



Skvamöz prekanseröz lezyonlarda terminoloji ve biomarkerler

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Patoloji Anabilim Dalı



25 Ulusal Patoloji Kongresi
6 Sitopatoloji Kongresi

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Skvamöz prekanseröz lezyonlar

- 1886 Sir John Williams

kansere komşu alanlarda noninvaziv epitelyal anormallikler

- 1900 Cullen

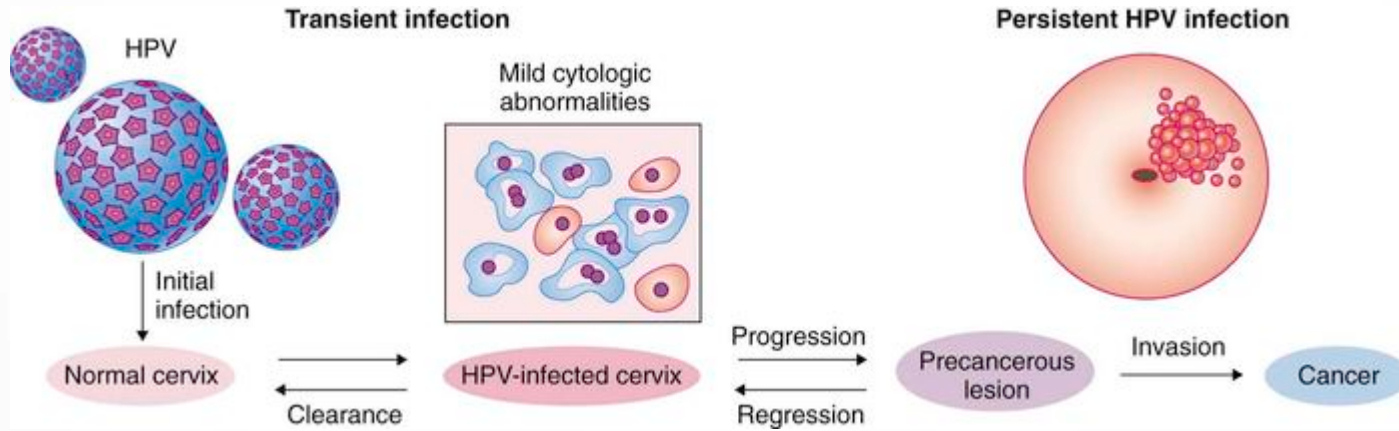
invaziv kansere histolojik benzerlikleri tanımlamış

- Schottlander ve Kermauner, 1930'da Broder karsinoma in situ (KİS) terminolojisi kullanmışlar

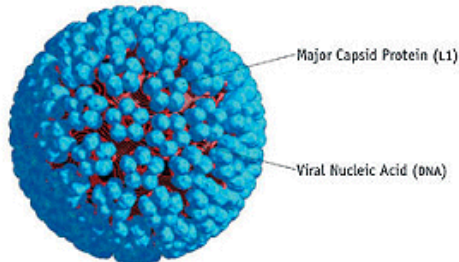
- Richart prekürsör lezyonların tek bir hastalığı temsil ettiğini ileri sürmüştü ve bu hastalığa “servikal intraepitelyal neoplazi (CIN)” CIN 1-2-3



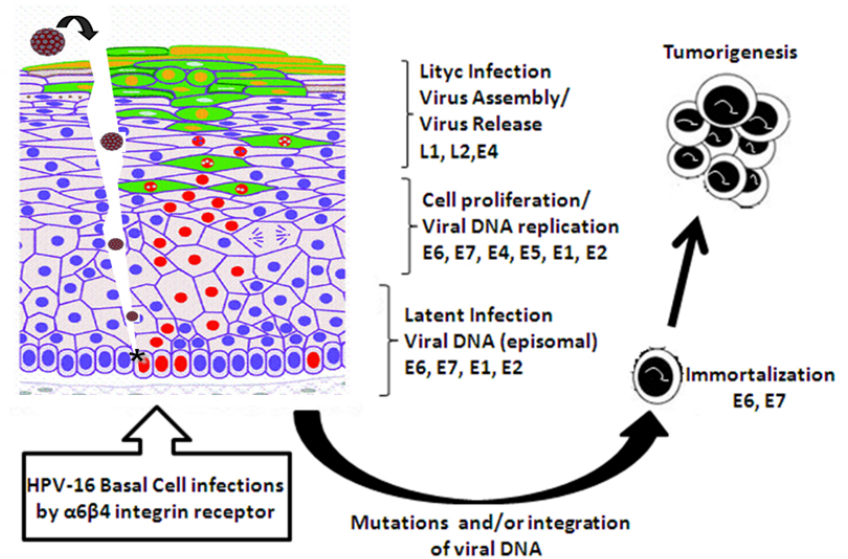
HPV ve Skuamöz neoplazi



THREE-DIMENSIONAL MODEL OF HUMAN PAPILLOMAVIRUS



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Published in The PNN Notebook, Volume 4, Number 3, September 2001 and The PNN Notebook Online at: www.pnn.org
Three-dimensional model of HPV created by Louis L. Henderson, Ph.D., Fredrick Cancer Research Center.

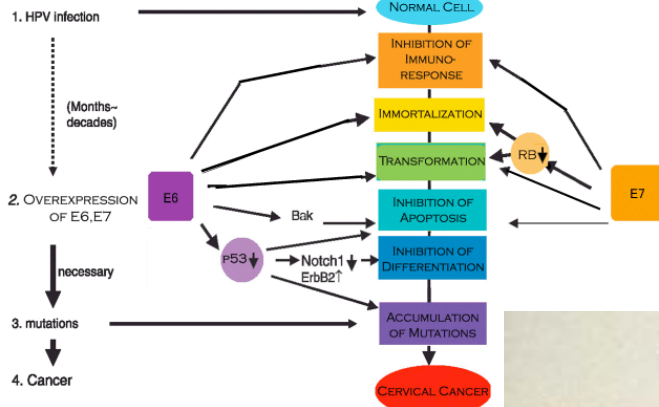


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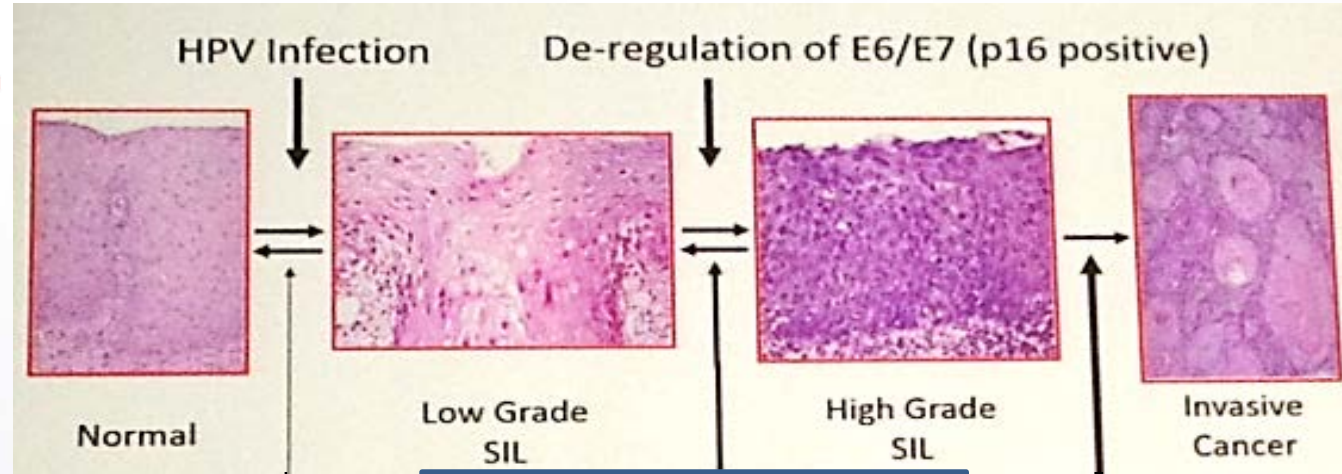
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MECHANISM OF E6/E7 IN CARCINOGENESIS OF CERVICAL CANCER



HPV ve Skuamöz neoplazi



Telomeraz aktivasyonu,
Apoptozis inhibisyonu,
Genetik değişiklikler,
İmmün cevap, Sigara



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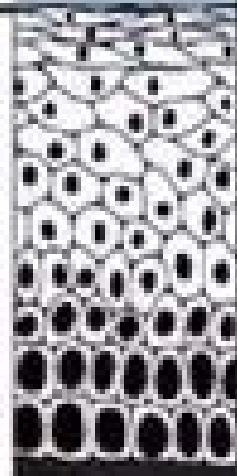
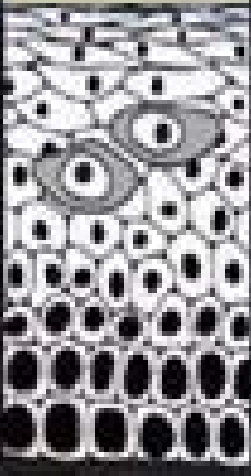
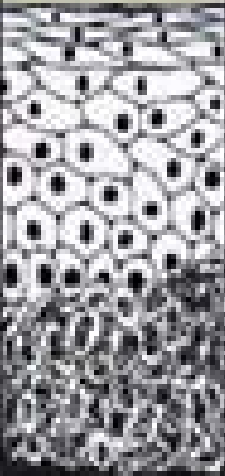
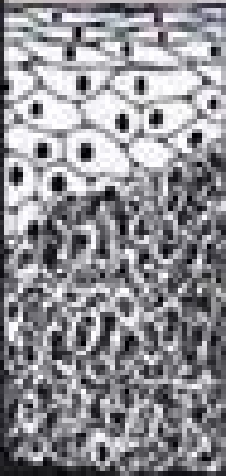
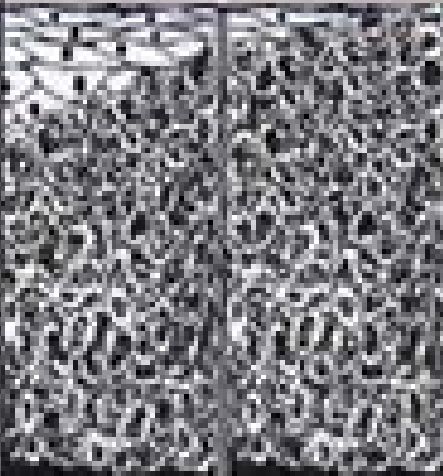
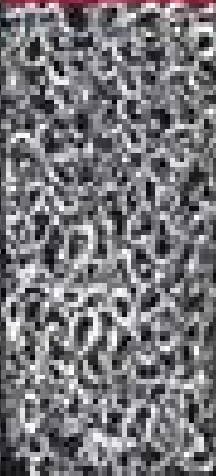
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Servikal intraepitelyal neoplazi (CIN)

