

CONVEGNO NAZIONALE GISCI

Roma 20-21 Aprile 2006

I Modelli di Screening e Nuove Prospettive
Massimo Confortini



IARC Handbook 2005

- There is sufficient evidence that screening for cervical cancer precursors every 3–5 years between the ages of 25 and 64 years by conventional cytology in a high-quality programme reduces the incidence of invasive cervical cancer by 80% or more among the women screened. .

PRESENTE

Citologia convenzionale

Lettura automatica
Citologia in fase liquida

Ripetizione citologica
per diagnosi borderline

Colposcopia

Triage con Test HPV
per diagnosi borderline



Gruppo Italiano Screening del Cervicocarcinoma

- Sulla base delle evidenze scientifiche Il GISCi ritiene di raccomandare l'applicazione del test per la ricerca dell'HPV HR nel triage della diagnosi citologica di atipia squamosa di significato indeterminato come una delle tre possibili opzioni insieme alla ripetizione del pap a sei mesi e della colposcopia immediata

Follow-up ASCUS

- **Colposcopia immediata**
- **Ripetizione del pap test a specifici intervalli**
- **HPV dna test per i tipi ad alto rischio**

TRIAGE ASCUS TBS 1991

	CSPO ASCUS-R	CSPO ASCUS-LSIL	Trento ASCUS
HPV+	12(41.4%)	85(51.8%)	78(25.2%)
HPV-	17(58.6%)	79(48.2%)	231(74.8%)
Totale	29	164	309

TRIAGE ASCUS TBS 2001

	Trento ASC-US	Trento ASC-H	ASL ROMAG ASC-US	ASL ROMAG ASC-H
HPV+	147(28.4%)	16(33.3%)	6(18.2%)	2(66.6%)
HPV-	371(71.6%)	32(66.6%)	27(81.8%)	1(33.3%)
Totale	518	48	33	3

IARC Handbook 2005

Efficacy of conventional cytology
has been demonstrated only for
squamous cell carcinoma

Changing rates of adenocarcinoma of the cervix in England-Sasieni et Al Lancet 2001

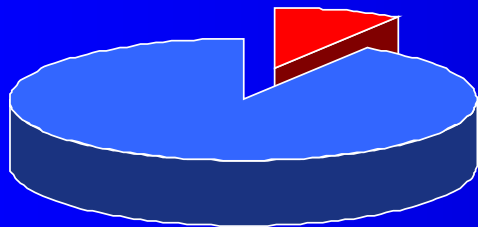
- L'aumento sostanziale di adenocarcinomi cervicali negli ultimi anni è in larga misura un effetto coorte legato alle nascite ed associato ad infezioni sessuali dopo la rivoluzione sessuale degli anni sessanta.
- La parziale diminuzione in giovani donne osservata in anni recenti suggerisce un effetto dei programmi di screening.

Ratio between Adenocarcinoma – Adenosquamous and Squamous cell Carcinoma

- **Area del RTT**

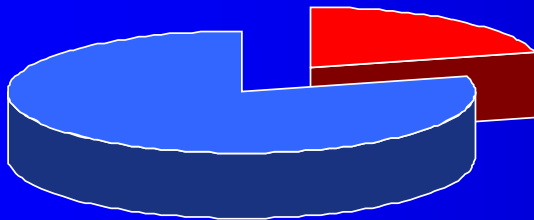
- 1985-88:

8.9% Adenok



- 1997-2000:

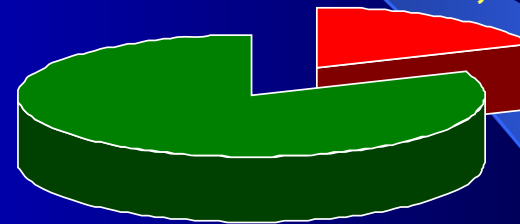
20.9% Adenok



- **SEER - USA**

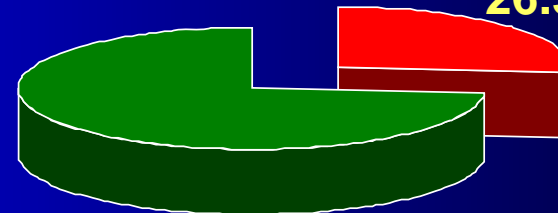
- 1985-88:

18,7% Adenok



- 1997-2000

26.3% Adenok



Odds Ratios (OR) of developing invasive cervical cancer by screening history (time since last Pap test), adjusted for civil status and birth place *Zappa et al Br J Cancer 2004, modificato*

Time since last test* (years)	Histologic type (OR 95% CI)		
	squamous	Adk and adksquamous	All cases
<3	0.15 (0.07-0.30)	0.65 (0.26-1.65)	0.25 (0.15-0.42)
3-<6	0.20 (0.10-0.39)	0.99 (0.43-2.29)	0.34 (0.21-0.56)
>= 6	0.56 (0.36-0.87)	0.54 (0.24-1.23)	0.56 (0.38-0.82)
Never screened	1.0	1.0	1.0

* excluding tests in the year before test

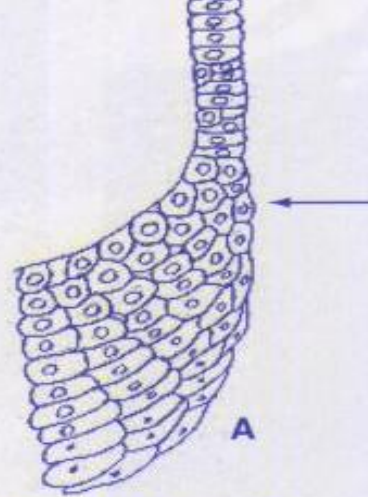
Can glandular lesion be diagnosed in Pap smear cytology?

Raab S.S. Diagn Cytopath2000

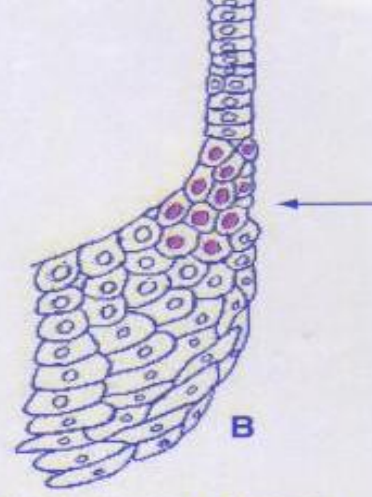
- Pur con qualche dato contraddittorio la maggior parte degli autori sostiene che la citologia abbia una buona sensibilità (65-80%) nella diagnosi di adenocarcinomi invasivi di origine endocervicale
- La sensibilità della citologia per Adenocarcinoma in situ (AIS) riportata in diverse casistiche varia dal 40 al 68%

Adenocarcinoma Endocervicale

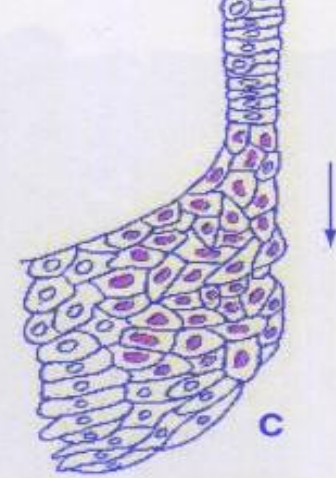
- La sensibilità non ottimale della citologia è legata soprattutto al prelievo ed **in misura minore a problematiche di interpretazione del quadro morfologico.**
- Da prendere in considerazione anche un “management” non corretto



