

Cervical Cytology and Pathology: Past, Present, and Future

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You can't really know where you are
going until you know where you
have been.

— *Maya Angelou* —

Objectives

- Review the history of the Bethesda System
- Provide an overview of Lower Anogenital Squamous Terminology
- Discuss evidence-based research studies
- Give a summary of QA findings
- Examine the relationship between HPV and cervical dysplasia
- Present the New ASCCP Risk Based-Management Guidelines

History of “the Bethesda system” (TBS)

- Bethesda, Maryland, December 1988
- Standardization of terminology
 - Relevant information communicated from the lab to the provider
 - Uniform and reasonably reproducible
 - Reflective of current understanding of cervical neoplasia

Evolution of Nomenclature

Richard RM. Cancer 19 1635, 1965

Bethesda: Cytology Report Example

Text(s) Ordered: Pap Smear (Liquid Based), Physician Read Pap
 Clinician Provided Cytology Info: ACC-62389 PID:142510
 Clinician Provided ICD Code(s) & Clinical History: 2309

Collected: 01/20/19 Pap Vial

INTERPRETATION

ASC-US EPITHELIAL CELL ABNORMALITY.
 ATYPICAL SQUAMOUS CELLS OF UNDETERMINED SIGNIFICANCE (ASC-US), IN. (91)
 Pathologist Provided ICD Code(s) (91)
 RB:610

Specimen Adequacy (91)
 Satisfactory for evaluation. Endocervical and/or squamous metaplastic cells (endocervical component) are present.

COMMENTS

14 The Pap smear is a screening test designed to aid in the detection of premalignant and malignant conditions of the uterine cervix. It is not a diagnostic procedure and should not be used as the sole means of detecting cervical cancer. Both false-positive and false-negative reports do occur. (91)

Performed by Britney Sefcik, Cytochemist (ASCP) (91)
 Electronically signed by Frank Lawrence Anderson, MD, Pathologist (91)
 CO-ATC(91) 19 15050160
 Clinical Info: SPC-Cervix
 Facility: No

PERFORMING LABS

91781 LabCorp Birmingham-Cytology 1801 First Avenue South, Birmingham, AL 35233-1033 Lab (205) 381-3000 Dr. Brian D. Ruppard MD
 For inquiries, the physician may contact the lab using the number(s) indicated above.

**Format of the Report:
Sample Type/Statement of
Adequacy**

- Specimen Adequacy-
Satisfactory/Unsatisfactory,
Presence/Absence of TZ, Quality
Indicators- blood, inflammation

**Format of the Report:
Sample Type/Statement of
Adequacy**

- Liquid based (Thin Prep) adequate
cellularity and smear quality
 - 5000 minimum absolute number of
cells
- TZ present: 10 metaplastic or
endocervical cells

**Format of the Report:
General Categorization**

- Negative for Squamous Intraepithelial
Lesion or Malignancy (NIL)
- Epithelial cell abnormalities
 - Squamous
 - Glandular
- Other- Endometrial cells > 45 yo

**Format of the Report:
Interpretation/Results**

- Squamous Cell Abnormalities
 - Atypical squamous cells
 - Of undetermined significance
 - Essentially equivalent to atypical
squamous cells, cannot exclude
LSIL
 - Cannot exclude a high grade
squamous intraepithelial lesion (ASC-
H)

**Format of the Report:
Interpretation/Results**

Squamous Cell Abnormalities

- LSIL
- HSIL
- Squamous cell carcinoma

**Format of the Report:
Interpretation/Results**

Glandular Cell Abnormalities

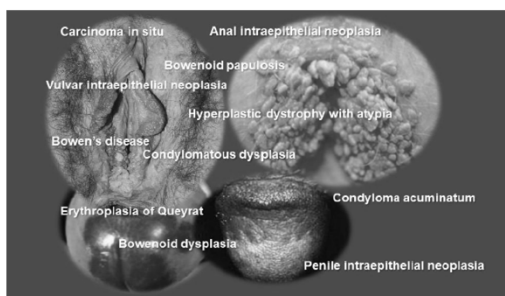
- | | |
|----------------|--|
| • Atypical | • Atypical |
| – Endocervical | – Endocervical
cells, favor
neoplastic |
| – Endometrial | |
| – Glandular | – Glandular cells,
favor
neoplastic |

Format of the Report: Interpretation/Results

- **Glandular Cell Abnormalities**
 - **Adenocarcinoma**
 - **Endocervical**
 - **Endometrial**
 - **Extrauterine**
 - **NOS**

Format of the Report: Interpretation/Results

- **Other Malignant Neoplasms (specify)**
- **Educational Notes and Suggestions**



