ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ
ATTIKON

Προσυμπτωματικός έλεγχος
HPV testing
Εμβολιασμός
Καρκίνος τραχήλου μήτρας

Χαράλαμπος Θεοφανάκης

Γυναικολόγος – Ογκολόγος (ESGO)

Επίκουρος Καθηγητής Μαιευτικής & Γυναικολογίας

Εθνικού & Καποδιστριακού Πανεπιστημίου Αθηνών

Γ' Μ/Γ Κλινική ΕΚΠΑ

ΠΓΝ Αττικόν

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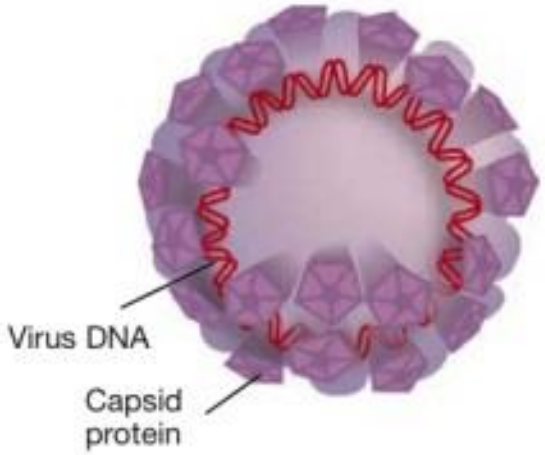
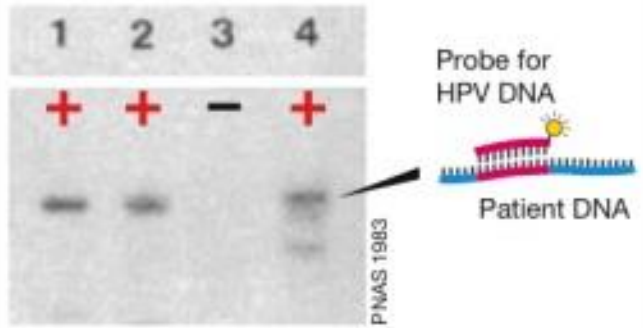
HPV– human papilloma virus

HPV has a circular, double stranded DNA, protected by capsid proteins.

More than 100 HPV-types are known. HPV16 and 18 cause 70% of all cervix cancers.



Discovery of HPV DNA in cancer cells



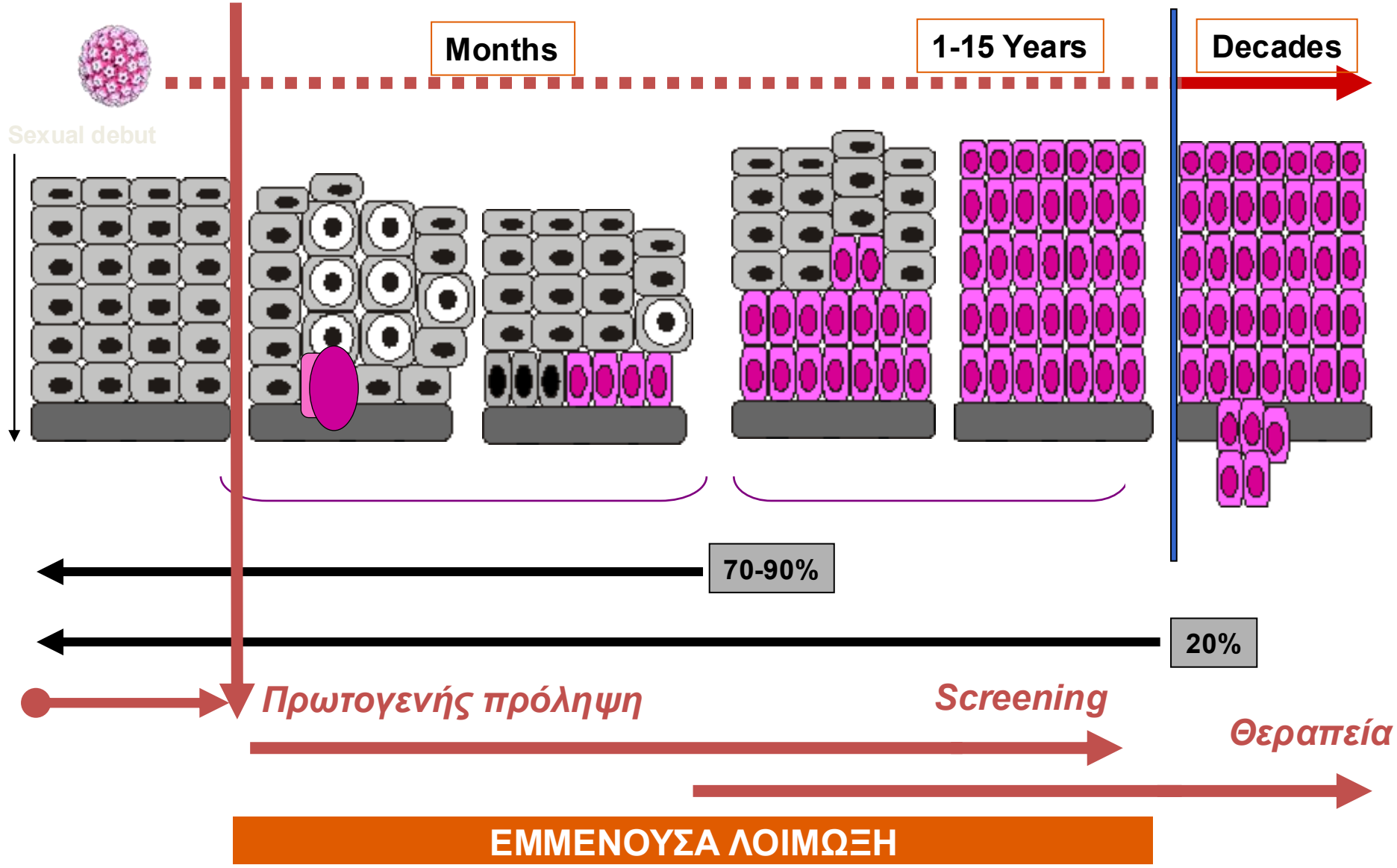
Harald zur Hausen found HPV DNA in patient DNA (+).

Infection by HPV

HPV infects epithelial cells in the cervical mucosa. HPV DNA integrates into the cellular genome when causing cancer.

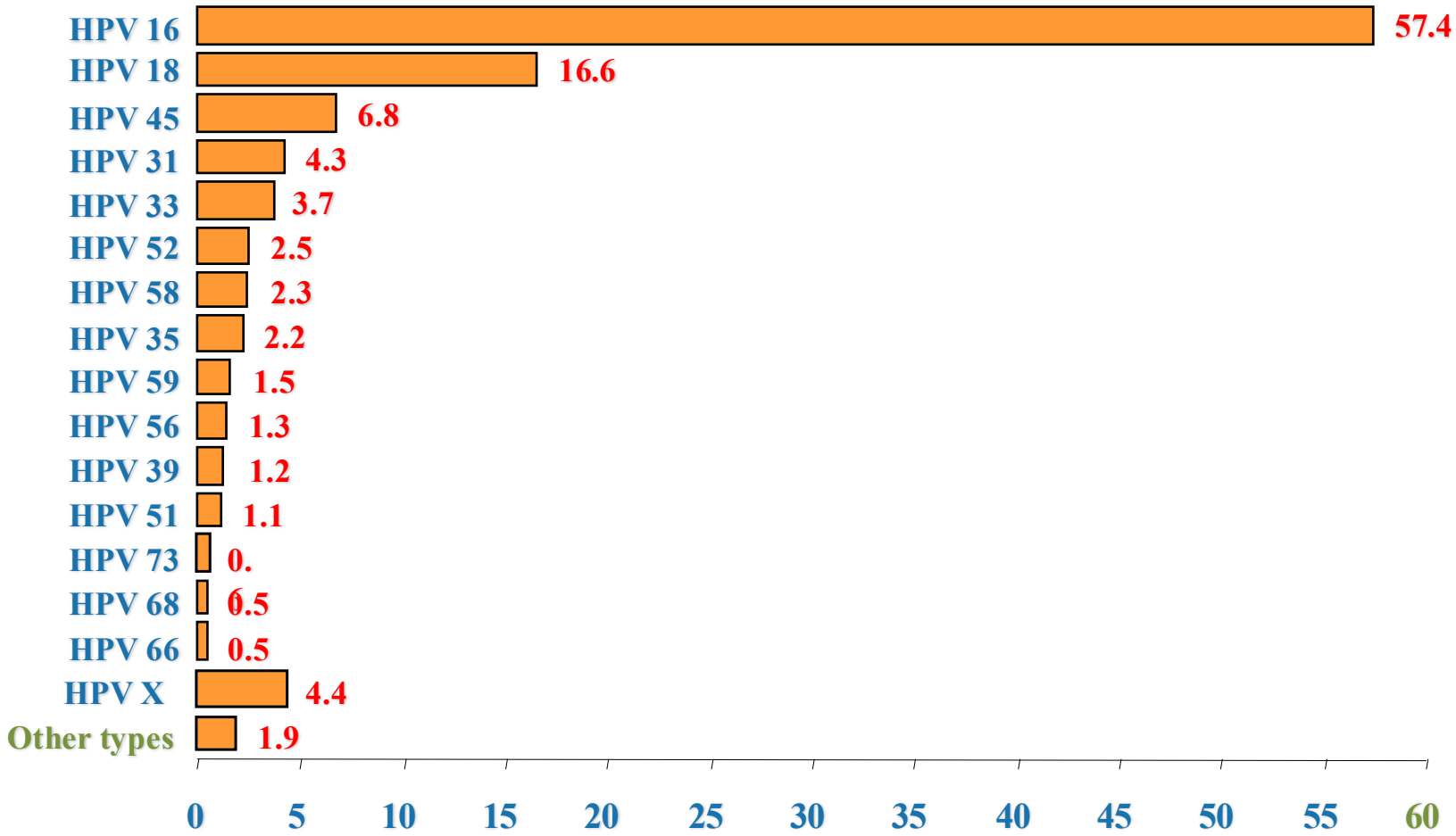
© The Nobel Committee for Physiology or Medicine 2008 Illustration: Annika Röhl

ΦΥΣΙΚΗ ΙΣΤΟΡΙΑ ΤΟΥ ΚΑΡΚΙΝΟΥ ΤΟΥ ΤΡΑΧΗΛΟΥ ΤΗΣ ΜΗΤΡΑΣ



CIN = Cervical Intraepithelial Neoplasia
SIL= Squamous Intraepithelial Lesion

Κατανομή των υποτύπων του ιού HPV



Munoz, Bosch, Castellsague et al., Int J Cancer 2004
Smith et al., Int J Cancer 2007

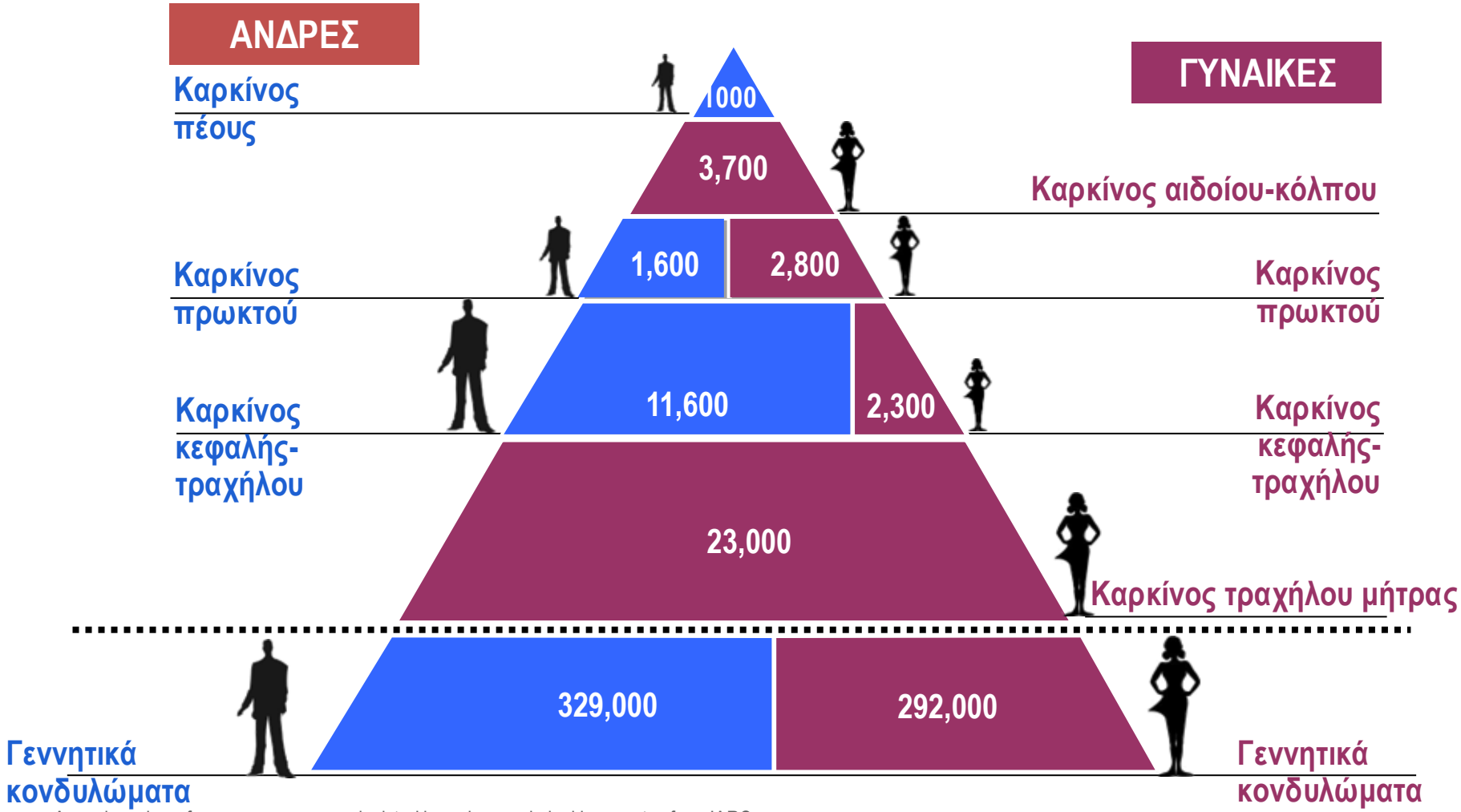
Καρκίνοι που συνδέονται με τον ιό HPV

	HPV+	HPV16/18 (among HPV+)
Καρκίνος τραχήλου μήτρας	100 %	71 %
Καρκίνος κόλπου	65 - 90 %	50 %
Καρκίνος πρωκτού (και στα 2 φύλα)	>80 %	92 %
Καρκίνος αιδοίου	30 - 35 %	80 %
Καρκίνος πέους	40 %	63 %
Καρκίνος φάρυγγα-λάρυγγα	25 %	89 %
Καρκίνος στοματικής κοιλότητας (και στα 2 φύλα)	10 %	95 %

