REVIEW

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Genotyping for Human Papillomavirus Types 16 and 18 in Women With Minor Cervical Lesions

A Systematic Review and Meta-analysis

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Background: High-risk human papillomavirus (hrHPV) testing to triage women with minor cervical lesions generates many referrals.

Purpose: To evaluate the accuracy of genotyping for HPV types 16 and 18 and its utility as a second triage step after hrHPV testing in women with minor cervical lesions.

Data Sources: Searches of 4 bibliographic databases, without language restrictions, from 1 January 1999 to 1 February 2016.

Study Selection: Studies involving women with atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesions (LSIL) who were triaged with tests for hrHPV and HPV 16/18 to find cervical intraepithelial neoplasia (grade ≥2 [CIN2+] or grade ≥3 [CIN3+]).

Data Extraction: Independent study selection, extraction of data, and quality assessment by 2 reviewers.

Data Synthesis: Twenty-four moderate- to good-quality studies involving 8587 women with ASC-US and 5284 with LSIL were found. The pooled sensitivity of HPV 16/18 genotyping for CIN3+ was about 70% for women with either ASC-US or LSIL. The pooled specificity (with a threshold of grade <2 CIN) was 83% (95% CI, 80% to 86%) for women with ASC-US and 76% (CI, 74% to 79%) for those with LSIL. The average risk for CIN3+ was 17% and 19% in HPV 16/18–positive women with ASC-US and LSIL, respectively, and was 5% in hrHPV-positive but HPV 16/18–negative women with either ASC-US or LSIL.

Limitation: Methodological and technical heterogeneity among studies; insufficient data to assess accuracy of separate assays.

Conclusion: Testing for HPV 16/18 to triage women with minor abnormal cytology is poorly sensitive but may be useful as a second triage test after hrHPV testing, with direct referral if the woman is positive for HPV 16/18. Whether colposcopy or repeated testing is recommended for hrHPV-positive but HPV 16/18–negative women depends on local decision thresholds that can be derived from pretest–posttest probability plots.

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Several countries have switched to human papillomavirus (HPV)–based screening for cervical cancer, but cytologic examination of a Papanicolaou (Pap) smear remains the primary form of cervical cancer screening in many other countries. Direct referral for diagnostic work-up with colposcopy and biopsy is usually recommended for women with high-grade lesions. However, women with minor cytologic abnormalities, including atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesions (LSIL), have only a modestly increased risk for cervical cancer (1). In the past, repeating the Pap test (repeated cytology) was the recommended follow-up for women with ASC-US or LSIL. Given the strong etiologic link between high-risk HPV (hrHPV) infection and cervical cancer, hrHPV testing has been proposed as an alternative triage method for women with equivocal or mildly abnormal cytology.

Randomized trials and systematic reviews show that, compared with repeated cytology, hrHPV testing has higher sensitivity and similar specificity in identifying underlying or incipient cervical precancer in women with ASC-US (2–4). Accordingly, triage by hrHPV testing has become standard practice (5–8). Low-grade squamous intraepithelial lesions are associated with a risk for precancer similar to that among hrHPV-positive women with ASC-US (9). Because most women with LSIL test positive for hrHPV (10), triage by hrHPV testing is inefficient (11, 12). The widespread practice of referring all women with hrHPV infection and ASC-US or with LSIL to colposcopy carries a considerable burden and cost. Because HPV types 16 and 18 cause about 70% of cervical cancer cases (8), genotyping for these types has been proposed as an additional tool to allow more fine-tuned management.

In this article, we present the results of a systematic review on the accuracy of genotyping for HPV types 16 and 18 to triage women with ASC-US or LSIL, including those who are hrHPV-positive. We also present a framework to assess the clinical utility of triage tests, based on the risk for cervical precancer before and after triage.