Normal epithelium



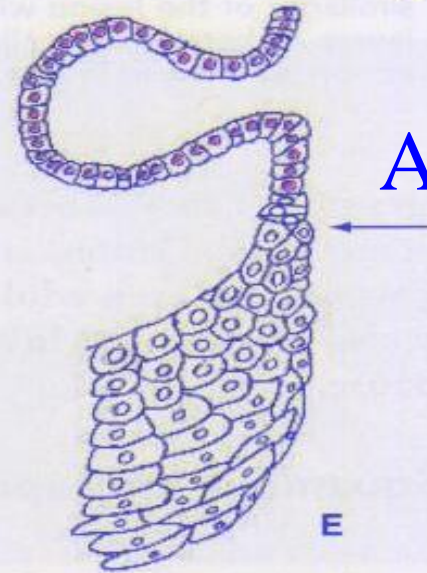
Development of early cancerous change



Lesions progressing in the direction of squamous epithelium



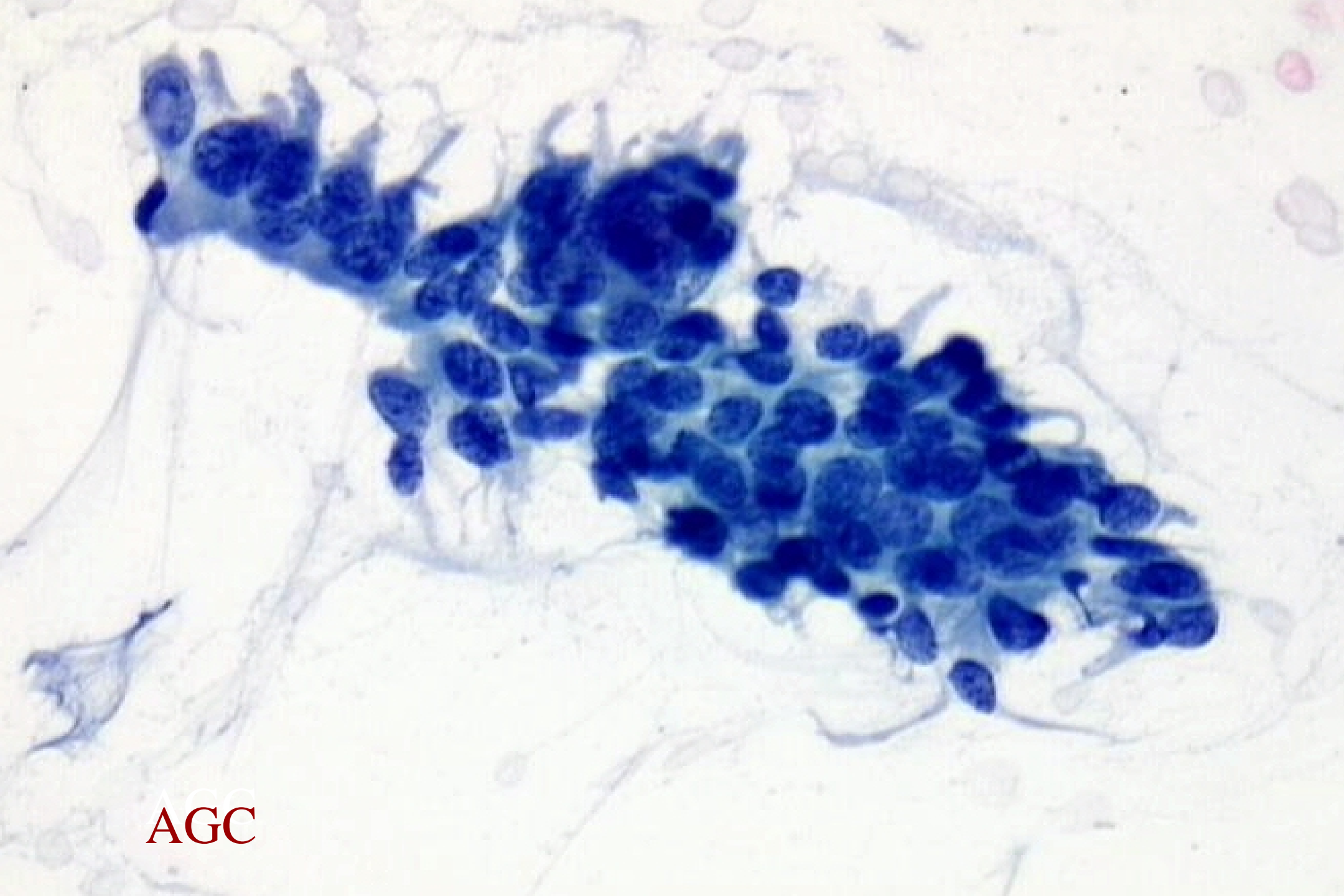
Lesions progressing in the direction of the endocervical canal



