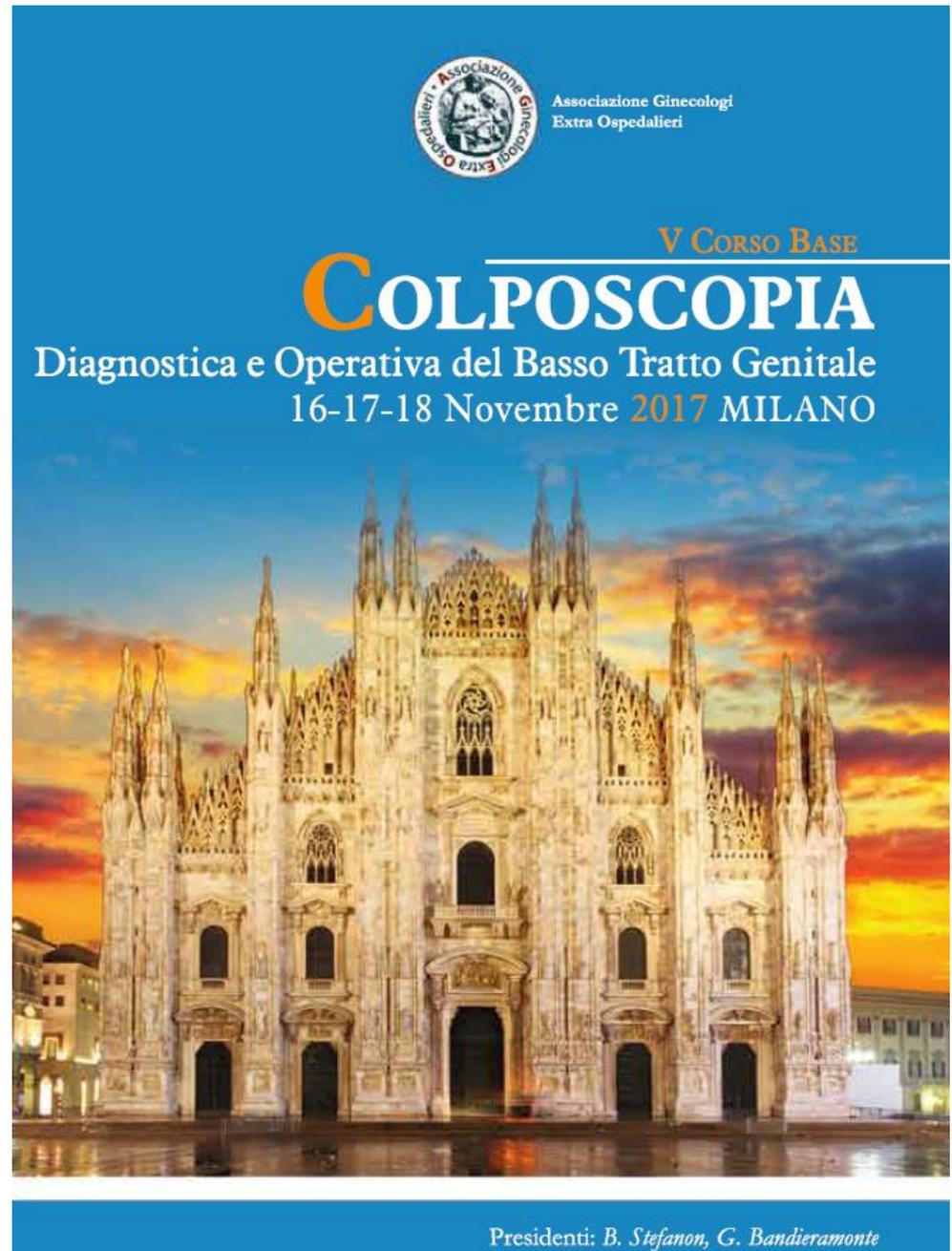


**Approccio diagnostico alla patologia cervicale:  
la colpocitologia tradizionale e su strato sottile.  
La classificazione Bethesda**

**C. Gentili**



Logo of the **Associazione Ginecologi Extra Ospedalieri** (Association of Hospital-based Gynecologists).

**V CORSO BASE**

# COLPOSCOPIA

Diagnostica e Operativa del Basso Tratto Genitale  
16-17-18 Novembre 2017 MILANO

Presidenti: *B. Stefanon, G. Bandieramonte*

PROCEEDINGS  
OF THE  
**Third Race Betterment Conference**  
January 2-6, 1928  

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*Under the Auspices of the*  
**Race Betterment Foundation**  
Battle Creek, Michigan



**NEW CANCER DIAGNOSIS**  
  
**Dr. George N. Papanicolaou**  
Cornell University Medical College



**American Journal of  
Obstetrics and Gynecology**  
Vol. 42                      AUGUST, 1941                      No. 2  

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**Original Communications**  

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**THE DIAGNOSTIC VALUE OF VAGINAL SMEARS IN  
CARCINOMA OF THE UTERUS\***  
**GEORGE N. PAPANICOLAOU, M.D., Ph.D., and HERBERT F. TRAUT, M.D.,**  
**NEW YORK, N. Y.**  
*(From the Departments of Anatomic and of Gynecology and Obstetrics of the  
Cornell University Medical College and the New York Hospital)*



AUREL BABES

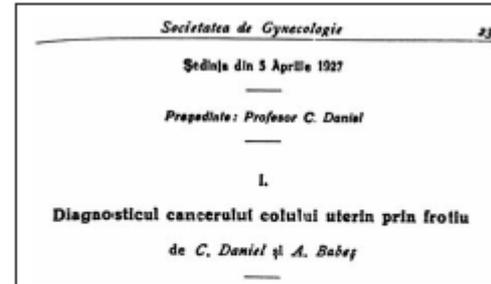


Figure 24 Title page of a paper by Professor M. Daniel and Dr. A. Babeș on the diagnosis of cervical cancer from smears, presented to the Bucharest Society of Gynecology on April 5, 1927.

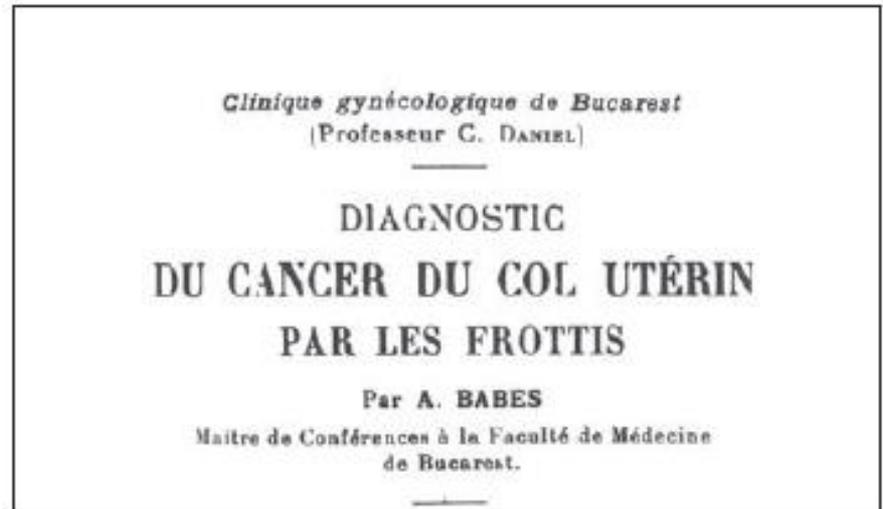
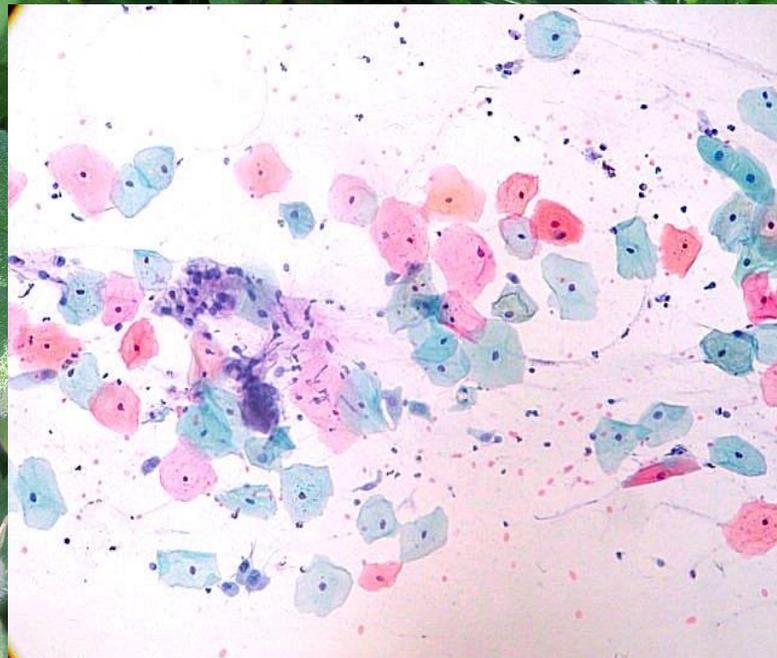


Figure 5 Title of the 1928 article by Dr. Babeș in *Presse Médicale* ("Diagnosis of Cancer of the Uterine Cervix by Means of Smears").



# La colorazione





The front of the 10 000-drachma note, showing George Papanicolaou (1883–1962), with his microscope and famous *Atlas of exfoliative cytology*, published in 1954.

**“Smears cannot always be judged as positive or negative.  
There are cases in which cytologic findings are inconclusive.**

A classification taking into consideration the relatively large group of questionable smear findings is therefore necessary. One may often experience great difficulty in classifying cells that deviate from the normal type but show no malignant characteristics.

**An intermediate class between the entirely normal and the suspicious groups appears to be necessary.**

A similar need for subdivision exists in the positive group. There are instances in which the results are of an overwhelmingly positive character, leaving no doubt as to their final interpretation.

On the other hand, there are cases in which there is strong but not fully convincing evidence of malignancy.

These considerations led us to the acceptance of the following system of classification for cytologic findings, consisting of five groups:

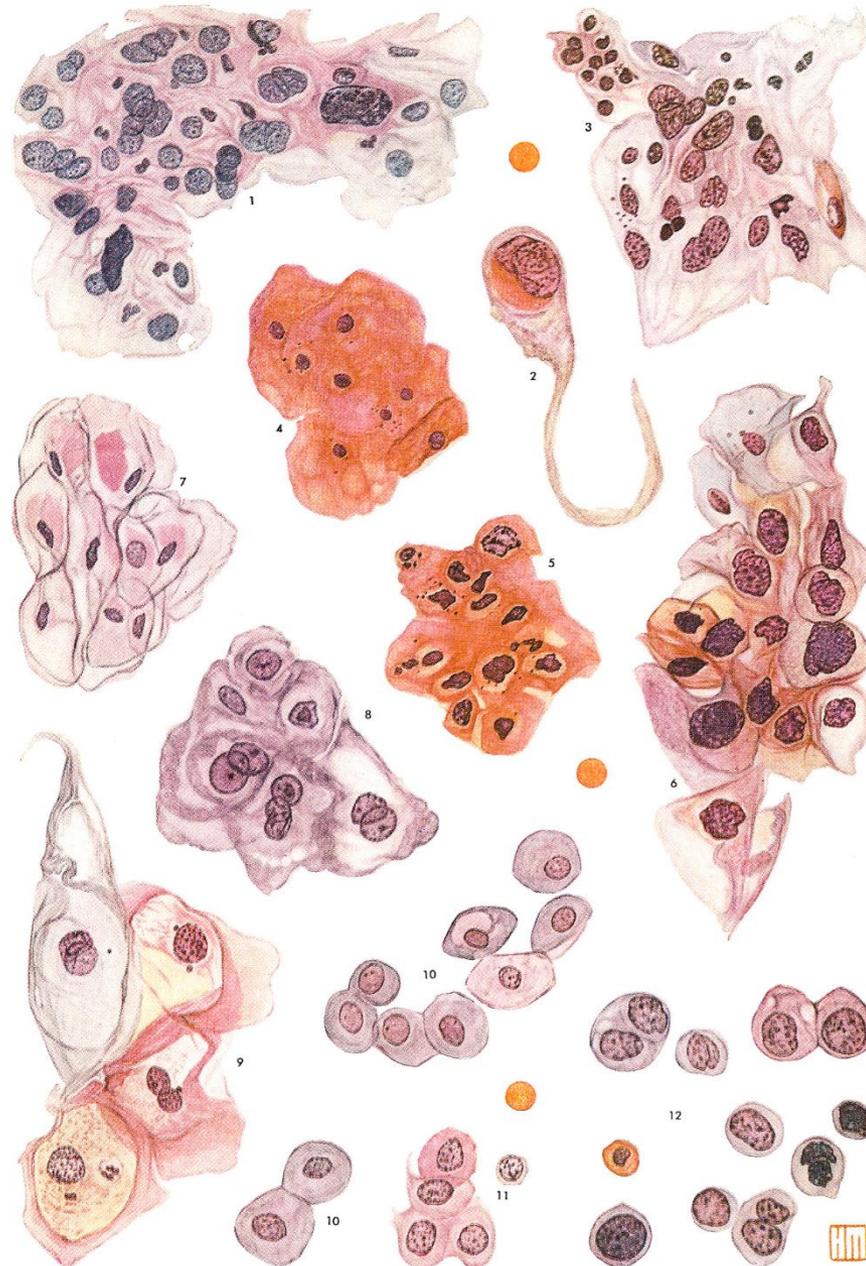
Class I: absence of atypical or abnormal cells