	HPV	CIN	Displazi	SIL
CIN I	Düşük- yüksek risk	Low grade CIN	Hafif	LGSIL
CIN 2	Yüksek risk	High grade CIN	Orta	HGSIL
CIN3	Yüksek risk	High grade CIN	Ağır/CIS	HGSIL

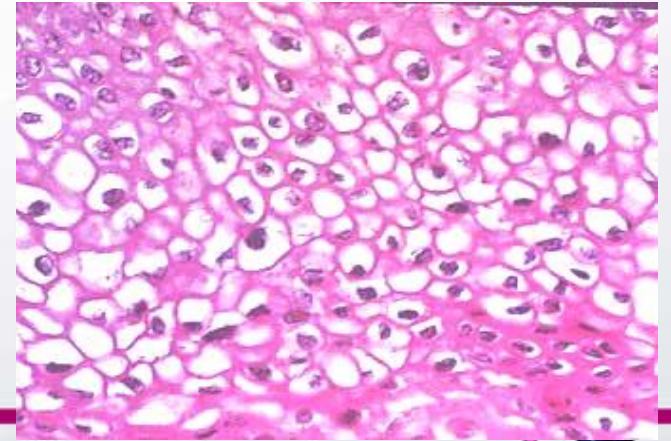
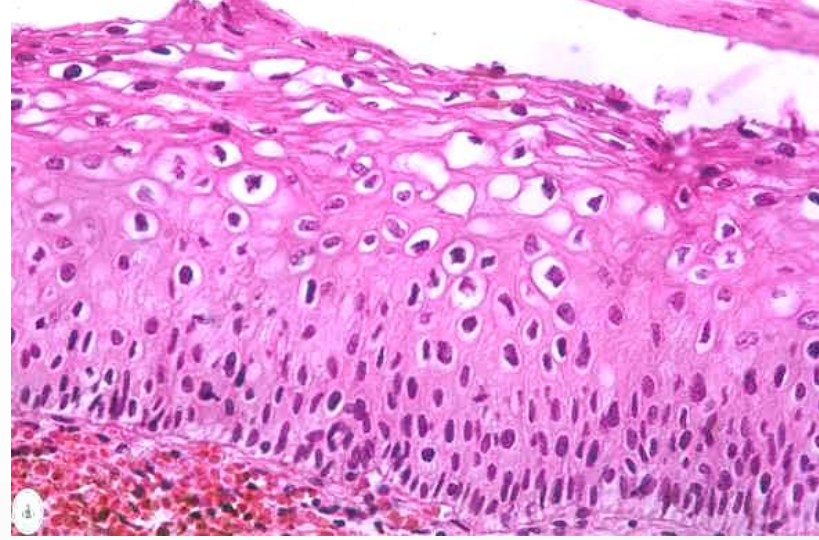


Normal	Low-grade squamous intra-epithelial lesion		High-grade squamous intra-epithelial lesion		Invasive cancer
Normal	Condyloma	CIN 1 (Mild dysplasia)	CIN 2 (Moderate dysplasia)	CIN 3 (Severe dysplasia, CIS)	Invasive cancer
					



LGSIL – CIN 1 – Hafif displazi

- Koilositoz
- Nükleer atipi
- Üst 2/3 maturasyon
- Alt 1/3 immatür, bazaloid hücre
- Alt 1/3 mitoz
- Anormal mitoz yok-nadir



CIN 1- LSIL ayırıcı tanı

- Reaktif atipi – inflamasyon
- Normal skuamöz epitel (belirgin sitoplazmik glikojen veya vakuolizasyon)

Koilositoz genellikle fokaldır

Benign epitelde nükleer irileşme, multinükleasyon, disorganizasyon, maturasyon bozukluğu en önemlisi gerçek nükleer atipi yoktur.

Park KJ, Soslow RA. Arch Pathol Lab Med 2009; 133: 729-738



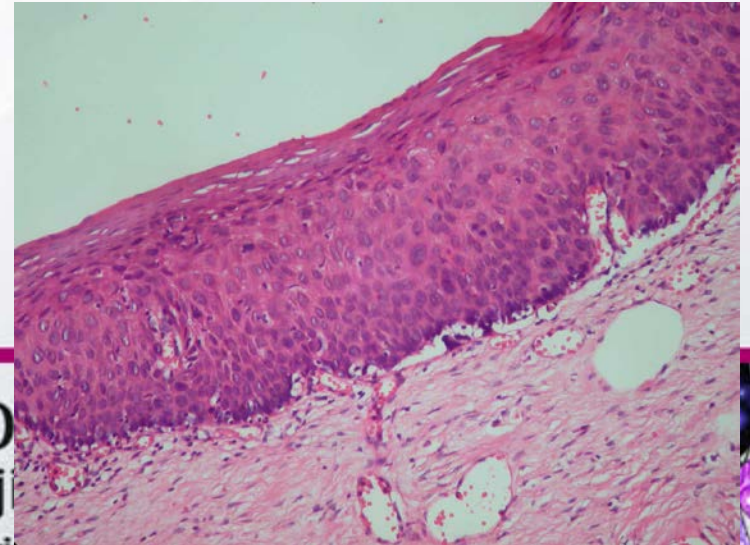
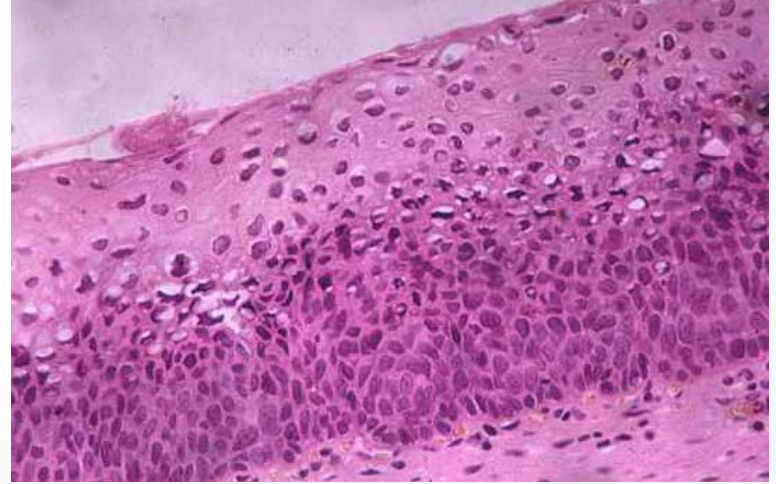
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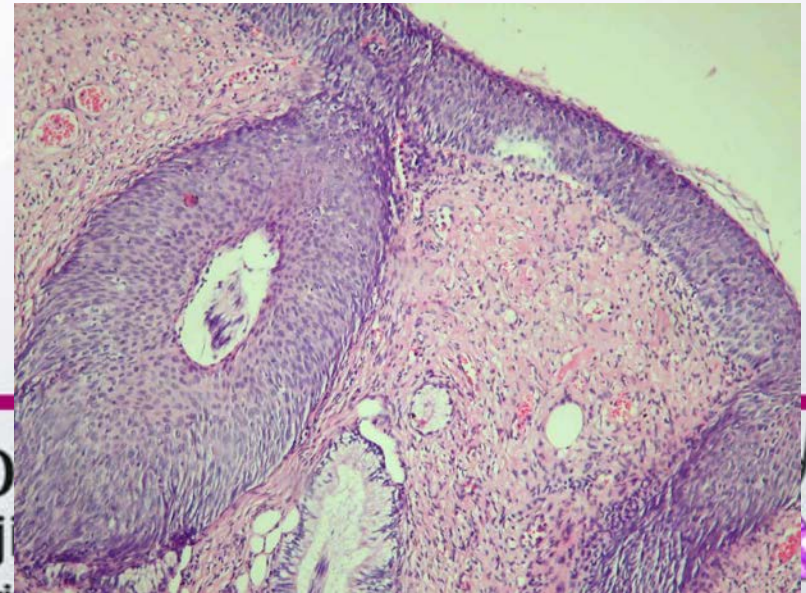
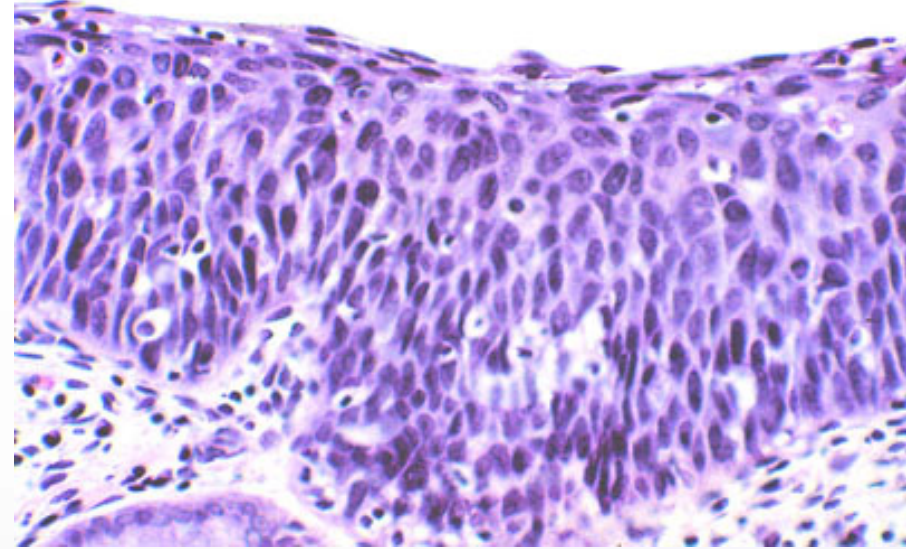
HGSIL – CIN 2 – Orta derecede displazi

- Üst 1/3-1/2 maturasyon
- Nükleer atipi
- Koilositoz
- Alt 2/3 immatür, bazaloid hücre
- Alt 2/3 mitoz
- Anormal mitoz nadir



HGSIL – CIN 3 – Ağır displazi/KİS

- Maturasyon yok yada yüzeyde
- Epitelin tamamında atipi ve mitoz
- Anormal mitoz



CIN 2 ∞ CIN 3

- CIN 2 ve CIN 3 ayırımı çok önemli ya da kritik değildir. İkisi de yüksek gradedir. İmmatür bazaloid hücrelerin kalınlığı aynı lezyon içinde değişkenlik gösterdiği için CIN 2 tanısının tekrarlanabilirliği düşüktür.