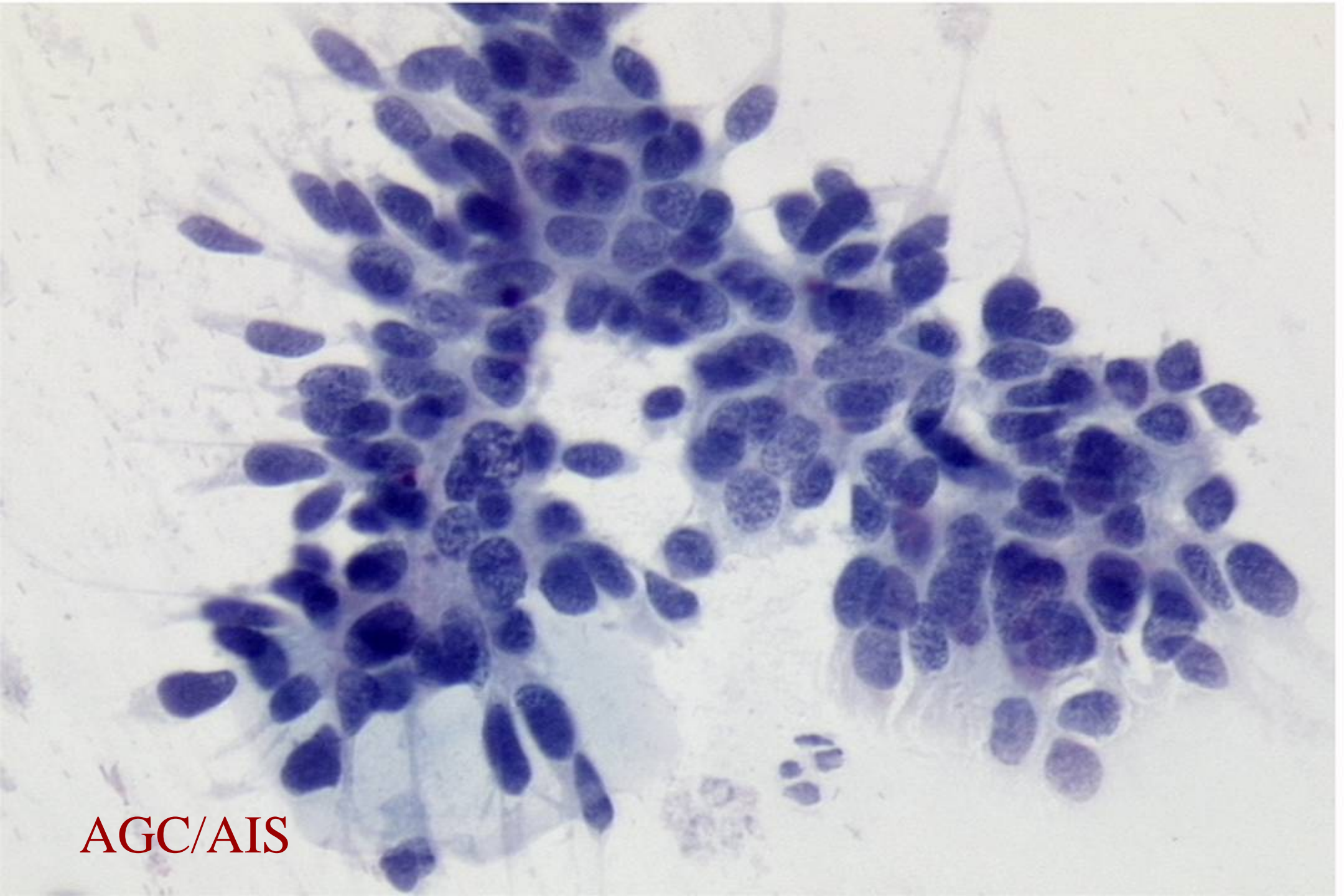
Adenocarcinoma in situ

AIS

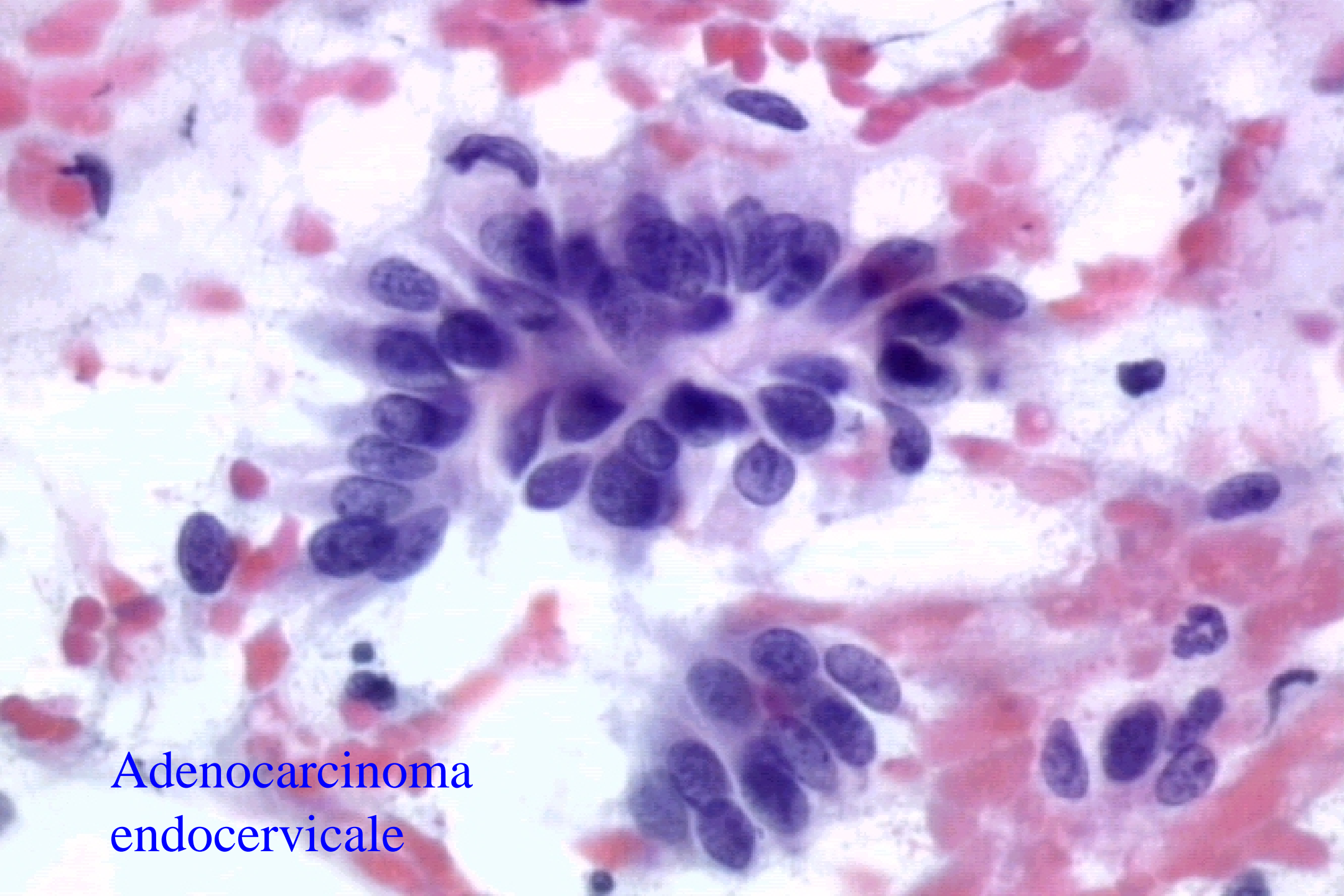
Sequence of events in the development of precancerous lesions of the uterine cervix. A. Normal cervix. Horizontal arrow indicates transformation zone (TZ). B. Early neoplastic changes (dysplastic cells) occurring in the TZ (horizontal arrow pointing down). Lesions may progress from the transformation zone in the direction of the squamous epithelium of the outer cervix (vertical arrow down), resulting in low-grade squamous intraepithelial lesions (LSIL). C. Lesions progressing in the direction of squamous epithelium (vertical arrow down). These lesions may progress to squamous carcinoma. D. Lesions progressing from the TZ in the direction of the endocervical canal (arrow up), resulting in high-grade squamous intraepithelial lesions (HSIL). E. Development of endocervical adenocarcinoma in situ (AIS) (horizontal arrow down). Events depicted in C-E may be reversed. (Drawing by Prof. Claude Gompel, University of Montreal.)



AGC



AGC/AIS

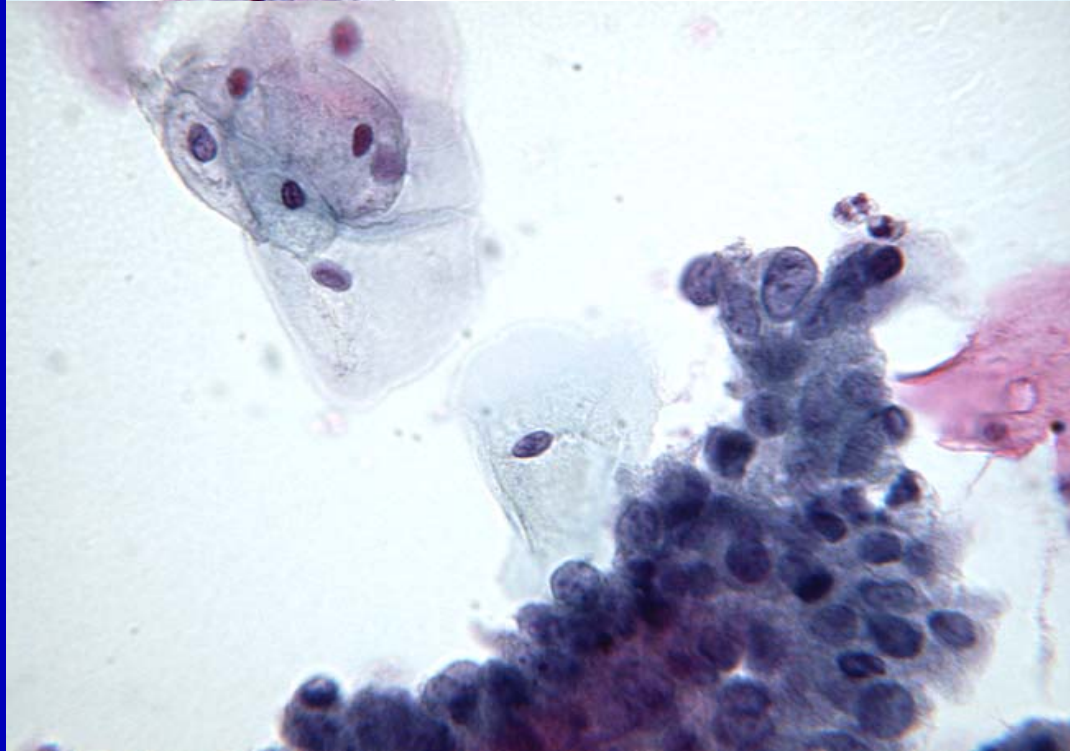
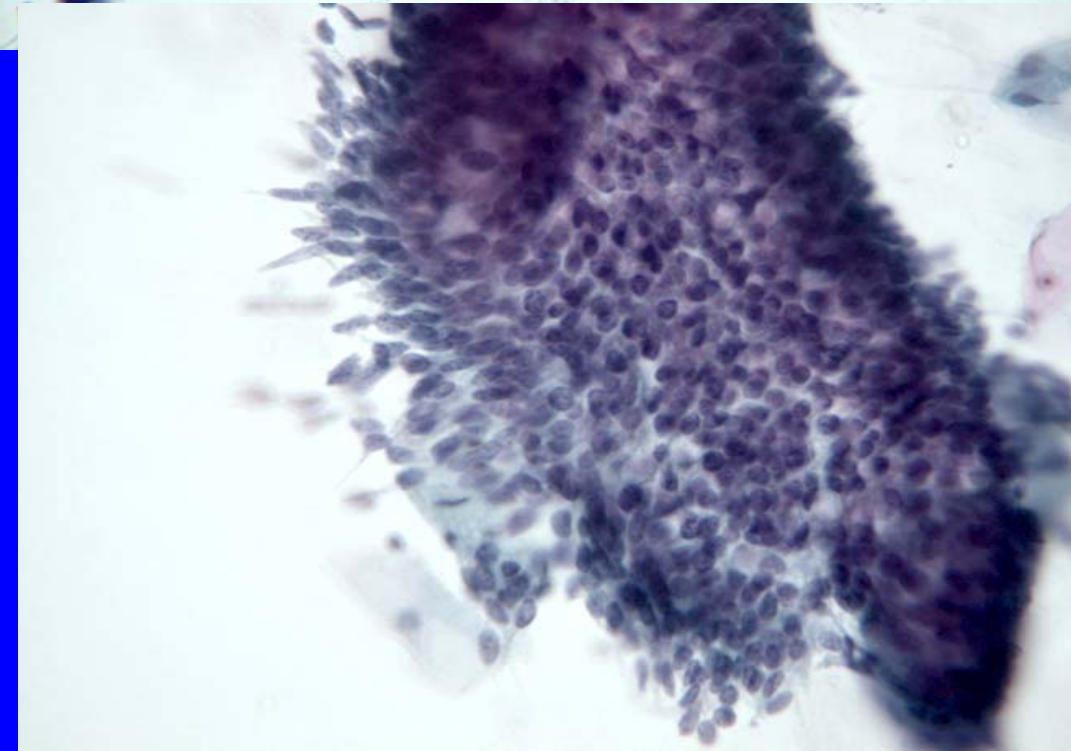