Class II: atypical cytology but no evidence of malignancy (flogosis)

Class III: cytology suggestive of, but not conclusive for, malignancy;

Class IV: cytology strongly suggestive of malignancy;

Class V: cytology conclusive for malignancy





**In the 1950s, a corps of technicians at the University of Tennessee Health Sciences Center study Pap smears**

## Comparazione delle terminologie usate in citologia ed istologia

Displasia/CIS 1954	CIN 1968	Bethesda System 1988	CIN modificata 1991
Displasia lieve	CIN1	LSIL	LGCIN(CIN1)
Displasia moderata	CIN2	HSIL	HGCIN(CIN2/3)
Displasia grave	CIN3		
Ca. in situ			
Ca. invasivo	Ca. invasivo	Ca. invasivo	Ca. invasivo
Reagan JW	Richart, R.M.	National Cancer Institute Workshop.	Richart, R.M.

# Perché il Bethesda

## LA TERMINOLOGIA DEVE:

1. trasmettere, dal laboratorio al clinico, informazioni chiare e pertinenti
2. essere omogenea, riproducibile, adattabile ad un'ampia gamma di settori lavorativi e di aree geografiche
3. tener conto e rispecchiare le conoscenze attuali relativamente alla neoplasia cervicale (due gradi di malattia)

# ***Evoluzione del Bethesda System***

1988	Primo Bethesda
1991	Prima Revisione
2001	Seconda revisione
2014	Terza revisione

# Preparato rifiutato/non processato



## Valutazione dell'adeguatezza:

- Non soddisfacente per la valutazione
- Soddisfacente per la valutazione



## Negative for intraepithelial lesion or malignancy

Non neoplastic findings (optional to report)

### Non neoplastic cellular variations:

- Squamous metaplasia
- Keratotic changes
- Tubal metaplasia
- Atrofia
- Pregnancy associated changes

### Reactive cellular changes associated with:

- Inflammation (includes typical repair)
- Radiation
- Intrauterine contraceptive device (IUD)
- Glandular cells status post hysterectomy

### Organisms:

- Trichomonas vaginalis*
- Fungal organisms morphologically consistent with *Candida spp*
- Shift in flora suggestive of bacterial vaginosis
- Bacteria morphologically consistent with *Actinomyces spp*
- Cellular changes consistent with Herpes simplex virus

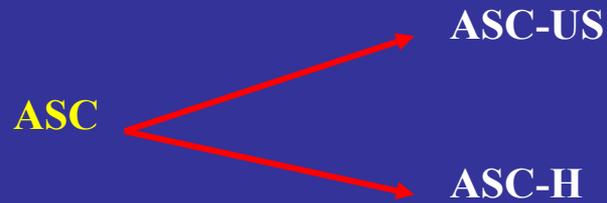
### Other:

- Endometrial cells (in a woman  $\geq$  45 years of age)

## Atypical squamous cells

LGSIL or LSIL (*encompassing* : HPV/ mild dysplasia /CIN1)

HGSIL or HSIL (*encompassing* : moderate and severe dysplasia /CIN 2-3-CIS )



BETHESDA 2001

Squamous cell carcinoma

## Atypical Glandular Cells



Adenocarcinoma *in situ* (AIS)

Adenocarcinoma

# Bethesda 2014: Time For An Update?

**Ritu Nayar, MD**

**Professor of Pathology**

**Northwestern University, Feinberg School of Medicine**

**Chicago, USA**

# Risultati .....

## Adeguatezza

- Chiarire i criteri di cellularità per i campioni post-irradiazione
- Aggiungere dati su interferenze di lubrificanti e sangue
- HPV test su campioni insoddisfacenti

## Cellule epiteliali squamose

- Come affrontare il problema LSIL con poche cellule HSIL (LSIL-H)
- Non è stata creata una nuova categoria
- Conservati 2 livelli terminologici: LSIL/HSIL

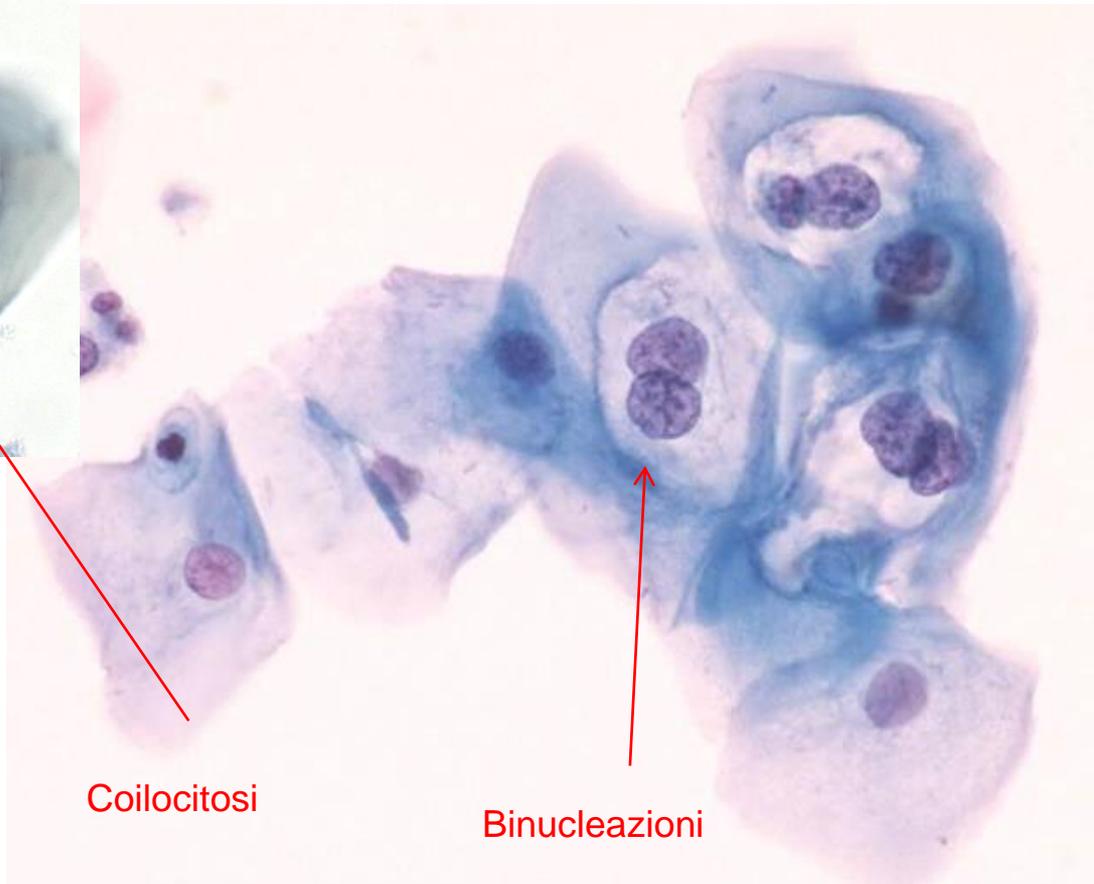
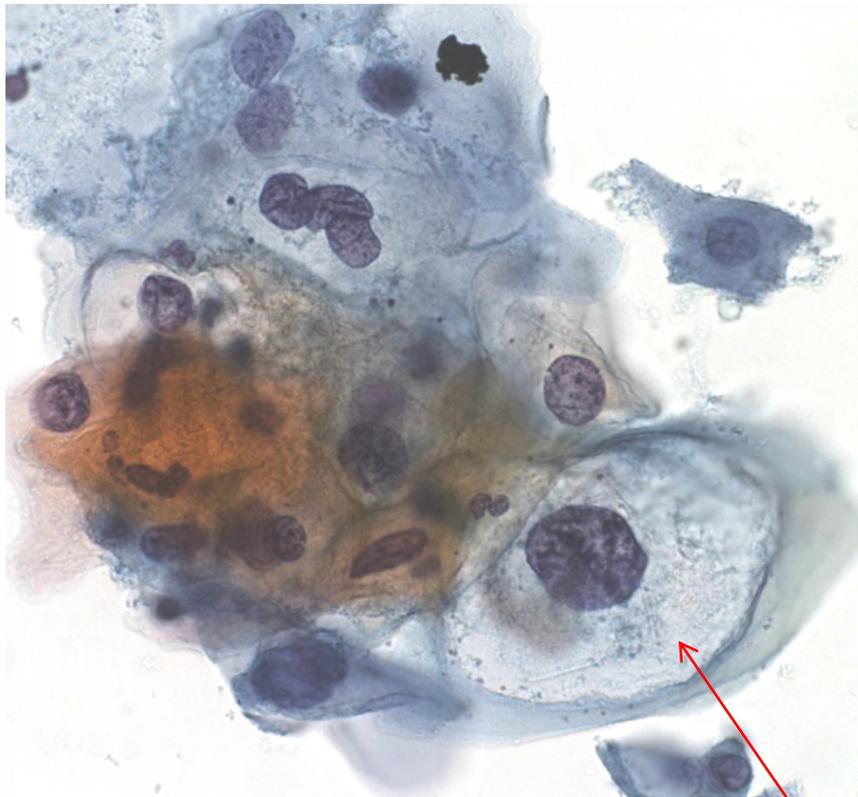
## Cellule endometriali

Segnalare la presenza di cellule endometriali in donne di età  $\geq$  45 anni (la valutazione solo in post menopausa)

