ASC-US/LSIL/CIN1: cytology, colposcopy, and histology with case studies and ASCCP 2019 Management Guidelines

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Disclosures

- Alan G. Waxman, MD, MPH– Faculty – No Disclosures
- Please see www.asccp.org/CompOnlineCME for full program disclosures

Images used with permission:

- Apgar B, Brotzman G, Spitzer M. Integrated Colposcopy: A Text and Atlas. Elsevier; 2002, 2008. (ABS)
- Ferris D, Cox T, O'Connor D, Wright C. Modern Colposcopy. Wolters Kluwer, ASCCP; 2002
- Personal collections as noted on slides

Objectives

- Discuss the epidemiology, cytologic characteristics, and recommended management of ASC-US and LSIL
- Understand the role of past history in management of low grade results
- Discuss 2019 ASCCP Risk-Based Management Consensus guideline recommendations for low grade precursor disease

2001 Bethesda terminology

Atypical squamous cells (ASC)

ASC-US

Undetermined significance

ASC-H

Cannot exclude HSIL

Atypical squamous cells (ASC) reporting rates for all methods

College of American Pathologists (CAP) 2006 survey found median rates of ASC in reporting labs of:

- Total ASC 4.6%
- ASC-US 4.3%
- ASC-H 0.3%

Chmara BA, et al. *Arch Path Lab Med.* 2010;134.3:331.

ASC interpretation

- ASC-US reports are poorly reproducible even among expert cytologists
- ALTS: only 42% of ASC-US was upheld by the pathology quality control group – 38% downgraded and 18% upgraded to SIL

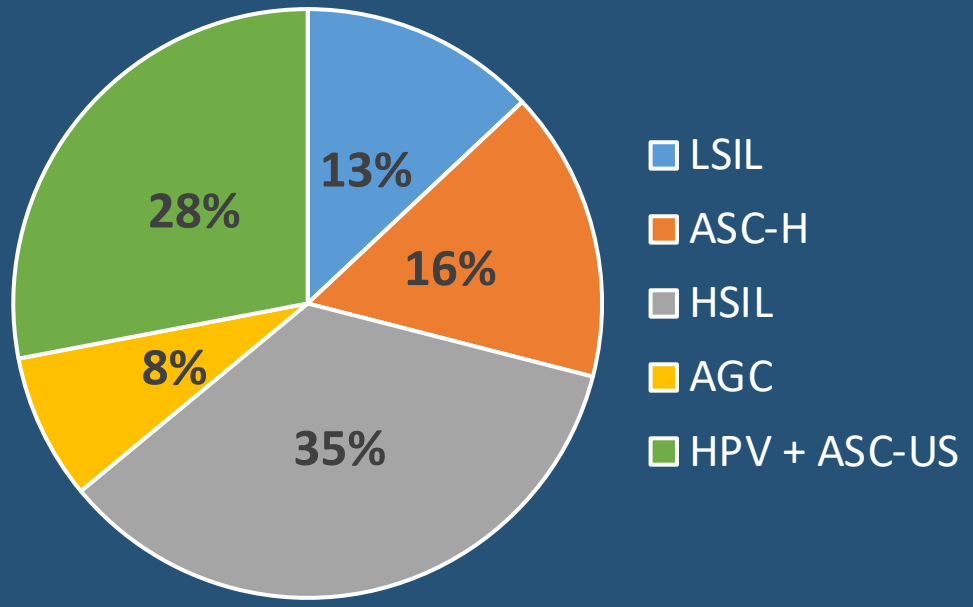
BUT

  - 5-17% of adult individuals with ASC-US have CIN 2+
  - Risk of invasion is low (0.1 - 0.2%)

Stoler, Schiffman. *J Am Med Assoc.* 2001;285:1500.
Solomon, Schiffman, Tarrone. *J Natl Cancer Instit.* 2001;93:293.

CIN 3+ - what was the referral cytology?

Distribution of CIN 3+ among individuals with abnormal cytology



Castle, et al. *Obstet Gynecol.* 2010;116:76-84.

5-year risk of CIN 3+ in individuals with ASC-US/HPV+

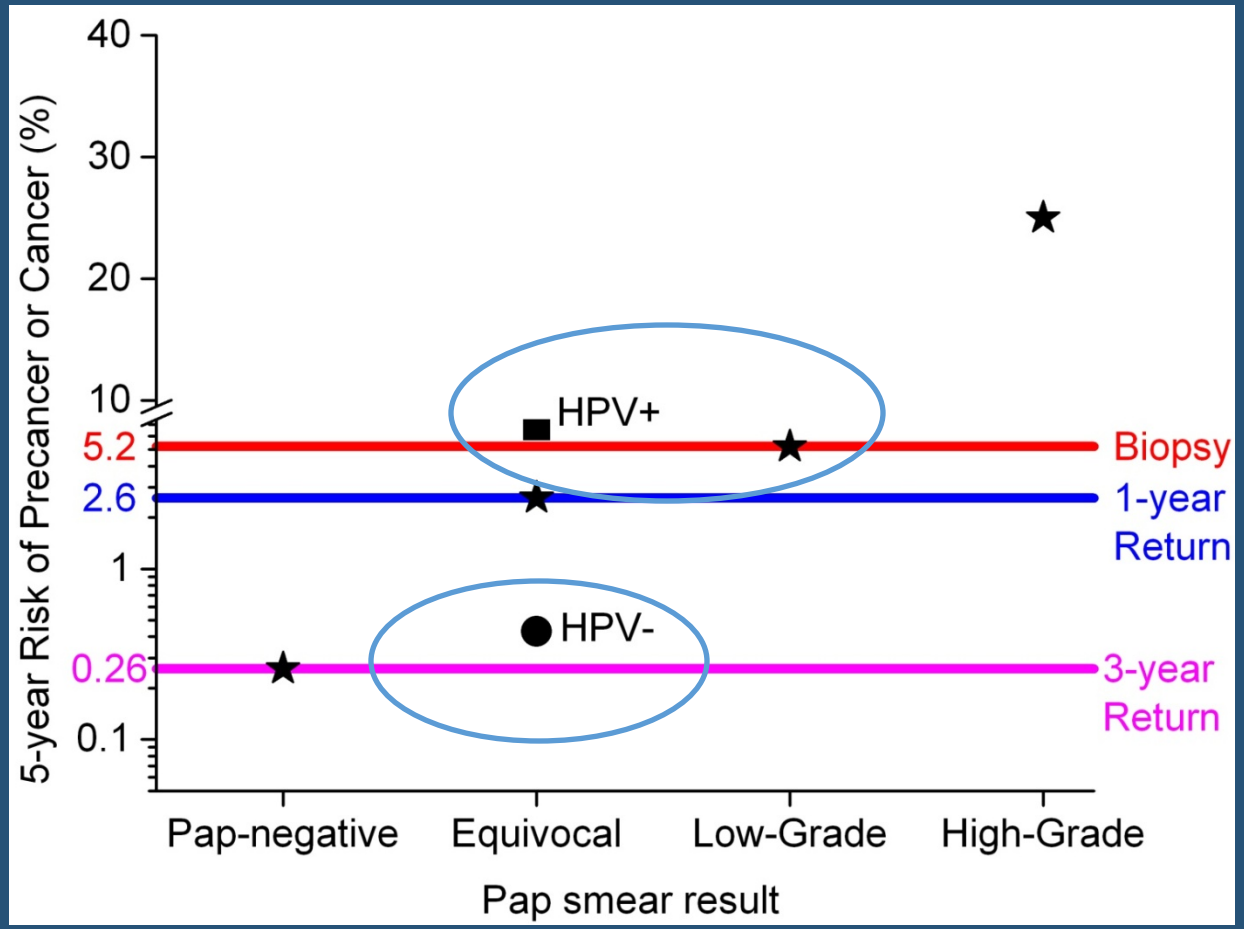
- Cumulative 5-year risk was 6.8% in KPNC* cohort
  - Slightly higher than LSIL (5.2%)
  - High enough to justify colposcopy irrespective of genotype result
    - Genotyping not recommended
- ASC-H confers substantially higher risk of CIN 3+ than ASC-US or LSIL but less than that of HSIL

Katki HA, et al. *JLGTD*. 2013;17:S36-S42.
*Kaiser Permanente Northern California

“Similar management of similar risks”

- Ensure simplified, consistent management for different test result combinations
- Can be initial management or follow-up

Risk of ASC-US*/HPV+ and HPV-

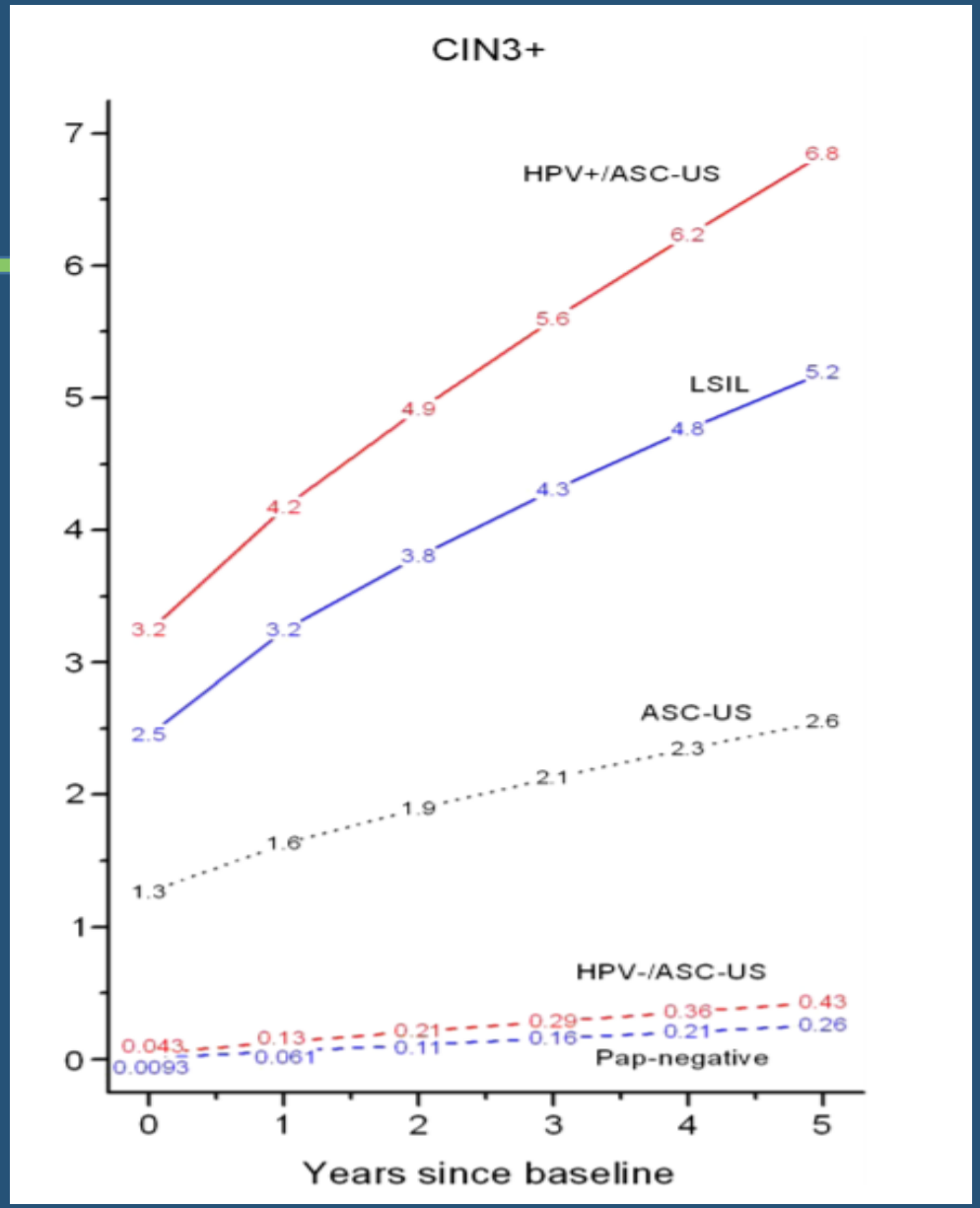


- ASC-US/HPV- has risk close to Cyto-, so similar management (too high for 5-year return, as in 2012 ACS screening guidelines)
- ASC-US/HPV+ has risk similar to LSIL, so similar management