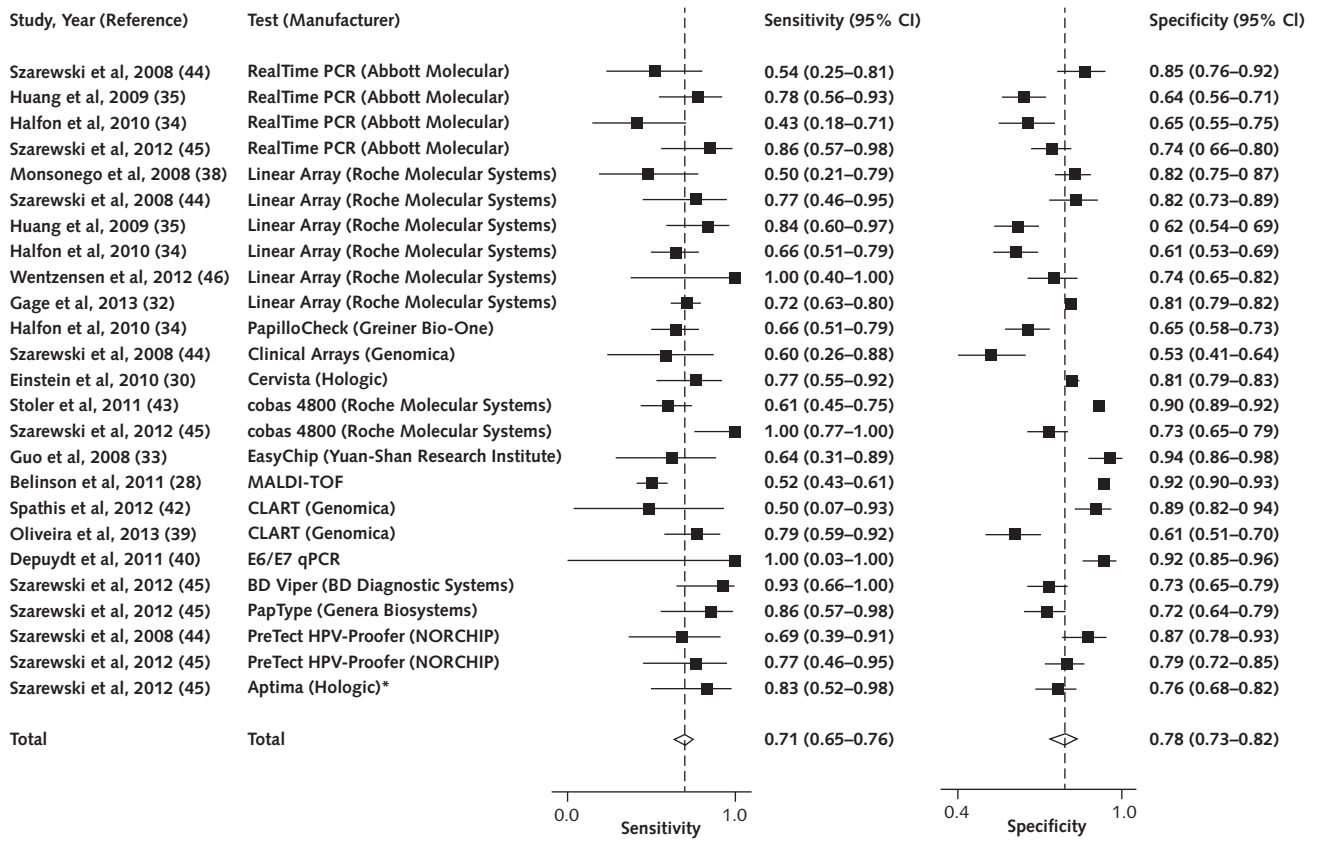
See also:

Web-Only
Supplement

Methods

We developed a protocol (**Supplement 1**, available at www.annals.org), followed standard procedures for

Figure 1. Meta-analysis of the sensitivity and specificity of genotyping for HPV 16/18 to detect CIN3+ in women with ASC-US.



ASC-US = atypical squamous cells of undetermined significance; CIN3+ = cervical intraepithelial neoplasia, grade ≥3; HPV = human papillomavirus; MALDI-TOF = matrix-assisted laser desorption/ionization time of flight; qPCR = quantitative polymerase chain reaction.
* Also included HPV 45 genotyping.

meta-analyses of diagnostic accuracy studies (12, 13), and reported processes and results according to standard guidelines (14).

Data Sources and Searches

Using the search strategies given in the protocol, we searched PubMed/MEDLINE, EMBASE, Scopus, and the Cochrane Central Register of Controlled Trials with no language restrictions from 1 January 1999 to 1 February 2016. We also culled reference lists of selected reports.

Study Selection

Two reviewers independently screened titles and abstracts to identify relevant studies. Studies had to involve 20 or more women with either ASC-US or LSIL who had cervical samples tested with an assay detecting hrHPV and HPV types 16 and 18, as well as a reference test to verify presence or absence of cervical intraepithelial neoplasia (grade ≥2 [CIN2+] or grade ≥3 [CIN3+]).

The ASC-US group comprised women with either ASC-US as defined according to the 1988 and 2001 editions of the Bethesda System (15, 16) or borderline dyskaryosis (17). The LSIL group included women with either LSIL (16) or mild dyskaryosis (17). Authors were contacted if no separate accuracy data were reported for ASC-US and LSIL or when CIN3+ was the only outcome reported.

