



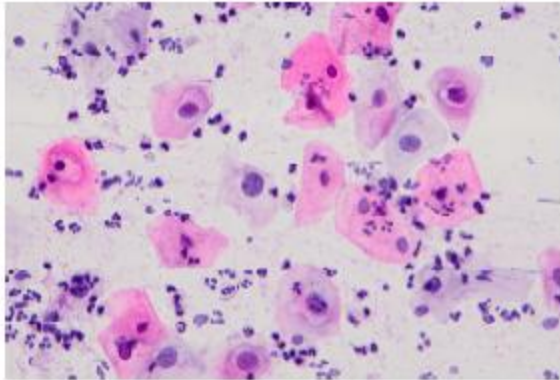
UNIVERZITET U NOVOM SADU
MEDICINSKI FAKULTET NOVI SAD



CENTAR ZA KONTINUIRANU
MEDICINSKU EDUKACIJU

EDUKATIVNI KURS

**CITOLOGIJA
CERVIKALNOG BRISA -
DILEME I PROBLEMI
U PRAKSI**



Kurs je akreditovan sa
12 bodova za predavače i
6 bodova za polaznike

21. jun 2025. godine

Amfiteatar bioskopske sale
Instituta u Sremskoj Kamenici
Put doktora Goldmana 4

Atipične pločaste ćelije - citolog neodređenog značenja



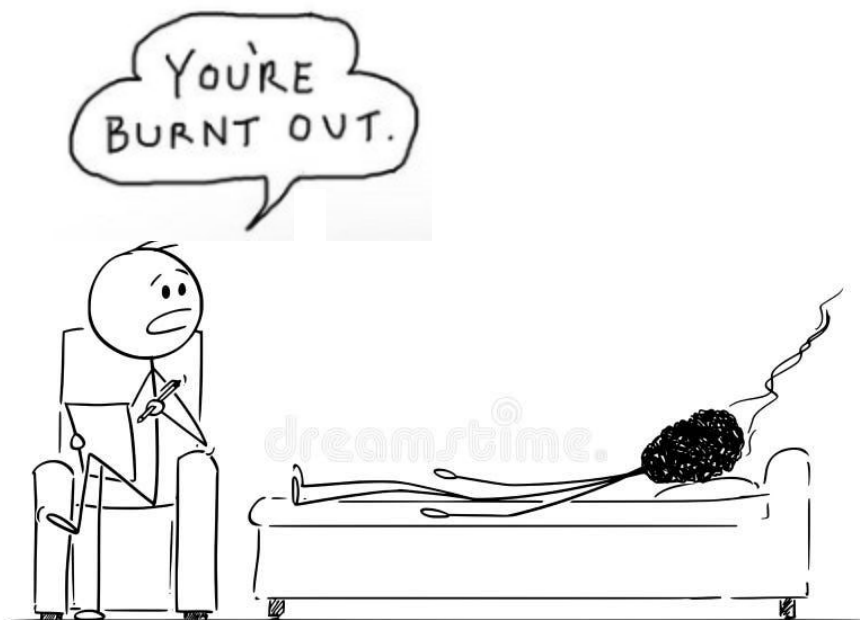
Dr sci. med Atila Fenjveši

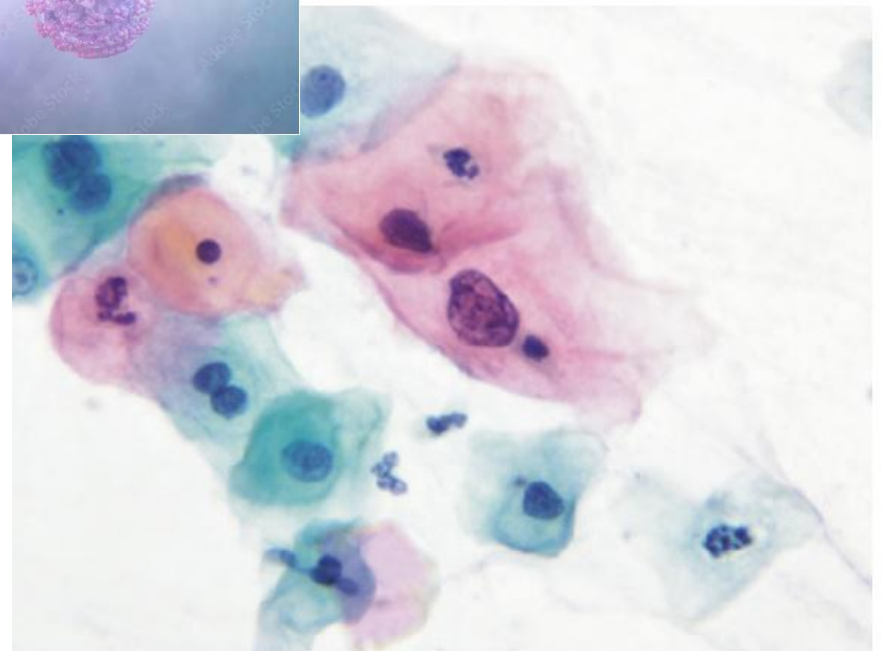
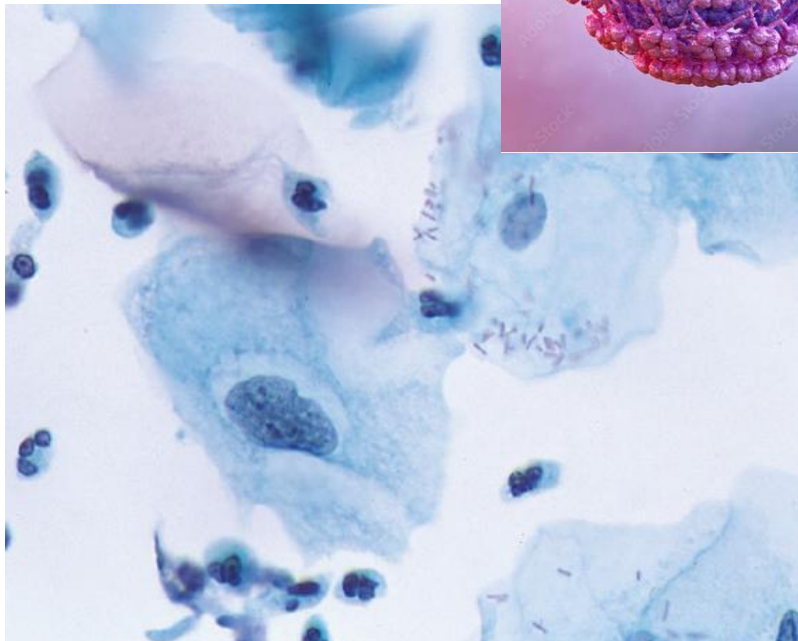
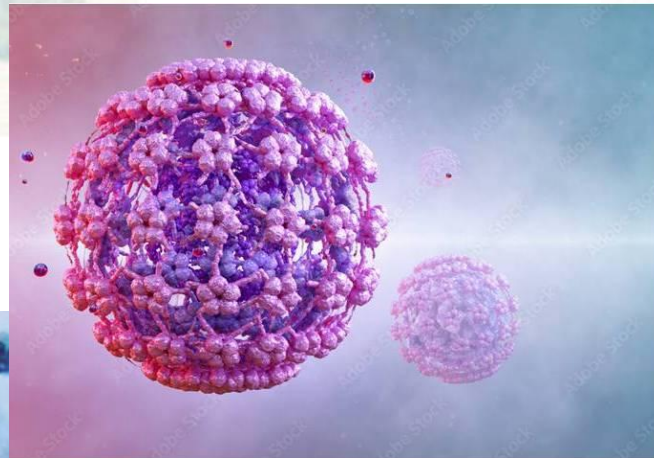
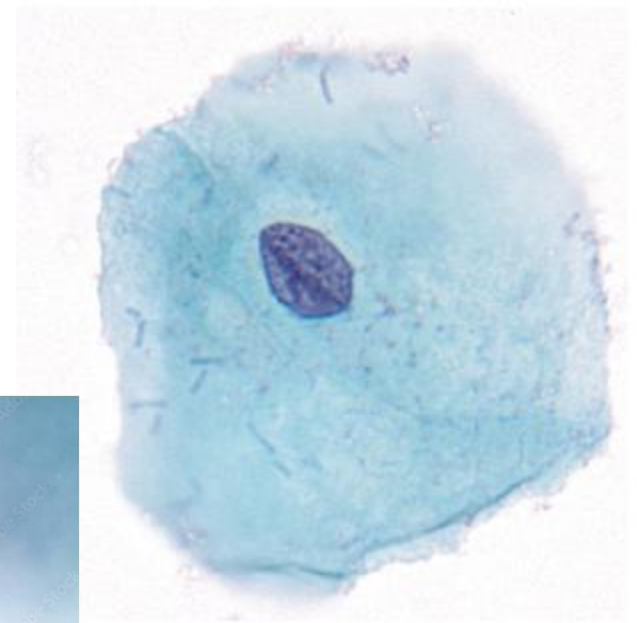
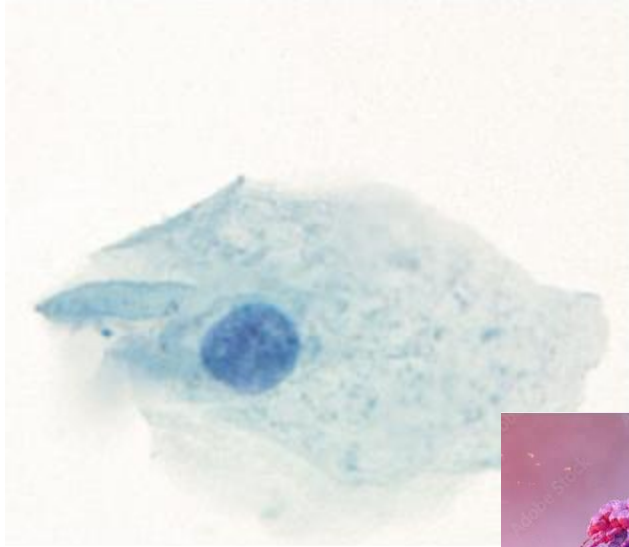


OPŠTA BOLNICA SENTA
ZENTAI KÖZKÓRHÁZ

ЗЗЈЗ КИКИНДА

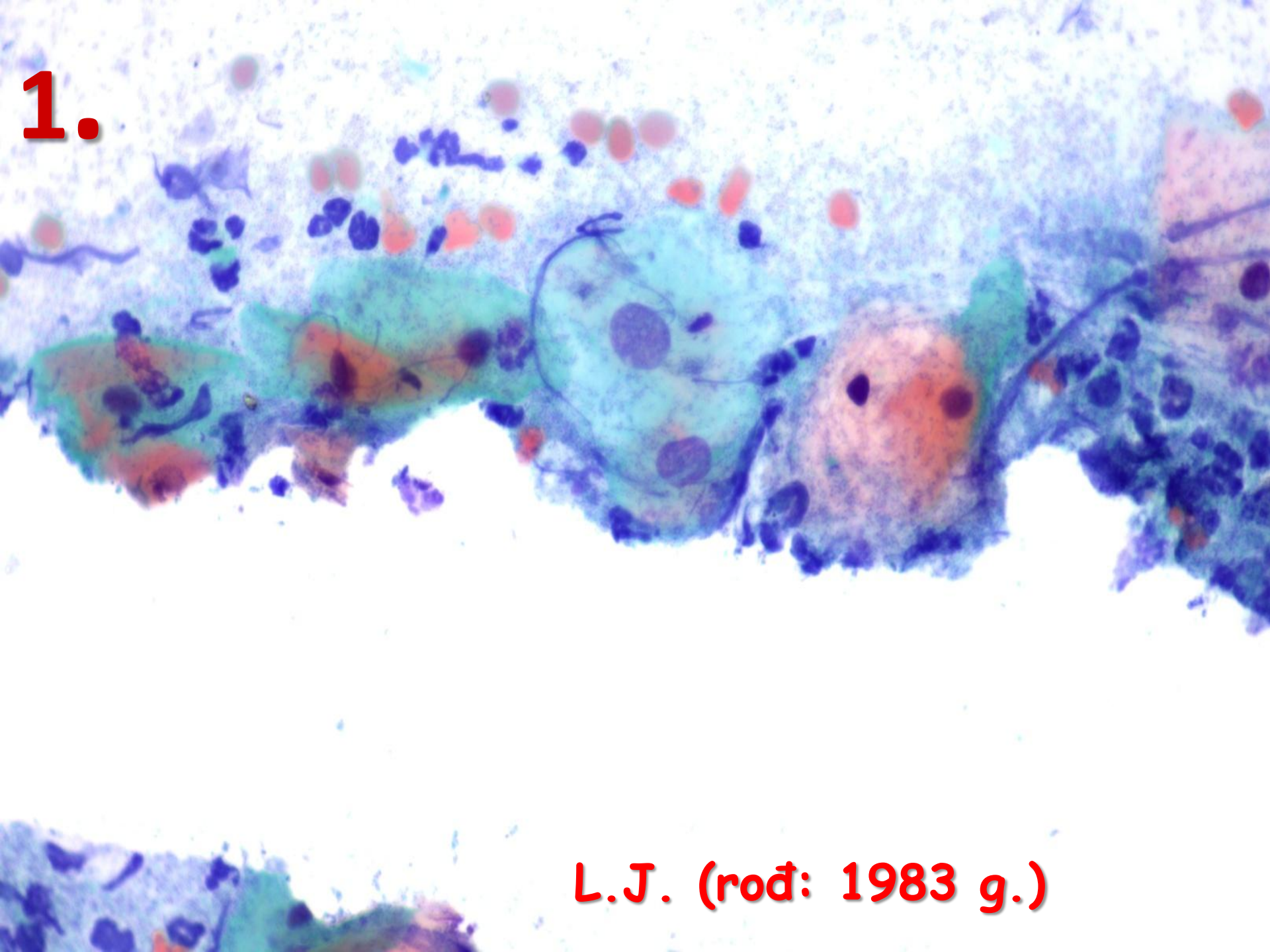
Завод за јавно здравље Кикинда





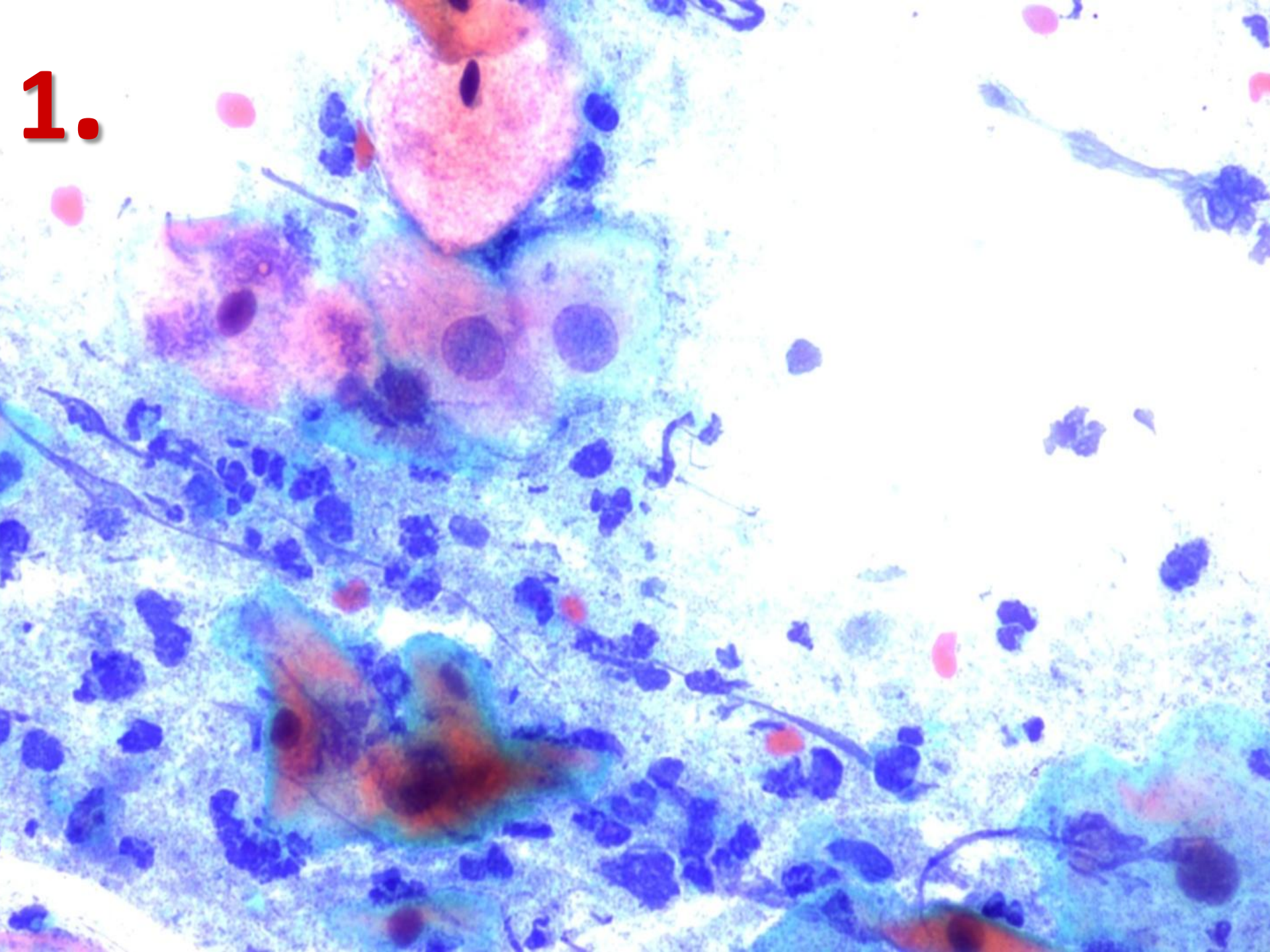


1.

