposcopy and histology as the gold standard test. An imperfect gold standard can influence the estimation of the sensitivity and specificity of a triage test, which can be assessed by examining the variation of accuracy by disease prevalence *(75)*. However, the accuracy did not change substantially, even over wide ranges of disease prevalence (Table 6). The sensitivity was higher when the colposcopist was aware of the triage test results (for repeat cytology at cutoff ASCUS or worse: 81% if unmasked versus 73% if masked; for HPV triage: 88% if unmasked versus 79% if masked). Although this difference was not statistically significant, it suggests variability in the validity of the gold standard. The specificities were similar for masked and unmasked evaluations.

Low Specificity of All Triage Methods

The specificity of triage with the Hybrid Capture II assay or by repeat Pap smears at a low cytologic threshold was moderate to poor. Colposcopy of all triage-positive women generates considerable costs. Therefore, there is a need for more specific tests with high predictive value that allow for the identification of women at increased risk for cervical cancer. Nevertheless, a recent cost–effectiveness simulation study of alternative scenarios for ASCUS management *(76)* indicated that Hybrid Capture II is more effective and cost-effective than repeat cytology. HPV DNA testing can be done on residual fluid if liquid-based cytology is performed or if an additional sample is collected with the first smear, both of which reduce costs. In contrast, repeat cytology requires multiple visits *(77)*. When evaluating the cost–effectiveness of HPV-based triage, it should be noted that the specificity of the test is highly age-dependent and that cost may therefore vary depending on the age of the population to be screened.

Cross-sectional Outcome: Detection of CIN2+

Our analysis was restricted to studies documenting accuracy of triage methods for the presence of moderate dysplasia or worse (CIN2+). In a subsequent study, we will assess triage considering severe dysplasia and carcinoma *in situ* (CIN3) as the outcome. CIN3+ may be a more relevant endpoint because its potential to regress spontaneously is more limited than in CIN2 *(15,78,79)*.

Our meta-analysis was further restricted to cross-sectional outcomes in which sensitivity and specificity were measured against a simultaneously applied gold standard (colposcopically directed biopsy). Longitudinal studies are required to assess the possibility of detecting missed lesions by repeat cytology before invasive cancer occurs *(80)*. The ALTS group recently published their longitudinal trial outcomes, defined in terms of cumulative incidence of histologic CIN3+ over a period of 2 years, in which all subjects were followed at 6-month intervals and finally submitted to a colposcopy/histology check-up *(81)*. The longitudinal sensitivity of HPV DNA testing only at enrollment for cumulative CIN3+ was estimated to be 92.4% (95% CI = 88.7% to 95.2%). Testing ASCUS women only once with Hybrid Capture II required referral of 53.1% (95% CI = 51.4% to 54.8%) of women in the HPV triage arm. However, repeat cytology at every visit with a threshold of ASCUS would potentially detect 97.2% (95% CI = 94.1% to 100%) of the cumulative CIN3+ cases. This repeat cytology scenario would refer 73% (95% CI = 70.1% to 75.4%) of all women for colposcopy and would require multiple successive visits and cytologic examinations. Nevertheless, our meta-analysis of cross-sectional accuracy for CIN2+ is relevant because women with ASCUS require a follow-up decision and CIN2+ is the usual threshold for treatment.

Delineation of the Categories of Atypical Squamous Cells According to the 2001 Bethesda Reporting System