Adenocarcinoma
endocervicale

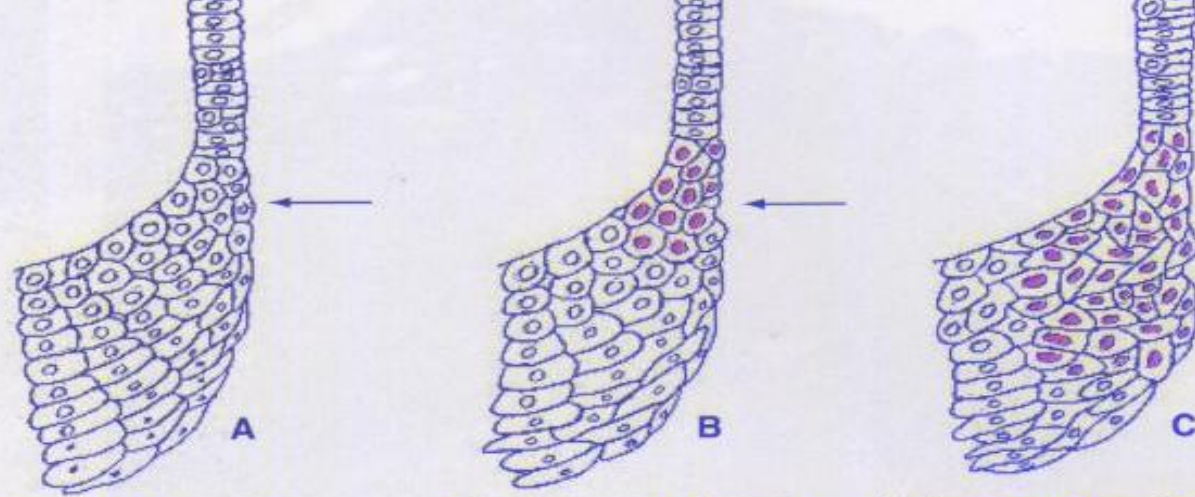
Trad



TP



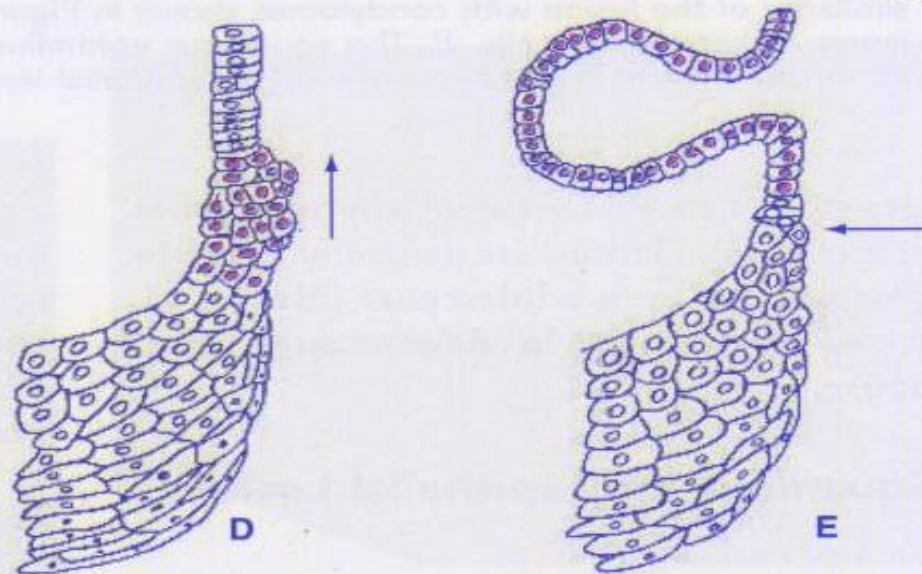
HSIL



Normal epithelium

Development of early cancerous change

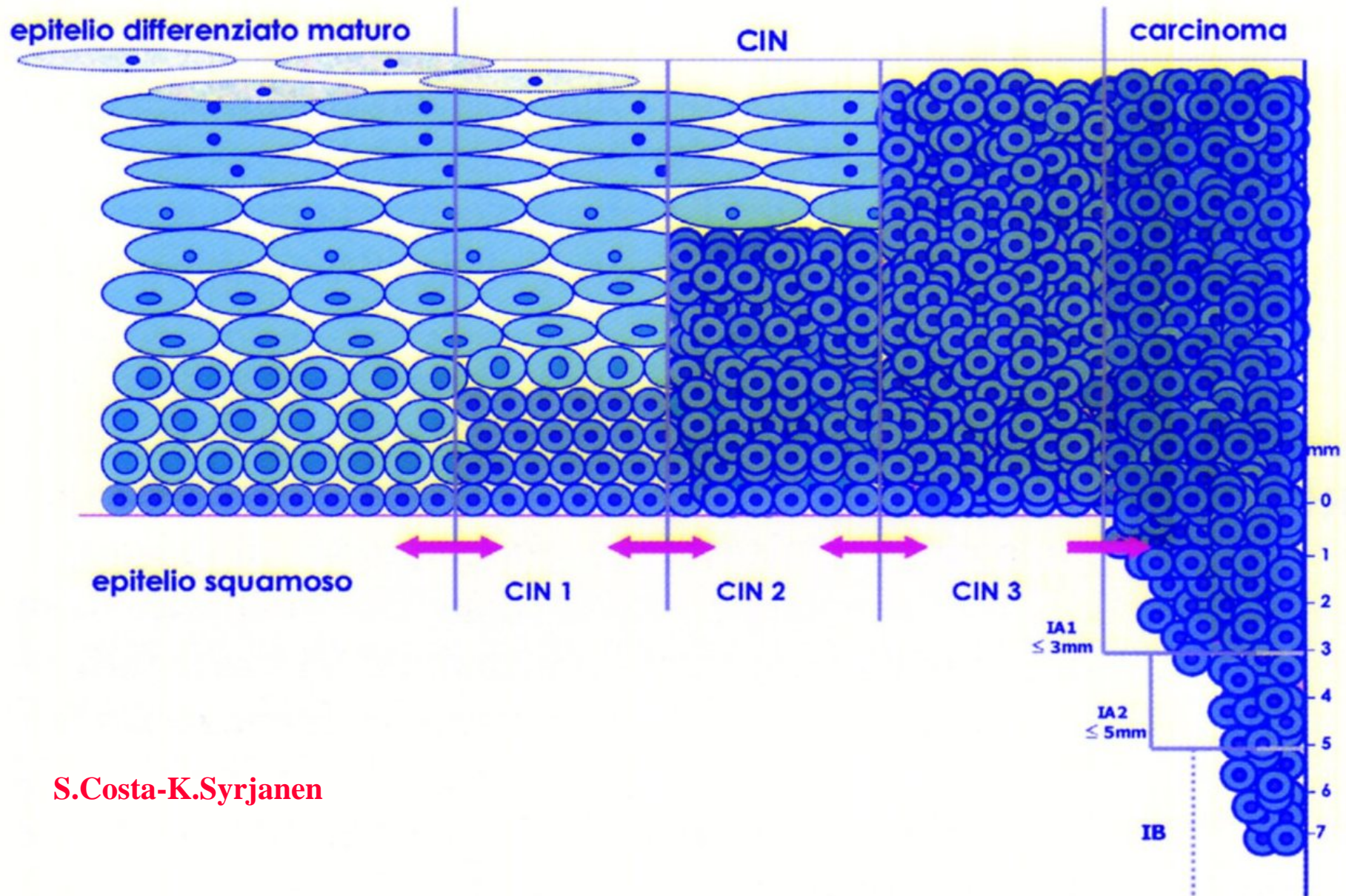
Lesions progressing in the direction of squamous epithelium