Katki et al, *JLGTD.* 2013;17:S28-S35.
*Equivocal = ASC-US

Cumulative risk of CIN 3+ among individuals ages 30-64

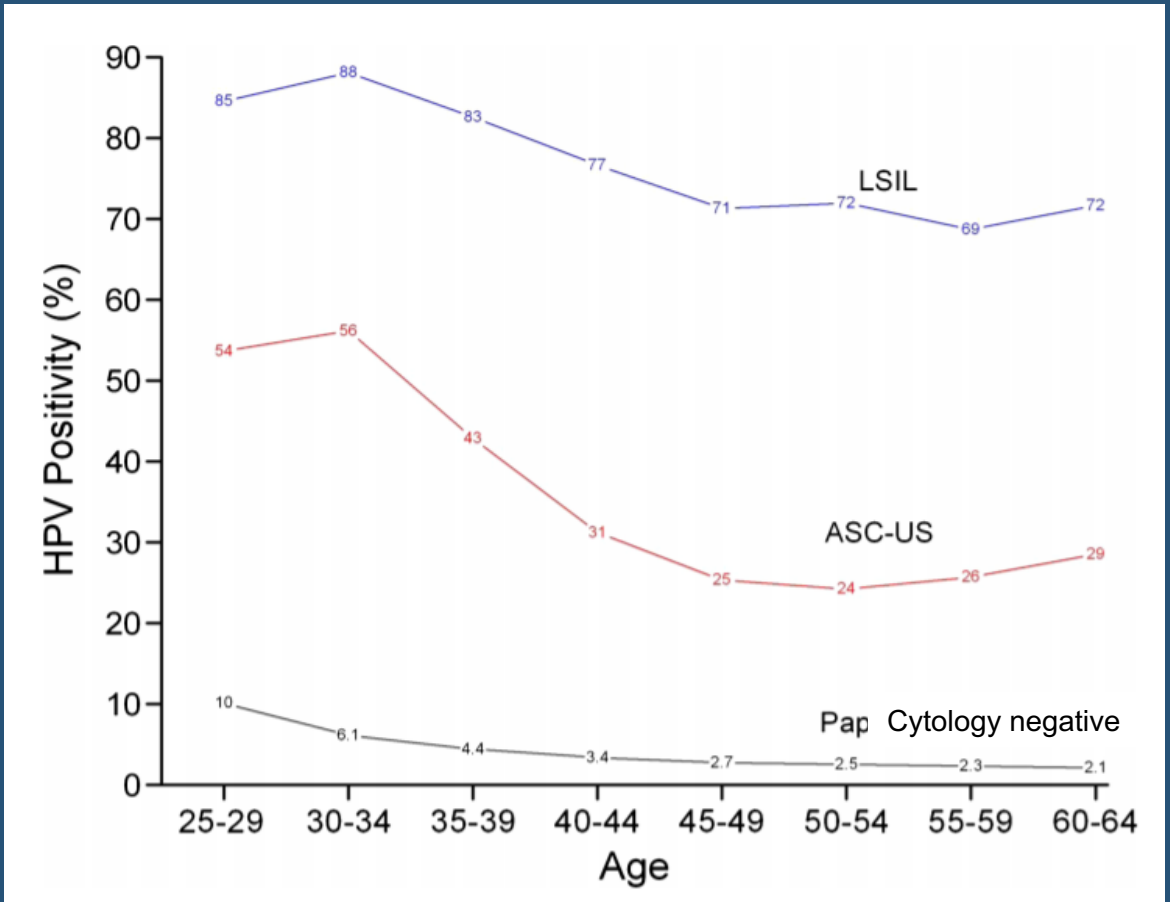
ASC-US and LSIL curves are for all results regardless of HPV status



Katki HA, et al. *JLGTD.* 2013;17:S36-S42.

Age specific prevalence of HPV+ results

ASC-US/HPV+ declined sharply from ages 30-34 to 55-59



Katki HA, et al. *JLGTD.* 2013;17:S36-S42.

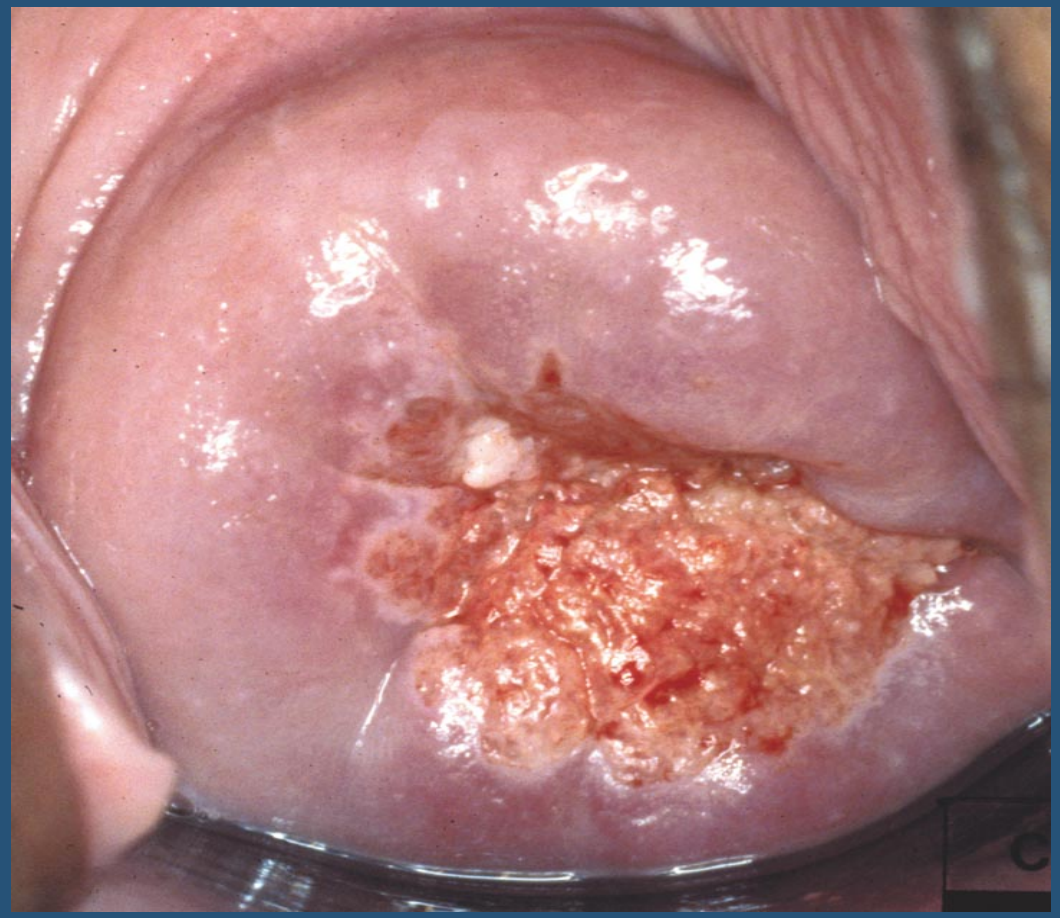
Rationale for continued follow-up of women with ASC-US

- In the ALTS study, 306 adult individuals presented with ASC-US and were ultimately found to have CIN 3
  - 58% diagnosed at initial assessment
  - 42% diagnosed during the 2 year follow-up period.

	Colpo	HPV testing	Repeat Cytol.	Total
Enrollment	58 (60%)	76 (75%)	44 (40%)	178 (58%)
Follow-up	14 (14%)	6 (6%)	22 (20%)	42 (14%)
Exit	25 (26%)	19 (19%)	42 (40%)	86 (28%)
Total (100%)	97 (100%)	101 (100%)	108 (100%)	306

The ALTS Group. Am J OG. 2003;188:1383-92.

What is ASC-US?

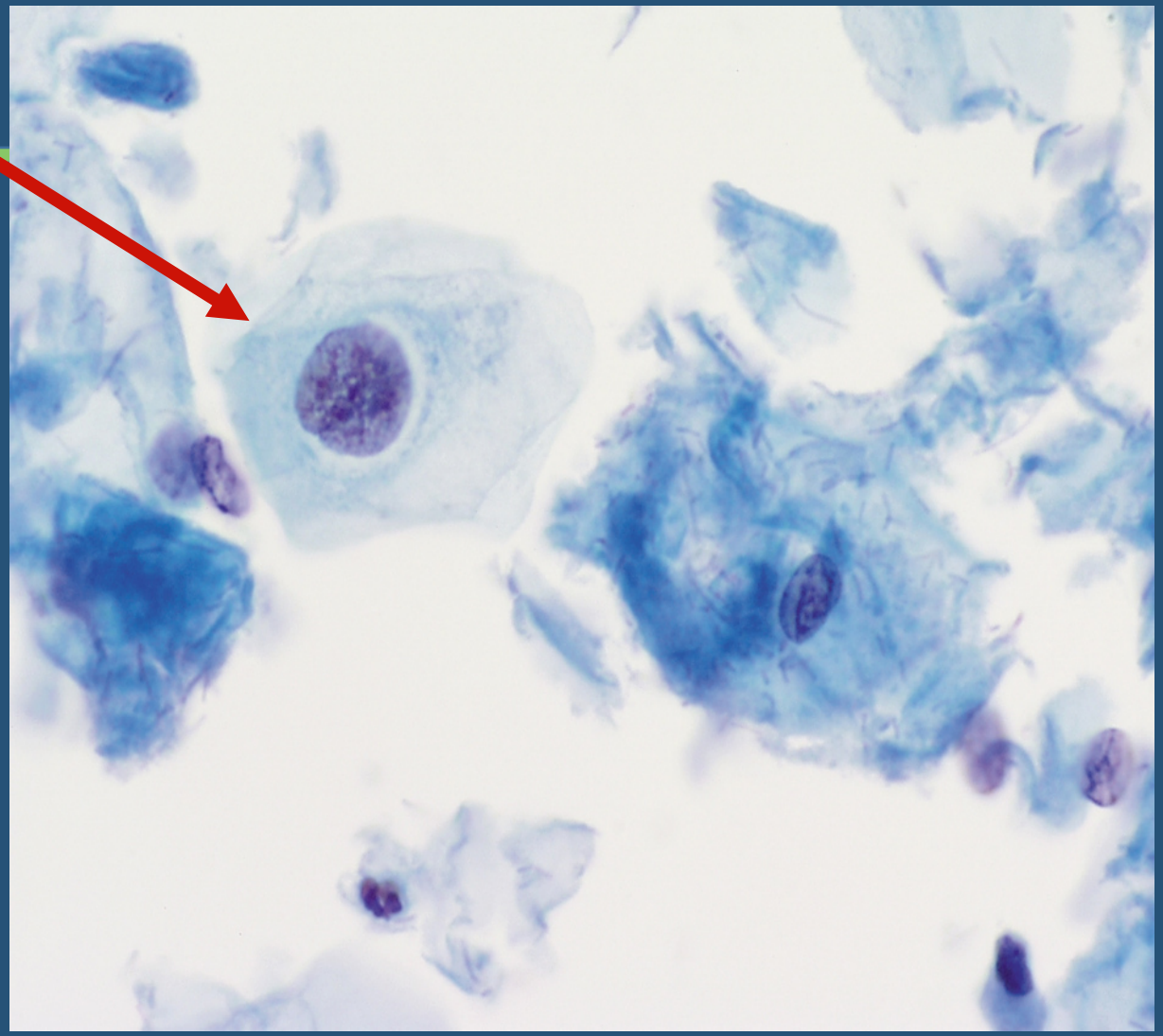


ASC-US cytology

- Cytologic changes suggestive of Squamous intraepithelial lesion (SIL) but lacking specific criteria
- Nuclear changes suggestive of but not totally consistent with SIL
- More than “reactive changes” but less than LSIL
- ALTS: 49% of ASC-US were hrHPV+
  - Rate of HPV+ depends on age and other factors!

