Systematic Review

Prediction of Treatment Failure After Excisional Treatment of Cervical Precancer

A Systematic Review and Meta-analysis

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OBJECTIVE: To evaluate the diagnostic accuracy and clinical utility of posttreatment tests to predict treatment failure after excisional treatment of cervical intraepithelial neoplasia grade 2 or worse (CIN 2+).

DATA SOURCES: Electronic databases (EMBASE, PubMed MEDLINE) were searched for studies published from January 1975 to August 2024 assessing the occurrence of treatment failure in women who underwent excisional treatment for histologically confirmed CIN 2+ lesion.

METHODS OF STUDY SELECTION: Previously published meta-analyses were extended and updated. A total of 1,802 studies were reviewed. Studies that assessed the diagnostic accuracy of the margin status, cytologic testing, combination of cytology and high-risk human papillomavirus (HPV), or combination of margin status and high-risk HPV compared with high-risk HPV testing were included. The primary outcome was treatment failure (residual or recurrent CIN 2+) and the absolute and relative diagnostic accuracy to predict this outcome. Studies with at least 18 months of follow-up were included.

TABULATION, INTEGRATION, AND RESULTS: Forty-six studies and 20,385 women were included in the analysis. Treatment failure occurred in 6.6% of patients. The pooled sensitivity and specificity of high-risk HPV testing were 86.8% and 80.5%, respectively. Cytology had a sensitivity of 70.8% and a specificity of 85.7%, pooled from 34 studies. Compared with high-risk HPV testing in the same studies, cytology was 6.5% more specific (95% CI, 1.024–1.108) but 21.3% less sensitive (95% CI, 0.702–0.882). Assessment of the margin status was 39.9% less sensitive (95% CI, 0.532–0.678) but similarly specific (95% CI, 0.970–1.069) to high-risk HPV testing in 29 studies, with a pooled sensitivity and specificity of 48.9% and 82.5%, respectively. Co-testing with cytology and high-risk HPV was similarly sensitive (95% CI, 0.992–1.061) but 10.5% less specific (95% CI, 0.850–0.944) compared with high-risk HPV testing in 16 studies, with a pooled sensitivity and specificity of 94.7% and 69.9%, respectively. The pooled sensitivity and specificity of co-testing with margin status and high-risk HPV were 96.9% and 55.7%, respectively, 6.6% more sensitive (95% CI, 1.021–1.114) but 26.7% less specific (95% CI, 0.637–0.844) than high-risk HPV testing in eight studies. Involved resection margins, abnormal cytology, and a positive high-risk HPV test

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The study was supported by the Risk-Based Screening for Cervical Cancer project (grant 847845) funded by the Horizon 2020 Framework Programme for Research and Innovation of the European Commission. Sciensano, the employer of Leandro Bomans and Marc Arbyn, received funding from the European Society of Gynaecological Oncology, the World Health Organization (through the Agreement for Performance of Work for Guidelines on Screening and Treatment of Preinvasive Cervical Disease), the European Commission Initiative on Cervical Cancer, and the German Guideline Program in Oncology (German Cancer Aid project through the University of Hannover, and the EUCanScreen project (grant 101079944) funded by the EU4Health Programme of the European Commission. Peter Hillemanns received support from the Comprehensive Cancer Center of State Lower Saxony (Germany).

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Each author has confirmed compliance with the journal's requirements for authorship.

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Financial Disclosure
The other authors did not report any potential conflicts of interest.

ISSN: 0029-7844/25

result were associated with a failure risk of 16.1%, 29.0%, and 26.1%, respectively. Women with negative margins, normal cytology, and a negative high-risk HPV test result had a failure risk of 3.6%, 2.3%, and 0.9%, respectively. The risk of treatment failure was highest for women with involved margins and a positive high-risk HPV test result (45.3%) and lowest for women with negative margins and a negative high-risk HPV test result (0.3%). Abnormal cytology and a positive high-risk HPV test result increased the risk of treatment failure to 42%, whereas normal cytology and a negative high-risk HPV test result decreased the risk to 0.6%.

CONCLUSION: High-risk HPV testing is highly sensitive and specific to predict residual or recurrent CIN 2+ after excisional treatment. Cytologic testing and assessment of the margin status are slightly more and similarly specific, respectively, but both are significantly less sensitive. High-risk HPV testing can sufficiently inform the posttreatment management based on the posttest risk of treatment failure, unlike both cytology and assessment of the margin status. High-risk HPV testing alone performs similarly to co-testing with cytology or margin status. Posttreatment high-risk HPV testing is therefore an accurate predictor of treatment failure in women treated for CIN 2+.

(Obstet Gynecol 2025;00:1–13)
DOI: 10.1097/AOG.0000000000005997

Cervical cancer is the fourth most common cancer in women globally and the most frequent cancer of the female reproductive system.[1] Invasive cervical cancer is preceded by precursor lesions called cervical intraepithelial neoplasia (CIN).[2] These premalignant lesions are graded according to histopathologic criteria and the risk of progression, correlated to the degree of CIN.[3–6] Women with CIN 3 have a long-lasting, significantly increased risk of developing invasive cervical cancer, and approximately one in three women with untreated CIN 3 progresses to invasive carcinoma.[5,7] Although spontaneous regression is more common for CIN 2, the risk of progression to CIN 3 or invasive cervical cancer remains significant; therefore, treatment is required.[2,8] Early detection and treatment of premalignant cervical lesions is a highly effective intervention to prevent cervical cancer.[9] Different treatment modalities are available for high-grade CIN, including excisional and ablative techniques or hysterectomy.[10] Excisional therapies such as large loop excision of the transformation zone, loop electrosurgical excision, laser conization, and cold-knife conization are the most commonly used and offer the ability to provide histopathologic evaluation of the excised tissue.[10–12] Histologic analysis of excised tissue helps ensure complete excision of the lesion through assessment of the lesion margins. In addition, rates of subsequent development of invasive cancer seem to be lower after excisional treatment compared with ablative techniques.[13] After treatment, women remain at an increased risk of developing invasive cervical cancer compared with the general population, and *treatment failure*, defined as residual or recurrent high-grade CIN, occurs in an average 7% of treated patients within 2 years, varying between 8% and 14% among studies.[14–18] Therefore, accurate prediction of treatment failure could enable effective posttreatment management.