Park KJ, Soslow RA. Arch Pathol Lab Med 2009; 133: 729-738



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Ayırıcı tanı

- Atrofi
- Transizyonel metaplazi
- İmmatür skuamöz metaplazi
- *Mitotik aktivite, pleomorfizm, hiperkromazi, polarite kaybı, kromatin kümelenmesi yoktur.*
- Reaktif - reperatif deęişiklik
- *Nükleer kontür düzenlidir, nukleol belirginlięi, hücre sınırları belirgin, inflamasyon vardır.*



Original Article

The Lower Anogenital Squamous Terminology Standardization Project for HPV-associated Lesions: Background and Consensus Recommendations From the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology

Teresa M. Darragh, M.D., Terence J. Colgan, M.D., J. Thomas Cox, M.D., Debra S. Heller, M.D., Michael R. Henry, M.D., Ronald D. Luff, M.D., Timothy McCalmont, M.D., Ritu Nayyar, M.D., Joel M. Palefsky, M.D., Mark H. Stoler, M.D., Edward J. Wilkinson, M.D., Richard J. Zaino, M.D., David C. Wilbur, M.D., and For Members of the LAST Project Work Groups

• Archives of Pathology and Laboratory Medicine:

- June 28, 2012. [Epub ahead of print]
- October 2012 – Volume 135 – p 1266-1297.

• Journal of Lower Genital Tract Disease:

- June 28, 2012. [Epub ahead of print]
- July 2012 – Volume 16 – p 205-242



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HPV ve Anogenital bölge kanserler

- Serviks kanseri >%99
- Vajinal kanser % 60-65
- Anal kanser % 83-95
- Vulva kanser % 20-50
- Penil kanser % 30-42
- Perianal kanser %28-80

Maniar KP, Nayar R. Adv Anat Pathol 21(5), 2014



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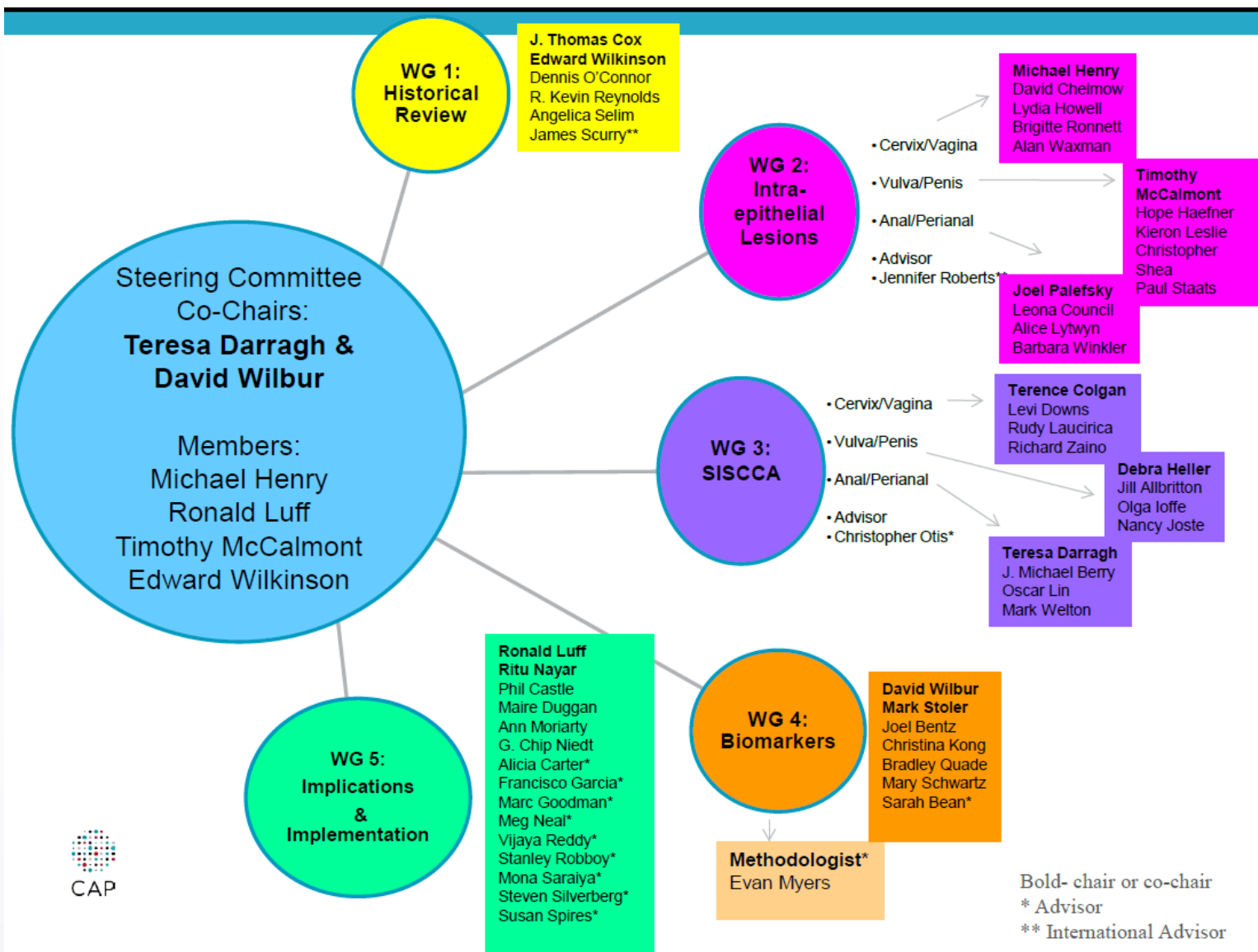
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LAST (Lower Anogenital Squamous Terminology)

- HPV ilişkili lezyonlarda biyolojik ve morfolojik benzerlik
- Ortak terminoloji oluşturma: Serviks, vulva, vajen, penis, anüs, perianüs, skrotum
- CAP – ASCCP





www.cap.org



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Terminoloji – Mukozal enfeksiyon/prekanser

- Displazi
 - Hafif, orta, ağır, karsinoma insitu
- İntraepitelyal neoplazi
 - CIN1-3
 - VaIN 1-3
 - AIN 1-3
- Skuamöz intraepitelyal lezyon
 - LSIL / HSIL

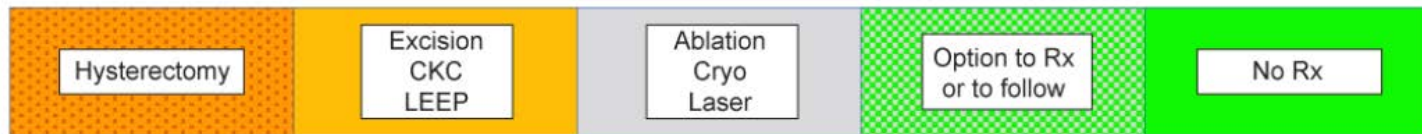
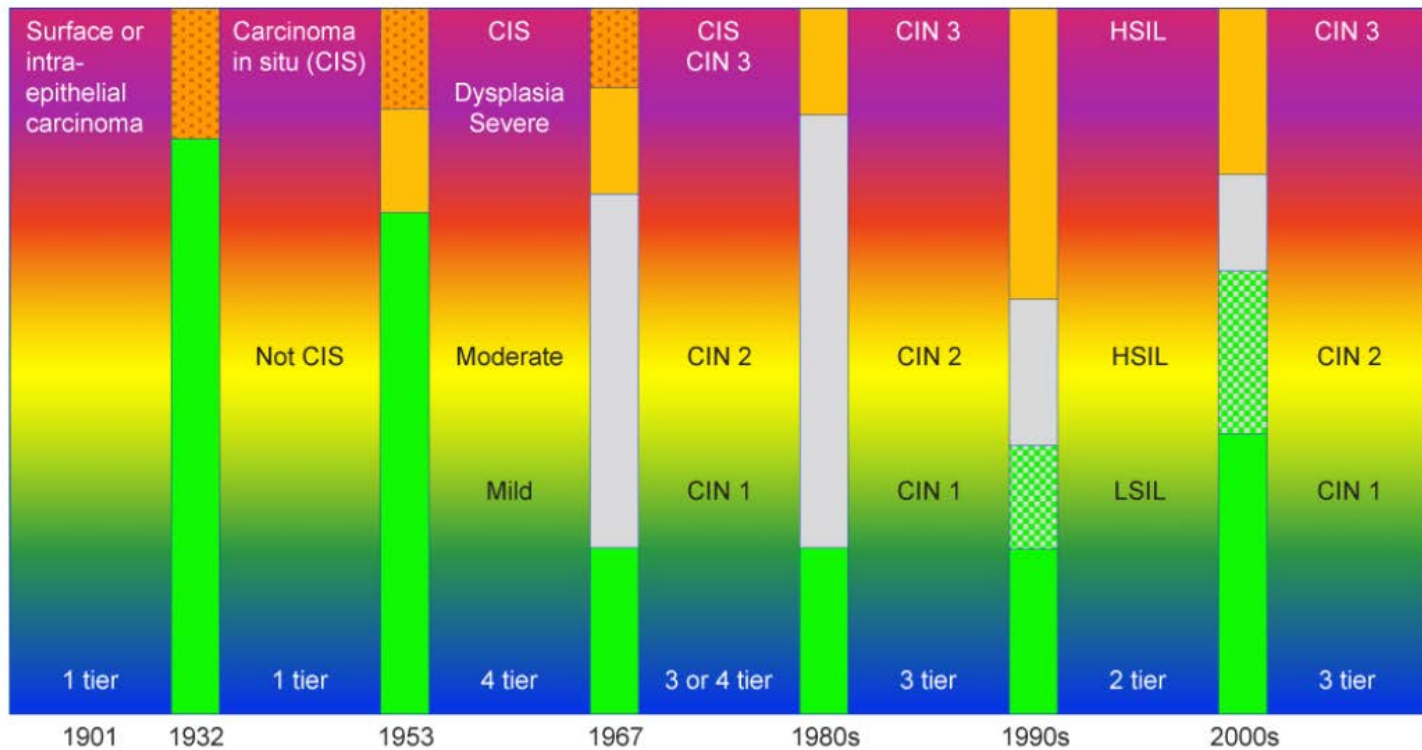


Terminoloji – Kutanöz enfeksiyon/prekanser

- VIN 1-3, PeIN 1-3, PAIN 1-3
- LSIL / HSIL
- VIN usual tip
- Karsinoma insitu
- Bowen hastl / Qeyrat eritroplazi
- Bowenoid papulosis