Source: Muñoz, Castellsagué, 2006; Parking & Bray 2006; Muñoz, Castellsagué et al., Vaccine 2006

Ο HPV σχετίζεται και με τα 2 φύλα

(καρκίνο πρωκτού, πέους, στοματοφάρυγγα και στοματικής κοιλότητας)[13]



Annual number of new cancer cases calculated based on crude incidence rates from IARC database (1998-2002) and population estimate Eurostat 2008; estimate Globocan 2008 for cervical cancer; published HPV prevalence rates were applied (for Europe, when available)

Genital warts estimates based on incidence rates in UK, HPA 2007

THE ARCHITECTURE TO ELIMINATE CERVICAL CANCER:

VISION: A world without cervical cancer

THRESHOLD: All countries to reach < 4 cases 100,000 women-years

2030 CONTROL TARGETS

90%

of girls fully vaccinated with HPV vaccine by 15 years of age

70%

of women screened with an **high precision test** at 35 and 45 years of age

90%

of women identified with cervical disease receive treatment and care

Launch

17 November 2020

SDG 2030: Target 3.4 – 30% reduction in mortality from cervical cancer

The 2030 targets and elimination threshold are subject to revision depending on the outcomes of the modeling and the WHO approval process

ESGO HYBRID MEETING European Gynaecological

World Health Organization

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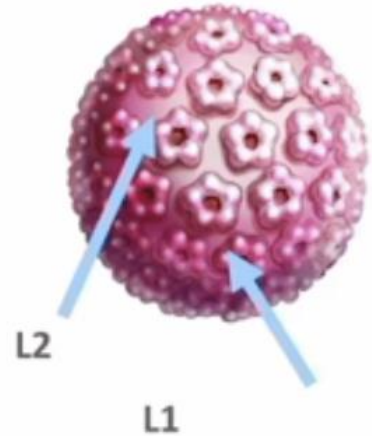
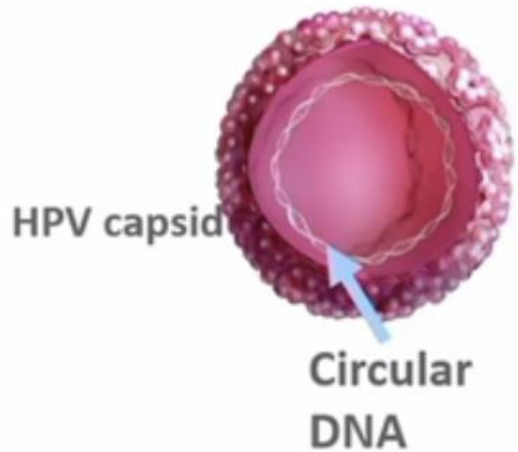
- Most common sexual transmitted disease (>%70)
- Unenveloped, dsDNA with capsid
- HPV Infection
  - Peak 20 years of age: 35%
  - Above age 30: 10%
  - 40-55 years 2. Peak
    - New Infection or Reactivation
- Transmission
  - Sexual, horizontal and vertical
    - Digital-Genital, Fomit (Sexual Toys), USG Probes, Reusable Speculum, Shared Clothing[1]
- >200 HPV Types
  - Low Risk : 6,11
    - Risk of Cervical Cancer x1
  - High Risk: **16, 18,** 45, 31, 33 52, 58, 35, 59, 56, 51, 39, 68, 73, 82
    - Risk of cervical cancer x300-500 (Tobacco-Lung Cancer Risk x10)
    - Cervical cancer is HPV Related in 99.7% of cases





[1]Sex Health. 2016;13(1):10–21

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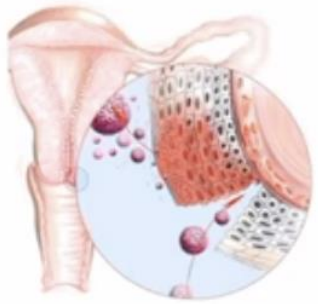
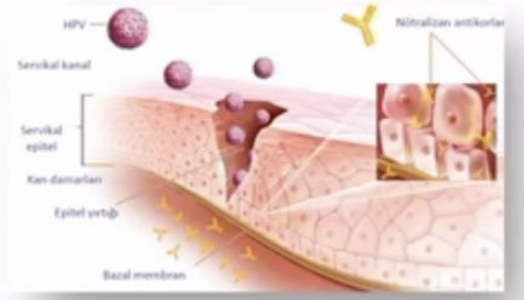
Natural Infection

- Most smart virus in the microbiology
- Your cellular immunity can make HPV negative in 2 years,
  - In 95-97% of the cases, HPV DNA becomes negative in 24 months
    - But negativity may not be forever
      - Re-activation is possible
  - In 3-5%, you have the persistent infection
- Antibody response (humoral immunity)
  - Seroconversion is in 50%
  - Treshold for protectivity ? Durability of Antibodies? Avidity of Antibodies ?
    - Re-infection is common





Costa Rica HPV Vaccine Trial and the PATRICIA study groups, *The Journal of Infectious Diseases, 2018, Nisan Richard B. S. Roden1, Nature, Nisan 2018*

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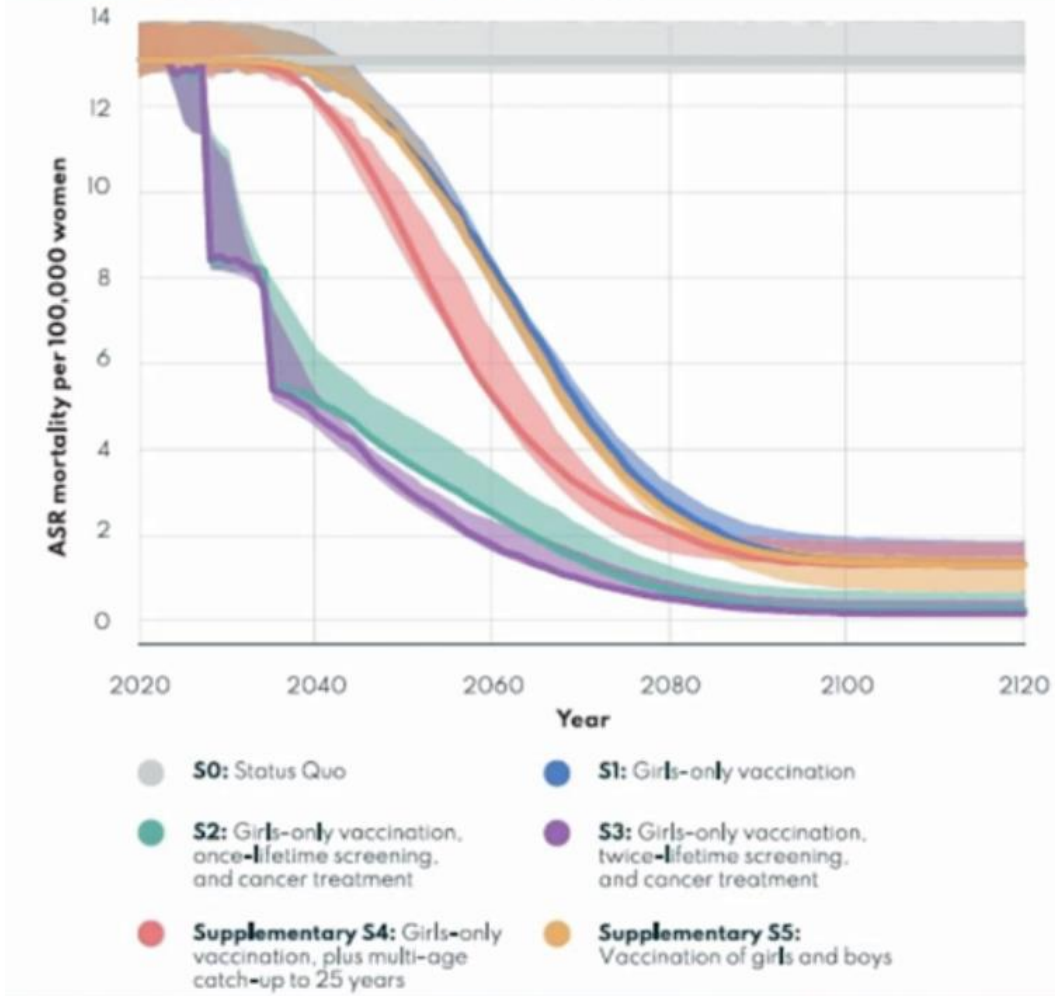
Modeling

Mortality over time for 78 LMICs, different scenarios for scaling-up cervical cancer control



Scenarios 1, 4, 5: Vaccination with or without screening can reduce mortality to <2 /100.000 in 80 - **100 years**

Scenario 2: Adding one time per life screening and adequate treatment, can achieve this target in **50 years**

Scenario 3: Two times per life screening and adequate treatment can achive this goal in **40 years with 34% reduction in mortality and 300.000 deaths averted until 2030**

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Move towards high performance tests

Complex or Low-Sensitivity

Cytology:

Successful in high-resource countries, but implementing quality cytology screening is challenging in middle and low resource countries

VIA:

Naked eye visual inspection with 3-5% acetic acid

High Performance Alternatives

- **HPV Testing**
  - No triage
  - Followed by treatment with cryotherapy or thermal ablation (not for WHIV)
- **HPV Testing**
  - Plus triage with HPV 16/18, VIA or other tests
  - Followed by treatment with cryotherapy or thermal ablation

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HPV Vaccines and Challenges

- Cost and availability
- Inequities in health care, poor awareness of HPV and cancer
- Myth that infectious disease is under control
- Ignorance and fear of vaccines in health care workers at all levels
- Underestimating anti-vaccine influence via social media

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Screening

- Objective Test
- Automated and centralized
- Man-power advantage
- Longer Screening Intervals
- No complex quality criteria
- Self/Urine/Point of Care Tests
- Vaccination era
- Decrease in incidence 40%, mortality 50% with better protection in adenocarcinoma
- Cost Effective

ASCO and ESGO RECOMMENDATION

For all resource settings;

HPV DNA SHOULD BE CONSIDERED

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Self tests: vaginal swaps, urinary samples, blood HPV

META ANALYSIS

COMPARATIVE PERFORMANCE ANALYSIS

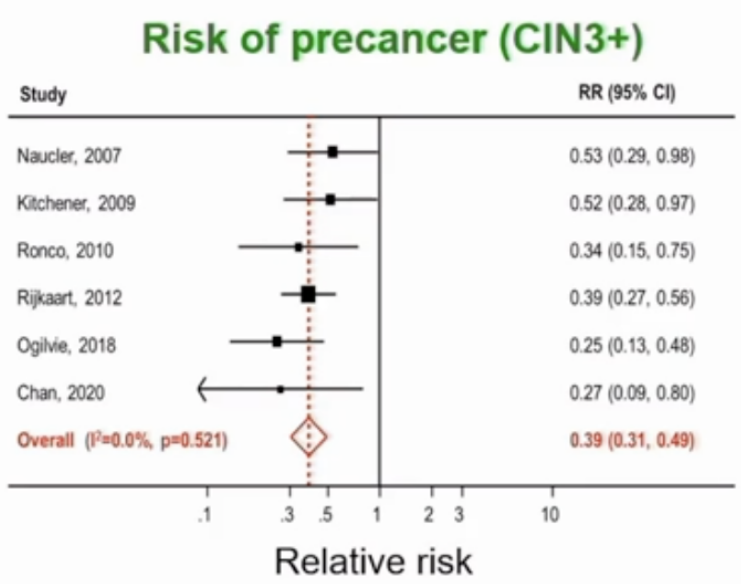
CLINICAL IMPLEMENTATION STUDIES

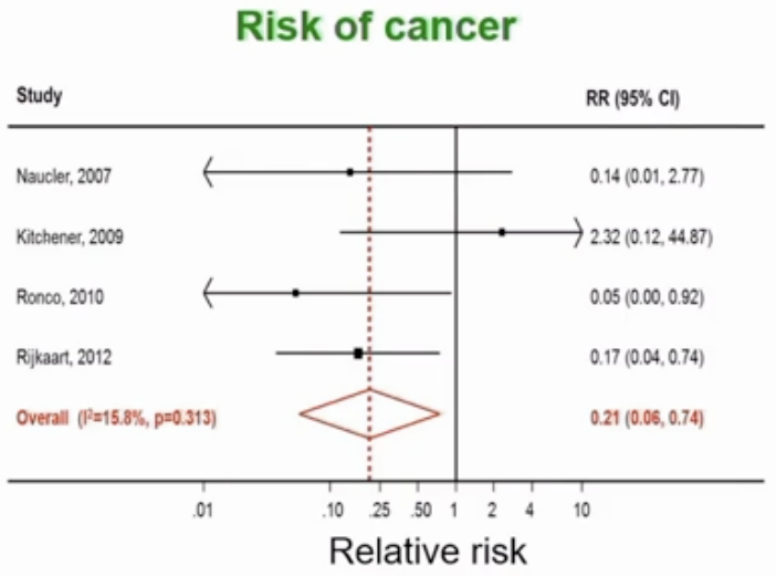
VALIDATION METHODOLOGY

Accuracy

Strong evidence: Screening with HPV DNA tests protects better against future pre-cancer and cancer than cytology-based screening

Randomised trials: risk of (pre-)cancer lower if HPV-negative compared to cytology-negative. Relative risk lower than one





Arbyn et al, Vaccine 2012, updated for IARC Handbook for cervical cancer screening (vol 18): 2022

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HPV DNA tests validated for primary screening (ESGO endorsed kits)

- 11 assays fulfil validation criteria
- Standard comparator test:
  - HC2, GP5+/6+
  - Abbott RT hrHPV
  - Alinity
  - Anyplex II HR HPV
  - Cobas 4800
  - HPV risk-assay
  - Onclarity
  - PapilloCheck HPV
  - Xpert HPV
  - Cobas 6800
- Newly validated:
  - CLART 4S, NeuMoDx

Arbyn, Clin Microbiol Infect 2021:

ELSEVIER

CMI CLINICAL MICROBIOLOGY AND INFECTION

ESCMID

2020 list of human papillomavirus assays suitable for primary cervical cancer screening

Marc Arbyn [1,2,*], Marie Simon [3], Eliana Peeters [1], Lan Xu [1,4], Chris J.L.M. Meijer [5], Johannes Berkhof [6], Kate Cuschieri [7], Jesper Bonde [8], Anja Ostrbenk Vanlencak [9], Fang-Hui Zhao [10], Remila Rezhake [1,10,11], Murat Gultekin [12], Joakim Dillner [13], Silvia de Sanjosé [14], Karen Canfell [15,16], Peter Hillemanns [17], Maribel Almonte [18], Nicolas Wentzensen [19,†], Mario Poljak [9,†]

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Screening policies in EU & UK (n=31)

- **Switched from cytology to HPV: 15 (48%)**
- **Plans to switch to HPV: 8 (19%)**
- **Cytology, no plans to switch to HPV: 6 (19%)**
- **Co-testing (cytology + HPV): 4 (GE, LU, CZ, PT)**
- **Self-sampling: 5 (13%) DK, FI, FR, NL, SE**

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Reaching the WHO CaCX elimination goals

- **Priority on coverage: HPV vaccination, screening & management of screen+ women**

- **Screening with HPV tests will assure sensitivity, adequate triage the specificity**

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hrHPV-based screening: DNA vs. mRNA assays

Lancet Oncol 2022; 23: 950–60

Accuracy and effectiveness of HPV mRNA testing in cervical cancer screening: a systematic review and meta-analysis

Marc Arbyn, Marie Simon, Silvia de Sanjosé, Megan A Clarke, Mario Poljak, Remila Rezhake, Johannes Berkhof, Victoria Nyaga, Murat Gultekin, Karen Canfell, Nicolas Wentzensen

Funding Horizon 2020 Framework Programme for Research and Innovation of the European Commission, through the RISCC Network; The UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP/WHO);, Haute Autorité de la Santé; European Society of Gynaecological Oncology; and the National Institute of Public Health and the Environment.

