

Elusive Diagnosis of HSIL on the Anal Pap Test

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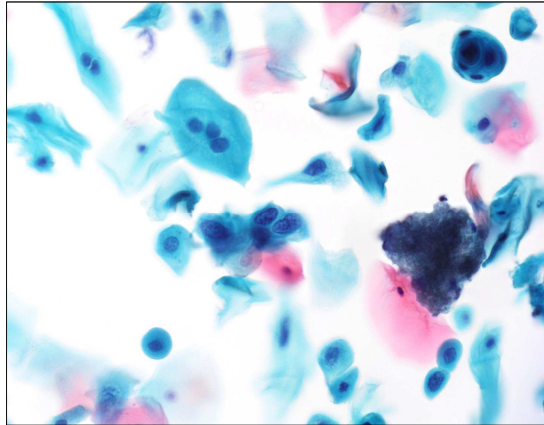
No Disclosures



Diagnostic Criteria of HSIL

Criteria for HSIL on anal cytology parallel cervical cytology:

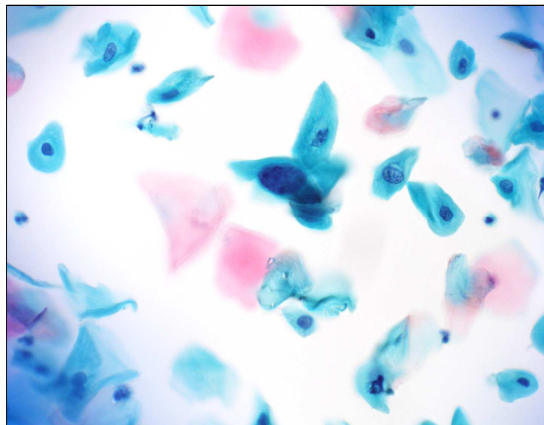
- Nuclear enlargement
- Hyperchromasia, coarse chromatin
- Irregular nuclear membrane, indented, groove
- High nuclear-cytoplasmic ratio
- Lack prominent nucleoli



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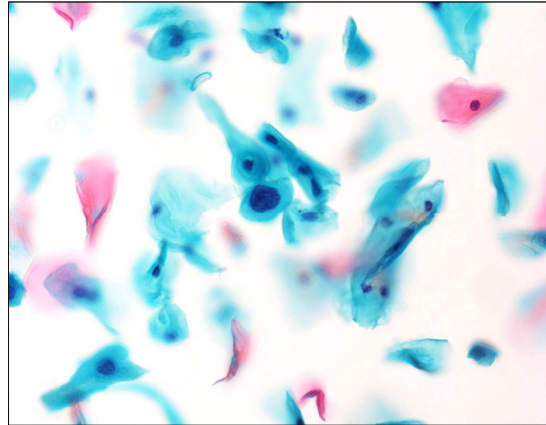
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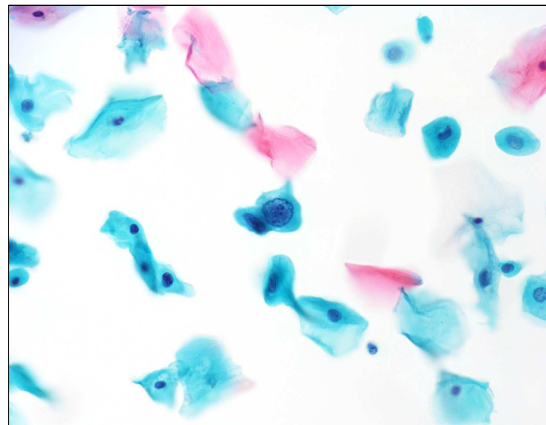