**LSIL**

Viareggio  
La darsena



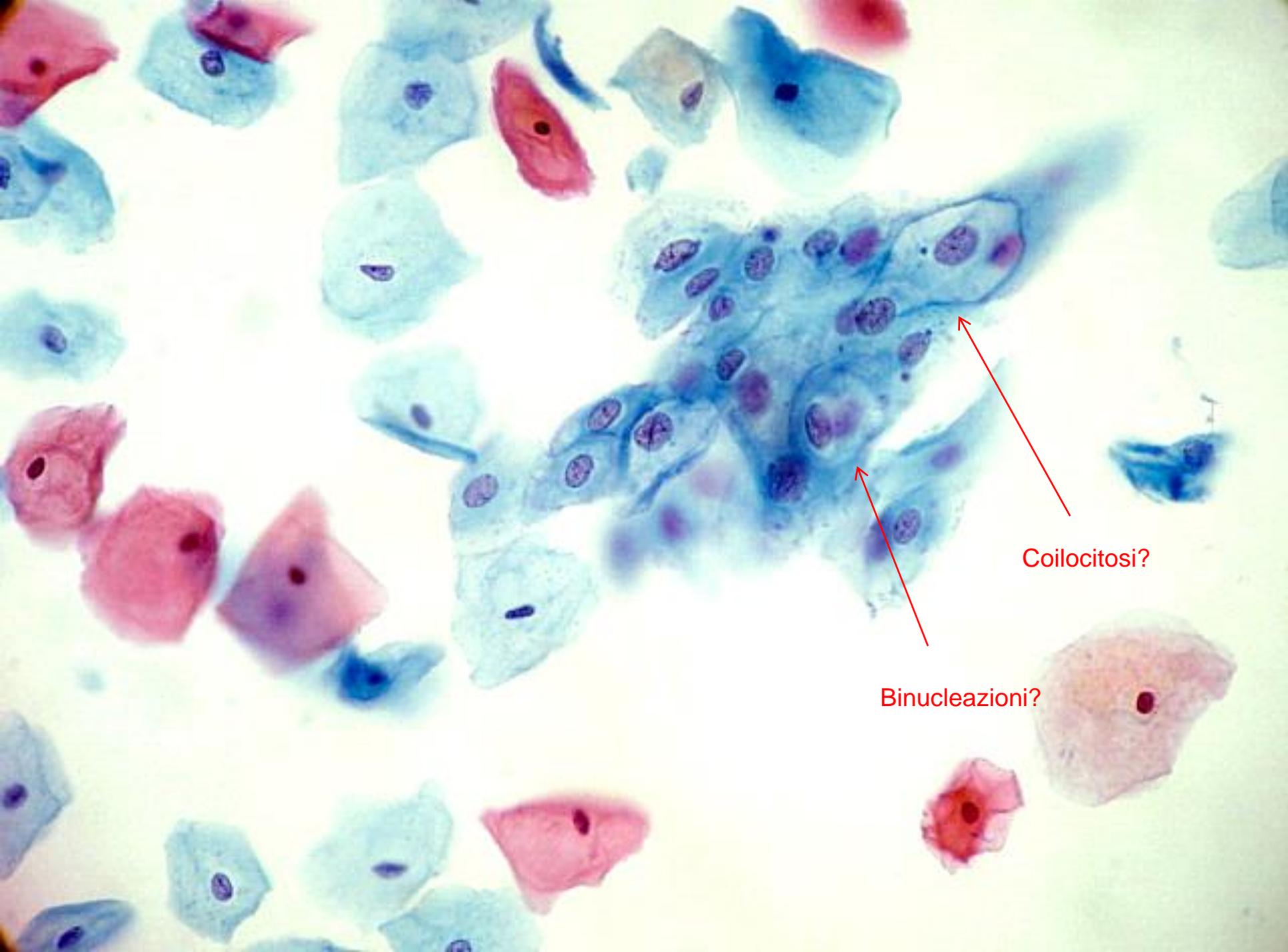


Coilocitosi

Binucleazioni

ASC-US





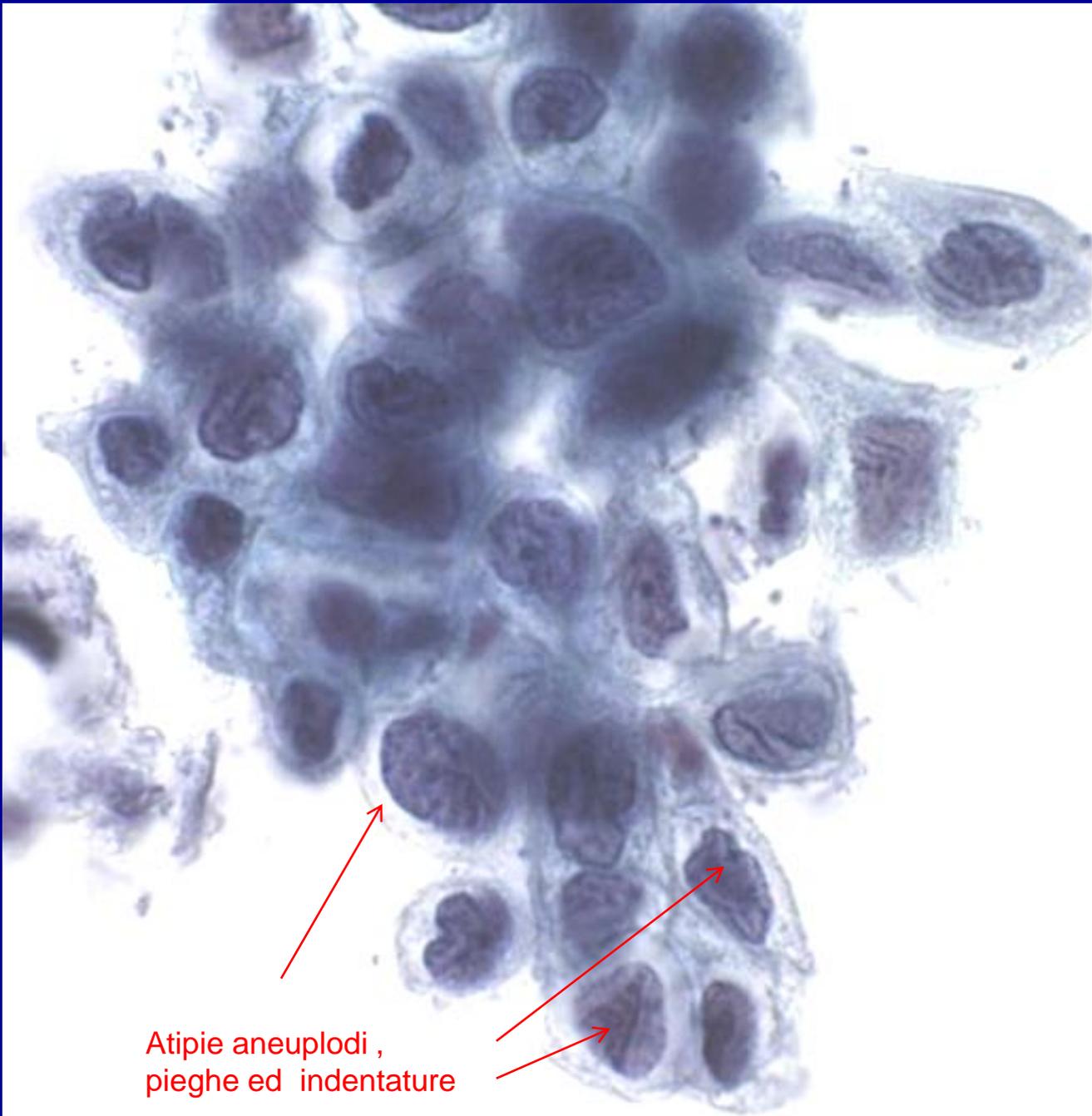
Koilocitosi?

Binucleazioni?

Monte Pisanino (1947m)

**HSIL**





Atipie aneuploidi ,  
pieghe ed indentature

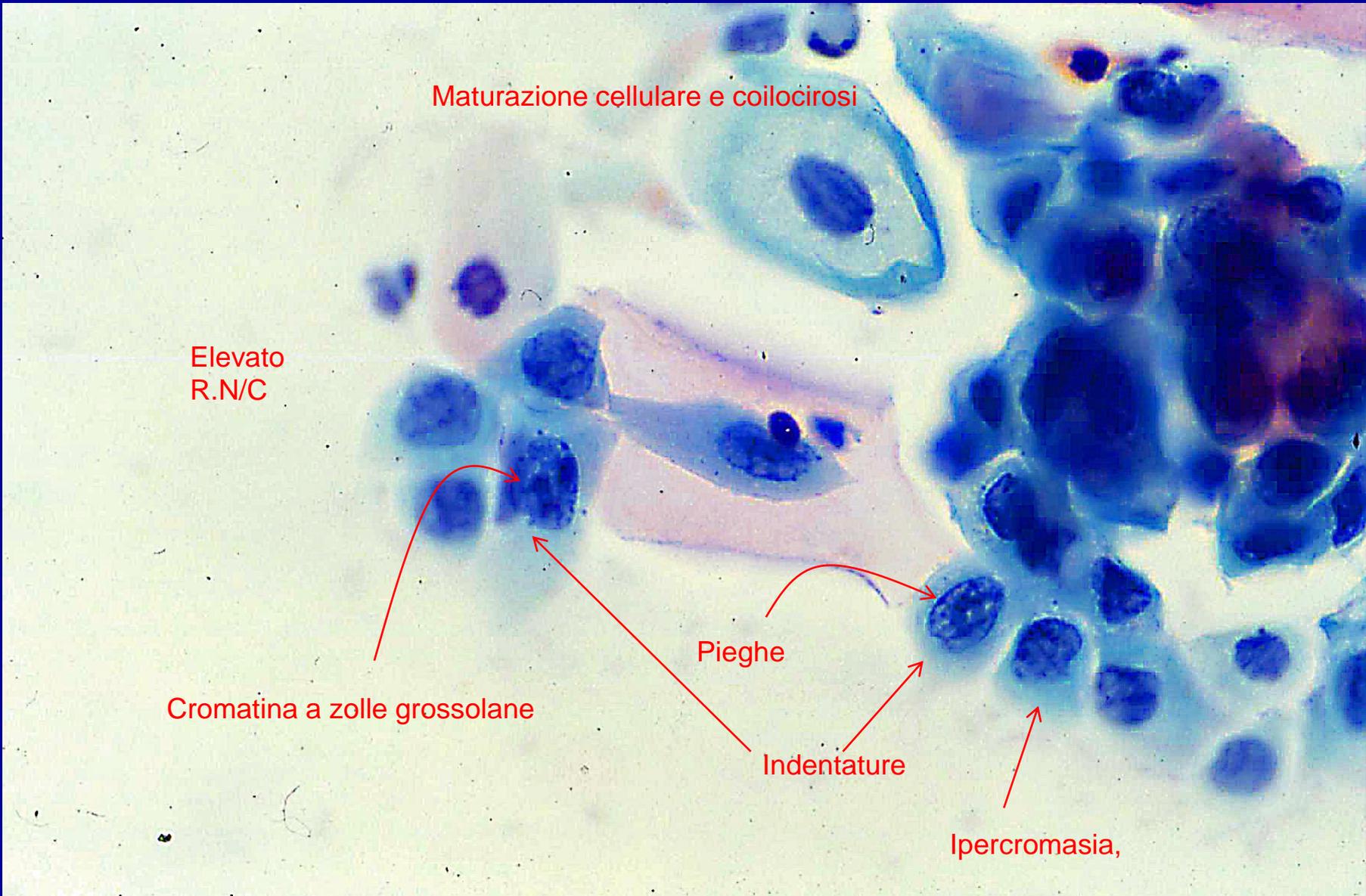
# ASC-H

Altissimo  
1589 m

Corchia  
1677 m

TONFANO





Maturazione cellulare e coilocirosi

Elevato  
R.N/C

Cromatina a zolle grossolane

Pieghe

Indentature

Ipercromasia,

**Carcinoma squamoso**  
**Adenocarcinoma in situ**  
**Adenocarcinoma cervicale**  
**Adenocarcinoma dell'endometrio**  
**Altre neoplasie maligne**

Pania della Croce (1859 m)

Sea

Prana

Lake of  
Massaciuccoli

Matanna





# Cellule ghiandolari atipiche AGC

## Atipiche

Cellule endocervicali (NAS o da specificare nel commento)