Terminology



Procedure

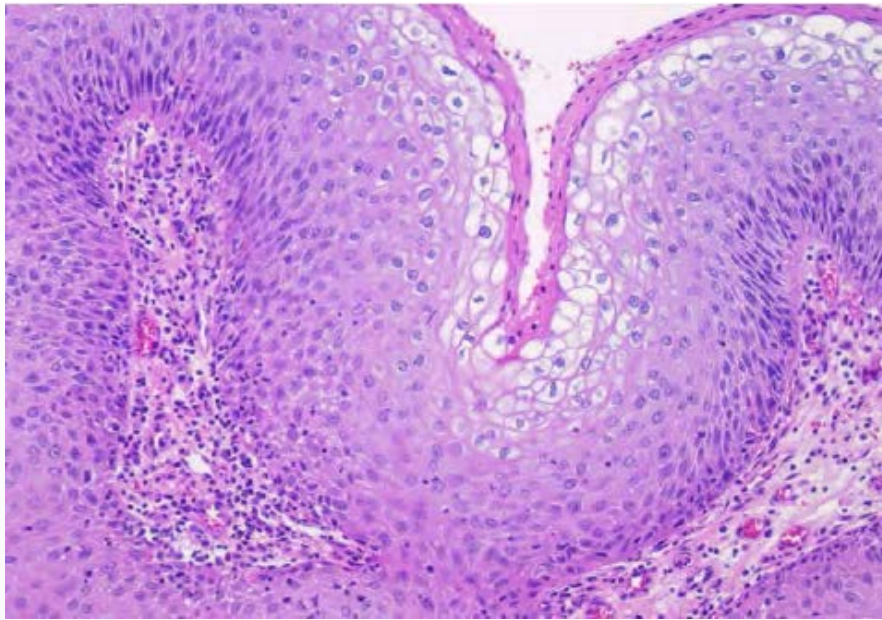


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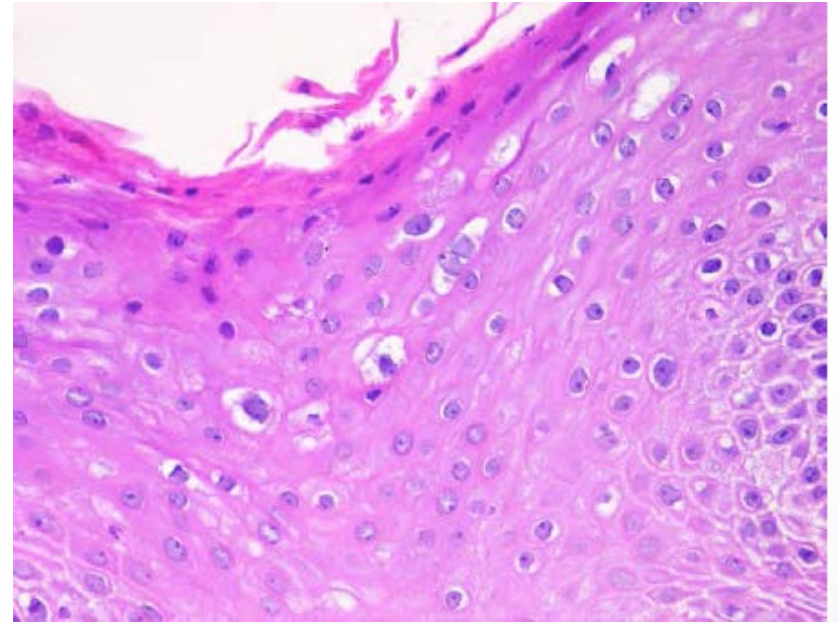
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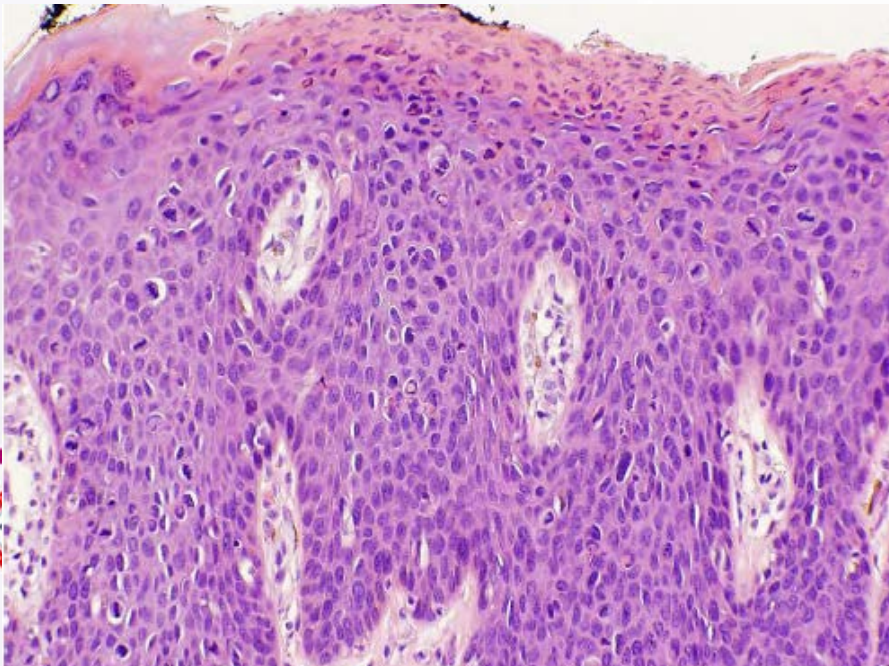
Perianal kondilom



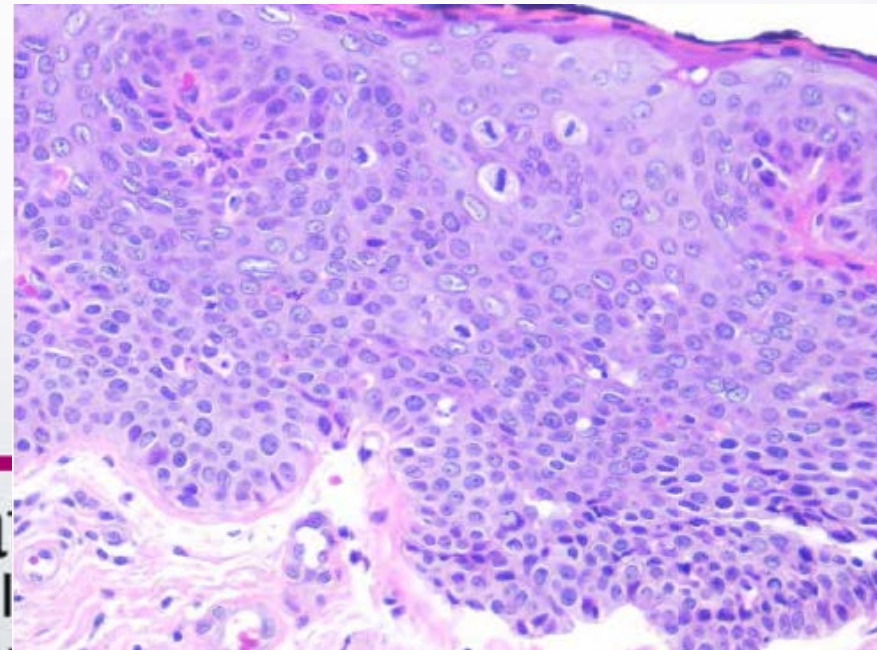
Serviks kondilom



VIN 3



PeIN 3



SIL Çalışma Grubu Önerileri

- Tüm bölgelerde HPV ilişkili preinvaziv skuamöz lezyonları için ortak terminoloji
 - Low grade skuamöz intraepitelyal lezyon-LSIL
 - High grade skuamöz intraepitelyal lezyon-HSIL
- Bölgeye ait –IN eklenmeli
 - CIN, VIN, VaIN, PeIN, PAIN, AIN
- HPV ilişkili olmayan skuamöz lezyonlar için ayrı terminoloji kullanılmalı örn: diferansiye VIN



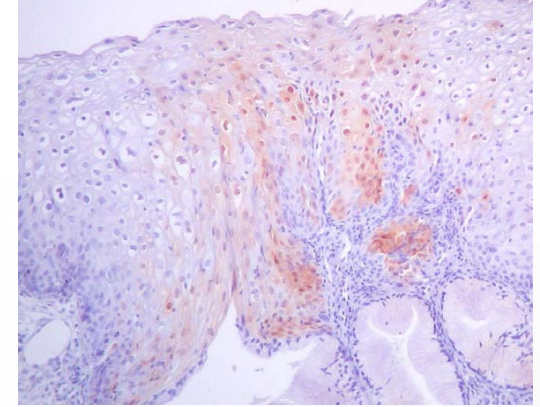
LAST

- İkili sistem günümüzde yaygın kullanılıyor
- Virus biyolojisi ile uyumlu
- Sitoloji terminolojisi ile uyumlu
- Tekrarlanabilirliği yüksek Kappa 0.30 – 0.71
(üçlü sistem kappa 0.12 – 0.58)
- Klinik yönetime uygun

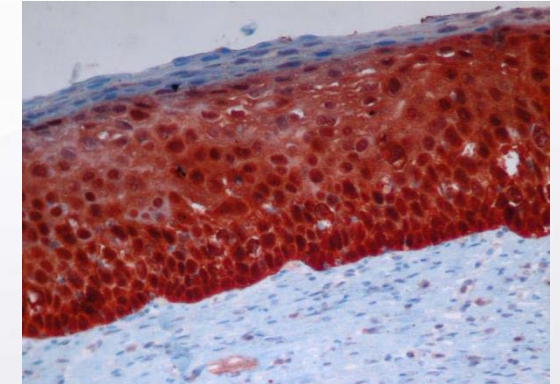


Biomarker Çalışma Grubu

- **p16**
- Ki 67
- ProExC
- HPV L1 protein
- HPV 16/18 mRNA
- Telomeraz
- HPV genotipleme



P16(-)