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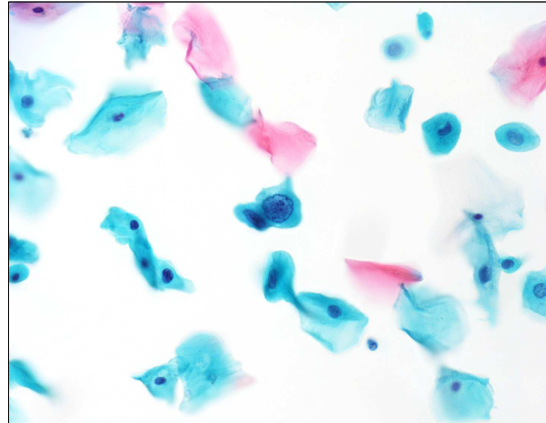


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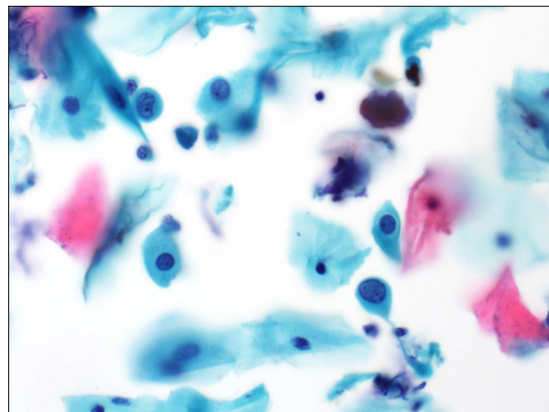
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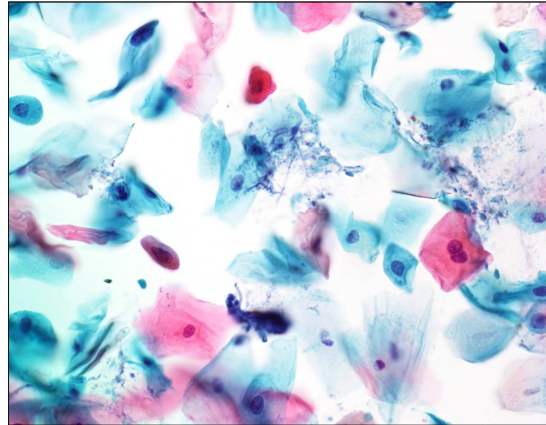
- Cytoplasm may be metaplastic
- May have small keratinized cell
- Often associated with atypical parakeratosis
- Often intermixed with LSIL



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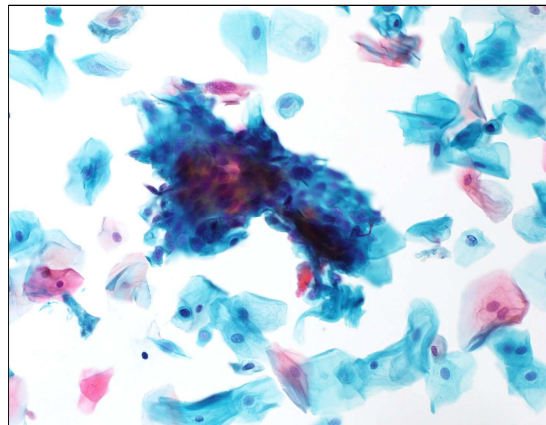
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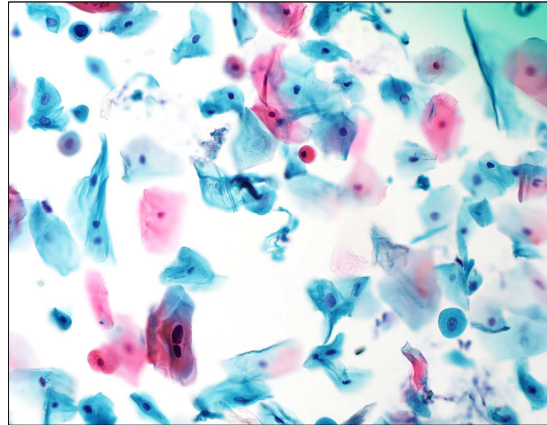
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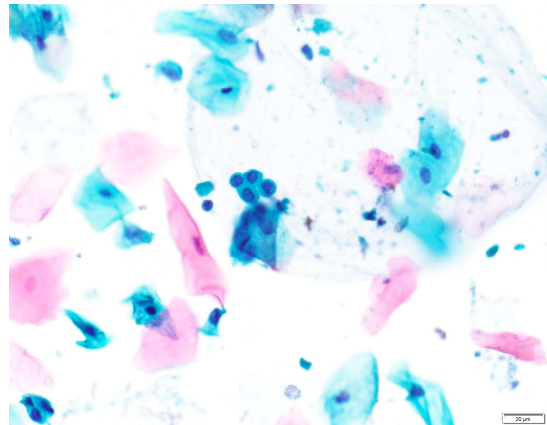
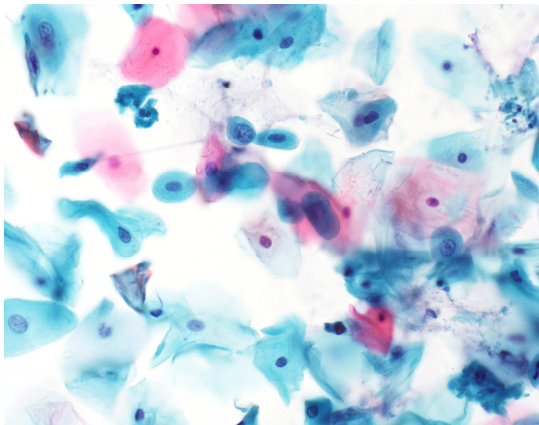
Morphologic variations of HSIL

