Enduring Guidelines Dual Stain Summary for Public Comments

Introduction

The Enduring Consensus Cervical Cancer Screening and Management Guidelines effort (Enduring Guidelines) is a standing committee to provide regular updates of the 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors for new technologies and approaches that were not includes in the 2019 guidelines process. Enduring guidelines includes experts in cervical cancer prevention, as well as representatives from 20 national organizations including patient advocacy groups. More details are available at: https://dceg.cancer.gov/research/cancer-types/cervix/enduring-guidelines

Risk-based approach: Following the approach of the 2019 consensus management guidelines, a risk-based approach is used to determine clinical actions. Specifically, the immediate and 3-year or 5-year risk of developing CIN3, AIS, or cancer (CIN3+) is estimated using prevalence-incidence mixture models.[1] Resulting clinical actions are based on risk thresholds determined by the 2019 guidelines.[2] Thresholds have been developed for return in 5 years, return in 3 years, return in 1 year, colposcopy, colposcopy or expedited treatment, and expedited treatment.[1–3] The risk threshold that is used most throughout the remainder of this document is the colposcopy risk threshold: colposcopy is recommended when the immediate risk of CIN3+ is 4-24%. As an extension to the 2019 process, 3-year risk thresholds have been developed to accommodate data on new technologies with shorter durations of follow-up.[5] When sufficient 5-year follow-up data are available, a 5-year risk threshold is used. For technologies evaluated in studies with shorter duration of follow-up, 3-year risk thresholds are used.

Exceptions to risk thresholds: During the 2019 process, exceptions were made to risk thresholds for certain situations. One example is an HPV18+ test result, which has an elevated cancer risk compared to the risk of CIN3. The decision was made to recommend colposcopy for HPV18+ due to elevated cancer risk although the CIN3+ risk was below the colposcopy threshold.[2]

Additional metrics for the Enduring Guidelines process: In addition, resource utilization metrics are computed for different approaches (Das et al. in preparation); these resource utilization metrics include number of colposcopy referrals, number of tests performed, and number of years of delayed diagnosis of CIN3+; costs are not explicitly considered.

Terminology and evidence evaluation metrics can be found in the Glossary at the end of this document.

Background on p16/Ki-67 Dual Stain and proposed recommendations

This remainder of this document describes background information on p16/Ki-67 Dual Stain (commercially available as CINTec Plus) and proposed guidelines for its use in clinical practice.

Background

p16/Ki-67 Dual Stain (DS) is a cytology-based test for detection of cervical precancer that has been approved by the FDA for triage of positive test results in HPV screening and HPV-cytology co-testing. DS detects a marker of HPV-related oncogene activity (p16) and a marker of cell proliferation (Ki-67) which, when detected in the same cell, are associated with precancerous cellular changes (CIN3+). This document summarizes risk-based recommendations for use of dual stain in management of abnormal cervical screening results by estimating risk for strata of DS results, screening test results, and screening history among individuals who test HPV+ and by evaluating resource utilization of DS for triage in comparison to established triage strategies.

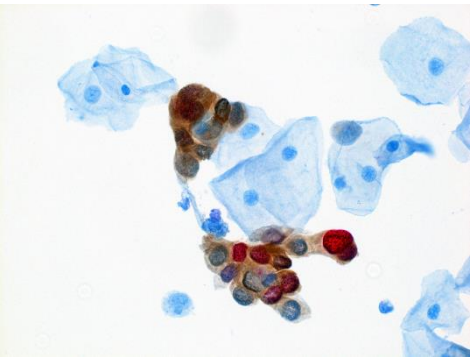

Figure 1: Dual stain positive cells; brown staining for p16; red staining for Ki-67

Dual Stain interpretation

A cell is considered Dual Stain Positive (DS+) if both stains (p16 and Ki-67) are present in the same cell. Slides with one or more DS+ cells are considered positive. DS was performed via manual review by a cytotechnologist with pathology sign-out or by manual DS review by cytotechnologist with full re-review of negative slides by a cytotechnologist.

Study populations

Risk estimates supporting the recommendations were calculated in two distinct populations, from Kaiser Permanente Northern California (KPNC) and from Mississippi (STRIDES Cohort). The inclusion of both populations is critical to ensure that recommendations for new technologies or management approaches provide a benefit for individuals in diverse settings.