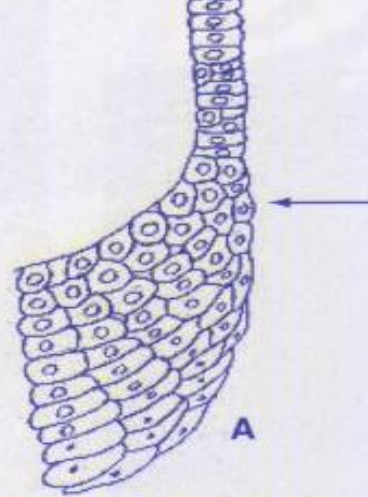
Lesions progressing in the direction of the endocervical canal

Adenocarcinoma in situ

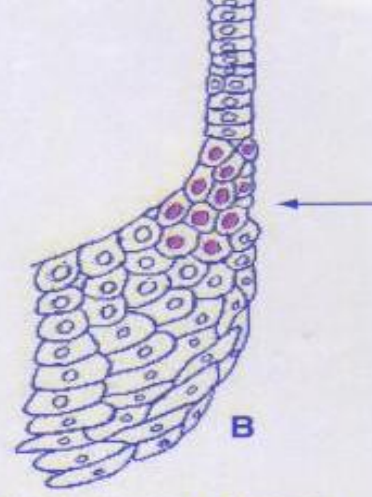
Sequence of events in the development of precancerous lesions of the uterine cervix. A. Normal cervix. Horizontal arrow indicates transition zone (TZ). B. Early neoplastic changes (dysplasia) occurring in the TZ (horizontal arrow pointing down). Lesions may progress from the transition zone in the direction of the squamous epithelium (horizontal arrow down) or in the direction of the endocervical canal (vertical arrow up). C. Lesions progressing in the direction of squamous epithelium. D. Lesions progressing in the direction of the endocervical canal. E. Development of endocervical adenocarcinoma in situ (TZ; horizontal arrow pointing down). Events depicted in C-E may be associated with HPV infection. (Drawing by Prof. Claude Gompel, University of Liège, Belgium.)



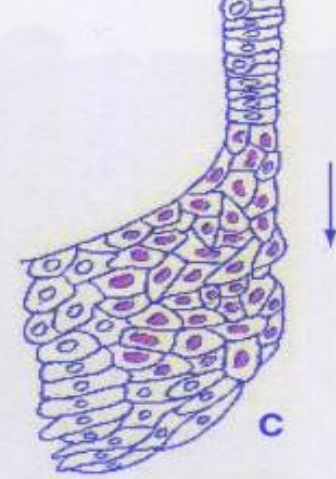
S.Costa-K.Syrjanen



Normal epithelium



Development of early cancerous change

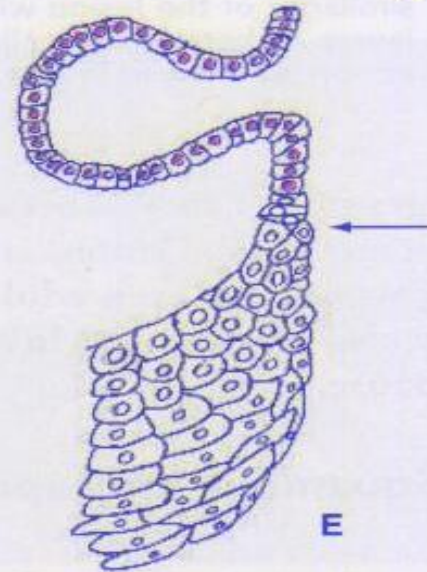


Lesions progressing in the direction of squamous epithelium

HSIL



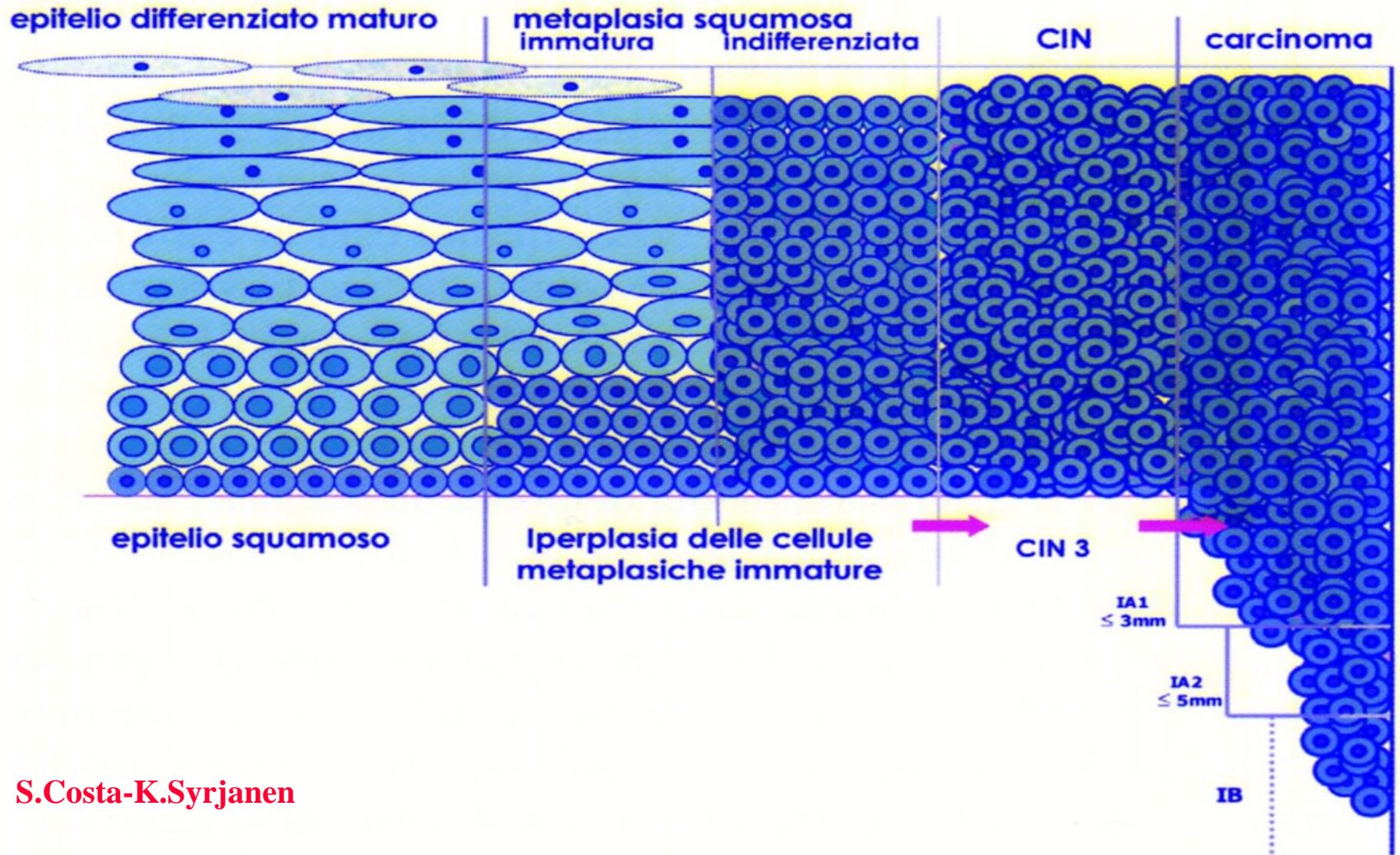
Lesions progressing in the direction of the endocervical canal