- Cytoplasm may be metaplastic
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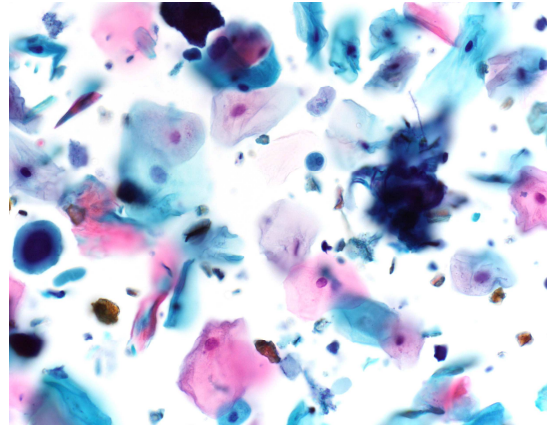
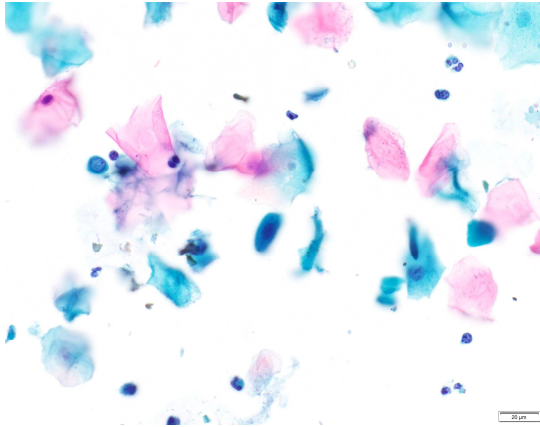
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Diagnostic Criteria of HSIL



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Diagnostic Criteria of HSIL



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CAP Interlaboratory Comparison

6 year evaluation of anal cytology:

- NILM: 91% concordance
- Abnormal: 90% concordance
- But, specific interpretive category: 68-72%
 - HSIL: 57.1% concordance
 - Squamous cell ca: 56.2% concordance

1. Darragh TM, Winkler B, Souers RJ, et al. Room for Improvement: Initial Experience With Anal Cytology: Observations From the College of American Pathologists Interlaboratory Comparison Program in Nongynecologic Cytology. Archives of Pathology & Laboratory Medicine 2013; 137: 1550-1554.