Our meta-analysis concerns women with a previous interpretation of ASCUS, such as that defined at the 1988 and 1991 Bethesda Workshops *(35,82)*. In 2001, a new version of the Bethesda Reporting System for Cervical Cytology was adopted that proposed a change in the subdivision of the global ASCUS class from three to two classes: ASC-US (atypical squamous cells of undetermined significance) and ASC-H (atypical squamous cells, HSIL cannot be ruled out) *(35,83)*. According to the new reporting system, the previous classification of atypical squamous cells favoring a benign reactive process (ASC-R) is now classified as negative for intraepithelial lesions or malignancy. The American Society for Colposcopy and Cervical Pathology has also recently updated its guidelines for the management of cervical cytologic abnormalities according to the new Bethesda terminology. Detection of high-risk HPV DNA was proposed as the first choice for triage of women with a liquid-based cytology result of ASC-US, whereas direct referral for colposcopic exploration is proposed as the optimal approach for women with ASC-H *(84,85)*. ASC-H is estimated to account for approximately 5%–10% of the ASC category *(83,86–88)*. In the ALTS, the prevalence of high-risk HPV types in the ASC-H group was 86%, and the proportion of women with ASC-H that contained CIN2+ was 41% *(87)*. HPV triage is therefore redundant for women with ASC-H.

It is not clear to what extent the elimination of ASC-R from the equivocal neoplastic changes will modify the conclusions of our meta-analysis. ASC-R account for approximately 20%–50% of all ASCUS results in U.S. women and a lower percentage in European women *(87–91)*. Because the prevalence of high-risk HPV types in ASC-R lesions is substantially lower than in other ASC lesions and because the positive predictive value of ASC-R for high-grade disease is minimal, HPV triage is probably not cost-effective for women with ASC-R results.

The accuracy of high-risk HPV DNA detection for triage of women with ASC results defined according to the 2001 Be-

thesda Reporting System guidelines is insufficiently documented. Nevertheless, we expect that restricting HPV triage to women with ASC-US will reduce the volume of HPV testing and considerably optimize its efficiency in the detection of women with CIN2+.

Recent Reviews and Meta-analyses

HPV triage has recently been reviewed *(28,92,93)*. Cuzick et al. *(28)* concluded that the available evidence did not support recommending widespread HPV testing in primary screening but that limited use, such as in management of women with borderline results, might be suggested. In the 2002 update of the French guidelines for management of women with cytologic abnormalities *(92)*, high-risk HPV DNA testing is recommended in triage of women with ASC-US. The Australian Medical Services Advisory Committee team reviewed literature regarding the management of women with low-grade epithelial abnormalities (LGEA) and concluded that there was insufficient evidence to support reimbursement for HPV triage of LGEA *(93)*. The authors remarked that international data did not match the particular Australian cytologic reporting system and that throughout the cytologic literature different thresholds for triage tests and outcomes were used, which made pooling data difficult *(93)*. However, no effort was made to pool data by separate test thresholds and histologic outcomes. The Australian LGEA category encompasses essentially low-grade squamous intraepithelial lesions. Our meta-analysis concerned the triage of women with ASCUS and not women with LSIL. However, in another systematic review *(34)* and also in the ALTS *(33,94,95)* it was found that HPV triage for LSIL had limited use because the test positivity rate was too high. Disparities between the Australian review and ours are likely the result of differences in the inclusion criteria for the index smear.

In conclusion, evidence is available indicating improved cross-sectional sensitivity of the Hybrid Capture II assay in comparison with the repeat Pap smear considered at cutoff ASCUS or worse for the outcome of high-grade CIN among women with equivocal cytologic results. The specificity of both triage methods is low. Cytologic triage of women with ASCUS that considers higher cytologic cutoffs yields unacceptably low sensitivity. We conclude that the Hybrid Capture II assay is a better triage method than repeat cytology for women with ASCUS.

References

(1) Franco EL, Rohan TE, editors. Cancer precursors. Epidemiology, detection and prevention. New York (NY): Springer-Verlag; 2002. p. 1–430.

(2) Kurman RJ, Henson DE, Herbst AL, Noller KL, Schiffman MH. Interim guidelines for management of abnormal cervical cytology. The 1992 National Cancer Institute Workshop. JAMA 1994;271:1866–9.

(3) Cox JT. HPV testing: is it useful in triage of minor Pap abnormalities? J Fam Pract 1998;46:121–4.

(4) Robertson JH, Woodend BE, Crozier EH, Hutchinson J. Risk of cervical cancer associated with mild dyskaryosis. BMJ 1988;297:18–21.