The status of the excisional margins is associated with the risk of residual or recurrent CIN, but its role as an accurate predictor of treatment failure is controversial. Positive margins have been described to increase the risk of treatment failure.[18–20] A recent meta-analysis found that involvement of the endocervical but not the ectocervical margins is a risk factor for residual or recurrent CIN.[14] However, the accuracy of the margin status as a test of cure is suboptimal; nearly half of all women with residual or recurrent CIN have clear margins, and approximately 15% of women considered cured have involved resection margins.[16,18] Follow-up with cytology screening has historically been a cornerstone of posttreatment management.[21] Women with consecutive negative Pap test results at posttreatment follow-up and women with normal cytology in population-based screening programs were found to have a similar risk of treatment failure, justifying a return to routine screening.[22–24]

The purposes of this systematic review and meta-analysis were to update the findings from previous reviews and to compare the diagnostic accuracy and clinical utility of different posttreatment tests to predict treatment failure. We compared the accuracy of the margin status and posttreatment cytology, alone or in combination with high-risk human papillomavirus (HPV) testing, with standalone posttreatment high-risk HPV testing as a method to predict residual or recurrent high-grade CIN. In addition, we evaluated the risk associated with each test result to inform the appropriate management, including referral to colposcopy, further surveillance, or return to routine screening.

DATA SOURCES

This review and meta-analysis follows the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analyses) guidelines for reporting of meta-

analyses.[25] The PICOS (population-intervention-comparator-outcome-study–type) components for the posed clinical questions and our literature search strategy, which included key words and MeSH terms pertinent to the defined PICOS, are described in Appendix 1, available online at http://links.lww.com/AOG/E211. We searched for published reviews and new studies from EMBASE and PubMed MEDLINE in the period of January 1, 1975, to August 1, 2024. Clinical trial registries were not consulted because our review focused on studies addressing a diagnostic test accuracy question. References were extracted from previously published reviews.[18,19] New references addressing the research question not yet included were extracted de novo. Reference lists of published reviews and selected reports were consulted.

STUDY SELECTION

For the purpose of this review, we searched for cohort studies assessing the occurrence of treatment failure, meaning recurrent or residual CIN grade 2 or worse (CIN 2+), in relation to the defined index and comparator tests. In addition, we searched for case–control studies assessing the index and comparator tests in women with treatment failure and women successfully treated. Studies were deemed eligible for inclusion if they included women who underwent excisional treatment for a histologically confirmed CIN 2+ lesion and 1) assessed the presence or absence of CIN at the resection margins, 2) performed cytologic testing between 3 and 9 months after treatment, 3) performed a combination of cytology and high-risk HPV, or 4) performed margin status and high-risk HPV testing between 3 and 9 months after treatment. Lastly, studies were included if they had a subsequent follow-up of at least 18 months after treatment, including histologic confirmation of CIN 2+ occurrence. The resection margins were considered positive if CIN 2+ was present at the resection margin and negative if margins were free of neoplasia. Covariates that were assessed include severity of the treated disease (CIN 2+, CIN 3+, or adenocarcinoma in situ), the method of treatment (large loop excision of the transformation zone, cold-knife conization, or laser conization), and localization of resection margin involvement (endocervical, ectocervical, or both).

For studies assessing the association of margin status with treatment failure published until December 31, 2006, data were extracted from the meta-analysis by Ghaem-Maghami et al.[19] Studies published in 2006–2016 regarding association of margin status and posttreatment high-risk HPV testing with treatment were extracted from the meta-analysis by Arbyn et al.[18] Study selection and data extraction for more recent studies published in 2016–2024 regarding the new accuracy questions were done by two authors (L.B. and A.T.R.). Possible conflicts were resolved by discussion and, if necessary, were resolved by third author (M.A). The quality of new included diagnostic accuracy studies was assessed with the QUADAS tool.[26]

The primary end point was treatment failure, defined as the occurrence of residual or recurrent CIN 2+ after treatment. Assessment of the absolute and relative diagnostic accuracy to predict this outcome was the primary objective.

For statistical analysis, the following data were extracted from included studies: study characteristics (author, year, country, study design), patient characteristics (sample size; mean age and range; mean, minimum, and maximum follow-up duration; treatment procedure; treated lesion), status of the resection margins, results of index and comparator tests, type of tests, timing of tests, and histologic grade of residual or recurrent lesions. Proportions (occurrence of treatment failure overall and in patients positive or negative for index or comparator test) were pooled with a random-effects meta-analysis model of binomial data with a Freeman–Turkey arcsine transformation.[27] A bivariate random-effects meta-analysis model was used to pool diagnostic accuracy data (sensitivity, specificity).[28] To pool relative risks (risk of residual or recurrent disease in women positive vs negative for index or comparator test), a random-effects inverse-variance model for ratios of proportions was used.[29] Interstudy heterogeneity was assessed by the I^2 index.[30] In place of the negative predictive value (NPV) the complement to the NPV (complement to the NPV=1−NPV) was reported. It quantifies the likelihood that a person receiving a negative test result is actually positive for the condition, with a higher complement to the NPV indicating poorer reliability of the negative test result. Pretest and posttest probability plots connect the pretest risk with the posttest risk after a positive or negative test result, calculated from positive and negative likelihood ratios. The gradient corresponds to the benchmarks, defined as risk levels of 2% and 20%. Risk levels exceeding 20% (red zone; high risk) warrant referral to colposcopy; risk levels below 2% (green zone; low risk) warrant return to routine screening. Risk levels between 2% and 20% (yellow zone; intermediate risk) warrant further surveillance. All statistical analyses were performed with Stata 16.1.