Data from Kaiser Permanente Northern California (KPNC) includes the DS Implementation Study[6,7] and a subset of the IRIS Cohort.[8] These cohorts include individuals undergoing co-testing for cervical screening with Surepath cytology who tested positive for HPV (either hc2 or cobas) in 2015 (Implementation Study) and 2017 (IRIS). Individuals were followed through Fall 2022, with a high follow-up rate for baseline risk and through 3 years. The KPNC population includes a diverse population from California (44% White, 24% Hispanic, 18% Asian/Pacific Islander and 8% Black), all of whom are members of Kaiser Permanente.

The STRIDES cohort in Mississippi[9] includes individuals undergoing co-testing for cervical screening using Thinprep cytology who tested positive for HPV (cobas) in 2018-2019. Individuals were followed through Fall 2022; follow-up is still ongoing for some baseline risk estimates. The STRIDES population includes a diverse population from Mississippi (60% Black, 26% White), over half of whom reside in rural areas, and two-thirds of whom receive publicly-funded screening services.

Data summary and proposed guidelines

The evidence summary is focused on ***DS triage of HPV-positive screening results based on HPV primary screening or HPV-cytology co-testing*** using data from US-based studies. DS is not proposed for primary screening or cytology triage at this point; nor is DS proposed for refining the management of women testing HPV-negative.

1. Dual Stain (DS) for triage of HPV-positives

PROPOSED RECOMMENDATION #1: ***Dual stain is acceptable for triage of HPV-positive individuals with management according to risk .(AII)***

Rationale:
Dual stain provides excellent discrimination between HPV-positive individuals requiring colposcopy and those who can be safely followed in 1 year. Performance is similar in the KPNC and STRIDES cohorts, indicating similar test performance in diverse populations. The risks for HPV+/DS+ exceeded the colposcopy threshold in all scenarios, even for those with prior HPV-negative screening results, indicating that past history does not change patient management when DS is used. In addition, compared to cytology, dual stain requires fewer colposcopies and detects CIN3 earlier.

Considerations:

- This is a recommendation for HPV tests without genotyping
- Primary screening HPV tests currently include limited genotyping
- When limited genotyping is available, please refer to guidelines for specific HPV genotypes
- This is a recommendation that can be used in settings when other risk information is not available

Evidence summary for Dual Stain (DS) for triage of HPV-positives
Tables 1 and 2 below show CIN3+ risks for HPV-positive individuals triaged with DS. In both the KPNC and STRIDES cohorts, and regardless of past history in KPNC, HPV-positive DS-positive results met the colposcopy threshold of 4%-24% immediate CIN3+ risk, and HPV-positive DS-negative results were below the colposcopy threshold and met criteria for a 1-year return.

Immediate CIN3+ risks of HPV-positive DS-positive were similar in the KPNC (9.5%) and STRIDES (11.5%) cohorts. Risks for HPV-positive DS-negative were also similar (1.5% KPNC, 0.7% STRIDES). A negative prior HPV test reduced the estimated immediate CIN3+ risk, however, the colposcopy threshold was still exceeded (4.9%).

Table 1: Dual Stain triage of HPV-positive individuals: KPNC

Prior history	Current Test Result	N	CIN3+ Cases	CIN3+ Immediate Risk	CIN3+ 3yr Cumulative Risk	Clinical management recommendation	Management Confidence Probability (%)
Not considered	HPV+/DS+	3,384	362	9.5%	12%	**colposcopy**	100%
Not considered	HPV+/DS-	3,458	44	0.75%	1.5%	**1-year return**	100%
HPV-neg	HPV+/DS+	710	48	4.9%	7.9%	**colposcopy**	86%
HPV-neg	HPV+/DS-	991	9	0.16%	1.2%	**1-year return**	97%

Table 2: Dual Stain triage of HPV-positive individuals: STRIDES

Prior history	Current Test Result	N	CIN3+ Cases	CIN3+ Immediate Risk*	Clinical management recommendation*
Not considered	HPV+/DS+	768	88	11.5%	**colposcopy**
Not considered	HPV+/DS-	1154	8	0.7%	**1-year return**

**Duration of follow-up in the STRIDES cohort is currently not sufficient to estimate cumulative 3-year risks and management confidence probabilities; follow-up is ongoing*