Tests and Reference Standards

The evaluated index tests were assays identifying DNA or RNA of HPV types 16 and 18, jointly or separately (HPV 16/18). An HPV 16/18 test result was considered positive if HPV 16 or HPV 18 was present and negative if both types were absent. The comparator tests were hrHPV assays identifying at least 8 hrHPV types (HPV 16, 18, 31, 33, 35, 45, 52, and 58). The HC2 assay (Qiagen) was used as the hrHPV comparator test if present. In studies where the HC2 assay was not used, other hrHPV assays or genotyping tests identifying separate hrHPV types were accepted as the comparator test. Details on test platforms and the panel of considered hrHPV types were noted. The cutoff proposed by the manufacturer of each assay was used as the positivity criterion.

In addition to use of HPV 16/18 genotyping as the sole triage test, a combined triage strategy was assessed, where HPV 16/18 genotyping as a second step

Table 1. Pooled Absolute Sensitivity and Specificity of HPV 16/18 Genotyping in Triage of Women With ASC-US or LSIL to Detect Underlying CIN2+ or CIN3+

Outcome, by Triage Group	Study/Test Reports, *n*	Pooled Value (95% CI), %	
		Sensitivity	Specificity
Women with ASC-US			
CIN2+	32	58.8 (54.6–62.9)	82.9 (79.6–85.7)
CIN3+	25	70.7 (64.9–76.0)	78.1 (73.3–82.3)
Women with LSIL			
CIN2+	28	55.5 (52.4–58.5)	76.3 (73.5–78.9)
CIN3+	24	70.0 (65.4–74.2)	72.5 (69.0–75.8)

ASC-US = atypical squamous cells of undetermined significance; CIN2+ = cervical intraepithelial neoplasia, grade ≥2; CIN3+ = cervical intraepithelial neoplasia, grade ≥3; HPV = human papillomavirus; LSIL = low-grade squamous intraepithelial lesions.

was restricted to women who were hrHPV-positive at the first triage test. All women underwent verification with colposcopy, colposcopy-directed biopsies (possibly supplemented with random biopsies), or endocervical curettage. The type of verification (reference standard) was recorded for each study. Two levels of the disease outcome were considered: CIN2+ and CIN3+. Adenocarcinoma in situ was included in the CIN3+ outcome.

Data Extraction and Quality Assessment

Two authors (M.A. and M.J.K.) independently checked the eligibility of references and extracted the number of true-positive, true-negative, false-positive, and false-negative results for each test, triage group, and outcome. Information on the study design, the clinical setting where patients were enrolled, the HPV assays, and the verification procedures was condensed into comprehensive tables. The quality of the selected studies was evaluated independently by 2 coauthors (L.X., F.V., or M.J.K.) using the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) checklist (18, 19).

Data Synthesis and Analysis

The absolute sensitivity and specificity were pooled by using a bivariate normal model for the logit transformations of sensitivity and specificity (20, 21). Summary receiver-operating characteristic curves and forest plots were created to show the joint overall and study-specific sensitivity and specificity of HPV 16/18 genotyping for triage of women with ASC-US or LSIL.

The relative sensitivity and specificity of the index tests versus the comparator tests were computed by including the test as a covariate in the bivariate model (22, 23). We used the Linear Array assay (Roche Molecular Systems) as the comparator to assess the relative accuracy of HPV 16/18 genotyping with different assays. Sources of heterogeneity of accuracy were assessed by including a series of potentially influential covariates in the bivariate model: QUADAS items, type of gold standard, HPV test platform used for hrHPV testing or HPV 16/18 genotyping, target of the HPV test (DNA or RNA), and number of HPV types targeted by the hrHPV test. The Deeks regression test, based on the regression of the log diagnostic odds ratio onto 1/(effective sample size), was used to assess small-study effects (publication bias) (24). Statistical significance was defined as a *P* value less than 0.05. However, for the assessment of the variation of accuracy over multiple categories, we applied a Bonferroni correction (0.05/k, where k was the number of categories) to adjust the significance level. We conducted the statistical analyses with Stata, version 13 (StataCorp), and SAS Enterprise Guide, version 5.1 (SAS Institute).

Pretest–posttest probability plots were constructed to help evaluate the utility of tests and testing strategies. Posttest risks were computed from the average prevalence of precancer in the reviewed studies. Decision thresholds were based on benchmark risk levels applied in Europe (1% and 10%) and the United States (2.6% and 5.2%) (25–27).

Role of the Funding Source

This review was funded by the Directorate-General for Research & Innovation of the European Commission (7th Framework Programme, grant no. 603019). The funders had no role in designing, conducting, or reporting the review.