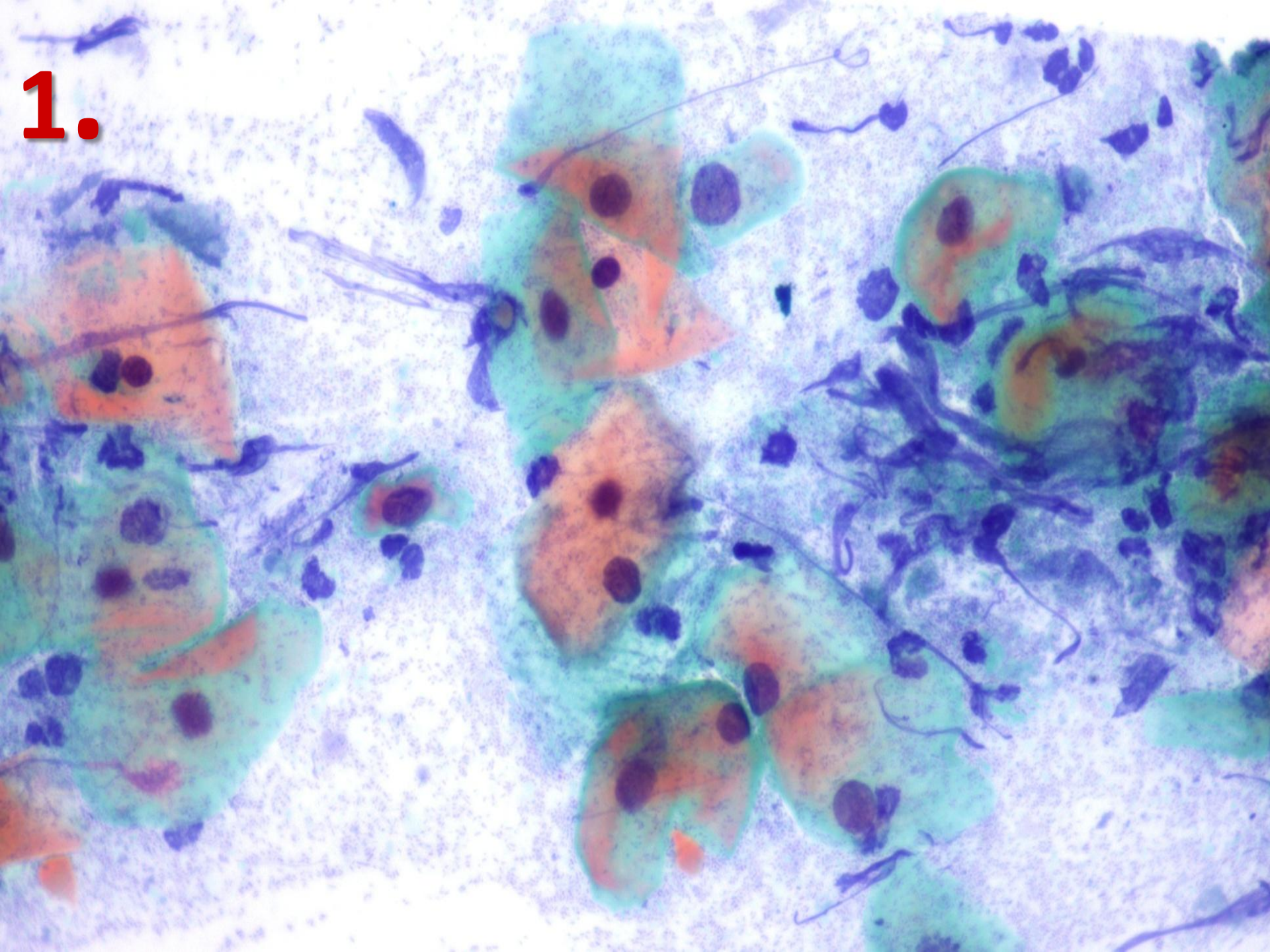


L.J. (rođ: 1983 g.)

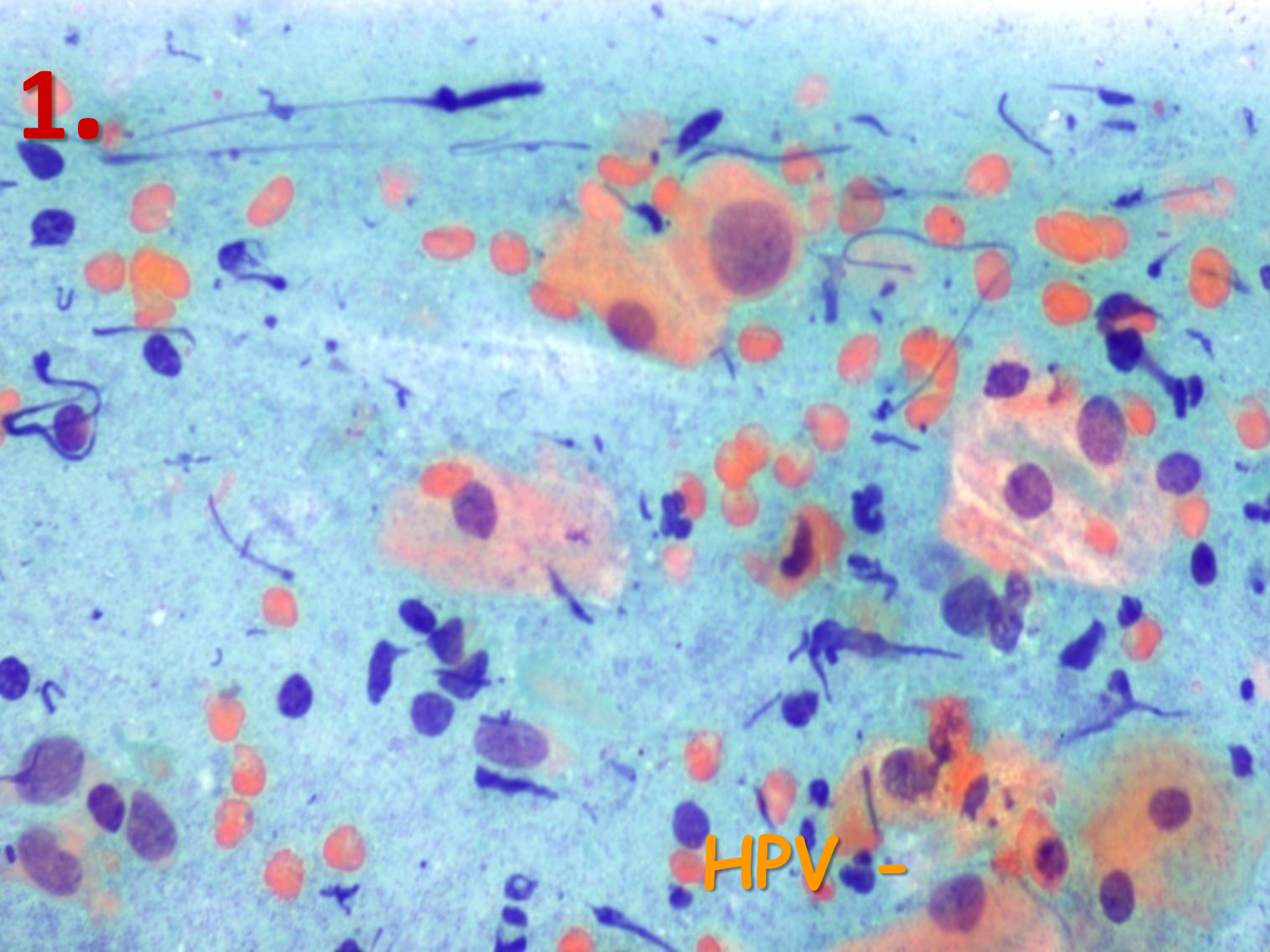
1.



1.



1.



HPV -

Category	BIRST-2	BIRST-1
Overall	62.8%	55.3%
NILM	73.7%	67.9%
LSIL	86.3%	54.1%
ASC-US	61.7%	39.9%
ASC-H	59.7%	22.4%
SCC	63.0%	~50%
HSIL	59.5%	~50%
Glandular abnormalities	33.2%	NR

Sherman ME, Dasgupta A, Schiffman M, Nayar R, Solomon D. The Bethesda Interobserver Reproducibility Study (BIRST): a web-based assessment of the Bethesda 2001 System for classifying cervical cytology. Cancer 2007;111:15-25.

Kurtycz DFI, Staats PN, Chute DJ, Russell D, Pavelec D, Monaco SE, Friedlander MA, Wilbur DC, Nayar R. Bethesda Interobserver Reproducibility Study-2 (BIRST-2): Bethesda System 2014. J Am Soc Cytopathol 2017;131-144.

ASC citološki nalaz ne sme prelaziti **5%** od ukupnih nalaza cervikalnih briseva opšte skriningirane populacije

Bethesda 2001 Workshop. Recommendations of the ASCUS Forum.
http://bethesda2001.cancer.gov/postwrkshp_recs.html

3% od ukupnih nalaza cervikalnih briseva (broj zavisi od lokalne rate LSIL i HSIL promena)

European guidelines for quality assurance in cervical cancer screening.

USA, 50.000.000 cervikalnog bris/god

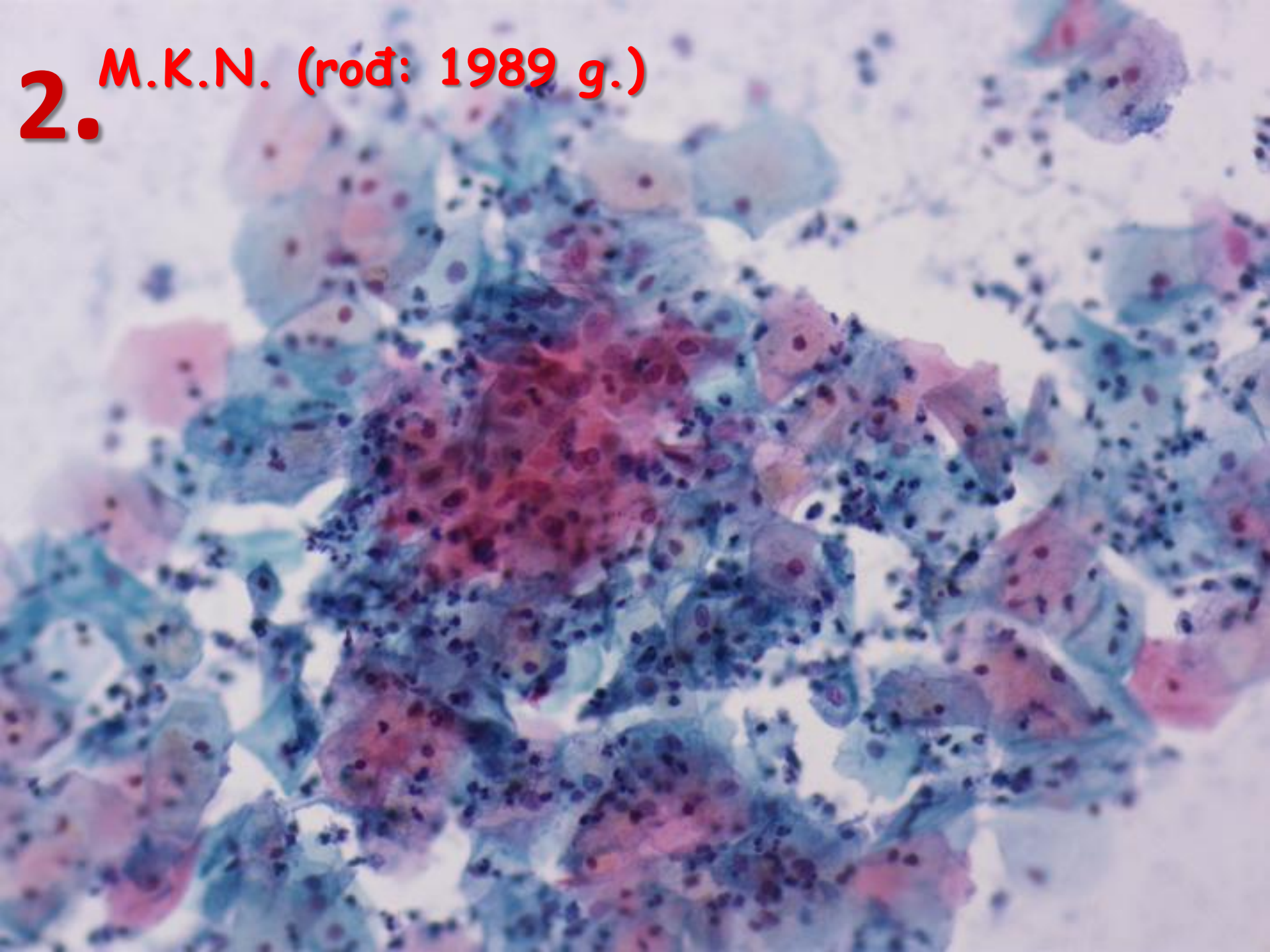
4-5% ASC-US

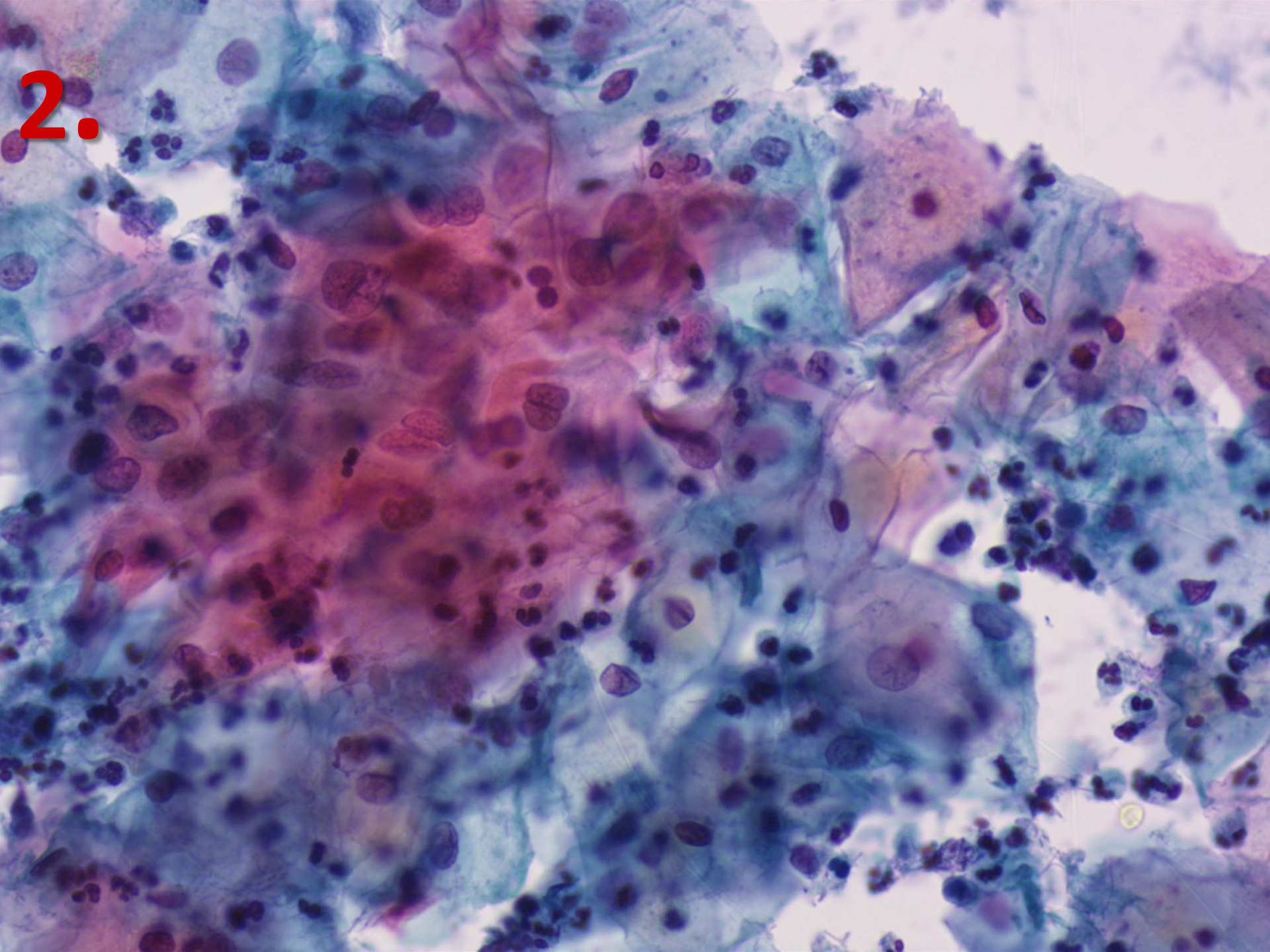
2.500.000/god

Bonfiglio TA. Atypical squamous cells of undetermined significance: a continuing controversy. Cancer 2002;96:125-7.

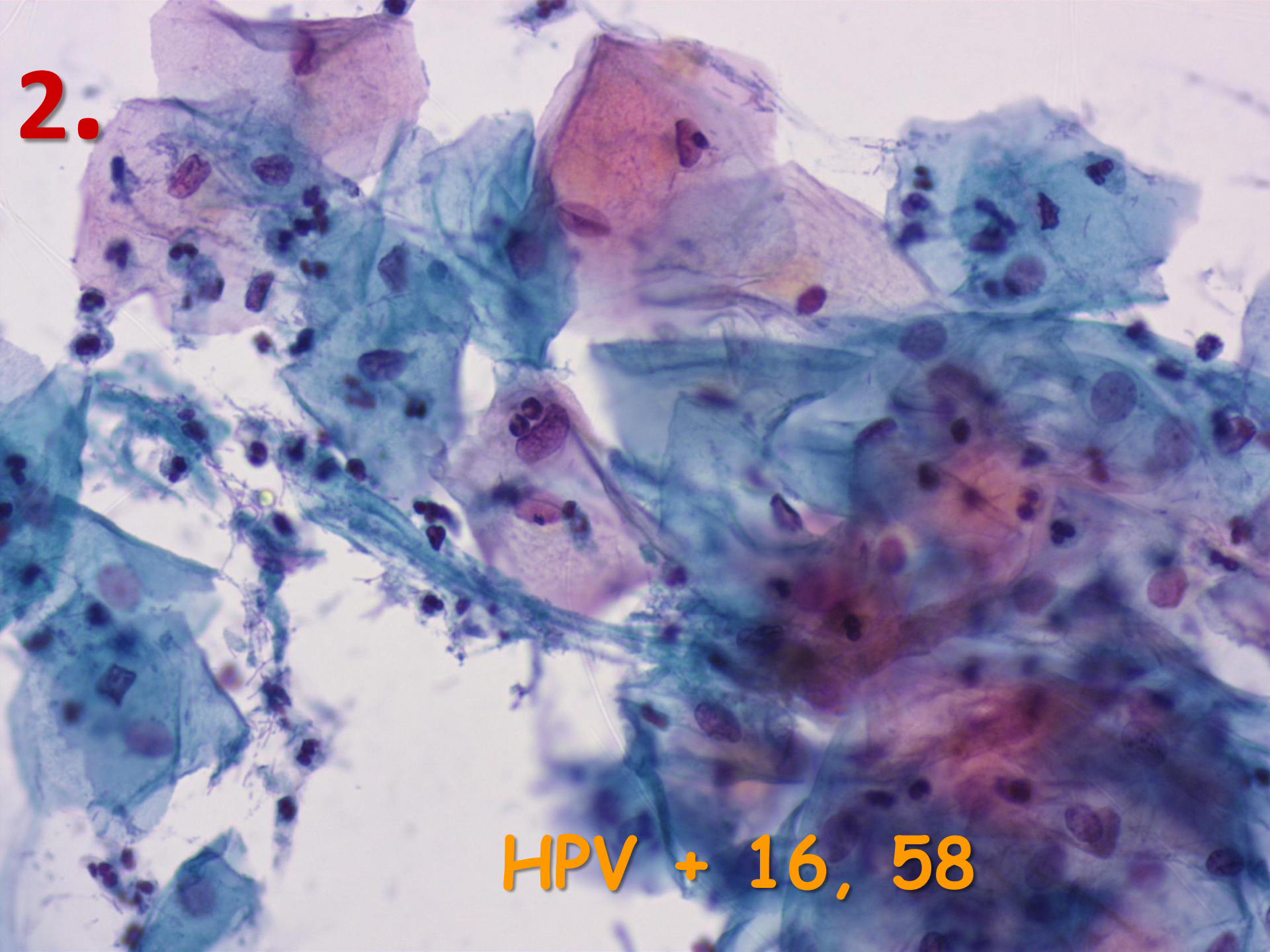
Procedure/test	Estimated cost, US
Office visit (screening)	\$55
Office visit (diagnostic)	\$65
Pap test	\$37
HPV test	\$49
Colposcopy	\$395
Biopsy (single)	\$65

2. M.K.N. (rođ: 1989 g.)





2.