Table 3 describes resource utilization for a hypothetical population of 100,000 individuals undergoing screening with primary HPV testing in scenarios where positive HPV test results are triaged with either DS or cytology, followed from the baseline HPV-positive result through three years of follow-up. The total number of colposcopies, visits at which HPV, DS, or cytology are performed for screening or follow-up, and cumulative years of delay of CIN3+ are compared. Clinical management in the model includes: HPV+/DS+ or HPV+/ASCUS or higher always receives colposcopy; HPV+/NILM or HPV+/DS- repeats testing in 1 year with colposcopy if HPV+/NILM or higher. The model uses ideal assumptions of full compliance with colposcopy and follow up, highly sensitive cytology, and 100% sensitivity for CIN3+ detection at colposcopy. ***In this model, triaging HPV+ results with cytology results in 18% more total colposcopies and 59% more years of delay in CIN3+ diagnoses compared to triage with DS***.

Table 3. Resource utilization comparing DS and cytology triage of HPV-positive results

Metric	DS	Cytology	Difference in metric cytology vs. DS
Total colposcopy referrals per 100k individuals after 3 years	6697	7892	+18%
Number of visits for HPV/DS/cytology testing	125,020	125,158	0%
Cumulative years of delay in CIN3+ per 100k individuals	128	203	+59%

2. Dual Stain (DS) for triage of HPV-positives when limited genotyping is provided by the screening test

PROPOSED RECOMMENDATION #2: ***A combination of dual stain and limited genotyping (provided by the screening HPV test) is acceptable for triage of HPV-positive individuals. All HPV16 and HPV18 positive individuals should be referred to colposcopy, until additional data on safety in HPV16+/DS- and HPV18+/DS- individuals become available. Women with HR12 should be managed according to risk. (AII)***

Rationale:
Dual stain provides excellent discrimination between HR12-positive individuals requiring colposcopy and those who can be safely followed in 1 year. Performance is similar in the KPNC and STRIDES cohorts. The risks for HPV HR12+/DS+ exceeded the colposcopy and HPV HR12+/DS- met the 1-year return threshold in all scenarios. Compared to cytology, dual stain requires fewer colposcopies and detects CIN3 earlier.

Considerations:
- Number of cancer outcomes is limited. Additional data and follow-up are needed to inform deferral strategies.
- Women positive for HPV16 and dual stain are at high risk, approaching the 25% threshold where expedited treatment is an option.
- HPV tests currently approved for HPV alone screening provide limited genotyping information as part of the test result. Resource utilization models assume that genotyping information is provided as part of the initial test result, not as an additional test.

Tables 4 and 5 below show CIN3+ risks for HPV-positive individuals triaged with DS when limited genotyping is provided by the screening test. Risk estimates are shown for DS-positive and DS-negative test results in strata of limited genotyping. Strata are ordered hierarchically, from the most to least carcinogenic HPV types: HPV16, else HPV18, else other 12 high-risk types (HR12). In both the KPNC and STRIDES cohorts, HPV16-positive DS-positive results, HPV18-positive DS-positive results, and HR12-positive DS-positive results met the colposcopy threshold of 4%-24% immediate CIN3+ risk. The CIN3+ risk of HPV-positive DS-negative results were below the colposcopy threshold for all genotype categories, and met criteria for a 1-year return. However, HPV16 and HPV18 are most strongly associated with cervical cancer, and currently, all HPV16 and HPV18-positive individuals are recommended to be referred to colposcopy, independent of cytology result. While the CIN3+ risks of HPV16-positive, DS-negative and HPV18-positive, DS-negative individuals are clearly below the colposcopy referral threshold, additional data on cancer outcomes are required to support risk-based management for this group. In the interim, it is recommended that all HPV16 and HPV18 positive results are referred to colposcopy, independent of DS result.

