

WORKSHOP
SCREENING DELLA CERVICE UTERINA:
STATO DELL'ARTE

Palazzo Partanna- Unione degli Industriali
P.zza Dei Martiri 56
27 giugno 2018

Da test di screening a test diagnostico:
la nuova sfida per la citologia di domani

Prof. Giancarlo Troncone

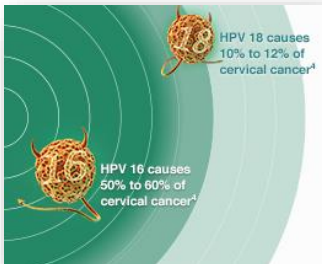


Programma Infradipartimentale di Biologia Molecolare in Citopatologia
Dipartimento di Sanità Pubblica - Università degli studi di Napoli "Federico II"



1941

OGGI

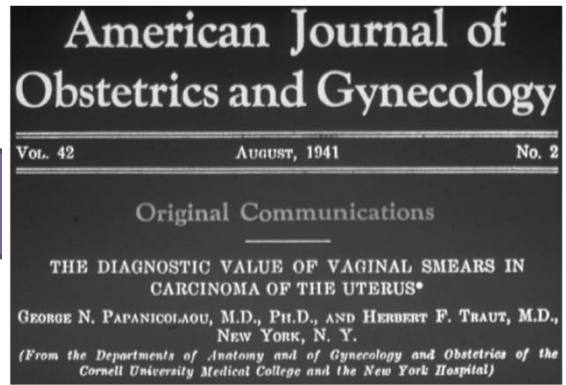




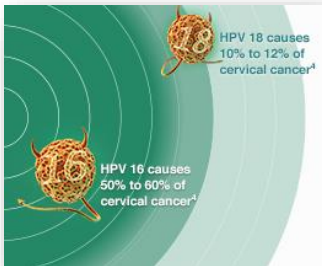
"The diagnostic value of vaginal smears in carcinoma of the uterus"
American Journal of Obstetrics and Gynecology

"Atlas of Exfoliative Cytology"

1941 1954



OGGI





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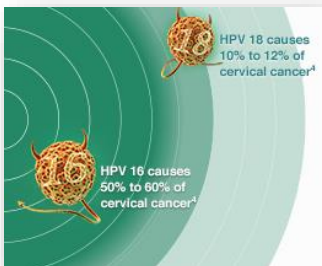
"Atlas of Exfoliative Cytology"

"The Bethesda System for reporting cervical cytology" - Atlas

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1988

OGGI



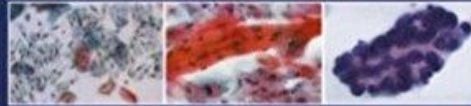
Robert J. Kurman Diane Solomon

THE
BETHESDA
SYSTEM
FOR REPORTING
CERVICAL / VAGINAL
CYTOLOGIC
DIAGNOSES

*Definitions, Criteria, and Explanatory Notes
for Terminology and Specimen Adequacy*



Springer-Verlag



Diane Solomon Ritu Nayar
EDITORS

The Bethesda System
for Reporting
Cervical Cytology

Definitions, Criteria, and
Explanatory Notes

Second Edition



The Bethesda System
for Reporting
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Definitions, Criteria,
and Explanatory Notes

Third Edition

Ritu Nayar
David C. Wilbur
Editors

 Springer



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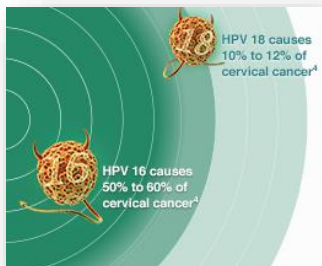
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1983 1988 1992

OGGI



Triage con HPV test per ASCUS

Isolamento e caratterizzazione di HPV 16 e 18
Harald zur Hausen – Premio Nobel 2008



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1941

1954

1983

1988

1992

1998

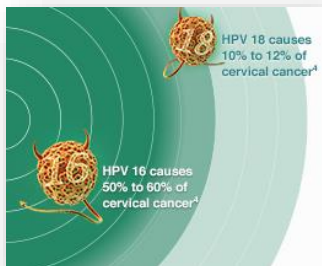
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Reflex HPV da liquid-based cervical cytologic

Triage con HPV test per ASCUS

Isolamento e caratterizzazione di HPV 16 e 18

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"The Bethesda System for reporting cervical cytology" - Atlas

1941 1954

1983

1988

1992

1998

2003

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Co-test screening

Reflex HPV da *liquid-based cervical cytologic*

Triage con HPV test per ASCUS

Isolamento e caratterizzazione di HPV 16 e 18
Harald zur Hausen – Premio Nobel 2008

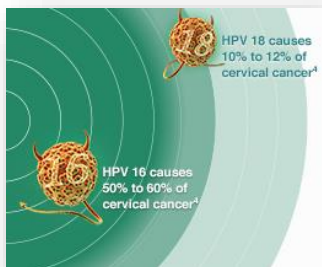
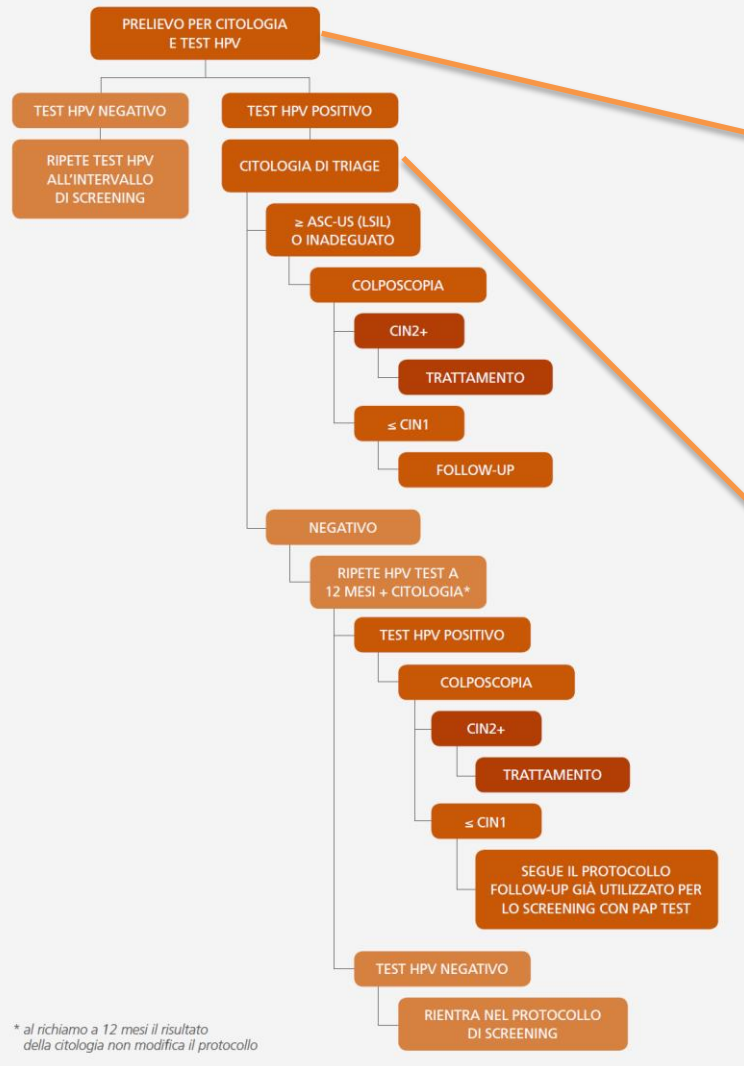