RESULTS

Selection of Studies and Study Characteristics

From 899 references, 24 studies were selected that met inclusion criteria (Figure 1 of Supplement 2, available at www.annals.org). The studies involved 8587 women with ASC-US and 5284 with LSIL (28–51). An overview of study designs, populations, and test characteristics is provided in Tables 1 and 2 of Supplement 2. Additional data were obtained from the authors of most of the studies, except for 8 articles that contained all of the absolute numbers required for computation of sensitivity and specificity (29, 30, 37, 47–51). Study settings included colposcopy clinics (30, 32, 34–36, 38, 40–42, 44–46, 49–51), primary screening settings (28, 29, 39, 43, 47), a maternity center (31), and pathology archives (33, 37). Fifteen HPV assays were evaluated.

Quality of Included Studies

Table 3 of Supplement 2 summarizes the methodological quality of the included studies. Most studies were of moderate or good quality; 3 were scored as probably free of bias (29, 32, 43), and 1 was scored as poor-quality (37). The most common potential sources of bias were failure to report on uninterpretable or equivocal test results (*n* = 12), failure to account for withdrawals (*n* = 9), and an unclear delay between tests (*n* = 8).

Absolute Sensitivity and Specificity

The summary receiver-operating characteristic curves (Figure 2 of Supplement 2) and forest plots (Figure 1) show the variation among studies and the pooled values of the sensitivity and specificity of genotyping for HPV 16/18 to detect CIN2+ or CIN3+ in women with ASC-US and LSIL. Genotyping for HPV

Table 2. Variation in Sensitivity and Specificity of HPV 16/18 Genotyping to Detect CIN2+ in Women With ASC-US or LSIL, by Test System

Test (Manufacturer)	Studies, *n*	Women With ASC-US				Women With LSIL			
		Sensitivity Ratio (95% CI)	*P* Value	Specificity Ratio (95% CI)	*P* Value	Sensitivity Ratio (95% CI)	*P* Value	Specificity Ratio (95% CI)	*P* Value
Linear Array (Roche Molecular Systems)*	10	1.00		1.00		1.00		1.00	
RealTime PCR (Abbott Molecular)	5	0.85 (0.61–1.17)	0.31	0.99 (0.93–1.05)	0.73	0.88 (0.64–1.19)	0.40	1.02 (0.97–1.07)	0.51
PapilloCheck (Greiner Bio-One)	1	0.97 (0.59–1.56)	0.87	1.02 (0.85–1.22)	0.85	1.03 (0.61–1.73)	0.92	1.08 (0.92–1.27)	0.35
Clinical Arrays (Genomica)	1	0.96 (0.52–1.79)	0.90	0.63 (0.50–0.81)	<0.001†	1.01 (0.69–1.48)	0.96	0.82 (0.71–0.95)	0.008
Cervista (Hologic)	2	1.14 (0.78–1.65)	0.50	1.00 (0.90–1.12)	0.95	–		–	
cobas 4800 (Roche Molecular Systems)	3	1.13 (0.92–1.39)	0.23	1.03 (0.97–1.08)	0.34	0.92 (0.74–1.14)	0.46	1.01 (0.96–1.07)	0.65
EasyChip (Yuan-Shan Research Institute)	1	1.09 (0.64–1.86)	0.74	1.16 (1.08–1.25)	<0.001†	0.78 (0.40–1.55)	0.48	1.17 (1.02–1.36)	0.030
MALDI-TOF	1	0.77 (0.46–1.30)	0.33	1.12 (1.00–1.21)	0.004	0.88 (0.64–1.21)	0.43	1.19 (1.09–1.29)	<0.001†
CLART (Genomica)	2	0.99 (0.64–1.54)	0.96	0.99 (0.89–1.12)	0.99	1.17 (0.89–1.54)	0.27	0.87 (0.76–1.01)	0.061
E6/E7 qPCR	1	1.39 (0.72–2.69)	0.33	1.12 (1.00–1.22)	0.004	0.60 (0.17–2.17)	0.44	0.95 (0.77–1.18)	0.66
BD Viper (BD Diagnostic Systems)	1	0.98 (0.15–6.32)	0.98	0.97 (0.73–1.29)	0.81	0.91 (0.59–1.42)	0.69	1.03 (0.91–1.16)	0.65
PapType (Genera Biosystems)	1	0.89 (0.13–6.30)	0.91	0.96 (0.72–1.29)	0.80	0.94 (0.61–1.45)	0.77	1.03 (0.91–1.17)	0.65
PreTect HPV-Proofer (NORCHIP)	2	0.96 (0.63–1.47)	0.85	1.05 (0.90–1.13)	0.27	0.86 (0.61–1.21)	0.39	1.10 (1.03–1.18)	0.003†
Aptima (Hologic)	1	0.85 (0.11–6.60)	0.88	1.00 (0.77–1.31)	0.98	0.91 (0.57–1.45)	0.68	1.00 (0.87–1.14)	0.94

ASC-US = atypical squamous cells of undetermined significance; CIN2+ = cervical intraepithelial neoplasia, grade ≥2; HPV = human papillomavirus; LSIL = low-grade squamous intraepithelial lesions; MALDI-TOF = matrix-assisted laser desorption/ionization time of flight; qPCR = quantitative polymerase chain reaction.
* Comparator test.
† Significant likelihood ratio test, which assesses whether the relative accuracy differs statistically from unity, with a significance level defined at 0.05/k (k = 14 [number of compared assays]; Bonferroni correction for multiple comparisons).