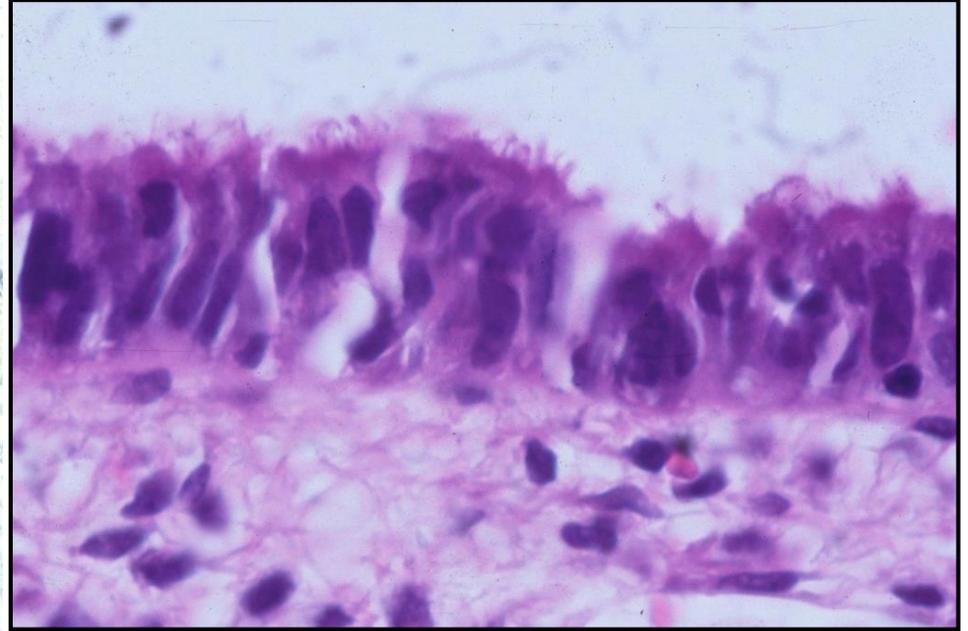
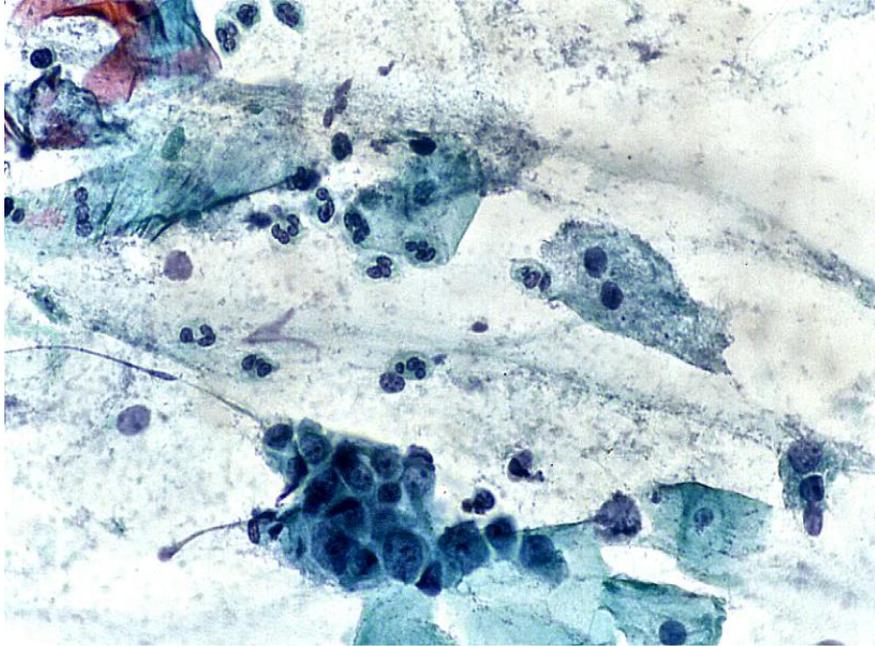
Cellule endometriali (NAS o da specificare nel commento)

Cellule ghiandolari (NAS o da specificare nel commento)

## Atipiche

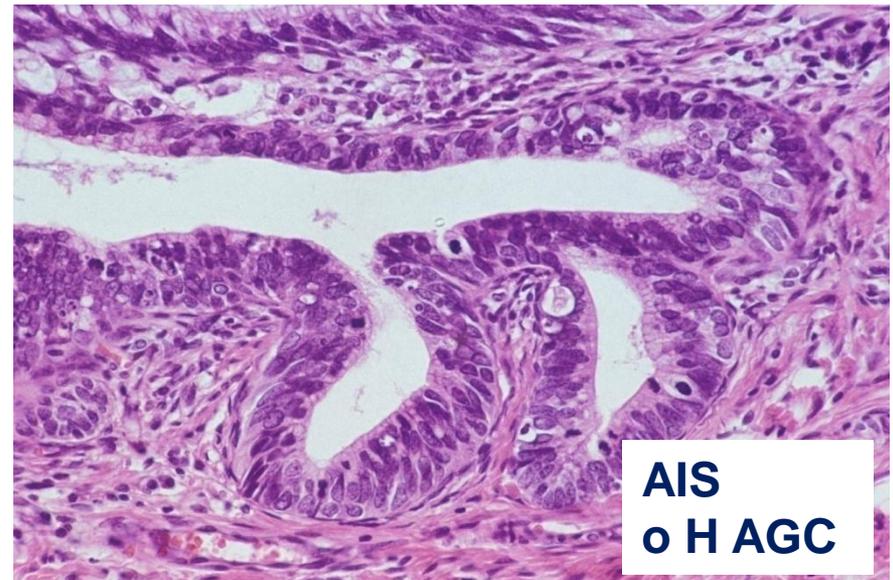
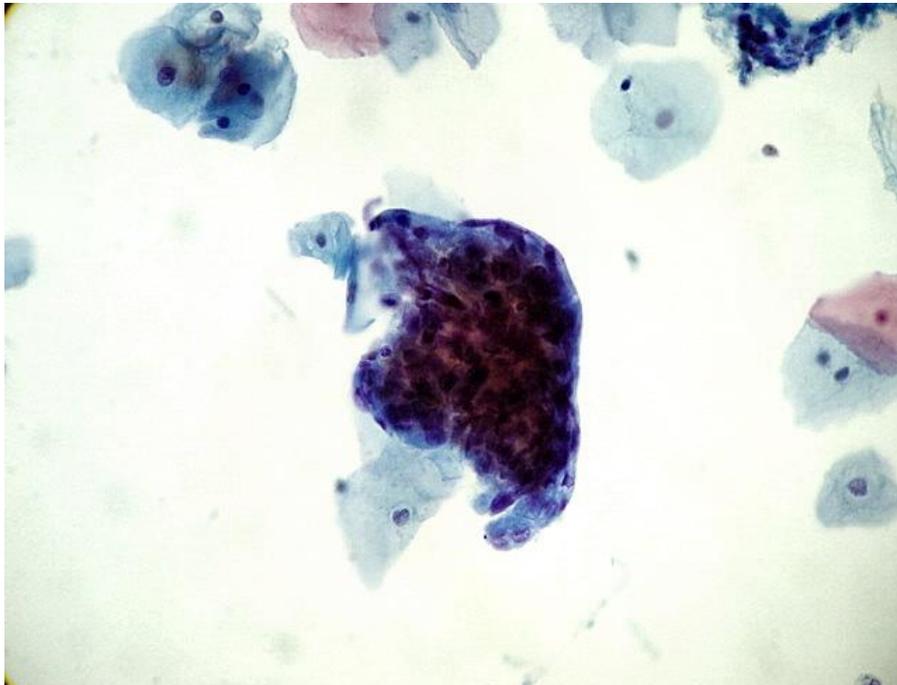
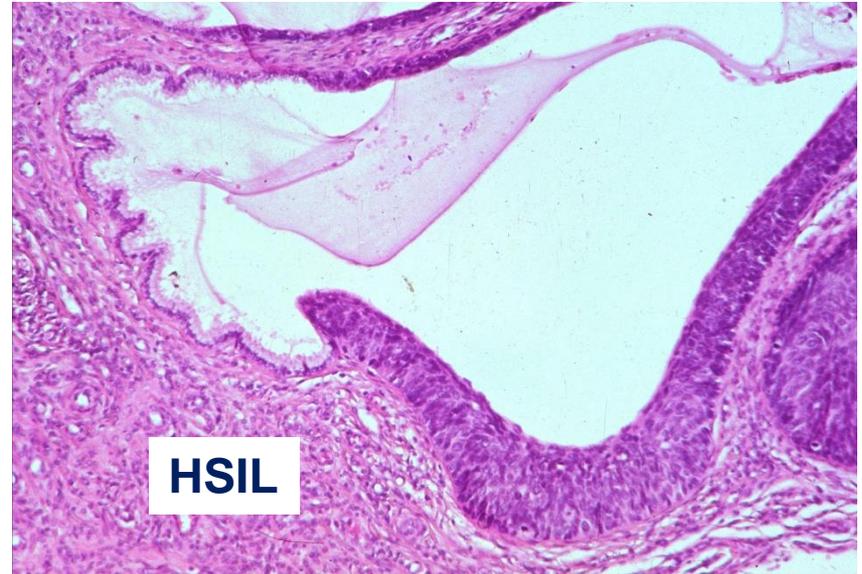
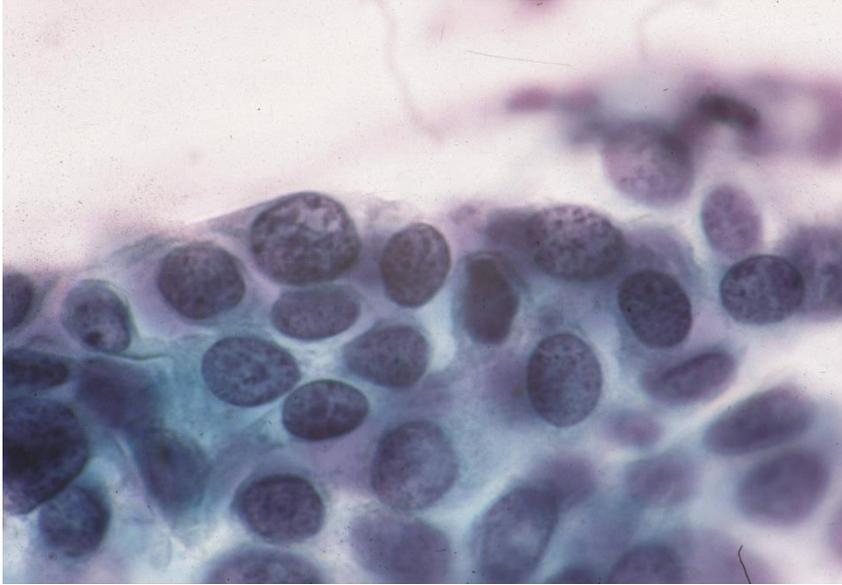
Cellule endocervicali, probabilmente neoplastiche

