# ASCCP Colposcopy Standards: Risk-Based Colposcopy Practice

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**Objectives:** The American Society for Colposcopy and Cervical Pathology (ASCCP) Colposcopy Standards recommendations address the role of and approach to colposcopy for cervical cancer prevention in the United States.

**Materials and Methods:** The recommendations were developed by an expert working group appointed by ASCCP's Board of Directors. This article describes the rationale, evidence, and recommendations related to risk-based colposcopy practice.

**Results:** Women referred to colposcopy have a wide range of underlying precancer risk, which can be estimated by referral screening tests including cytology and human papillomavirus testing, in conjunction with the colposcopic impression. Multiple targeted biopsies, at least 2 and up to 4, are recommended to improve detection of prevalent precancers. At the lowest end of the risk spectrum, untargeted biopsies are not recommended, and women with a completely normal colposcopic impression can be observed. At the highest end of the risk spectrum, immediate treatment is an alternative to biopsy confirmation.

**Conclusions:** Assessing the risk of cervical precancer at the colposcopy visit allows for modification of colposcopy procedures consistent with a woman's risk. Implementation of these recommendations is expected to lead to improved detection of cervical precancers at colposcopy, while providing more reassurance of negative colposcopy results.

**Key Words:** biopsy, cervical cancer screening, colposcopy, precancer, risk

(*J Low Genit Tract Dis* 2017;21: 230–234)

Despite its central role in cervical cancer screening, the accuracy and reproducibility of colposcopy-directed biopsy are limited. Important factors that may contribute to these limitations in the United States (US) include the following: (1) the lack of standardized terminology and (2) the lack of recommendations for colposcopy practice and procedures, and (3) the lack of quality assurance measures. Recognizing the limitations of current colposcopy approaches in the US, the American Society for Colposcopy and Cervical Pathology (ASCCP), in collaboration with investigators from the US National Cancer Institute, set out to review evidence and develop recommendations for US colposcopy practice.[1] This article describes the evidence and recommendations related to risk-based colposcopy.

Several studies have shown that taking a single biopsy from the cervix may miss up to 40% of prevalent precancers.[2–5] Recently, multiple-biopsy protocols have been proposed and implemented mainly in research studies and clinical trials. The role of random biopsies is controversial: some studies have reported increased detection of cervical precancers by random biopsy sampling,[3,6] whereas others have shown no benefit of adding random biopsies to multiple targeted biopsies.[4,5] Due to the lack of formal guidance, there is currently a wide variety of colposcopy practice in the US, ranging from single targeted biopsy to 4-quadrant random biopsy protocols.

Currently, the discussion about colposcopy practice does not sufficiently consider that the risk of cervical precancer varies widely among women referred because of abnormal screening tests. The risk of precancer can be estimated based on various screening and triage tests, for example, cytology and human papillomavirus (HPV) testing, especially with HPV 16/18 genotyping, in combination with the colposcopic impression at the colposcopy visit.[5] An optimal colposcopy strategy may be different for women at the lowest risk versus women at much higher risk. This suggests that instead of a one-size-fits-all approach to colposcopy, the procedures undertaken during the colposcopy visit should be modified based on the underlying risk.[7]

To develop risk-based colposcopy standards, the following charges were addressed by working group 2 of the ASCCP-sponsored Colposcopy Standards effort and are reported in this article: (1) define risk-based colposcopy, (2) identify markers that can be used to guide colposcopy practice, (3) identify dependable risk strata for risk-based colposcopy, and (4) define thresholds for different colposcopy practice.

## MATERIALS AND METHODS

The goal of Working Group 2 was to develop recommendations on how colposcopy practice should be modified based on assessment of underlying risk, which includes the severity of findings before colposcopic referral (screening and triage tests) and the colposcopic impression. Colposcopy practice includes the complete colposcopy visit, from visual assessment of the cervix to biopsy sampling if indicated. To support the recommendations, an extensive literature review was conducted. Data were pooled from published and unpublished studies for a systematic review and meta-analysis evaluating (1) the incremental benefit of taking multiple targeted and nontargeted biopsies and (2) the risk of precancer in various strata based on cytology, HPV testing, and colposcopy impression.

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The authors have declared they have no conflicts of interest.

Logistical and meeting support was provided by the ASCCP.