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3 clinical questions

1. Cross-sectional accuracy of hrHPV DNA vs mRNA
2. Longitudinal performance of hrHPV DNA vs mRNA

} clinician samples

3. Cross-sectional accuracy of mRNA on self- vs mRNA

on clinician samples

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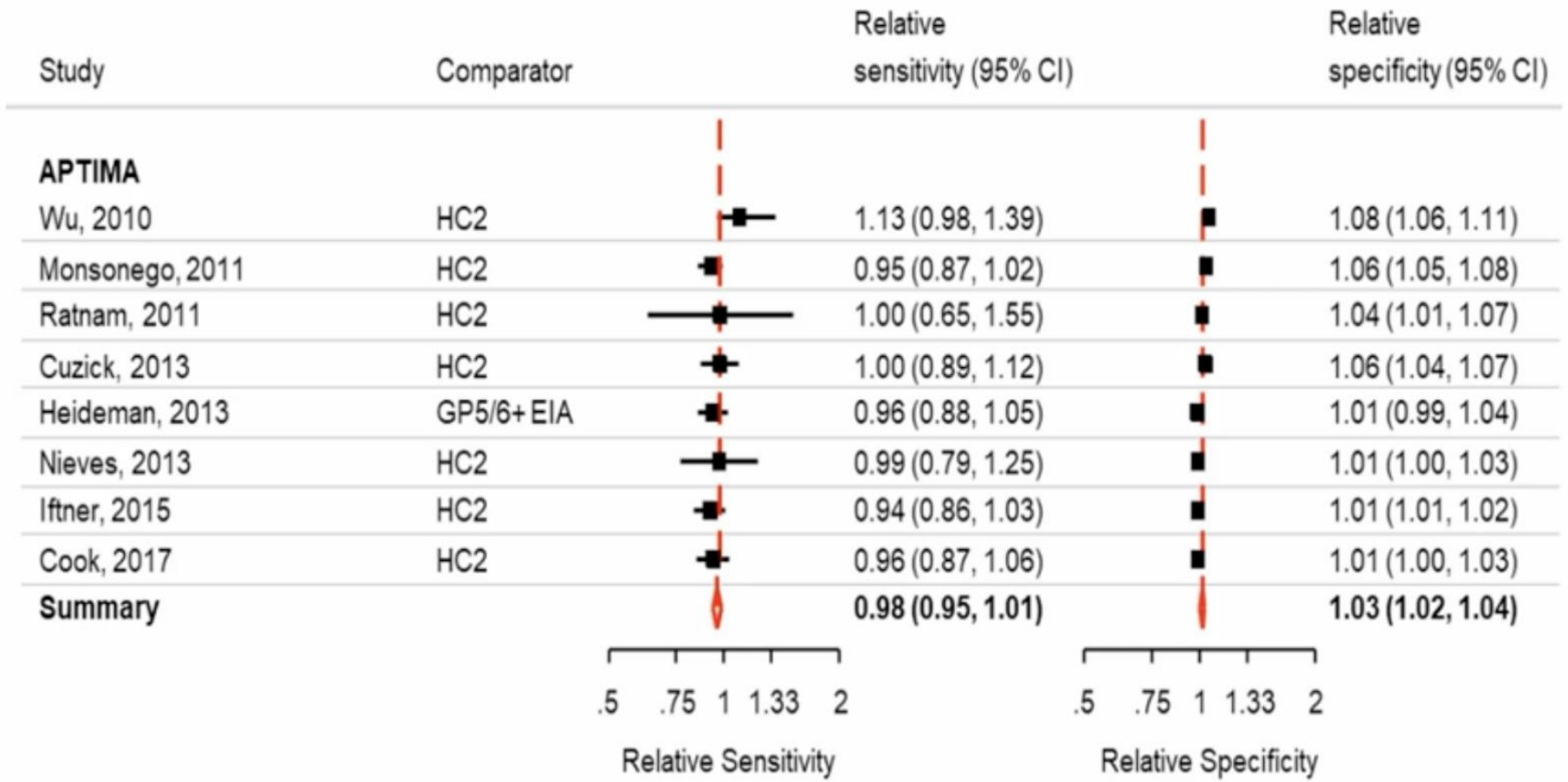
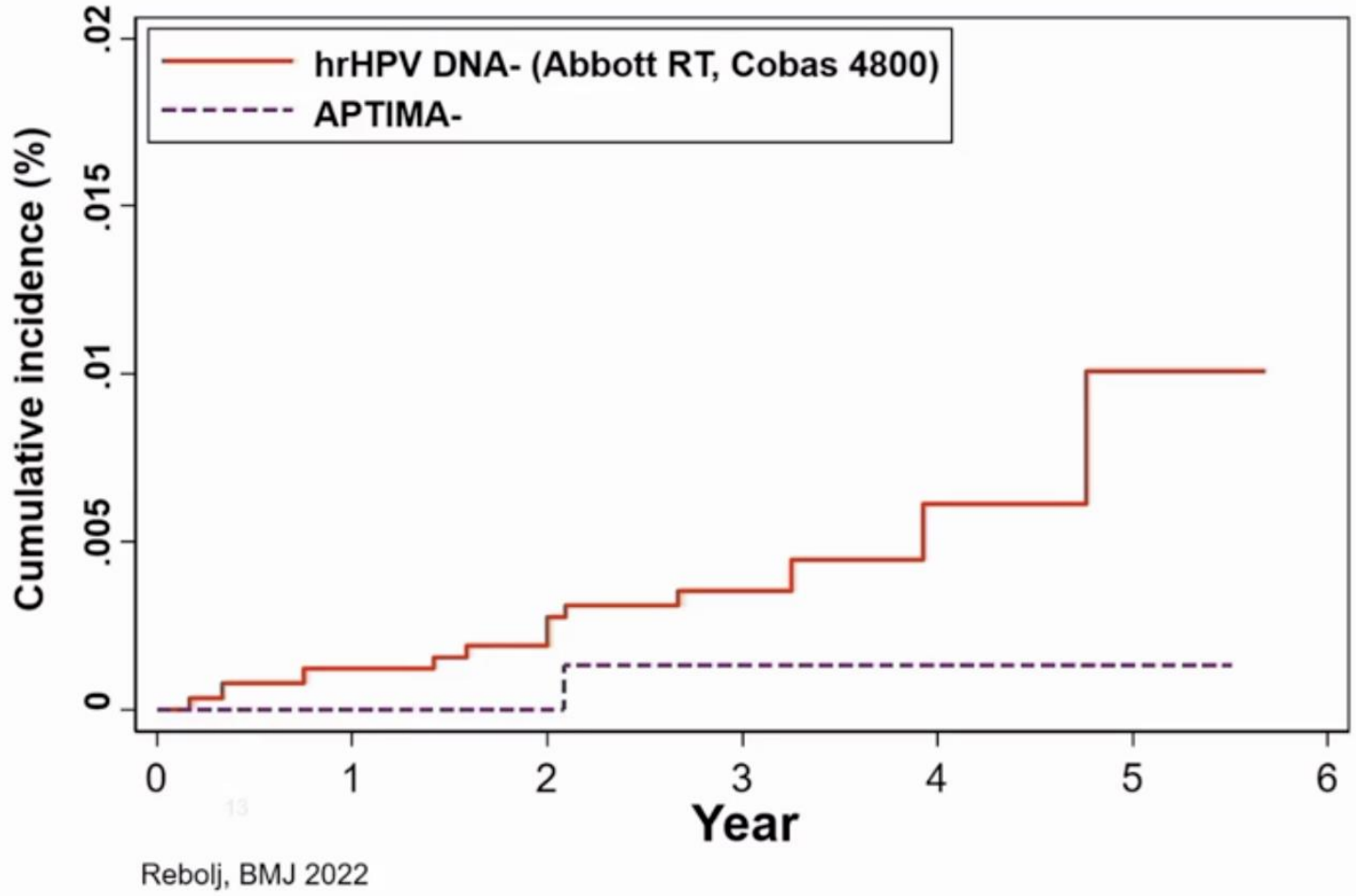
APTIMA vs. hrHPV DNA comparator tests to detect CIN2+ (cervical specimens in screening)



Cumulative detection of cervical cancer after negative APTIMA vs. after negative hrHPV DNA tests



HR: 0.18 (95% CI 0.03-1.38)

Rebolj, BMJ 2022

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Conclusions: APTIMA

- Similar cross-sectional clinical accuracy as hrHPV DNA assays (on cervical specimens)
- Few longitudinal studies (5-10Y): no evidence of inferior longitudinal performance
- APTIMA on self-samples is less sensitive than on clinician sample

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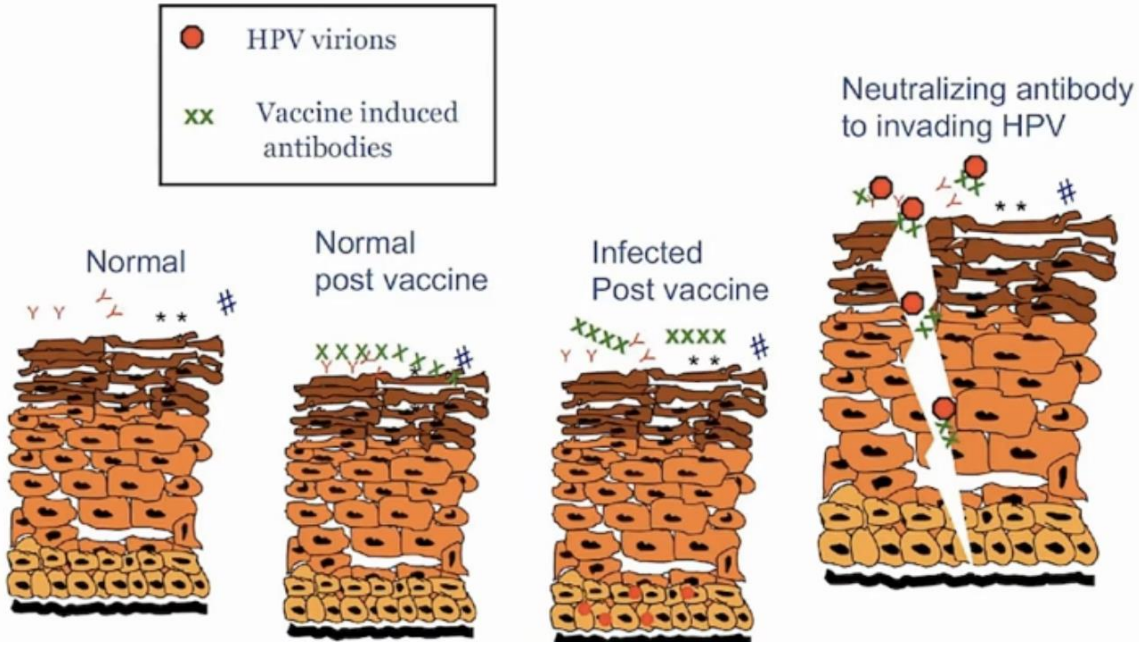
HPV Vaccines: What do we know from clinical trials? – Level A

HPV vaccines

- highly efficacious in preventing HPV infections - cervical, vaginal, vulvar, anal pre-invasive and invasive disease, anogenital warts (GARDASIL)
- does NOT lead to clearance or reduced persistence with ongoing infections at the time of the vaccine



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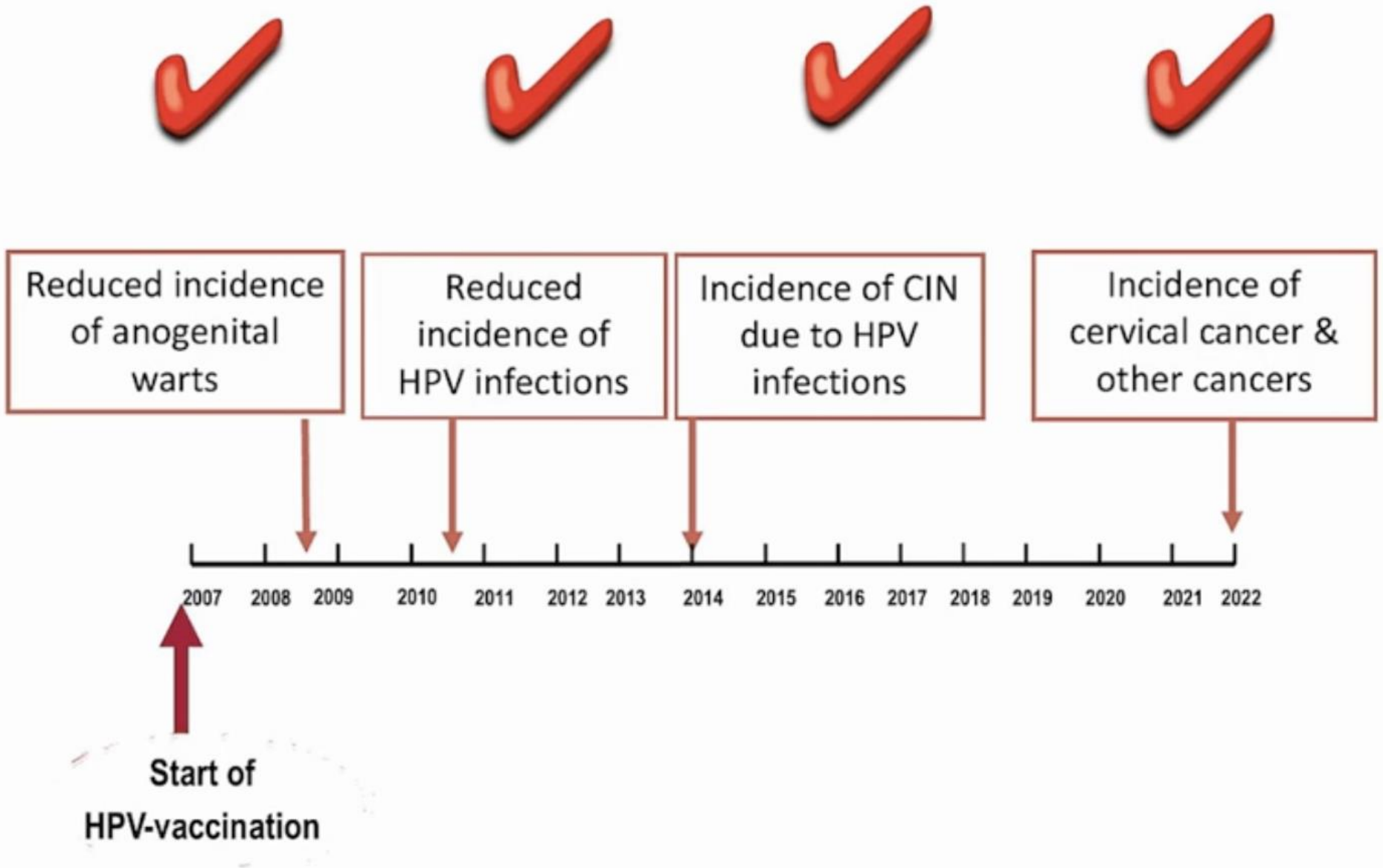