FIGURA 1

PROTOCOLLO SCREENING CERVICALE
CON TEST HPV PRIMARIO E CITOLOGIA DI TRIAGE



PRELIEVO PER CITOLOGIA
E TEST HPV

CITOLOGIA DI TRIAGE

RACCOMANDAZIONI SUL TEST HR-HPV COME
TEST DI SCREENING PRIMARIO - *GISCI 2017*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

OCTOBER 18, 2007

VOL. 357 NO. 16

Human Papillomavirus DNA versus Papanicolaou Screening Tests for Cervical Cancer

Marie-Hélène Mayrand, M.D., Eliane Duarte-Franco, M.D., Isabel Rodrigues, M.D., Stephen D. Walter, Ph.D., James Hanley, Ph.D., Alex Ferenczy, M.D., Sam Ratnam, Ph.D., François Coutlée, M.D., and Eduardo L. Franco, Dr.P.H., for the Canadian Cervical Cancer Screening Trial Study Group*

Sensitivity, specificity, PPV and NPV for CIN 2+, for various combinations of primary cervical screening options evaluated in the randomized Canadian Cervical Cancer Screening Trial of over 10,000

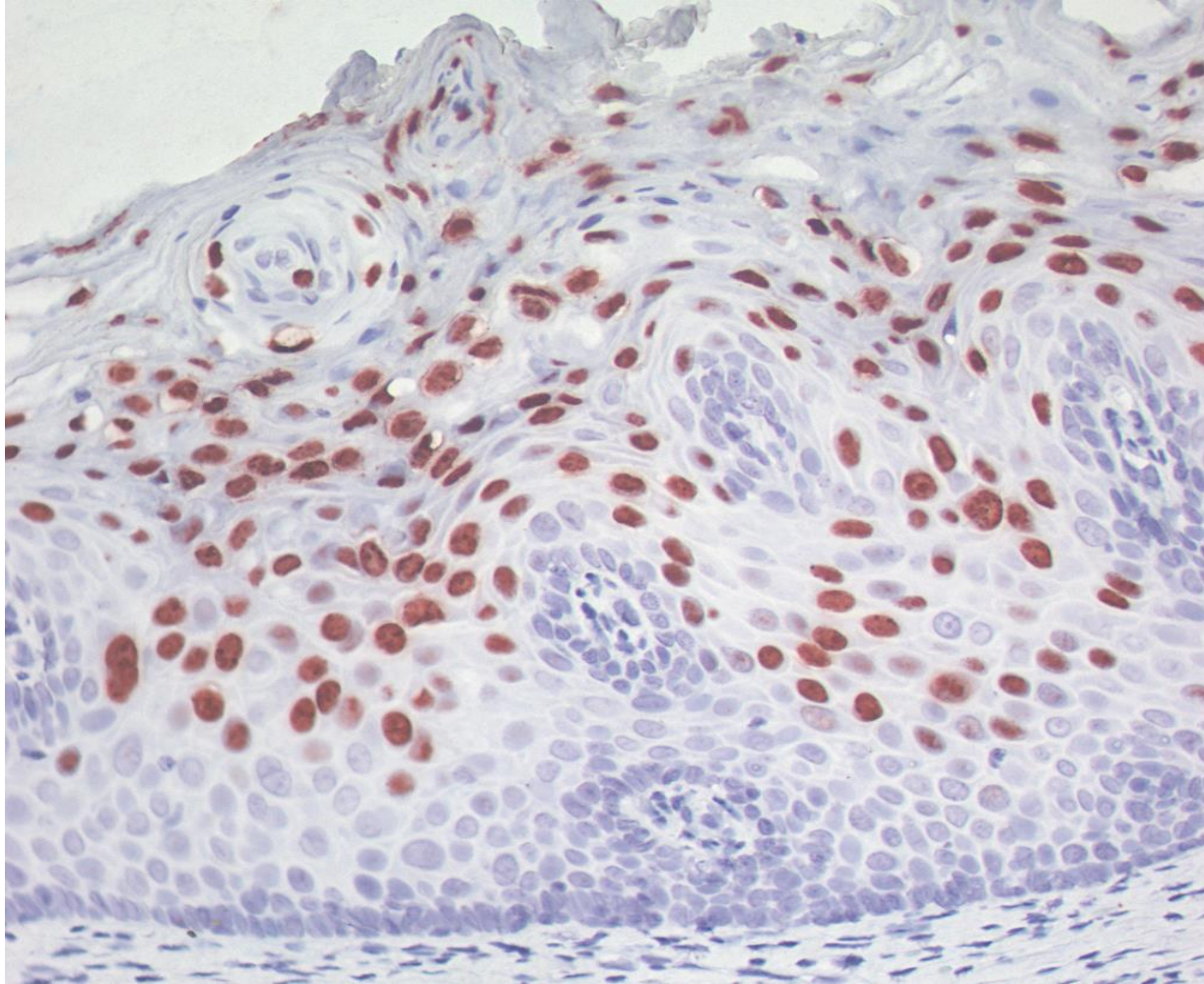
Test	Sens	Spec	PPV	NPV	% to Colpo ^a
HPV alone	97.4	94.3	7.0	100.0	6.1
Pap alone	56.4	97.3	8.5	99.8	2.9
Pap with reflex HPV	53.8	98.7	14.9	99.8	1.6
HPV with reflex Pap	53.8	99.1	21.4	99.8	1.6
HPV plus Pap	100.0	92.5	5.5	100.0	7.9

^a Colpo = colposcopy.