Table 4: Dual Stain triage of HPV-positive individuals when limited genotyping is provided by the screening test: KPNC

Current Test Result	N	CIN3+ Cases	CIN3+ Immediate Risk	CIN3+ 3-year Cumulative Risk	Clinical management recommendation	Management Confidence Probability%
DS+/HPV16+	681	172	23%	29%	**colposcopy**	88%
DS-/HPV16+	325	15	2.6%	5.0%	**1-year return**	99%
DS+/HPV18+	200	26	11%	15%	**colposcopy**	100%
DS-/HPV18+	137	2	1.1%	2.4%	**1-year return**	99%
DS+/HR12+	2,503	164	5.6%	7.6%	**colposcopy**	100%
DS-/HR12+	2,996	27	0.53%	1.1%	**1-year return**	100%

Table 5: Dual Stain triage of HPV-positive individuals when limited genotyping is provided by the screening test: STRIDES

Current Test Result	N	CIN3+ Cases	CIN3+ Immediate Risk	Clinical management recommendation*
DS+/HPV16+	178	43	24.2%	**colposcopy**
DS-/HPV16+	110	2	1.8%	**1-year return**
DS+/HPV18+	72	4	5.6%	**colposcopy**
DS-/HPV18+	84	0	0%	**1-year return**
DS+/HR12+	518	41	7.9%	**colposcopy**
DS-/HR12+	919	4	0.5%	**1-year return**

**Duration of follow-up in the STRIDES cohort is currently not sufficient to estimate cumulative 3-year risks and management confidence probabilities; follow-up is ongoing*

Table 6 uses the same approach to utilization modeling as Table 3, now incorporating limited genotyping. A hypothetical population of 100,000 individuals undergoes screening with primary HPV testing which provides limited genotyping for HPV-positives. Clinical management in the model includes: HPV16+ or HPV18+ always receives colposcopy irrespective of DS or cytology result; HR12-positive, DS positive is referred to colposcopy; HR12-positive and ASC-US or greater is referred to colposcopy; HR12+/NILM or HR12+/DS- repeats testing in 1 year with colposcopy if HPV+/NILM or higher at the 1-year follow-up visit. The total number of colposcopies, visits at which HPV, DS, or cytology are performed for screening or follow-up, and cumulative years of delay of CIN3+ are compared over 3 years of follow-up. The model uses ideal assumptions of full compliance with colposcopy and follow up, highly sensitive cytology, 100% sensitivity for CIN3+ detection at colposcopy. ***In this model, triaging HPV HR12+ results with cytology results in 10% more total colposcopies and 29% more years of delay in CIN3+ diagnoses compared to triage with DS.***

Table 6: Resource utilization comparing dual stain triage and cytology triage for HPV-positives when limited genotyping is provided by the HPV screening test

Metric	DS	Cytology	Difference in metric cytology vs. DS
Total colposcopy referrals per 100k individuals after 3 years	8545	9407	+10%
Number of visits for HPV/DS/cytology testing	111379	111403	0%
Cumulative years of delay in CIN3+ per 100k individuals	103	133	+29%

3. Dual Stain (DS) for triage of HPV-positive NILM, ASC-US, and LSIL in co-testing

PROPOSED RECOMMENDATION #3: *In a co-testing setting, dual stain is acceptable for triage of HPV-positive individuals with NILM, ASC-US, or LSIL with management according to risk. (AII)*

Rationale: Dual stain provides excellent risk stratification for NILM, ASC-US, and LSIL in a co-testing setting**.** Performance is similar in the KPNC and STRIDES cohorts. Dual stain triage of NILM, ASC-US, LSIL in a co-testing setting results in a reduction of colposcopies and reduced delay of CIN3+ detection, while additional tests are required.

Considerations:

- In individuals with ASC-H, AGC, HSIL, dual stain should not be performed
- When primary screening test includes limited genotyping, individuals with HPV16/18 should receive colposcopy; individuals with HR12 can be managed as above

Tables 7 and 8 below show CIN3+ risks for HPV-positive individuals with NILM, ASC-US and LSIL in a co-testing setting. Risk estimates are shown for DS-positive and DS-negative test results among individuals with HPV-positive NILM, ASC-US, and LSIL. In both the KPNC and STRIDES cohorts, ASC-US and LSIL with DS-positive results met the colposcopy threshold of 4%-24% immediate CIN3+ risk, and all HPV-positive ASC-US and LSIL with DS-negative results were below the colposcopy threshold and met criteria for a 1-year return. HPV-positive NILM with DS-positive results met the colposcopy threshold and HPV-positive NILM with DS-negative results met criteria for a 1-year return in KPNC; follow-up is still underway for HPV-positive NILM in STRIDES.

Table 7: Dual stain triage of NILM, ASC-US, LSIL in a co-testing setting in KPNC.