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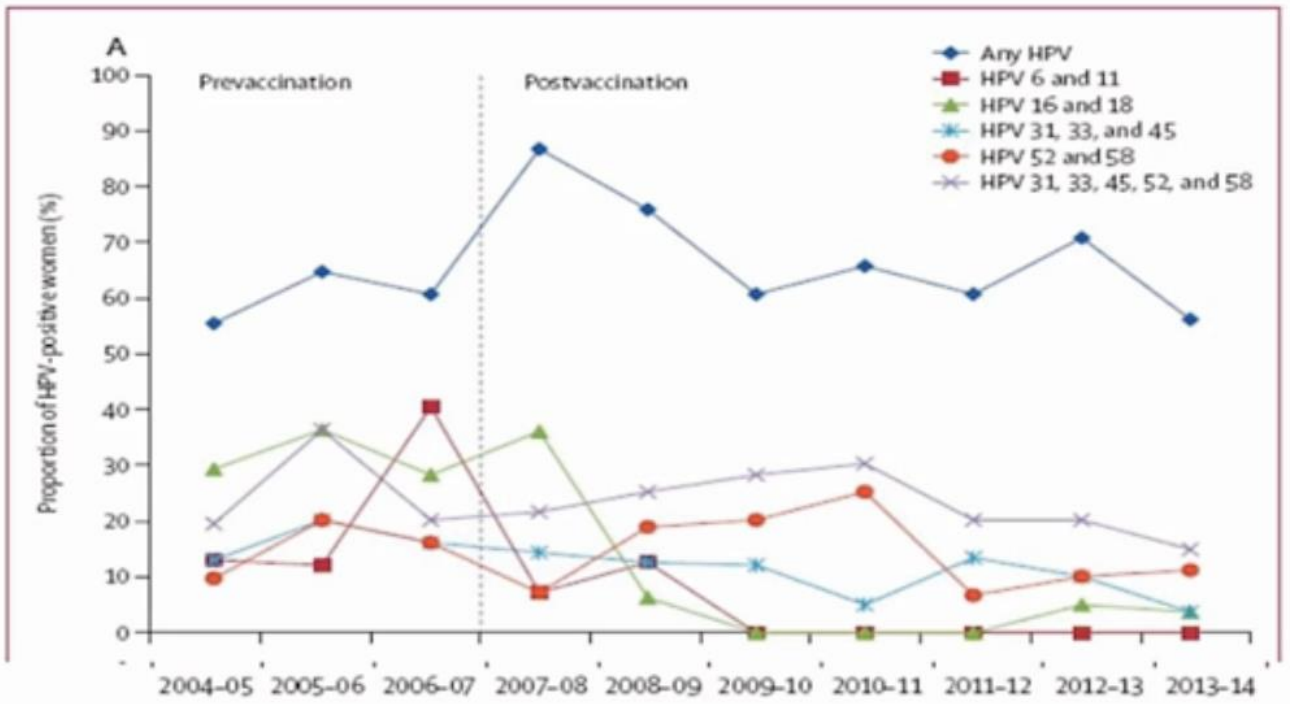
HPV prevalence in women up to 21 years old in Australia following vaccination program implementation with Gardasil with near elimination of HPV types 6, 11, 16, 18



Data from Australia-born women who proceeded in Melbourne Centre of Sexual Health diagnosed with clamydia, in whom a cervical sample was obtained

Chow E, et al. Lancet 2015

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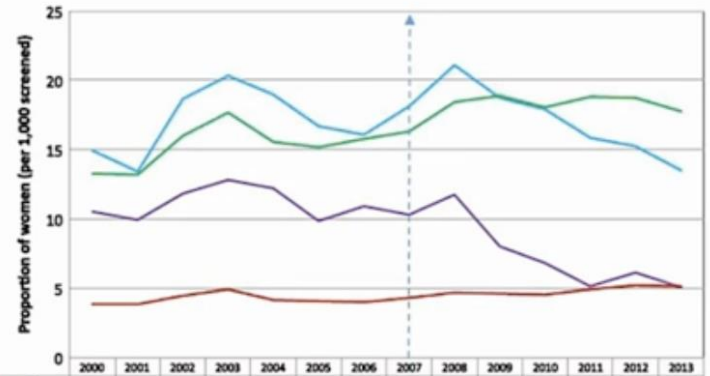
Australia: data on high-grade cervical abnormalities

Brotherton J M L Saville A M et al. Human papillomavirus vaccination is changing the epidemiology of high-grade cervical lesions in Australia
Cancer Causes Control 2015.

Trends in high grade cervical abnormalities (histologically confirmed) by age group, 2000-2013, Victorian Cervical Cytology Registry (Data as held on 20th May 2014. HPV Vaccination programme commenced April 2007)

Incidence of high-grade cervical abnormalities in girls aged <18 years



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
<20 yrs	10.6	9.9	11.8	12.8	12.2	9.8	10.9	10.3	11.8	8.0	6.8	5.1	6.1	5.0
20-24 yrs	15.0	13.4	18.6	20.3	18.9	16.7	16.1	18.1	21.1	18.7	17.9	15.8	15.3	13.5
25-29 yrs	13.3	13.2	16.0	17.7	15.5	15.1	15.8	16.3	18.4	18.9	18.1	18.8	18.8	17.7
30+ yrs	3.8	3.8	4.4	4.9	4.1	4.1	4.0	4.3	4.7	4.6	4.5	4.9	5.2	5.2

Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study

2019

thebmj

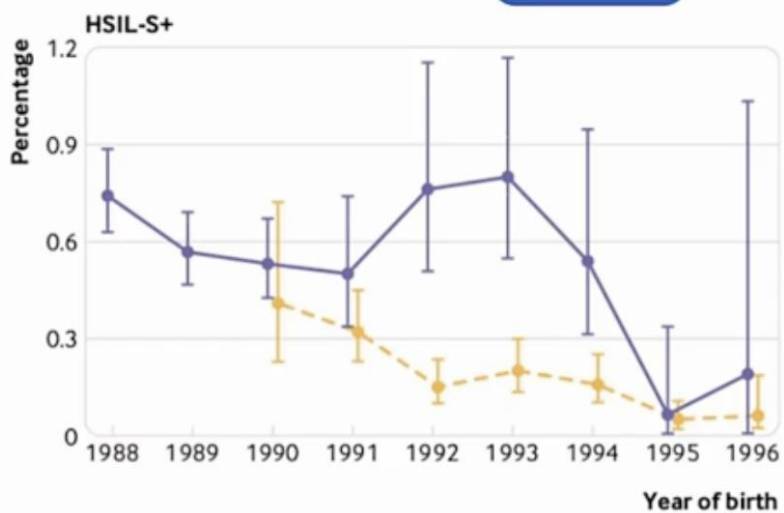
Tim Palmer,[1] Lynn Wallace,[2] Kevin G Pollock,[3,4] Kate Cuschieri,[5] Chris Robertso
Kim Kavanagh,[7] Margaret Cruickshank[8]

Reduction

- CIN3+: 89%
- CIN2+: 88%
- CIN1+: 79%

Vaccination at younger age increasing vaccine effectiveness:

- 12-13y: 86%
- 17y: 51%



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ORIGINAL ARTICLE FREE PREVIEW

HPV Vaccination and the Risk of Invasive Cervical Cancer

Jiayao Lei, Ph.D., Alexander Ploner, Ph.D., K. Miriam Elfström, Ph.D., Jiangrong Wang, Ph.D., Adam Roth, M.D., Ph.D., Fang Fang, M.D., Ph.D., Karin Sundström, M.D., Ph.D., Joakim Dillner, M.D., Ph.D., and Pär Sparén, Ph.D.

Abstract

BACKGROUND The efficacy and effectiveness of the quadrivalent human papillomavirus (HPV) vaccine in preventing high-grade cervical lesions have been shown. However, data to inform the relationship between quadrivalent HPV vaccination and the subsequent risk of invasive cervical cancer are lacking.

METHODS We used nationwide Swedish demographic and health registers to follow an open population of 1,672,983 girls and women who were 10 to 30 years of age from 2006 through 2017. We assessed the association between HPV vaccination and the risk of invasive cervical cancer, controlling for age at follow-up, calendar year, county of residence, and parental characteristics, including education, household income, mother's country of birth, and maternal disease history.

RESULTS During the study period, we evaluated girls and women for cervical cancer until their 31st birthday. Cervical cancer was diagnosed in 19 women who had received the quadrivalent HPV vaccine and in 538 women who had not received the vaccine. The cumulative incidence of cervical cancer was 47 cases per 100,000 persons among women who had been vaccinated and 94 cases per 100,000 persons among those who had not been vaccinated. After adjustment for age at follow-up, the incidence rate ratio for the comparison of the vaccinated population with the unvaccinated population was 0.51 (95% confidence interval [CI], 0.32 to 0.82). After additional adjustment for other covariates, the incidence rate ratio was 0.37 (95% CI, 0.21 to 0.57). After adjustment for all covariates, the incidence rate ratio was 0.12 (95% CI, 0.00 to 0.34) among women who had been vaccinated before the age of 17 years and 0.47 (95% CI, 0.27 to 0.75) among women who had been vaccinated at the age of 17 to 30 years.

CONCLUSIONS Among Swedish girls and women 10 to 30 years old, quadrivalent HPV vaccination was associated with a substantially reduced risk of invasive cervical cancer at the population level. (Funded by the Swedish Foundation for Strategic Research and others.)

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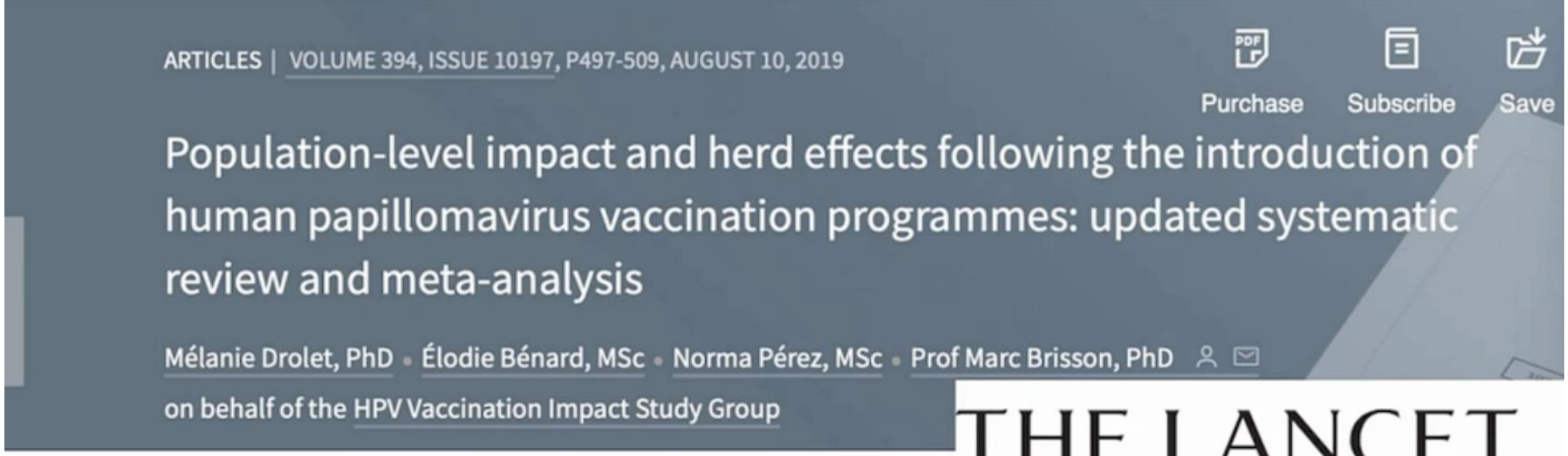

- This updated systematic review and meta-analysis includes data from 60 million individuals and up to 8 years of post-vaccination follow-up
- Our results show compelling evidence of the substantial impact of HPV vaccination programmes on HPV infections and CIN2+ among girls and women, and on anogenital warts diagnoses among girls, women, boys, and men.
- Additionally, programmes with multi-cohort vaccination and high vaccination coverage had a greater direct impact and herd effects.

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How can we achieve better impact?

- Increase coverage: school-based
- Vaccinate Men
- Vaccinate Older Women
- Vaccinate women with previous or current HPV infections
- Vaccinate women after cone

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What is the logic behind vaccinating women with previous cervical disease?

Human Vaccines 5:10, 696-704; October 2009; © 2009 Landes Bioscience

Evaluation of quadrivalent HPV 6/11/16/18 vaccine efficacy against cervical and anogenital disease in subjects with serological evidence of prior vaccine type HPV infection

Sven-Eric Olsson,[1*] Susanne K. Kjaer,[2] Kristján Sigurdsson,[3] Ole-Erik Iversen,[4] Mauricio Hernandez-Avila,[5] Cosette M. Wheeler,[6] Gonzalo Perez,[7,27] Darron R. Brown,[8] Laura A. Koutsky,[9] Eng Hseon Tay,[10] Patricia Garcia,[11] Kevin A. Ault,[12] Suzanne M. Garland,[13] Sepp Leodolter,[14] Grace W.K. Tang,[15] Daron G. Ferris,[16] Jorma Paavonen,[17] Matti Lehtinen,[18] Marc Steben,[19] F. Xavier Bosch,[20] Joakim Dillner,[21] Elmar A. Joura,[22] Slawomir Majewski,[23] Nubia Muñoz,[24] Evan R. Myers,[25] Luisa L. Villa,[26] Frank J. Taddeo,[26] Christine Roberts,[26] Amha Tadesse,[26] Janine Bryan,[26] Roger Maansson,[26] Scott Vuocolo,[26] Teresa M. Hesley,[26] Alfred Saah,[26] Eliav Barr[26] and Richard M. Haupt[26]

- Vaccines also effective in women and men with previous but cleared infections

- Analysis 2,617 women - 3 clinical studies
  HPV seropositive but DNA negative subjects receiving:
- HPV 6/11/16/18 vaccine: NO subject developed disease to vaccine type
- Placebo: 7 cases cervical disease and 8 cases of external genital disease related to a vaccine HPV type

- Vaccine confers protection from re-infection or re-activation, natural immunity from induced antibodies does not protect overtime

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Should older women be vaccinated?...
Should women in colposcopy be vaccinated?...
Should women be vaccinated after local excision?...