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CAP Interlaboratory Comparison

- HSIL often “under-called” LSIL (25%)
- Or “over-called” squamous cell ca (14%)
- And no improvement over 6-year evaluation

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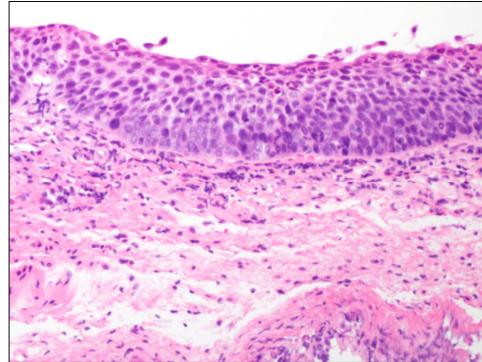
Why is HSIL Challenging?

- 1) Is HSIL being sampled?
- 2) If present, are we finding it?
- 3) If we find it, can we recognize it?
- 4) If we find it, and we call it HSIL, will others agree?
- 5) If we find it, and we call it HSIL, will the biopsy agree?
- 6) If we find it, and we call it HSIL, and the biopsy does not agree, who is right?
- 7) Are the criteria really the same as cervicovaginal cytology?



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1) Is HSIL being sampled?



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- 5-10% of cases are unsatisfactory
- 12-18% of ASCUS, LSIL revised to HSIL+
- Performance dependent on extent of disease
 - Increased quadrants of disease improves HSIL sampling/detection

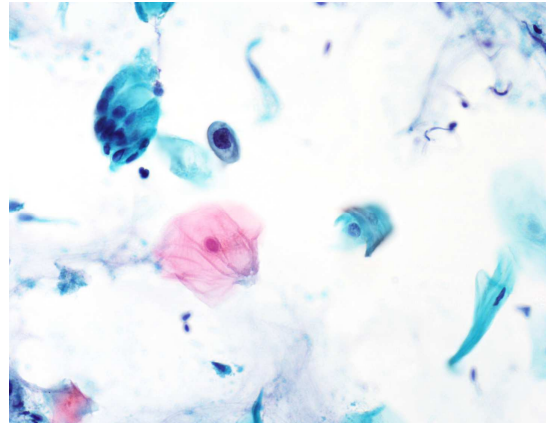
1. Templeton DJ, et al.; SPANC Study Team. Prevalence and predictors of unsatisfactory anal cytology tests in a cohort of gay and bisexual men in Sydney, Australia: baseline findings from the Study of the Prevention of Anal Cancer (SPANC). *Eur J Cancer Prev.* 2017; 26(3): 212-216.
2. Morency EG et al. Anal Cytology: Institutional Statistics, Correlation With Histology, and Development of Multidisciplinary Screening Program With Review of the Current Literature. *Arch Pathol Lab Med.* 2019 Jan;143(1):23-29.
3. Nathan M, Singh N, Garrett N, et al. Performance of anal cytology in a clinical setting when measured against histology and high-resolution anoscopy findings. *Aids* 2010;24:373-379.



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2) If present, are we finding it?

- Rare cells
- Obscured by inflammation or fecal debris
- Poor preservation/air drying artifact
- Associated with LSIL



1. Arain S, Walts AE, Thomas P, et al. The Anal Pap smear : Cytomorphology of squamous intraepithelial lesions. CytoJournal 2005;2:4.
2. Friedlander MA, Stier E, Lin O. Anorectal cytology as a screening tool for anal squamous lesions. Cancer Cytopathology 2004;102:19–26.



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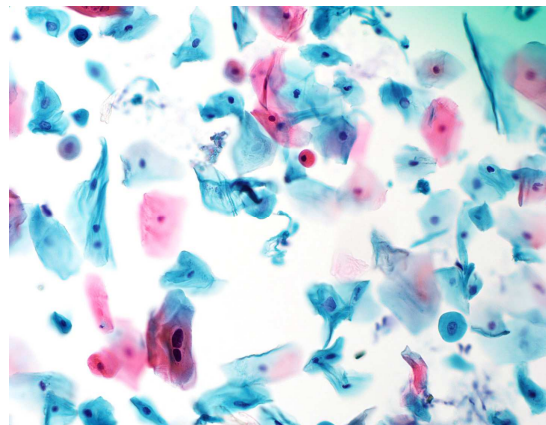