16/18 identified, on average, 70.7% (95% CI, 64.9% to 76.0%) of CIN3+ cases in women with ASC-US and 70.0% (CI, 65.4% to 74.2%) in women with LSIL (Table 1). The sensitivity of HPV 16/18 genotyping for CIN2+ was lower (difference of 12% to 14%) than for CIN3+. The pooled specificity to exclude CIN2+ was 82.9% (CI, 79.6% to 85.7%) in women with ASC-US and 76.3% (CI, 73.5% to 78.9%) in those with LSIL.

Table 2 shows the variation in the accuracy of genotyping for HPV 16/18 by test system, with the Linear Array assay as the comparator. No statistically significant differences in sensitivity were observed. However, a higher specificity ($P < 0.001$) was noted for EasyChip (Yuan-Shan Research Institute) in triage of women with ASC-US and for PreTect HPV-Proofer (NORCHIP) and MALDI-TOF (matrix-assisted laser desorption/ionization time of flight) in triage of women with LSIL, whereas a lower specificity was noted for Clinical Arrays (Genomica) in triage of women with ASC-US.

Relative Accuracy of Genotyping for HPV 16/18 Versus hrHPV Testing

The relative sensitivity of HPV 16/18 genotyping compared with hrHPV testing for detecting CIN3+ was 0.75 (CI, 0.68 to 0.83) in women with ASC-US and 0.70 (CI, 0.63 to 0.77) in those with LSIL (Table 3). The specificity of HPV 16/18 genotyping to exclude CIN2+ was substantially higher than for hrHPV testing (1.70 [CI, 1.51 to 1.90] in women with ASC-US and 3.14 [CI, 2.83 to 3.48] in those with LSIL). Results for HPV 16 genotyping compared with hrHPV testing and compared with HPV 16/18 genotyping are provided in Table 5 and Figure 5 of Supplement 2.

Table 3. Meta-analysis of the Relative Sensitivity and Specificity of HPV 16/18 Genotyping Versus High-Risk HPV Testing

Outcome, by Triage Group	Comparisons, *n*	Relative Sensitivity (95% CI)	*P* Value	Relative Specificity (95% CI)	*P* Value
Women with ASC-US					
CIN2+	29	0.59 (0.54–0.65)	<0.001	1.70 (1.51–1.90)	<0.001
CIN3+	15	0.75 (0.68–0.83)	<0.001	1.87 (1.64–2.12)	<0.001
Women with LSIL					
CIN2+	19	0.56 (0.51–0.62)	<0.001	3.14 (2.83–3.48)	<0.001
CIN3+	15	0.70 (0.63–0.77)	<0.001	3.49 (3.01–4.05)	<0.001

ASC-US = atypical squamous cells of undetermined significance; CIN2+ = cervical intraepithelial neoplasia, grade ≥2; CIN3+ = cervical intraepithelial neoplasia, grade ≥3; HPV = human papillomavirus; LSIL = low-grade squamous intraepithelial lesions.

Table 4. Accuracy and Pretest and Posttest Probabilities of CIN2+ and CIN3+ for Triage With hrHPV Testing or HPV 16/18 Genotyping

Outcome, by Triage Group	Pretest Risk, %*	Pooled Sensitivity, %	Pooled Specificity, %	Likelihood Ratio		Test Positivity Rate, %	Posttest Risk, %	
				Positive	Negative		If Result Is Positive	If Result Is Negative†
Women with ASC-US								
hrHPV testing								
CIN2+	10.1	95.0	48.6	1.85	0.10	55.8	17.2	1.1
CIN3+	6.0	96.6	45.0	1.76	0.08	57.5	10.1	0.5
HPV 16/18 genotyping								
CIN2+	10.1	58.8	82.9	3.43	0.50	21.3	27.7	5.3
CIN3+	6.0	70.7	78.1	3.23	0.38	24.8	16.9	2.4
hrHPV-positive women with ASC-US								
HPV 16/18 genotyping								
CIN2+	17.2	60.1	67.3	1.84	0.59	37.4	27.5	11.0
CIN3+	10.1	73.8	61.7	1.93	0.42	41.9	17.9	4.5
Women with LSIL								
hrHPV testing								
CIN2+	21.1	96.9	24.8	1.29	0.12	79.7	25.6	3.4
CIN3+	8.6	97.7	22.4	1.26	0.10	79.3	10.6	1.0
HPV 16/18 genotyping								
CIN2+	21.1	55.5	76.3	2.34	0.58	30.4	38.5	13.5
CIN3+	8.6	70.0	72.5	2.55	0.41	31.1	19.3	3.8
hrHPV-positive women with LSIL								
HPV 16/18 genotyping								
CIN2+	25.6	60.2	64.6	1.70	0.62	41.7	36.9	17.5
CIN3+	10.6	72.6	60.7	1.85	0.45	42.8	18.0	5.1