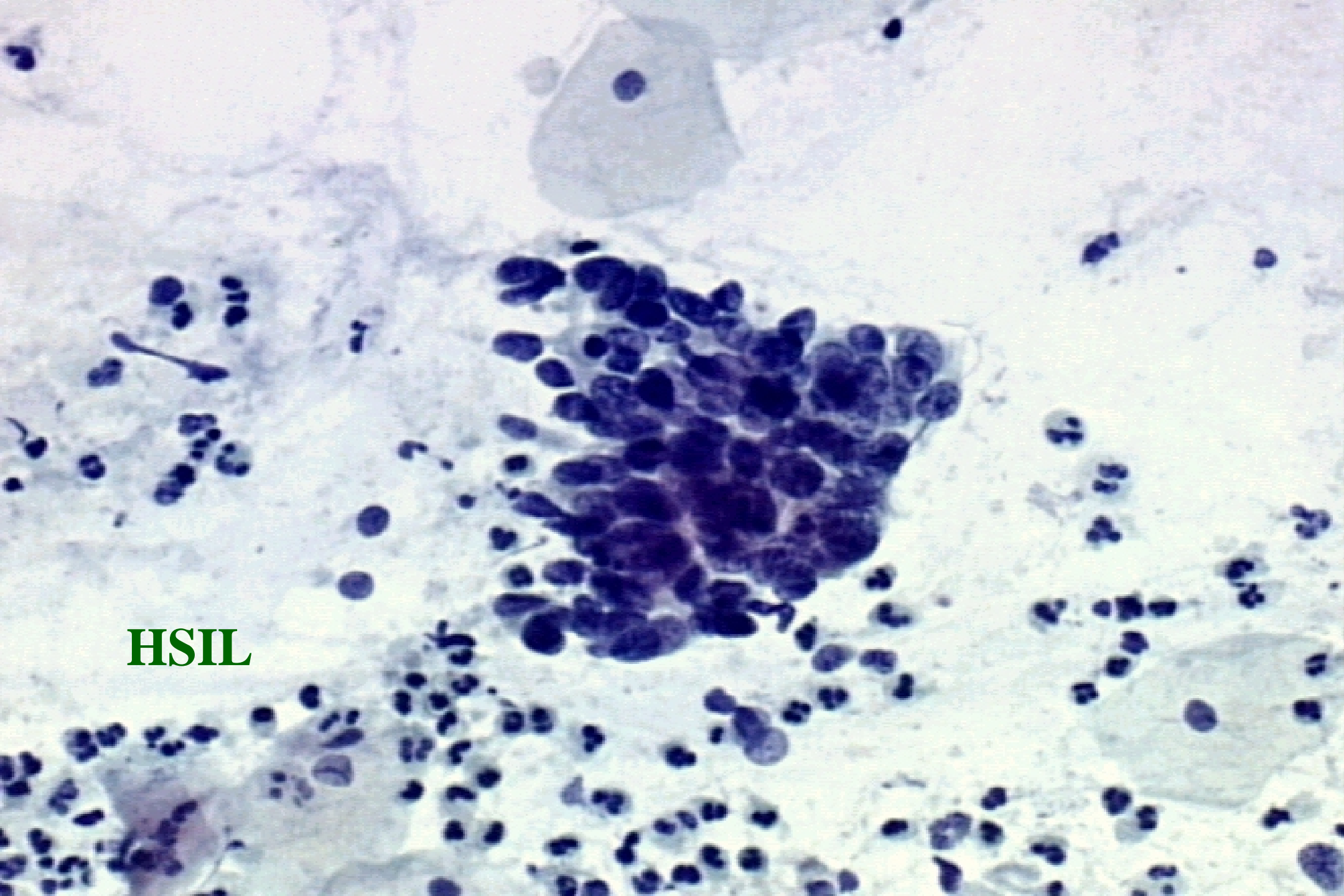
Adenocarcinoma in situ

Sequence of events in the development of precancerous lesions of the uterine cervix. A. Normal cervix. Horizontal arrow indicates transformation zone (TZ). B. Early neoplastic foci (red dots) occurring in the TZ (horizontal arrow pointing from the transformation zone to the squamous epithelium of the outer cervix). C. Progression to low-grade squamous intraepithelial lesions (LSIL) (vertical arrow down). These lesions may progress to squamous carcinoma. D. Progression from the TZ in the direction of the endocervical canal (arrow up), resulting in high-grade squamous intraepithelial lesions (HSIL). E. Development of endocervical adenocarcinoma in situ (TZ; horizontal arrow down). Events depicted in C-E may be reversed. (Drawing by Prof. Claude Gompel, University of Liège, Belgium.)