ASC-US

- Nuclear enlargement and atypia + increase in chromatin
- Reserved for cells in which a clear distinction between reactive and SIL cannot be made



Apgar, Brotzman, Spitzer

What is LSIL?

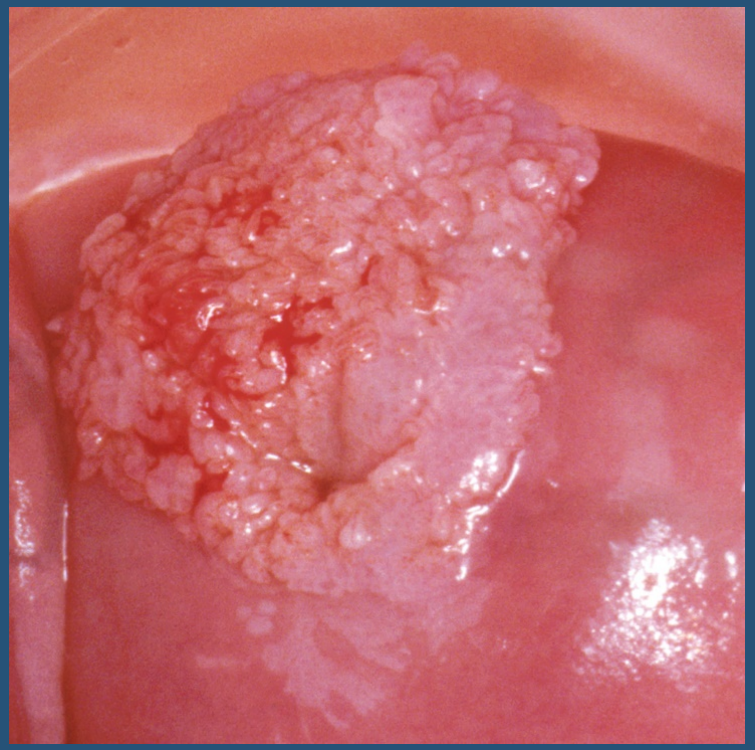
- Morphologic manifestation of a generally transient viral infection
- Non-neoplastic manifestations of HPV infection
  - Raised condyloma acuminata
  - Flat acetowhite lesions
  - 43% of HPV naive college females acquired HPV over 3 years

Ho et al. *NEJM.* 1998;338:423.

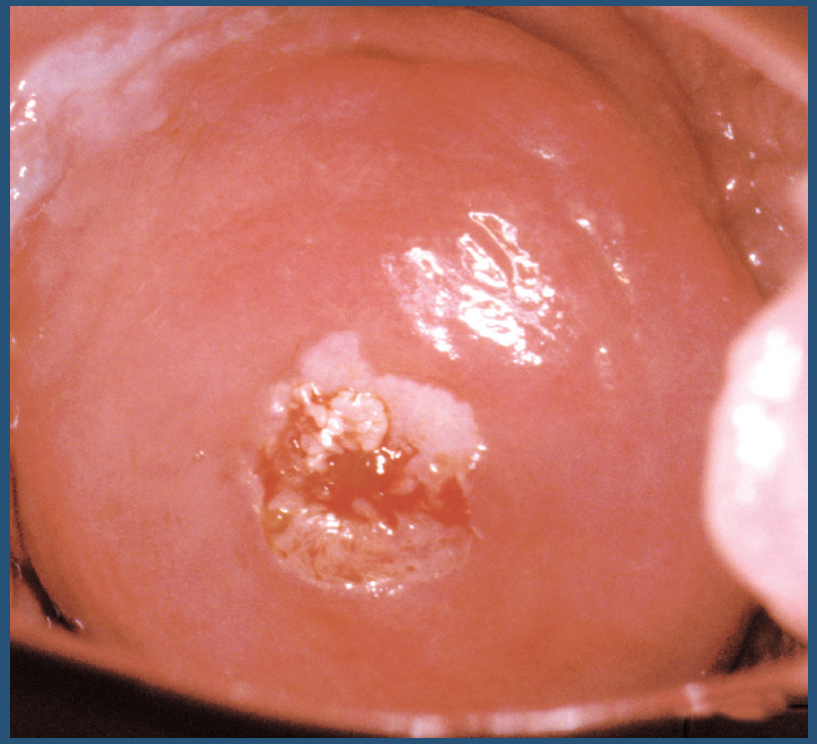
HPV infection of the cervix (LSIL)

Lesion with 2 morphologic presentations

Condyloma acuminata



Squamous intraepithelial lesion



Clinical importance of LSIL

- 77% of individuals with LSIL are HPV+
- 118 individuals with LSIL followed for 53 months
  - 88.1% regressed to ASC-US or negative
  - 9.2% progressed to HSIL
- Young females more likely to have incident infections

Arbyn M, et al. *Vaccine*. 2006;24(Suppl 3):S78-S89.
Schlecht, et al. *J Nat Cancer Inst.* 2003;95:1336.

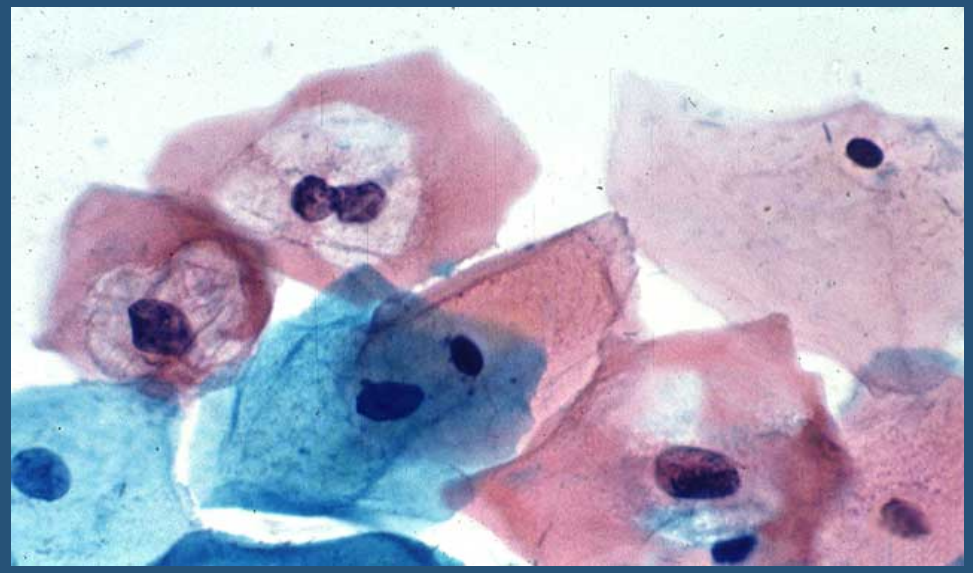
Individuals with LSIL at colposcopy

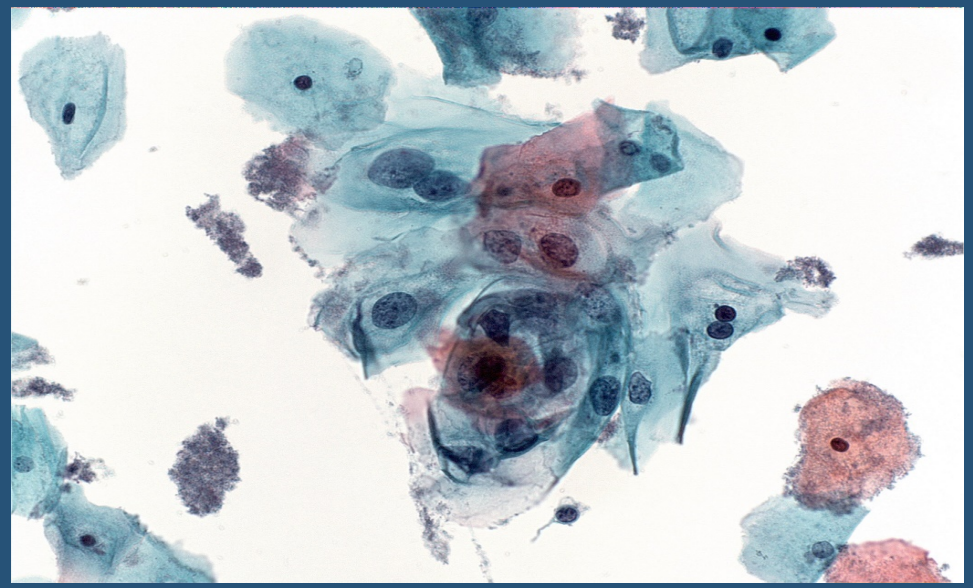
- ~85.0% of individuals with LSIL have biopsy-confirmed CIN at colposcopy
  - 67.0% have (LSIL) CIN 1
  - 18.0% have (HSIL) CIN 2+
- 14.0% have no lesion
- 0.3% have invasive cervical cancer

Jones and Novis.1996;120:523-31.

LSIL cytology

- Peri-nuclear clearing or halo
- Nuclear atypia
- Considerable amount of cytoplasm
- Higher nuclear/cytoplasmic ratio