RESULTS

A total of 46 studies published between 1997 and 2024 were included in the meta-analysis of diagnostic test accuracy (Appendix 2, available online at http://links.lww.com/AOG/E211). Four studies[31–34] addressing the accuracy of the margin status, cytology, or high-risk HPV testing to predict residual or recurrent CIN 2+ were extracted from the meta-analysis by Ghaem-Maghami et al.[19] Twenty-eight studies were included in the meta-analysis by Arbyn et al,[18,22,35–60] and 14 new studies were added that addressed the same question.[61–74] The detailed characteristics of newly included studies are described in Appendix 3, available online at http://links.lww.com/AOG/E211.The initial search identified 1,727 publications, and 75 potentially eligible studies were identified in previous meta-analyses. Of the 89 total studies assessed for inclusion after primary screening based on title and abstract, 43 were excluded from the meta-analysis. Among these, 32 studies had residual or recurrent CIN 1 as the sole outcome, six of which also had insufficient follow-up (less than 18 months). Four studies included solely patients treated for CIN 1 and were therefore excluded. Seven studies were excluded for insufficient follow-up, and one study evaluated only high-risk HPV testing without a comparator test. Twenty-nine studies provided data for the accuracy of posttreatment high-risk HPV testing and accuracy of the margin status for the outcome of CIN 2+. Thirty-four studies evaluated accuracy of cytology and high-risk HPV testing. Eight studies looked at the accuracy of high-risk HPV testing and co-testing of margin status with high-risk HPV testing. Sixteen studies had information about the accuracy of high-risk HPV testing and co-testing with cytology and high-risk HPV. The main results from the meta-analysis are summarized in Table 1.

A total of 20,385 women treated for CIN 2+ were enrolled across all included studies. The quality of newly included studies was assessed with the QUADAS tool and varied from moderate to good (Appendix 4, available online at http://links.lww.com/AOG/E211). The most problematic items were reporting of uninterpretable results for the index or comparator test and for the reference test: 6 of the 14 studies (42.8%) did not report uninterpretable results for the index or comparator test, and in two studies (14.3%), reporting was unclear. Two of the 14 studies (14.3%) did not report uninterpretable results for the reference test, and reporting was unclear in 10 studies (71.4%). Masking of the outcome was scored as problematic in five studies (35.7%), and partial and differential verification was problematic in four studies (28.6%) and three studies (21.4%), respectively.

Across all 42 included cohort studies, the pooled occurrence of treatment failure (residual or recurrent CIN 2+) in women treated for cervical precancer (CIN 2 or CIN 3) was 6.6% (95% CI, 5.6–7.7%). The prevalence of residual or recurrent CIN 2+ was heterogeneous across all studies (range 1.4–15.8%, I^2=85.80%, P=.00) (Fig. 1). The failure rates did not differ by severity of the treated disease: 6.7% for CIN 2+ (95% CI, 5.6–7.8%) and 5.6% for CIN 3+ (95% CI, 3.9–7.7%) (P=.376) (Appendix 5, available online at http://links.lww.com/AOG/E211).

The sensitivity and specificity to predict residual or recurrent CIN 2+ were pooled for each index test and compared with high-risk HPV testing alone. The sensitivity and specificity, pooled from 46 studies that performed high-risk HPV testing, were 86.8% (95% CI, 81.2–92.5%) and 80.5% (95% CI, 77.2–83.7%), respectively. Of 34 studies that performed cytology testing, the pooled sensitivity and specificity were 70.8% (95% CI, 60.4–81.2%) and 85.7% (95% CI, 83.0–88.4%), respectively. Cytology was 21.3% less sensitive than high-risk HPV testing (sensitivity ratio 0.787, 95% CI, 0.702–0.882) but 6.5% more specific (specificity ratio 1.065, 95% CI, 1.024–1.108), taking only the studies that performed both these tests into account. Involvement of the resection margins was assessed in 29 studies and showed the lowest absolute pooled sensitivity (48.9%, 95% CI, 40.1–57.6%) with a specificity of 82.5% (95% CI, 78.9–86.0%). Compared with high-risk HPV testing in these studies, assessment of the margin status was 39.9% less sensitive (sensitivity ratio 0.601, 95% CI, 0.532–0.678) and similarly specific (specificity ratio 1.018, 95% CI, 0.970–1.069). The pooled sensitivity of co-testing with cytology and high-risk HPV or co-testing with margin status and high-risk HPV testing was 94.7% (95% CI, 92.3–97.1%) for cytology and high-risk HPV testing and 96.6% (95% CI, 94.1–99.7%) for margin status and high-risk HPV testing. However, specificity was low for both co-tests: 69.9% (95% CI, 63.6–76.2%) for cytology and high-risk HPV and 55.7% (95% CI, 47.3–64.0%) for margin status and high-risk HPV. Compared with high-risk HPV testing alone, co-testing with cytology was similarly sensitive (sensitivity ratio 1.026, 95% CI, 0.992–1.061) but 10.5% less specific (specificity ratio 0.895, 95% CI, 0.850–0.944). Margin status and high-risk HPV testing, although 6.6% more sensitive (sensitivity ratio 1.066, 95% CI, 1.021–1.114), was 26.7% less specific (specificity ratio 0.733, 95% CI, 0.637–0.844) (Fig. 2 and Appendices