(5) Coleman D, Day N, Douglas G, Farmery E, Lynge E, Philip J, et al. European Guidelines for Quality Assurance in Cervical Cancer Screening. Europe against cancer programme. Eur J Cancer 1993;29A Suppl 4:S1–38.

(6) Flannelly G, Anderson D, Kitchener HC, Mann EM, Campbell M, Fisher P, et al. Management of women with mild and moderate cervical dyskaryosis. BMJ 1994;308:1399–403.

(7) Arbyn M, Albertyn G, De Groof V. Consensus on follow-up recommendations in cervical cancer screening (in Dutch). Tijdschr voor Geneeskunde 1996;52:709–15.

(8) Noumoff JS. Atypia in cervical cytology as a risk factor for intraepithelial neoplasia. Am J Obstet Gynecol 1987;156:628–31.

(9) Richart RM. Causes and management of cervical intraepithelial neoplasia. Cancer 1987;60(8 Suppl):1951–9.

(10) Richart RM, Wright TC Jr. Controversies in the management of low-grade cervical intraepithelial neoplasia. Cancer 1993;71(4 Suppl):1413–21.

(11) Soutter WP. Management of women with mild dyskaryosis. Immediate referral to colposcopy is safer. BMJ 1994;309:591–2.

(12) Ferenczy A. Viral testing for genital human papillomavirus infections: recent progress and clinical potentials. Int J Gynecol Cancer 1995;5:321–8.

(13) Wilkinson C, Jones JM, McBride J. Anxiety caused by abnormal result of cervical smear test: a controlled trial. BMJ 1990;300:440.

(14) Narod SA, Thompson DW, Jain M, Wall C, Green LM, Miller AB. Dysplasia and the natural history of cervical cancer: early results of the Toronto Cohort Study. Eur J Cancer 1991;27:1411–6.

(15) Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. Int J Gynecol Pathol 1993;12:186–92.

(16) Melnikow J, Nuovo J, Willan AR, Chan BK, Howell LP. Natural history of cervical squamous intraepithelial lesions: a meta-analysis. Obstet Gynecol 1998;92:727–35.

(17) Murdoch JB, Grimshaw RN, Morgan PR, Monaghan JM. The impact of loop diathermy on management of early invasive cervical cancer. Int J Gynecol Cancer 1992;2:129–33.

(18) Cox JT, Lorincz AT, Schiffman MH, Sherman ME, Cullen A, Kurman RJ. Human papillomavirus testing by hybrid capture appears to be useful in triaging women with a cytologic diagnosis of atypical squamous cells of undetermined significance. Am J Obstet Gynecol 1995;172:946–54.

(19) Wright TC, Sun XW, Koulos J. Comparison of management algorithms for the evaluation of women with low-grade cytologic abnormalities. Obstet Gynecol 1995;85:202–10.

(20) Kinney WK, Manos MM, Hurley LB, Ransley JE. Where's the high-grade cervical neoplasia? The importance of minimally abnormal Papanicolaou diagnoses. Obstet Gynecol 1998;91:973–6.

(21) zur Hausen H. Molecular pathogenesis of cancer of the cervix and its causation by specific human papillomavirus types. Curr Top Microbiol Immunol 1994;186:131–56.

(22) Bosch FX, Manos MM, Munoz N, Sherman M, Jansen AM, Peto J, et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International Biological Study on Cervical Cancer (IBSCC) Study Group. J Natl Cancer Inst 1995;87:796–802.

(23) Munoz N. Human papilloma virus and cervical cancer: epidemiological evidence. In: Franco E, Monsonego J, editors. New developments in cervical cancer screening and prevention. Oxford (UK): Blackwell Science; 1997. p. 3–13.

(24) Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999;189:12–9.

(25) Bosch FX, Lorincz A, Munoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol 2002; 55:244–65.