Cellule ghiandolari, probabilmente neoplastiche

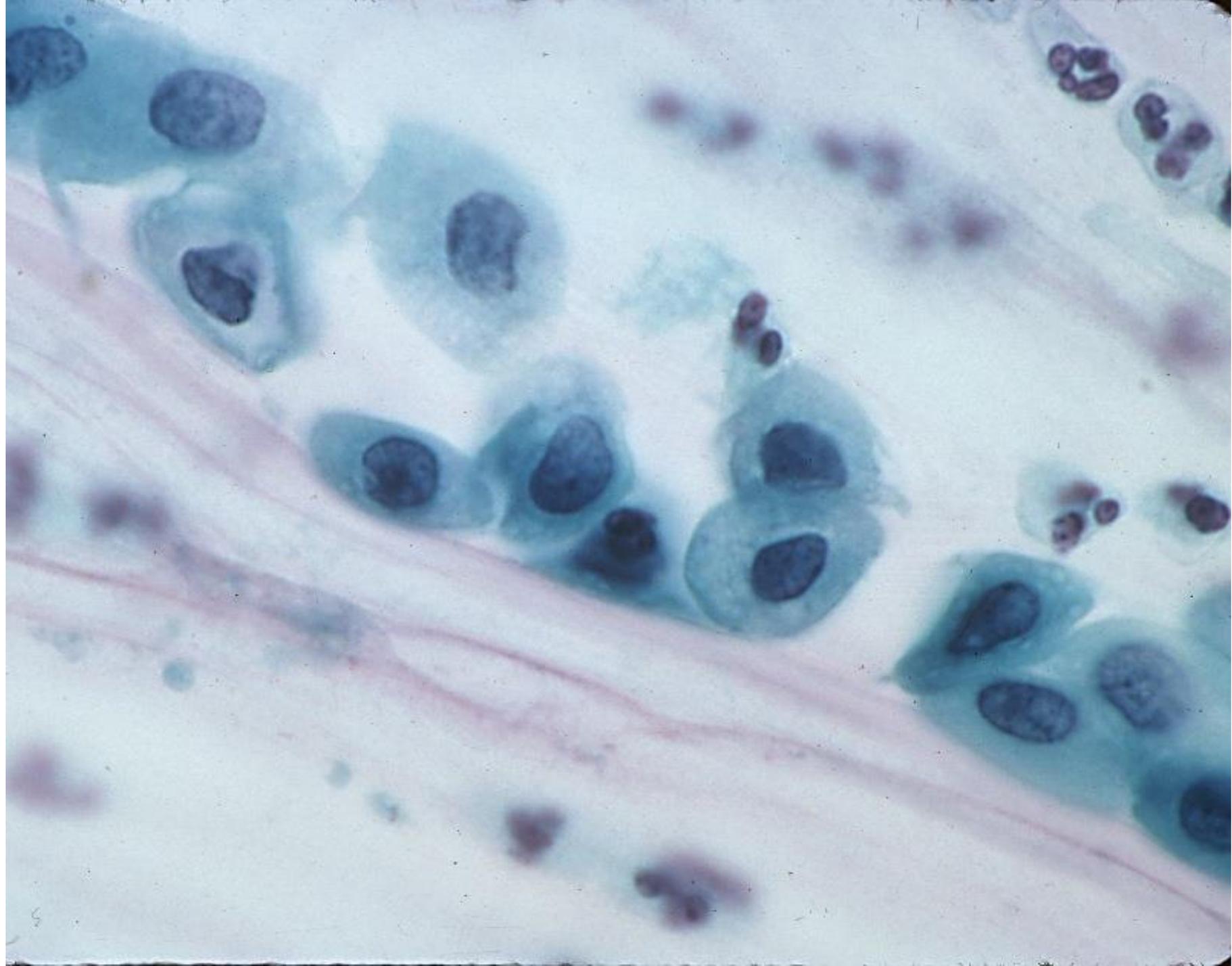


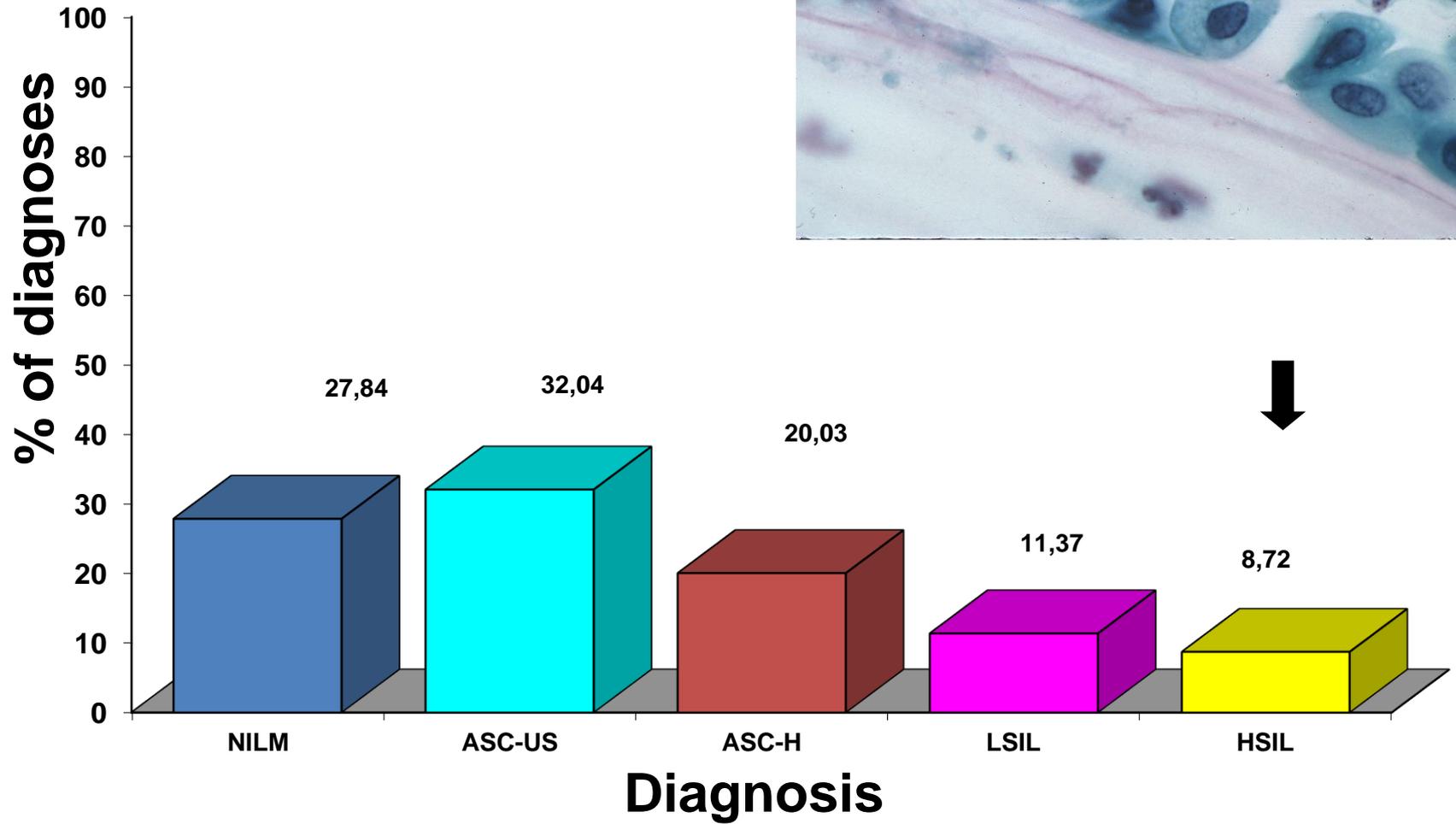
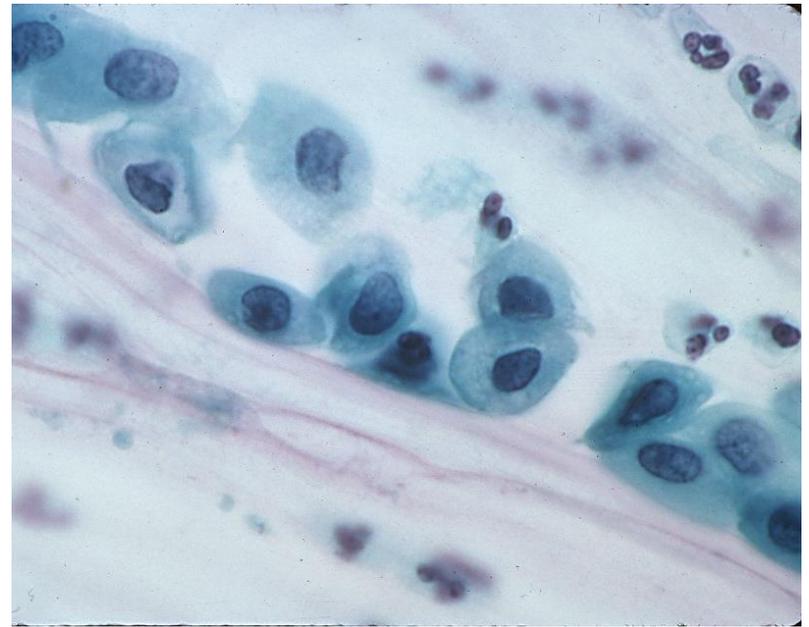
AGC