- At present it remains an individual choice
  - Real world data confirm trial data: lower protection in adult vs younger females
  - Vaccination of women >=30Y not cost-effective
  - There is no harm and it is safe…but not funded

- Prophylactic … vaccines do not prevent progression of HPV infection to disease, decrease time to clearance of HPV infection, or treat HPV-related disease.

- Ideally, should be given in early adolescence …. For 27 through 45, clinicians can consider discussing HPV vaccination with persons who are most likely to benefit.

- Vaccine effectiveness might be low among persons with risk factors for HPV infection or disease (e.g., adults with multiple lifetime sex partners and likely previous infection with vaccine-type HPV), as well as among persons with certain immunocompromising conditions.

- After local excision: Promising data but at risk of bias
  - Well designed RCT is required to assess effectiveness… and cost-effectiveness
  - Before this can be introduced in national vaccination programmes
  - Extended to multi-focal disease etc

ESGO
European Society of Gynaecological Oncology

BJC
British Journal of Cancer
www.nature.com/bjc

CONSENSUS STATEMENT

Cervical screening: ESGO-EFC position paper of the European Society of Gynaecologic Oncology (ESGO) and the European Federation of Colposcopy (EFC)

Maria Kyrgiou[1,2], Marc Arbyn[3], Christine Bergeron[4], F. Xavier Bosch[5,6,7], Joakim Dillner[8], Mark Jit[9,10,11], Jane Kim[12], Mario Poljak[13], Pekka Nieminen[14], Peter Sasieni[15], Vesna Kesic[16], Jack Cuzick[17] and Murat Gultekin[18]

Table 1. Summary of European Union Guidelines for Quality Assurance in Cervical Screening, completed with ESGO/EFC expert opinion.

1	Screening needs to identify the target population that is to be screened. This is the basis of population-based programs and is usually done by obtaining a list of individuals from a population registry belonging to the target age range. EU guidelines accept starting screening in the range 20–29 years but do not recommend screening before 25 years. Screening of cohorts vaccinated against HPV can start later but currently no specific European-wide guidelines exist for vaccinated cohorts.
2	The target population that is due for screening should have a personalised invitation to screening. This is the basis of organised screening programs. In addition to the lists with the target population, lists with actually performed screening tests (from whom and when) should be obtained from the screening laboratories. In order to be able to provide a time, date and place for a personalised appointment, an organisation that can take the samples is also needed. Main Quality Indicator: Invitation coverage—number of women in the target population due for screening that receive a personalised invitation with specified time and place/all women in the target population due for screening
3	Women who do not attend their screening appointment should be sent a new personalised invitation next year. Main Quality Indicator: Renewed invitation coverage—number of non-attending women who receive a new annual invitation/All non-attending women.
4	Women who have not attended after repeated invitations could be sent an HPV self-sampling kit. Main Quality Indicators: Test coverage—number of women in the target population that are recommended to be screened that are actually screened in the recommended interval/all women in the target population that are recommended to be screened. Test coverage can be calculated for any given length of time. When monitoring the effect of repeat invitations and sending of self-sampling kits calculating test coverage at increased lengths such as 5-year or 10-year test coverage is useful.
5	Organised screening with HPV testing is recommended until the age of 65 years. Women who have had a negative screening test at age 65 can exit the program, whereas non-attenders still could receive invitations beyond the age of 65. There is no current agreement on the age of initiation of screening.
7	Double screening with both HPV and cytology is recommended against. Primary HPV testing outside of an organised programme is also recommended against.
8	Sending of self-sampling kits to the entire population (i.e. not only to non-attenders) is currently not recommended.
9	It is recommended to prolong the screening interval for HPV-negative women, to ensure that the annual proportion of the population that require gynaecological investigation is kept reasonably low (to save resources and avoid possible side effects). The interval can be prolonged.
10	Women who are HPV-positive in primary screening should be triaged with cytology. Women with abnormal cytology should be referred for gynaecological investigation. Direct referral to colposcopy of all HPV-positive women is recommended against. Main Quality Indicator: Proportion of women HPV-positive in primary screening who are cytology-positive and are referred/all women who are HPV-positive in primary screening. HPV-positive women with negative reflex cytology should have a new triage test some time later, which could be cytology or a hrHPV test. Other options can be considered.
11	In age groups where primary cytology screening is used (below 30 years), women with high-grade cytology or worse should be directly referred. Women with equivocal or mildly abnormal may have a reflex HPV-test and be referred to colposcopy if HPV-positive. Screening programs should monitor the results of the program and allow for incremental optimisations in the program: Repeat testing of women with inconclusive screening (e.g. HPV + /cytology−), referral policies and compliance to referral, results of triage tests, colposcopies, biopsies and treatment of precancers. The efficiency of the program should be continuously monitored to ensure optimal use of resources that results in a maximal protection against cervical cancer. Key factors to monitor are the proportion of screen-positive women (the prevalence of HPV infections), the number and cost of invitations, sampling, testing and repeat testing, colposcopies and CIN treatments, in the context of the observed reduction in the incidence of cervical cancers.
12	All laboratories performing cytology or HPV testing should be accredited and take part in an official quality assurance program. The screening program should audit cancer cases.
13	When purchasing HPV tests for primary screening, programs should only ask for HPV tests that have been clinically validated.

Παθολογία Τραχήλου & Κολποσκόπηση:
Κυτταρολογία - Βιοδείκτες - Κολποσκόπηση
Ιστολογία & περαιτέρω διαχείριση
17-20 Οκτωβρίου 2024

Review

ACTA CYTOLOGICA

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Published online: May 19, 2015

The Pap Test and Bethesda 2014

"The reports of my demise have been greatly exaggerated."
(after a quotation from Mark Twain)

Ritu Nayar[a, b] David C. Wilbur[c, d]

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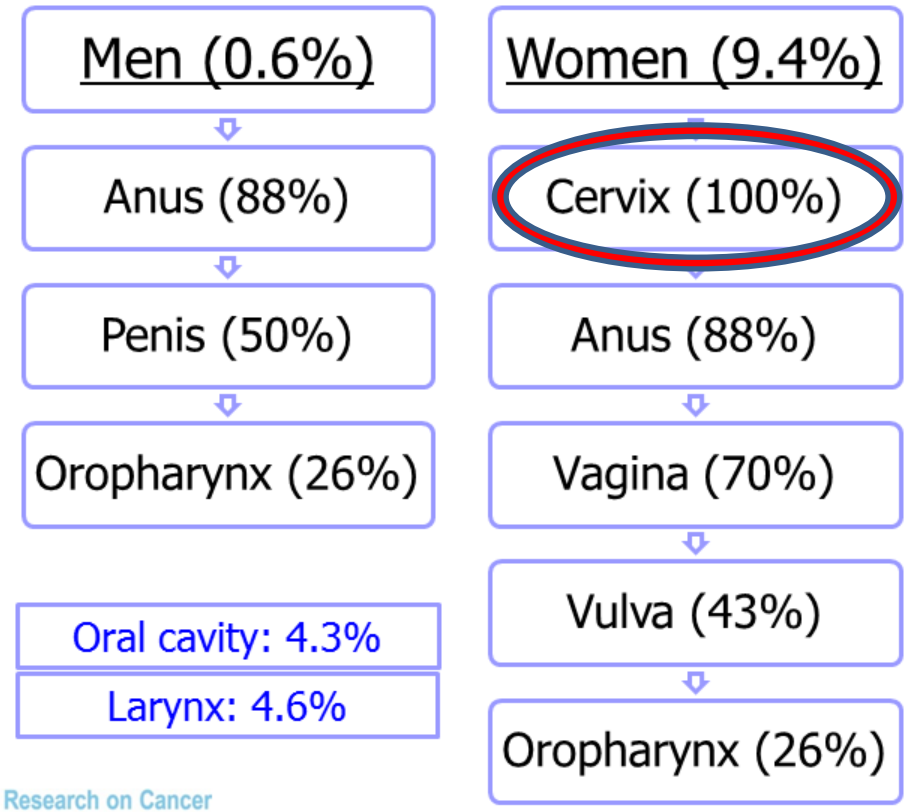
EPITHELIAL CELL ABNORMALITIES

SQUAMOUS CELL

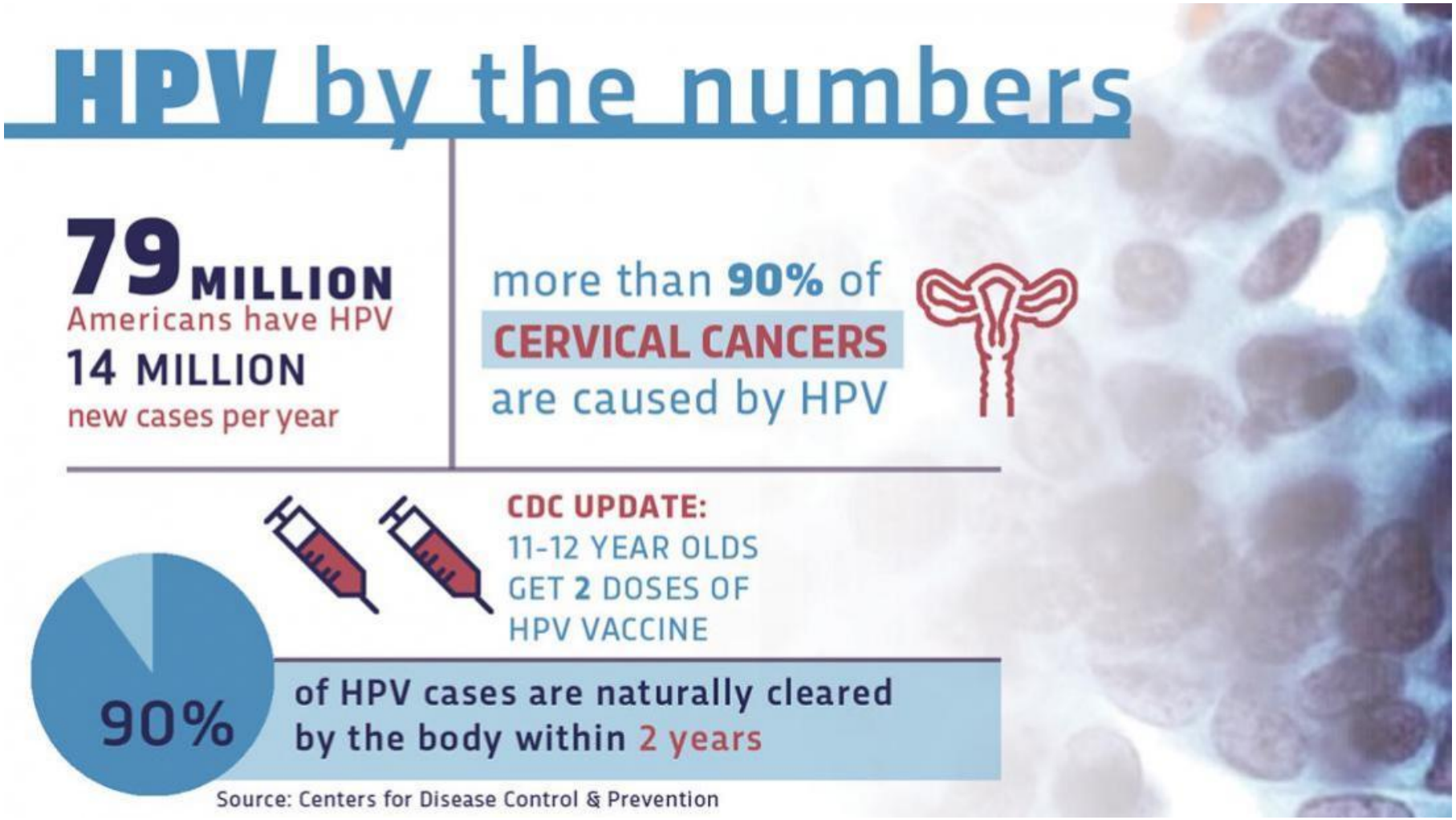
- Atypical squamous cells
  - of undetermined significance (ASC-US)
  - cannot exclude HSIL (ASC-H)
- Low-grade squamous intraepithelial lesion (LSIL)
  (encompassing: HPV/mild dysplasia/CIN 1)
- High-grade squamous intraepithelial lesion (HSIL)
  (encompassing: moderate and severe dysplasia, CIS; CIN 2 and CIN 3)
  - with features suspicious for invasion (*if invasion is suspected*)
- Squamous cell carcinoma

Cancers Attributed to HPV



International Agency for Research on Cancer
World Health Organization

de Martel C. Lancet Oncol 2012
Plummer Lancet Glob Health 2016;


HPV by the numbers
79 MILLION
Americans have HPV
14 MILLION
new cases per year
more than 90% of
CERVICAL CANCERS
are caused by HPV
CDC UPDATE:
11-12 YEAR OLDS
GET 2 DOSES OF
HPV VACCINE
90%
of HPV cases are naturally cleared
by the body within 2 years
Source: Centers for Disease Control & Prevention

Ταξινόμηση

Παλαιά ταξινόμηση	Ταξινόμηση κατά WHO (2003)	Ταξινόμηση κατά WHO (2014)
Ήπια δυσπλασία	CIN 1	Χαμηλόβαθμη πλακώδης ενδοεπιθηλιακή αλλοίωση (LSIL)
Μέτρια δυσπλασία / βαριά δυσπλασία / καρκίνωμα in citu	CIN2 CIN3	Υψηλόβαθμη πλακώδης ενδοεπιθηλιακή αλλοίωση (HSIL)

- Atypical squamous cells-undetermined significance" (ASC-US): 90-95%
- Atypical squamous cells-cannot exclude a high-grade squamous intraepithelial lesion" (ASC-H): 5-10%
- The ASC-H category was developed to highlight the minor subset of ASC considered suspicious for a cancer precursor lesion, that is, HSIL.
- This indicates that definite LSIL is present as well as some cells suggest the possibility of HSIL.