From: Mayrand MH et al. N Engl J Med 2007;357:1579–88. Copyright © 2007 Massachusetts Medical Society. All rights reserved.



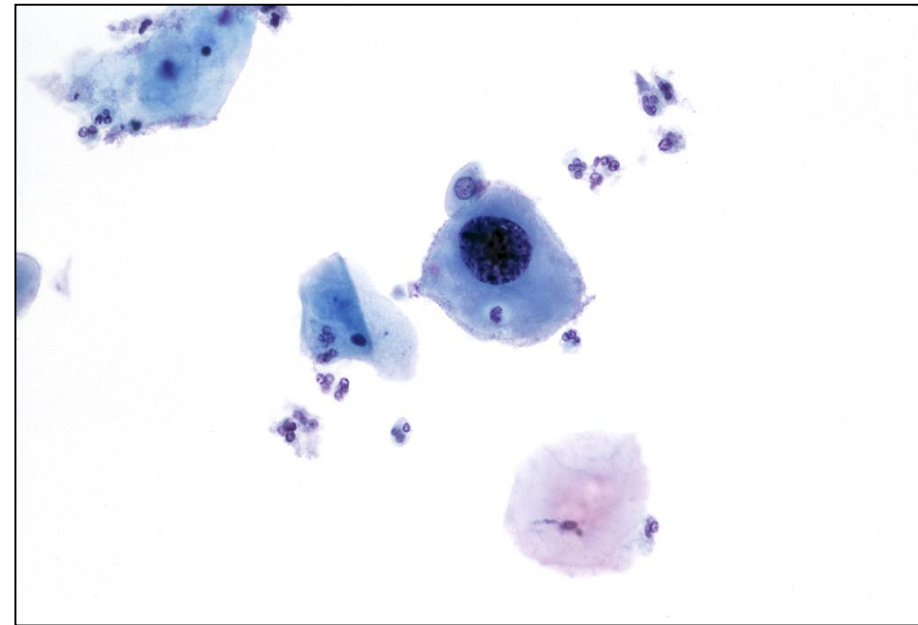
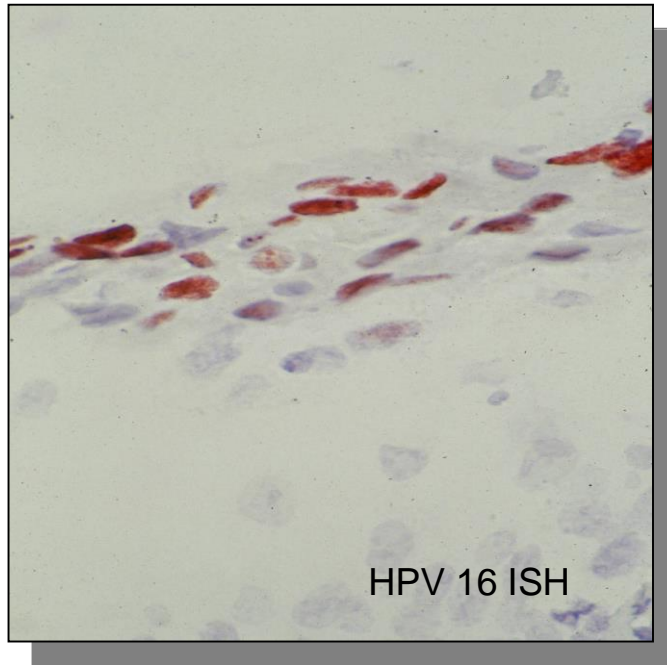
LSIL= differentiated and virally productive



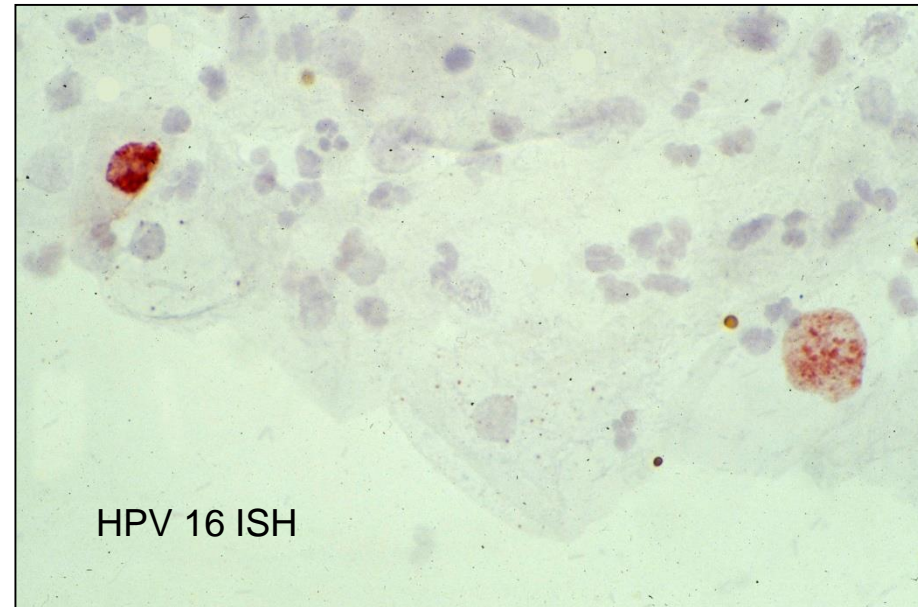
HPV 45 ISH



LSIL= permissive HPV infection



The nuclear enlargement and hyperchromasia of LSIL are direct results of productive HPV infection



Stoler MH.