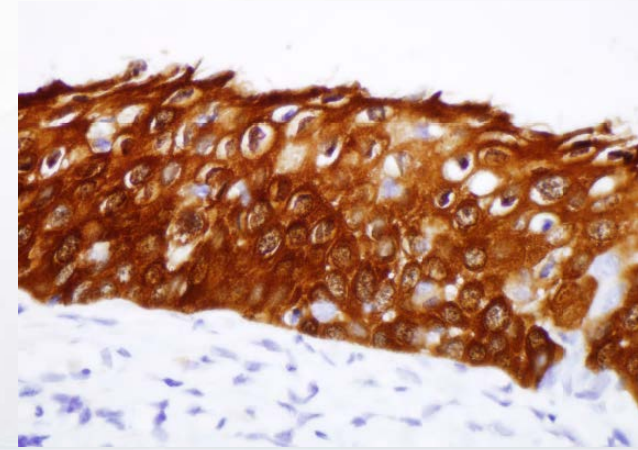
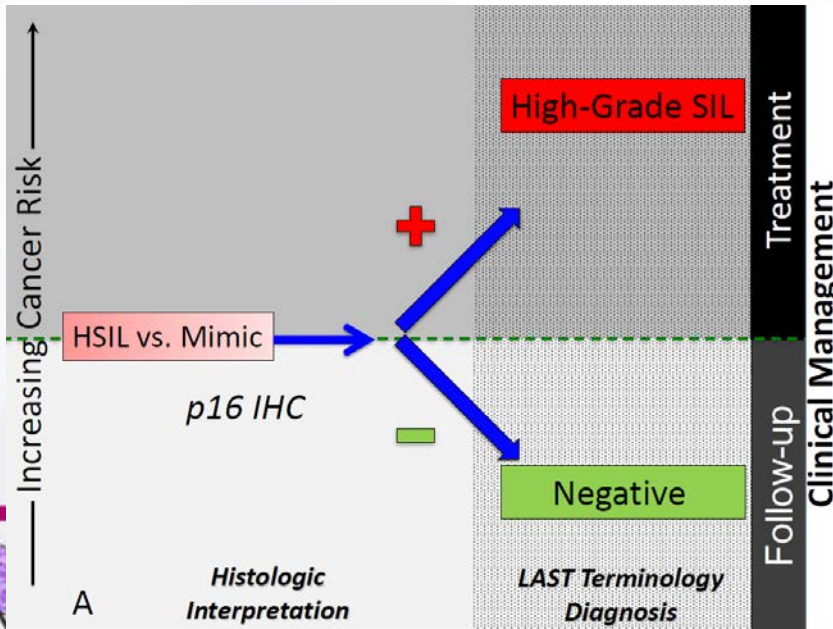


P16(+)



Biomarker Çalışma Grubu

- p16 HSIL (-IN2-3) ile immatür metaplazi, atrofi, reperatif değişiklikler, tanjant kesit ayırımında kullanılmalı
- p16 güçlü, diffüz, “*blok*” boyanma



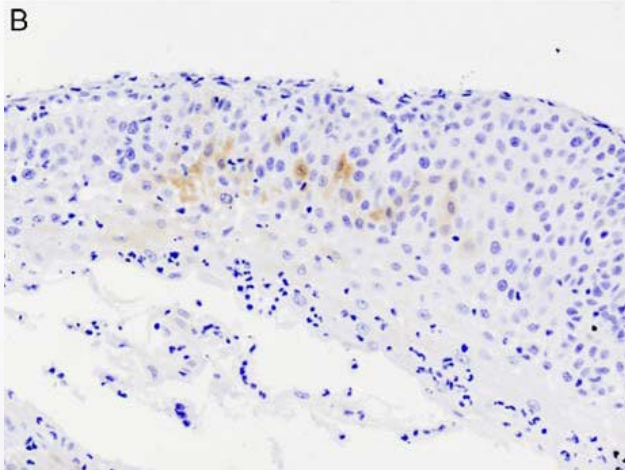
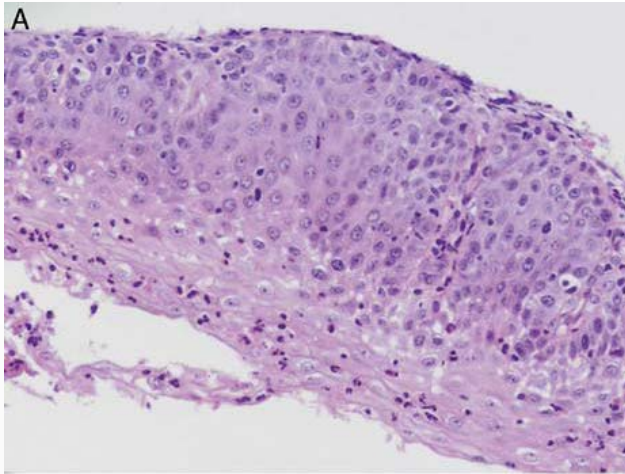
loji Kongresi

Sitopatoloji Kongresi

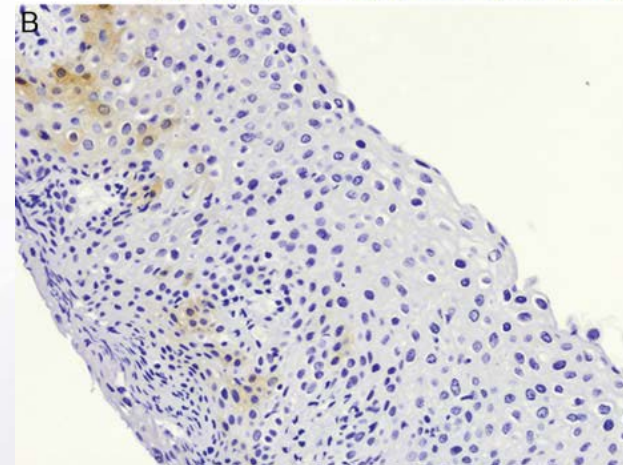
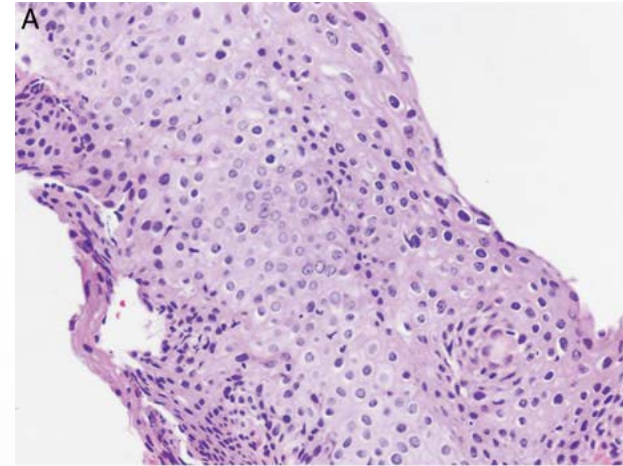
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İnflamasyon & HSIL



HSIL & LSIL



International Journal of Gynecological Pathology
32:76-115, Lippincott Williams & Wilkins, Baltimore
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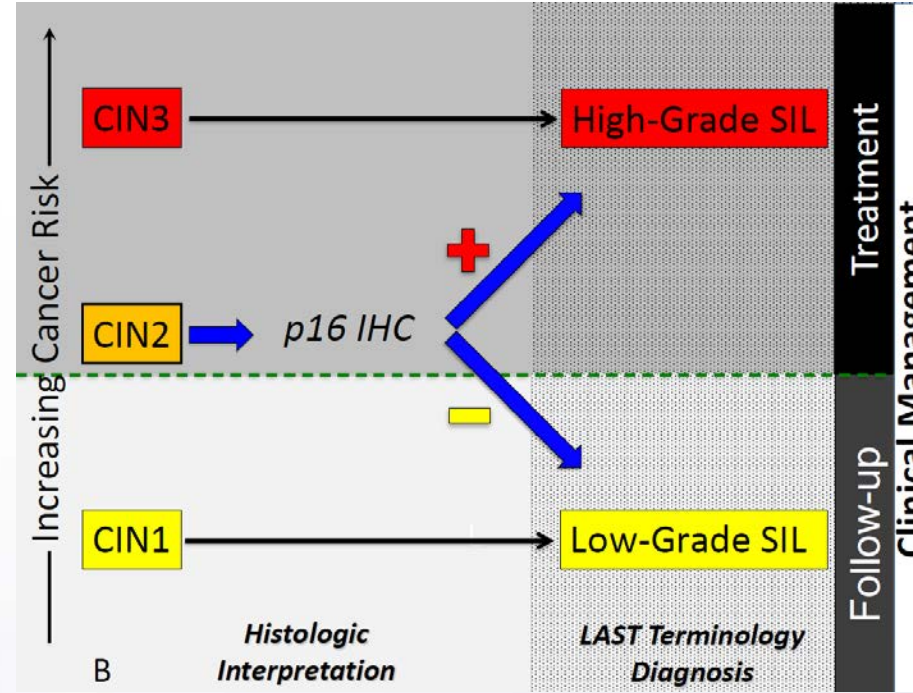
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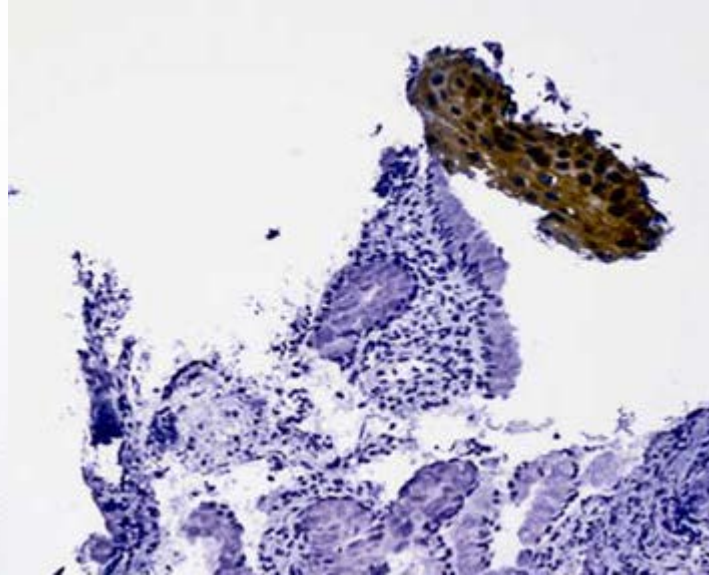
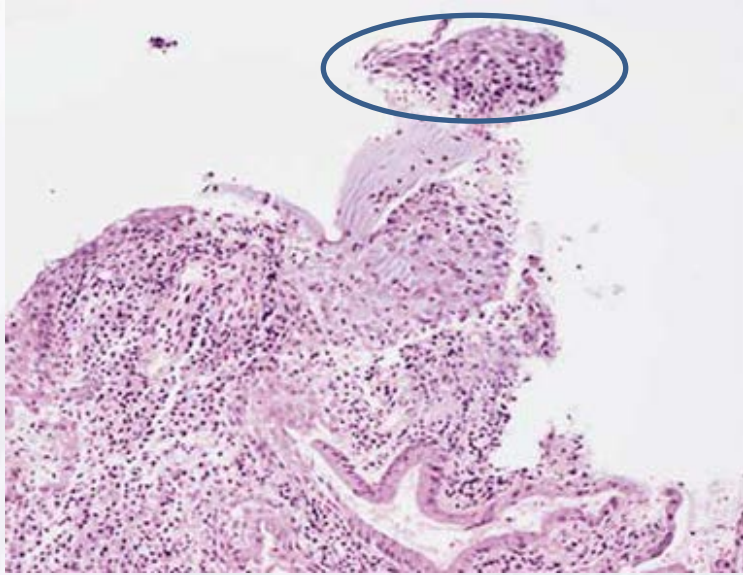
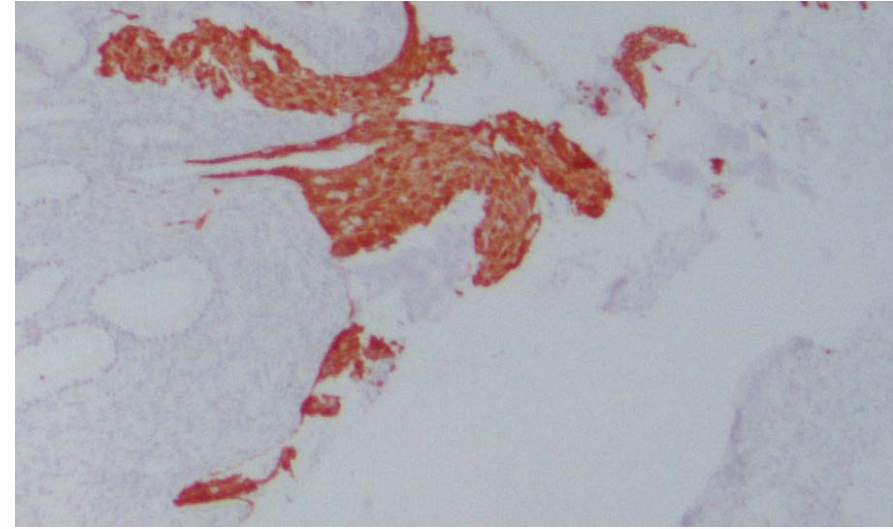