Solomon D et al., JAMA 2002

ASC-cannot rule out HSIL (ASC-H)

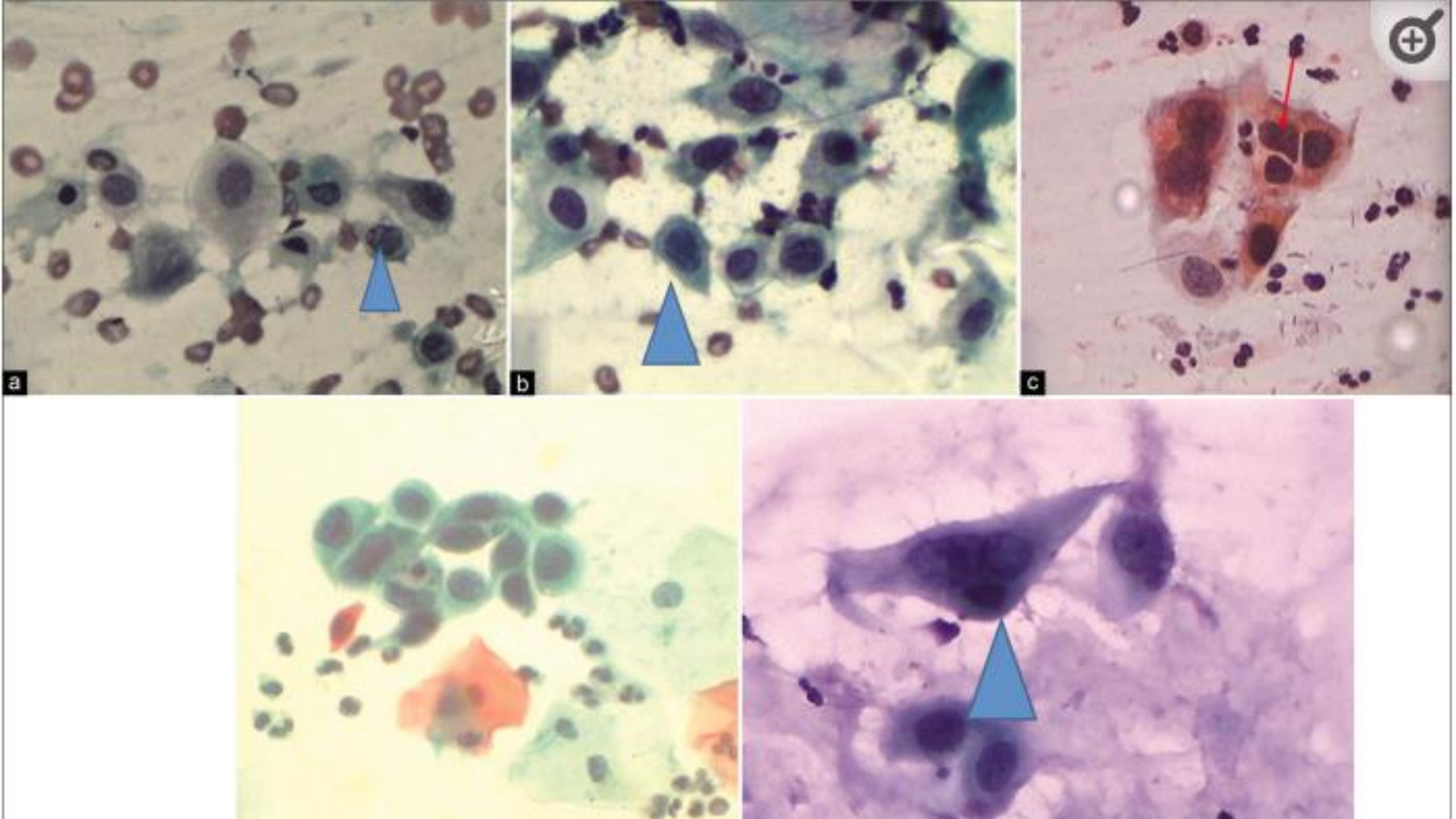
- ASC-H is a designation reserved for the minority of ASC cases (<10%), in which the cytology changes are suggestive of HSIL
- Cases classified as ASC-H are associated with a higher predictive value for detecting an underlying CIN2 or CIN3 than ASC-US
- It warrants ***immediate colposcopy to confirm or exclude the presence of HSIL***. ASC-H does not represent single biologic entity
- Studies show 35–50% of women with ASC are infected with hrHPV, and the remaining non-infected women are not at increased risk

Kattoor J, Kamal MM. Cytojournal. 2022

Cytomorphology

- ASC-H usually affects immature squamous metaplastic cells
- Immature squamous metaplasia is one of the most common mimics of ASC-H
- ASC-H cells demonstrate nuclear enlargement at least 1.5–2.5 times of metaplastic cells
- High N: C ratio, coarse chromatin pattern, as well as some degree of hyperchromasia, abnormal nuclear shapes, and nuclear membrane irregularity favor HSIL over benign metaplasia

Kattoor J, Kamal MM. Cytojournal. 2022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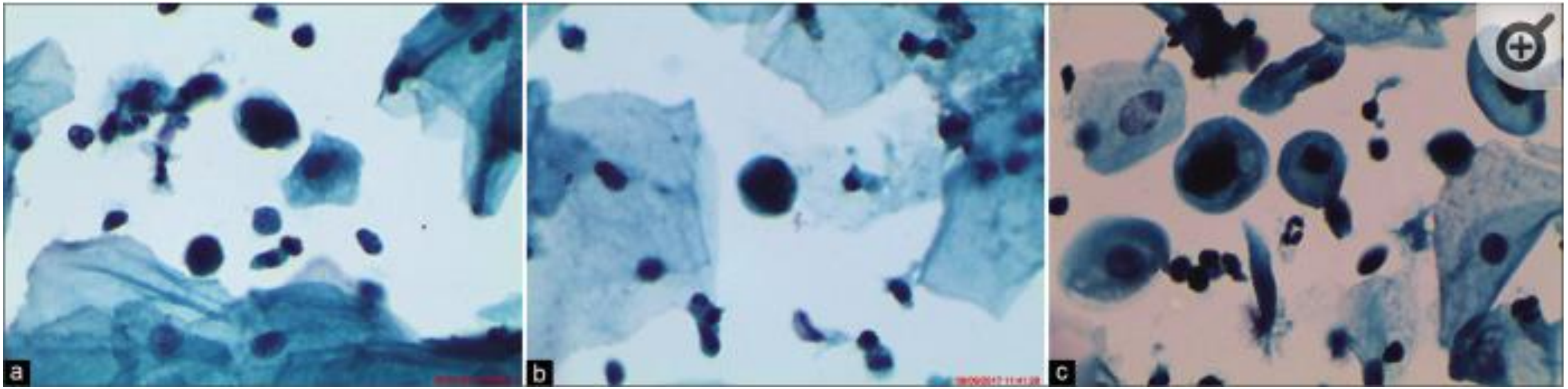
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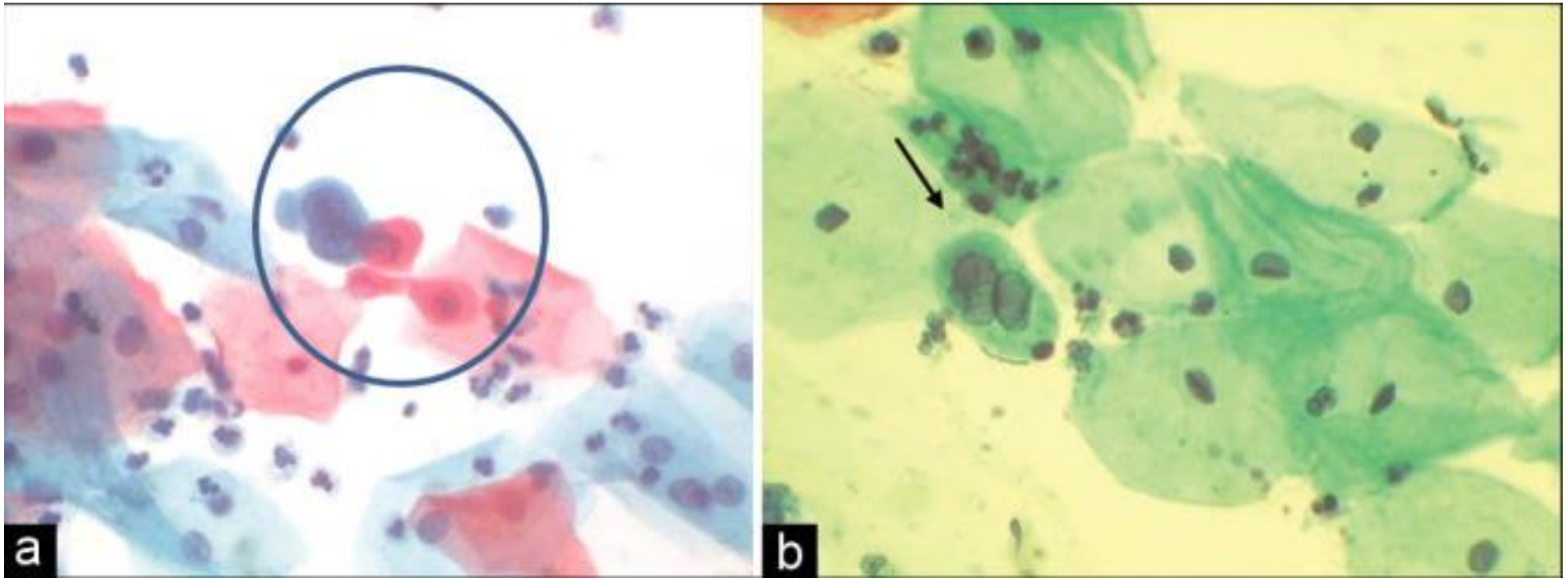
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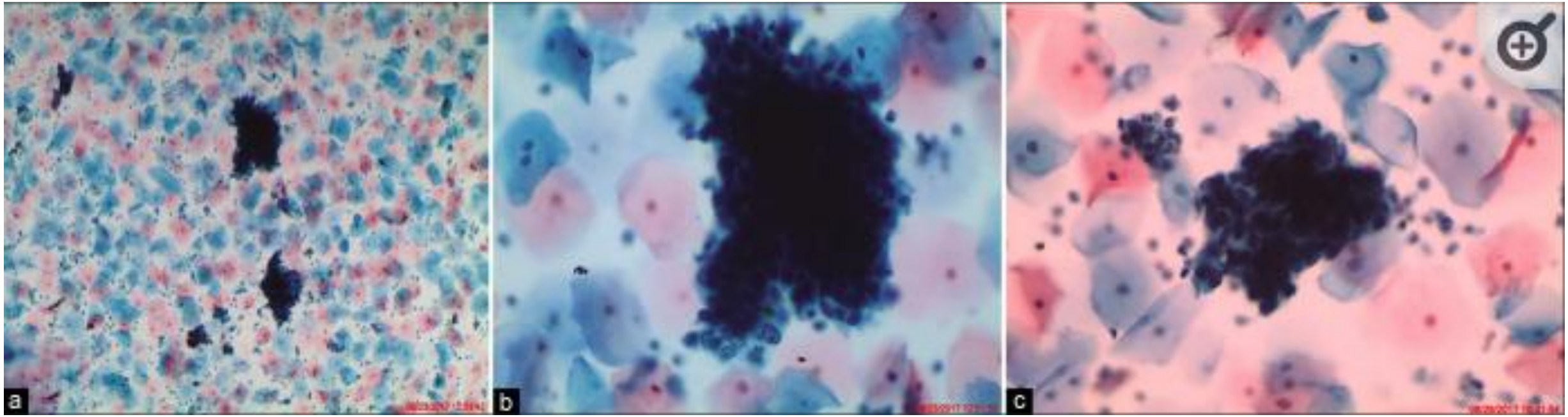
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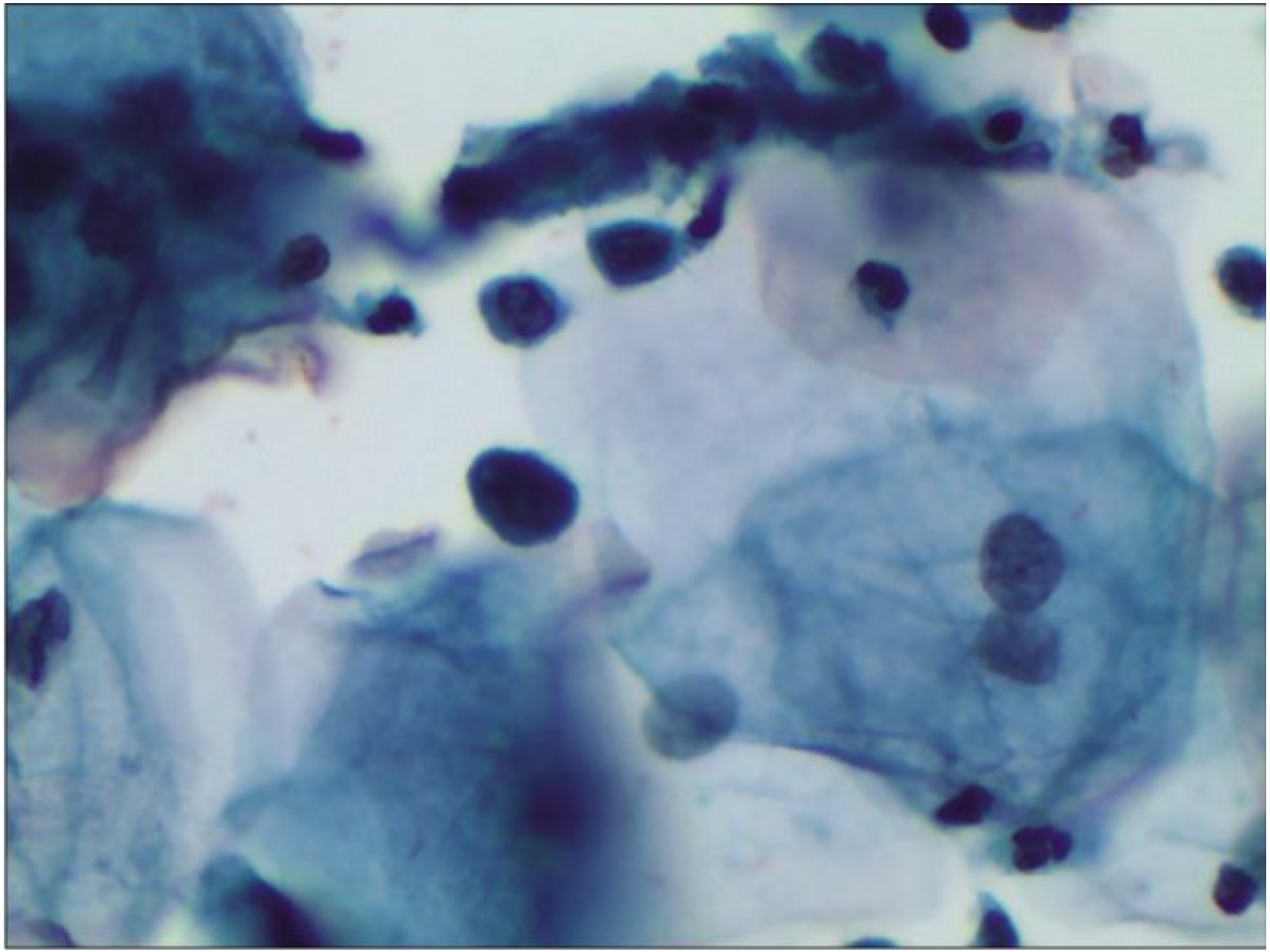