Arch Pathol Lab Med 2003; 127:935-939

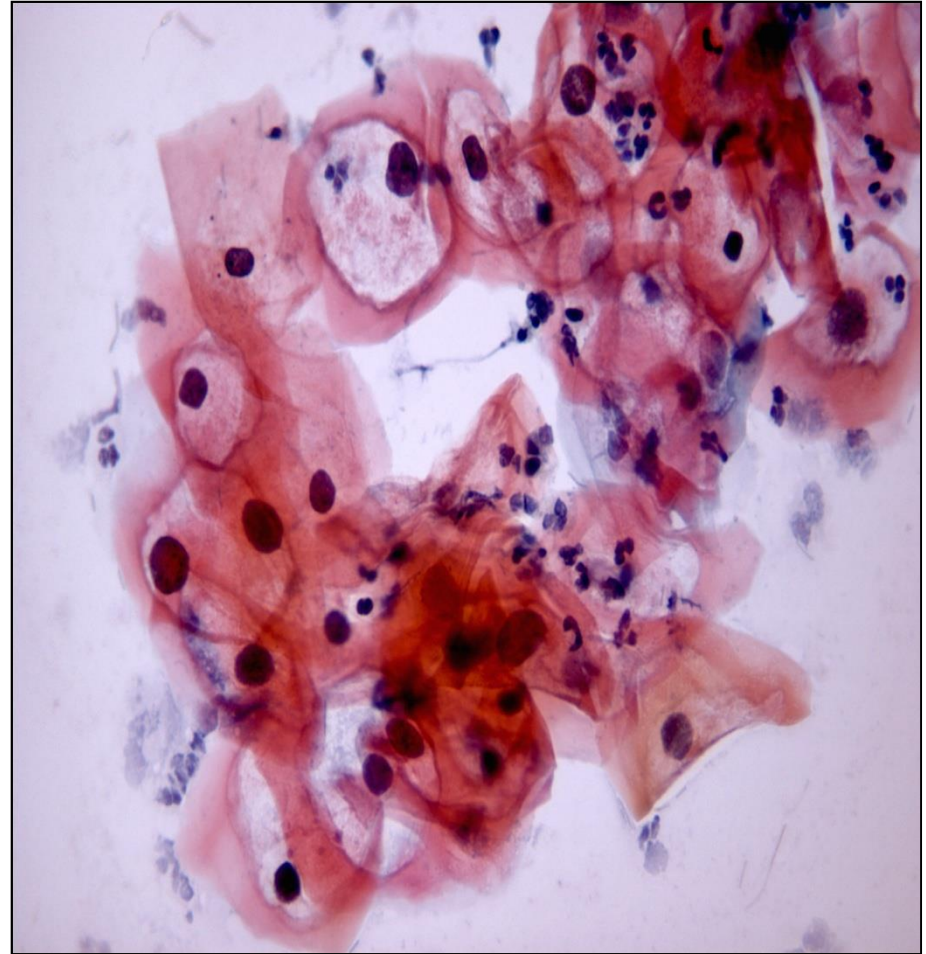


Koilocyte: permissive HPV infection

If the cells have also the correct amount and form of cytokeratin binding E4, then they appear as koilocytes.

Stoler MH.

Arch Pathol Lab Med 2003; 127:935-939

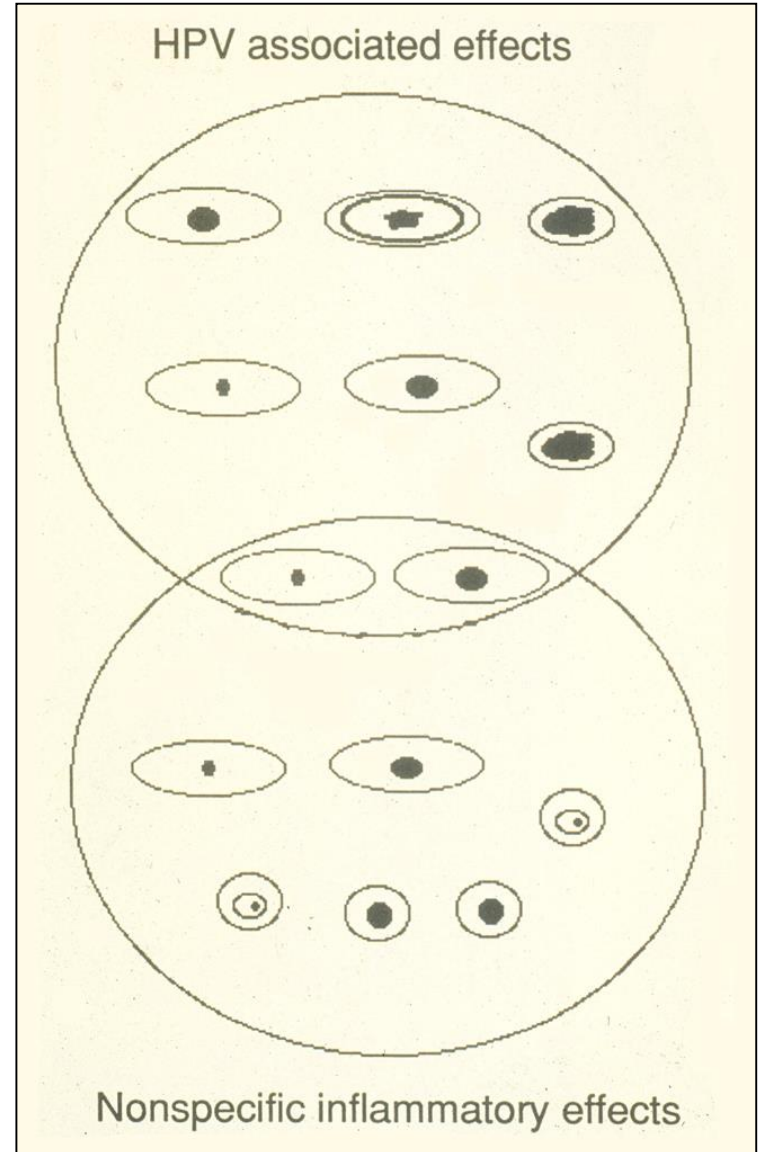
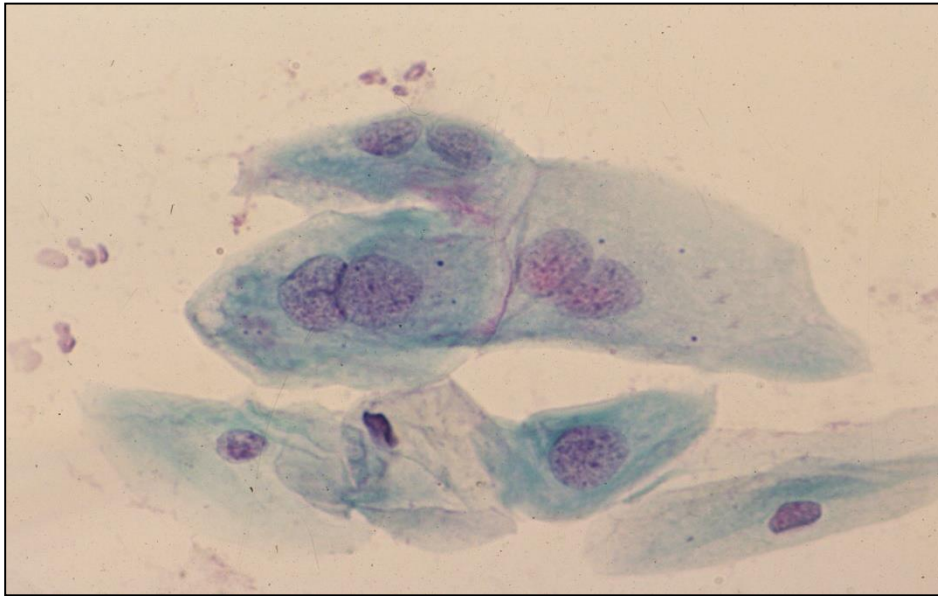