ASC-US = atypical squamous cells of undetermined significance; CIN2+ = cervical intraepithelial neoplasia, grade ≥2; CIN3+ = cervical intraepithelial neoplasia, grade ≥3; HPV = human papillomavirus; hrHPV = high-risk human papillomavirus; LSIL = low-grade squamous intraepithelial lesions.
* Average of the prevalence or short-term cumulative incidence of CIN2+ or CIN3+ pooled from the studies included in the meta-analysis. For 2-step triage, the pretest risk corresponds to the posttest risk after hrHPV testing.
† 1 – negative predictive value.

Influence of Study and Test Characteristics and Small-Study Effects

Few study-quality items influenced the accuracy of HPV 16/18 genotyping to detect underlying precancer (Table 6 of Supplement 2). In women with ASC-US, the specificity of HPV 16/18 genotyping was higher when withdrawal of cases was unclear and in cases of partial verification. In women with LSIL, the sensitivity was higher and the specificity was lower when an inappropriate reference test was used or when withdrawal of cases was not explained.

Genotyping for HPV 16/18 in triage of women with ASC-US was less sensitive when the reference standard involved additional random biopsies or a mix of gold standard tests, and was more specific when only 1 biopsy specimen from the most suspect area was taken compared with when multiple colposcopy-targeted biopsy specimens were taken (Table 7 of Supplement 2). In general, the choice of hrHPV testing platform (HC2 or other platform, panel of targeted hrHPV types, or DNA or RNA testing) did not influence the relative accuracy of HPV 16/18 genotyping compared with hrHPV testing. However, in triage of women with LSIL, the magnitude of the relative specificity was higher with the HC2 assay than with other hrHPV test platforms as comparators (Table 8 of Supplement 2). The relative accuracy of an RNA-based assay targeting HPV types 16/18/45 versus hrHPV testing did not differ from that of an assay targeting HPV 16/18 (Table 9 of Supplement 2).

The Deeks regression test for funnel plot asymmetry did not reveal small-study effects (Table 10 and Figure 6 of Supplement 2).

Meta-analysis of the Accuracy of HPV 16/18 Genotyping in hrHPV-Positive Women With ASC-US or LSIL

For women with ASC-US or LSIL who tested positive for hrHPV in a first-step triage test, the pooled sensitivity was similar or slightly higher and the specificity was lower (Table 11 and Figure 7 of Supplement 2) compared with all women with ASC-US or LSIL (Table 1).

Pretest and Posttest Risks for Cervical Precancer

Table 4 displays accuracy measures and pretest and posttest probabilities of CIN2+ and CIN3+. Before triage testing, the average pretest risk for CIN3+ was 6% among women with ASC-US. A positive hrHPV test result increased the average risk to 10.1%, and a negative result decreased the risk to 0.5%. A positive HPV 16/18 test result in women with ASC-US increased the risk to 16.9%, and a negative result decreased it to