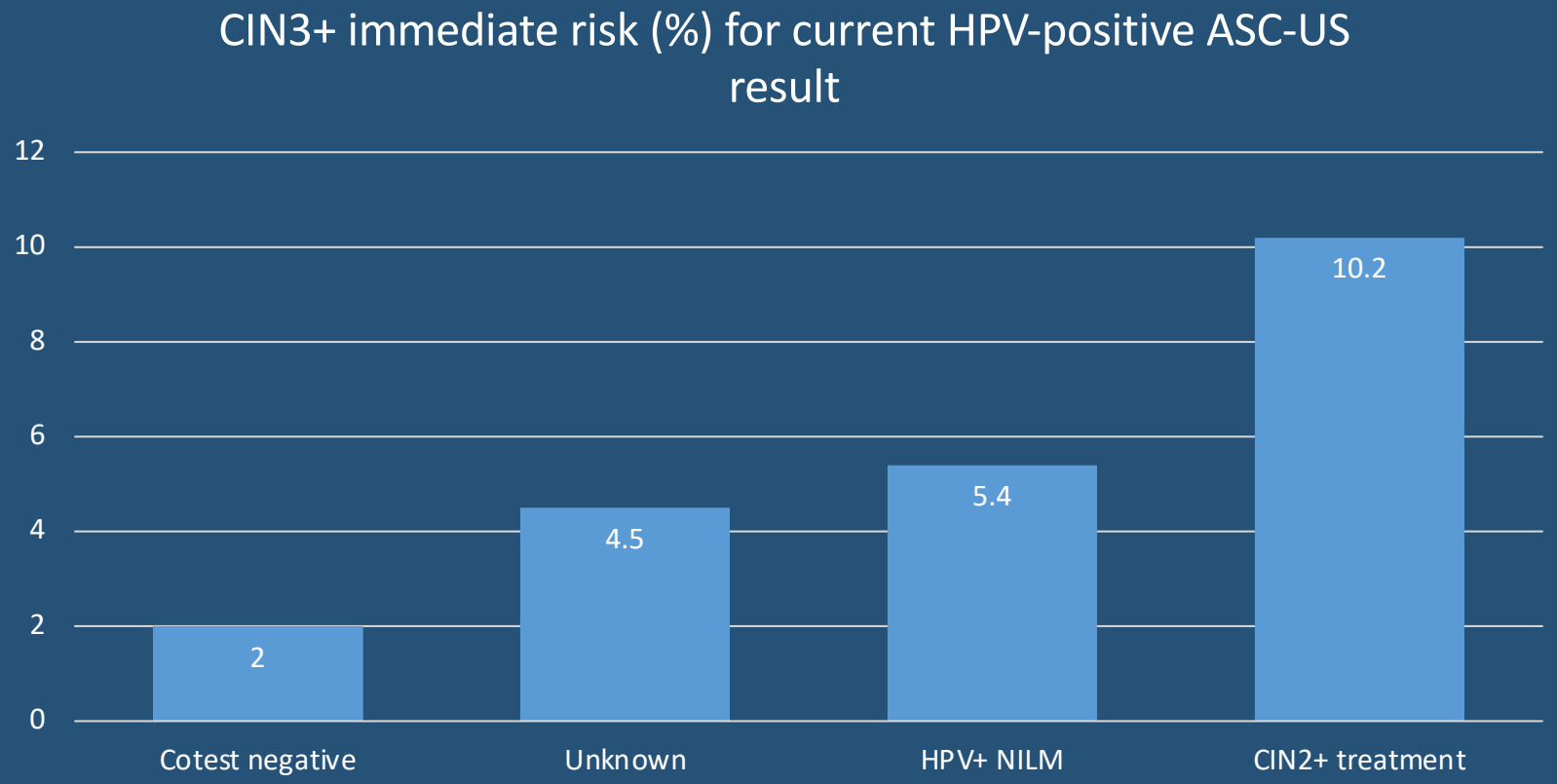




Fundamental concept of 2019 guidelines: Management is based on risk, not results

- Recommendations of colposcopy, treatment, or surveillance will be based on a patient's risk of CIN3+ determined by a combination of **current results** and **past history** *(including unknown history)*.
- A current HPV-positive ASC-US or LSIL test result may yield a different management recommendations depending on the history of recent past test results.

Past history influences current risk



Demarco et al. *JLGTD.* 2020.

Colposcopy Threshold

When individuals have an estimated immediate risk of diagnosis of CIN3+ of 4.0% or greater based on prior history and current results, referral to colposcopy is recommended.

Immediate CIN3+ Risk by Co-test (KPNC)

HPV	Pap	N	%	Immediate Risk (%)	Colposcopies per CIN3+ diagnosis
Pos	HSIL+	3980	0.3%	48.86	2.1
Pos	ASC-H	3766	0.2%	25.73	2.8
Neg	HSIL+	183	0.0%	25.21	2.8
Pos	ASC-US	20506	2.0%	4.45	8.6
Pos	LSIL	23659	1.5%	4.27	11.3
Pos	NILM	63541	4.1%	2.13	18.3
Neg	LSIL	3300	0.2%	1.05	19.0
Neg	ASC-US	25331	1.6%	0.04	22.6
Neg	NILM	1388153	89.8%	0.002	219.4

Demarco et al. *JLGTD.* 2020.

Documented prior negative HPV (KPNC)

HPV	Pap	Immediate risk (%) after prior HPV neg	Immediate risk (%) no prior HPV test
Pos	HSIL+	32.28	48.86
Pos	ASC-H	13.56	25.73
Neg	HSIL+	13.80	25.21
Pos	LSIL	2.10	4.27
Pos	ASC-US	2.03	4.45
Pos	NILM	0.74	2.13
Neg	LSIL	0.44	1.05
Neg	ASC-US	0.014	0.04
Neg	NILM	0.001	0.002

LSIL/ASCUS no longer meets colposcopy threshold

Demarco et al. *JLGTD.* 2020.

Negative HPV testing lowers risk

- Negative HPV test or cotest within past 5 years (e.g. normal screening at normal interval) reduces risks of minimally abnormal results
  - *Negative HPV or cotest followed by HPV+ ASC-US or LSIL returns in 1 year (no colposcopy)*
  - *Prior negative HPV testing lowers risk from 4% to 2%*

Medium risk results are still referred for colposcopy

- HPV-positive ASC-US and LSIL in all situations other than the ones we just reviewed
- Any HPV+ result 2 times in a row
- Anything concerning for high-grade:
  - ASC-H, AGC, HSIL
- HPV 16 or 18 infections
  - HPV 16 or 18 positive needs colposcopy, even if Pap result is normal

Patient case #1

- 38 year-old presents for screening. She has had regular cervical cancer screening, with her last test at age 33, which was a negative cotest.
- This year her screening tests are ASC-US HPV+. What do you do?

Patient case #1

- 5 years ago: negative cotest
- Current year: ASC-US HPV+
- Her prior negative cotest reduces her risk of having precancer now.
- The recommendation is: return in 1 year

Patient case #1

- 5 years ago: negative cotest
- Current year: ASC-US HPV+
- Her prior negative cotest reduces her risk of having precancer now.
- The recommendation is: return in 1 year

- One year follow-up: ASC-US HPV+
- She now has HPV that has persisted over 2 consecutive tests.
- The recommendation is: colposcopy to check for precancer.

Patient case #2

- 30 year-old presents for screening. She had an LSIL Pap test last year, followed by a colposocpy that confirmed CIN1.
- This year her follow-up cotest is ASC-US HPV+. What do you do?

Patient case #2

- Last year: LSIL Pap with colposcopy showing CIN1
- Current year: ASC-US HPV+
- Her prior colposcopy where precancer (CIN2/3) was not found reduces her risk of having precancer now.
- The recommendation is: return in 1 year

Patient case #2

- Last year: LSIL Pap with colposcopy showing CIN1
- Current year: ASC-US HPV+
- Her prior colposcopy where precancer (CIN2/3) was not found reduces her risk of having precancer now.
- The recommendation is: return in 1 year
- One year follow-up: ASC-US HPV+
- She now has HPV that has persisted over 2 consecutive tests.
- The recommendation is: colposcopy to check for precancer.

Negative colposcopy lowers risk

- Colposcopy that excludes high-grade precancer (i.e. confirms a diagnosis <CIN2) reduces risk of subsequent minimally abnormal result
  - Colposcopy confirming the absence of high grade disease followed by HPV+ ASC-US or LSIL returns in 1 year (not colposcopy)
  - Prior negative colposcopy lowers risk from 4% to 2%

Other low-risk results are managed the same as before

- ASC-US HPV negative → return in 3 years
  - 5-year risk of CIN3+ is 0.40%
- NILM HPV positive → return in 1 year
  - Immediate risk of CIN3+ is 2%
- LSIL HPV negative → return in 1 year
  - Immediate risk of CIN3+ is 1%

Histologic LSIL (CIN1) is low risk

- Even when diagnosed several years in a row, CIN1 does not have a high risk of hiding an occult precancer
- Observation is preferred to treatment for CIN1
  - Treatment remains an option after shared decision-making

Natural history of CIN 1

- CIN 1 is a histologic expression of productive HPV infection
- Approximately 90% regress
  - Regression rates decrease with age, duration
  - Regression rates are lowest for HPV 16
- 13% diagnosed with CIN 2+ after 2 years (ALTS)

Clifford et al. *Cancer Epidemiol Biomarkers Prev.* 2006;14:1157-64.

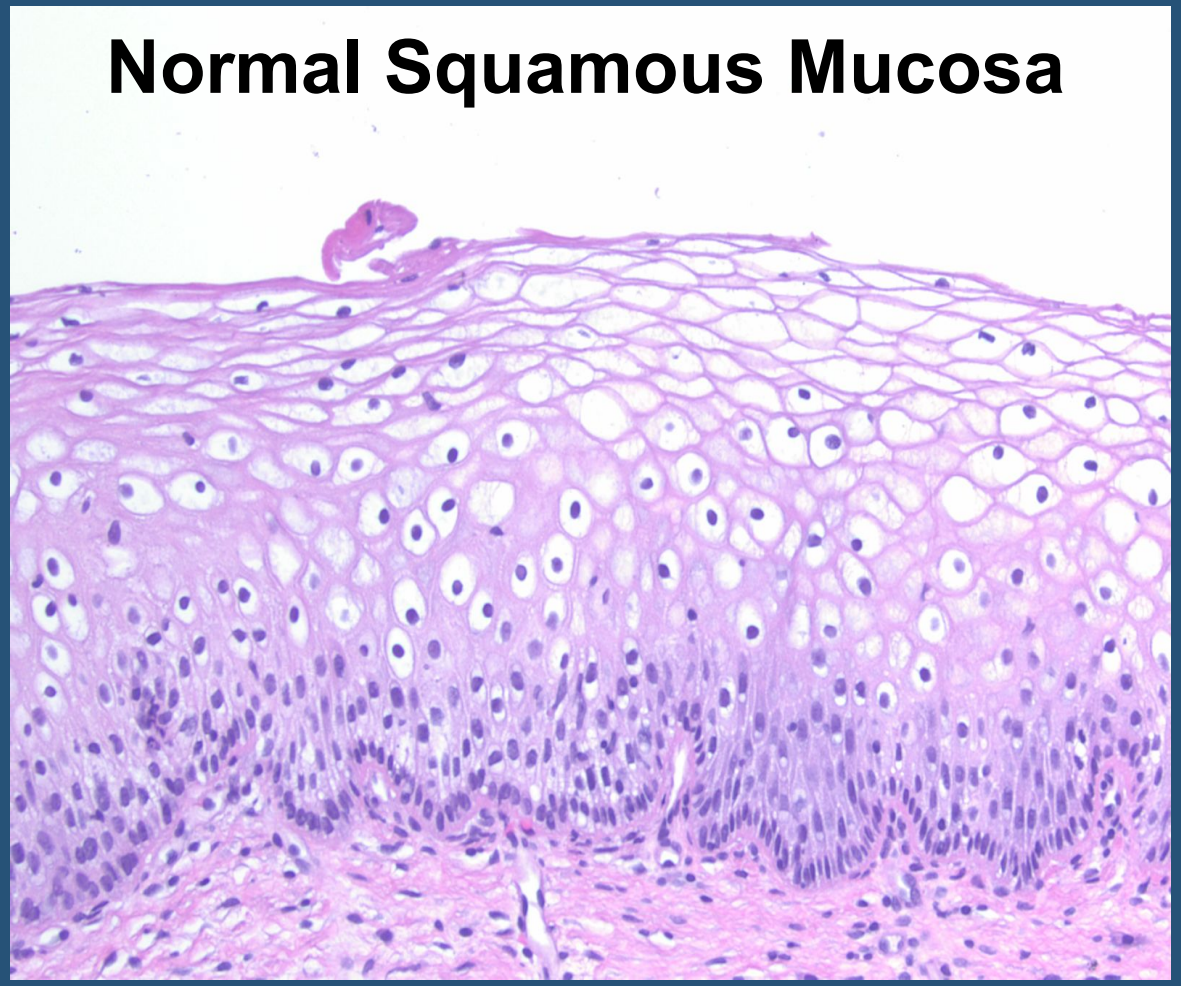
Is CIN 1 a true cancer precursor?