Table 1. Summary of Meta-analysis Results

Test	No. of Studies	Sensitivity, %	Specificity, %	Relative Sensitivity vs HPV	Relative Specificity vs HPV	PPV, %	cNPV, %
HPV	46	86.8 (81.2–92.5)	80.5 (77.2–83.7)	—	—	26.1 (22.5–29.7)	0.9 (0.6–1.2)
Margins	29	48.9 (40.1–57.6)	82.5 (78.9–86.0)	0.60 (0.53–0.68)	1.02 (0.97–1.07)	16.1 (12.5–19.7)	3.6 (2.9–4.3)
Cytology	34	70.8 (60.4–81.2)	85.7 (83.0–88.4)	0.79 (0.70–0.88)	1.07 (1.02–1.11)	29.0 (24.1–33.8)	2.3 (1.6–3.0)
Margins and HPV	8	96.0 (94.1–99.7)	55.7 (47.3–64.0)	1.07 (1.02–1.11)	0.73 (0.64–0.84)	12.8 (9.4–16.1)	0.3 (0.0–0.6)
Cytology and HPV	16	94.7 (92.3–97.1)	69.9 (63.6–76.2)	1.03 (0.99–1.06)	0.90 (0.85–0.94)	21.6 (17.2–26.0)	0.6 (0.3–0.9)

HPV, human papillomavirus; PPV, positive predictive value; cNPV, complement to the negative predictive value.
Data in parentheses are 95% CIs.

6–9, available online at http://links.lww.com/AOG/E211).

The risk of residual or recurrent CIN 2+ after treatment was highest for women with abnormal cytology (atypical squamous cells of undetermined significance or worse) (29.0%, 95% CI, 24.1–33.8%). Women with a positive high-risk HPV test result had a posttreatment CIN 2+ risk of 26.1% (95% CI, 22.5–29.7%). In women with involved resection margins, the risk of a residual or recurrent CIN 2+ lesion was 16.1% (95% CI, 12.5–19.7%). Conversely, the risk of residual or recurrent CIN 2+ after a normal cytology result was 2.3% (95% CI, 1.6–3.0%), and the risk after a negative high-risk HPV test result decreased to only 0.9% (95% CI, 0.6–1.2%) (Fig. 3A and 3B). For women with negative margins, the risk was 3.6% (95% CI, 2.9–4.3%) (Fig. 3C). Sixteen studies had information about the accuracy of cytology and high-risk HPV co-testing to predict residual or recurrent CIN 2+. One study evaluating co-testing was a case–control study and therefore excluded from analyses of predictive values. The risk of a posttreatment CIN 2+ lesion after a positive cytology or high-risk HPV test result was 21.6% (95% CI, 17.2–26.0%); the risk after a negative cytology and a negative high-risk HPV test result decreased to 0.6% (95% CI, 0.3–0.9%) (Fig. 4A).

Eight studies evaluated the combination of margin status and high-risk HPV testing. The risk of residual or recurrent CIN 2+ with involved resection margins or a positive high-risk HPV test result was 12.8% (95% CI, 9.4–16.1%); for women with clear margins and a negative high-risk HPV test result, this decreased to 0.3% (95% CI, 0.0–0.6%) (Fig. 4B). The relative risk of CIN 2+ was highest for women with involved margins or a positive high-risk HPV test (co-test) result compared with women with clear margins and a negative high-risk HPV test result (32.03, 95% CI, 17.32–59.22). The relative risk was 18.17 (95% CI, 14.14–23.34) for women with a positive compared with negative high-risk HPV test result, 16.28 (95% CI, 11.63–22.78) for women with a positive compared with negative cytology and high-risk HPV co-test result, 12.48 (95% CI, 8.45–18.43) for women with abnormal compared with normal cytology, and 4.34 (95% CI, 3.36–5.60) for women with involved compared with clear resection margins (Appendices 10–14, available online at http://links.lww.com/AOG/E211).

The pretest–posttest probability plots show the risks of posttreatment CIN 2+ for women with a positive and a negative test result (Fig. 3). Involved resection margins result in a risk not exceeding 20%, and clear margins are associated with a risk higher than 2%. Although abnormal cytology exceeds the risk level of 20%, normal cytology is still associated with an intermediate risk level higher than 2%. For a high-risk HPV test alone, a positive result indicates a risk of treatment failure exceeding 20%; a negative result reduces this risk to well below the 2% threshold. Only cytology and high-risk HPV co-testing performs similarly to high-risk HPV testing alone (Fig. 3). For co-testing with margin status and high-risk HPV, a positive result does not exceed the 20% risk level for a residual or recurrent lesion, but after a negative result, the risk level decreases to less than 2% (Fig. 4). Stratifying the risk of residual or recurrent CIN 2+ by joint margin and high-risk HPV status allows the identification of several groups ranging from low to high risk of treatment failure. Patients who are either margin-negative and high-risk HPV–positive or margin-positive and high-risk HPV–