Biomarker Çalışma Grubu

- **Morfolojik olarak (-), -IN1 ve -IN3 ise p16 yapma**
- -IN2 p16 uygulanmalı
- p16 (-) veya fokal zayıf (+) ise LSIL veya HPV ilişkisiz patoloji
- -IN2 ve -IN3 ayırımı
- <-IN1 ancak sitoloji HSIL, ASC-H, ASC-US/p16(+), AGC (NOS)



- Ezilme, koter artefaktı gibi HE ile değerlendirilmesi zor fokal odaklarda p16 yararlı



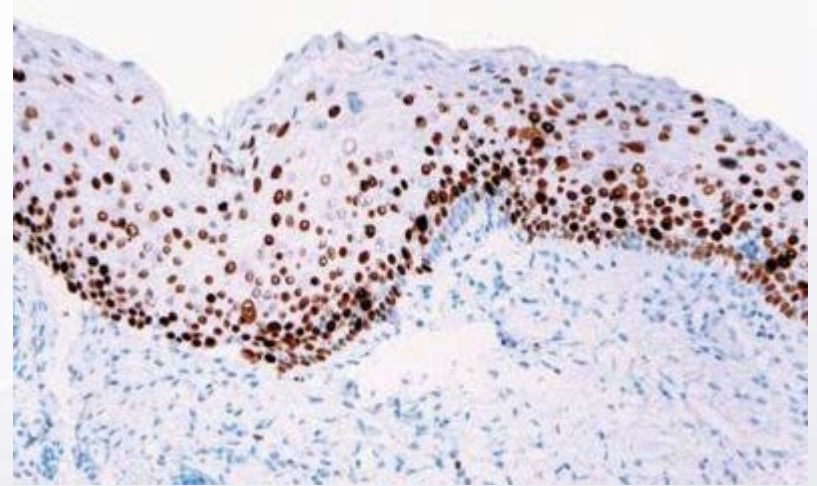
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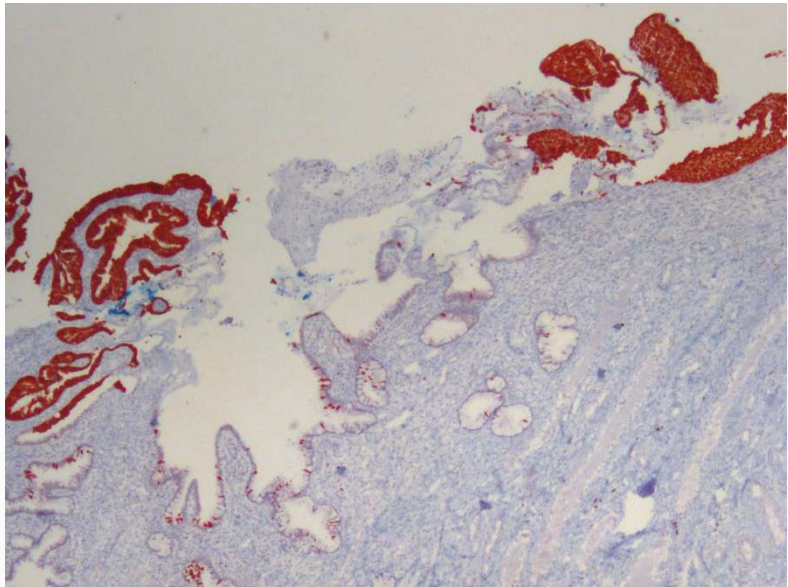
Biomarker Çalışma Grubu

- Ki 67 ve ProExC benzer
- p16 yoksa, teknik yetersizse Ki 67 ve/veya ProExC kullanılabilir

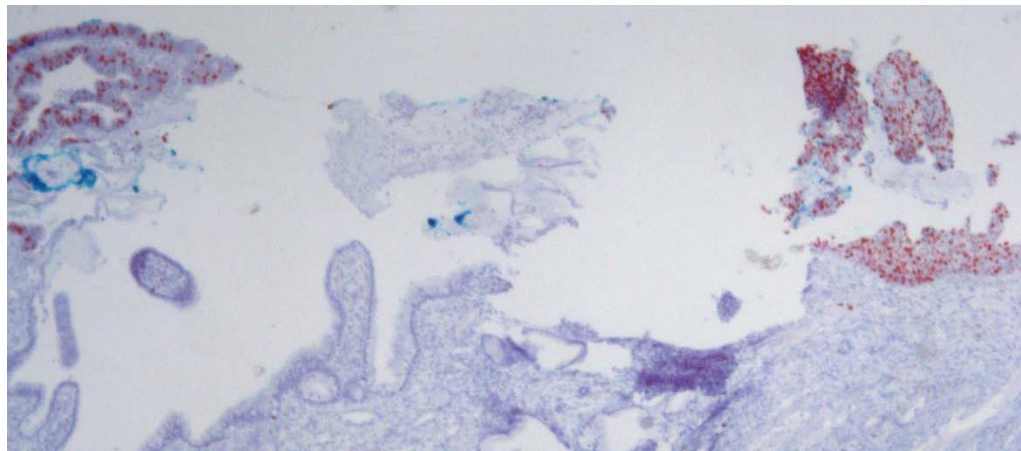


ProExC

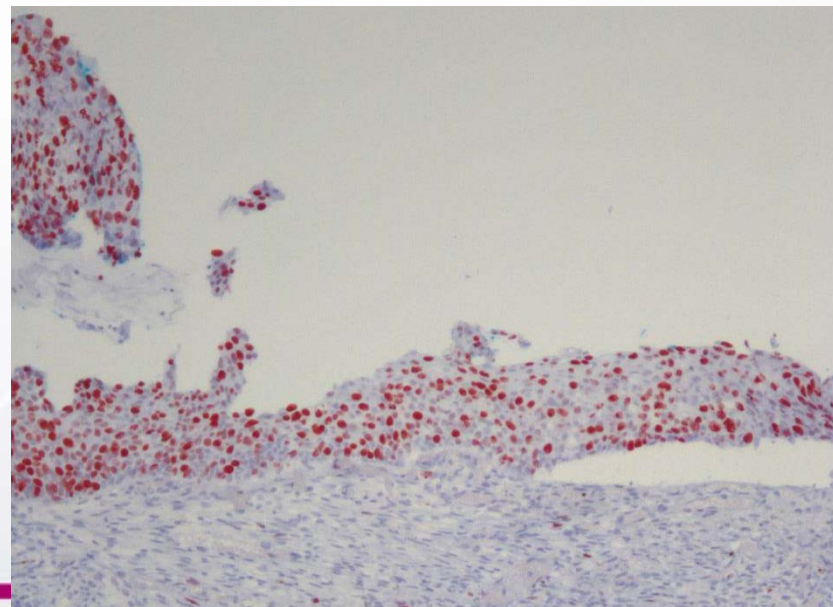
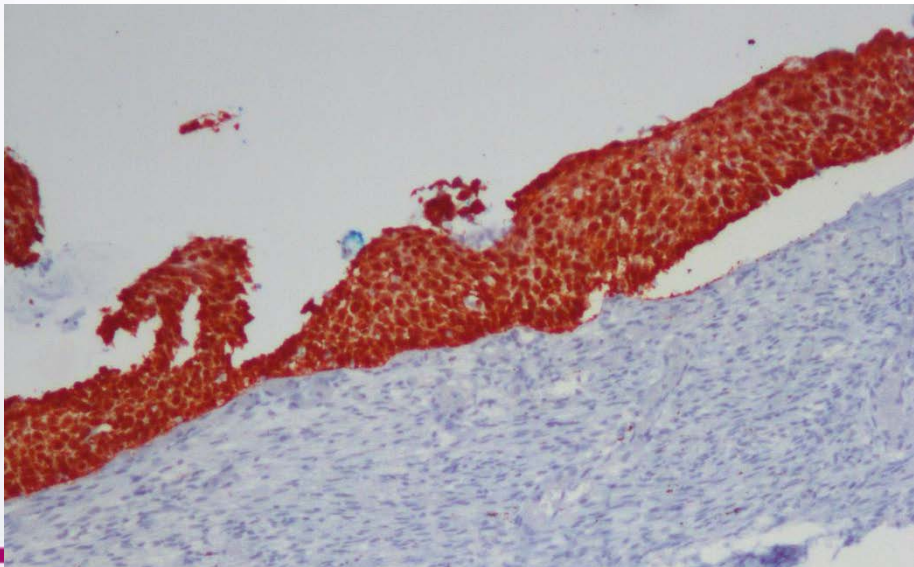