- Goal of cervical cytology is to facilitate identifying true cancer precursors
  - CIN 2+ are true cancer precursors
  - CIN 1 is not considered a true cancer precursor
- Concern about individuals with CIN 1 is that they may have unrecognized CIN 2+

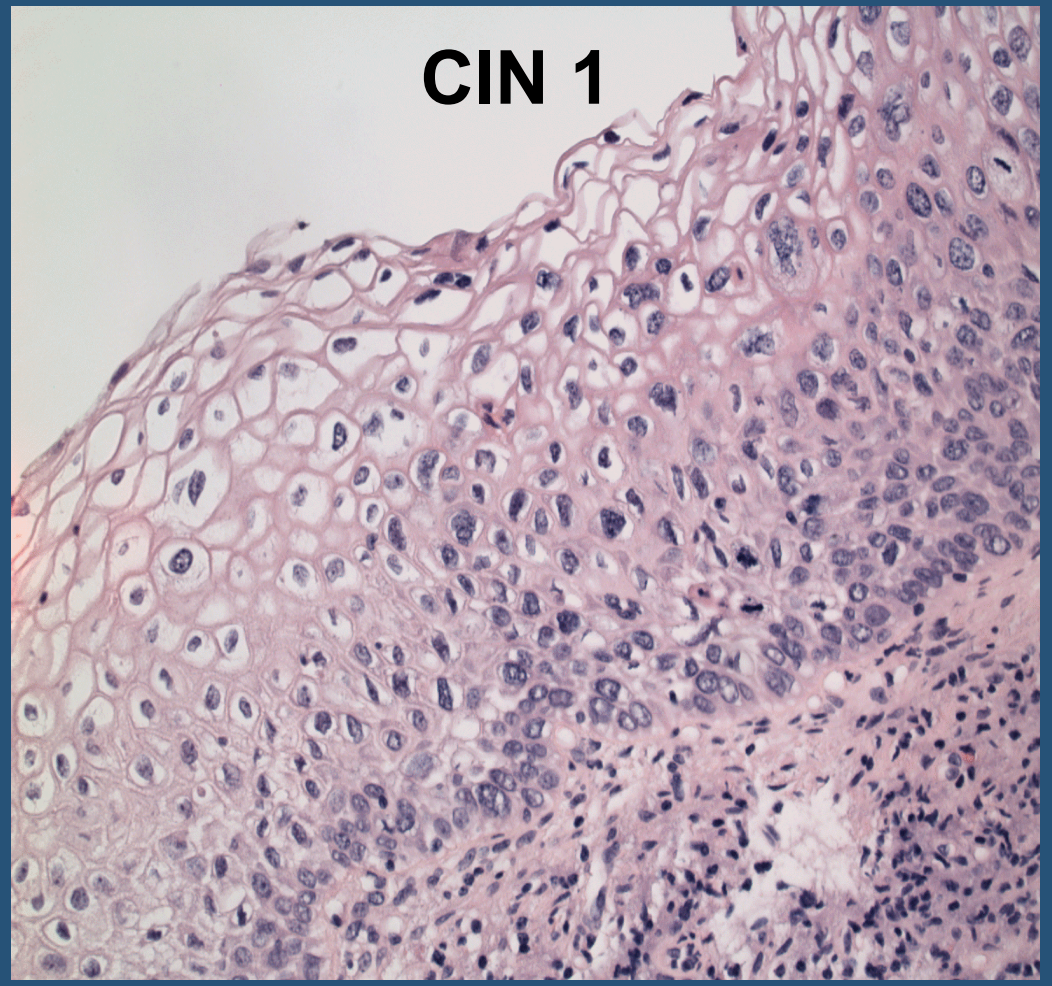
Histology of CIN 1

- Lower 1/3 of epithelium involved
- Koilocytosis in the superficial layers
- No abnormal mitotic figures

Normal Squamous Mucosa



CIN 1



Nancy Joste, MD, UNM Dept of Pathology

Colposcopy of Histologic LSIL (CIN 1)

Margin of CIN 1

- Irregular, feathered
- Angular, jagged, geographic
- Satellite lesions, usually multifocal

28-year-old with LSIL cytology

Biopsy = CIN 1

Apgar, Brotzman, Spitzer

32-year-old with LSIL cytology

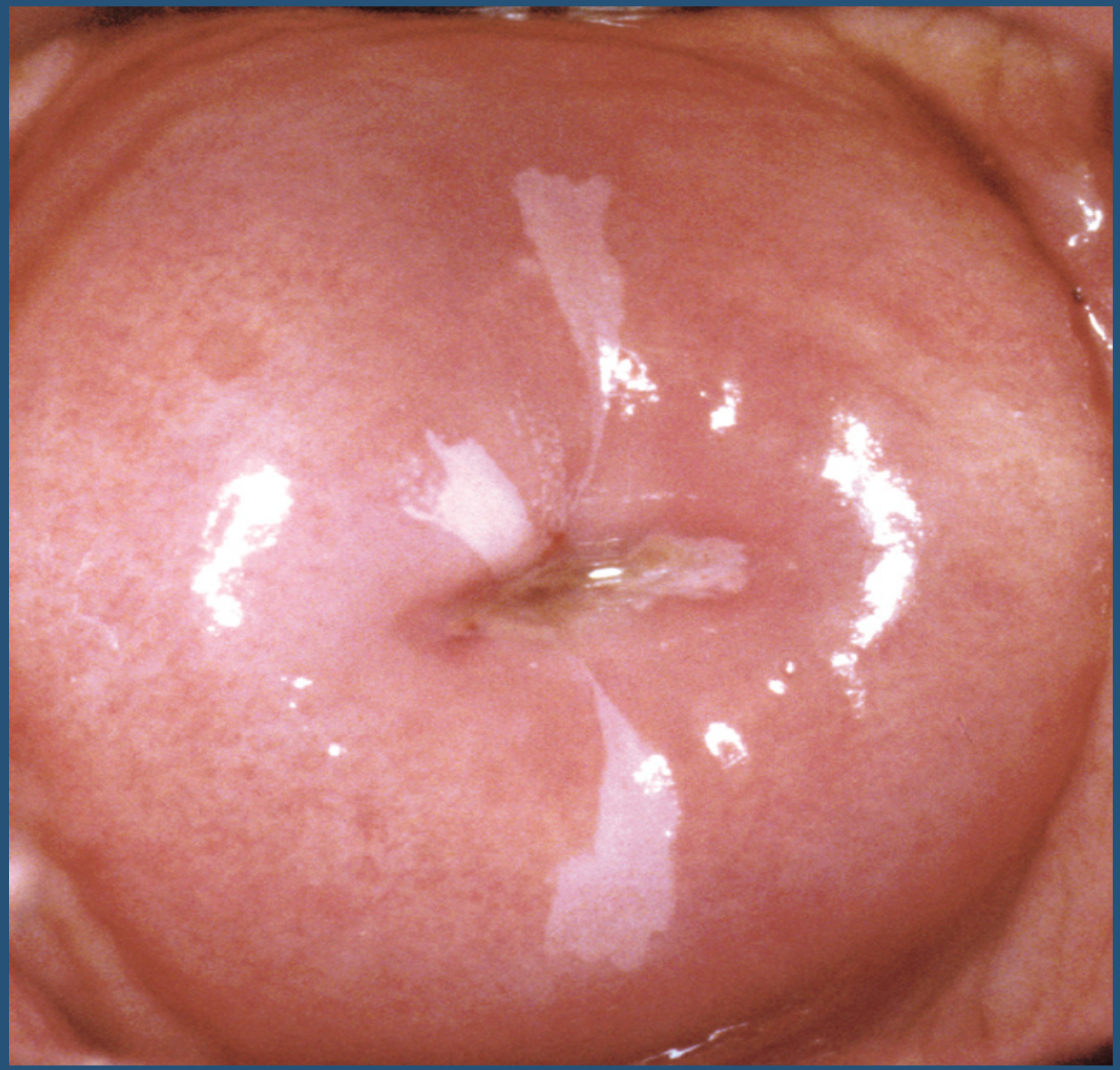
Geographic margin

Satellite lesions

Mild acetowhiteness

Full SCJ not visualized

Biopsy = CIN 1



Apgar, Brotzman, Spitzer

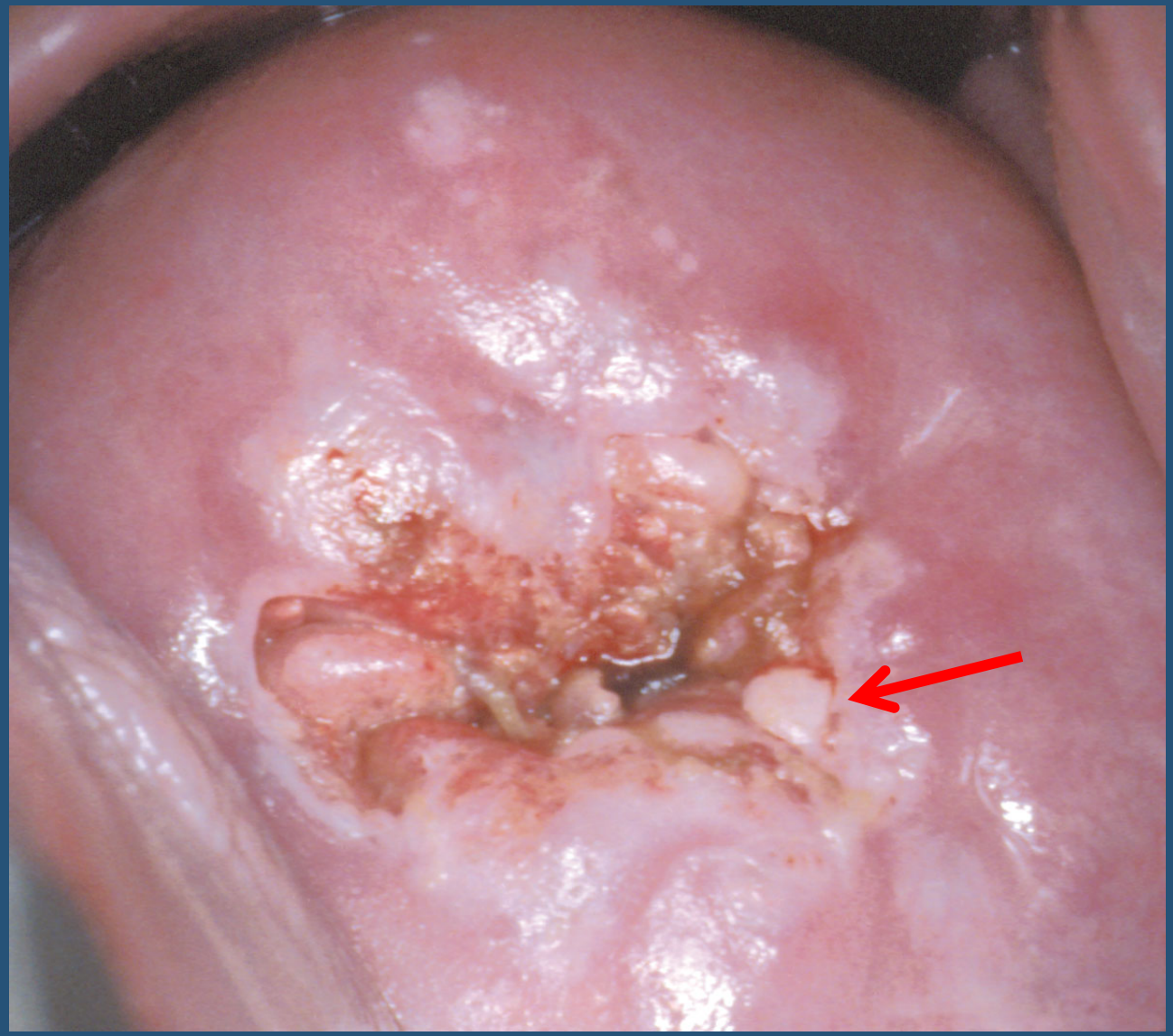
Color of CIN 1

- Shiny surface
- Translucent
- Indistinct acetowhitening
- Snow-white acetowhiteness
- Acetowhite reaction fades quickly