# AGC verso neoplasia

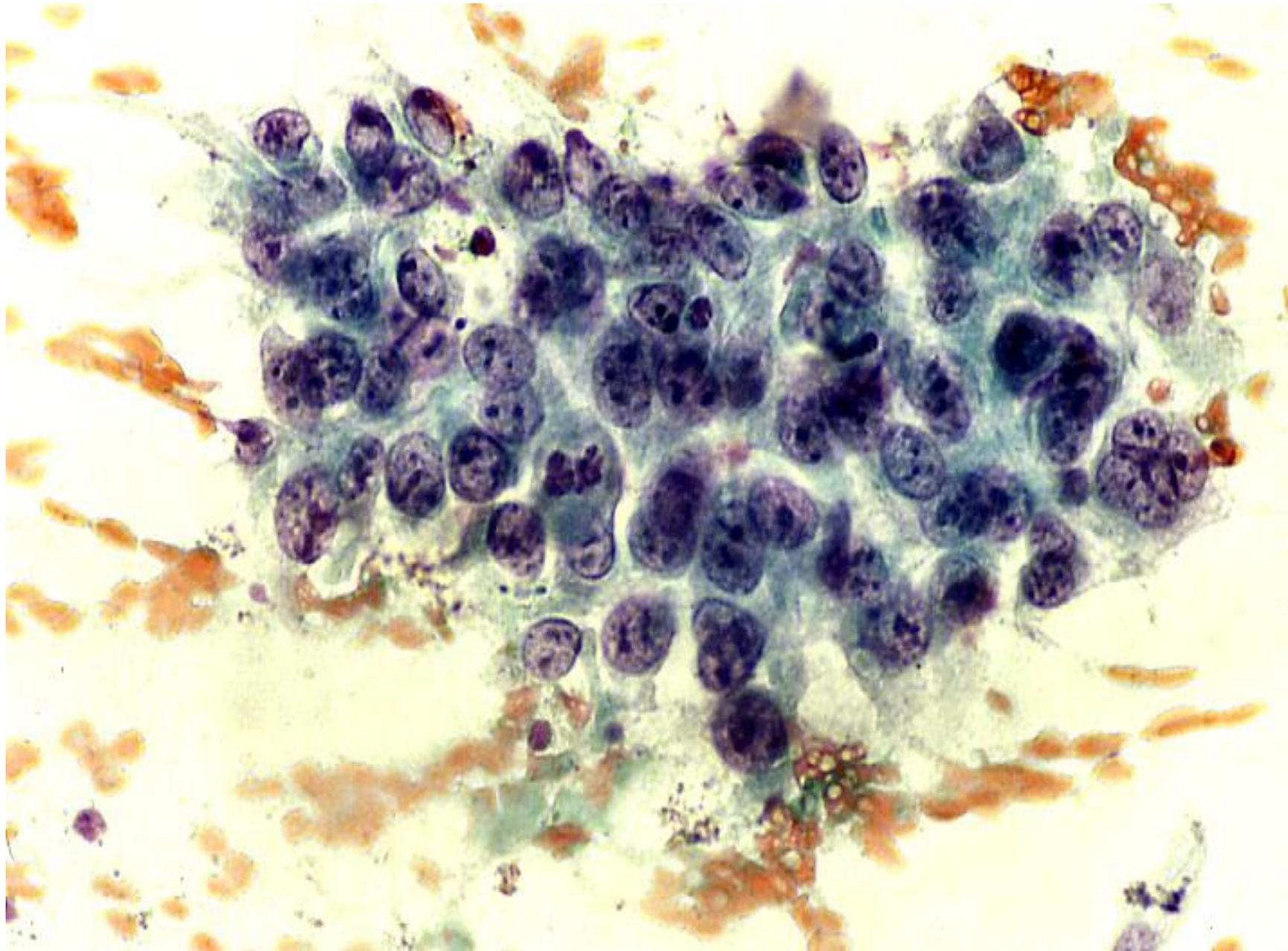


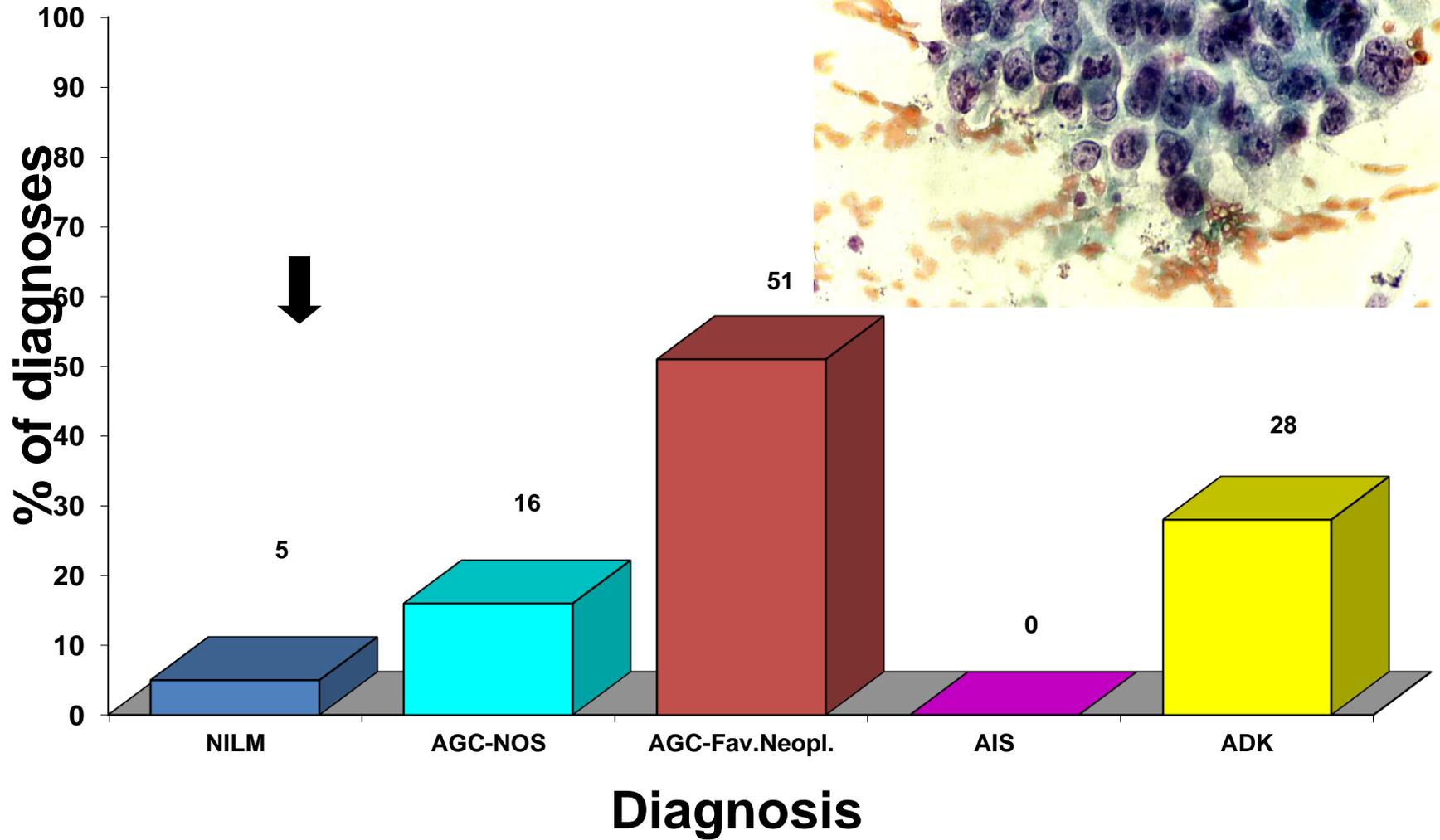
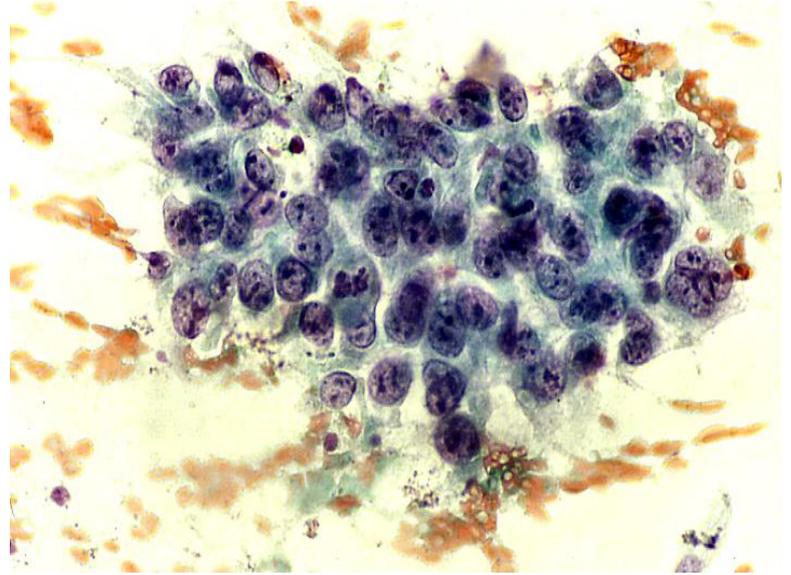
Tutto chiaro?