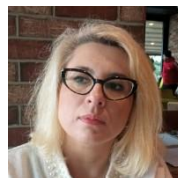


HPV + 16, 58

Analiza je rađena testom Sacace Biotechnologies na Sacace aparatu. To je in vitro test za amplifikaciju u stvarnom vremenu, za otkrivanje i genotipizaciju humanog papiloma virusa (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68)

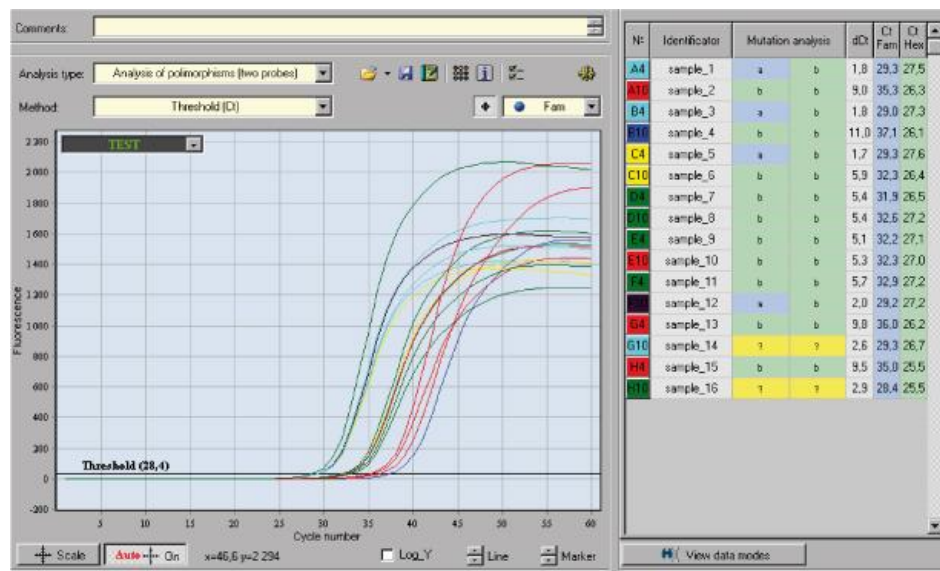


Завод за јавно здравље Кикинда



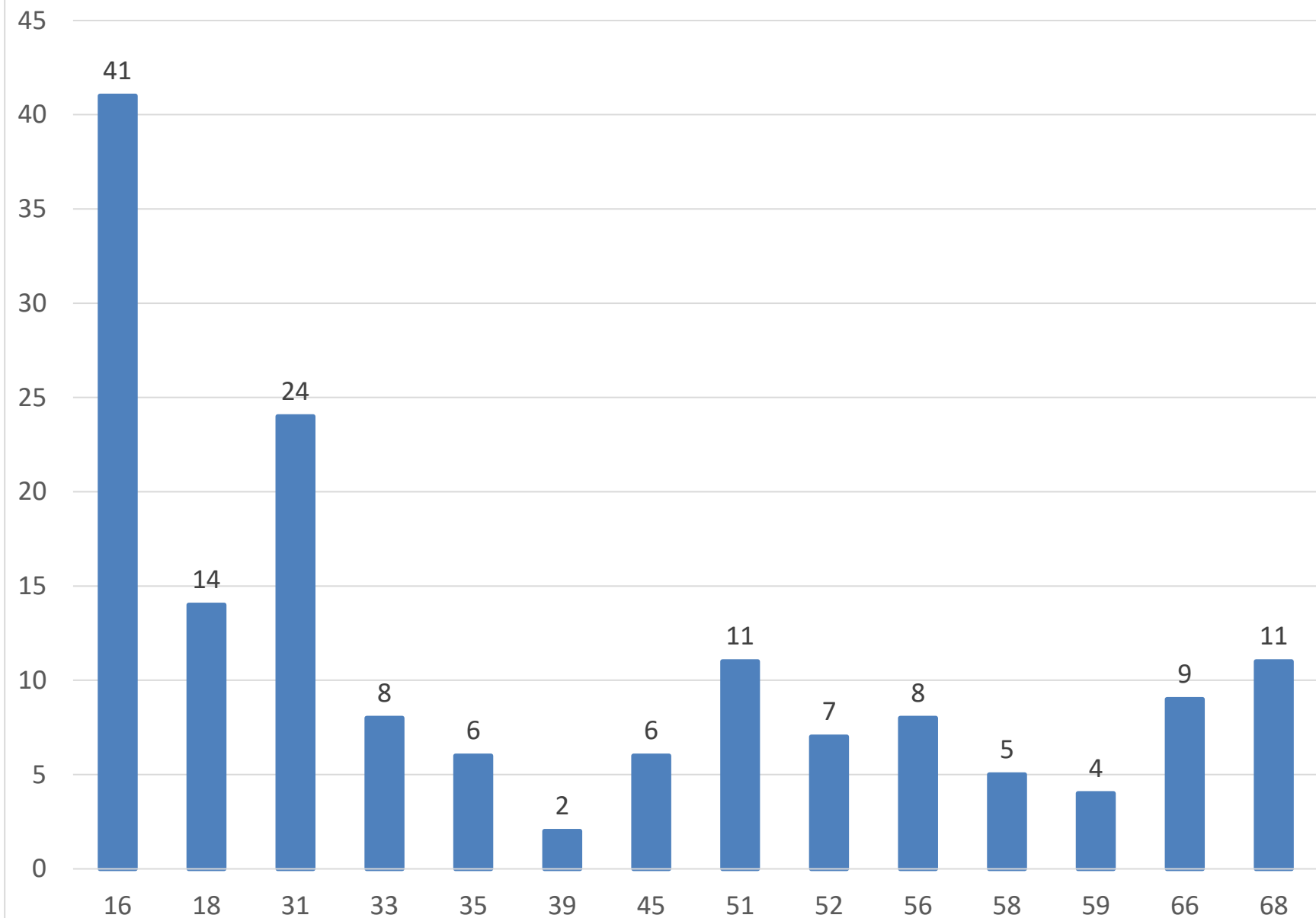
DR NATAŠA NEDELJKOV TEŠIN

CENTAR ZA MIKROBIOLOGIJU, ZZJZ KIKINDA



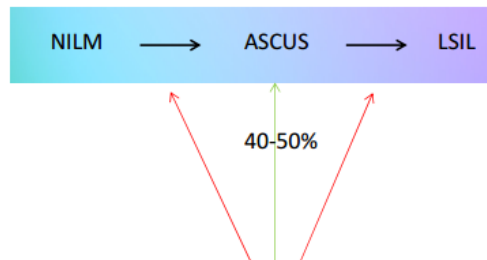
UČESTALOST DETEKCIJE GENOTIPA

Brojčana vrednost



Genotipovi

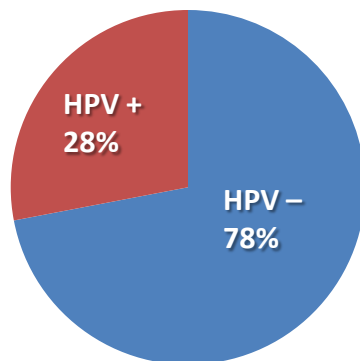
Kontrola kvaliteta rada citološke laboratorije

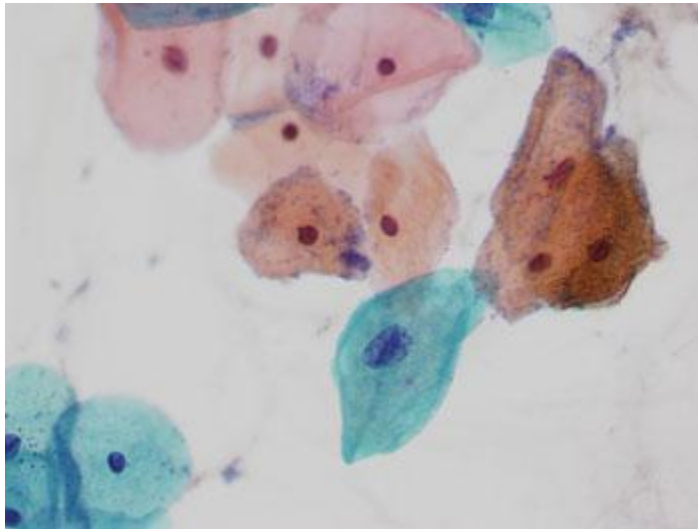


citološka-virusološka korelacije

Postotak od **30–35%** HPV pozitivnih ASC-US citoloških nalaza se smatra za prihvatljivim.

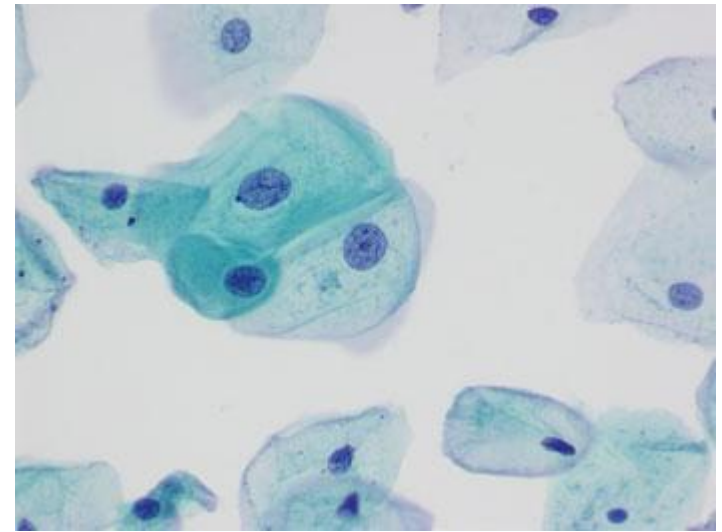
Thrall MJ. A Practical Approach to Squamous Abnormalities on Cervical Cytology: Overview of Interpretive Criteria and Guidance for Altering Thresholds in Response to Quality Assurance Findings. Acta Cytol. 2023;67(2):129-142. doi: 10.1159/000528531. Epub 2023 Jan 26. PMID: 36702101.



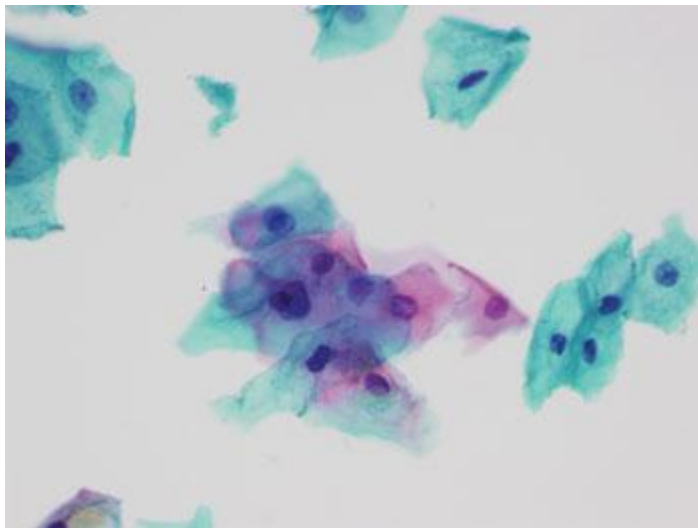


**HPV–
negativ
ASCUS**

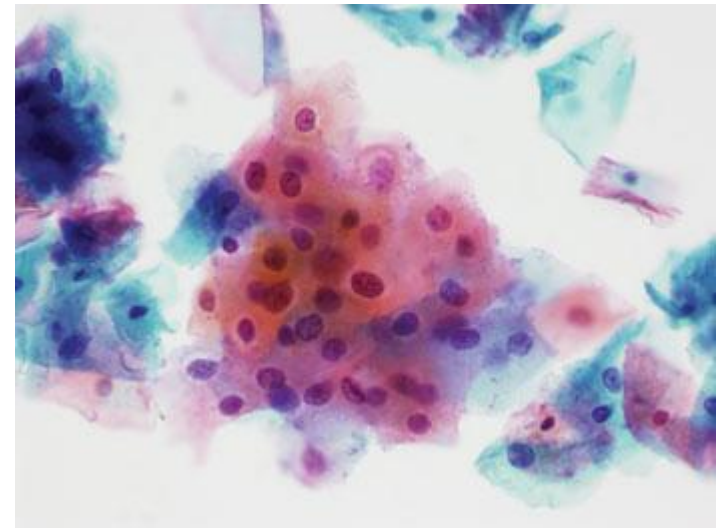
Some **nuclear enlargement** and **hyperchromasia** in an intermediate-type cell that also has cytoplasmic enlargement in HR-HPV DNA–negative ASCUS. Background of bacterial vaginosis (400).



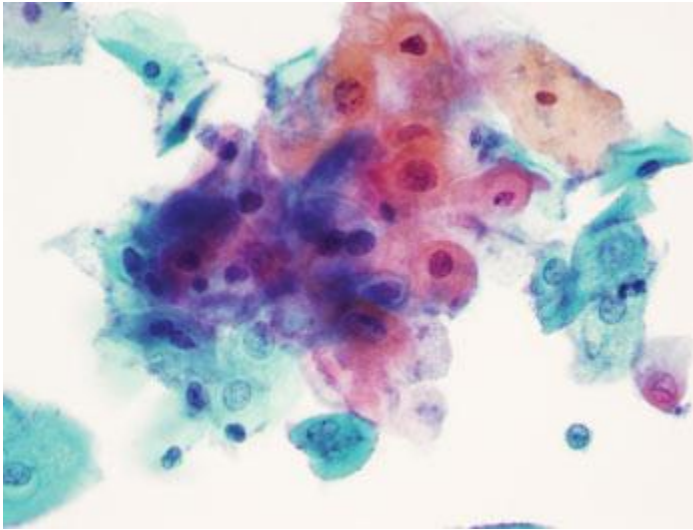
Nuclear and cytoplasmic enlargement in a large cell with increased cytoplasm. HR-HPV DNA–negative ASCUS (400).



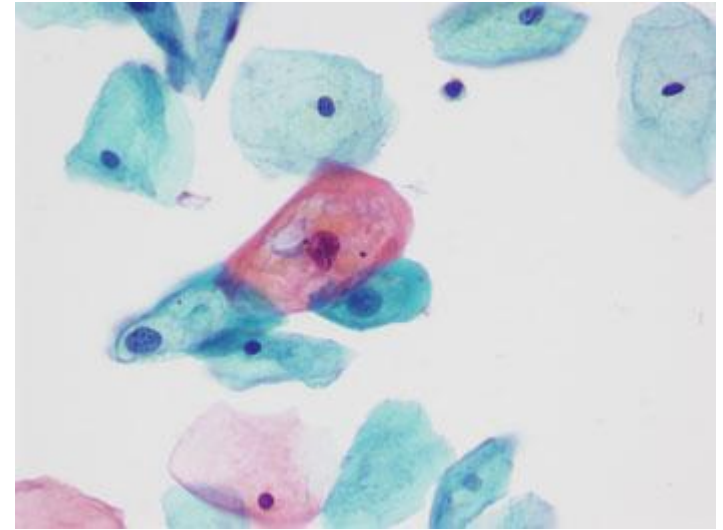
Nuclear and cytoplasmic enlargement in an HPV-negative ASCUS case (400).



Hyperchromasia, nuclear enlargement and small halos with some **parakeratosis** in HR-HPV DNA–negative ASCUS (400).



Koilocytelike changes in HR-HPV DNA–positive ASCUS
(ThinPrep, Papanicolaou stain, 400).

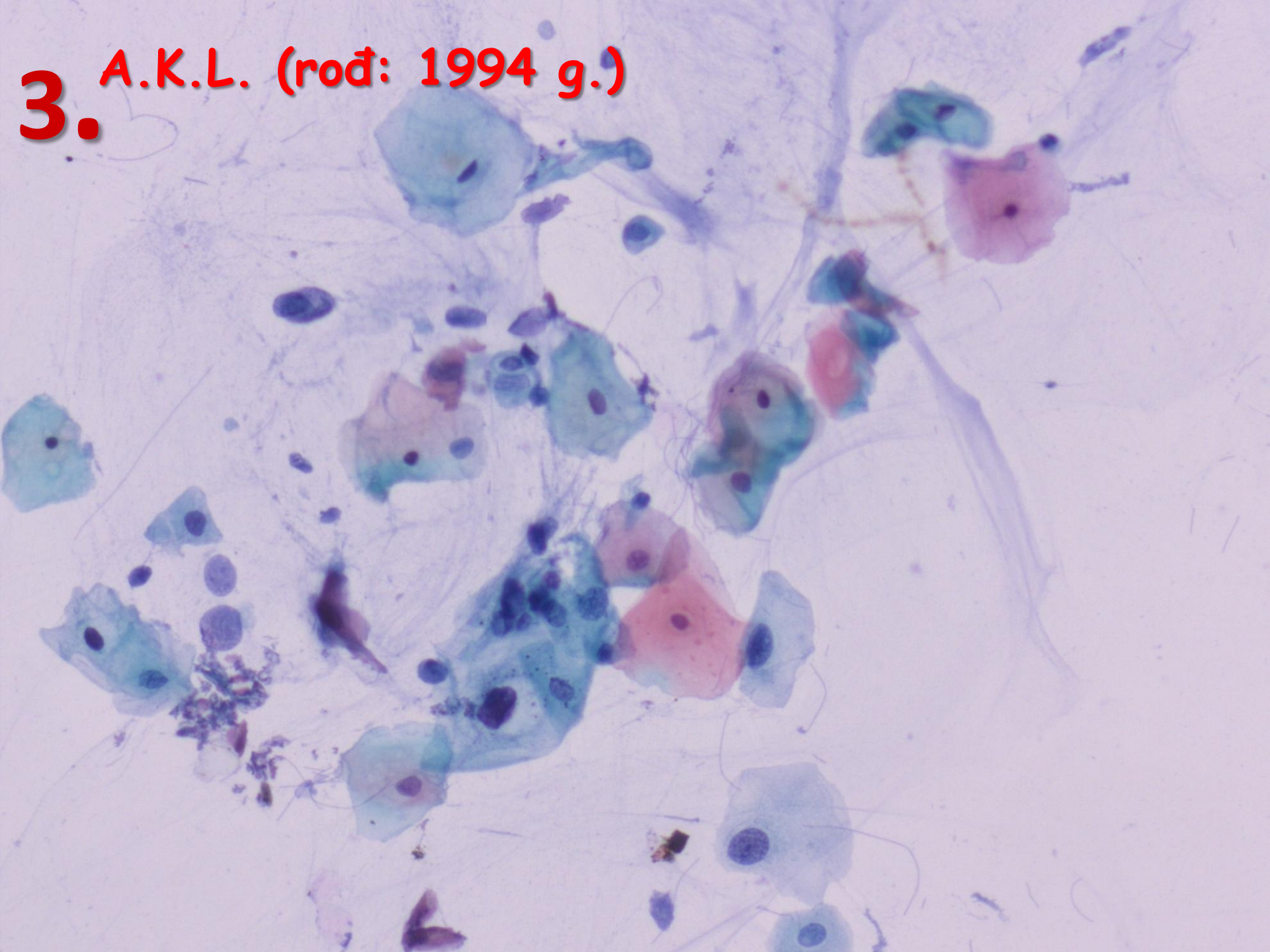


Koilocytelike changes in HR-HPV DNA–positive ASCUS
(ThinPrep, Papanicolaou stain, 400).