Koilocytes

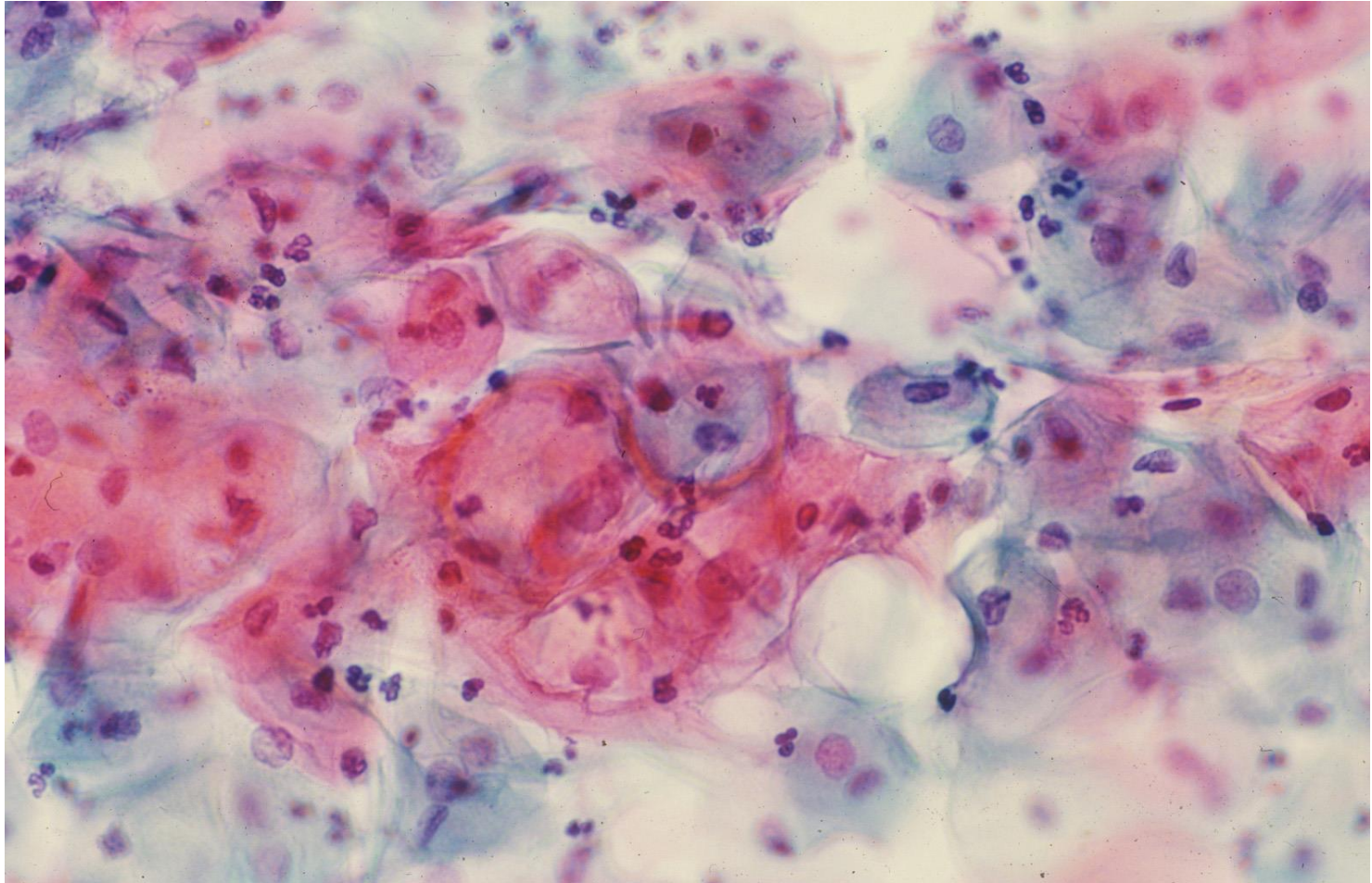


Early or regressive HPV infection: a component of ASC-US

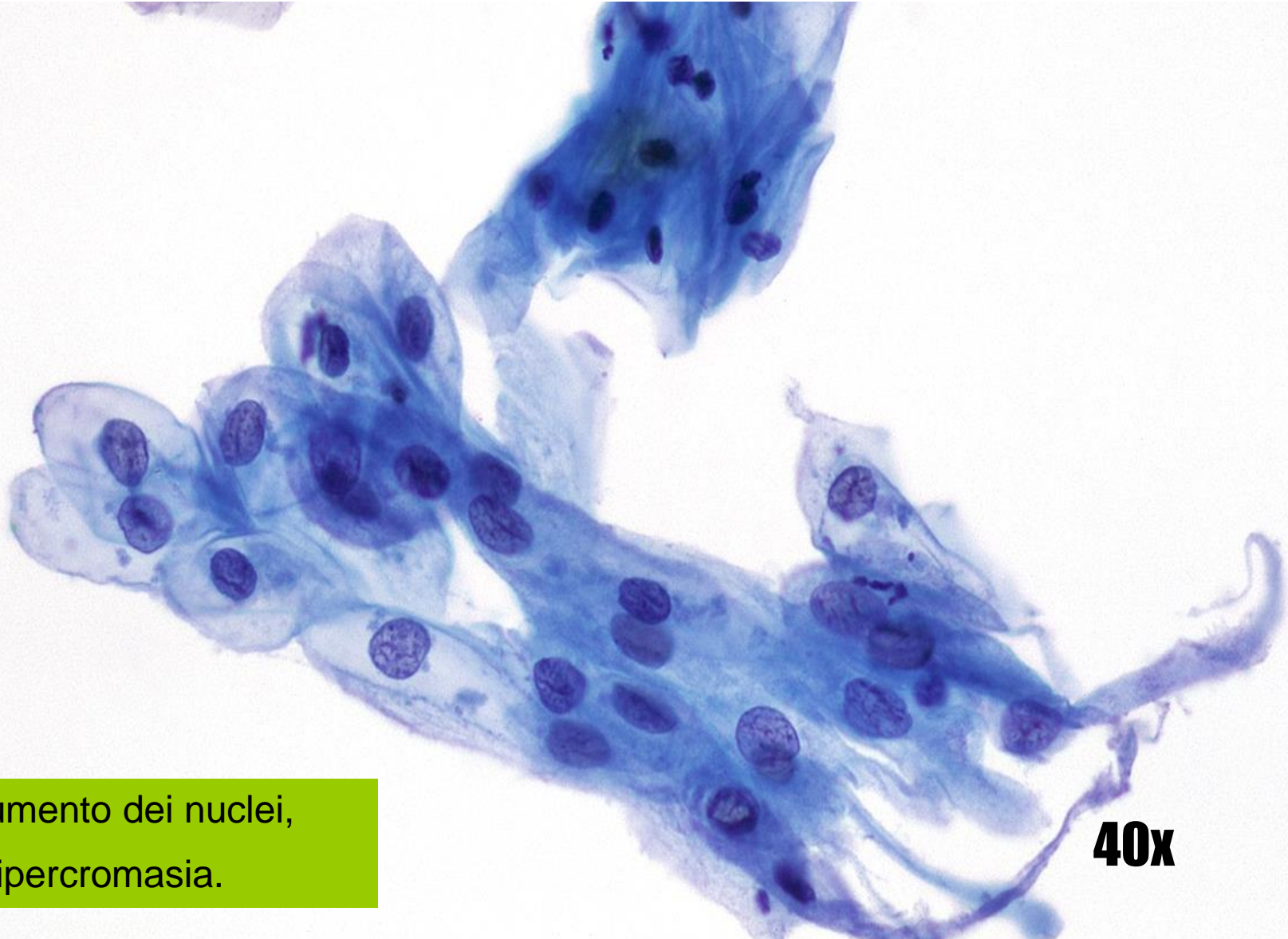
In not fully developed or regressing HPV infection the cells derived from the surface have less nuclear abnormalities.



Prima ASCUS ora FU 1 year



Prima ASCUS ora FU 1 year



Lieve aumento dei nuclei,
minima ipercromasia.

40x

Colposcopia

A microscopic image of a Pap smear. The background is light pink. There are several large, flat, squamous epithelial cells. One large cell in the