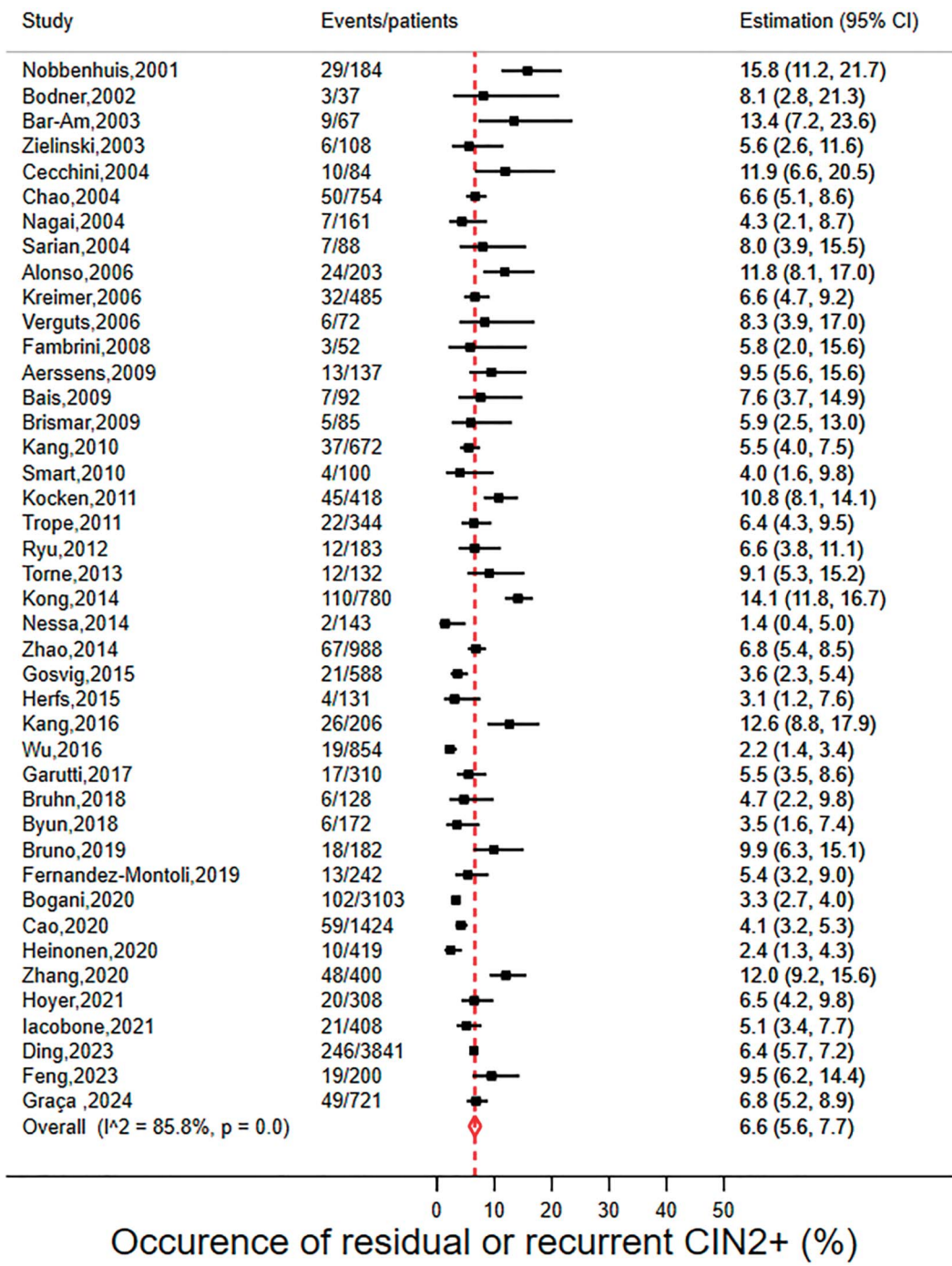

Fig. 1. Occurrence of treatment failure (residual or recurrent cervical intraepithelial neoplasia grade 2 or worse [CIN 2+]) in patients treated for cervical precancer (CIN 2 or CIN 3). *Error bars* represent 95% CIs. The *vertical line* and *diamond* at the bottom correspond with the overall pooled estimate.

Bomans. Prediction of Cervical Precancer Recurrence. Obstet Gynecol 2025.

negative can be classified as at intermediate risk (11.1% and 3.0% respectively). Double-negative patients are at low risk of treatment failure (0.3%, Fig. 4), whereas patients with positive margins and a positive high-risk HPV test result have a significantly increased risk of 45.3% (Appendix 15, available online at http://links.lww.com/AOG/E211). Similarly for joint cytology and high-risk HPV status, two