Lower Anogenital Squamous Terminology (LAST)

- **Two tiered terminology**
 - **Low grade squamous intraepithelial lesions**
 - **High grade squamous intraepithelial lesions**
- **Terms used for all sites in male and female LGT**

LAST Standardization Project

- **CIN/VAIN/VIN/AIN- Grade 2 lesions are poorly reproducible among pathologists**
- **Variable behavior**
 - **Some progress to HSIL**
 - **Some regress to LSIL**

LAST Standardization Project

- **Use old terminology with the new**
 - **LSIL (CIN 1)**
 - **HSIL (CIN 2)**
 - **HSIL (CIN 3)**

Terminology

Natural history model	Histology			Cytology	
	Dysplasia nomenclature	CIN nomenclature	LAST nomenclature	Papanicolaou classification	The Bethesda system
	Negative	Negative		I	NILM
	Squamous atypia	Squamous atypia		II	ASC-US
Infection	Mild dysplasia	CIN1	LSIL	III	LSIL
Precancer	Moderate dysplasia	CIN2		IV	HSIL
	Severe dysplasia Carcinoma <i>in situ</i>	CIN3	HSIL	V	Carcinoma
Cancer	Carcinoma	Carcinoma			



The ASCUS/LSIL Triage Study for Cervical Cancer (ALTS)

- ASCUS/LSIL = 3 Million results per year
- 5,000 Study Participants from 1996-2000
- Funded by National Cancer Institute

The ASCUS/LSIL Triage Study for Cervical Cancer (ALTS)

- UAB 1 of 4 Centers
- Comparing efficacy and cost-effectiveness of management strategies
- Data analysis is ongoing

ALTS Management Strategies

1. Immediate Colposcopy of all women
2. Repeat cytology with colposcopy only if high grade lesion
3. Co-testing with referral for colpo if HPV is positive or cytology show high grade lesion

ALTS Study Findings

- HPV testing is sensitive in detecting underlying precancerous lesions
- HPV testing is not useful with diagnosis of LSIL
- Expert interpretations of Paps vary

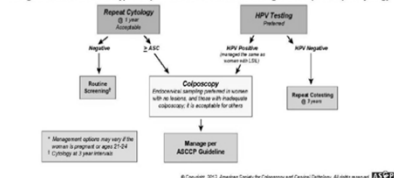
Kaiser Permanente Northern California (KPNC)

- 1.5 Million women ages 25-65 years
 - 591 cancers, 8473 CIN3+, 21395 CIN2+
- Cotesting and HPV genotyping data
- Vaccination status
- Comparison CDC NBCCEDP data



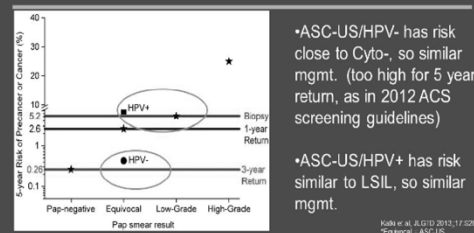
Cytology ASCUS/HPV Negative

Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US) on Cytology*



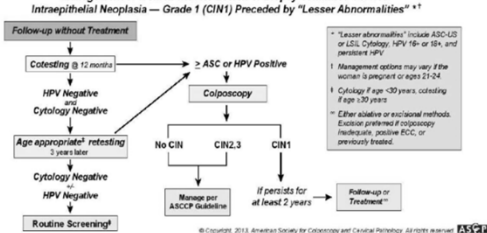
- ASC-US is the most common cytologic abnormality, but it carries the lowest risk of CIN 3+, partly because one-third to two-thirds are not HPV-associated.
- With two consecutive ASC-US HPV- negative findings consult for guidance

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



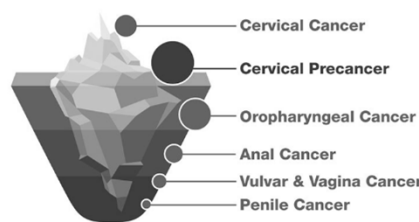
Post Colposcopy Follow-Up

Management of Women with No Lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 1 (CIN1) Preceded by “Lesser Abnormalities” **



- All women with LSIL will be referred for colposcopy
- HPV- test are not done on LSIL due to approximately 80% of these results are associated with HPV

