

## ASCCP Colposcopy Standards; WG2: Risk-based colposcopy

### Draft recommendations and supporting evidence

#### Recommendation #1:

Colposcopy-biopsy practice may be modified based on prior risk levels 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. The risk can be estimated from screening and triage tests (e.g. cytology and HPV with HPV16/18 genotyping), and the colposcopic impression at the colposcopy visit. Risk markers can be combined to stratify the population in groups with very different risk. Depending on the underlying risk, colposcopy-biopsy practice could be usefully modified. For example, when the risk of precancer is very high, immediate treatment may be recommended. Conversely, if the risk is very low, more expectant management may be warranted. For intermediate risks, multiple biopsies of acetowhite lesions lead to increased detection of precancer.*

**Recommendation #2:**

Multiple biopsies targeting all areas with acetowhitening, metaplasia or higher abnormalities are recommended. Usually, at least two and up to four 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 up to a third of prevalent precancers (Table 1). In all studies, there was a substantial increase moving from one to two targeted biopsies. In the NCI 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 second to third biopsies. A fourth targeted biopsy, or an additional non-targeted biopsy (random biopsy) only provided a minimal increase in disease yield.*

**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. Obstet Gynecol 2006             | ALTS trial, multiple centers in the USA | 2-year CIN3+           | 142/208 (68.3%) | 108/132 (81.8%) | 35/42 (83.3%)   | NA             |
| Pretorius et al. J Low Genit Tract Dis 2011 | SPOCCS, China                           | Cross-sectional, CIN3+ | 141/222 (63.5%) |                 |                 | 198/222 (89%)  |
| Van der Marel et al. Gynecol Oncol 2014     | EVAH study, Netherlands and Spain       | Cross-sectional, CIN2+ | 136/263 (51.7%) | 159/263 (60.4%) |                 |                |
| Wentzensen et al. J Clin Oncol 2015         | Biopsy Study, USA                       | Cross-sectional, HSIL+ | 157/252 (60.6%) | 222/252 (85.6%) | 246/252 (95.6%) | 252/252 (100%) |

**Recommendation #3:**

For women fulfilling the following criteria: less than HSIL cytology, no known HPV16/18 positivity, and who have a completely normal colposcopic impression (i.e. no acetowhitening, metaplasia, or other visible abnormality), biopsy may be deferred.

**Rationale and supporting evidence:**

*Multiple studies have shown that women with a low prior risk and a completely normal colposcopy impression (<acetowhitening) have a very low risk of prevalent precancer (Table 2). A prospective study from the UK showed that women with normal colposcopy impression and borderline-mild cytology findings have a very low risk of precancer in the following years (Table 3).*

**Table 2:** Risk of cervical precancer in women with normal colposcopy and low prior risk**Low-risk group: <HSIL, HPV 16/18-, normal colposcopy**

| Study  | Manuscript                          | N    | CIN2+ | CIN3+ | Proportion CIN2+ | Proportion CIN3+ |
|--------|-------------------------------------|------|-------|-------|------------------|------------------|
|        | Huh et al. Obstet Gynecol 2014      | 1225 | 8     | 2     | 0.0065           | 0.0016           |
| ATHENA | in preparation                      | 373  | 4     | 2     | 0.0107           | 0.0054           |
| ALTS   | in preparation                      | 1572 | 25    | 11    | 0.0159           | 0.0070           |
| BD     | Wentzensen et al. J Clin Oncol 2015 | 19   | 0     | 0     | 0.0000           | 0.0000           |
| Biopsy |                                     |      |       |       |                  |                  |
| Total  |                                     | 3189 | 37    | 15    | 0.0116           | 0.0047           |

**Table 3:** Prospective UK data (Kelly et al. BJOG 2012)**Cumulative disease at 1, 2, 3, >3 years after negative colposcopy in women with low-grade cytology**

| Years since negative colposcopy | Negative    | Abnormal cytology | CIN1      | CIN2      | CIN3      | Total |
|---------------------------------|-------------|-------------------|-----------|-----------|-----------|-------|
| 1                               | 912 (95.4%) | 10 (1.0%)         | 18 (1.9%) | 6 (0.6%)  | 10 (1.0%) | 956   |
| 2                               | 869 (90.9%) | 19 (2.0%)         | 33 (3.5%) | 16 (1.7%) | 19 (2.0%) | 956   |
| 3                               | 851 (89.0%) | 25 (2.6%)         | 38 (4.0%) | 19 (2.0%) | 23 (2.4%) | 956   |
| >3                              | 826 (86.4%) | 30 (3.1%)         | 49 (5.1%) | 23 (2.4%) | 28 (2.9%) | 956   |

#### Recommendation #4:

In non-pregnant women age 25 and older with very high risk of precancer (at least two of the following: HSIL cytology, HPV16 and/or HPV18 positive, high grade colposcopy impression), immediate treatment without biopsy confirmation is preferred but colposcopy with multiple targeted biopsies is acceptable. Endocervical sampling should be conducted according to the 2012 ASCCP management guidelines. If biopsies are taken and do not show precancer, increased surveillance according to the 2012 ASCCP management guidelines is recommended.