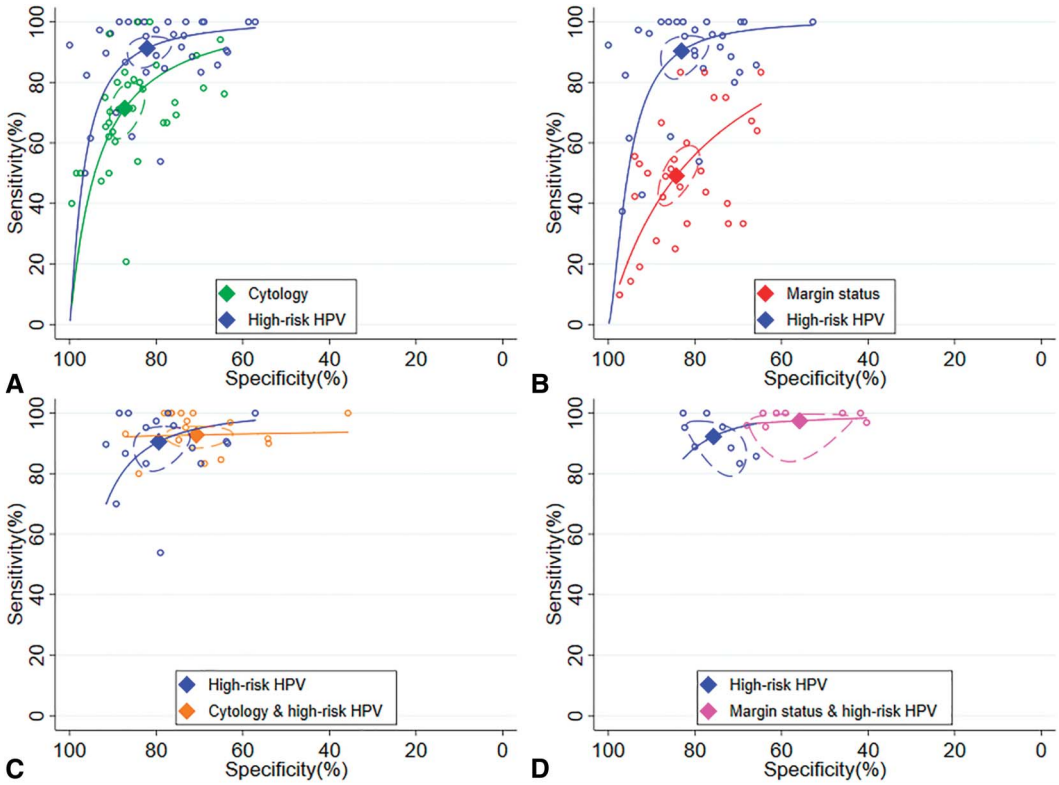

Fig. 2. Summary receiver operating characteristic plot of sensitivity as a function of the specificity for residual or recurrent cervical intraepithelial neoplasia grade 2 or worse (CIN 2+) in women treated for CIN 2+ for cytologic testing 3–9 months after treatment (**A**), histologic evaluation of the resection margins (**B**), co-testing with cytology and high-risk human papillomavirus (HPV) (**C**), and co-testing with evaluation of the resection margins and high-risk HPV (**D**) compared with high-risk HPV testing alone (**A–D**).

Bomans. Prediction of Cervical Precancer Recurrence. Obstet Gynecol 2025.

groups of women at intermediate risk of residual or recurrent CIN 2+ can be identified: Women with either a positive cytology followed by a negative high-risk HPV test result or a negative cytology followed by a positive high-risk HPV test result have a risk level of 4.4% and 11.9%, respectively. Women with positive cytology and a positive high-risk HPV test result are at high risk (42.3%); women who test negative for both are at low risk (0.6%, Fig. 4) (Appendix 16, available online at http://links.lww.com/AOG/E211).

DISCUSSION

Our meta-analysis found that treatment failure after excisional treatment of high-grade CIN occurs in approximately 7% of cases. We also assessed the accuracy of the margin status, cytologic testing, and high-risk HPV testing in the posttreatment setting. Posttreatment high-risk HPV testing performs well as a predictor of treatment failure owing to both a high sensitivity and specificity of 87% and 81%, respectively. Cytologic testing 3 to 9 months after treatment showed a pooled sensitivity of 71% and specificity of 86%. Compared with high-risk HPV DNA testing after treatment, cytologic testing had a substantially lower sensitivity with only a minor gain in specificity. We also evaluated two forms of co-testing: cytology in combination with high-risk HPV and assessment of the margin status in combination with high-risk HPV testing. Both showed high sensitivity but low specificity compared with high-risk HPV testing. Although the combination of margin status and high-risk HPV testing was only slightly more sensitive but substantially less specific than high-risk HPV testing alone, the combination of cytology and high-risk HPV was equally as sensitive but 10% less specific. The added layer of detection inherent to co-testing might lead to an increase in false-positive results because subtle reactive or inflammatory changes that may not be attributable to true precancerous lesions that were not detected by standalone high-risk HPV testing are identified, resulting in a lower specificity.