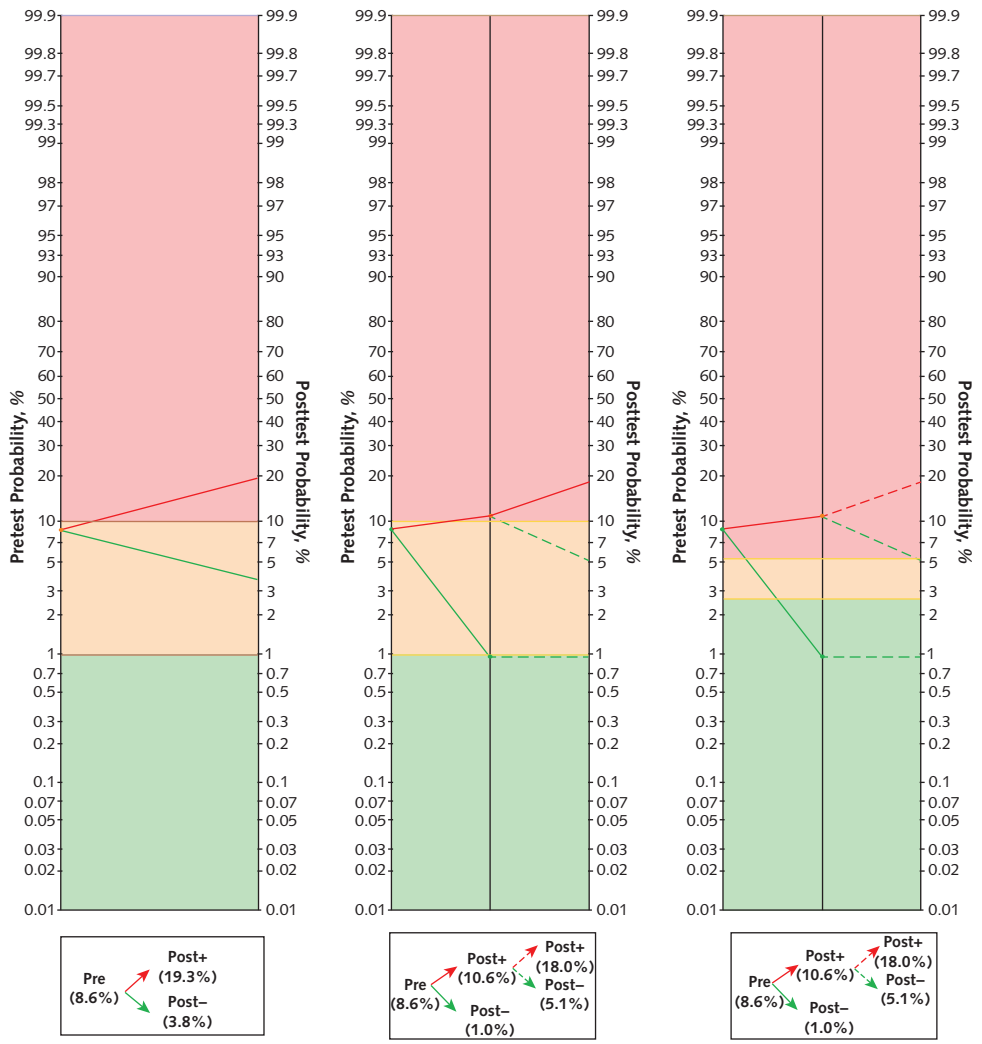
2.4%. In women with LSIL, the pretest probability of CIN3+ was 8.6%, whereas the posttest probabilities after triage were 10.6% in hrHPV-positive women, 19.3% in HPV 16/18–positive women, 1.0% in hrHPV-negative women, and 3.8% in HPV 16/18–negative women. With the 2-step triage, the risks for CIN3+ among women with ASC-US were 17.9% for those who were HPV 16/18–positive and 4.5% for those who were HPV 16/18–negative; for women with LSIL, the corresponding risks were 18.0% and 5.1%.

Pretest–Posttest Probability Plots

The utility of scenarios to triage women with LSIL, using the European (1% and 10%) and U.S. (2.6% and 5.2%) decision thresholds, is displayed in **Figure 2**. A positive HPV 16/18 test result would reclassify 30% of patients with LSIL as needing a colposcopy referral (**Figure 2**, *left* [*red zone*]), whereas the other 70% would need repeated testing (**Figure 2**, *left* [*yellow zone*]). The middle plot in **Figure 2** displays shifts in risk when hrHPV testing is followed by HPV 16/18 genotyping. Testing for hrHPV minimally increases the risk for CIN3+ (from 9% to 11%) for hrHPV-positive women with LSIL but decreases the risk to 1% for hrHPV-negative women with LSIL. Adding HPV 16/18 genotyping to hrHPV-positive women with LSIL would reclassify 43% as needing immediate referral (**Figure 2**, *middle* [*red zone*]). Repeated surveillance testing would be recommended for the remaining 57% who carry other hrHPV types (**Figure 2**, *middle* [*yellow zone*]).

In the United States, the pretest risk for CIN3+ in women with LSIL is considered sufficiently high to justify referral (**Figure 2**, *right*). Women who are negative for hrHPV could be followed conservatively (*green zone*), whereas those who are positive for HPV 16/18

Figure 2. Pretest and posttest probabilities of CIN3+ after triage in women with LSIL.



Use of HPV 16/18 genotyping as a single triage test (*left*) and use of a 2-step triage with hrHPV testing followed by HPV 16/18 genotyping in hrHPV-positive women (*middle* and *right*). Benchmarks are defined at risk levels of 1% and 10% (applied in Europe) (*left* and *middle*) and 2.6% and 5.2% (applied in the United States) (*right*). CIN3+ = cervical intraepithelial neoplasia, grade ≥3; HPV = human papillomavirus; hrHPV = high-risk human papillomavirus; LSIL = low-grade squamous intraepithelial lesions.

would require referral (**Figure 2**, *red zone*). Women who are hrHPV-positive but HPV 16/18–negative could be recommended for either colposcopy or retesting because their risk level is borderline (**Figure 2**, *between red and yellow zones*). Additional plots for diverse triage situations are shown in **Figures 8** to **13** of **Supplement 2**.