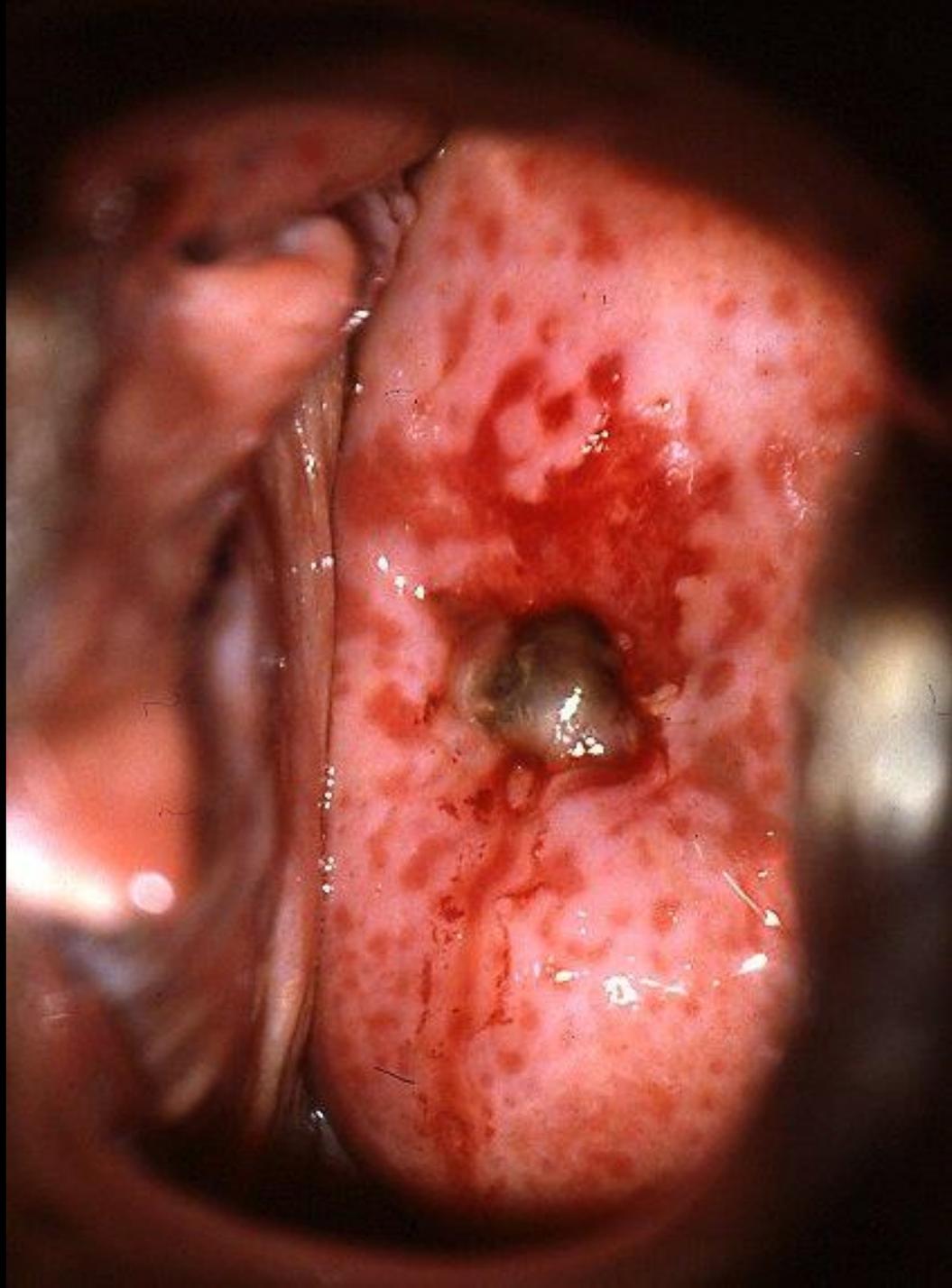












Normale

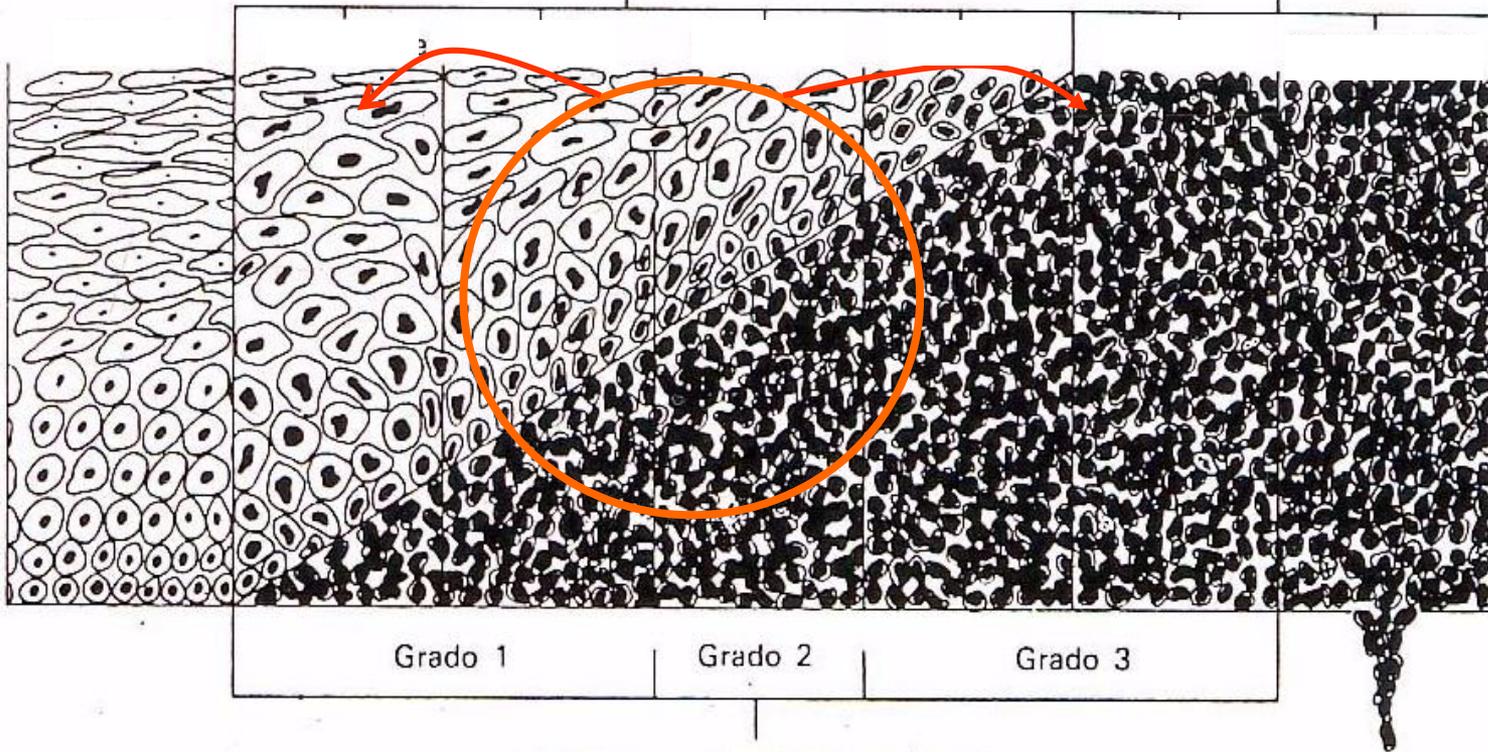
ASC-US

LSIL

ASC-H

HSIL

Carcinoma



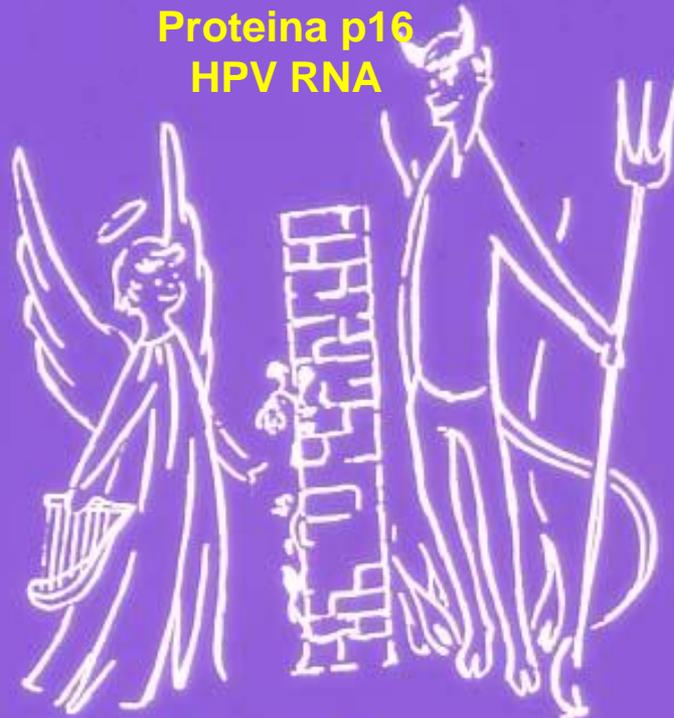
Grado 1

Grado 2

Grado 3

Neoplasia intraepiteliale cervicale

Proteina p16  
HPV RNA



NEG



ASC-US



LSIL



a

ASC-H



HSIL



CAS

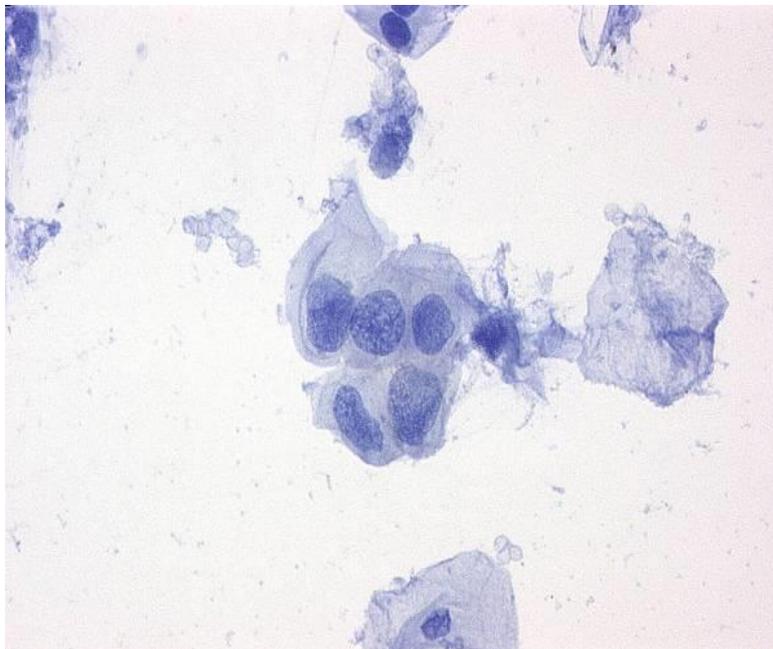


# La proteina p16



Marina di Carrara

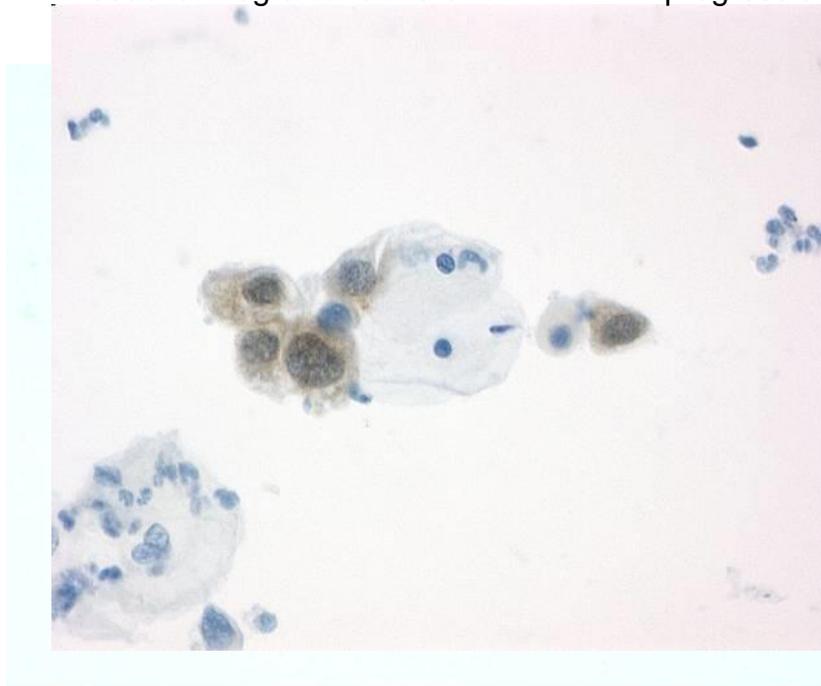
P16 neg



↓  
Follow-up

P16 pos    K67 pos

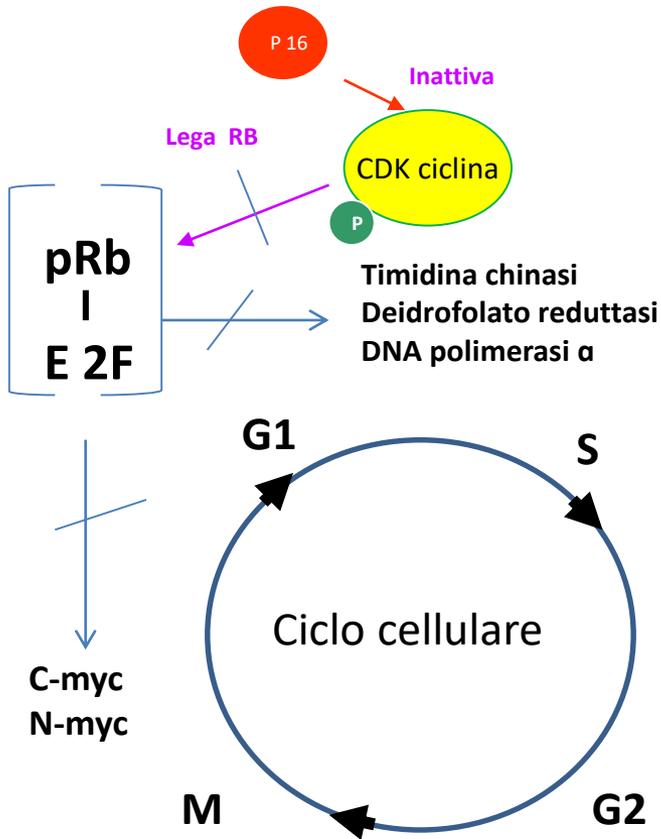
Probabile integrazione virale → progressione



↓  
Trattamento

# Condizioni fisiologiche

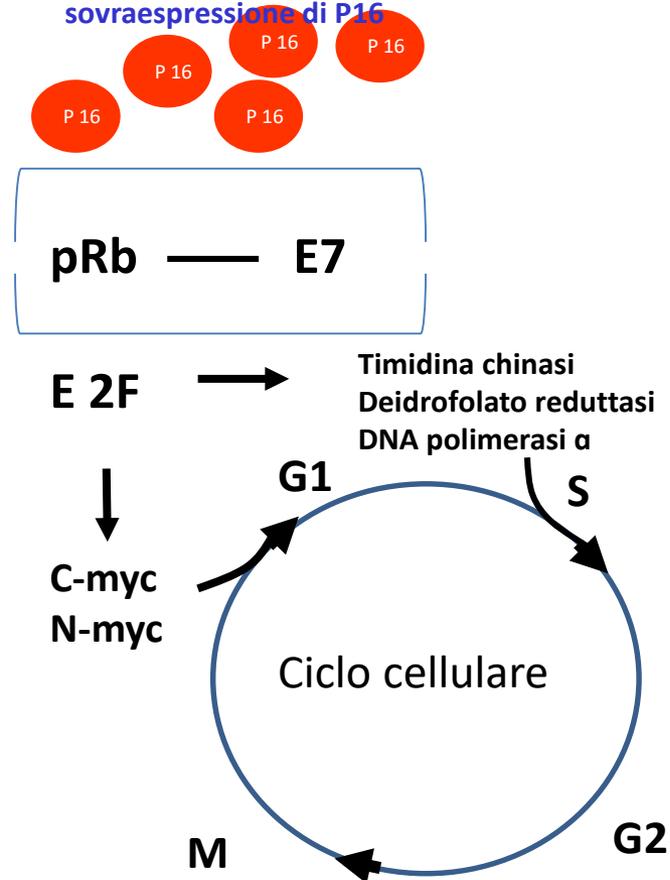
P16 inibisce la ciclina D, che lega RB liberando E2F che promuove la divisione cellulare



Inibizione del ciclo cellulare

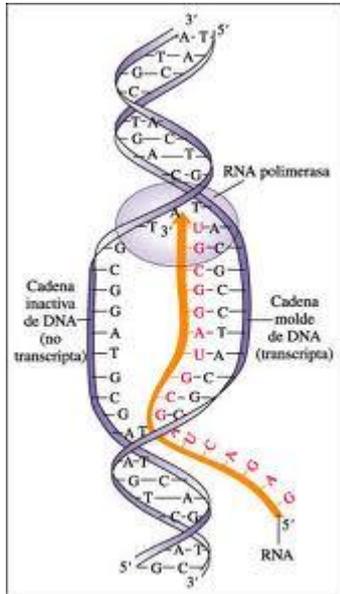
# Infezione da HPV ad alto rischio

E7 si lega a pRb, liberando E2F, potente stimolatore del ciclo cellulare. La CDK ciclina non esercita più la sua azione su RB con conseguente accumulo e sovraespressione di P16



Stimolazione del ciclo cellulare

# HPV RNA



E6-E7

mRNA cellulare

Presenza E6-E7  
Integrazione  
virale

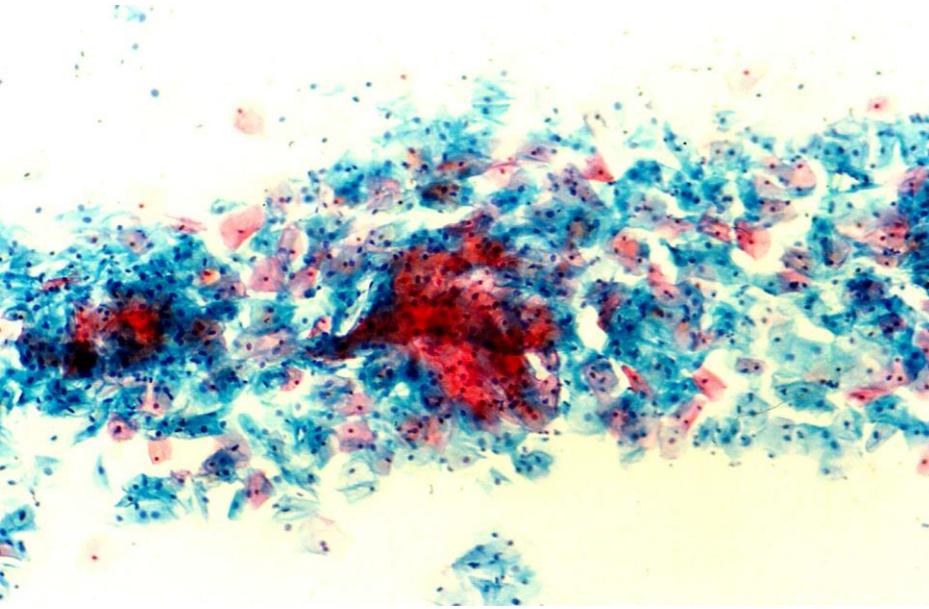
# Cytology report

THE MANCHESTER CYTOLOGY CENTRE, M13 9WL		Slide No. [REDACTED].08
<b>Patient</b> [REDACTED] [REDACTED] [REDACTED] [REDACTED] D.O.B. [REDACTED] NHS No. [REDACTED] Serial No. [REDACTED]	<b>LMP:</b> [REDACTED] <b>Test Date:</b> 11 Jan 2008 <b>Specimen Type:</b> LBC (SurePath) <b>Reason for Smear:</b> Routine call <b>Condition:</b> Pregnant	
<b>Sender</b> HOE1 Dr Elizabeth HOLT SALFORD ROYAL HOSPITAL CLAIRE DUNNE, GYNAE DEPT., * STOTT LANE SALFORD M6 8HD HOSP	<b>Clinical Details:</b> Cervix appears normal Pre TOP -308416	
<b>G.P.</b> Dr M TYRRELL ST ANDREWS MEDICAL CENTRE RUSSELL STREET ECCLES MANCHESTER M30 0NU	<b>Cytology Report:</b> MILD DYSKARYOSIS High risk HPV NOT DETECTED by HC2 test. Routine recall is recommended.	
<b>HA</b> Salford & Trafford H A PEEL HOUSE ALBERT STREET ECCLES MANCHESTER M30 0NJ	<b>Pattern:</b> MILD DYSKARYOSIS <b>Infection:</b> High risk HPV NOT DETECTED [0] <b>Suggest:</b> Routine recall [A]	
	<b>Authoriser:</b> [REDACTED] <b>Date authorised:</b> [REDACTED] 1st print date: 22 Jan 2008      Date: 22 Jan 2008	