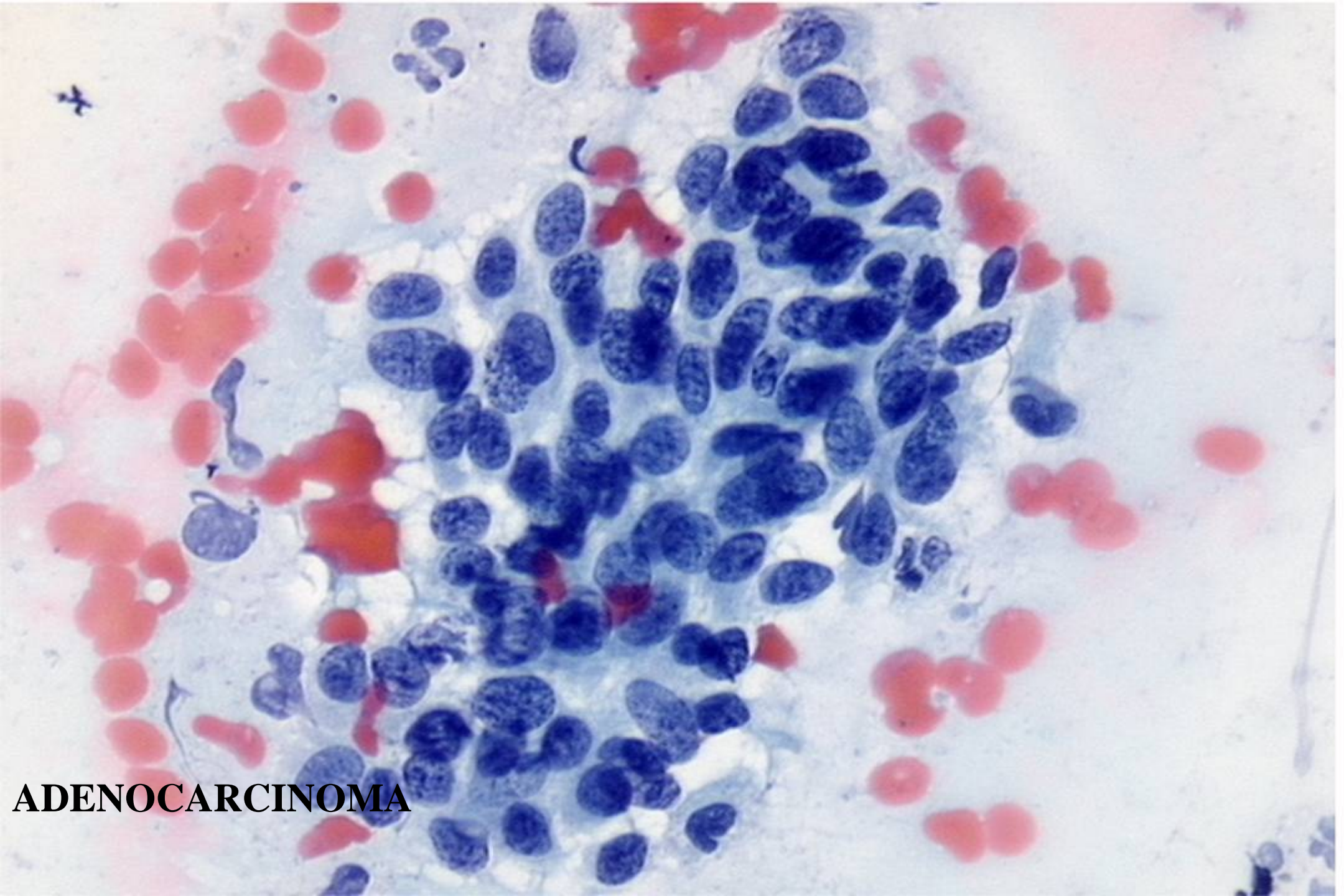
C



S.Costa-K.Syrjanen

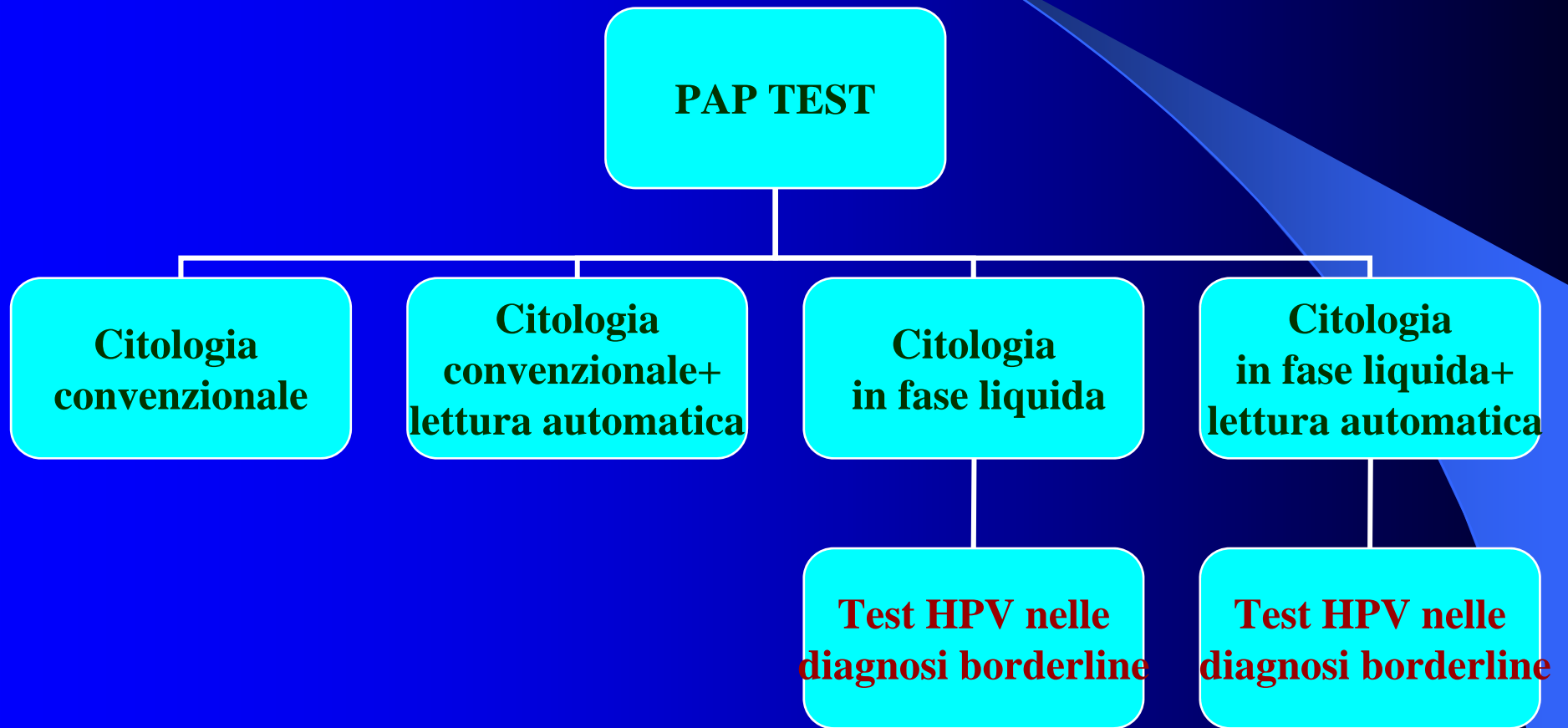


HSIL



ADENOCARCINOMA

TRA PRESENTE E FUTURO



IARC Handbook

There is **sufficient evidence** that screening by liquid-based cytology **can** reduce cervical cancer incidence and mortality rates.

There is **sufficient evidence** that screening by automated cytology **can** reduce cervical cancer incidence and mortality rates.

CITOLOGIA IN FASE LIQUIDA

Costi diretti

- Training
- Strumentazione
- Reattivi (vial , filtri ecct)
- Personale per preparazione strisci

Possibili risparmi

- Tempo di lettura
- Minor numero di richiami per strisci insoddisfacenti
- Minor numero di colposcopie ?

LBC

- L'utilizzo della citologia in fase liquida deve permettere successive indagini molecolari garantendo la conservazione e stabilità delle molecole presenti (DNA , mRNA ecct) a temperatura ambiente per un tempo congruo all'esecuzione degli esami stessi.

Prelievo per HPV Dna Test

- **Prelievo citologico tradizionale**

➔ strisciato (PCR)

➔ provetta (PCR, HC*)

*(HC sistema di prelievo in STM con un dispositivo che si lascia in provetta)

- **Prelievo per citologia in fase liquida**

(PCR, HC)



LETTURA AUTOMATICA

LETTURA COMPUTER-ASSISTITA

The AutoPap Primary Screening System

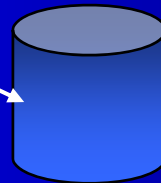


Slide Processor

PREP or Conventional Slide



**SlideWizard Field
Relocation and Review**



Copy service application

AutoPap

- A feasibility study of the use of the AutoPap screening System as a primary screening and location-guided rescreening device.

Confortini e Coll. Cancer Cytopathology 2003

Analisi dei costi (studio)

	Convenzionale	Autopap NFR =20%	Convenzionale	Autopap NFR =20%
	25.000 pap/anno		60.000 pap/anno	
Costo Autopap	No	216,912	No	216,912
Personale tecnico	No	4,000	No	10,000
Lettura	233,333 €	151,547	560,000	363,713
Ripetizioni-approfon.	11,500 €	8,000	27,600	19,200
	15,00 €	12,500	36,000	30,000
Totale	259,833 €	392,959	623,600	639,825
CIN 2 + trovati	55	53	132	126
Costo x CIN 2 +	4,724	7,414	4,724	5,077

LBC e Lettura Automatica

- L'introduzione di queste metodiche può essere fatta sulla base di valutazioni locali basate sull'analisi dei costi , del gradimento da parte degli operatori e della funzionalità e disponibilità del personale di lettura

LETTURA AUTOMATICA E STRATO SOTTILE

- ACCURATEZZA
- COSTI
- RISPARMIO TEMPI DI LETTURA

ACCURATEZZA

LBC+LETTURA AUTOMATICA

- Non esistono dati di letteratura, con end-point l'istologia, che indichino un aumento di accuratezza utilizzando la lettura automatica su strato sottile

RISPARMIO TEMPI DI LETTURA LBC+LETTURA AUTOMATICA

?

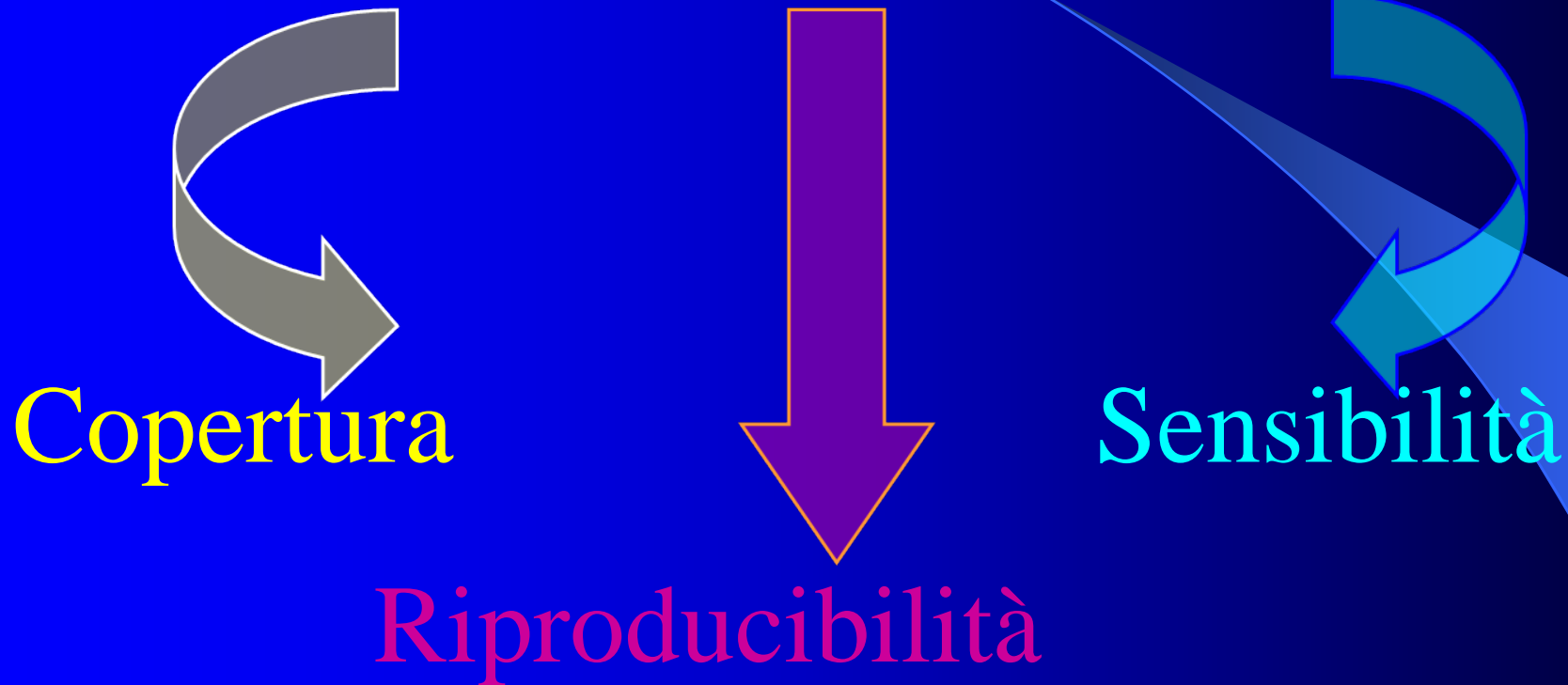
Thin-layer cervical cytology: a new meta-analysis

Lancet 2006

- It appears that new technology will not be the answer to the remaining incidence and mortality rates of cervical cancer.
- Increasing the coverage rate, as done in England since 1988, has been shown to be the key to success.