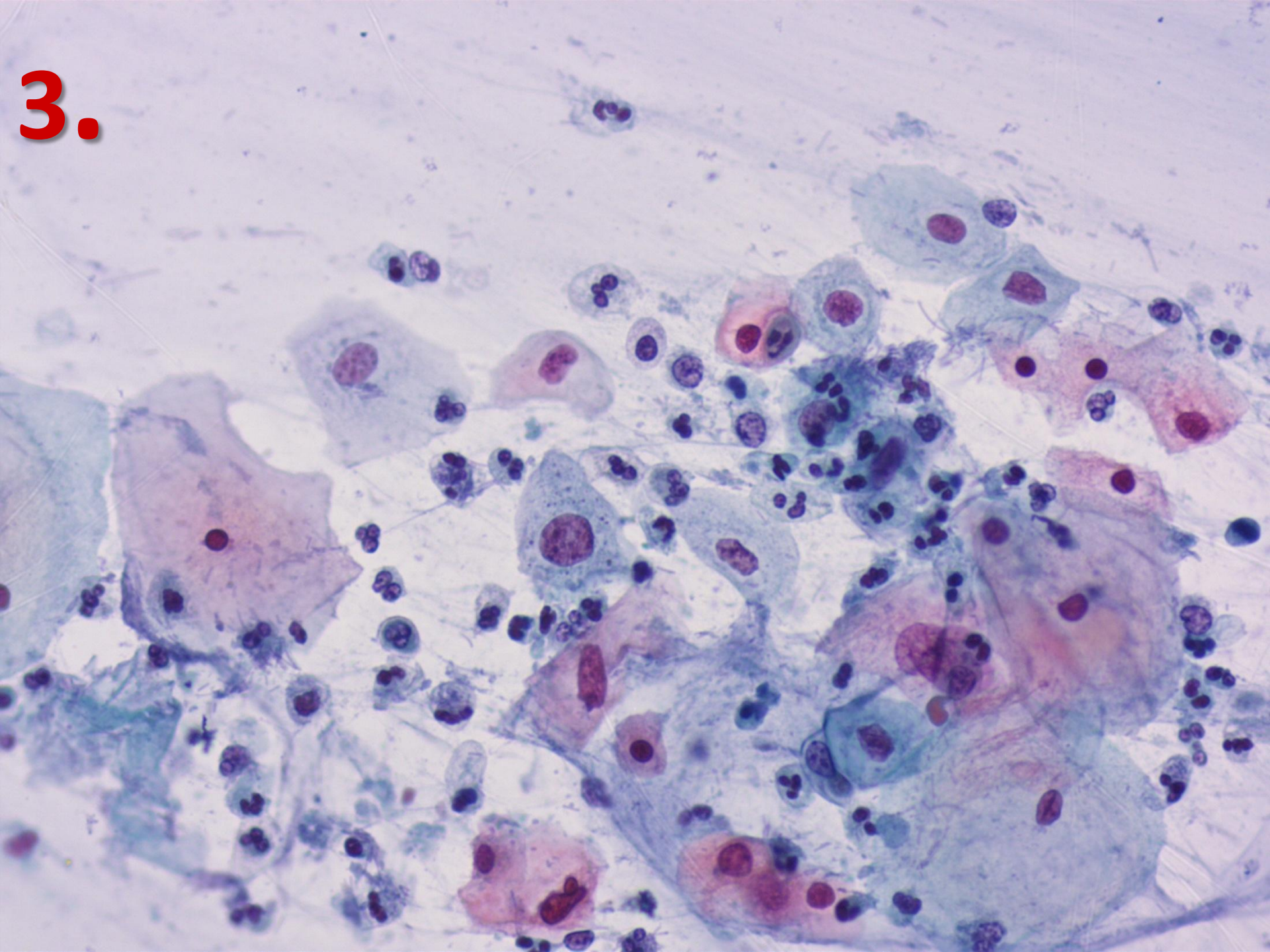
**HPV–
positiv
ASCUS**

Steinman S, Smith D, Chandler N, Dhurandhar B, Di Filippo L, Scheiber-Pact M, Mody D. Morphologic. Patient and Interpreter Profiles of High-Risk Human Papillomavirus–Positive vs. – Negative Cases of Atypical Squamous Cells of Undetermined Significance. Acta Cytol 2008;52:279–285

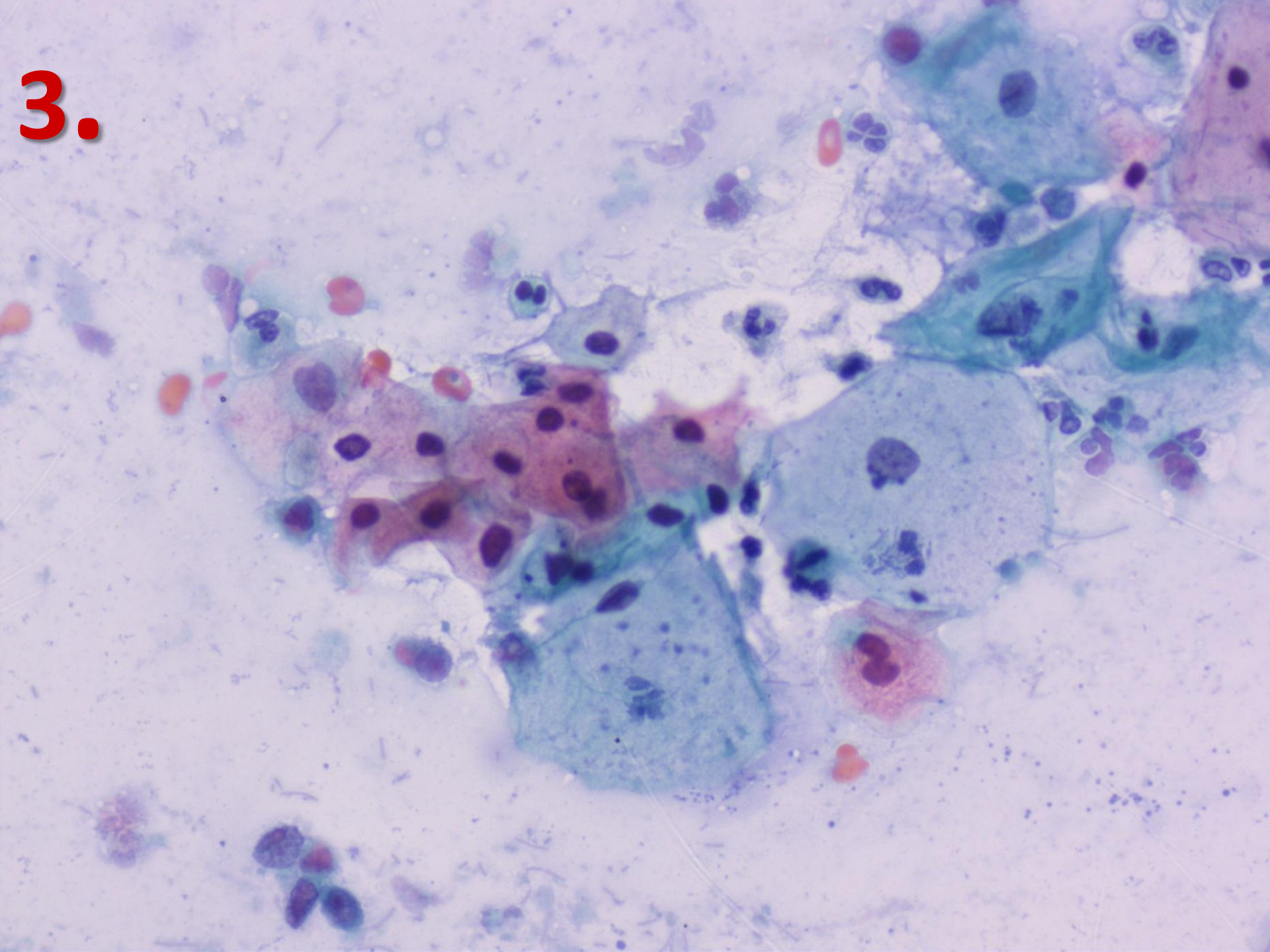
3. A.K.L. (roď: 1994 g.)



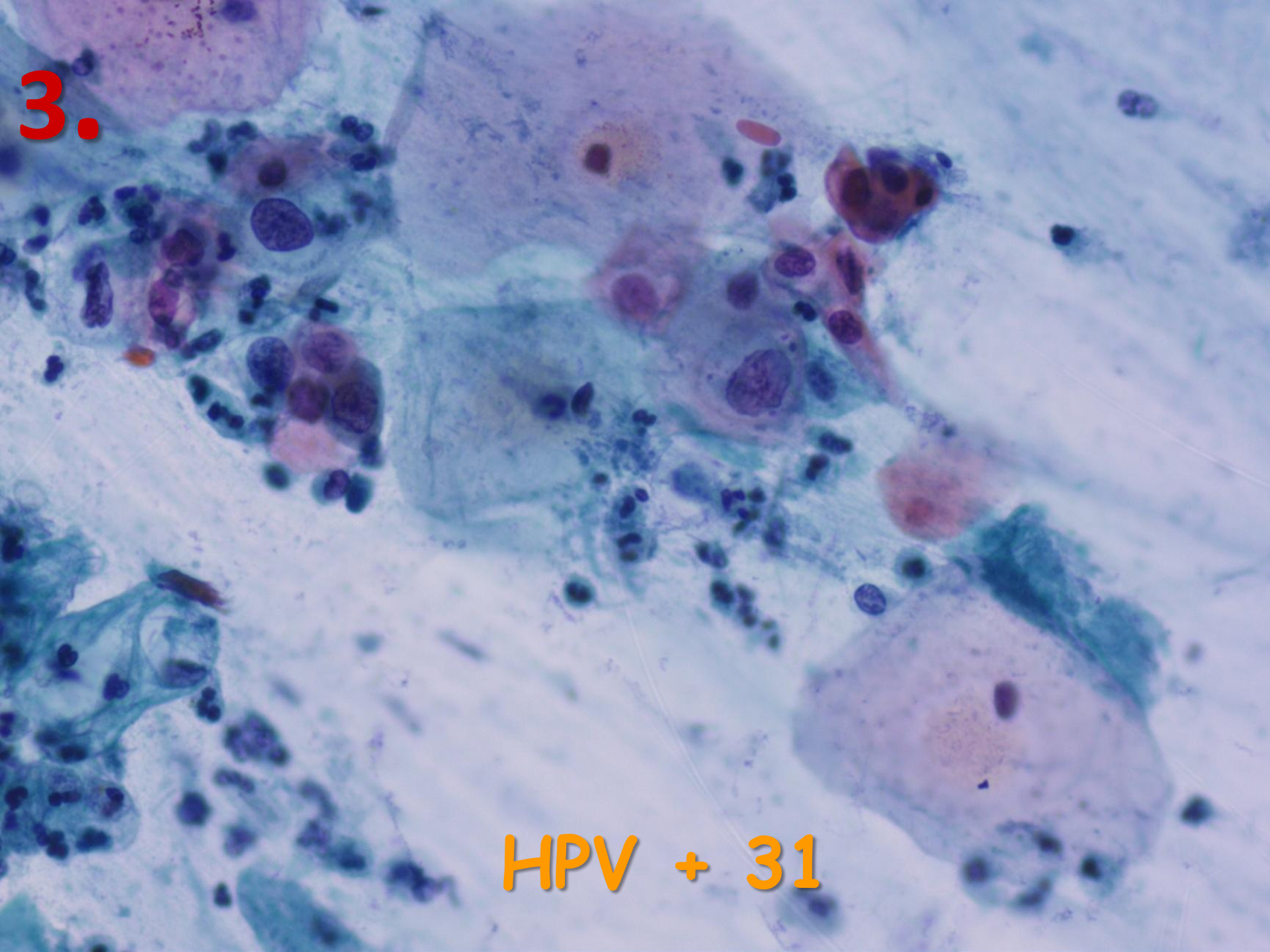
3.



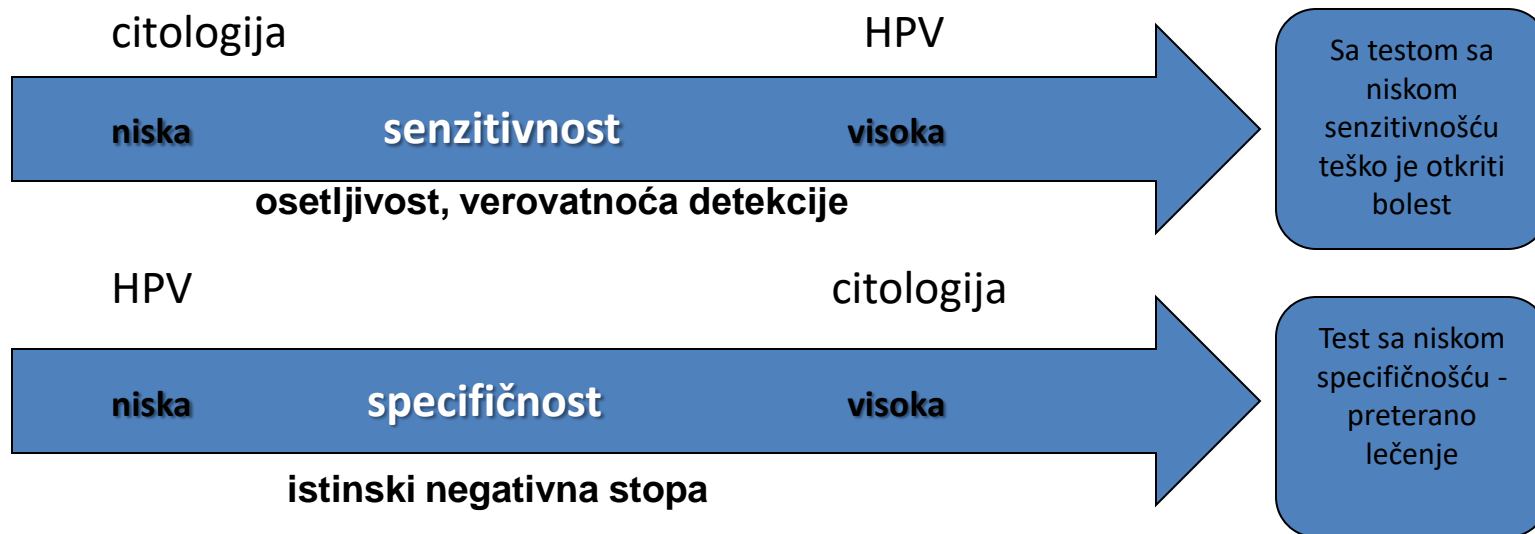
3.



3.



HPV + 31



30,606 ispitivanih **sensitivnost HPV 98.1%** (69%-100%)
specifičnost HPV 88.7% (79%-97%).

Ramírez AT, Valls J, Baena A, Rojas FD, Ramírez K, Álvarez R, et al.; on behalf of the ESTAMPA Study Group. Performance of cervical cytology and HPV testing for primary cervical cancer screening in Latin America: an analysis within the ESTAMPA study. Lancet Reg Health Am, Published online 20 September 2023; <https://doi.org/10.1016/j.lana.2023.100593>

Sensitivnost HPV 94.6%/ Pap testing was **55.4%**.

Specifičnost HPV 94.1%/Pap smears **96.8%**.

Mustafa RA, Santesso N, Khatib R, Mustafa AA, Wiercioch W, Kehar R, Gandhi S, Chen Y, Cheung A, Hopkins J, Ma B, Lloyd N, Wu D, Broutet N, Schünemann HJ. Systematic reviews and meta-analyses of the accuracy of HPV tests, visual inspection with acetic acid, cytology, and colposcopy. Int J Gynaecol Obstet 2016;132:259-65.

Lažno pozitivan Hpv test

specifičnost testa (88%-94%)

(visoko specifični testovi daju mali broj lažno pozitivnih rezultata)

- testiranje na poznate ne-kancerogene tipove HPV-a
- upotreba ultrasensitivnih testova
- uključivane marginalno kancerogenih tipova HPV-a
- unakrsna reaktivnost marginalno kancerogenih tipova

Schiffman M, de Sanjose S. False positive cervical HPV screening test results. Papillomavirus Res 2019;7:184-187.

Lažno negativan Hpv test

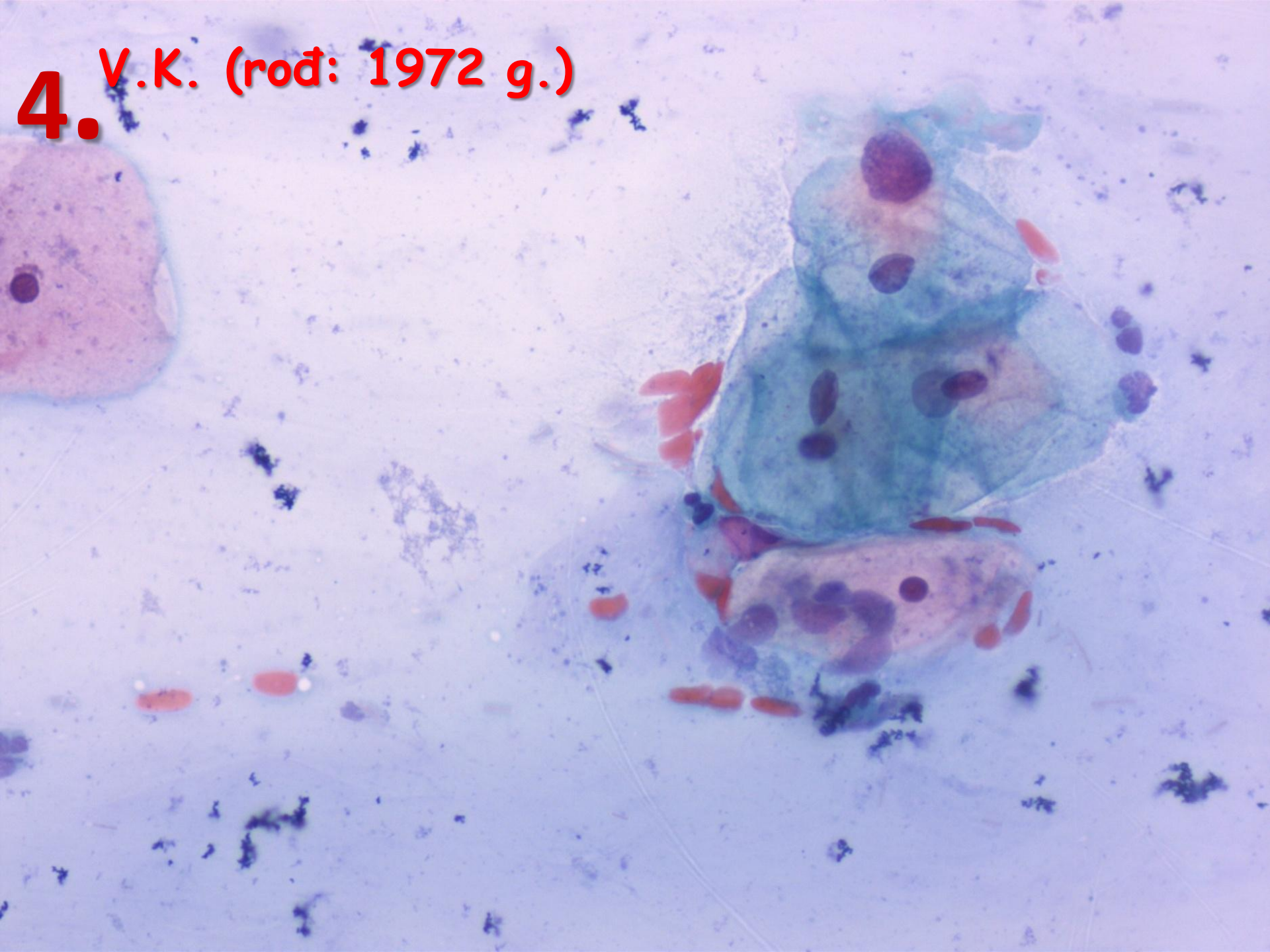
senzitivnost testa (94%-98%)