DISCUSSION

This meta-analysis found that genotyping for HPV 16/18 detects about 7 of 10 CIN3+ cases and about 6 of 10 CIN2+ cases in women with minor abnormal cytology. The pooled specificity (with a threshold of grade <2 CIN) was 83% in women with ASC-US and 76% in those with LSIL. Genotyping for HPV 16/18 was substantially more specific but less sensitive than testing for hrHPV. The average risks for underlying CIN3+ were 17% and 19% in HPV 16/18–positive women with ASC-US or LSIL, respectively; 2% and 4% among HPV 16/18–negative women with ASC-US or LSIL, respectively; and 5% in hrHPV-positive but HPV 16/18–negative women with either ASC-US or LSIL.

These findings, particularly the posttest risks for precancer, are useful for deciding how to incorporate HPV 16/18 genotyping results into patient management. Until recently, genotyping was done after hrHPV testing on women who tested positive. Several platforms are now available that allow inexpensive, high-throughput, 1-step genotyping. These platforms often give a readout of HPV 16/18 genotyping results separate from the other hrHPV testing, allowing the clinician immediate access to a secondary triage test. Our findings suggest that such partial genotyping tests can be used for risk stratification of hrHPV-positive women to immediate colposcopy or delayed follow-up. Local decision thresholds should help inform decisions about the clinical usefulness of the secondary triage strategy. According to European guidelines, a risk for CIN3+ greater than 10% is considered the threshold for referring a woman to colposcopy. In the United States, this threshold is greater than 5.2%; surveillance testing 6 to 12 months later is proposed if the risk for CIN3+ is 2.6% to 5.2%, and testing at longer intervals is proposed if the risk is less than 2.6% (25, 26). Women with ASC-US or LSIL who are hrHPV-positive but HPV 16/18–negative have a risk for underlying CIN3+ of around 5%, which U.S. guidelines would classify as borderline. This means that both immediate referral to colposcopy and retesting would be plausible options, with no clear preference (**Figure 2**, *right*). The utility of genotyping is more obvious in a European setting, where delayed retesting could be proposed for women with minor cytologic abnormalities who carry high-risk types other than HPV 16 and 18.

A strength of this meta-analysis is the inclusion of more than 8000 women with ASC-US and more than 5000 with LSIL from 24 studies. Our group previously reviewed the utility of hrHPV testing in triage of women with borderline and low-grade cytologic abnormalities (3, 4, 12, 52), but no group has performed a systematic review of HPV 16/18 genotyping as a primary or secondary triage test. This study helps clinicians to understand the underlying risks associated with HPV 16/18 positivity, which is now routinely reported in many newer HPV testing platforms.

In addition to our meta-analysis, we assessed the accuracy of triage using genotyping only for HPV 16, the most carcinogenic type. Genotyping for HPV 16/18 was 8% more sensitive for CIN3+ in both women with ASC-US and those with LSIL but 5% and 8% less specific, respectively, compared with HPV 16 genotyping (**Figure 5** and **Table 5** of **Supplement 2**).

Only 8 of the 24 included studies contained all of the required data in the published reports, but we obtained the data from the other studies directly from the authors. The studies were of moderate to good methodological quality, giving us confidence in the reliability of our sensitivity and specificity estimates. We found no evidence of publication bias or small-study effects. We found consistent and precise estimates of all relative accuracy estimates of HPV 16/18 genotyping compared with hrHPV testing.

Our review identified several limitations in the available data, including the lack of age-stratified data and too few data to precisely assess the accuracy of separate assays. Studies of test accuracy are observational in design, with short-term outcomes that do not provide evidence on effectiveness with respect to prevention of cancer (53). Randomized trials assessing cumulative incidence of CIN3+ or cancer among women who are negative at triage are needed to provide high-quality evidence on the efficacy of alternative management options. Studies had methodological and technical heterogeneity, although study quality and test characteristics seemed to have limited influence on estimates of test accuracy.

In conclusion, triage of women who have minor cytologic abnormalities with partial genotyping for HPV 16/18 increases efficiency compared with hrHPV testing, but at the expense of a loss in sensitivity. Whether a test has good triaging capability can be shown by plotting risks for precancer on pretest and posttest probability plots. Women testing positive for HPV 16 and 18 are at high risk and should be referred for colposcopy. Women carrying other high-risk HPV types cannot be released to routine screening. Whether the risk is sufficiently low in these women to avoid referral to colposcopy or to propose repeated testing depends on local decision thresholds.

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