Screening e PAP TEST

PUNTI CRUCIALI



Screening del carcinoma della cervice uterina

Partecipazione

Tra i parametri che possono influenzare l'efficacia dello screening sulla popolazione (% di casi totali di cancro prevenibili) la partecipazione (copertura) risulta di gran lunga quello con la maggiore influenza

screening ogni	età	totale test	% casi prevenibili		
			copertura %		
			60%	85%	100%
1 anno	20-64	45	56	79	93
3 anni	20-64	15	54	77	91
3 anni	25-64	13	53	76	89
5 anni	25-64	8	49	69	81

AUMENTO DELLA COPERTURA

- E' in atto in Olanda uno studio su donne "non rispondenti" che prevede l'invio a casa di un KIT per eseguire da sole il test HPV da inviare successivamente al laboratorio molecolare
- Sorprendentemente il 30% di queste donne ha eseguito il test ed ha inviato l'esame al laboratorio

IARC Handbook

- There is *sufficient evidence*, based on surrogate markers, that the efficacy of HPV testing, using a validated system, as the primary screening modality can be expected to be at least as good as that of conventional cytology.

Worldwide Human Papillomavirus etiology of cervical adenocarcinoma and its cofactors: implications for screening and prevention

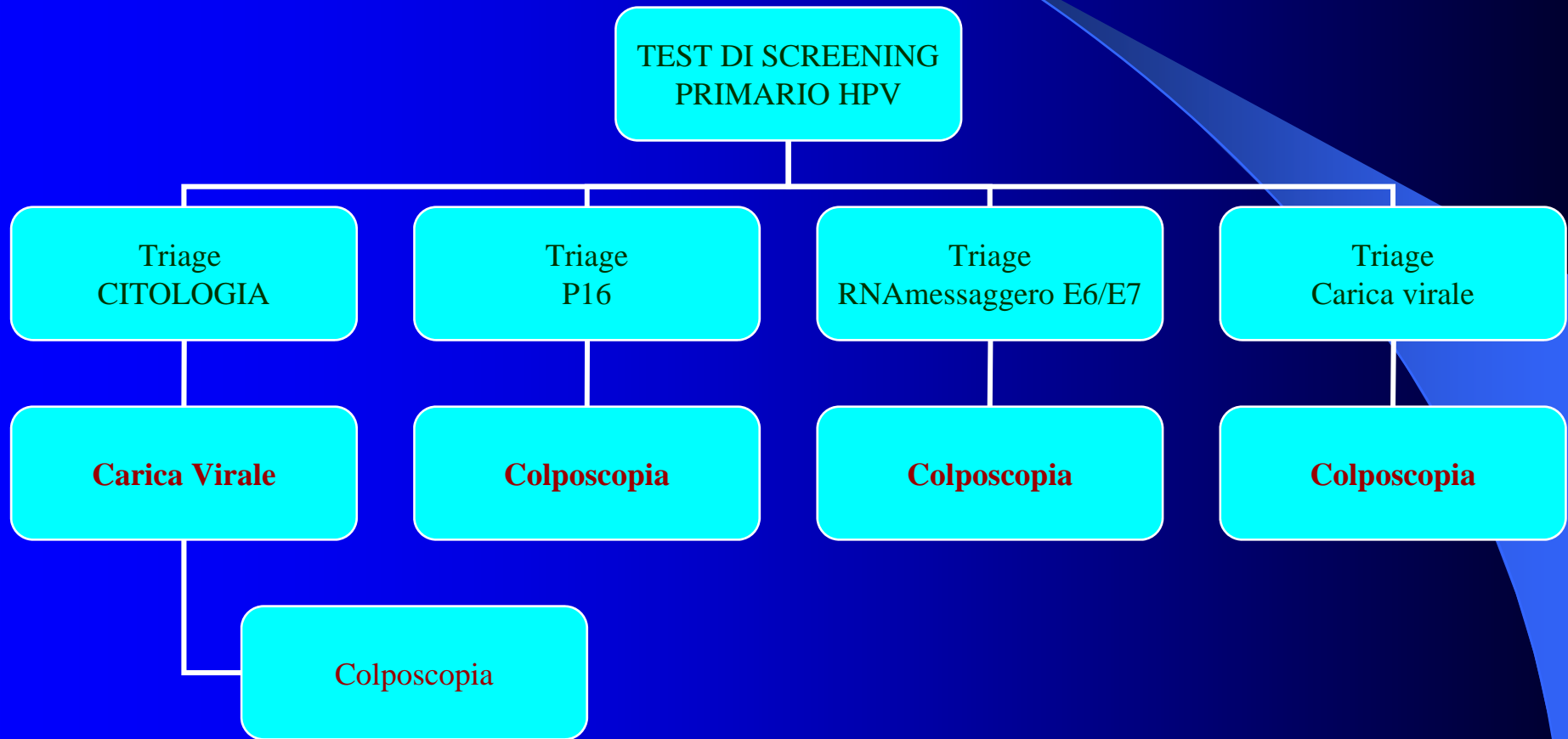
X.Castellsaguè et Al JNCI March 2006

- The confirmation from our findings that HPV is the central cause of cervical adenocarcinoma and that the same HPV types that are known to be involved in squamous cell cervical carcinoma are involved in cervical adenocarcinoma further implies that the introduction of HPV testing to primary screening should improve the efficiency of these programs at detecting precancerous glandular lesions

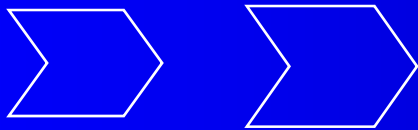
STUDIO MULTICENTRICO NAZIONALE

NUOVE TECNOLOGIE NELLA
PREVENZIONE DEL CARCINOMA
CERVICALE

FUTURO PROSSIMO

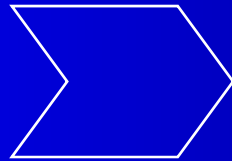


In situ hybridization
Southern blot



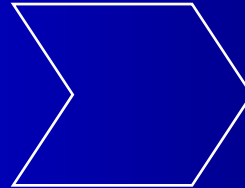
Direct probes

HCI



Signal
amplification

PCR



Target amplification

Real-Time PCR

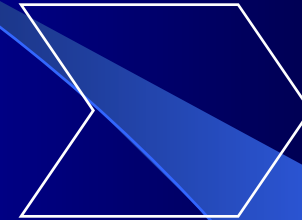


Fig.2 Sensibilità relativa delle tecniche di analisi degli acidi nucleici

SENSIBILITA' E SPECIFICITA' ANALITICA

- **SENSIBILITA' ANALITICA:** la proporzione di donne HPV pos correttamente individuate da un test
- **SENSIBILITA' CLINICA:** la proporzione di donne con malattia (lesioni \geq cin2) che sono correttamente identificate da un test HPV

SENSIBILITA' E SPECIFICITA' CLINICA

- SPECIFICITA' ANALITICA : la proporzione di donne HPV HR negative che sono correttamente identificate da un risultato negativo
- SPECIFICITA' CLINICA: la proporzione di donne senza lesioni \geq cin2 che sono che sono correttamente identificate da un risultato negativo

Host and viral factors in cervical pathogenesis

Viral factors

Host specific factors



Caratterizzazione di markers di interazione HPV-DNA e DNA cellulare che potrebbero segnalare lo stato di latenza, persistenza e progressione a neoplasia

Strategie di vaccinazione nel trattamento e prevenzione del cancro cervicale

- Vaccinazione profilattica
- Vaccinazione terapeutica
- Vaccini combinati

FUTURO IN EPOCA VACCINALE