(26) Kaufman RH, Adam E. Does typing of human papillomavirus assist in the triage of women with repeated low-grade, cervical cytologic abnormalities? Gynecol Oncol 1998;70:317–8.

(27) Kaufman RH, Adam E. Is human papillomavirus testing of value in clinical practice? Am J Obstet Gynecol 1999;180:1049–53.

(28) Cuzick J, Sasieni P, Davies P, Adams J, Normand C, Frater A, et al. A systematic review of the role of human papillomavirus testing within a cervical screening programme. Health Technol Assess 1999;3:i–iv, 1–196.

(29) Ferris DG, Wright TC Jr, Litaker MS, Richart RM, Lorincz AT, Sun XW, et al. Triage of women with ASCUS and LSIL on Pap smear reports: management by repeat Pap smear, HPV DNA testing, or colposcopy? J Fam Pract 1998;46:125–34.

(30) Ferris DG, Wright TC Jr, Litaker MS, Richart RM, Lorincz AT, Sun XW, et al. Comparison of two tests for detecting carcinogenic HPV in women with Papanicolaou smear reports of ASCUS and LSIL. J Fam Pract 1998; 46:136–41.

(31) Morin C, Bairati I, Bouchard C, Fortier M, Roy M, Moore L, et al. Managing atypical squamous cells of undetermined significance in Papanicolaou smears. J Reprod Med 2001;46:799–805.
(32) Solomon D, Schiffman M, Tarone R; ALTS Study group. Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. J Natl Cancer Inst 2001;93:293–9.
(33) Sherman ME, Schiffman M, Cox JT; Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study Group. Effects of age and human papilloma viral load on colposcopy triage: data from the randomized Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study (ALTS). J Natl Cancer Inst 2002;94:102–7.
(34) Arbyn M, Buntinx F, Van Ranst M, Cortiñas Abrahantes J. Triage of women with atypical or low-grade cytological abnormalities of the cervix by HPV testing: systematic review and meta-analysis. Brussels (Belgium): Institute of Public Health/Epidemiology Reports No. 2001–019[D/2001/2505/34]. 2002. p. 1–244.
(35) Luff RD. The Bethesda System for reporting cervical/vaginal cytologic diagnoses: report of the 1991 Bethesda workshop. The Bethesda System Editorial Committee. Hum Pathol 1992;23:719–21.
(36) Richart RM. Cervical intraepithelial neoplasia. Pathol Annu 1973;8:301–28.
(37) Galbraith RF. A note on graphical presentation of estimated odds ratios from several clinical trials. Stat Med 1988;7:889–94.
(38) Light RJ, Singer JD, Willet JB. The visual presentation and interpretation of meta-analysis. In: Cooper H, editor. The handbook of research synthesis. New York (NY): Russell Sage Foundation; 1994. p. 439–54.
(39) Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. Methods for meta-analysis in medical research. Chichester (UK): John Wiley & Sons, Ltd.; 2000. p. 1–317.
(40) Cochran WG. The combination of estimates from different experiments. Biometrics 1954;10:101–29.
(41) Dersimonian R, Laird NM. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
(42) Sharp S, Sterne J. Meta-analysis. Stata Technical Bulletin 1997;38:9–14.
(43) Shlay JC, Dunn T, Byers T, Baron AE, Douglas JM Jr. Prediction of cervical intraepithelial neoplasia grade 2–3 using risk assessment and human papillomavirus testing in women with atypia on Papanicolaou smears. Obstet Gynecol 2000;96:410–6.