28-year-old with LSIL cytology

Translucent white lesion on anterior lip = CIN 1

Dense white at 4:00 = CIN 3

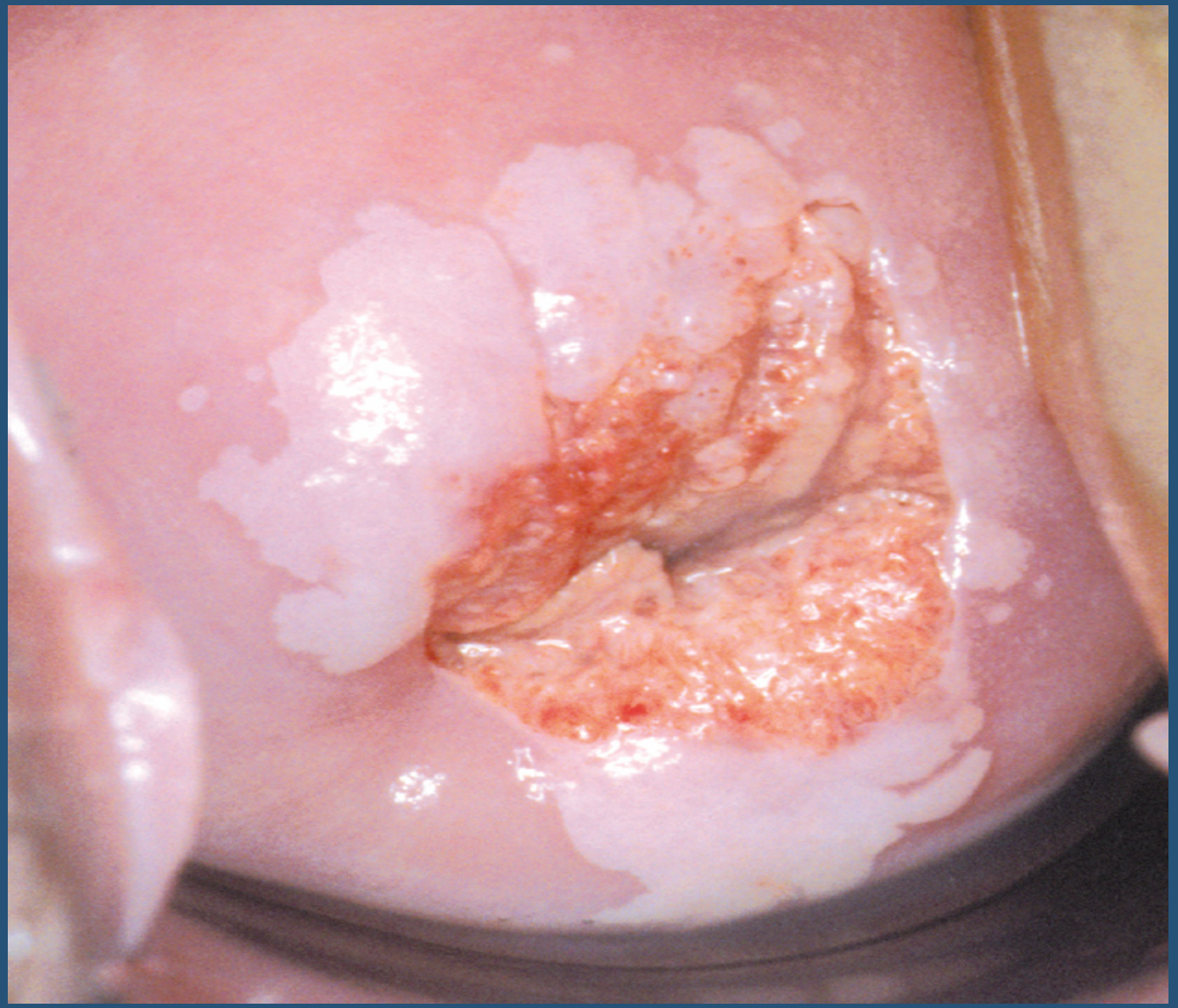


Apgar, Brotzman, Spitzer

31-year-old with LSIL cytology

Shiny white
Satellite lesions
Geographic margins

Biopsy = CIN 1

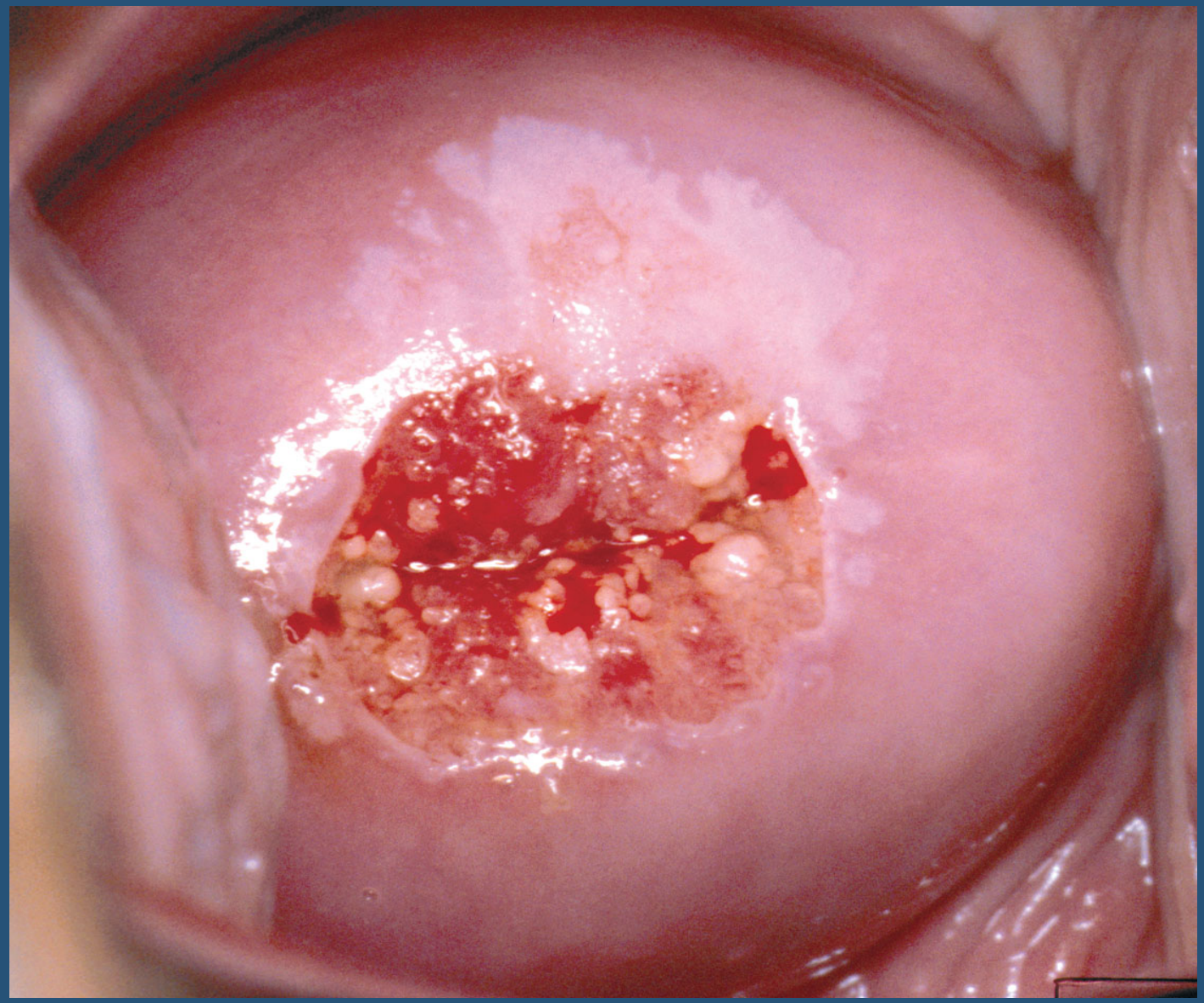


Apgar, Brotzman, Spitzer

29-year-old with LSIL cytology

Translucent white
Geographic borders
Satellite lesions

Biopsy = CIN 1

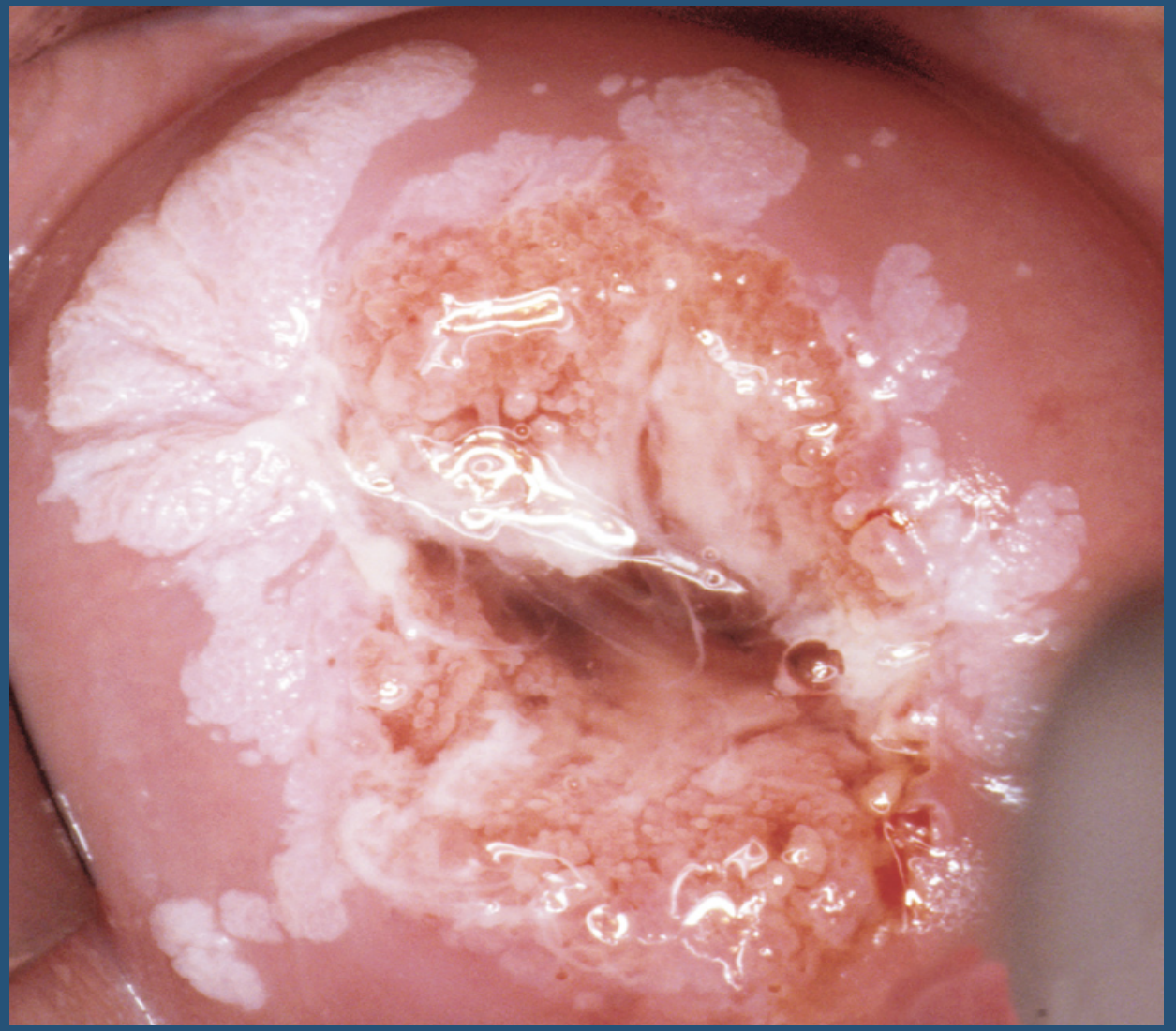


Apgar, Brotzman, Spitzer

21-year-old with LSIL cytology

Lesion has “texture”
Geographic margin

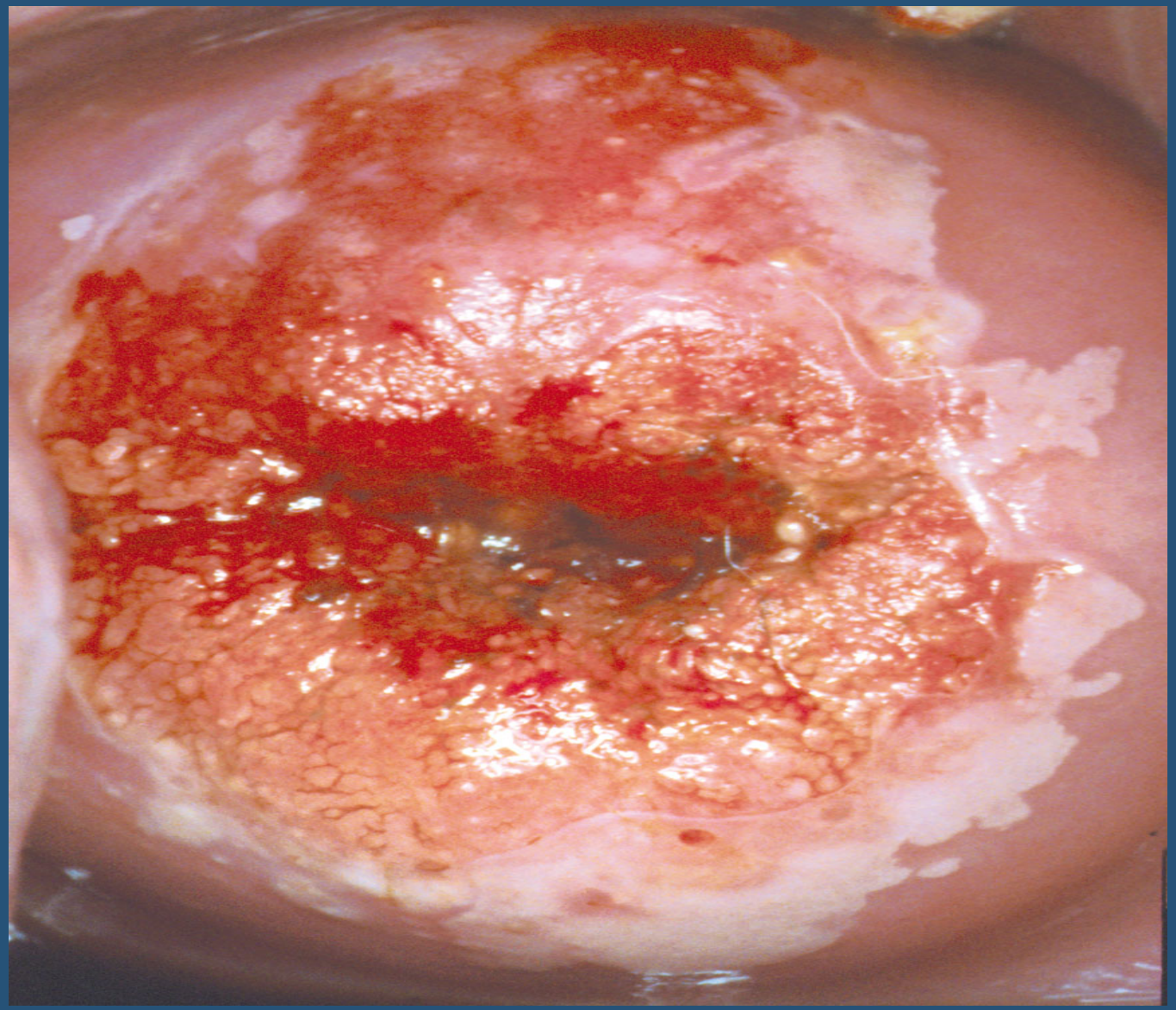
Biopsy = CIN 1



Apgar, Brotzman, Spitzer

22-year-old with LSIL cytology

Biopsy (3:00) = CIN 1



Apgar, Brotzman, Spitzer

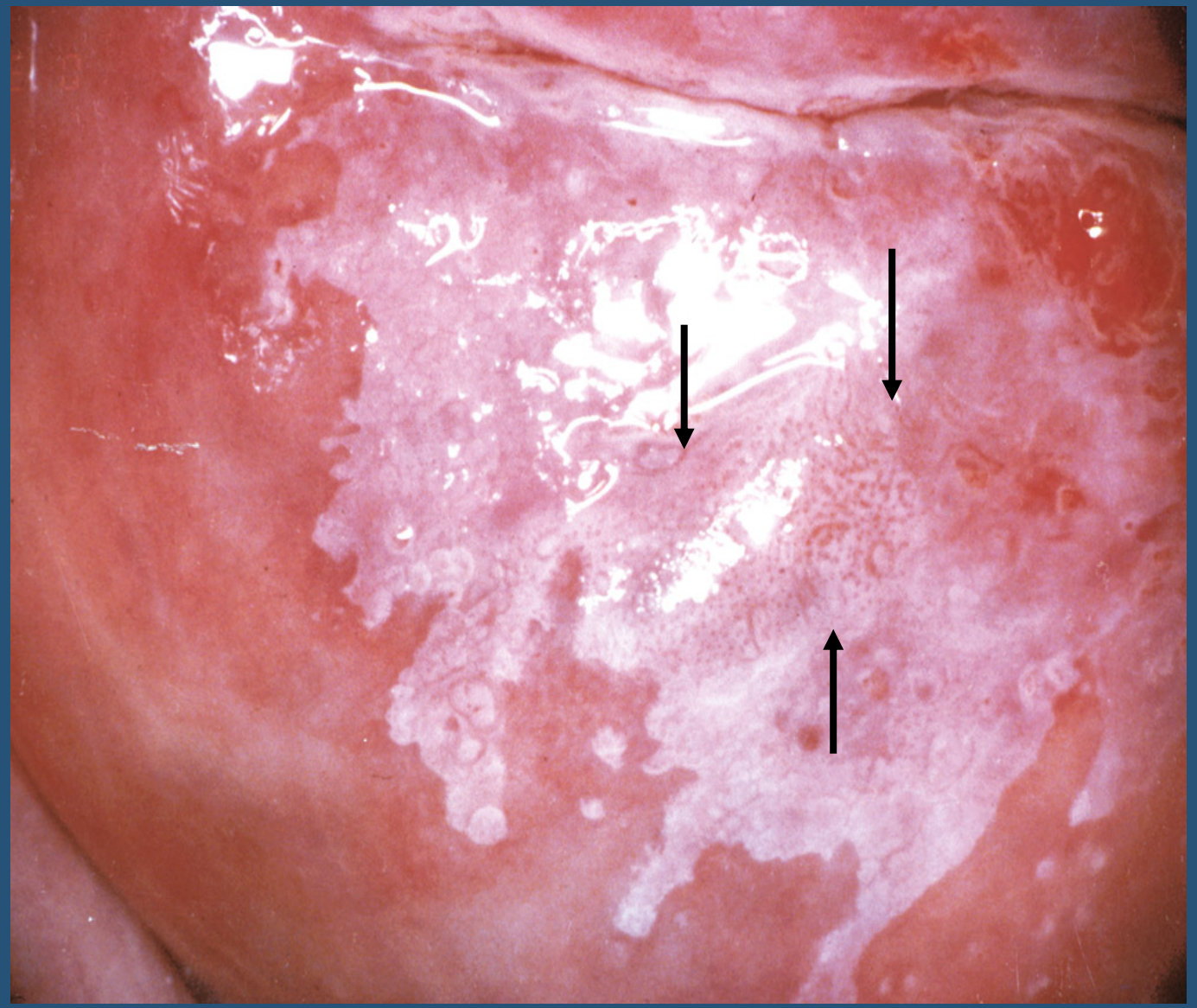
Vessel pattern of CIN 1