p16

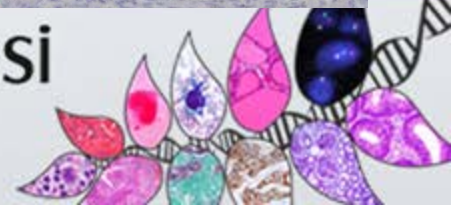


Ki 67

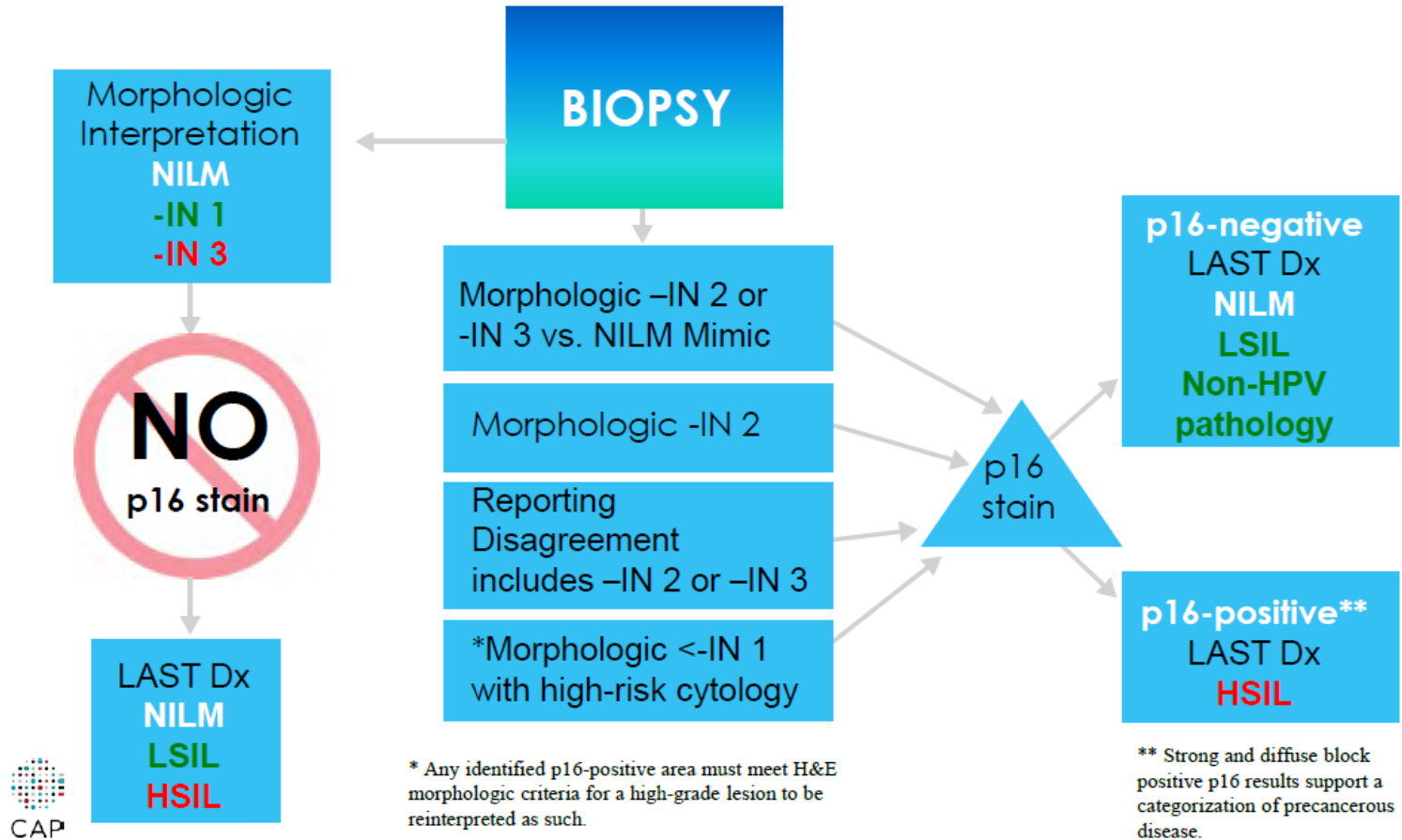


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Summary of Algorithms for Management of Biopsy Results with LAST Terminology



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Problemler

- P16 pozitif low grade lezyonlar
- P16 negatif high grade lezyonlar
 - Gen delesyon
 - Gen “silencing”
- Up-grade eğilimi
- Gereksiz fazla tedavi
- Aşırı p16 kullanımı (maliyet↑, tanıda geçikme)



	Regresyon	Kalıcılık	CIN 3'e ilerleme	İnvazyon
CIN 1	%60	%30	%10	%1
CIN 2	%40	%40	%20	%5
CIN 3	%30	%60		%12

Jordan LB, Monaghan H. *Clinical Oncology*, 2004;16:248-254

Hangi lezyonlar progresyon gösterecek?
Takip mi? Eksizyon/ablasyon mu?



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Laboratory Management of Cervical Intraepithelial Neoplasia: Proposing a New Paradigm

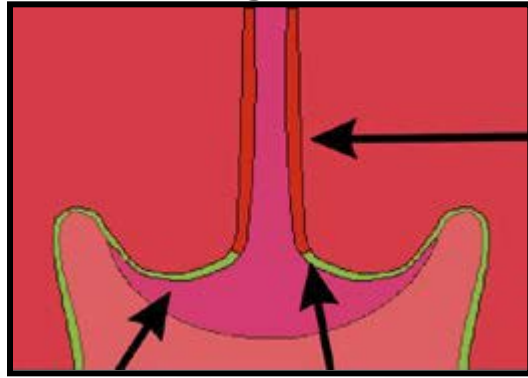
Michael Herfs, PhD† and Christopher P. Crum, MD**

Adv Anat Pathol • Volume 20, Number 2, March 2013

- LSIL
- HSIL
- QSIL (Questionable grade of squamous intraepithelial lesion)
 - “SIL of uncertain/questionable grade”
 - 6 ay takip ve değerlendirme



Doğumda

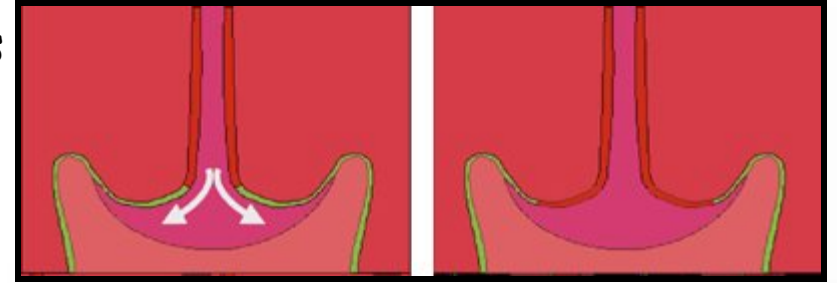


Endoserviks

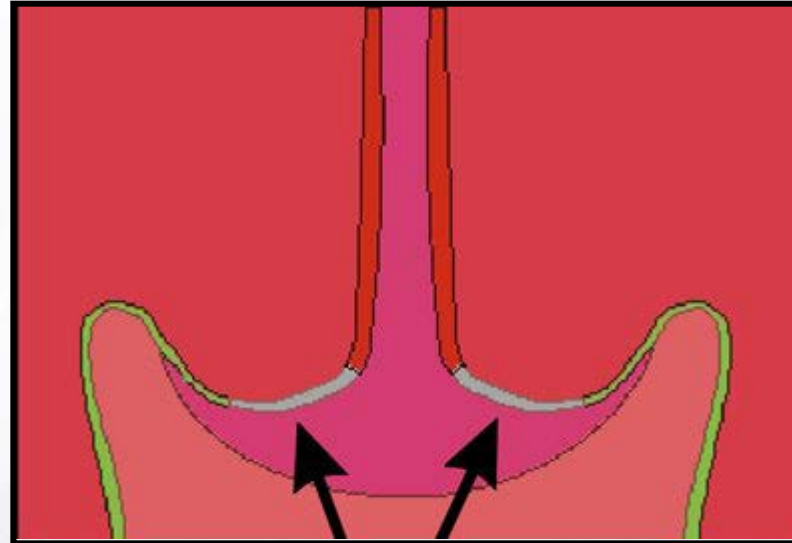
Ektoserviks

Skvamokolumnar
bileşke

Puberte, adolesans



Endoservikal eversiyon, ektopi, ektropion



Transformasyon zonu



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Skuamokolumnar junction hücreleri

Laboratory Management of Cervical Intraepithelial Neoplasia: Proposing a New Paradigm

Michael Herfs, PhD*† and Christopher P. Crum, MD*

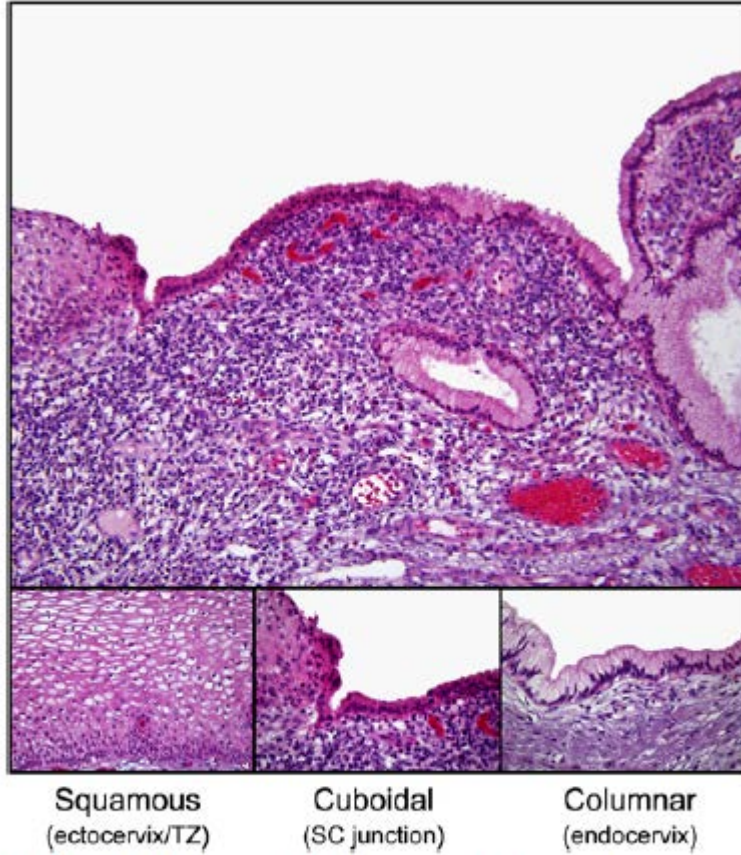


FIGURE 1. Histology of the human adult cervical squamocolumnar junction with squamous (ectocervix), cuboidal (junction), and columnar (endocervix) cells. SC indicates squamocolumnar.