(44) Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
(45) Steichen TJ. Tests for publication bias in meta-analysis. Stata Technical Bulletin 1998;7:125–33.
(46) Goff BA, Muntz HG, Bell DA, Wertheim I, Rice LW. Human papillomavirus typing in patients with Papanicolaou smears showing squamous atypia. Gynecol Oncol 1993;48:384–8.
(47) Slawson DC, Bennett JH, Simon LJ, Herman JM. Should all women with cervical atypia be referred for colposcopy: a HARNET study. Harrisburgh Area Research Network. J Fam Pract 1994;38:387–92.
(48) Fait G, Daniel Y, Kupferminc MJ, Lessing JB, Niv J, Bar-Am A. Does typing of human papillomavirus assist in the triage of women with repeated low-grade, cervical cytologic abnormalities? Gynecol Oncol 1998;70:319–22.
(49) Manos MM, Kinney WK, Hurley LB, Sherman ME, Shieh-Ngai J, Kurman RJ, et al. Identifying women with cervical neoplasia: using human papillomavirus DNA testing for equivocal Papanicolaou results. JAMA 1999;281:1605–10.
(50) Bergeron C, Jeannel D, Poveda J, Cassonnet P, Orth G. Human papillomavirus testing in women with mild cytologic atypia. Obstet Gynecol 2000;95:821–7.
(51) Fait G, Kupferminc MJ, Daniel Y, Geva E, Ron IG, Lessing JB, et al. Contribution of human papillomavirus testing by hybrid capture in the triage of women with repeated abnormal pap smears before colposcopy referral. Gynecol Oncol 2000;79:177–80.
(52) Lin CT, Tseng CJ, Lai CH, Hsueh S, Huang HJ, Law KS. High-risk HPV DNA detection by Hybrid Capture II. An adjunctive test for mildly abnormal cytologic smears in women > or = 50 years of age. J Reprod Med 2000;45:345–50.
(53) Rebello G, Hallam N, Smart G, Farquharson D, McCafferty J. Human papillomavirus testing and the management of women with mildly abnormal cervical smears: an observational study. BMJ 2001;322:893–4.
(54) Zielinski DG, Snijders PJ, Rozendaal L, Voorhorst FJ, Runsink AP, de Schipper FA, et al. High-risk HPV testing in women with borderline and mild dyskaryosis: long-term follow-up data and clinical relevance. J Pathol 2001;195:300–6.
(55) Cox JT, Schiffman MH, Winzelberg AJ, Patterson JM. An evaluation of human papillomavirus testing as part of referral to colposcopy clinics. Obstet Gynecol 1992;80:389–95.
(56) Hatch KD, Schneider A, Abdel-Nour MW. An evaluation of human papillomavirus testing for intermediate- and high-risk types as triage before colposcopy. Am J Obstet Gynecol 1995;172:1150–5; discussion 1155–7.
(57) Herrington CS, Evans MF, Hallam NF, Charnock FM, Gray W, McGee JD. Human papillomavirus status in the prediction of high-grade cervical intraepithelial neoplasia in patients with persistent low-grade cervical cytological abnormalities. Br J Cancer 1995;71:206–9.
(58) Ferenczy A, Franco E, Arseneau J, Wright TC, Richart RM. Diagnostic performance of Hybrid Capture human papillomavirus deoxyribonucleic acid assay combined with liquid-based cytologic study. Am J Obstet Gynecol 1996;175:651–6.