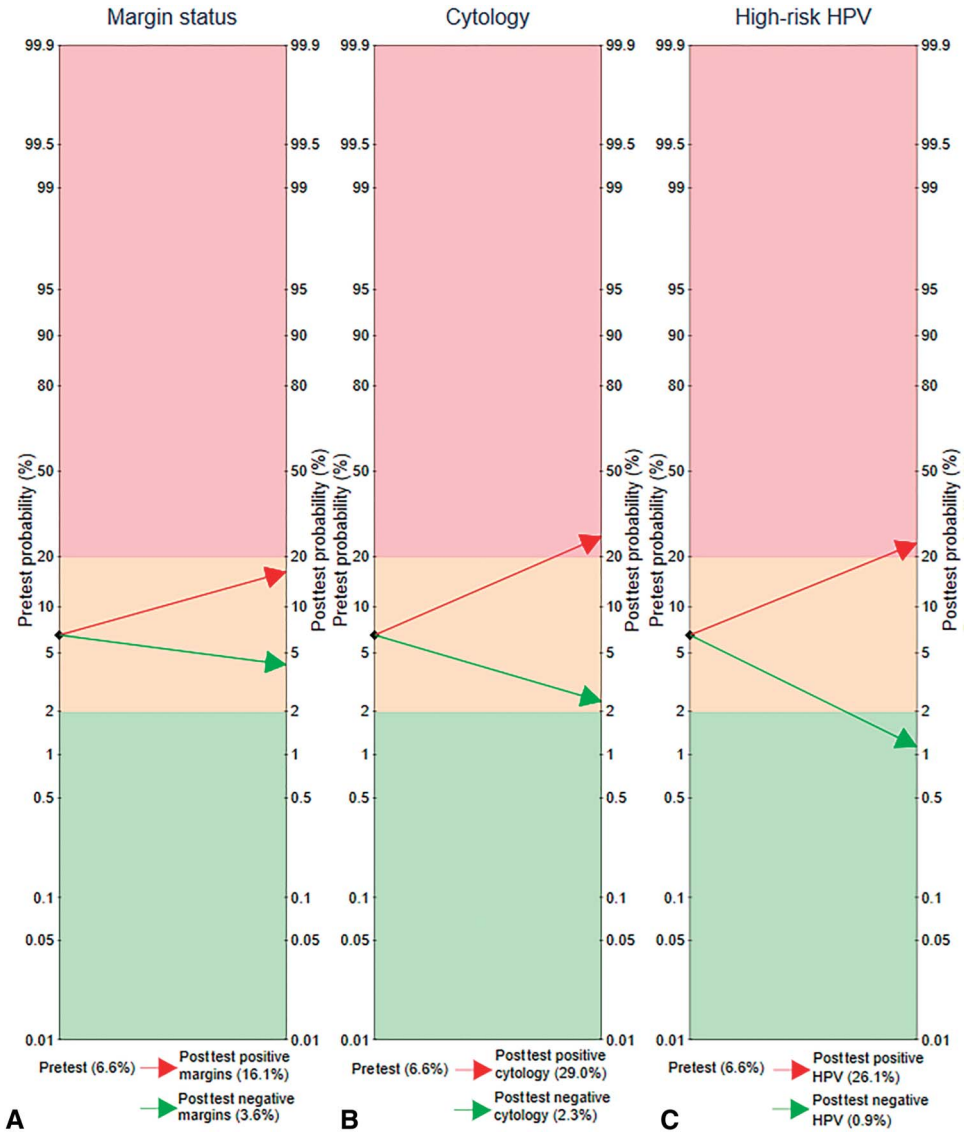

Fig. 3. Pretest and posttest probability plots for residual or recurrent cervical intraepithelial neoplasia grade 2 or worse (CIN 2+) after treatment of CIN 2+ assessed by histologic evaluation of the resection margins (**A**), cytologic testing 3–9 months after treatment (**B**), or high-risk human papillomavirus (HPV) testing 3–9 months after treatment (**C**).

Bomans. Prediction of Cervical Precancer Recurrence. Obstet Gynecol 2025.

As previously described,[14,16,18,19] incomplete excision of cervical precancer was associated with an increased risk of a residual or recurrent high-grade lesion. In our meta-analysis, the risk was five times higher than in women with complete removal of neoplastic tissue. In comparison, the risk for women with abnormal compared with normal cytology was 13 times higher and the risk for women who tested positive for high-risk HPV was 33 times higher compared with those who tested negative. Women with negative margins still have a 4% risk of treatment failure, explained by a low sensitivity of 49%. Conversely, approximately 17% of women with involved resection margins were considered cured after a period of at least 18 months. Despite the close association with risk of failure, assessment of the margin status is therefore not an accurate predictor of treatment failure compared with other available tests. In accordance with previous meta-analyses, our findings confirm the performance of posttreatment high-risk HPV testing as an accurate predictor of treatment failure. A previous meta-analysis by Arbyn et al[18] found a similar risk of residual or recurrent CIN 2+ associated with the margin status while describing the improved performance of posttreatment high-risk HPV testing to predict treatment failure. Here, we confirm these findings in a larger sample size from more recent studies and expand on the analysis by including cytology and co-testing in the equation.

The pretest–posttest probability plots give information on the clinical utility of tests and allow easily

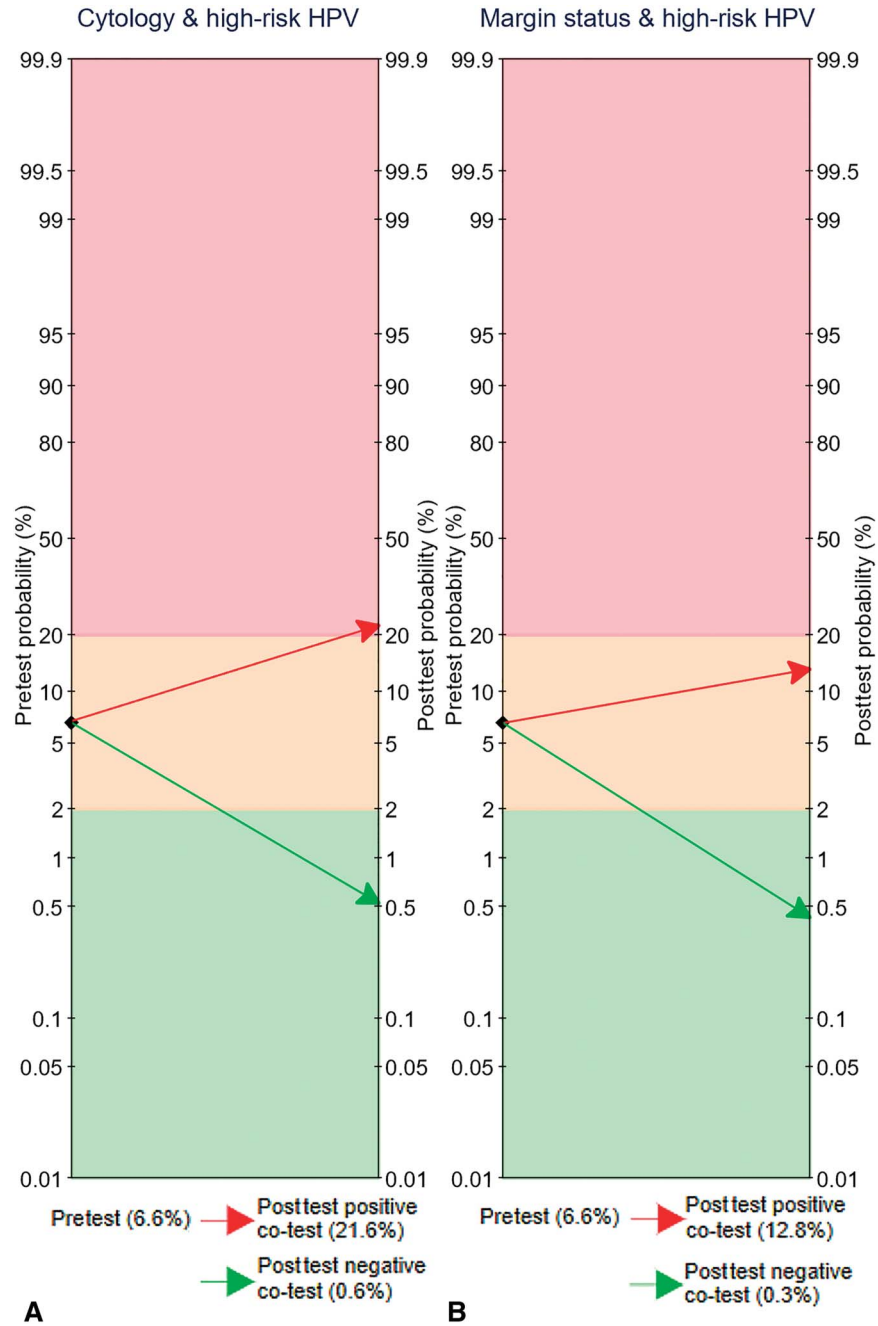

Fig. 4. Pretest and posttest probability plots for residual or recurrent cervical intraepithelial neoplasia grade 2 or worse (CIN 2+) after treatment of CIN 2+ assessed by co-testing with cytology and high-risk human papillomavirus (HPV) (**A**) and co-testing with evaluation of the resection margins and high-risk HPV (**B**).