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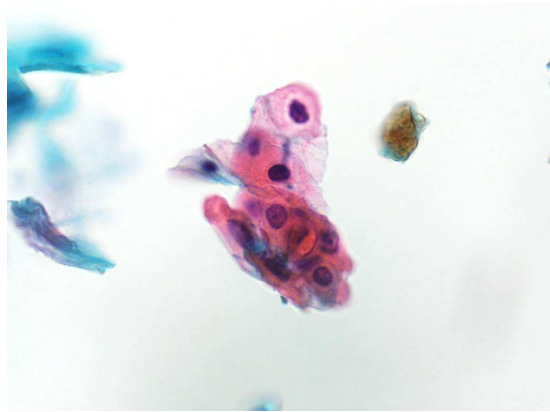


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3) If we find it, can we recognize it?

- Often “under-grade” compared to consensus
- 12-18% of ASCUS, LSIL revised to HSIL+
- HSIL interpreted as LSIL > ASCUS > NILM
- Misinterpreting atypical squamous metaplasia
- May be due to lack of experience



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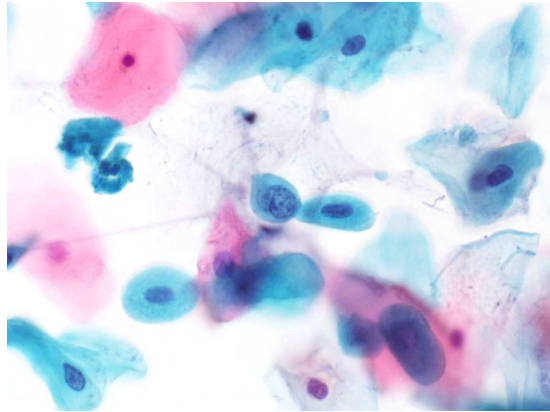
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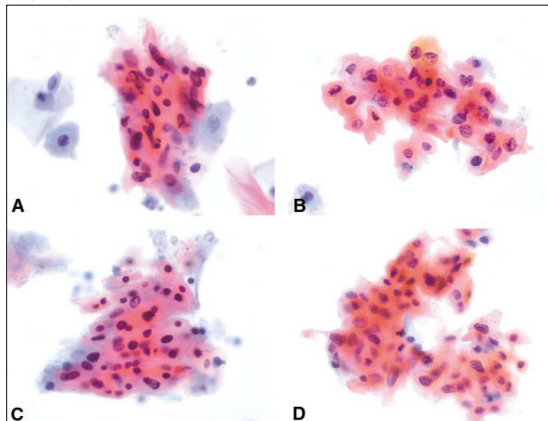


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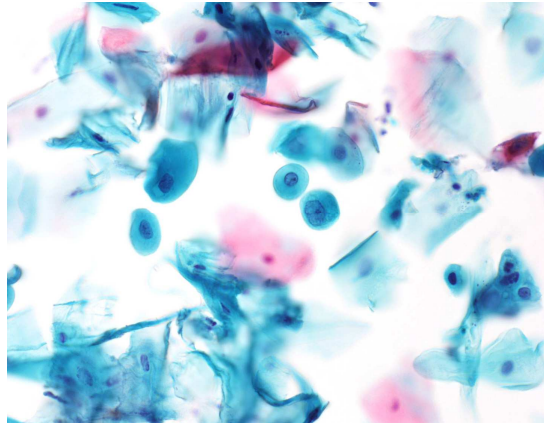


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4) If I call it HSIL, will others agree?

CAP study

- Concordance of interpretation with slide dx
- 57.1% for HSIL
- 56.2% for squamous cell ca
- No improvement of HSIL concordance over time



1. Darragh TM, et al. Room for Improvement: Initial Experience With Anal Cytology: Observations From the College of American Pathologists Interlaboratory Comparison Program in Nongynecologic Cytology. Archives of Pathology & Laboratory Medicine 2013;137:1550-1554.



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4) If I call it HSIL, will others agree?