center has a very dark, dense nucleus. There are also many smaller, round cells with dark nuclei scattered throughout. The overall appearance is consistent with low-grade squamous intraepithelial lesion (LSIL) and inflammation.

Cellule
infiammatorie

LSIL

nuclei scuri ed ipercromatici

40x



LSIL

LSIL

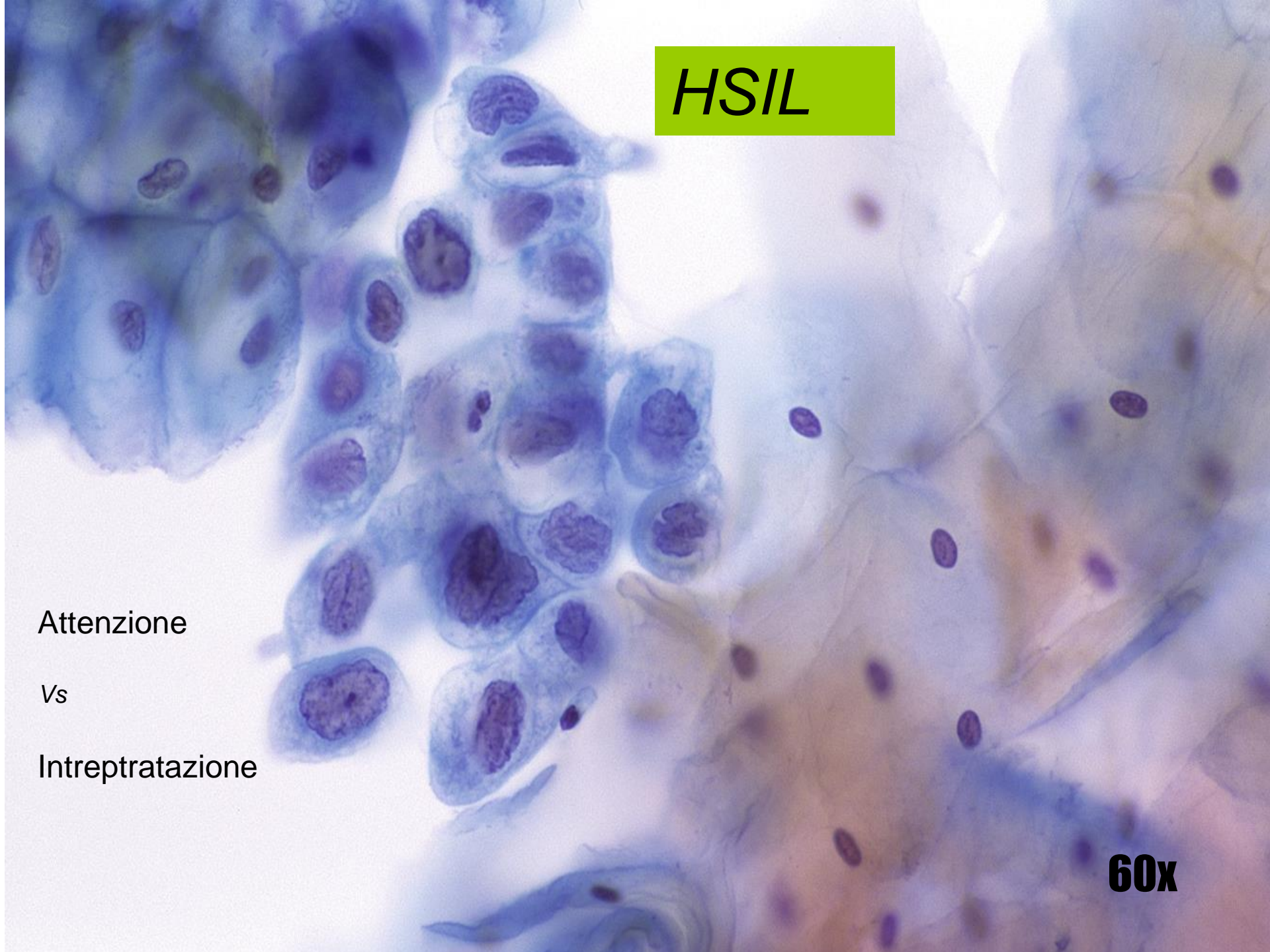
nuclei scuri ed ipercromatici

40x

HSIL

Attenzione
Vs
Intrepretazione

60x



The Tahoe Study

Bias in the Interpretation of Papanicolaou Test Results When Human Papillomavirus Status Is Known