DOI: 10.1097/LGT.0000000000000334

A systematic literature search was conducted to identify studies with relevant information about number of biopsies and colposcopy risk strata. The following search term was used: ((("uterine cervical neoplasms"[MeSH Terms] OR ("uterine"[All Fields] AND "cervical"[All Fields] AND "neoplasms"[All Fields]) OR "uterine cervical neoplasms"[All Fields] OR ("cervical"[All Fields] AND "cancer"[All Fields]) OR "cervical cancer"[All Fields]) AND ("diagnosis"[Subheading] OR "diagnosis"[All Fields] OR "screening"[All Fields] OR "mass screening"[MeSH Terms] OR ("mass"[All Fields] AND "screening"[All Fields]) OR "mass screening"[All Fields] OR "screening"[All Fields] OR "early detection of cancer"[MeSH Terms] OR ("early"[All Fields] AND "detection"[All Fields] AND "cancer"[All Fields]) OR "early detection of cancer"[All Fields])) AND "female"[MeSH Terms] AND "adult"[MeSH Terms]) AND (("Colposcopy/methods"[Mesh] OR "Colposcopy/statistics and numerical data"[Mesh] OR "Colposcopy/utilization"[Mesh]) AND "female"[MeSH Terms] AND "adult"[MeSH Terms]) AND ("female"[MeSH Terms] AND "adult"[MeSH Terms]).

The PubMed search was performed on June 1, 2016, and yielded 340 abstracts. All abstracts were rapidly screened by working group members and 196 references were identified for detailed abstraction. Four studies that evaluated the increased detection of precancer with increasing number of biopsies were identified (see Table 1). However, due to the heterogeneity of study design, biopsy procedures, and endpoints, these data could not be combined and are reported individually. To combine studies reporting on disease outcomes in risk strata, an abstraction sheet was developed to capture information on risk markers (cytology, HPV status with partial genotyping, colposcopy impression, age), number of women in different risk strata, and number of cervical intraepithelial neoplasia (CIN) 2, CIN 3, and cancer in these strata to calculate absolute risk estimates. Eight references with risk information were abstracted.[2–6,8–10] In addition, unpublished primary data were obtained from 3 studies and included in the meta-analysis: The ASCUS-LSIL Triage Study (ALTS) trial,[11] the Biopsy Study,[5] and the BD Onclarity trial. Atypical squamous cells cannot rule out high-grade (ASC-H) and atypical glandular cells were included with high-grade squamous intraepithelial lesion (HSIL) or worse (HSIL+) cytology. The following risk strata were used to develop the recommendations: (1)less than HSIL cytology, HPV 16/18 negative, normal colposcopy for the lowest risk group; (2) combinations including at least 2 of 3 of HSIL+, HPV 16/18 positive, high-grade colposcopy impression for the highest risk groups; and (3) an intermediate risk group between the lowest and highest.

Draft recommendations were developed based on the abstracted evidence and expert consensus. The recommendations were presented to the steering committee in October 2016 and reviewed for content and consistency. Revisions were presented to all working group members for discussion and further revision in January 2017, and a vote among working group members was held shortly after. Sixty-seven percent affirmative votes were required for approval of individual recommendations. All recommendations were approved at the first vote and most were approved unanimously with only minor comments. After further editing and notification of stakeholder professional organizations, recommendations were posted on the ASCCP web site for public comments between March 13 and 22, 2017, which resulted in additional modifications in response to the comments. Finally, recommendations were presented at the International Federation for Cervical Pathology and Colposcopy's 16th World Congress in Orlando, Florida, on April 5, 2017, followed by a plenary discussion. Final revisions were made by the steering committee based on comments received at this meeting.[1]

## RESULTS

### Adapting Colposcopy Practice to Previous Risk and Colposcopy Impression

#### Recommendation

Colposcopy practice may be modified based on the risk level (which can be viewed as the probability of finding precancer/cancer at the time of the procedure), based on reason for referral and colposcopy impression.

#### Rationale and Supporting Evidence

Women referred to colposcopy because of abnormal cervical cancer screening results have a wide range of underlying risk of cervical precancer.[5] The risk can be estimated from screening and triage tests (e.g., cytology and HPV with HPV 16/18 genotyping) and the colposcopic impression at the colposcopy visit. Risk markers can be combined to stratify the population into groups with very different risk. Depending on the underlying risk, colposcopy practice can be usefully modified to account for these risk differences. For example, when the risk of precancer is very high, immediate treatment may be recommended to minimize costs and avoid loss to follow-up across multiple visits. Conversely, if the risk is very low, expectant management with serial cytology and HPV testing but no biopsy may be warranted. For intermediate risks, multiple biopsies of acetowhite lesions lead to increased detection of precancer.