(testovi sa visokom senzitivnošću daju mali broj lažno negativnih rezultata)

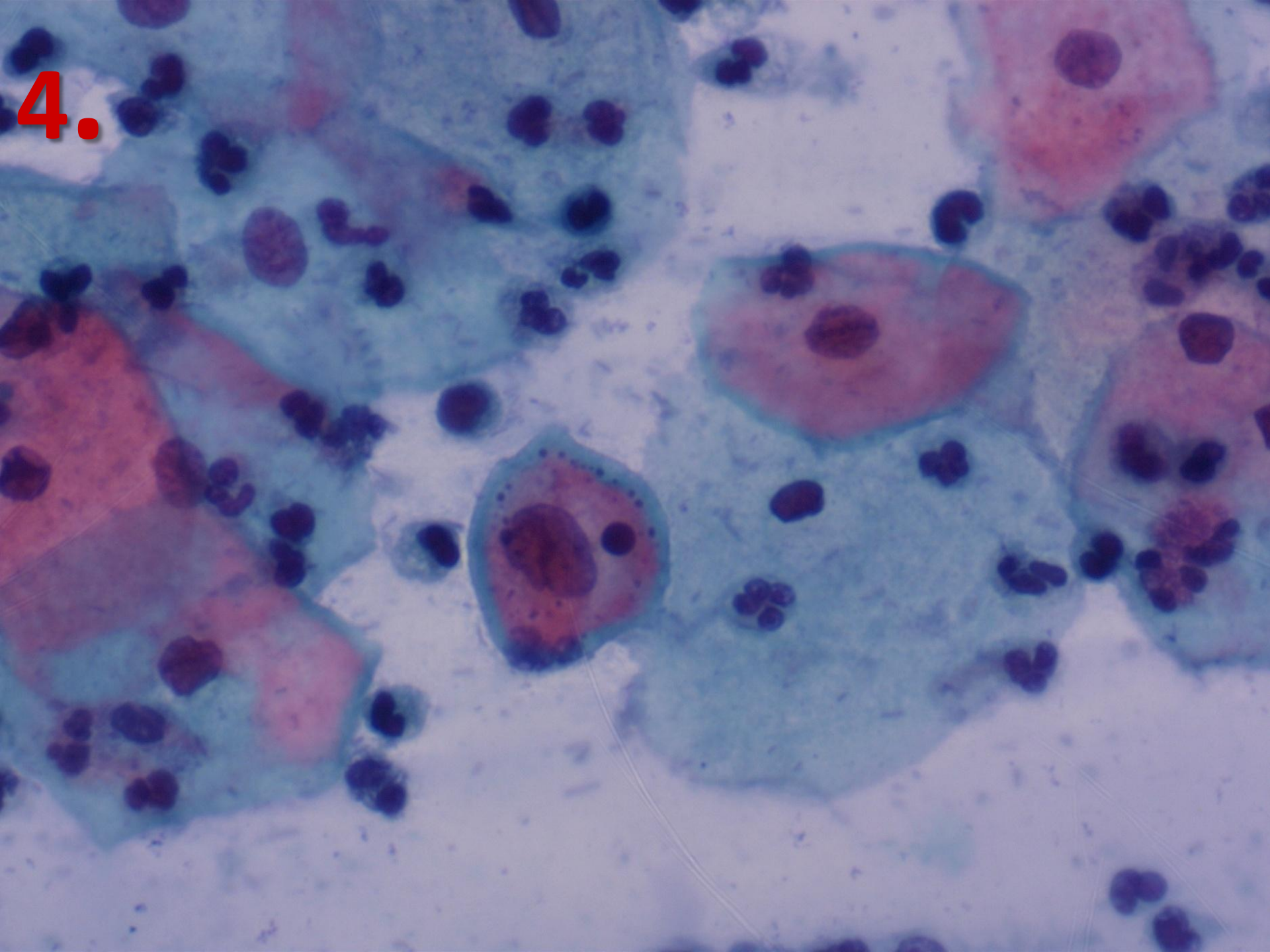
- latentna (dormant) HPV infekcija
- mogućnost nastanka promena izazvanih HPV infekcijom sa ne visokoonkogenim tipovima HPV-a
- nepravilno uzorkovanje (gubitak ciljnog fragmenta DNK) (nekroza, krv, zapaljenje)
- neodgovarajuće laboratorijske procedure
- loše obučeno osoblje

Zazove P, Reed BD, Gregoire L, Ferenczy A, Gorenflo DW, Lancaster WD. Low false-negative rate of PCR analysis for detecting human papillomavirus-related cervical lesions. J Clin Microbiol 1998;36:2708-13.

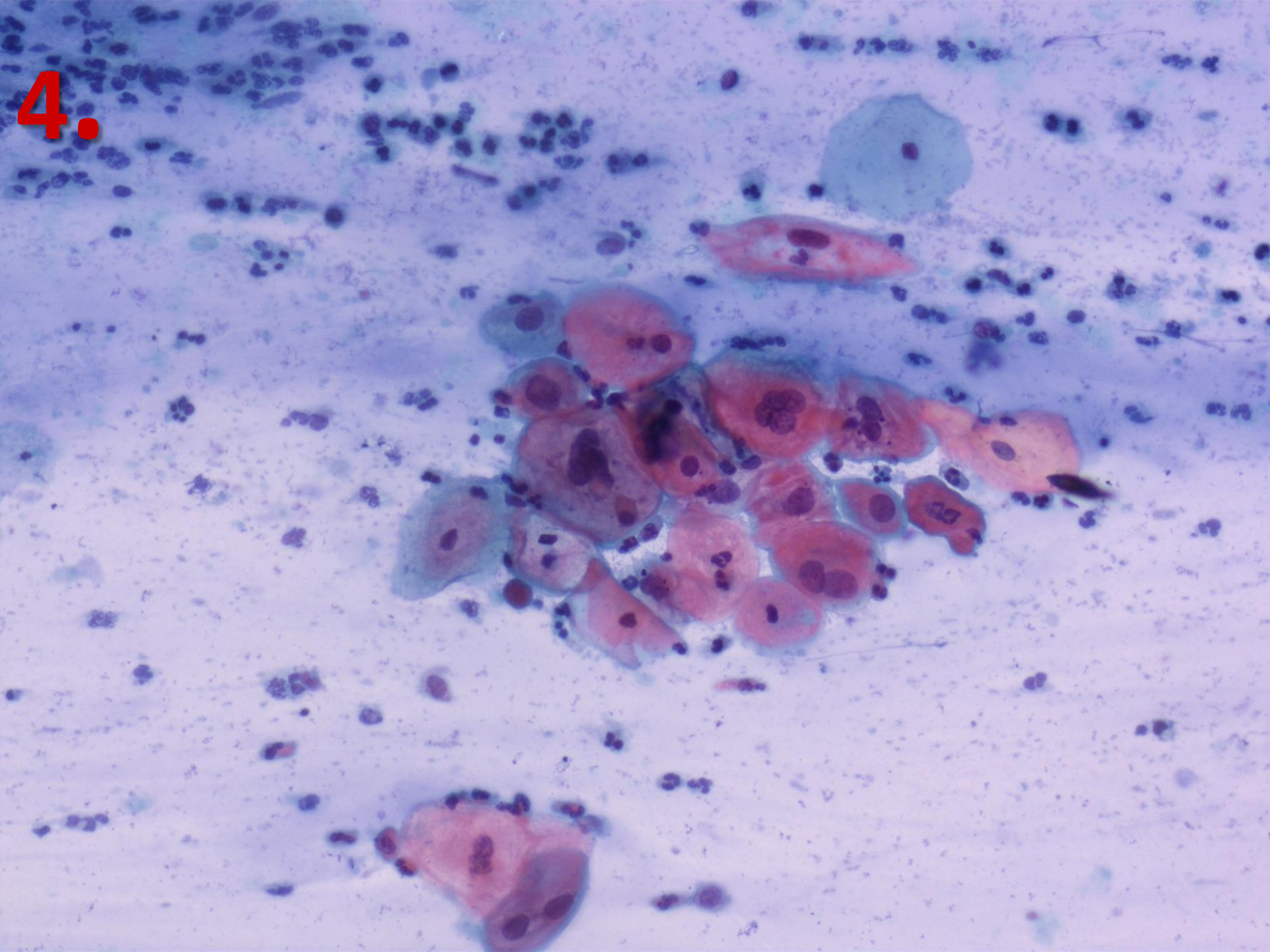
4. V.K. (rođ: 1972 g.)



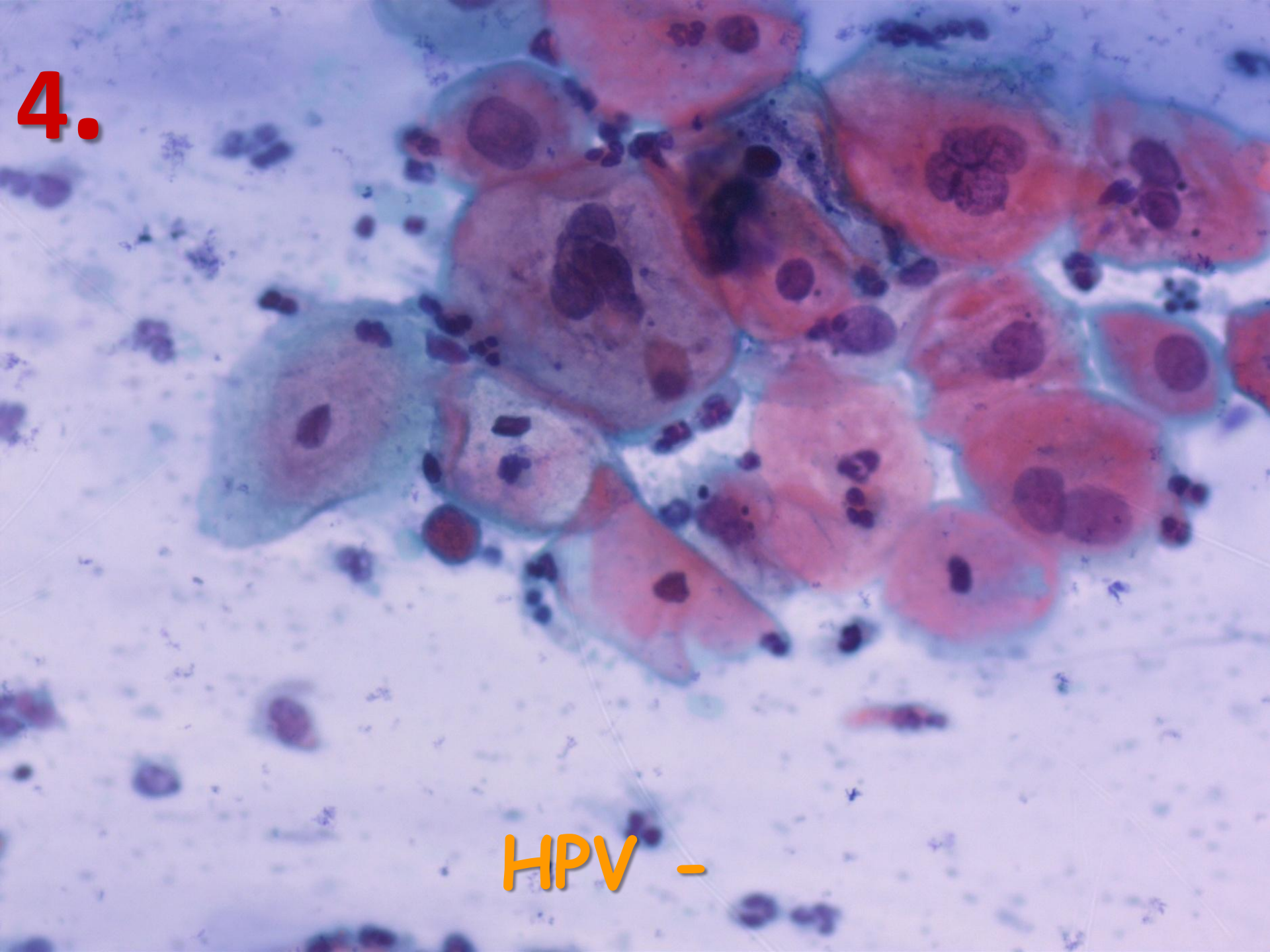
4.



4.



4.



HPV -

HPV pozitivnost

1990–1999 - 85.9%

2000–2005 - 87.9%,

2006–2010 - 92.9%

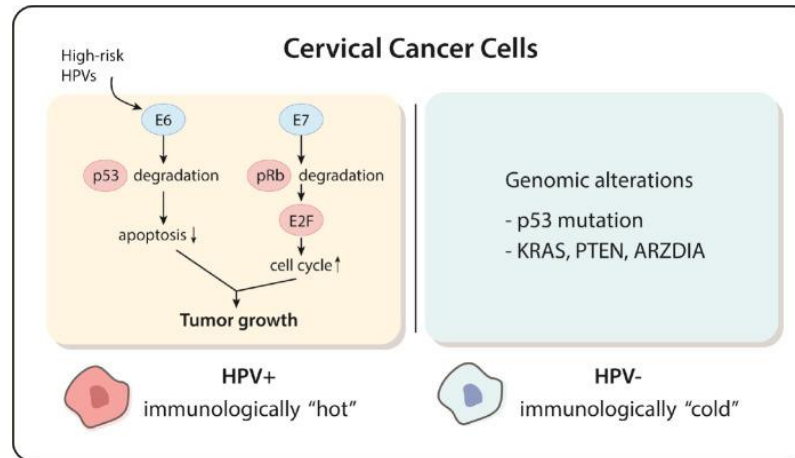
Korišćenjem najmodernije metode sekvenciranja sledeće generacije (next-generation sequencing) oko 5% primarnih karcinoma cerviksa je HPV negativno.

Xing B, Guo J, Sheng Y, Wu G, Zhao Y. Human Papillomavirus-Negative Cervical Cancer: A Comprehensive Review. Front Oncol. 2021 Feb 17;10:606335. doi: 10.3389/fonc.2020.606335. PMID: 33680928; PMCID: PMC7925842.

U literaturi se navodi oko **3-8%** slučajeva HPV negativnih cervikalnih neoplazmi.

Lee JE, Chung Y, Rhee S, Kim TH. Untold story of human cervical cancers: HPV-negative cervical cancer. BMB Rep 2022;55:429-438.

Molekularna etiologija HPV negativnog cervikalnog kancera je nejasna ali se smatra da je mutacija p53, KRAS i PIK3CA-PTEN gena uključena u patogenezu.



Liebrich C, Brummer O, Von Wasielewski R, Wegener G, Meijer C, Iftner T, Petry KU. Primary cervical cancer truly negative for high-risk human papillomavirus is a rare but distinct entity that can affect virgins and young adolescents. Eur J Gynaecol Oncol 2009;30:45-8.

Xing B, Guo J, Sheng Y, Wu G, Zhao Y. Human Papillomavirus-Negative Cervical Cancer: A Comprehensive Review. Front Oncol. 2021 Feb 17;10:606335. doi: 10.3389/fonc.2020.606335. PMID: 33680928; PMCID: PMC7925842.

Lee JE, Chung Y, Rhee S, Kim TH. Untold story of human cervical cancers: HPV-negative cervical cancer. BMB Rep 2022;55:429-438.

Ovi tumori se obično dijagnostikuju u uznapredovanijem stadijumu bolesti sa većim postotkom limfonodalnih metastaza.

Nicolás I, Marimon L, Barnadas E, Saco A, Rodríguez-Carunchio L, Fusté P, Martí C, Rodríguez-Trujillo A, Torne A, Del Pino M, Ordi J. HPV-negative tumors of the uterine cervix. Mod Pathol. 2019 Jul;32(8):1189-1196.

Udruženi sa lošijom prognozom kako u pogledu ukupnog preživljavanja (overall survival) i preživljavanje bez znakova bolesti (disease-free survival).

Lee JE, Chung Y, Rhee S, Kim TH. Untold story of human cervical cancers: HPV-negative cervical cancer. BMB Rep 2022;55:429-438.

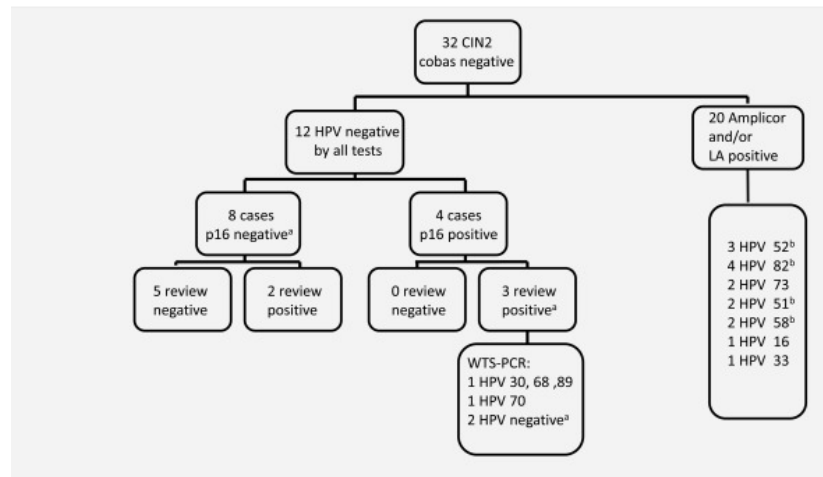
Takođe se objavljena studija sa oko 15% teškostepene displazije bez prisustva HPV na osnovu retrospektivne mult institucionalne studije italijanskih autora na osnovu analize 1738 konizata (1478 (85%) HR-HPV-positive i 260 (15%) HR-HPV-negative high-grade cervical dysplasia).

Bogani G, Supracordevole F, Di Donato V, Ciavattini A, Ghelardi A, Lopez S et al. High-risk HPV-positive and -negative high-grade cervical dysplasia: Analysis of 5-year outcomes. Gynecol Oncol 2021;161:173-178.