# Lo strato sottile



## Pap test convenzionale



## Pap test su strato liquido



- Perdita di materiale nel trasferimento da campione a vetrino
- Cattiva fissazione
- Aggregazione, sovrapposizione cellulare
- Presenza di materiale oscurante

- Tutto il campione viene raccolto nel contenitore
- Ottima fissazione
- Distribuzione uniforme delle cellule
- Assenza di materiale oscurante



Cesare, what  
do you think  
about LBC?

I don't see  
any future in it

Long Island 1997

## Situation

**In the United States at least 80% percent of all Pap tests are LBC**

**LBC is widely used in Europe.**

- LBC is the standard-of-care in England
- LBC is >60% Pap tests in Switzerland.
- LBC is >70% Pap tests in Belgium

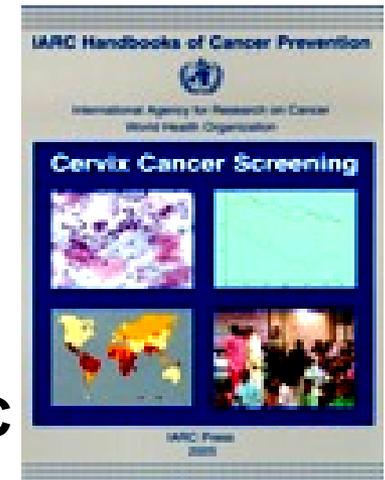
**LBC is the only screening test used in Scotland and Ireland**

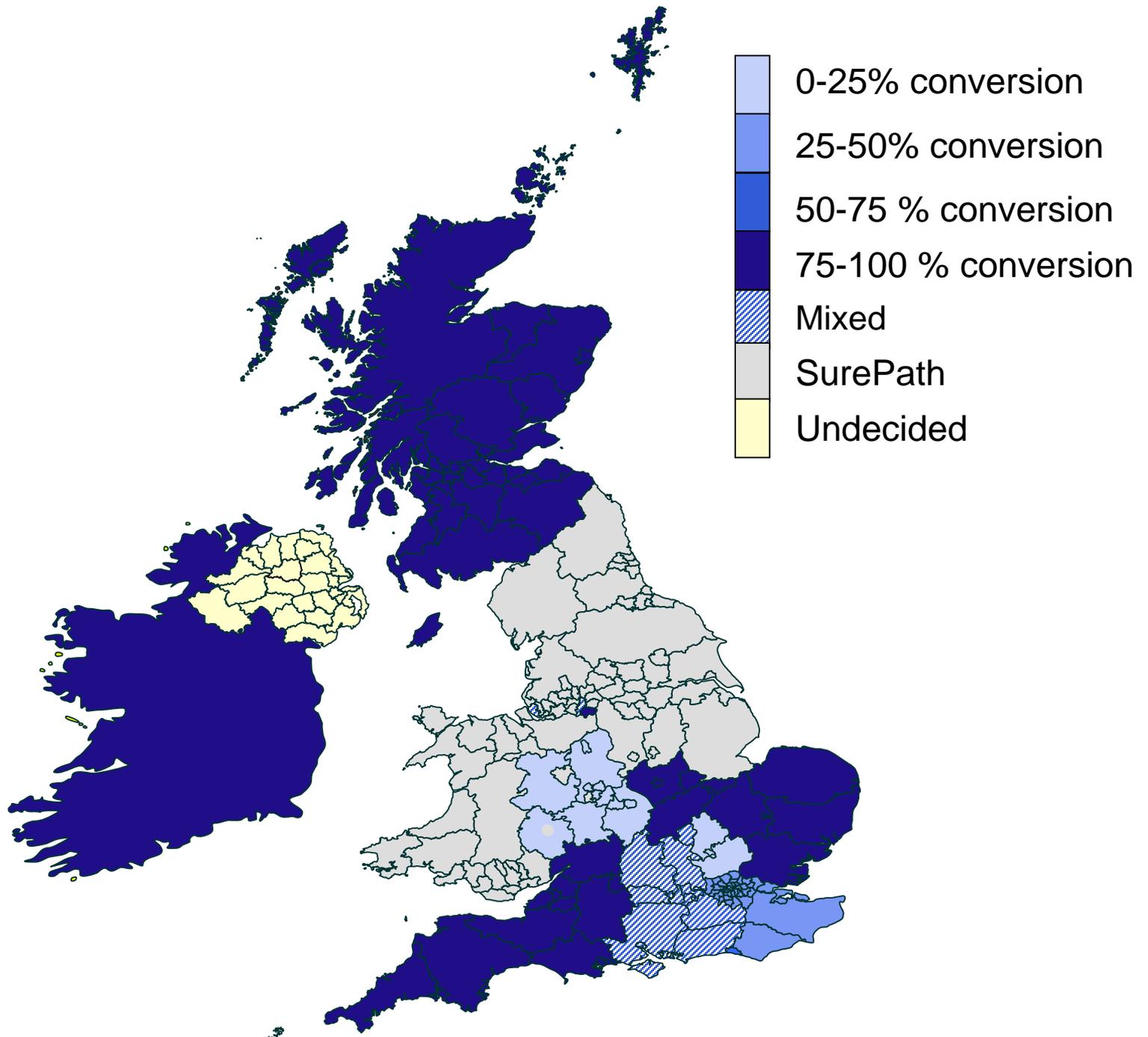
**LBC approved for routine screening in Hong Kong and Canada**

**Ontario, Canada, Screening Guidelines recommend LBC**

**IARC / WHO (2005) approved liquid based cytology as an “effective method of cervical cancer control”**

**European Guidelines for Cervical cancer Screening approve LBC**





# Tramonto in Versilia

**Dimezza i tempi di lettura**

**Riduce il numero degli inadeguati**

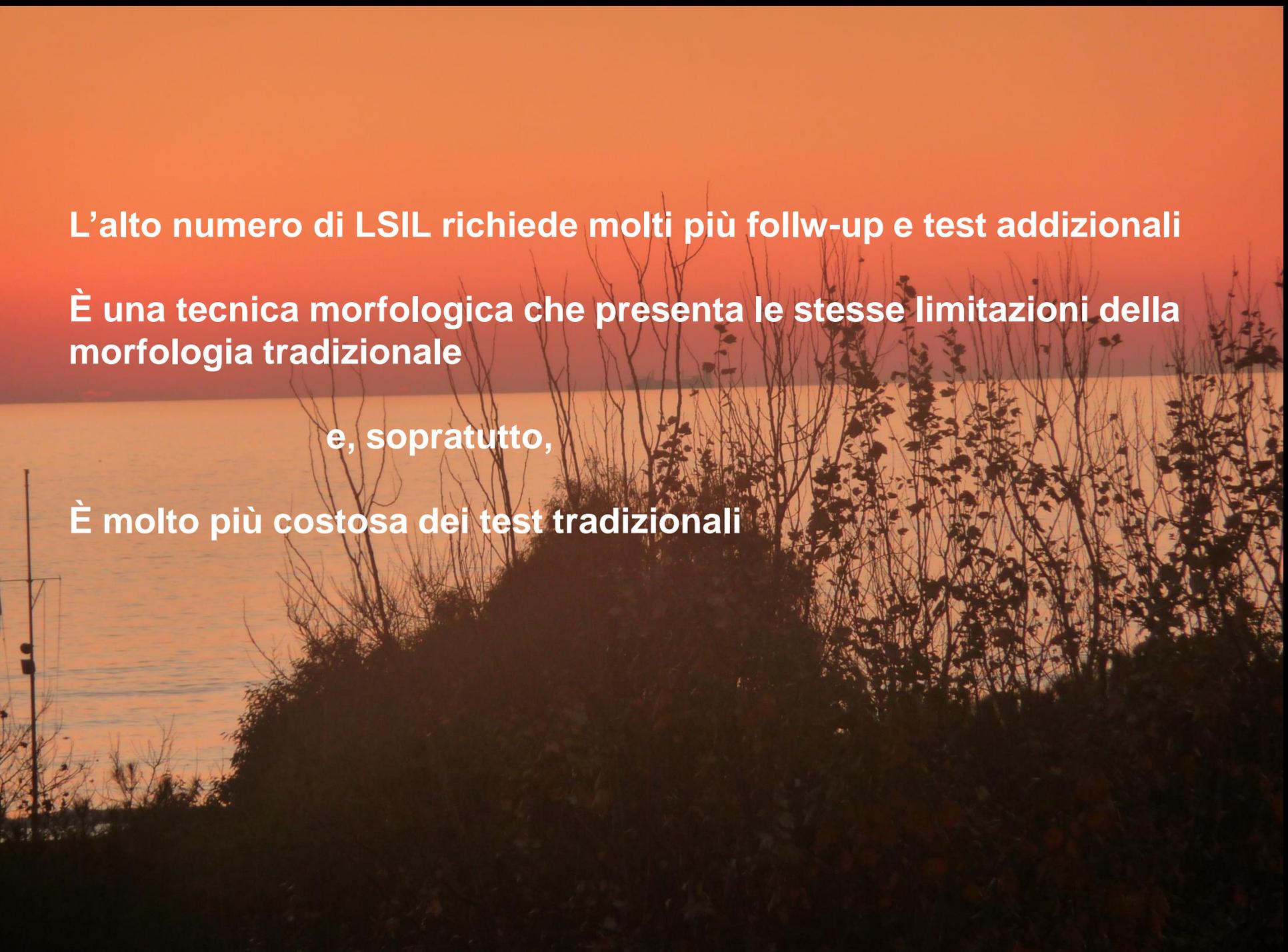
**Individua un numero maggiore di LSIL statisticamente significativo**

**Individua un numero maggiore di HSIL non statisticamente significativo**

**Permette di eseguire altri test sul materiale residuo,  
adatto per lo screening primario con HPV**

**È il metodo più adatto per l'automazione**

**Ma**

The background of the slide is a photograph of a sunset or sunrise. The sky is a gradient of orange and red, transitioning into a lighter yellow near the horizon. A calm body of water reflects the light from the sky. In the foreground, there are dark silhouettes of trees and bushes, some with sparse leaves. The overall mood is serene and natural.

**L'alto numero di LSIL richiede molti più follw-up e test addizionali**

**È una tecnica morfologica che presenta le stesse limitazioni della morfologia tradizionale**

**e, soprattutto,**

**È molto più costosa dei test tradizionali**

**Thank you  
very much  
for your  
attention**