Current Test Result	N	CIN3+ Cases	CIN3+ Immediate Risk	CIN3+ 3-year Cumulative Risk	Clinical management recommendation	Management Confidence Probability%
NILM/DS+	1,003	73	4.6%	8.6%	**colposcopy**	79%
NILM/DS-	1,864	20	0.60%	1.5%	**1-year return**	100%
ASC-US/DS+	978	82	6.6%	9.9%	**colposcopy**	100%
ASC-US/DS-	954	15	0.9%	1.6%	**1-year return**	100%
LSIL/DS+	942	46	4.1%	5.9%	**colposcopy**	58%
LSIL/DS-	595	7	0.5%	0.9%	**1-year return**	100%

Table 8: Dual stain triage of NILM, ASC-US, LSIL in a co-testing setting in STRIDES.

Current Test Result	N	CIN3+ Cases	CIN3+ IR	Clinical management recommendation
NILM/DS+	332	*7*	*Follow-up still underway*	
NILM/DS-	929	*5*	*Follow-up still underway*	
ASC-US/ DS+	145	11	7.5%	**colposcopy**
ASC-US/ DS-	95	1	1.1%	**1-year return**
LSIL/DS+	150	12	8.0%	**colposcopy**
LSIL/DS-	68	0	0.0%	**1-year return**

**Duration of follow-up in the STRIDES cohort is currently not sufficient to estimate risks associated with NILM/DS+, cumulative 3-year risks, and management confidence probabilities; follow-up is ongoing*

Similar to Tables 3 and 6, Table 9 describes resource utilization for a hypothetical population of 100,000 individuals. Table 9 describes screening with co-testing in scenarios where positive HPV test results with NILM, ASC-US or LSIL cytology are triaged with DS, in comparison to management by co-testing alone. Clinical management in the model includes: Referral of HPV+/NILM DS-positive, HPV+/ASC-US DS-positive, and HPV+/LSIL DS-positive to colposcopy while DS-negatives are retested after 1 year. The total number of colposcopies, visits at which HPV, DS, or cytology are performed for screening or follow-up, the total number of tests, and cumulative years of delay of CIN3+ are compared. The model uses ideal assumptions of full compliance with colposcopy and follow up, highly sensitive cytology, 100% sensitivity for CIN3+ detection at colposcopy. ***In this model, co-testing alone results in 17% more total colposcopies and 64% more years of delay in CIN3+ diagnoses compared to triage of NILM, ASC-US, LSIL with DS. Additional DS triage results in a 6% increase of number of tests over three years.***

Table 9: Resource utilization comparing dual stain triage of NILM, ASC-US, LSIL in a co-testing setting to co-testing without additional triage

Metric	DS triage of NILM, ASC-US, LSIL in co-testing	Co-testing alone	Difference in metric cytology vs. DS
Total colpo referrals per 100k individuals after 3 years	6761	7888	+17%
Number of visits	111475	111550	0.0%
Number of tests over three years	236462	223101	-6%
Cumulative years of delay CIN3+	126	207	+64%

4. Use of Dual Stain (DS) in follow-up after abnormal results, colposcopy, or treatment (surveillance settings)

PROPOSED RECOMMENDATION #4: ***When patients are being followed after an abnormal screening test result, after colposcopy, or after treatment, it is acceptable to use DS according to the guidelines outlined for screening (e.g., to triage a positive HPV test result or a co-test result of HPV-positive NILM, ASCUS, or LSIL).*** **(CIII)**

Rationale:
Data in the screening setting indicate that DS provides greater risk discrimination than cytology and that past history therefore has less impact on the risk estimate of a DS result than a cytology result. Therefore, it follows that DS can be used in the settings of follow-up after abnormal screening tests, colposcopy, or treatment using the same recommendations outlined for the screening settings. Specifically, DS can be used for triage of HPV-positive test results when primary HPV testing is used, or for triage of HPV-positive NILM, ASCUS, or LSIL results when co-testing is used.

5. Unsatisfactory Dual Stain (DS) results

PROPOSED RECOMMENDATION #5: ***When a DS result is unsatisfactory, repeating the sample is recommended. Repeat sampling can occur as soon as is convenient.*** **(CIII)**

Rationale:
DS involves examination of cervical cells, and therefore may be unsatisfactory due to insufficient cellularity of the specimen. In this case, precancer cannot be excluded, and the sample should be repeated.