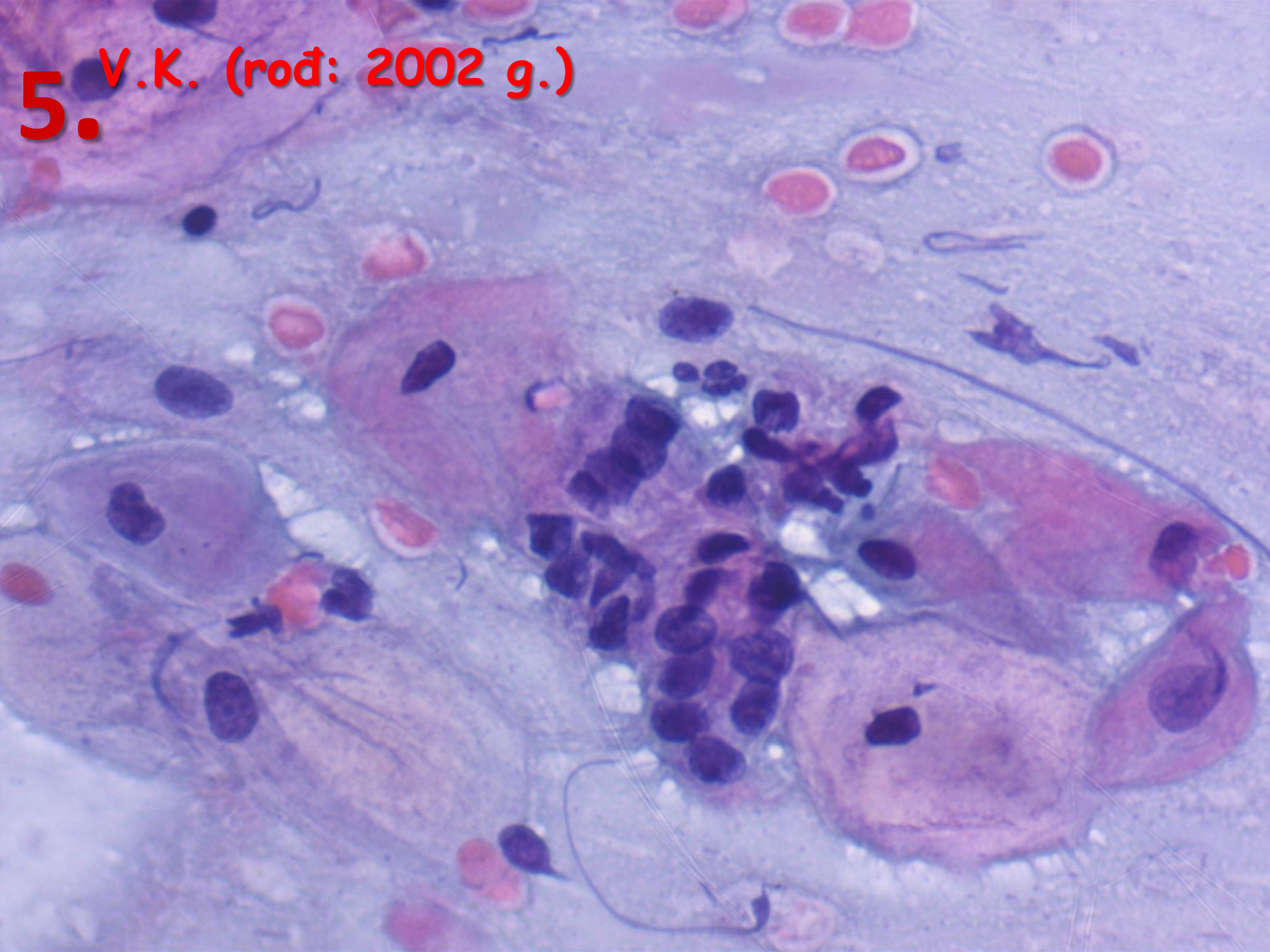
419 teškostepena displazija i 92 invazivnog karcinoma
Isključivanjem dijagnostičkih grešaka u svim potvrđenim slučajevima
CIN 3 promena je dokazano prisustvo HPV.

Böhmer G, van den Brule AJ, Brummer O, Meijer CL, Petry KU. No confirmed case of human papillomavirus DNA-negative cervical intraepithelial neoplasia grade 3 or invasive primary cancer of the uterine cervix among 511 patients. Am J Obstet Gynecol 2003;189:118-20.

>47,000/497 CIN2+/305 CIN3+ nije nađen ni jedan slučaj CIN3 promene koja nije udružena sa infekcijom sa HPV.

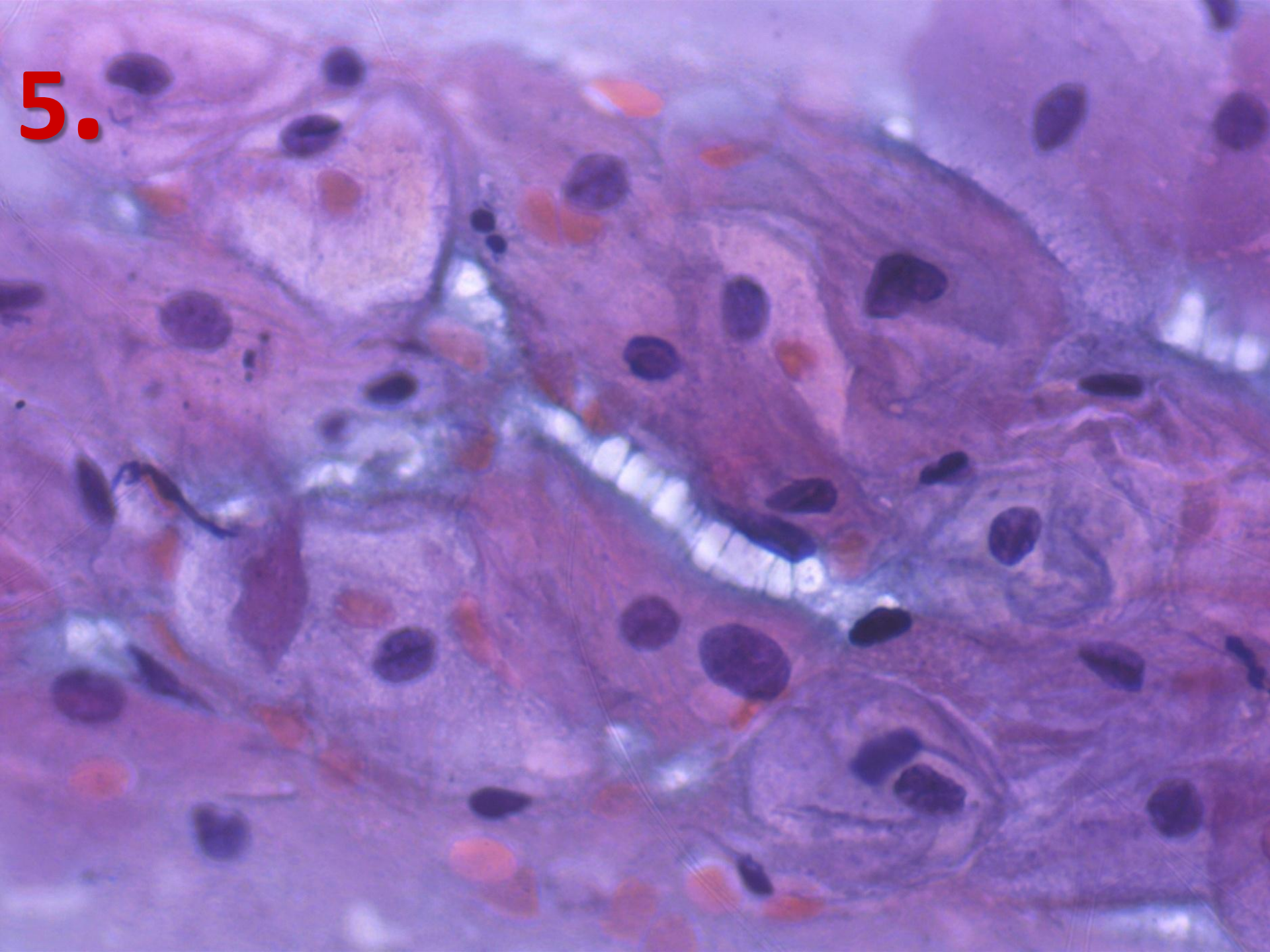


Petry KU, Cox JT, Johnson K, Quint W, Ridder R, Sideri M, Wright TC Jr, Behrens CM. Evaluating HPV-negative CIN2+ in the ATHENA trial. Int J Cancer 2016;138:2932-9.



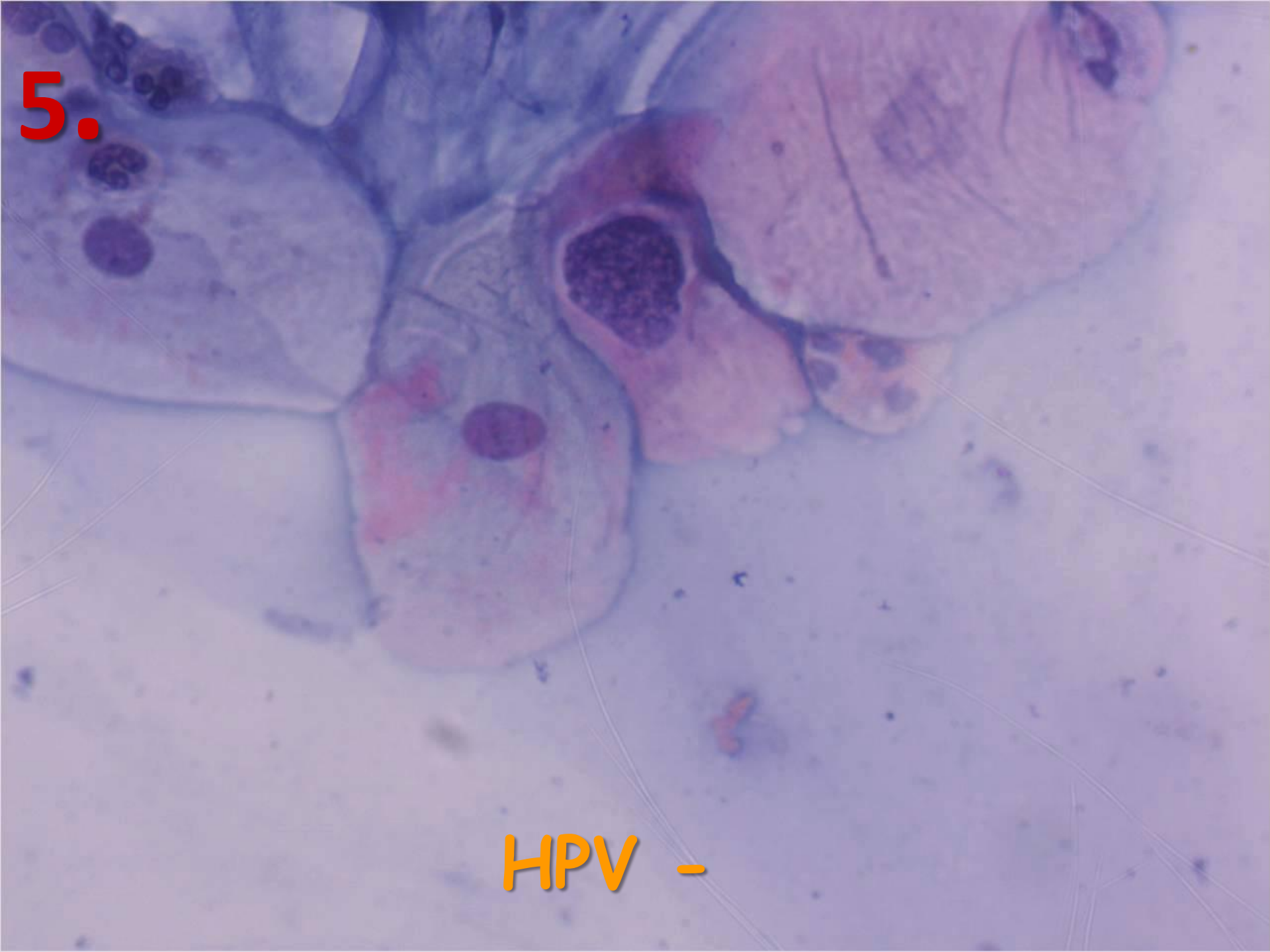
5. V.K. (rođ: 2002 g.)

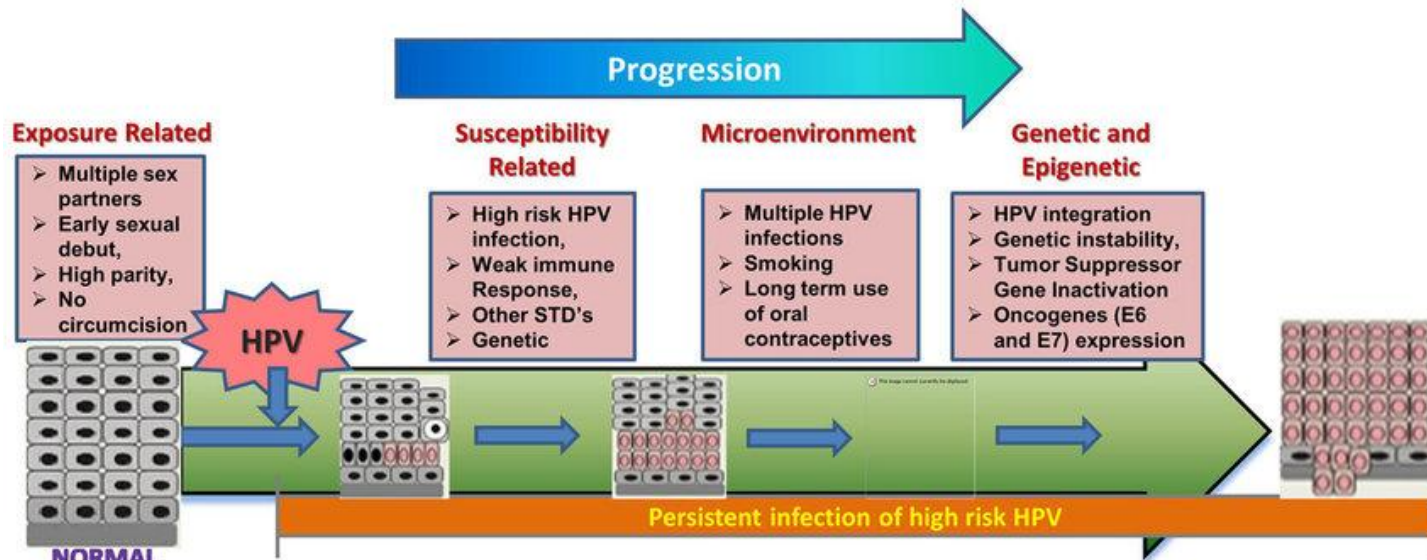
5.



5.

HPV -





HPV INFECTED CERVIX

>1 year

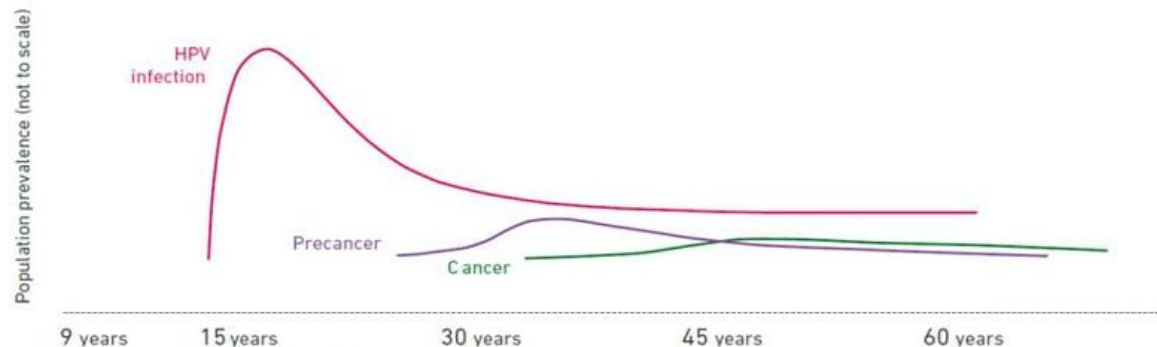
LOW GRADE SQUAMOUS LESIONS
(Representing CIN1)

>4-5 years

HIGH GRADE SQUAMOUS LESIONS
(Representing CIN2/3)

>10 years

CERVICAL CANCER



Nestanak virusa za 6 meseci: 55%-64% (prosečno 224 dana)
za 12 meseci: 67%-80%

Rodriguez AC, Schiffman M, Herrero R, et al. Rapid clearance of human papillomavirus and implications for clinical focus on persistent infections. J Natl Cancer Inst 2008; 100: 513–517.

Moscicki AB, Widdice L, Ma Y, et al. Comparison of natural histories of human papillomavirus detected by clinician- and self-sampling. Int J Cancer 2010; 127: 1882–1892.

Nestanak virusa: za 6 meseci 46% (NILM); 29% (ASC-US/L-SIL)
za 18 meseci: 65% (NILM); 41% (ASC-US/L-SIL)
44102 žena cervikalnog skiring programa Nizozemske
Najniža rata clearenca za HPV 16, HPV 18, HPV 31 i HPV 33

Bulkmans NW, Berkhof J, Bulk S, Bleeker MC, van Kemenade FJ, Rozendaal L, Snijders PJ, Meijer CJ; POBASCAM Study Group. High-risk HPV type-specific clearance rates in cervical screening. Br J Cancer 2007;96:1419-24.

Više od 90% HPV infekcije nestane za 2 godine.

Huber J, Mueller A, Sailer M, Regidor PA. Human papillomavirus persistence or clearance after infection in reproductive age. What is the status? Review of the literature and new data of a vaginal gel containing silicate dioxide, citric acid, and selenite. Womens Health (Lond). 2021 Jan-Dec;17:17455065211020702. doi: 10.1177/17455065211020702. PMID: 34096424; PMCID: PMC8785287.

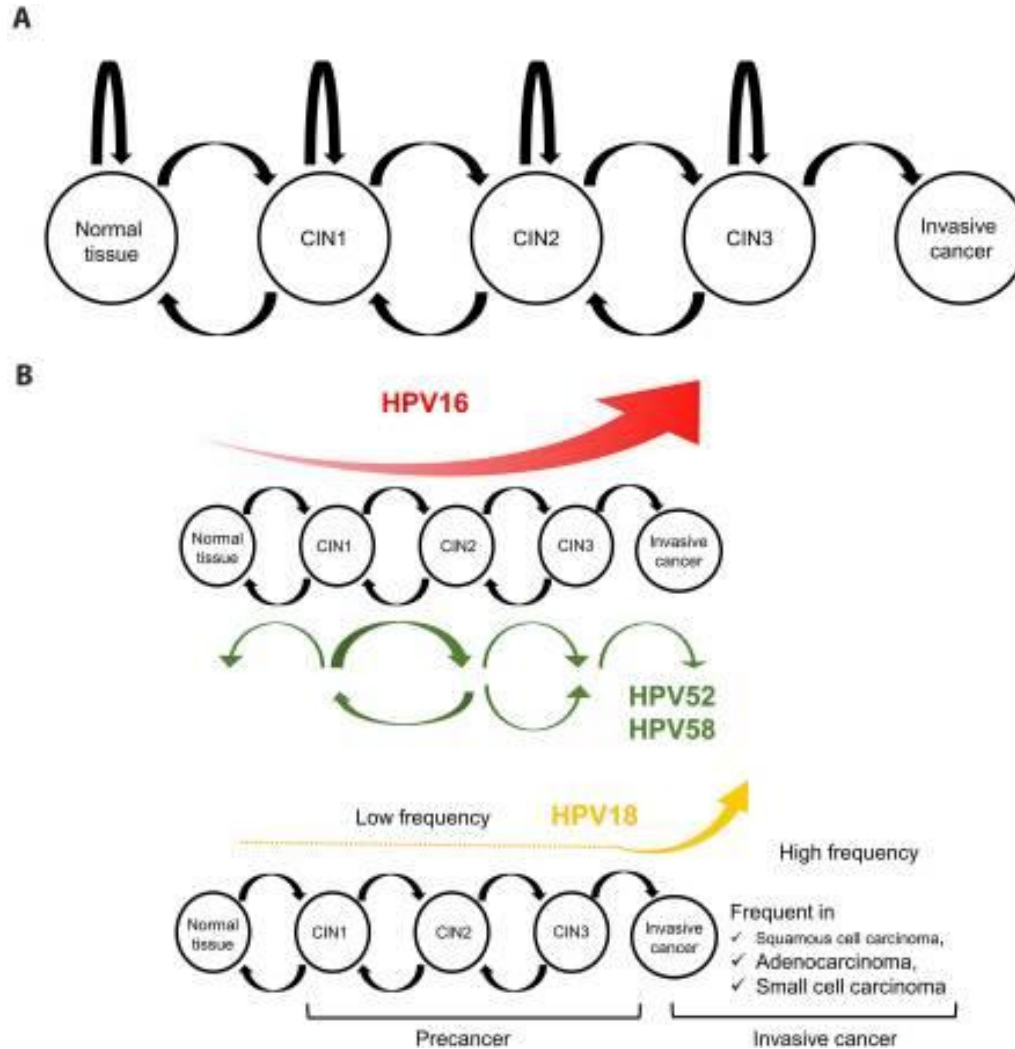
Inficiranost HPV skoro uvek nestaju same u roku od 1 do 2 godine bez nastanka bilo kakvih promena na ćelijama. Ako dođe do promena, ćelije se skoro uvek vraćaju u normalu.