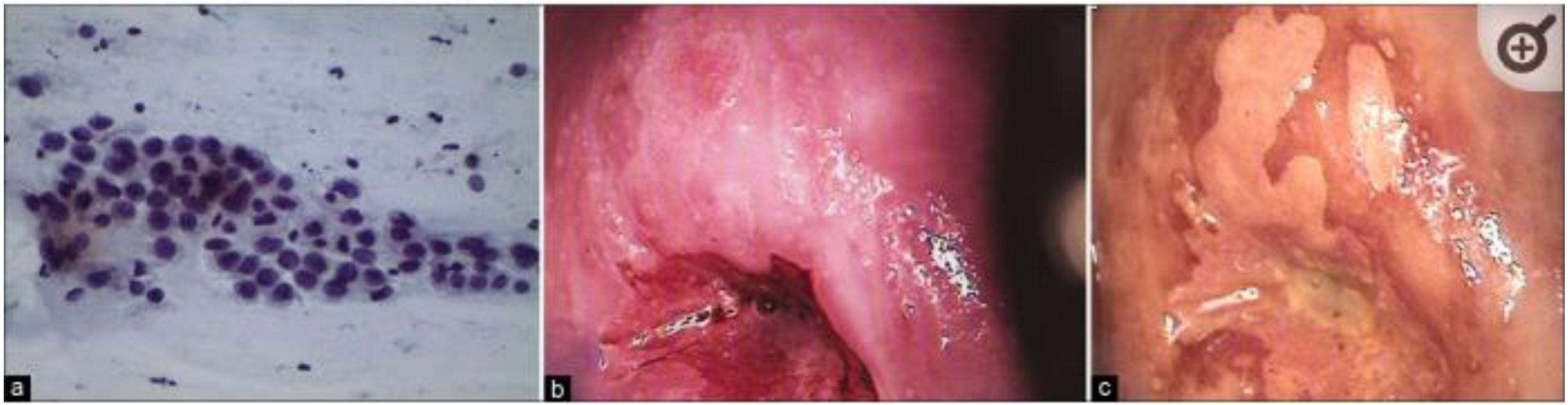
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ASC-H is associated with higher risk of oncogenic HPV DNA detection and greater risk of underlying CIN2 or worse (30–40%) compared to ASC-US (10–15%).

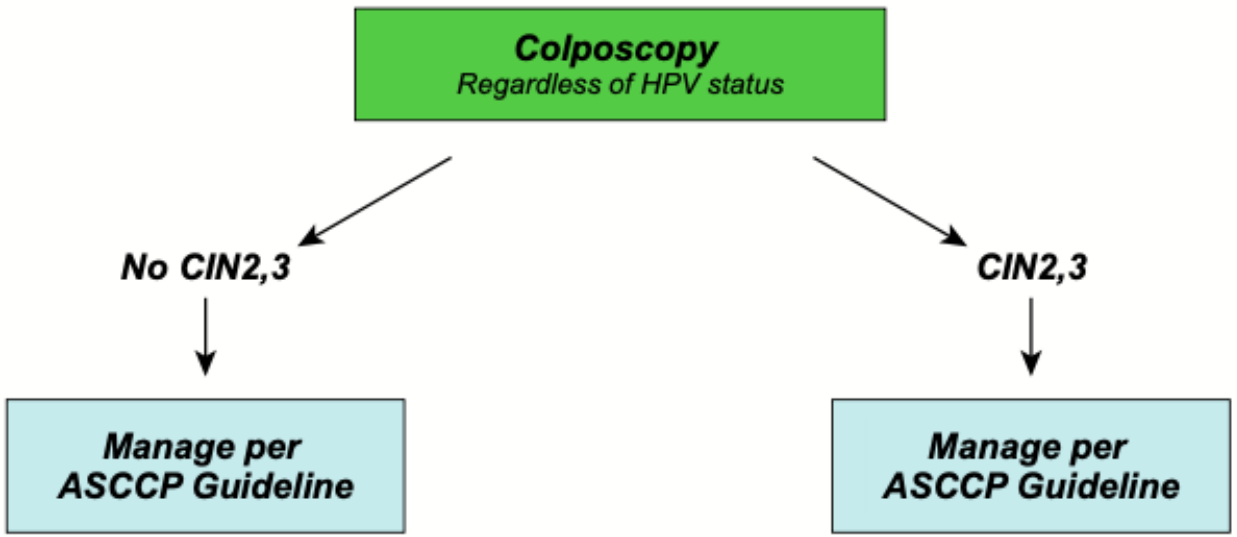
Massad LS et al., Obstet Gynecol 2013

Διαχείριση ASC-H

- HPV testing is not recommended for triage of ASC-H
- The recommended management of ASC-H is colposcopy
- Management of women with ASC-H and colposcopy that does not result in histologic diagnosis of CIN2 or more severe lesion should be individualized based on review of all pathologic or clinical findings
- Careful follow-up is required either with HPV testing at 12 months or cytology testing at 6 and 12 months
- In contradistinction to definitive interpretation of HSIL, immediate treatment without colposcopy is not possible.

Stoler MH *Clin Lab Med* 2003
Massad LS et al., Obstet Gynecol 2013

*Management of Women with Atypical Squamous Cells: Cannot Exclude High-grade SIL (ASC-H)**



* Management options may vary if the woman is ages 21-24

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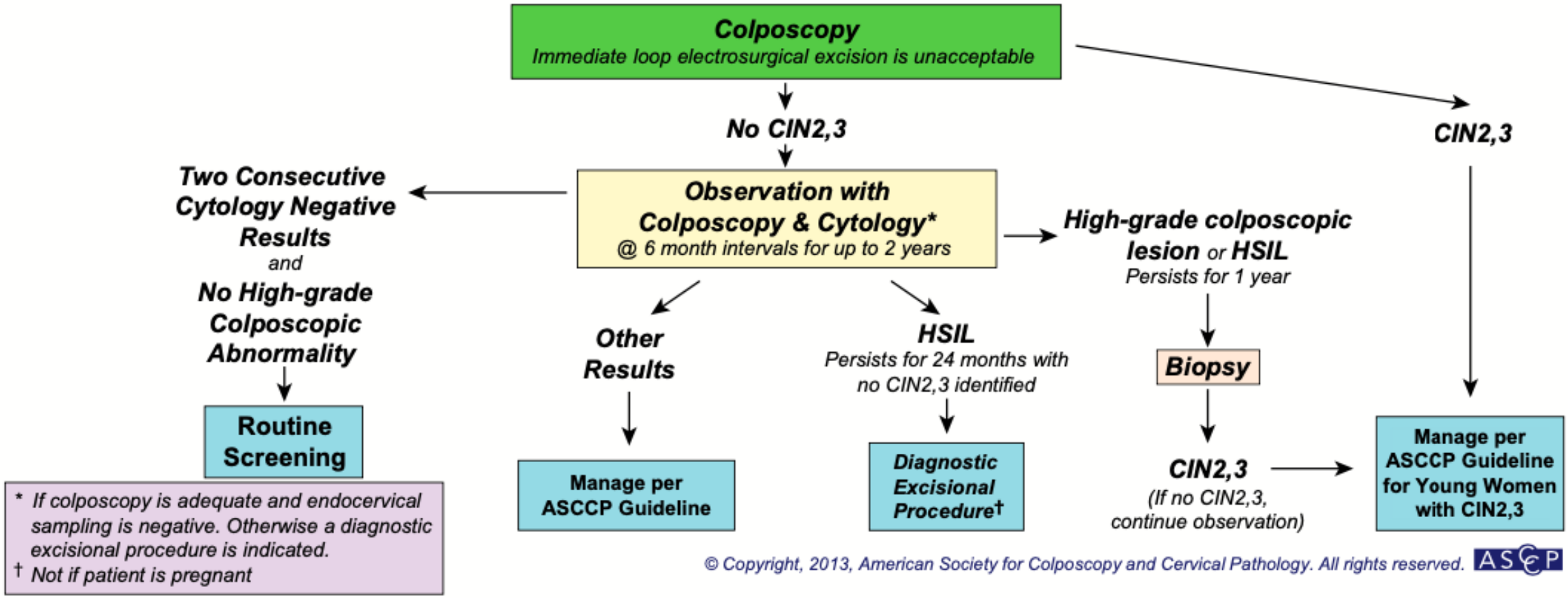
Management of Women Ages 21-24 yrs with Atypical Squamous Cells, Cannot Rule Out High Grade SIL (ASC-H) and High-grade Squamous Intraepithelial Lesion (HSIL)



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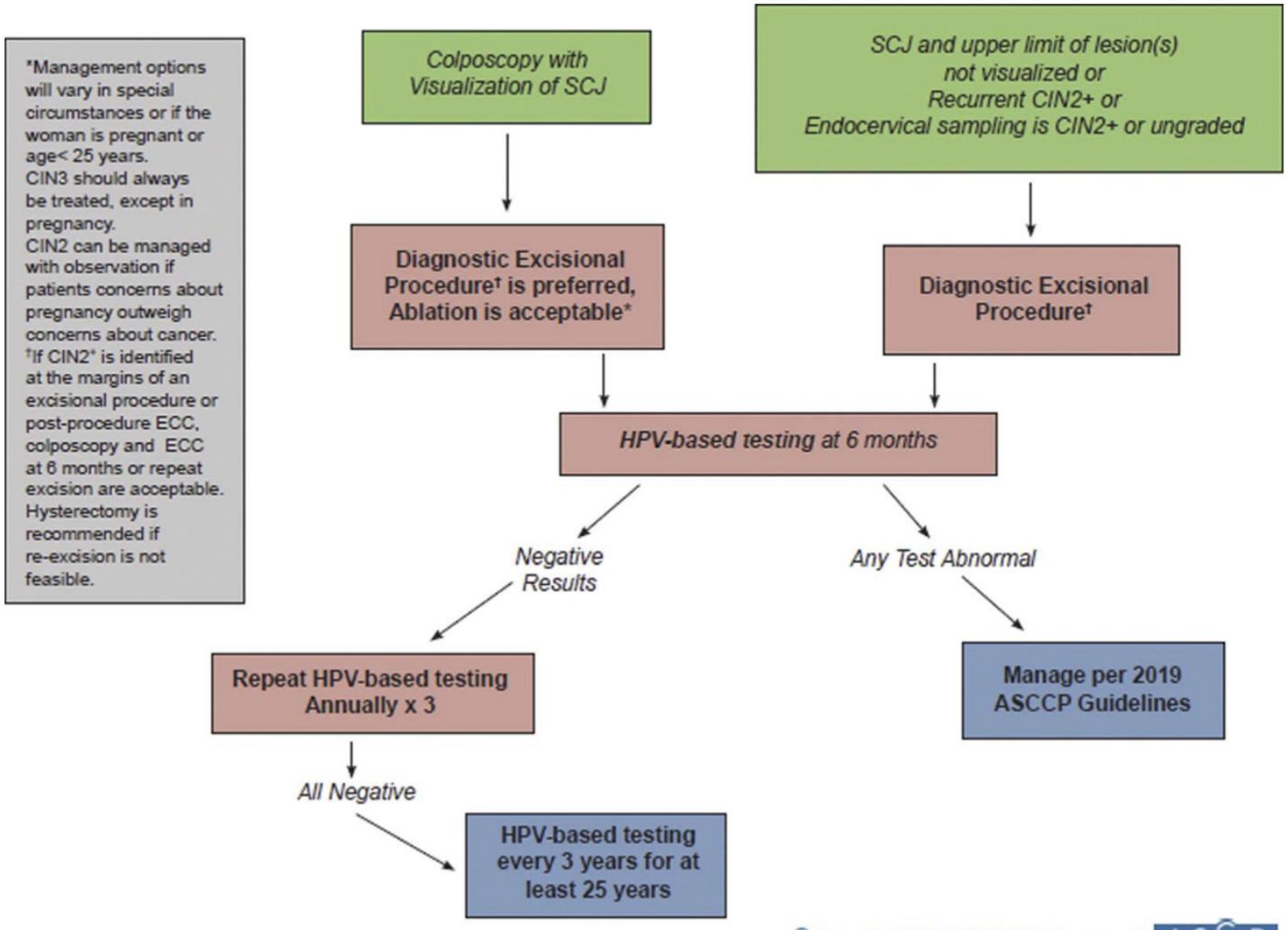

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Management of Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 2 and 3 (CIN2,3)*

* Management options will vary in special circumstances or if the woman is pregnant or ages 21-24

† If CIN2,3 is identified at the margins of an excisional procedure or post-procedure ECC, cytology and ECC at 4-6mo is preferred, but repeat excision is acceptable and hysterectomy is acceptable if re-excision is not feasible.

Adequate Colposcopy

↓

Either Excision† or Ablation of T-zone*

↓

2x Negative Results

↓

Repeat cotesting
@ 3 years

↓

Routine Screening

Inadequate Colposcopy or Recurrent CIN2,3 or Endocervical sampling is CIN2,3

↓

Diagnostic Excisional Procedure†

↓

Cotesting
@ 12 & 24 months

↓

Any Test Abnormal

↓

Colposcopy
With endocervical sampling

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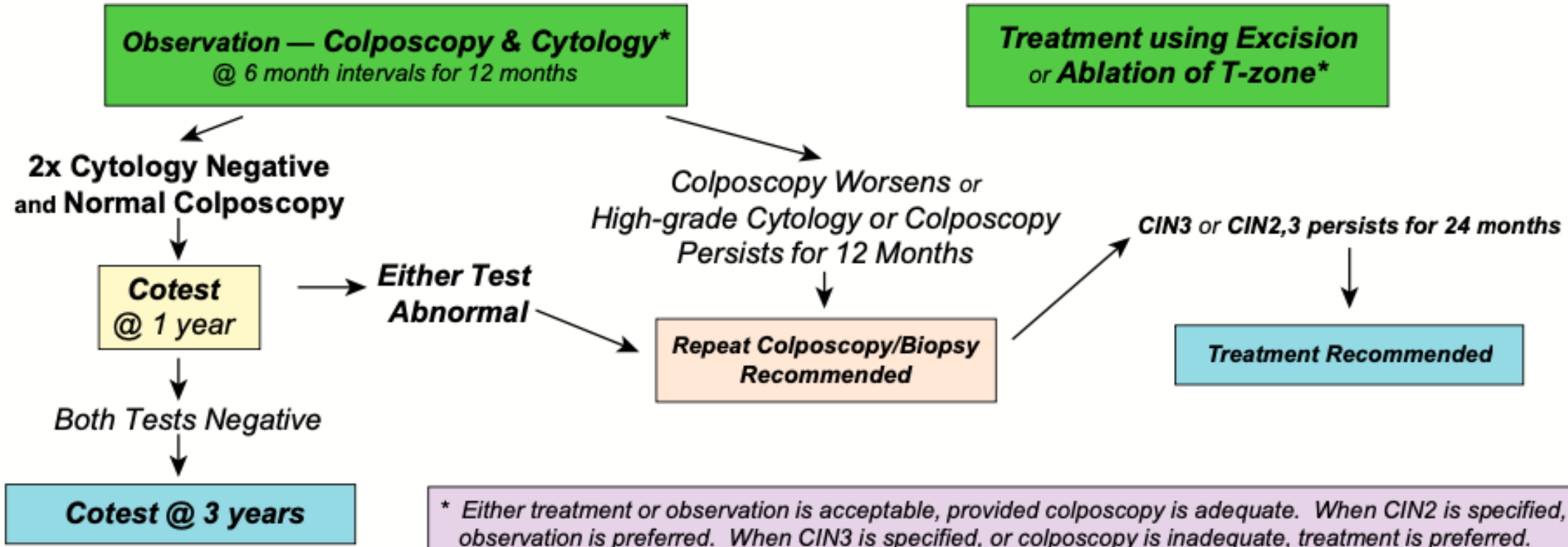
Management of Young Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 2,3 (CIN2,3) in Special Circumstances*



* Either treatment or observation is acceptable, provided colposcopy is adequate. When CIN2 is specified, observation is preferred. When CIN3 is specified, or colposcopy is inadequate, treatment is preferred.