**TABLE 1.** Increased Detection of Cervical Precancer With Increasing Number of Biopsies

| Study | Population | Endpoints | 1 biopsy | 2 biopsies | 3 biopsies | 4 biopsies |
|---|---|---|---|---|---|---|
| Gage et al.[2] | ALTS trial, multiple centers in the US | 2-year CIN 3+ | 142/208 (68.3%) | 108/132 (81.8%) | 35/42 (83.3%) | NA |
| Pretorius et al.[3] | SPOCCS, China | Cross-sectional, CIN 3+ | 141/222 (63.5%) | | | 198/222 (89%) |
| van der Marel et al.[4] | EVAH study, The Netherlands and Spain | Cross-sectional, CIN 2+ | 136/263 (51.7%) | 159/263 (60.4%) | | |
| Wentzensen et al.[5] | Biopsy Study, US | Cross-sectional, HSIL+ | 157/252 (60.6%) | 222/252 (85.6%) | 246/252 (95.6%) | 252/252 (100%) |

ALTS indicates ASCUS-LSIL Triage Study; US, United States; NA, not applicable; CIN,cervical intraepithelial neoplasia; SPOCCS,Shanxi Province Cervical Cancer Screening Study; EVAH,Evaluating the Visual Appearance of cervical lesions in relation its histological diagnosis, human papillomavirus genotype and other viral parameters; HSIL,high-grade squamous intraepithelial lesion.

## Number and Type of Biopsies Taken at Colposcopy

### Recommendation

Multiple biopsies targeting all areas with acetowhitening, metaplasia, or higher abnormalities are recommended. Usually, at least 2 and up to 4 targeted biopsies from distinct acetowhite lesions should be taken.

### Rationale and Supporting Evidence

Many studies have shown that taking a single biopsy targeting the worst-appearing lesion may miss a third and up to half of prevalent precancers (see Table 1). In all studies, there was a substantial increase moving from 1 to 2 targeted biopsies. In the National Cancer Institute Biopsy Study, which used a very low threshold of colposcopic abnormality (any acetowhitening), the yield of precancer increased substantially from the first to second and from second to third biopsies. A fourth targeted biopsy, or an additional nontargeted biopsy (random biopsy), provided only a minimal increase in disease yield. Targeted biopsies should be taken from women with any degree of acetowhitening.

## Biopsy Practice in Women With Low Risk of Precancer

### Recommendation

Nontargeted biopsies are not recommended for women referred to colposcopy at the lowest end of risk, that is, those with less than HSIL cytology, no evidence for HPV16/18, and a completely normal colposcopic impression (i.e., no acetowhitening, metaplasia, or other visible abnormality).

### Rationale and Supporting Evidence

Multiple studies have shown that women with a low previous risk and a completely normal colposcopy impression (<acetowhitening) have a very low risk of prevalent precancer (see Table 2). A prospective study from the United Kingdom showed that women with normal colposcopy impression and borderline-mild cytology findings have a very low risk of precancer in the following years.[12]

In many studies, "random biopsies" are not well defined. They often refer to biopsies taken of normal-appearing cervix, but these normal areas can include areas of acetowhitening or metaplasia. It is more appropriate to differentiate targeted biopsies, that is, biopsies targeting any visible change, including acetowhitening, metaplasia, and other changes within the normal and abnormal spectrum, from completely nontargeted biopsies. Studies that have systematically evaluated the incremental yield of nontargeted biopsies in addition to targeted biopsies have shown very limited additional benefit for detection of precancer.[4,5,13] Biopsies are recommended even when the colposcopic impression is negative but any degree of acetowhitening, metaplasia, or other abnormality is present. Failing to do so may risk missing CIN 3+ and allowing untreated progression.