Screening Won't Protect Your Patients from Most HPV Cancers



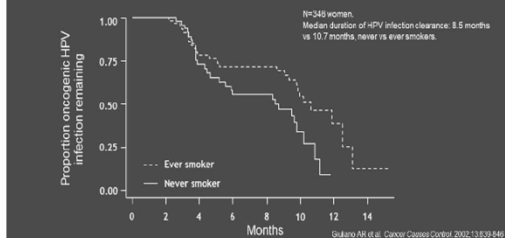
High-risk HPV and Cervical Cancer

- HPV is the necessary (but not sufficient) agent in the pathogenesis of cervical cancer
- Present in 99.7% of cervical cancers worldwide
- HPV positive detection in cancers of the oropharyngeal, tonsillar, base of tongue, oral cavity, larynx
- Vaccination females and males

HPV Infection: 3 Courses

- 1) Sustained Remission
 - Immune response contains infection
- 2.) Productive Infection
 - Co-factors present, HPV replicates
 - Cigarette smoking, Chlamydia, OCs, Nutrition, Immunosuppression
- 3.) Neoplastic Transformation
 - Persistent infection

Smoking History Increases the Time to Clearance of HPV



Addressing THE Need for Advanced HPV Diagnostics-ATHENA Study

- 47,000 women, >21 yo
- 1st screening trial for HPV genotyping
 - 16, 18, and 12 additional hrHPV types
- FDA Approved for Primary Screening
- Can be considered an alternative to traditional screening
- Primary hrHPV only every 5 years

Characteristics of Cervical Cancer Screening Tests



Method	Every	If started at 30, reduction in the number of cervical cancer deaths from 8.34 to
Cytology	3 yrs	0.76 deaths per 1000 women
hrHPV-only	5 yrs	0.29 deaths per 1000 women
Co-testing	5 yrs	0.30 deaths per 1000 women

Kim JJ, Burger EA, Regan C, Sy S. Screening for Cervical Cancer in Primary Care: A Decision Analysis for the US Preventive Services Task Force. JAMA. 2018 Aug 21;320(7):706-714

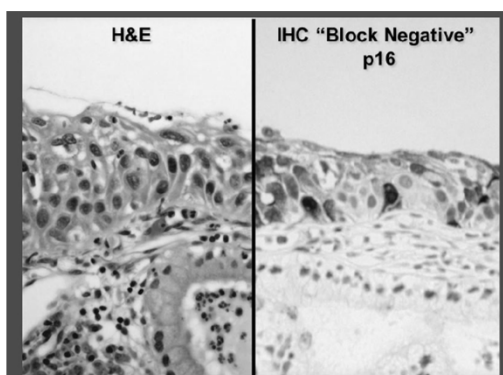
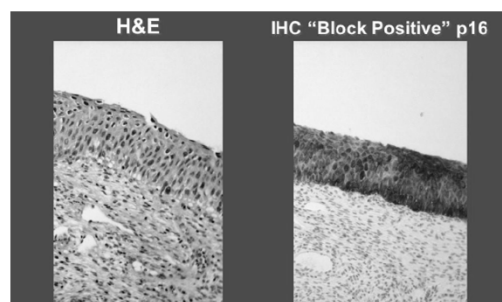
Pathology Report

Additional Information:
Fasting No
Clinical Info: SRC: Curettage

Pathology Report	Tests Ordered:	Clinician Provided ICD Code(s) & Clinical History:
Material Submitted: (01)		N87.0 (01)
Cervix - ECC		CIN (01)
Gross Description: (01)		ECC: Received is an aggregate of mucoid and hemorrhagic material measuring 1.0 x 0.5 x 0.1 cm. Submitted in cassette(s) A1. SHU/SHU 09/21/2019 0442 Local (01)
Diagnosis: (01)		
ENDOCERVICAL CURETTAGE: - FRAGMENTS OF SQUAMOUS MUCOSA WITH FOCAL CHANGES SUGGESTIVE OF MODERATE DYSPLASIA (CIN II, HSIL). - FRAGMENTS OF BENIGN ENDOCERVICAL GLANDS. COMMENT: THE BODY IS MORE DEFINITE FOR DYSPLASIA THAN THE CELLS REPRESENTED IN THE PREVIOUS PAP SMEAR. EOR: 09/24/2019 1220 Local		
Pathologist Provided ICD Code(s): (01)		
N87.1 (01)		
CPT Codes: (01)		
883051 (01)		
Comments: (01)		
ADDENDUM: A P16 IMMUNOSTAIN SUPPORTS THE DIAGNOSIS OF FOCAL MODERATE DYSPLASIA. THE ORIGINAL DIAGNOSIS REMAINS UNCHANGED. EOR:09/30/2019		

p16 Immunostain

- Tumor suppressor gene/biomarker for transforming HPV infection
- Positive results of block staining with p16 indicative of high grade disease
- Improves accuracy of interpretation and prediction of risk for high grade disease
- Clarify discrepancies between cytology and pathology, biopsies/curettage