*Ann T. Moriarty, MD; Ritu Nayar, MD; Terry Arnold, CT(ASCP); Lisa Gearries, CT(ASCP); Andrew Renshaw, MD;
Nicole Thomas, MPH, CT(ASCP); Rhona Souers, MS*

**Table 3. Specific Reference Category With Knowledge of the HPV Status (Biased)
and Without Knowledge of the HPV Status (Unbiased) ($P = .002$)**

Variable	Response Category, No. (%)				Total
	NILM	ASC-US	LSIL	HSIL	
Observers know positive HPV status	131 (31.3)	114 (27.2)	94 (22.4)	80 (19.1)	419
Observers do not know the HPV status	181 (43.1)	101 (24.0)	65 (15.5)	73 (17.4)	420

Knowledge of the HPV Status Biases Cytotechnologists' Interpretation of Pap Tests Originally Diagnosed as Negative for Intraepithelial Lesion or Malignancy

Erika E. Doxtader, MD; Jennifer A. Brainard, MD; Dawn Underwood, MS, CT(ASCP); and Deborah J. Chute, MD

HPV-positive	Noto	Sconosciuto
ASCUS	48%	36%

HPV-negative	Noto	Sconosciuto
ASCUS	29%	29%

Similarly, Doxtader et al¹⁹ showed that knowledge of HPV-HR positivity biased cytotechnologists' interpretation of Pap tests originally diagnosed as NILM to upgrade to ASCUS or worse. HPV-HR positive cases

Increased Rate of ASCUS Diagnosis With Concomitant Request for High-Risk Human Papillomavirus Reflex Testing May Be Due to Cognitive Bias

Avani A. Pendse, MD, PhD,^{1,2} Anna E. Bauer, PhD,³ Leslie Dodd, MD,² and Lori Scanga, MD, PhD²

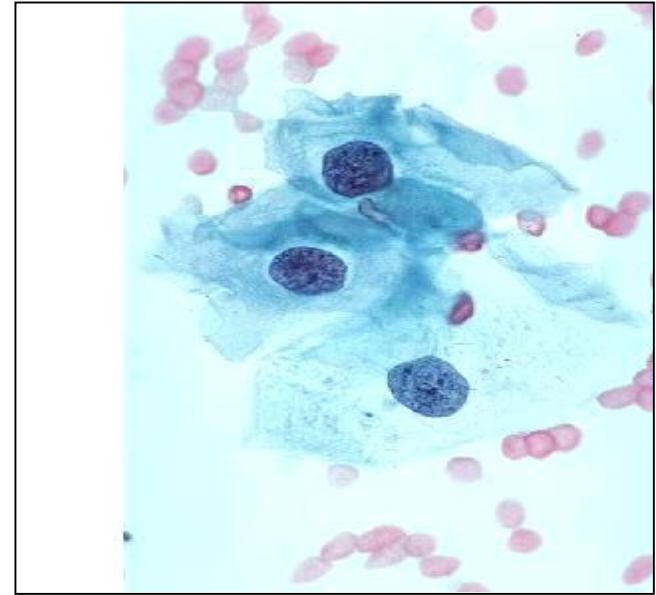
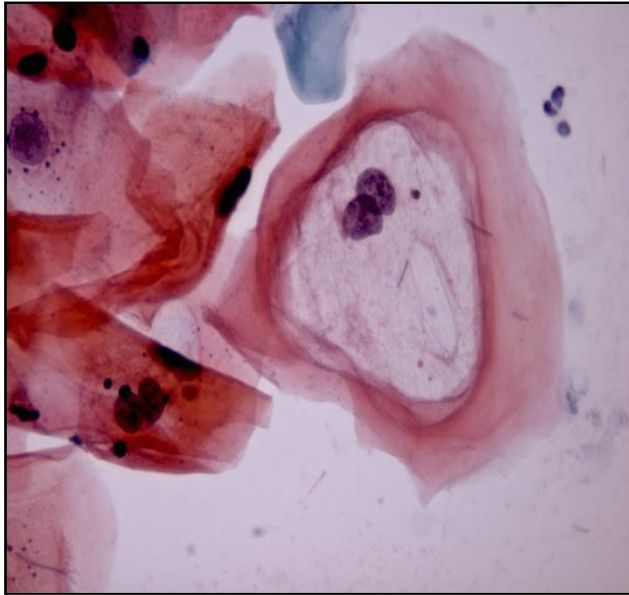
From the ¹Department of Pathology, Duke University Medical Center, Durham, NC; and Departments of ²Pathology and Laboratory and ³Psychiatry, School of Medicine, University of North Carolina at Chapel Hill.

Key Words: Pap test; ASCUS; Reflex HPV testing; Bias

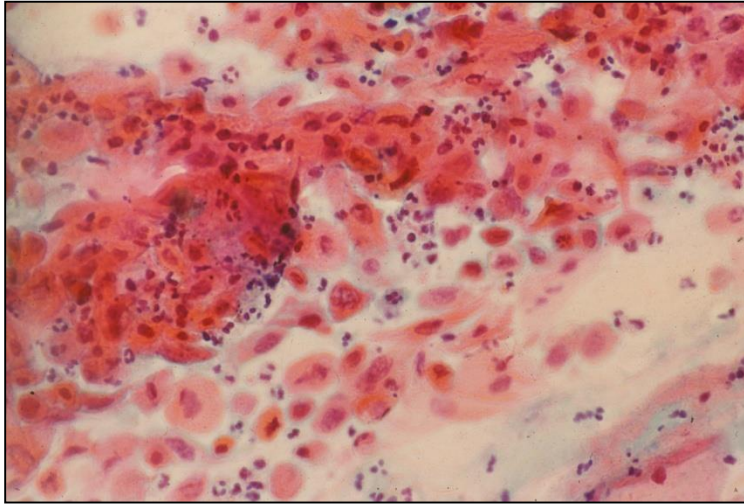
Am J Clin Pathol 2018;00:1–9

	Cotesting	Reflex
Total, No. (%)	516 (67.7)	246 (32.3)
Diagnosis, No. (%)		
NILM	132 (25.6)	53 (21.5)
ASCUS	170 (33.0)	102 (41.5)