## Biopsy Practice in Women With Very High Risk of Precancer

### Recommendation

In nonpregnant women 25 years and older with very high risk of precancer (at least 2 of the following: HSIL cytology, HPV 16 and/or HPV 18 positive, high-grade colposcopy impression), either immediate excisional treatment without biopsy confirmation or colposcopy with multiple targeted biopsies is acceptable. Endocervical sampling should be conducted according to the 2012 ASCCP Management Guidelines.[14] If biopsies are taken and do not show precancer, management according to the 2012 ASCCP Management Guidelines is recommended.[14]

### Rationale and Supporting Evidence

A systematic review of see-and-treat management strategies for women with HSIL cytology found that 89% of all women with HSIL had CIN 2+,[15] whereas other studies have shown somewhat lower risk (see Table 3).[5,11] Currently, 2012 ASCCP Management Guidelines give the option of immediate treatment for women with HSIL cytology.[14] Table 3 shows that in each study, the risk of precancer in women with HSIL and high-grade colposcopy impression or HPV 16 and high-grade colposcopy impression substantially exceeds the current HSIL risk threshold at which immediate treatment is acceptable, suggesting that immediate treatment can be recommended particularly for these women. If the alternate strategy of taking multiple targeted biopsies shows no precancer despite the high previous risk, increased surveillance is recommended according to the 2012 ASCCP Management Guidelines.[14] Data from the Biopsy Study suggest that finding no precancer after a multiple biopsy protocol has a high negative predictive value.

## DISCUSSION

As part of the ASCCP Colposcopy Standards effort, recommendations for risk-based colposcopy practice were developed. Women referred to colposcopy have a wide range of risk of cervical precancer, which can be estimated using morphological (cytology), molecular (HPV testing and genotyping), and visual (colposcopic impression) risk markers measured at screening, triage, and the colposcopy visit. Depending on the risk of precancer as determined by these markers, colposcopy practice can be modified. Generally, at least 2 and up to 4 targeted biopsies are recommended for accurate detection of prevalent precancers. In women at lowest risk (no high-grade cytology, no HPV16/18, normal colposcopic impression), nontargeted (random) biopsies are not recommended. There is currently insufficient evidence for or

**TABLE 2.** Risk of Cervical Precancer in Women With Normal Colposcopy and Low Previous Risk

**Low-risk group: <HSIL, HPV 16/18-, normal colposcopy**

| Study | Article | *n* | CIN 2+ | CIN 3+ | Proportion CIN 2+ | Proportion CIN 3+ |
|---|---|---|---|---|---|---|
| ATHENA | Huh et al.[6] | 660 | 15 | 6 | 0.0227 | 0.0091 |
| ALTS trial | | 402 | 4 | 2 | 0.0100 | 0.0050 |
| BD Onclarity trial | | 1,572 | 25 | 11 | 0.0159 | 0.0070 |
| Biopsy Study | | 38 | 3 | 0 | 0.0789 | 0.0000 |
| Pooled estimate | | 2,672 | 47 | 19 | 0.015 (0.007–0.026) | 0.004 (0.002–0.008) |

HSIL indicates high-grade squamous intraepithelial lesion; HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; ATHENA, Addressing The Need for Advanced HPV Diagnostics; ALTS, ASCUS Low-grade Triage Study; BD, Becton Dickinson.

**TABLE 3.** Risk of CIN 2+ in Women With High Previous Risk Strata

| Strata | Study | Reference | Population | *n* | CIN 2+ | Proportion CIN 2+ |
|---|---|---|---|---|---|---|
| HSIL only (reference) | | Aue-Aungkul et al.[8] | HSIL | 133 | 119 | 0.89 |
| | | Bosgraaf et al.[9] | HSIL | 1,781 | 1,643 | 0.92 |
| | ALTS | | ASCUS/LSIL | 411 | 246 | 0.60 |
| | BD | | HPV+ | 124 | 105 | 0.85 |
| | Biopsy Study | Wentzensen et al.[5] | ASCUS+ | 206 | 127 | 0.62 |
| | Pooled estimate | | | 2,655 | 2,240 | 0.79 (0.61–0.93) |
| High-grade colposcopy and HSIL+ | | Aue-Aungkul et al.[8] | HSIL | 110 | 102 | 0.93 |
| | | Bosgraaf et al.[9] | HSIL | 1,543 | 1,473 | 0.95 |
| | ALTS | | | 155 | 122 | 0.79 |
| | BD | | | 17 | 13 | 0.76 |
| | Biopsy Study | | | 108 | 81 | 0.75 |
| | Pooled Estimate | | | 1,933 | 1,791 | 0.86 (0.73–0.95) |
| High-grade colposcopy and HPV 16/18+ | DSI trial | Zaal et al.[10] | BMD twice | 18 | 17 | 0.94 |
| | ALTS | | | 182 | 133 | 0.73 |
| | BD | | | 31 | 19 | 0.61 |
| | Biopsy Study | | | 83 | 65 | 0.78 |
| | Pooled estimate | | | 314 | 234 | 0.76 (0.66–0.85) |
| HSIL and HPV 16/18+ | ALTS | | | 171 | 128 | 0.75 |
| | BD | | | 46 | 31 | 0.67 |
| | Biopsy Study | | | 91 | 67 | 0.74 |
| | Pooled estimate | | | 308 | 196 | 0.73 (0.54–1.0) |
| High-grade colposcopy and HSIL and HPV 16/18+ | ALTS | | | 105 | 90 | 0.86 |
| | BD | | | 9 | 8 | 0.89 |
| | Biopsy Study | | | 57 | 45 | 0.79 |
| | Pooled estimate | | | 171 | 143 | 0.85 (0.78–0.90) |