Procenjuje se da će oko 10-20% žena imati perzistentnu HPV infekciju sa mogućim nastankom raka grlića materice nakon 15 do 20 godina. (imunosuprimirani, HIV može se razviti za 5 do 10 godina)

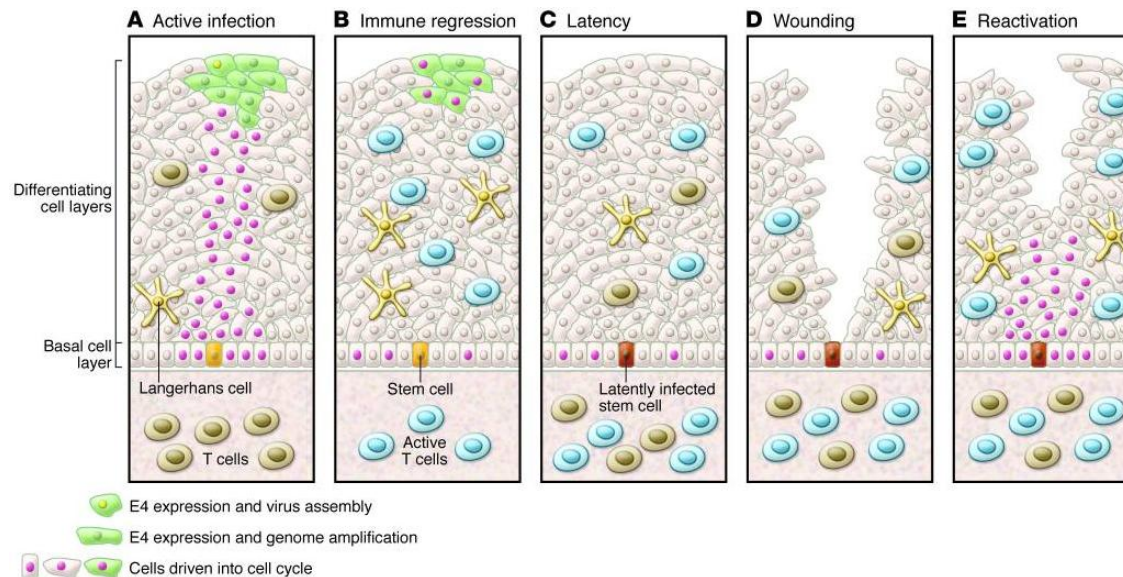
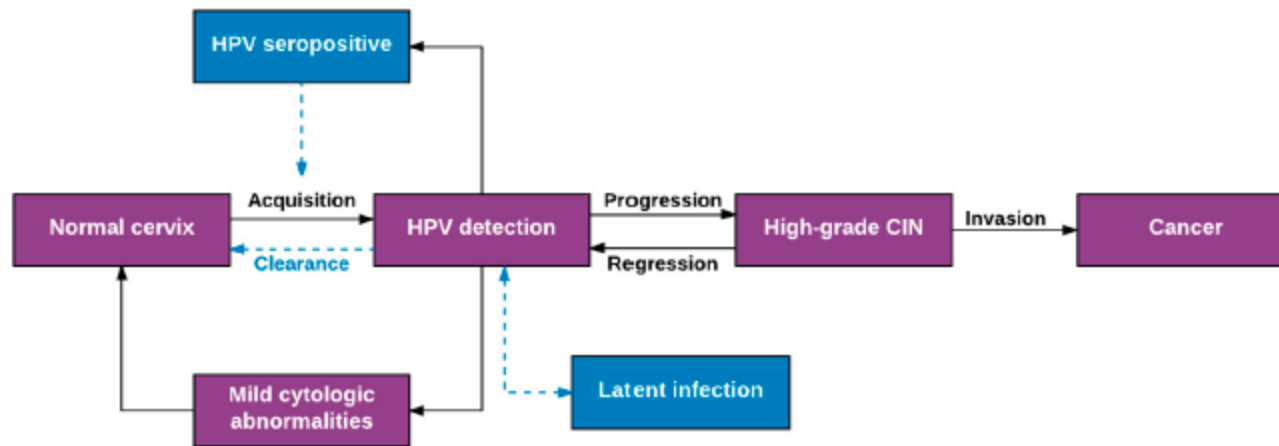
Illah O, Olaitan A. Updates on HPV Vaccination. Diagnostics (Basel). 2023 Jan 9;13(2):243. doi: 10.3390/diagnostics13020243. PMID: 36673053; PMCID: PMC9857409.

U jednoj studiji 7% adolescenata je razvio HSIL ubrzo nakon infekcije sa što sugeriše da neke žene mogu razviti HSIL promene bez dugotrajne perzistirajuće infekcije.

Argyri E, Papaspyridakos S, Tsimplaki E, Michala L, Myriokefalitaki E, Papassideri I, Daskalopoulou D, Tsiaoussi I, Magiakos G, Panotopoulou E. A cross sectional study of HPV type prevalence according to age and cytology. BMC Infect Dis. 2013 Jan 30;13:53. doi: 10.1186/1471-2334-13-53. PMID: 23363541; PMCID: PMC3575232.

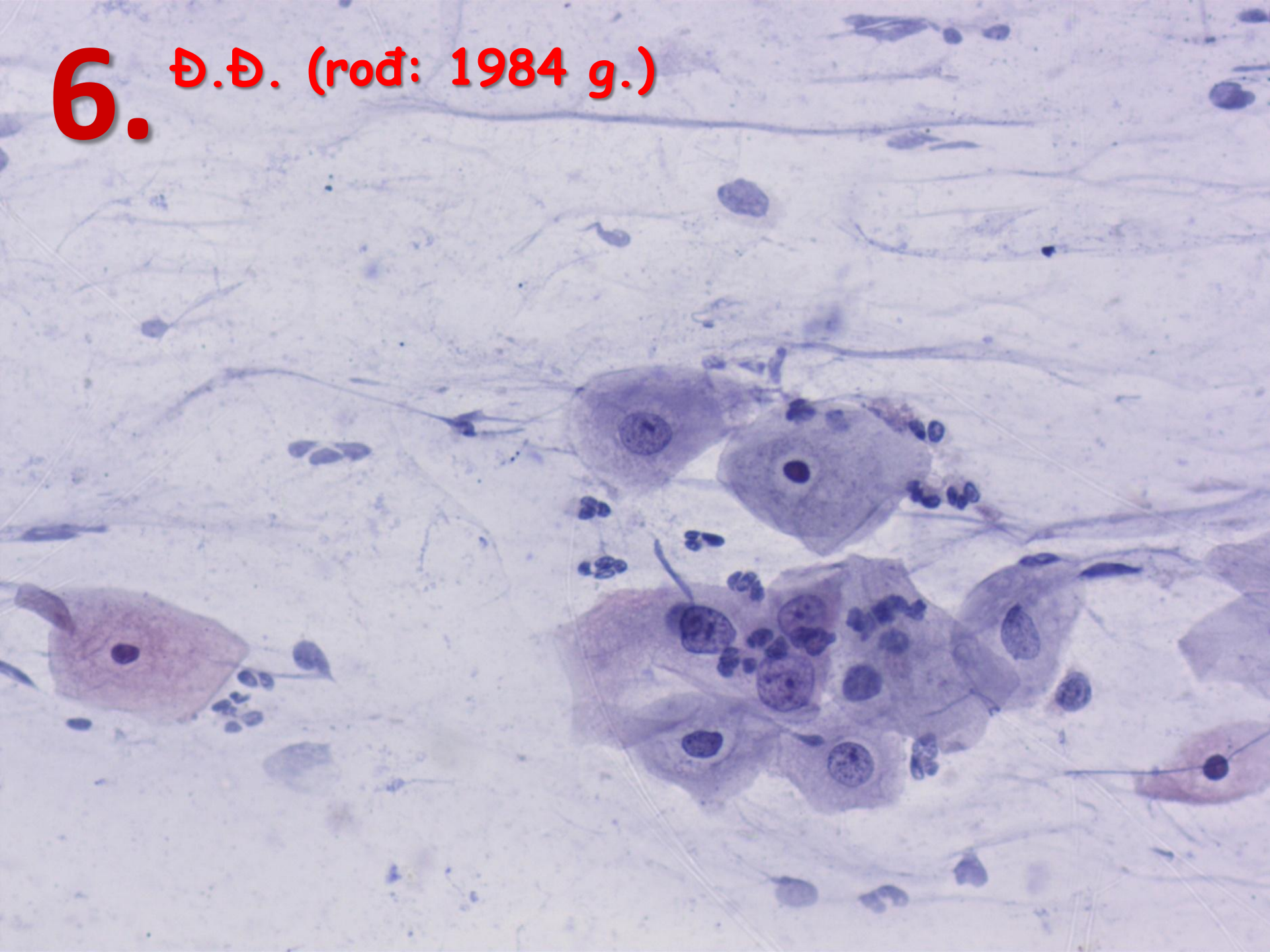


Kusakabe M, Taguchi A, Sone K, Mori M, Osuga Y. Carcinogenesis and management of human papillomavirus-associated cervical cancer. *Int J Clin Oncol* 2023;28:965-974.

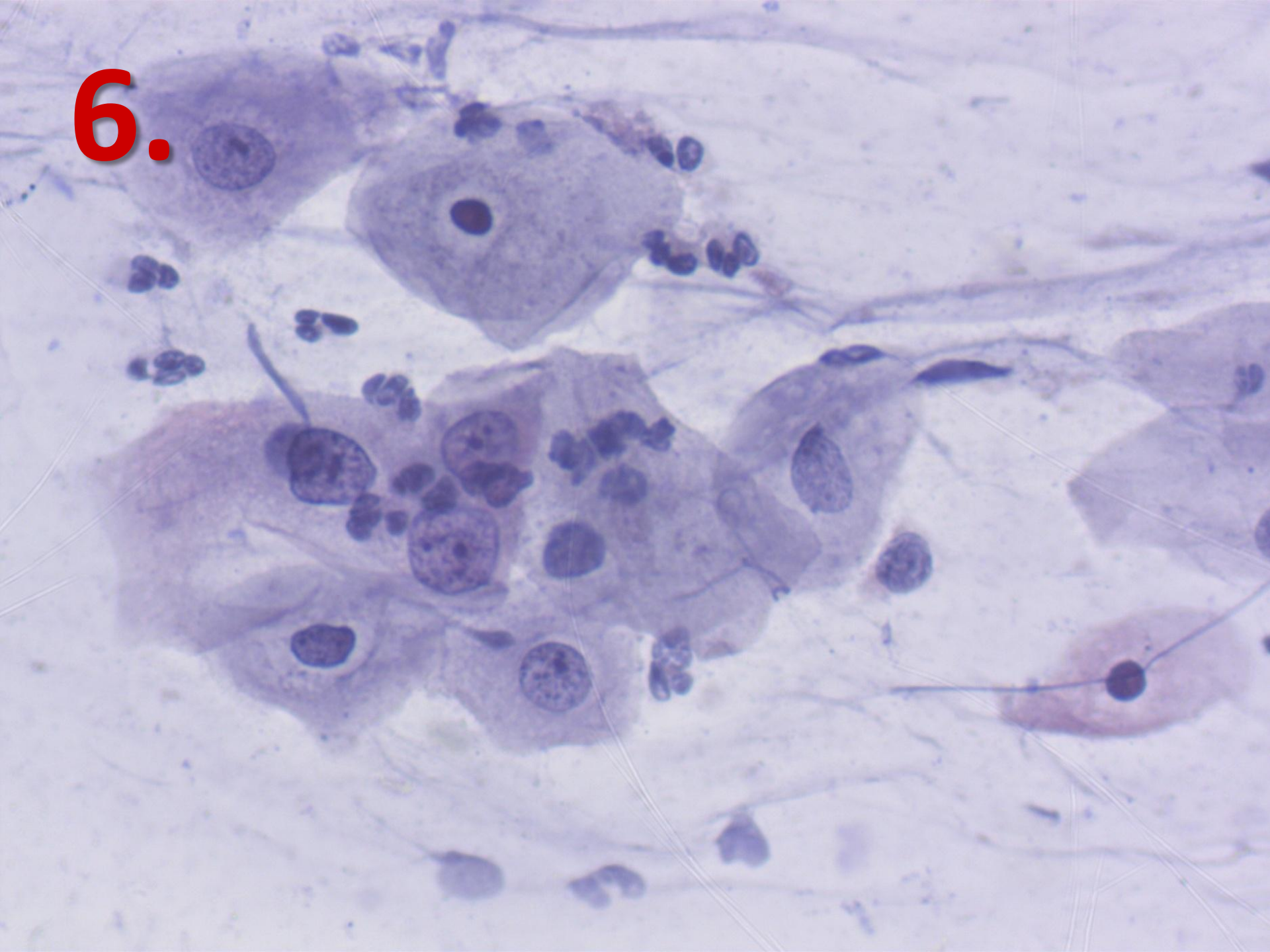


Gravitt PE, Winer RL. Natural history of HPV infection across the lifespan: role of viral latency. Viruses 2017 Sep 21;9(10):267. doi: 10.3390/v9100267. PMID: 28934151; PMCID: PMC5691619.

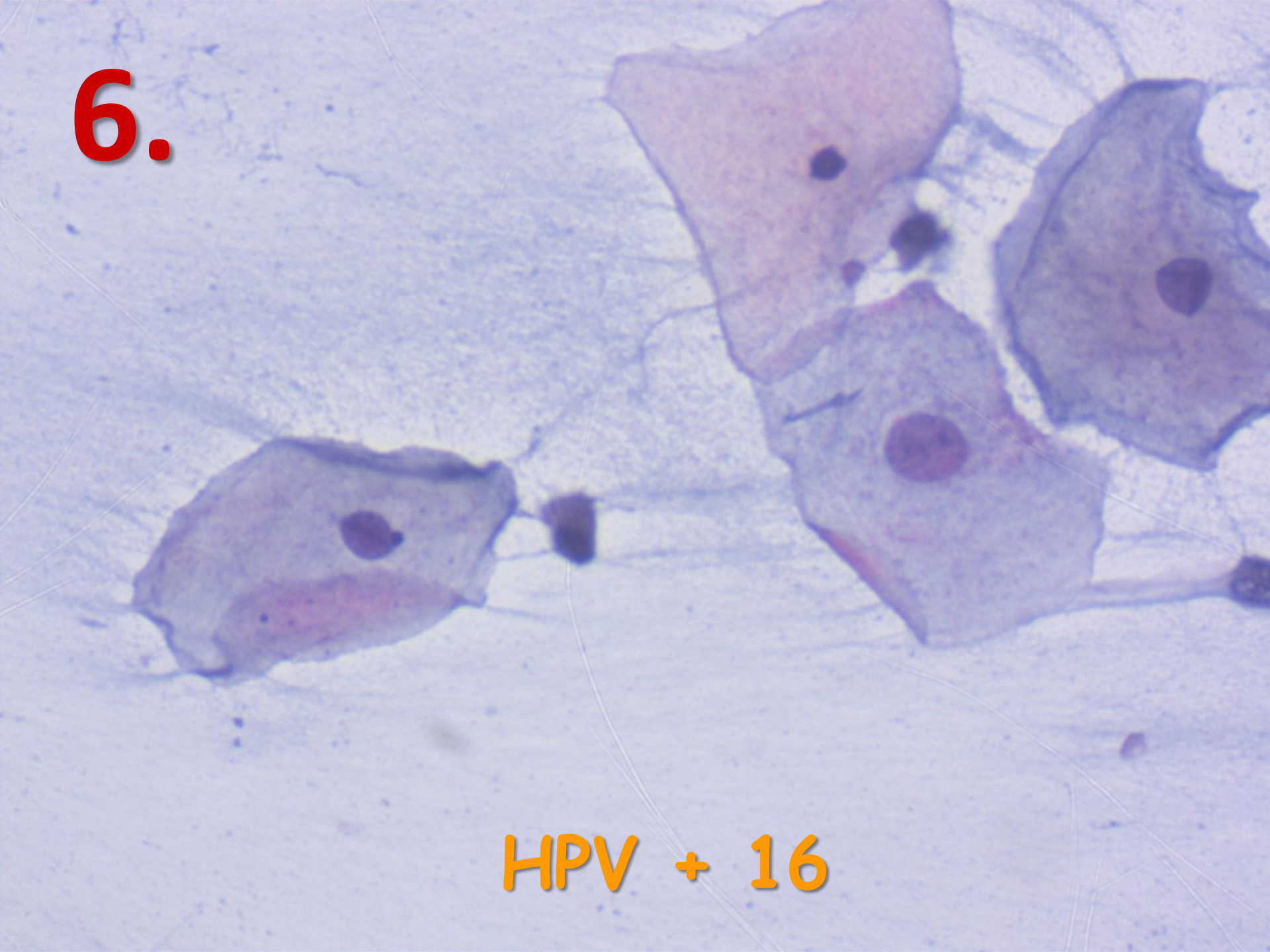
6. Đ.Đ. (rođ: 1984 g.)



6.