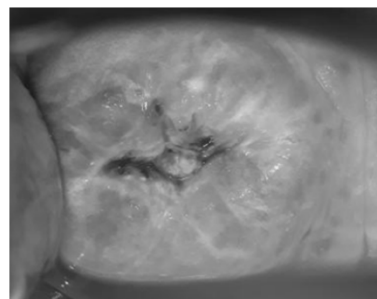
Case Example

23 yo G1P1 with pap history including:
 2019- ASCUS
 2018- LSIL/HPV positive (outside provider),
 age 22
 2017- LSIL, age 21

Case Example

- Colposcopy findings:
 - External genitalia normal, no gross lesions
 - SCJ not fully visualized
 - Ectocervix unremarkable
 - No mosaicism or punctations noted
 - ECC obtained

EVA Image



Pathology Report

Additional Information:
 Fasting: No
 Clinical Info: SRC: Curettage

Pathology Report	Tests Ordered:	Clinician Provided ICD Code(s) & Clinical History:
Material Submitted: cervix - ECC		N67.0 CIN
Diagnosis: ENDOCERVICAL CURETTAGE: - FRAGMENTS OF SQUAMOUS MUCOSA WITH FOCAL CHANGES SUGGESTIVE OF MODERATE DYSPLASIA (CIN II, HSIL). - FRAGMENTS OF BENIGN ENDOCERVICAL GLANDS. COMMENT: THE BODY IS MORE DEFINITIVE FOR DYSPLASIA THAN THE CELLS REPRESENTED IN THE PREVIOUS PAP SMEAR. BDR: 09/24/2019 1220 Local		Gross Description: ECC. Received is an aggregate of mucoid and hemorrhagic material measuring 1.0 x 0.5 x 0.1 cm. Submitted in cassette(s) A1. SNU/SNU, 09/21/2019 0452 Local
Pathologist Provided ICD Code(s): N67.1		
CPT Codes: 883051		

Comments:
ADDENDUM:
 A P18 PINKINGSTAIN SUPPORTS THE DIAGNOSIS OF FOCAL MODERATE DYSPLASIA. THE ORIGINAL DIAGNOSIS REMAINS UNCHANGED.
 BDR:09/30/2019



Future Guidelines

5-year Risk of CIN 3 by Age and Pap Result

Baseline Pap and HPV test result	CIN 3+ risk, %		
	21-24	25-29	30-64
HSIL	28	28	47
ASC-H	16	24	18
AGC	6.9	14	8.5
LSIL	3.0	5.0	5.2
ASC-US	3.0	3.9	7.6
HPV-positive/ASC-US	4.4	7.1	6.8
HPV-negative/ASC-US	0.57	0.59	0.43
Pap-negative	0.2	0.36	0.26

Adapted from Kelloff MA et al. AJGTD 2013;17(6):556-555

Risk Bar

Management: 5-year return 3-year return 1-year return Colposcopy Treatment

- Immediate CIN3+ risks of 25% or above, both colposcopy or immediate treatment are acceptable.
 - Immediate CIN3+ risks of 50% or above, both colposcopy or immediate treatment are acceptable but immediate treatment should be strongly considered.

New Guidelines: Equal Management of Equal Risk Principle

What is the patient's risk?

- Guideline Committees
- Research based
- Clinical action and reassurance
- Treatment

New Guidelines: Equal Management of Equal Risk Principle

What is the patient's risk?

- Colpo
- Short interval surveillance (1 or 3 years)
- 5 year screening

New Risk-Based Guidelines

- Patient's current test results and past history
- Risk matrix is used to calculate her risk of CIN2/3
- Computer program generates risk score
- Recommends next step in management based on risk thresholds suggested by working groups and ratified through consensus process

Risk of CIN3+

- 50-100%
- 25-50%
- 4-24%
- 0.5-4%
- 0.1-0.5%
- <0.1%

ASCP 2019 Annual Scientific Meeting on Anogenital & HPV-Related Diseases

New Guidelines

- HPV Status
- Cytology
- Past History
- New Screening Technology
 - HPV typing
- Vaccination Status
- Patient Characteristics
 - Age, prior negative HPV, etc.

Resulting management achieves precision and simplicity

Enter risk data

Patient: Doe, Jane
Age: 42
HPV: Positive
Cervix: LSIL
Colposcopy: LSE
Vaccine: No
Last screen: Negative

High risk: Treatment

Medium risk: Colposcopy

Low risk: Triage or repeat testing

Minimal risk: Regular screening interval

Recommendation: COLPOSCOPY/ REFERRAL

A 42 year old woman with LSIL, cytology and HPV16 has a 4% risk of CIN3+ which is above the colposcopy referral threshold of 4%