Inter-rater Reliability

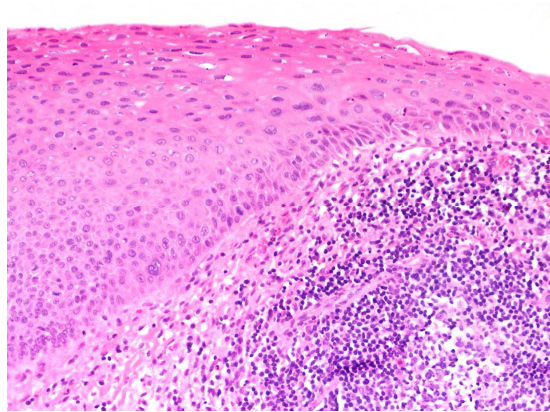
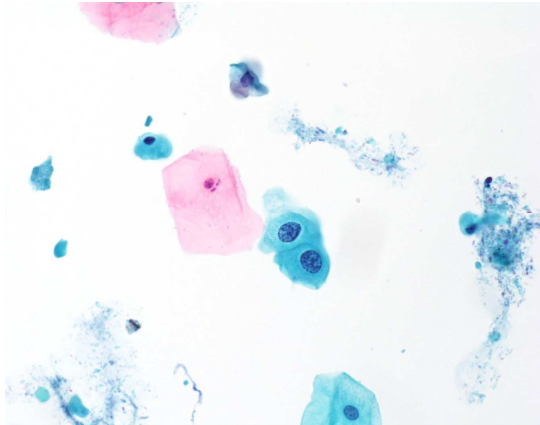
- 77% of cases, at least 3/4 pathologists agree
- Cohen's kappa: 0.54-0.69
- For HSIL, kappa: 0.45 (NILM kappa: 0.84)
- Inter-rater reliability, moderate agreement

1. Lytwyn A, Salit IE, Raboud J, et al. Interobserver agreement in the interpretation of anal intraepithelial neoplasia. Cancer 2005;103:1447-1456.
2. Scholefield JH, et al. Guidelines for anal cytology—to make cytological diagnosis and follow up much more reliable. Cytopathology: Official Journal Of The British Society For Clinical Cytology 1998;9:15-22.
3. Darragh TM, Tokugawa D, Castle PE, et al. Interrater agreement of anal cytology. Cancer Cytopathol 2013;121:72-78.



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5) I call it HSIL, will the biopsy agree?



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Correlation with Anal Biopsy

- 8-44% bx HSIL “under-called” as LSIL or less
- 3-46% of cyto HSIL was bx LSIL or less
- 12% cyto ASCUS, LSIL were revised HSIL+
- 10% cyto HSIL revised to LSIL
- Cytology “under-called” compared to HRA and biopsy

1. de Ruiter A, Carter P, Katz DR, et al. A comparison between cytology and histology to detect anal intraepithelial neoplasia. *Genitourin Med* 1994;70:22–25.
2. Nathan M, Singh N, Garrett N, et al. Performance of anal cytology in a clinical setting when measured against histology and high-resolution anoscopy findings. *Aids* 2010;24:373–379.
3. Nahas C, et al. Screening Anal Dysplasia in HIV-Infected Patients: Is There an Agreement Between Anal Pap Smear and High-Resolution Anoscopy-Guided Biopsy? *Diseases of the Colon & Rectum* 2009;52:1854–1860.
4. Mathews W, et al. Measurement Characteristics of Anal Cytology, Histopathology, and High-Resolution Anoscopic Visual Impression in an Anal Dysplasia Screening Program. *Jacids Journal of Acquired Immune Deficiency Syndromes* 2004;37:1610–1615.