#### **Rationale and supporting evidence:**

*A large systematic review of see-and-treat management strategies for women with HSIL cytology found that 89% of all women with HSIL had CIN2+, while some clinical trials have shown somewhat lower risk. Currently, 2012 ASCCP management guidelines give the option of immediate treatment for women with HSIL cytology. Table 4 shows that in each study, the risk of precancer in women with HSIL and high grade colposcopy impression or HPV16 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 biopsies show no precancer despite the high prior risk, increased surveillance is recommended.*

**Table 4:** Risk of CIN2+ or HSIL+ in women with high prior risk strata

| Strata                              | Study        | Reference                           | Population | N    | CIN2+ | CIN3+ | HSIL + | Proportion CIN2+ | Proportion HSIL+ |
|-------------------------------------|--------------|-------------------------------------|------------|------|-------|-------|--------|------------------|------------------|
| HSIL only (reference)               | Syst. review | Ebisch et al. BJOG 2016             | HSIL       | 3777 | 3351  |       |        | 0.89             |                  |
|                                     | ALTS         | in preparation                      | ASCUS/LSIL | 314  | 177   |       |        | 0.56             |                  |
|                                     | BD           | in preparation                      | HPV+       | 133  | 65    | 34    |        | 0.49             |                  |
|                                     | Biopsy       | Wentzensen et al. J Clin Oncol 2015 | ASCUS+     | 236  | --    | --    | 125    |                  | 0.53             |
|                                     | Total        |                                     |            | 4460 | 3593  | 34    | 125    | 0.85             | 0.53             |
| High-grade colpo + HSIL +           | Syst. review | Ebisch et al. BJOG 2016             |            | 3403 | 3077  |       |        | 0.90             |                  |
|                                     | ALTS         | in preparation                      |            | 103  | 80    |       |        | 0.78             |                  |
|                                     | BD           | in preparation                      |            | 17   | 13    | 10    |        | 0.76             |                  |
|                                     | Biopsy       | Wentzensen et al. J Clin Oncol 2015 |            | 109  | --    | --    | 77     |                  | 0.71             |
|                                     | Total        |                                     |            | 3632 | 3170  | 10    | 78     | 0.90             | 0.71             |
| High-grade colpo + HPV16/18+        | DSI trial    | Zaal et al. BJOG 2012               | BMD twice  | 18   | 17    | 14    |        | 0.94             |                  |
|                                     | ALTS         | in preparation                      |            | 101  | 76    |       |        | 0.75             |                  |
|                                     | BD           | in preparation                      |            | 31   | 19    | 13    |        | 0.61             |                  |
|                                     | Biopsy       | Wentzensen et al. J Clin Oncol 2015 |            | 84   | --    | --    | 65     |                  | 0.77             |
|                                     | Total        |                                     |            | 234  | 112   | 27    | 65     | 0.75             | 0.77             |
| HSIL + HPV16/18+                    | ALTS         | in preparation                      |            | 153  | 103   |       |        | 0.67             |                  |
|                                     | BD           | in preparation                      |            | 46   | 31    | 20    |        | 0.67             |                  |
|                                     | Biopsy       | Wentzensen et al. J Clin Oncol 2015 |            | 83   | --    | --    | 65     |                  | 0.78             |
|                                     | Total        |                                     |            | 282  | 134   | 20    | 65     | 0.67             | 0.78             |
| High-grade colpo + HSIL + HPV16/18+ | ALTS         | in preparation                      |            | 55   | 47    |       |        | 0.85             |                  |
|                                     | BD           | in preparation                      |            | 9    | 8     | 6     |        | 0.89             |                  |
|                                     | Biopsy       | Wentzensen et al. J Clin Oncol 2015 |            | 58   | --    | --    | 45     |                  | 0.78             |
|                                     | Total        |                                     |            | 122  | 55    | 6     | 45     | 0.86             | 0.78             |