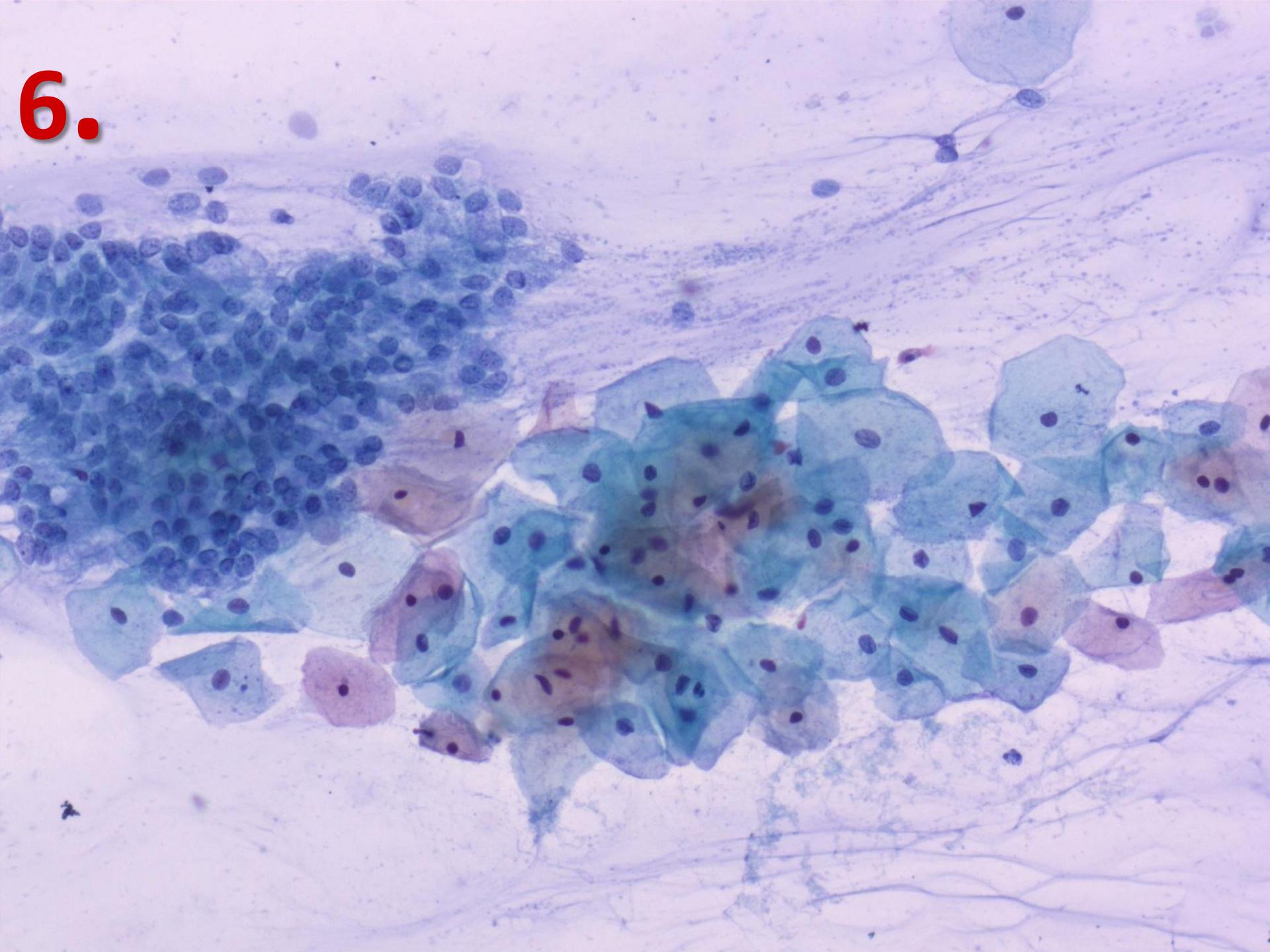


6.

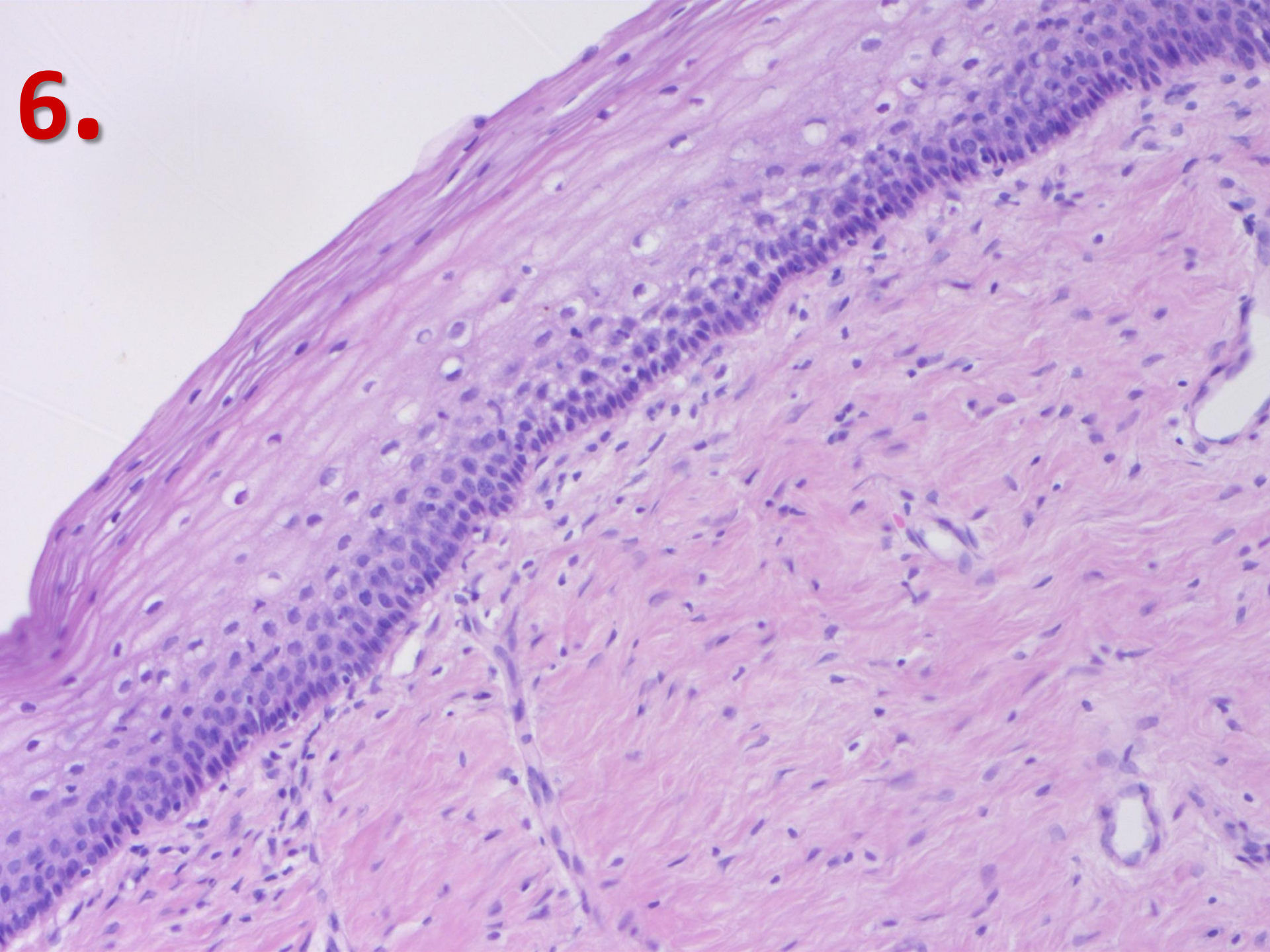


HPV + 16

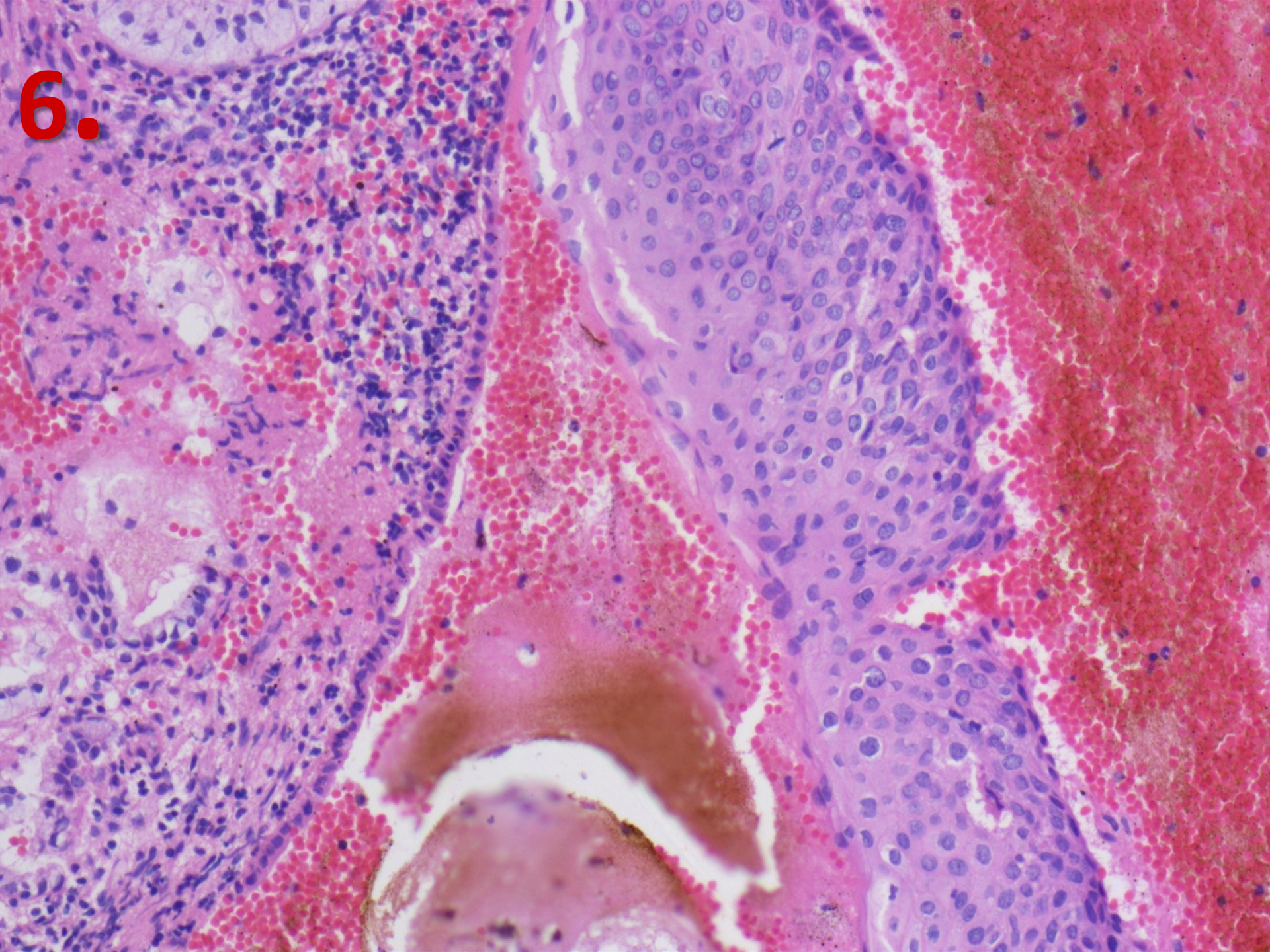
6.



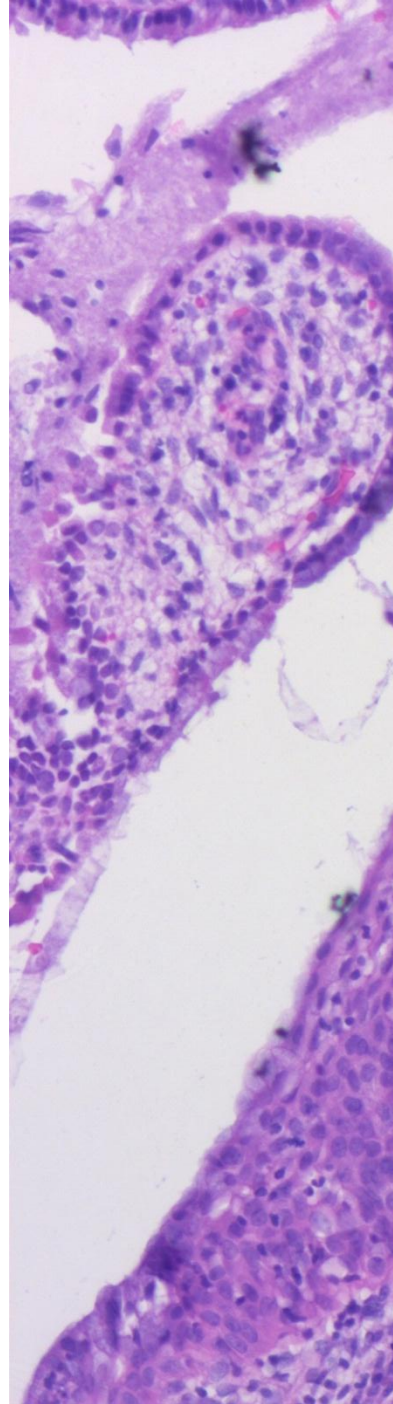
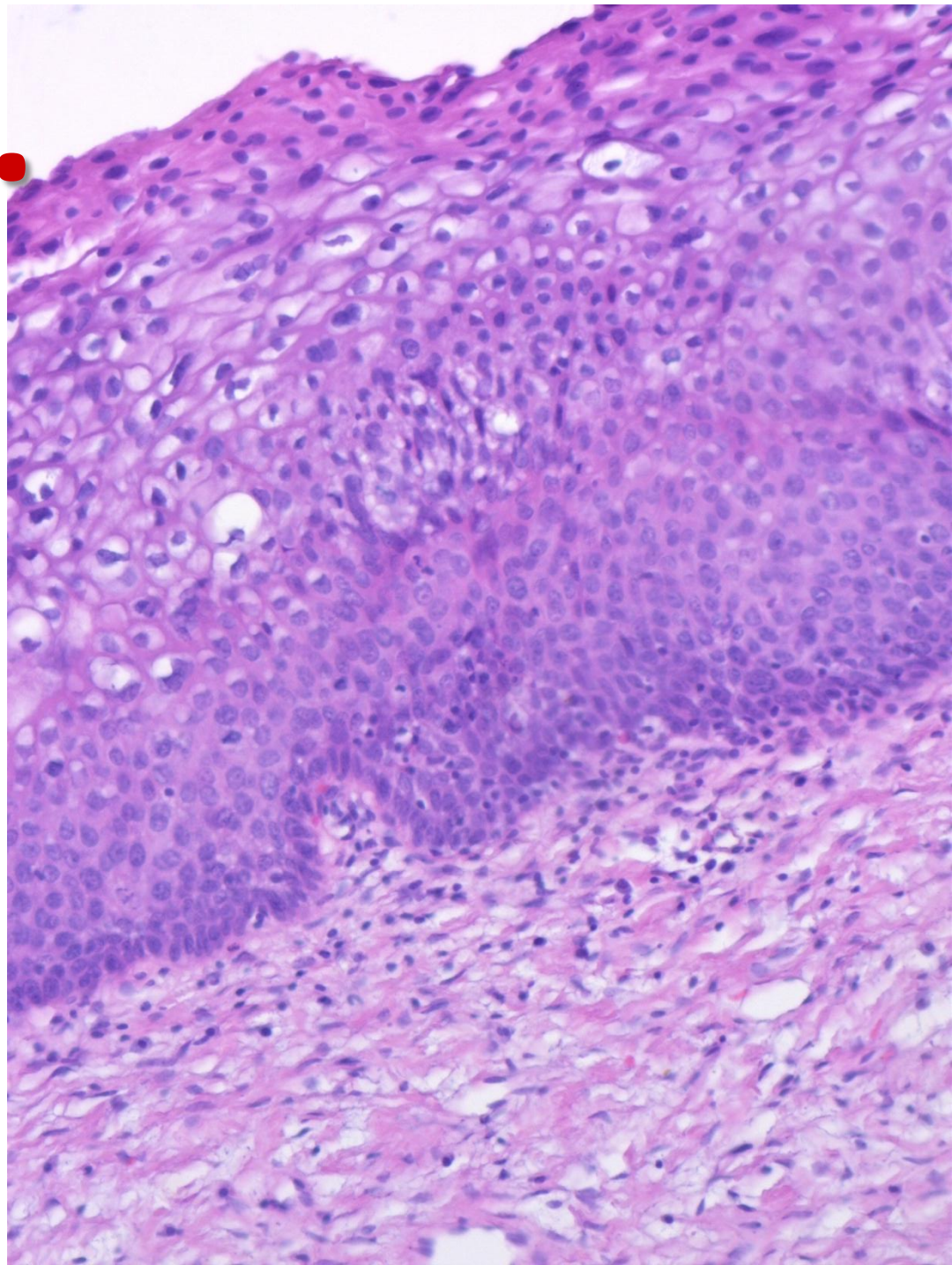
6.



6.



6.



od **10** do **20%** ASCUS slučajeva histološki se nalaze CIN2 i CIN3

10.037 žena kategorisanih kao ASCUS

1017 (10.1%) slučajeva CIN 2/3 promena

62 (0.62%) slučajeva invazivni karcinom

Nygård JF, Sauer T, Skjeldestad FE, Skare GB, Thoresen SØ. CIN 2/3 and cervical cancer after an ASCUS pap smear. A 7-year, prospective study of the Norwegian population-based, coordinated screening program.

Acta Cytol 2003;47:991-1000.

65.191 ASC citološki nalaz

19.7% žena nađena CIN2 ili veća lezija

Raab SS, Jones BA, Souers R, Tworek JA. The effect of continuous monitoring of cytologic-histologic correlation data on cervical cancer screening performance.

Arch Pathol Lab Med 2008;132:16-22.

Kaiser Permanente Northern California (KPNC) – 2003-2017

1.5 miliona žena (25 – 65) HPV/ citologija svake tri godine, praćene najmanje 10 godina.

Cytologic interpretation	Immediate risk of CIN3+	
	HR-HPV (-)	HR-HPV (+)
NILM	0.00	2.1
ASC-US	0.04	4.4
LSIL	1.1	4.3
ASC-H	3.4	25
HSIL	25	48

Egemen D, Cheung LC, Chen X, Demarco M, Perkins RB, Kinney W, Poitras N, Befano B, Locke A, Guido RS, Wiser AL, Gage JC, Katki HA, Wentzensen N, Castle PE, Schiffman M, Lorey TS. Risk Estimates Supporting the 2019 ASCCP Risk-Based Management Consensus Guidelines. J Low Genit Tract Dis 2020;24:132-143.

HPV Type	PAP Category	CIN3+ Immediate risk (%)	Cancer Immediate risk (%)
HPV16+	ASC-US	5.34	0.33
HPV 16+	LSIL	6.70	0.89

**HPV16 positive ASC-US and LSIL still exceed 4% threshold*

Perkins RB, Guido RS, Castle PE, Chelmow D, Einstein MH, Garcia F, Huh WK, Kim JJ, Moscicki AB, Nayar R, Saraiya M, Sawaya GF, Wentzensen N, Schiffman M; 2019 ASCCP Risk-Based Management Consensus Guidelines Committee. 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. J Low Genit Tract Dis 2020;24:102-131.

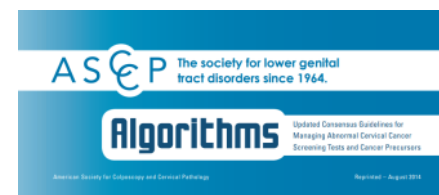
OPEN

2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors

Rebecca B. Perkins, MD, MSc,¹ Richard S. Guido, MD,² Philip E. Castle, PhD,³ David Chelmow, MD,⁴ Mark H. Einstein, MD, MS,⁵ Francisco Garcia, MD, MPH,⁶ Warner K. Huh, MD,⁷ Jane J. Kim, PhD, MSc,⁸ Anna-Barbara Moscicki, MD,⁹ Ritu Nayar, MD,¹⁰ Mona Saraiya, MD, MPH,¹¹ George F. Sawaya, MD,¹² Nicolas Wentzensen, MD, PhD, MS,¹³ and Mark Schiffman, MD, MPH¹⁴ for the 2019 ASCCP Risk-Based Management Consensus Guidelines Committee

Key Words: cervical cytology, HPV testing, management of abnormal cervical cancer screening tests, guidelines

(*J Low Genit Tract Dis* 2020;24: 102–131)



dalje praćenje ➡ na osnovu citološke dijagnoze

dalje praćenje ➡ na osnovu procene rizika

MINIMALNO POTREBNI PODACI:

- dob pacijentkinje
- sadašnji citološki nalaz
- citološki rezultati u zadnjih 5 godina
- intervencije zbog prekanceroznih promena u zadnjih 25 godina
- HPV
- specijalne grupe pacijentkinja (mlađe od 25 godina, trudnice, imunosuprimirane pacijentkinje)