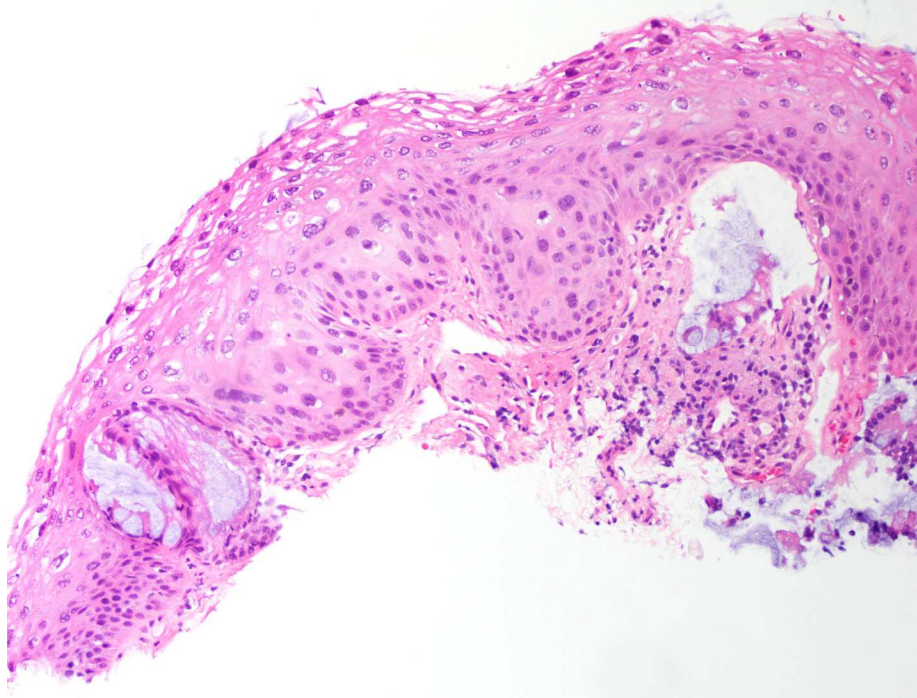
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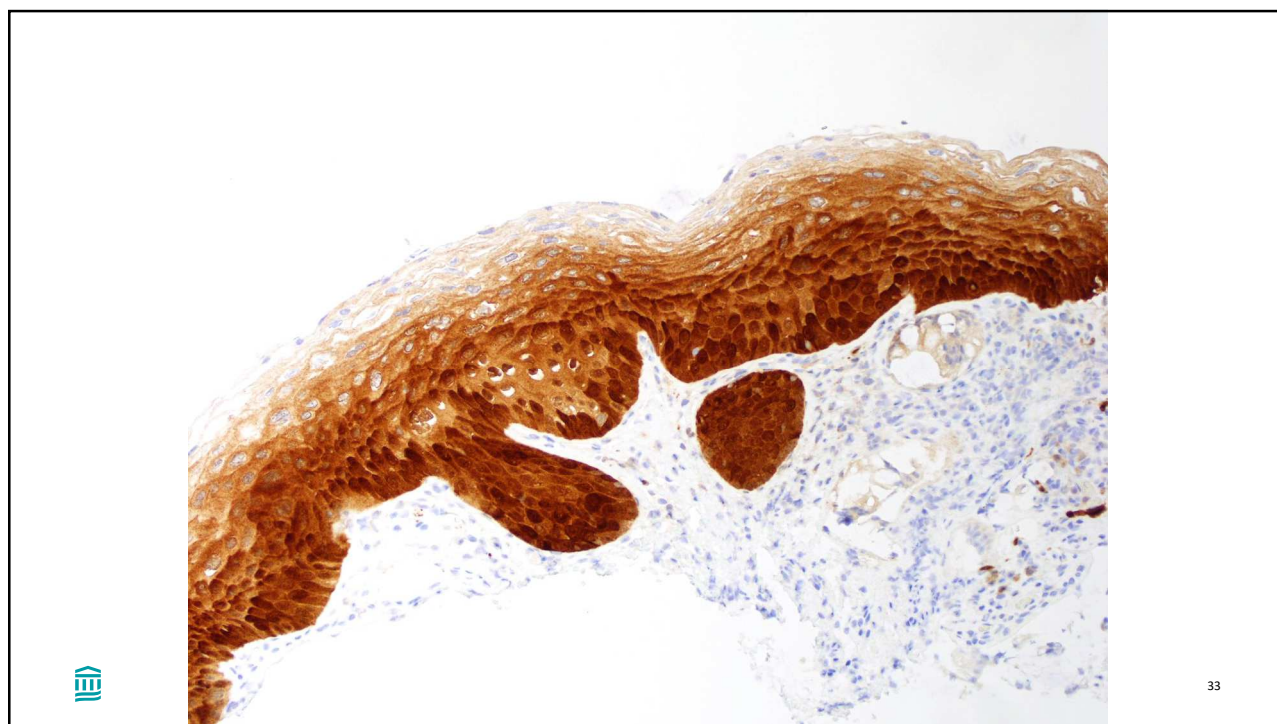
Cytology versus Biopsy, who is right?