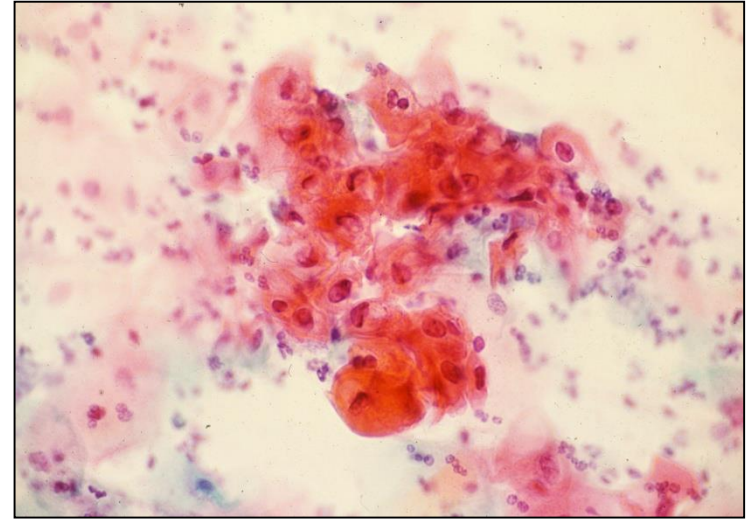
Search for nuclear atypia !



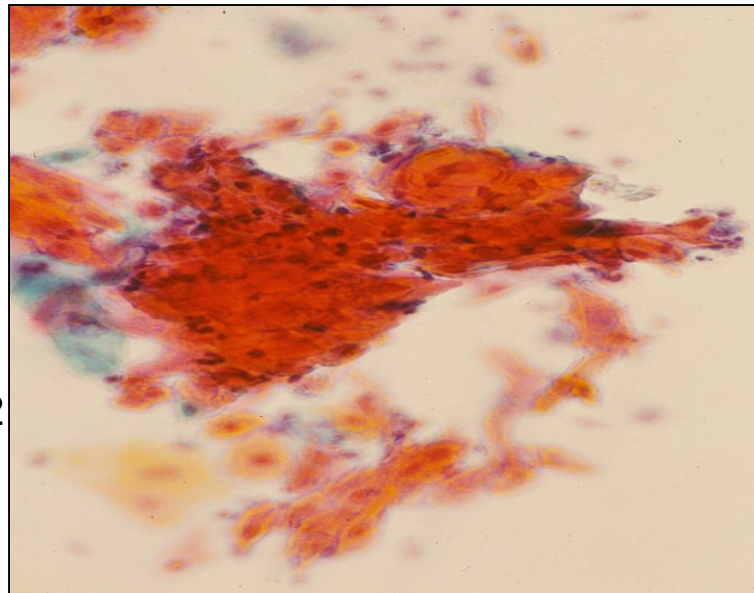
Abnormal keratinization: a component of both ASC-US and ASC-H



parakeratosis



dyskeratosis



hyperkeratosis

Troncone G, Gupta PK.
Acta Cytol 1995 39:659-62





UNIVERSITÀ DEGLI STUDI DI NAPOLI
FEDERICO II

Master

Citologia esfoliativa e screening di popolazione

- > Livello: 1
- > **Struttura responsabile:** Dipartimento di Sanità Pubblica
- > **Coordinatore:** Prof. Giancarlo TRONCONE
- > **N° posti:** Numero massimo: 25 - Numero minimo: 10
- > **Costo:** € 1000,00 (2 rate)
- > **Durata:** 1 anno
- > **Crediti formativi:** 60
- > **Requisiti per l'ammissione:** vedi regolamento





UNIVERSITÀ DEGLI STUDI DI NAPOLI
FEDERICO II

Master

Metodologie di anatomia patologica per lo studio di biomarcatori predittivi di risposta terapeutica

- > Livello: 1
- > Struttura responsabile: Dipartimento di Sanità Pubblica
- > Coordinatore: Prof. Giancarlo TRONCONE
- > N° posti: Numero massimo: 25 - Numero minimo: 10
- > Costo: € 1500,00 (2 rate)
- > Durata: 1
- > Crediti formativi: 60
- > Requisiti per l'ammissione: vedi regolamento



Main genotyping techniques

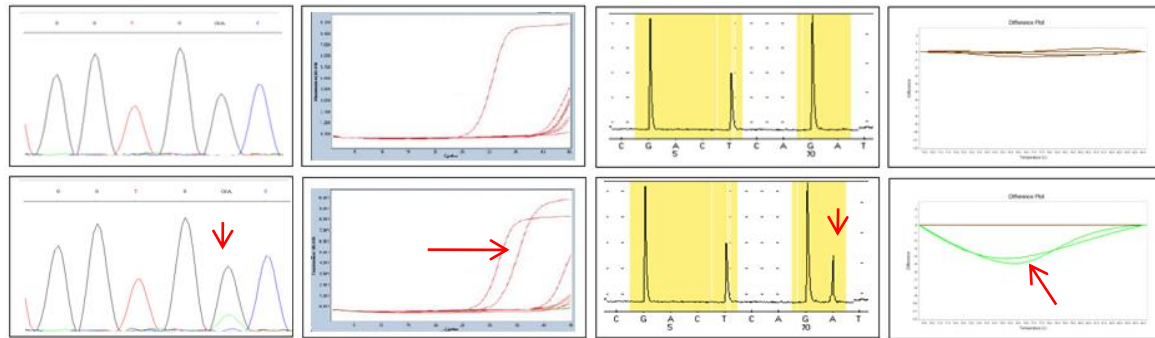


Sanger

TheraScreen

Pyrosequencing

HRMA



LOD = 15-20%

1-5%

5-10%

3-5%

DNA input = 10 ng/μl

80 ng/μl

10 ng/μl

5ng/μl



Da test di screening a test diagnostico: la nuova sfida per la citologia di domani

Il patrimonio della citologia di screening

Le basi morfo-molecolari dell'infezione
da HPV

Le nuove regole della citologia di triage

Il ruolo della formazione morfo-
molecolare