Bomans. Prediction of Cervical Precancer Recurrence. Obstet Gynecol 2025.

interpretable visualization of pretest and posttest risk of treatment failure. Using previously described decision thresholds of 2% and 20% for low risk and high risk, respectively, allows effective stratification of patients based on their posttest risk of treatment failure.[75] From these decision thresholds, we find that high-risk HPV testing alone and co-testing with cytology are associated with a sufficiently increased or decreased risk to stratify patients into distinct post-treatment management categories. Compared with high-risk HPV testing alone, however, co-testing is associated with a higher cost because the inferior specificity and increased number of tests performed. Involved margins, although associated with an increased risk of treatment failure, do not necessarily warrant referral to colposcopy; clear margins do not sufficiently lower the risk to warrant a return to routine screening. The increase and reduction in risk are

more pronounced if patients are stratified by joint margin or cytology and high-risk HPV status, only if women are double negative or double positive. However, joint margin or cytology and high-risk HPV testing do not provide significantly improved protection against treatment failure compared with high-risk HPV testing alone.

Novel biomarkers for cervical precancer have been emerging in recent years such as host or viral DNA methylation, including DNA promoter methylation of tumor suppressor genes such as cell adhesion molecule 1 (*CADM1*) and myelin and lymphocyte (*MAL*) or viral capsid genes, as well as dual staining for overexpressed p16 and Ki67 proteins or detection of high-risk HPV mRNA.[47,76–79] However, the literature describing the performance of these tests in a posttreatment setting is limited, and the majority of the identified studies did not meet our inclusion criteria. Two studies assessed the diagnostic accuracy of high-risk HPV mRNA tests to predict a residual or recurrent CIN 2+ lesion after excisional treatment of CIN 2+ with a follow-up of at least 18 months.[47,76] Among a total of 451 patients treated, the pooled sensitivity and specificity of high-risk HPV mRNA detection were 55% and 90%, respectively. One study evaluated dual staining for p16 and Ki67 with different cutoffs for positivity ranging from one or more up to six or more dual-stain–positive cells with sensitivities ranging from 69% to 49% and specificities ranging from 90% to 96%.[77] Because of the limited number of studies in the context of posttreatment follow-up and the large interstudy heterogeneity, the evidence for their diagnostic accuracy is limited.

Multiple studies have reported increased risk of treatment failure in patients with type-specific HPV persistence, particularly in the case of HPV16 or 18.[44,45,55,57,80] HPV16 is associated with lower clearance and higher CIN 3 recurrence rates than other high-risk HPV types.[57,81,82] Genotyping for HPV might therefore increase the specificity of HPV testing by identifying the same genotype in pretreatment and posttreatment specimens or stratifying patients by high-risk genotypes, although the effect on sensitivity is inconclusive.[57,82] In our present analysis, only a minority of studies reported data on genotyping and type-specific persistence, and the findings were highly heterogeneous, both statistically and clinically, leading us to exclude these variables from the analysis.

The strengths of this study include a comprehensive evaluation of the available evidence from a large number of studies that assessed the diagnostic accuracy and the risk-based assessment of the clinical utility of different predictors of recurrence. We included nearly 50 studies with a population of more than 20,000 women in our meta-analysis. In addition, we adhered to strict criteria of inclusion, specifically selecting comparative studies that performed high-risk HPV testing in conjunction with other tests over an extensive follow-up period, allowing us to more definitively answer the proposed clinical questions. However, studies were often statistically and clinically heterogeneous. For pooled estimates of diagnostic accuracy, disease occurrence, and predictive values, large interstudy heterogeneity was observed. In particular, sensitivity of the margin status and cytologic testing varied substantially across studies, underlying the subjective character of these latter tests involving human interpretation. Our analysis was done on aggregated data extracted from published data, limiting the amount of potentially influential covariates such as age, lesion size, or smoking status that we could incorporate. More in-depth analyses could be performed in meta-analyses of individual patient data.[18] Future analyses could further investigate the diagnostic accuracy of other markers such as methylation or high-risk HPV mRNA in a posttreatment setting, for which there is limited and poor-quality evidence included in the present meta-analysis. The role of the HPV genotype and type-specific persistence is also an important question that should be addressed in future research.

In conclusion, we reaffirm previous findings that high-risk HPV testing after treatment is capable of accurately predicting residual or recurrent CIN 2+. Although positive excisional margins or abnormal cytologic results are associated with an increased risk of treatment failure, both are less sensitive than high-risk HPV testing and fail to accurately inform risk-based management of treated patients. Co-testing with cytology and high-risk HPV performs similarly to high-risk HPV testing alone, with higher sensitivity but significantly lower specificity. In groups at high risk such as women recently treated for a cervical lesion, increased sensitivity at the cost of specificity might be warranted. Assessment of the margin status is a poor predictor of outcomes after treatment of CIN 2+ characterized by a very low sensitivity.

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PEER REVIEW HISTORY

Received February 6, 2025. Received in revised form April 2, 2025. Accepted April 10, 2025. Peer reviews and author correspondence are available at http://links.lww.com/AOG/E212.