- Usually absent
- Fine mosaic and punctation
- Small intercapillary distance
- No atypical vessels
- Afferent and efferent loops may be exaggerated with condyloma

28-year-old with LSIL cytology

Geographic margin
Fine mosaic
Fine punctuation

Biopsy = CIN 1

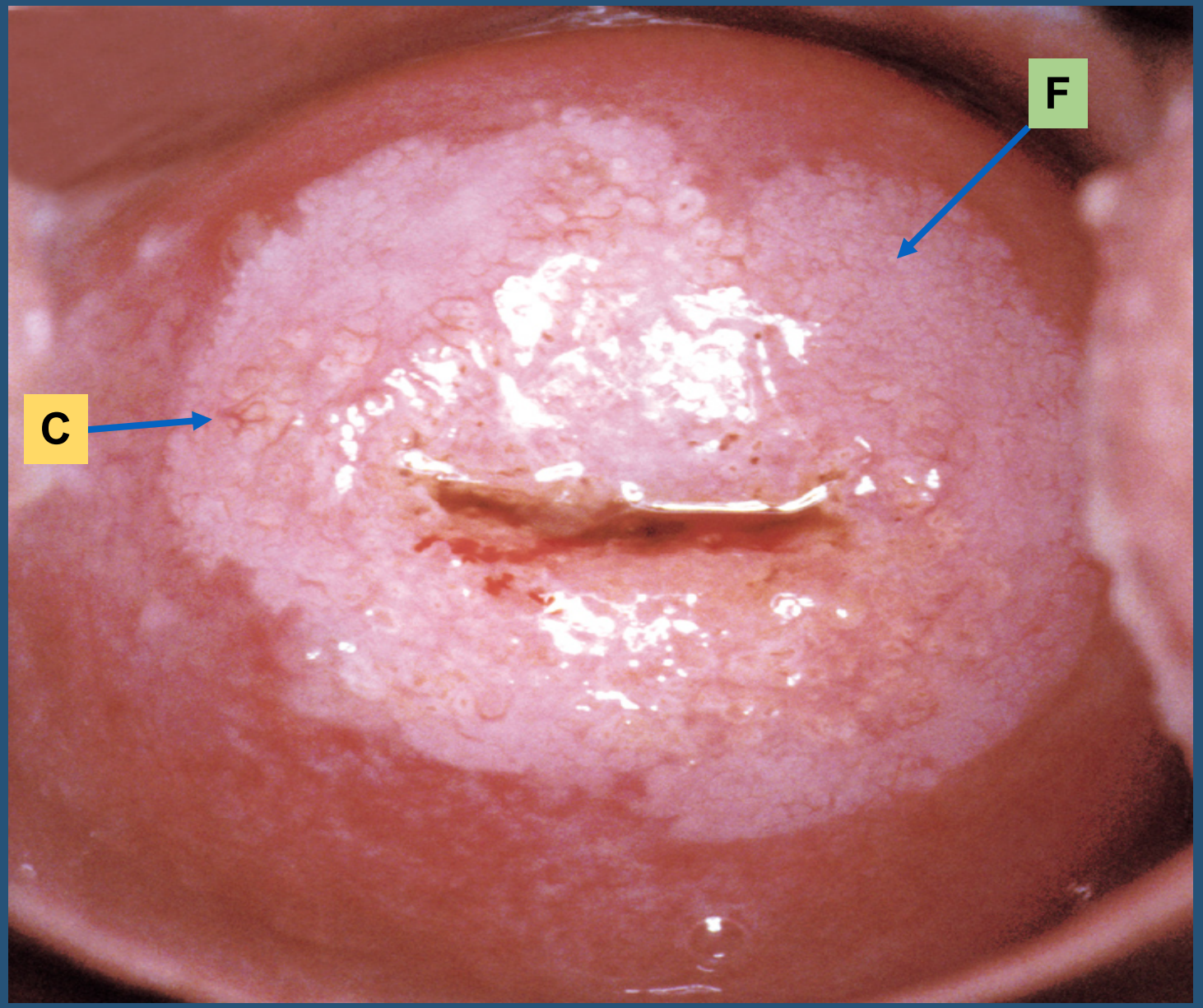


Apgar, Brotzman, Spitzer

38-year-old with LSIL cytology

Coarse (C) and Fine (F) mosaic pattern

Biopsy = CIN 1



Apgar, Brotzman, Spitzer

Colposcopy Standards

- Biopsies should be taken of all acetowhite areas
- Generally 2-4 biopsies are recommended
- Biopsy may be deferred only if TZ is fully visualized, colposcopic impression is normal with no acetowhitening, and prior risk is low (<HSIL cytology, no HPV16/18 positivity)
- Endocervical sampling preferred for LSIL if SCJ not fully visualized.