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6) If we find it, and we call it HSIL, and the biopsy does not agree, who is right?

Cytology versus Biopsy, who is right?

- What is the gold-standard?
- Anal biopsy interpretation also suffers from inter-observer variability
 - Especially with 3-tier AIN system



7) Are the criteria really the same as cervicovaginal cytology?

- Abnormal cells have a high nucleus-to-cytoplasmic ratio
- Nuclear changes similar to those seen in LSIL – enlargement, hyperchromasia, and nuclear chromatin and/or membrane irregularities
- However, cytoplasm scant, and may be metaplastic or keratinized
- Mixture of both LSIL and HSIL on the same sample is frequently seen on anal cytology
- Squamous lesions with prominent orangeophilic cytoplasmic keratinization are common
- Degenerative changes with nuclear karyorrhexis more frequent than in cervical specimens.
- Very small cells (highlighted by IHC) may hide in background



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Conclusions

- HSIL on anal cytology parallel cervix
- Identification of rare HSIL cells
- Utilize Bethesda criteria to avoid “under-calling”
- QA review of cytology and biopsy with discordance



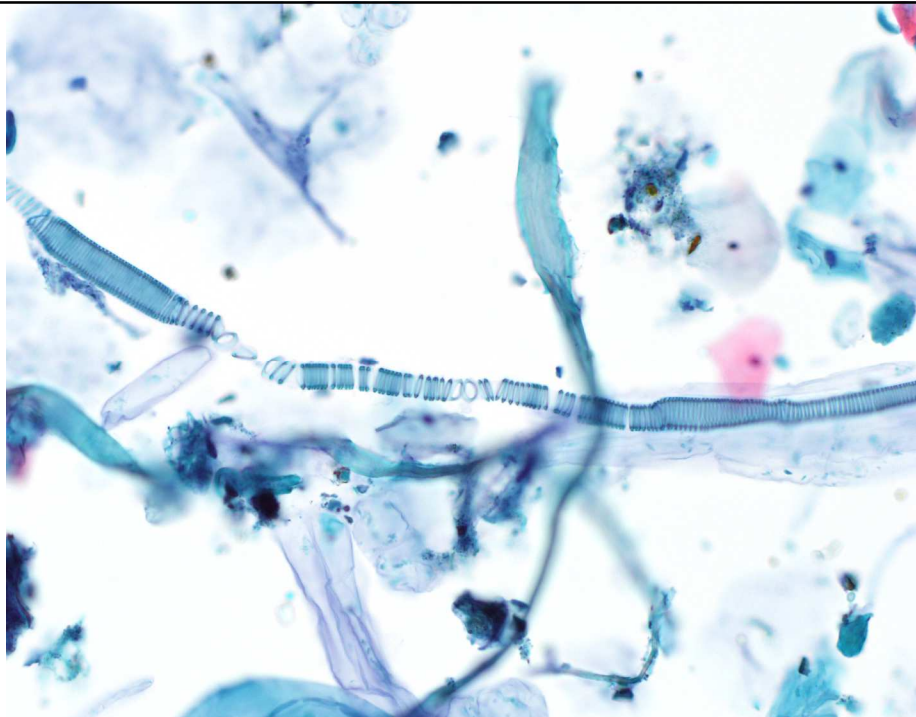
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Future Considerations

P16/Ki67 IHC; molecular testing
HPV testing
HIV-treatment
HPV-vaccine



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