REFERENCES

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GUIDELINES TERMINOLOGY, EVIDENCE EVALUATION, AND GLOSSARY

Terminology: As in prior guidelines,[2,4] the following terminology is used for recommendations:

Recommended: Good data to support use when only one option is available.
Preferred: Option is the best (or one of the best) when there are multiple options
Acceptable: One of multiple options when there is either data indicating that another approach is superior or when there are no data to favor any single option
Not recommended: Weak evidence against use and marginal risk for adverse consequences
Unacceptable: Good evidence against use

Note: "preferred" is used when there are multiple options and some are considered preferable to others. "Acceptable" is used when there are multiple options and all are considered equally beneficial.

Evidence evaluation for Rating the Recommendations (carried forward from 2012 and 2019 guidelines processes)

Strength of recommendation

A. Good evidence for efficacy and substantial clinical benefit support recommendation for use.
B. Moderate evidence for efficacy or only limited clinical benefit supports recommendation for use.
C. Evidence for efficacy is insufficient to support a recommendation for or against use, but recommendations may be made on other grounds.
D. Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use.
E. Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use.

Quality of evidence

I. Evidence from at least one randomized, controlled trial.
II. Evidence from at least one clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies, or dramatic results from uncontrolled experiments.
III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Terminology used for recommendations

Recommended. Good data to support use when only one option is available.
Preferred. Option is the best (or one of the best) when there are multiple options
Acceptable. One of multiple options when there is either data indicating that another approach is superior or when there are no data to favor any single option
Not recommended. Weak evidence against use and marginal risk for adverse consequences
Unacceptable. Good evidence against use

GLOSSARY

Dual Stain (DS): p16/Ki-67 Dual Stain (DS) is a cytology-based test for detection of cervical precancer that has been approved by the FDA for triage of positive test results in HPV screening and HPV-cytology co-testing. DS detects a marker of HPV-related oncogene activity (p16) and a marker of cell proliferation (Ki-67) which, when detected in the same cell, are associated with precancerous cellular changes (CIN3+).

Management Confidence Probability (%): This metric describes the likelihood that, if risk estimates were recalculated in a similar population, the clinical management recommendation would be the same.

Cervical Intraepithelial Neoplasia (CIN and CIN3+) CIN is a pathologic diagnosis of squamous cervical abnormalities detected on histopathologic analysis of a cervical biopsy, endocervical curettage (ECC) or excisional biopsies such as cold knife cone or Loop Electrosurgical Excision Procedure (LEEP). CIN terminology is a 3-tiered system (CIN1, CIN2, CIN3) but a 2-tier system (LSIL/HSIL) is now recommended. Both systems are currently in use by pathology laboratories. CIN1 in the 3-tiered system corresponds to LSIL in the 2-tiered system. CIN2 (when supported by p16 immunohistochemistry) and CIN3 in the 3-tiered system both correspond to HSIL in the 2-tiered system. **CIN3+**, used as the endpoint for risk estimates in this document, includes CIN3, AIS (adenocarcinoma in situ, a glandular cancer precursor), and cervical cancer.

The *Bethesda system* is a *system* for reporting cervical or vaginal cytologic diagnoses, used for reporting cervical cytology (Pap test) results. It was introduced in 1988 and revised in 1991, 2001, and 2014. The name comes from the location (*Bethesda*, Maryland) of the conference where this terminology was developed.

Cervical cytology terms:

Negative for intraepithelial lesion or malignancy (NILM) *normal result*

Atypical Squamous Cells of Uncertain Significance (ASCUS) *minimally abnormal result*

Atypical Squamous Cells of Uncertain Significance cannot exclude high grade squamous intraepithelial lesion (SIL) (ASC-H) *has features of high grade SIL but not fully developed; considered as a high-grade result in risk estimates*

Low grade Squamous Intraepithelial Lesion (LSIL) *minimally abnormal result that is the cytologic expression of HPV infection*

High Grade Squamous Intraepithelial Lesion (HSIL) *considered as a high-grade result in risk estimates*

Atypical Glandular Cells (AGC) are managed *as a high grade result, AGC reporting is subclassified in Bethesda by cell type (glandular, endocervical, endometrial) and further stratified by risk as "favor neoplastic" (higher risk) or "not otherwise specified/NOS" for glandular and endocervical cell types.*