(59) Hall S, Lorincz A, Shah F, Sherman ME, Abbas F, Paull G, et al. Human papillomavirus DNA detection in cervical specimens by hybrid capture: correlation with cytologic and histologic diagnoses of squamous intraepithelial lesions of the cervix. Gynecol Oncol 1996;62:353–9.
(60) Bollen LJ, Tjong-A-Hung SP, Van der Velden J, Brouwer K, Mol BW, ten Kate FJ, et al. Human papillomavirus deoxyribonucleic acid detection in mildly or moderately dysplastic smears: a possible method for selecting patients for colposcopy. Am J Obstet Gynecol 1997;177:548–53.
(61) Kaufman RH, Adam E, Icenogle J, Reeves WC. Human papillomavirus testing as triage for atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesions: sensitivity, specificity, and cost-effectiveness. Am J Obstet Gynecol 1997;177:930–6.
(62) Kaufman RH, Adam E, Icenogle J, Lawson H, Lee N, Reeves KO, et al. Relevance of human papillomavirus screening in management of cervical intraepithelial neoplasia. Am J Obstet Gynecol 1997;176:87–92.
(63) Adam E, Kaufman RH, Berkova Z, Icenogle J, Reeves WC. Is human papillomavirus testing an effective triage method for detection of high-grade (grade 2 or 3) cervical intraepithelial neoplasia? Am J Obstet Gynecol 1998;178:1235–44.
(64) Nyirjesy I, Billingsley FS, Forman MR. Evaluation of atypical and low-grade cervical cytology in private practice. Obstet Gynecol 1998;92:601–7.
(65) Lytwyn A, Sellors JW, Mahony JB, Daya D, Chapman W, Ellis N, et al. Comparison of human papillomavirus DNA testing and repeat Papanicolaou test in women with low-grade cervical cytologic abnormalities: a randomized trial. HPV Effectiveness in Lowgrade Paps (HELP) Study No. 1 Group. CMAJ 2000;163:701–7.
(66) Mould TA, Singer A, Gallivan S. Quantitative detection of oncogenic HPV DNA using hybrid capture to triage borderline and mildly dyskaryotic Papanicolaou smears. Eur J Gynaecol Oncol 2000;21:245–8.
(67) Lorincz AT. Methods of DNA hybridisation and their clinical applicability to human papillomavirus detection. In: Franco E, Monsonego J, editors. New developments in cervical cancer screening and prevention. Oxford (UK): Blackwell Science; 1997. p. 325–37.
(68) O'Sullivan JP, Ismail SM, Barnes WS, Deery AR, Gradwell E, Harvey JA, et al. Interobserver variation in the diagnosis and grading of dyskaryosis in cervical smears: specialist cytopathologists compared with non-specialists. J Clin Pathol 1994;47:515–8.
(69) Sherman ME, Schiffman MH, Lorincz AT, Manos MM, Scott DR, Kuman RJ, et al. Toward objective quality assurance in cervical cytopathology. Correlation of cytopathologic diagnoses with detection of high-risk human papillomavirus types. Am J Clin Pathol 1994;102:182–7.
(70) Gatscha RM, Abadi M, Babore S, Chhieng D, Miller MJ, Saigo PE. Smears diagnosed as ASCUS: interobserver variation and follow-up. Diagn Cytopathol 2001;25:138–40.
(71) Stoler MH, Schiffman M; Atypical Squamous Cells of Undetermined Significance-Low-grade Squamous Intraepithelial Lesion Triage Study (ALTS) Group. Interobserver reproducibility of cervical cytologic and histologic interpretations: realistic estimates from the ASCUS-LSIL Triage Study. JAMA 2001;285:1500–5.