CIN indicates cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; ALTS, ASCUS Low-grade Triage Study; BD, Becton Dickinson; DSI, Dynamic Spectral Imaging; BMD, borderline mild dyskariosis.

against non-targeted biopsies in women with HSIL, ASC-H or AGC; however, usually there is some degree of acetowhitening associated with these cytology results. In women at highest risk (either 2 or all 3 of high-grade cytology, HPV 16/18 positivity, and high-grade colposcopic impression), the risk of precancer is high enough that immediate treatment without biopsy confirmation is an alternative to biopsy confirmation. These recommendations clarify the content of the colposcopy encounter but do not change 2012 ASCCP Guidelines for Management of Abnormal Cervical Cancer Screening Tests.[14]

These recommendations follow the principles of risk-based management and precision medicine.[7,16] Instead of using a general approach to a larger population with varying risk of cervical precancer, risk assessment at colposcopy allows better tailoring of colposcopy practice to a woman's individual risk. For a risk-based strategy to be successful, several important conditions need to be met: (1) risk assessment tools need to be dependable and reproducible: the risk measures for the high-risk categories, HSIL cytology and high-grade colposcopy impression, and normal colposcopy impression for the low-risk category, are more reproducible than intermediate categories of cytology and colposcopy impression. (2) Risk estimates for specific strata should be portable across populations: our systematic literature review demonstrated that variability of risk estimates for the various strata was low across US studies. (3) The strategy must be readily implementable in clinical practice: rather than predicting individual risk in fine detail, it is clinically most practical to divide the population into a few strata with different risks that allow different clinical management. Thus, the 3 risk levels separated in the recommendations fulfill these criteria.

The evidence underlying these recommendations is based on data primarily from women screened with cytology. Cervical cancer screening is currently undergoing a major transition, with 3 primary screening strategies approved in the US (cytology alone, HPV alone, and cytology-HPV co-testing)[17,18] and many triage strategies under evaluation.[19,20] The combination of screening and triage results defines the overall risk in the colposcopy population. Screening strategies with primary HPV testing are more sensitive and may refer to colposcopy more women with small, incipient lesions that are harder to detect.[21] However, most currently established and evaluated strategies include cytology and HPV testing with partial genotyping. Therefore, the same strata will be applicable to different screening strategies. It is important to point out that dependable risk strata can be defined without HPV genotyping, which is currently not universally available. Our systematic review indicates that the risk within strata is comparable across studies, even between the studies with cytology screening and the single HPV screening trial. In the future, because new screening and triage strategies become available, risk strata can be adapted and benchmarked to currently established risk thresholds.

It is important to consider the implementation of risk-based colposcopy in clinical practice. Screening and triage test results, which are important components of risk stratification, are available to colposcopists at the time of the examination. This information is usually included in paper charts or, preferably, in electronic medical records. Colposcopy impression further modifies the previous risk estimates based on those tests and completes the risk assessment. New colposcopy forms and charts to be developed based on the ASCCP Colposcopy Standards should include the relevant risk information to standardize the risk assessment process.

In summary, assessing the risk of cervical precancer at the colposcopy visit allows for modification of colposcopy

procedures consistent with a woman's risk. This strategy allows observation without biopsy when risk is low and treatment without biopsy confirmation when risk is highest. For women in all other risk groups, taking multiple targeted biopsies including areas of even minimal acetowhitening is important to improve detection of cervical precancer at the colposcopy visit. It is expected that implementation of these recommendations will lead to improved detection of cervical precancers at colposcopy, while at the same time providing more reassurance of negative colposcopy results.

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