Management of CIN 1

- The risk of occult CIN 2+ among individuals with ≤CIN 1 at colposcopic biopsy or no lesion is linked to the risk conveyed by prior cytology
- “Lesser Abnormalities” include ASC-US, LSIL, HPV 16 or 18 positivity, persistent HPV
- Higher risk abnormalities include ASC-H, HSIL and AGC

Risk of CIN 2+ among individuals with CIN 1 after Lesser Abnormalities

- After initial colposcopy for LSIL or ASC-US/HPV+, the risk for subsequent CIN 2+ over 2 years is 10-13%
- The risk of CIN 2+ does not vary regardless of whether CIN 1 or no lesion is found
- The post-colposcopy management for CIN 1 should be repeat HPV test or cotest in 1 year

Perkins RB et al. J Low Genit Tract Dis. 2020;24(2):102-131.

Management of CIN 1 or no lesion preceded by "Lesser Abnormalities"

- Co-testing at one year is recommended
- If both tests are negative age-appropriate retesting in 3 years is recommended
  - Cytology if < 25
  - HPV based testing if ≥ 25
- If those tests are negative return to in 3 years
- If any test is abnormal, consult ASCCP Guidelines via app or web

Perkins RB et al. J Low Genit Tract Dis. 2020;24(2):102-131.

Persistent CIN 1 after "Lesser Abnormalities"

- Persistent CIN 1 reflects a persistent HPV infection
- If CIN 1 persists for at least 2 years, continued follow-up is preferred but treatment is acceptable
  - If treatment is selected, excision and ablation are options depending on whether or not SCJ is fully visualized.
  - If SCJ is not fully visualized and colposcopy or endocervical sampling contains CIN 2 or CIN 3, or patient was previously treated, ablation is unacceptable

Perkins RB et al. J Low Genit Tract Dis. 2020;24(2):102-131.

Unacceptable options for managing CIN 1

- Ablative procedures in individuals with CIN 1 where SCJ not fully visualized.
- Topical treatments such as Podophyllin or podophyllin-related products for use in the vagina or on the cervix
- Hysterectomy as primary/principal treatment for CIN 1

Wright TC, et al. *AJOG.* 2007;197(4):340-345.

Management of CIN 1 or no lesion preceded by ASC-H, HSIL

- Higher risk than when preceded by a lesser abnormality
- Differs by whether preceding diagnosis was ASC-H or HSIL

Perkins RB et al. J Low Genit Tract Dis. 2020;24(2):102-131.

Figure 10: Management of Histologic LSIL (CIN1) or Less Preceded by ASC-H Cytology

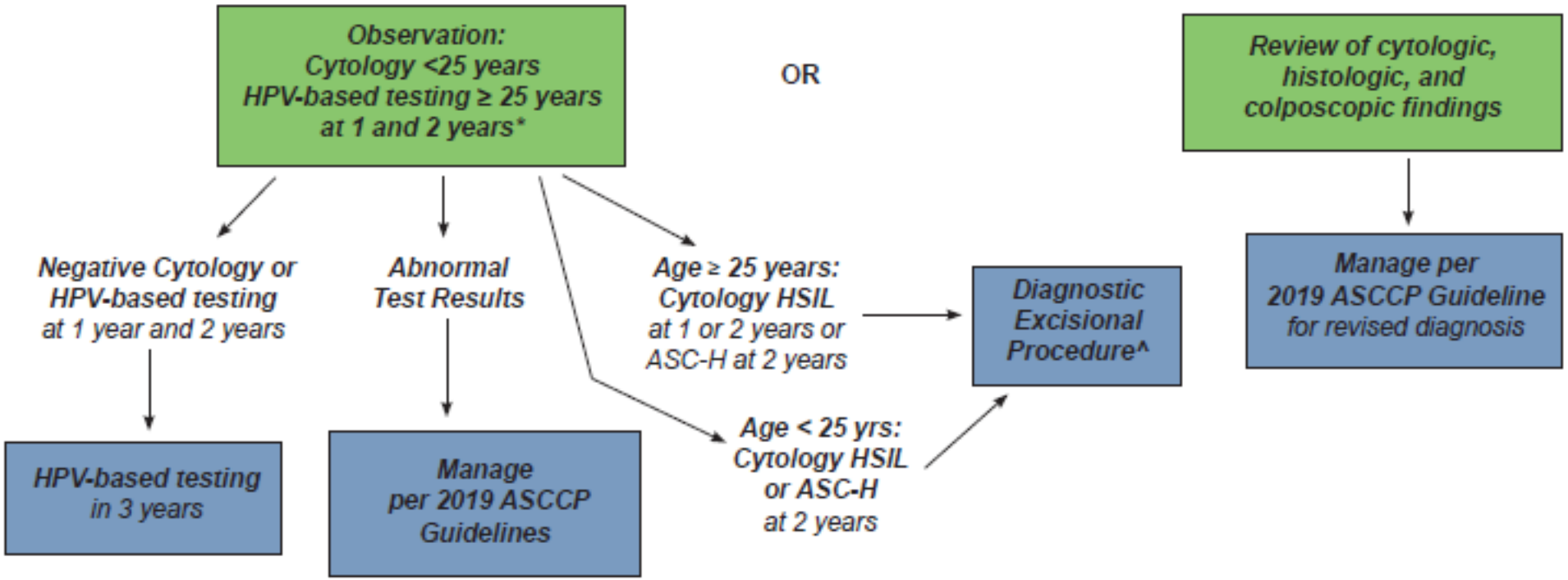
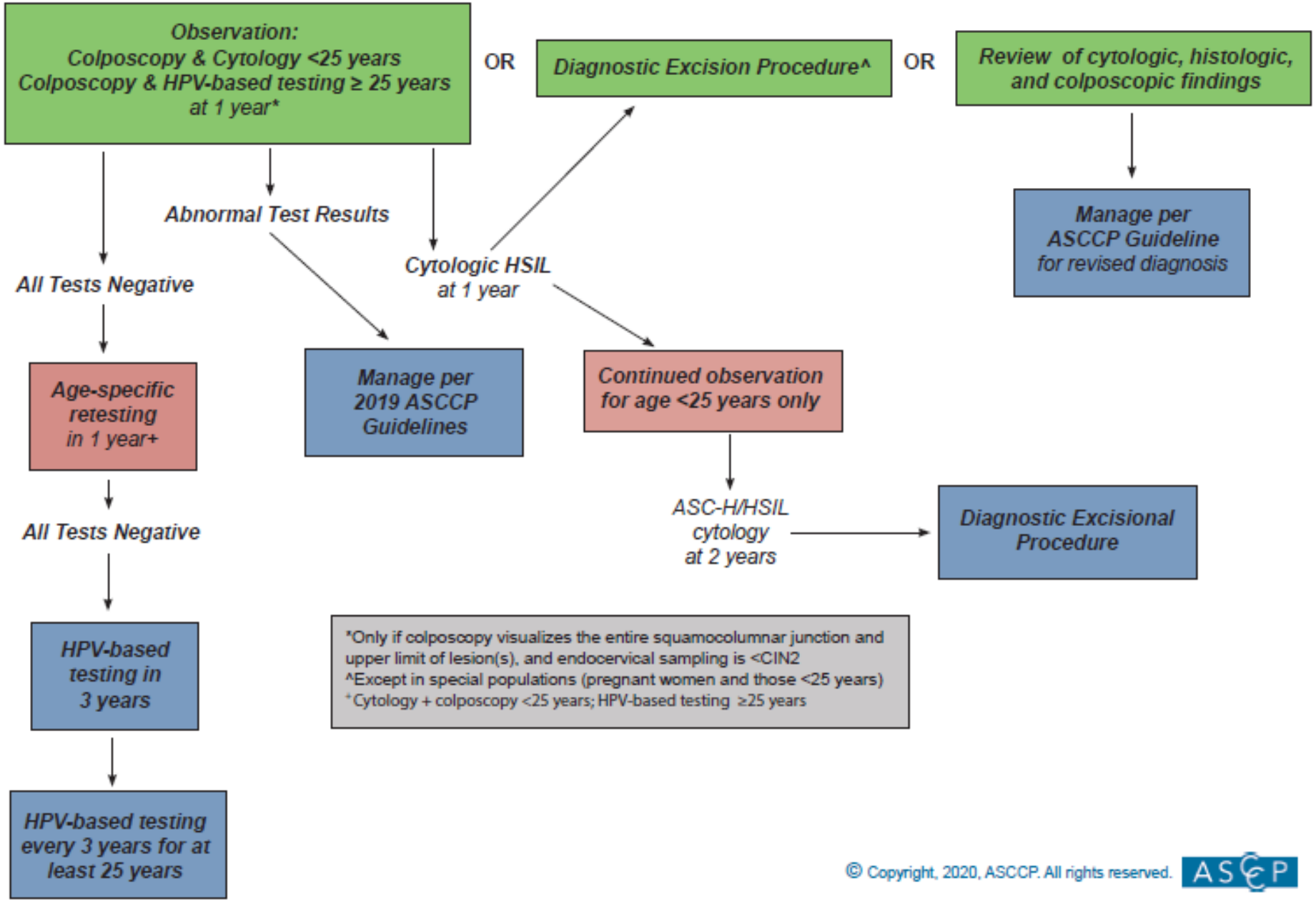


Figure 9: Management of Histologic LSIL (CIN1) or Less Preceded by HSIL Cytology



Management of CIN 1 on endocervical sampling

- When CIN 1 is detected on endocervical sampling after “Lesser Abnormalities” and NO CIN 2+ is detected, follow guidelines with the addition of repeat endocervical sampling in 12 months
- When CIN 1 is detected on endocervical sampling after ASC-H, HSIL, AGC-NOS and follow up is chosen, repeat endocervical sampling at follow up visits

Perkins RB et al. J Low Genit Tract Dis. 2020;24(2):102-131.

Summary

- Discussed the epidemiology, cytologic characteristics, and recommended management of ASC-US and LSIL
- Reviewed colposcopic and histologic characteristics of LSIL (CIN 1)
- **Discussed 2019 ASCCP Risk-Based Management Consensus guideline recommendations for low grade precursor disease**