(72) Castle PE, Lorincz AT, Mielzynska-Lohnas I, Scott DR, Glass AG, Sherman ME, et al. Results of human papillomavirus DNA testing with the hybrid capture 2 assay are reproducible. J Clin Microbiol 2002;40:1088–90.
(73) Woodman CB, Collins S, Winter H, Bailey A, Ellis J, Prior P, et al. Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. Lancet 2001;357:1831–6.
(74) Schiffman M, Adrianza ME. ASCUS-LSIL Triage Study. Design, methods and characteristics of trial participants. Acta Cytol 2000;44:726–42.
(75) Boyko EJ. Re: "Meta-analysis of Pap test accuracy". Am J Epidemiol 1996;143:406–7.
(76) Kim JJ, Wright TC, Goldie SJ. Cost-effectiveness of alternative triage strategies for atypical squamous cells of undetermined significance. JAMA 2002;287:2382–90.
(77) Wright TC Jr, Lorincz A, Ferris DG, Richart RM, Ferenczy A, Mielzynska I, et al. Reflex human papillomavirus deoxyribonucleic acid testing in women with abnormal Papanicolaou smears. Am J Obstet Gynecol 1998; 178:962–6.
(78) Morrison SA. Screening in chronic disease. In: Kelsey JL, Marmot MG, Stolley PD, Vessey MP, editors. Series Monogr Epidemiol Biostat. Vol 19. 2nd ed. Oxford (UK): Oxford University Press; 1992. p. 1–254.
(79) Schiffman M, Kjaer SK. Chapter 2: Natural history of anogenital human papillomavirus infection and neoplasia. J Natl Cancer Inst Monogr 2003; 31:14–9.
(80) Sherman ME, Wang SS, Tarone R, Rich L, Schiffman M. Histopathologic extent of cervical intraepithelial neoplasia 3 lesions in the atypical squamous cells of undetermined significance low-grade squamous intraepithelial lesion triage study: implications for subject safety and lead-time bias. Cancer Epidemiol Biomarkers Prev 2003;12:372–9.
(81) ASCUS-LSIL Triage Study (ALTS) Group. Results of a randomized trial on the management of cytology interpretations of atypical squamous cells of undetermined significance. Am J Obstet Gynecol 2003;188:1383–92.
(82) The 1988 Bethesda System for reporting cervical/vaginal cytologic diagnoses. National Cancer Institute Workshop. JAMA 1989;262:931–4.
(83) Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA 2002;287:2114–9.
(84) Wright TC Jr, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ; ASCCP-Sponsored Consensus Conference. 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. JAMA 2002;287:2120–9.
(85) Stoler MH. New Bethesda terminology and evidence-based management guidelines for cervical cytology findings. JAMA 2002;287:2140–1.
(86) Sherman ME, Tabbara SO, Scott DR, Kurman RJ, Glass AG, Manos MM, et al. "ASCUS, rule out HSIL": cytologic features, histologic correlates, and human papillomavirus detection. Mod Pathol 1999;12:335–42.
(87) Sherman ME, Solomon D, Schiffman M; ASCUS LSIL Triage Study Group. Qualification of ASCUS. A comparison of equivocal LSIL and equivocal HSIL cervical cytology in the ASCUS LSIL Triage Study. Am J Clin Pathol 2001;116:386–94.
(88) Quddus MR, Sung CJ, Steinhoff MM, Lauchlan SC, Singer DB, Hutchinson ML. Atypical squamous metaplastic cells: reproducibility, outcome, and diagnostic features on ThinPrep Pap test. Cancer 2001;93:16–22.
(89) Quddus MR, Zhang S, Sung CJ, Liu F, Neves T, Struminsky J, et al. Utility of HPV DNA detection in thin-layer, liquid-based tests with atypical squamous metaplasia. Acta Cytol 2002;46:808–12.
(90) Hughes SA, Sun D, Gibson C, Bellerose B, Rushing L, Chen H, et al. Managing atypical squamous cells of undetermined significance (ASCUS): human papillomavirus testing, ASCUS subtyping, or follow-up cytology? Am J Obstet Gynecol 2002;186:396–403.
(91) Scott DR, Hagmar B, Maddox P, Hjerpe A, Dillner J, Cuzick J, et al. Use of human papillomavirus DNA testing to compare equivocal cervical cytologic interpretations in the United States, Scandinavia, and the United Kingdom. Cancer 2002;96:14–20.
(92) Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES). Management of a patient with an abnormal cervical smear. Service Recommandations et Références Professionnelles et Service Evaluation Economique. Paris (France): ANAES; 2002. p. 1–92.
(93) Medical Services Advisory Committee (MSAC). Human papillomavirus testing in women with cytological prediction of low-grade abnormality. MSAC reference 12b, Canberra (Australia): 2003. p. 1–97.
(94) Human papillomavirus testing for triage of women with cytologic evidence of low-grade squamous intraepithelial lesions: baseline data from a randomized trial. The Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study (ALTS) Group. J Natl Cancer Inst 2000;92:397–402.
(95) ASCUS-LSIL Triage Study (ALTS) Group. A randomized trial on the management of low-grade squamous intraepithelial lesion cytology interpretations. Am J Obstet Gynecol 2003;188:1393–400.

NOTES

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