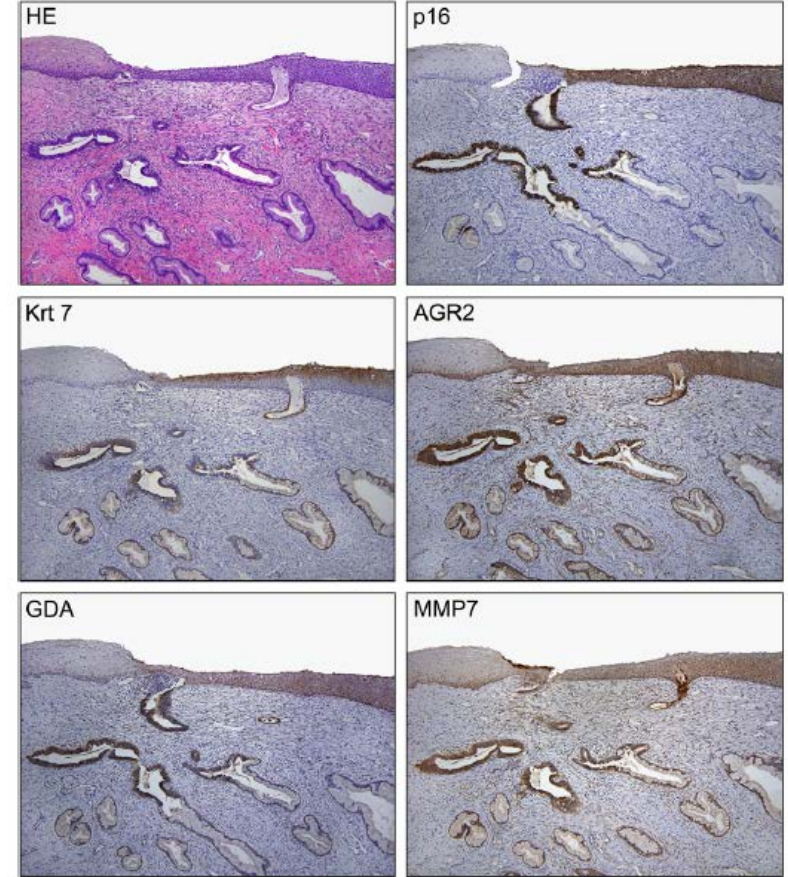


FIGURE 2. Immunostaining of HNSIL and adenocarcinoma in situ with p16ink4 and SC junction-specific antibodies. Note that both squamous and columnar HPV-related lesions are observed in the SC junction. AGR2 indicates anterior gradient 2; GDA, guanine deaminase; HE, hematoxylin-eosin; HPV, human papillomavirus; HNSIL, high-grade squamous intraepithelial lesion; Krt 7, keratin 7; MMP 7, matrix metalloproteinase 7; SC, squamocolumnar.

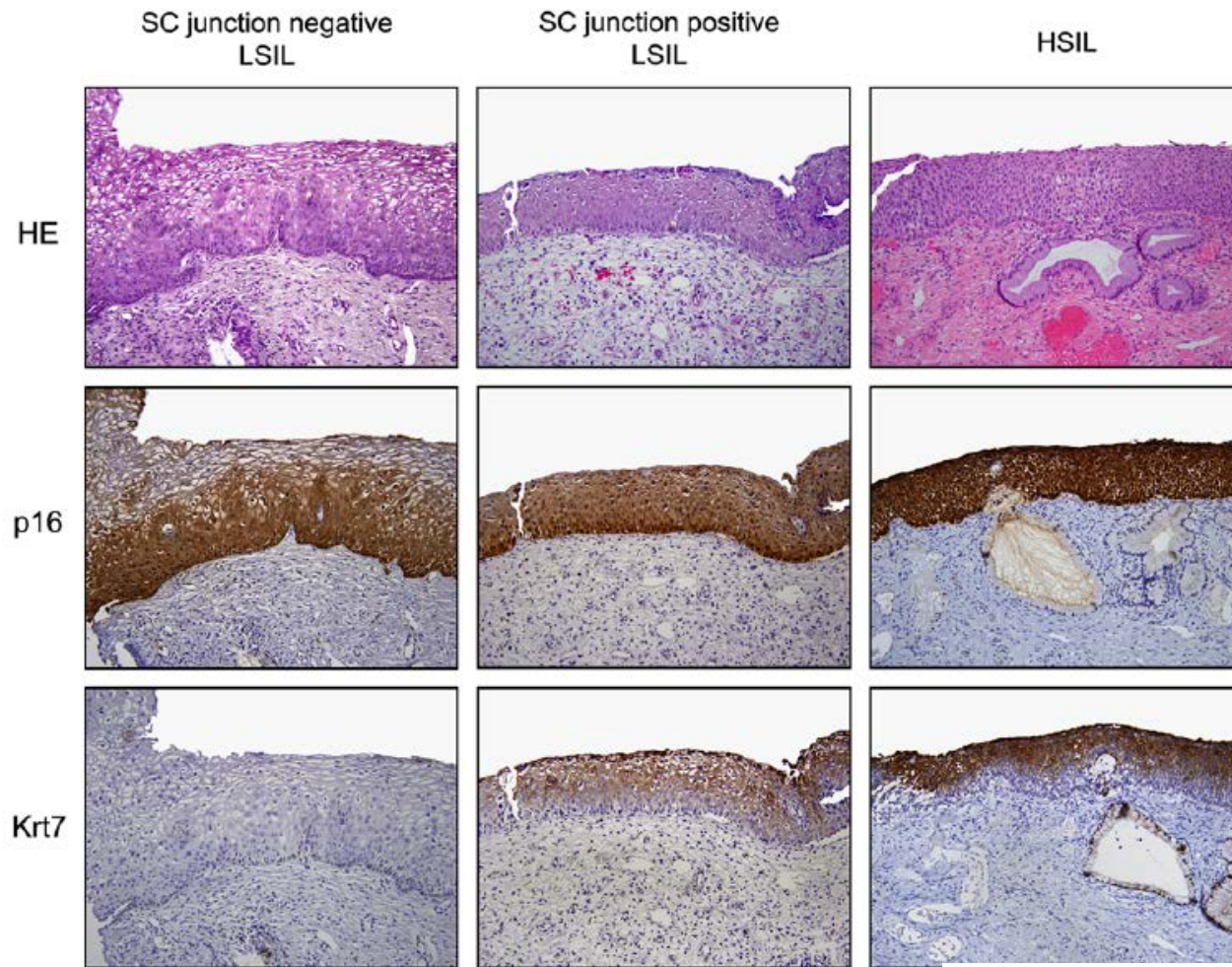


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Skuamokolumnar junction marker



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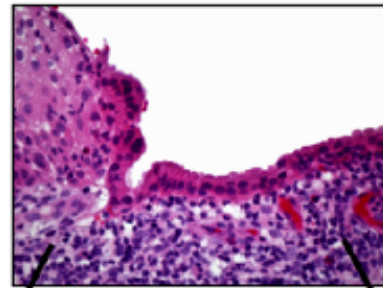


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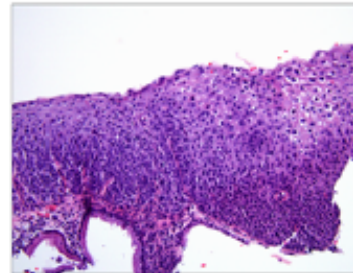
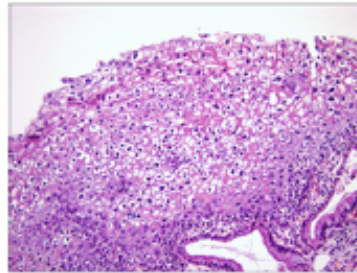
Skvamokolumnar junction marker



HPV Infection

Ectocervical/TZ LSIL

SC-Junction LSIL (QSIL)



SC-junction marker (-)
Full-thickness p16+ = 30%
High risk HPV infection = 50%
Diagnostic agreement = high
HSIL outcome = rare

SC-junction marker (+)
Full-thickness p16+ = 90%
High risk HPV infection = 95%
Diagnostic agreement = low
HSIL outcome = ~20%

Monitor less closely

Monitor more closely

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Laboratory Management of Cervical Intraepithelial Neoplasia: Proposing a New Paradigm

Michael Herfs, PhD† and Christopher P. Crum, MD**

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- LSIL
- HSIL
- QSIL (Questionable grade of squamous intraepithelial lesion)
 - “SIL of uncertain/questionable grade”
 - 6 ay takip ve değerlendirme



2003

WHO histological classification of tumours of the uterine cervix

2014

WHO Classification of tumours of the uterine cervix^{a,b}

Epithelial tumours	
Squamous tumours and precursors	
Squamous cell carcinoma, not otherwise specified	8070/3
Keratinizing	8071/3
Non-keratinizing	8072/3
Basaloid	8083/3
Verrucous	8051/3
Warty	8051/3
Papillary	8052/3
Lymphoepithelioma-like	8092/3
Squamotransitional	8120/3
Early invasive (microinvasive) squamous cell carcinoma	8076/3
Squamous intraepithelial neoplasia	
Cervical intraepithelial neoplasia (CIN) 3/	8077/2
squamous cell carcinoma in situ	8070/2
Benign squamous cell lesions	
Condyloma acuminatum	
Squamous papilloma	8052/0
Fibroepithelial polyp	
Glandular tumours and precursors	
Adenocarcinoma	
Mucinous adenocarcinoma	8140/3
Endocervical	8480/3

Epithelial tumours	
Squamous cell tumours and precursors	
Squamous intraepithelial lesions	
Low-grade squamous intraepithelial lesion	8077/0
High-grade squamous intraepithelial lesion	8077/2
Squamous cell carcinoma, NOS	
Keratinizing	8071/3
Non-keratinizing	8072/3
Papillary	8052/3
Basaloid	8083/3
Warty	8051/3
Verrucous	8051/3
Squamotransitional	8120/3
Lymphoepithelioma-like	8082/3
Benign squamous cell lesions	
Squamous metaplasia	
Condyloma acuminatum	
Squamous papilloma	8052/0
Transitional metaplasia	
Glandular tumours and precursors	
Adenocarcinoma in situ	8140/2
Adenocarcinoma	8140/3

Other epithelial tumours	
Adenosquamous carcinoma	
Glassy cell carcinoma	
Adenoid basal carcinoma	
Adenoid cystic carcinoma	
Undifferentiated carcinoma	
Neuroendocrine tumours	
Low-grade neuroendocrine tumour	
Carcinoid tumour	
Atypical carcinoid tumour	
High-grade neuroendocrine carcinoma	
Small cell neuroendocrine carcinoma	
Large cell neuroendocrine carcinoma	
Mesenchymal tumours and tumour-like lesions	
Benign	
Leiomyoma	
Rhabdomyoma	
Others	
Malignant	
Leiomyosarcoma	
Rhabdomyosarcoma	



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LAST Project Resources

- Links to articles
- Summary of recommendations
- FAQs
- Biomarker Algorithms
- LAST Project PowerPoint presentation
- www.cap.org
- www.asccp.org



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