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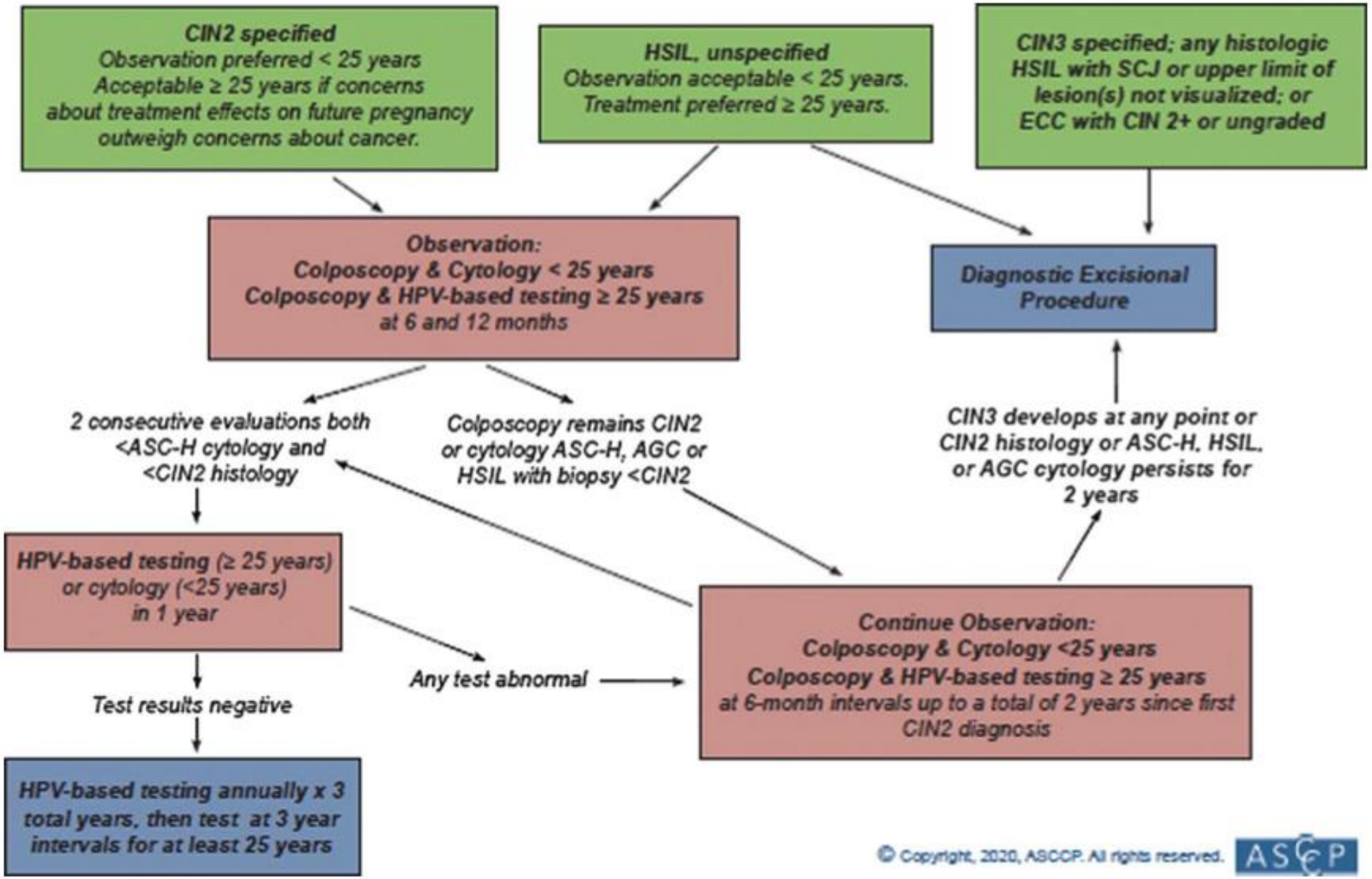
CIN2 σε νεαρές ηλικίες



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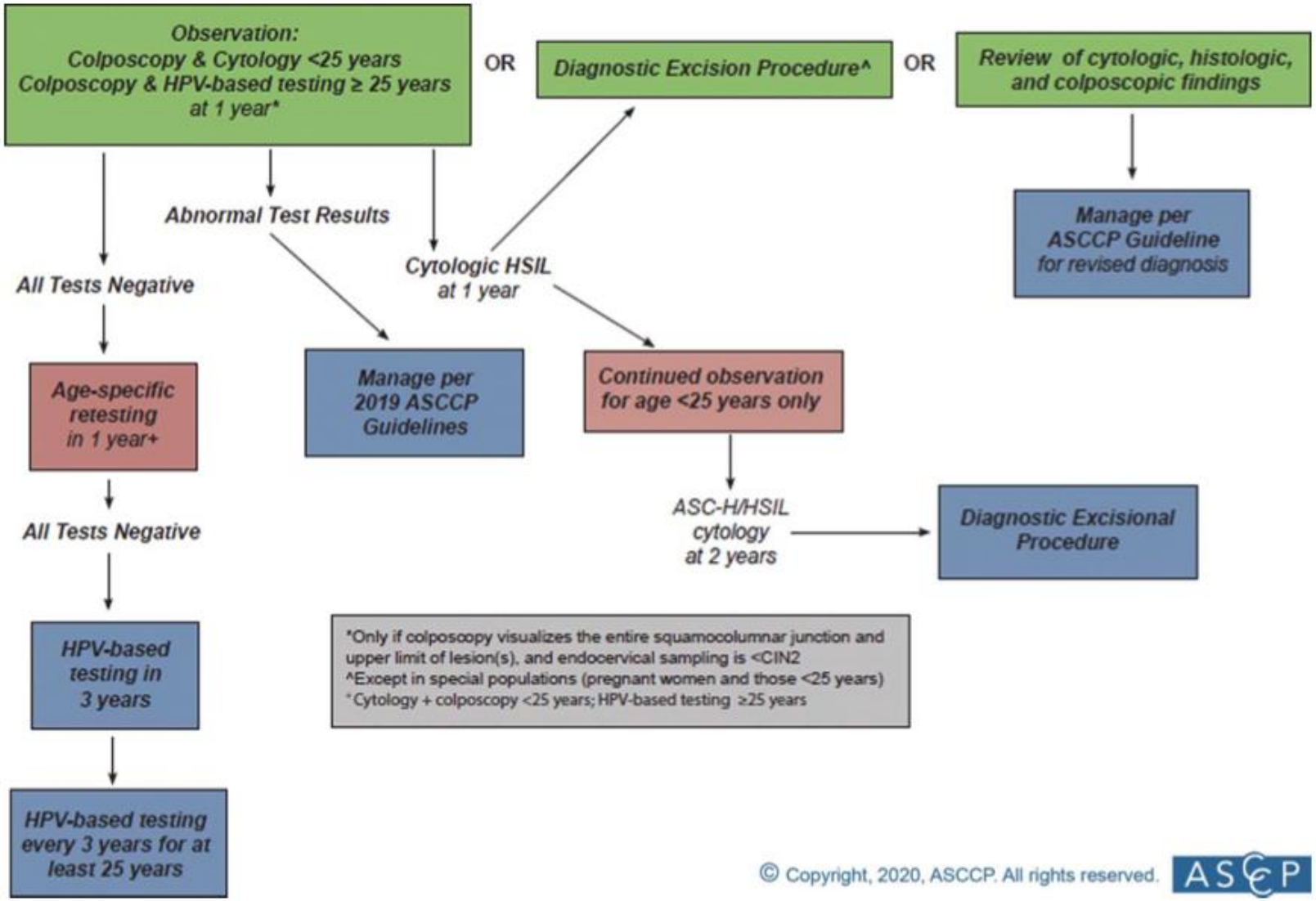
Ιστολογία LSIL μετά από κυτταρολογία



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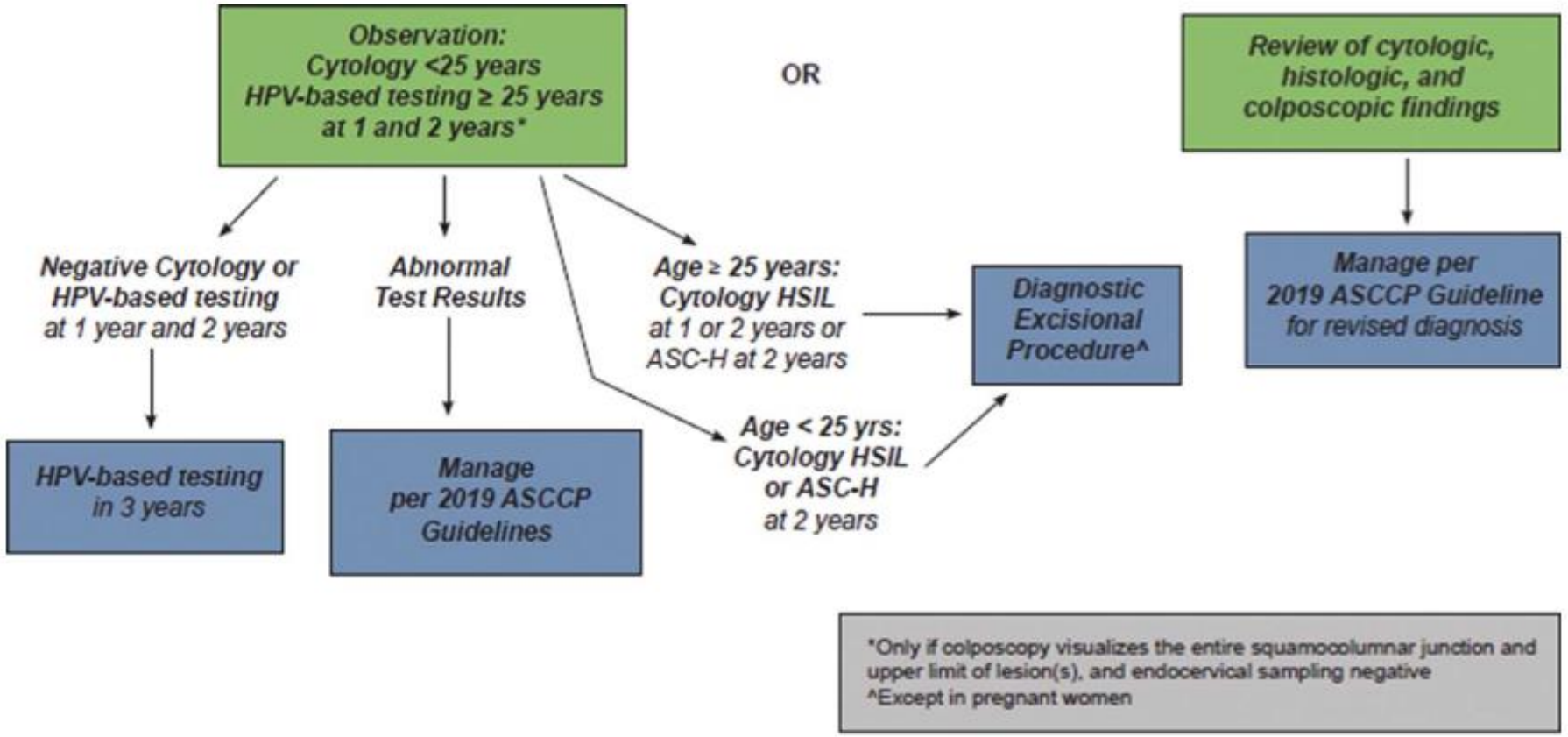
Ιστολογία LSIL μετά από κυτταρολογία AC-
''



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Παραπομπή για κολποσκόπηση (1)

- Σε υψηλόβαθμη κυτταρολογία (HSIL ή ASC-H)

- Σε χαμηλόβαθμη κυτταρολογία (LSIL)

✓ Αν έχει πραγματοποιηθεί και HPV testing (co-testing), το δεύτερο μπορεί να λειτουργήσει και σαν διαλογή.

✓ Αν το HPV testing είναι θετικό → κολποσκόπηση

✓ Αν το HPV testing είναι αρνητικό → επανάληψη του co-testing σε 12 μήνες και κολποσκόπηση αν οποιοδήποτε τεστ βγει θετικό

✓ Επίσης αποδεκτή η άμεση διενέργεια κολποσκόπησης χωρίς επανάληψη

Παραπομπή για κολποσκόπηση (2)

- ASC-US κυτταρολογία

✓ HPV testing για διαλογή ακόμα και σε γυναίκες < 25 ετών

✓ Αν το HPV testing είναι θετικό → κολποσκόπηση άμεσα

✓ Αν το HPV testing είναι αρνητικό → τακτικός έλεγχος

✓ Αν το HPV testing δεν είναι εφικτό → επανάληψη της κυτταρολογίας σε 12 μήνες και κολποσκόπηση αν η κυτταρολογία εξακολουθεί να είναι ASC-US+

- Φυσιολογική κυτταρολογία και θετικό HPV testing

✓ Επανάληψη του co-testing σε 12 μήνες και παραπομπή για κολποσκόπηση να οποιοδήποτε τεστ βγει θετικό

✓ Γονοτύπηση για τους υπότυπους 16/18. Αν βγει θετική → κολποσκόπηση άμεσα ενώ αν βγει αρνητική → επανάληψη του co-testing σε 12 μήνες

Παραπομπή για κολποσκόπηση (3)

- Φυσιολογική αλλά ανεπαρκής κυτταρολογία

✓ Σε γυναίκες < 30 ετών ή > 30 ετών με αρνητικό HPV testing → καμία ενέργεια

✓ Σε γυναίκες > 30 ετών με θετικό HPV testing = φυσική κυτταρολογία με θετικό HPV testing

✓ Σε γυναίκες > 30 ετών χωρίς διαθέσιμο HPV testing → επανάληψη της κυτταρολογίας σε 3 χρόνια

Παραπομπή για κολποσκόπηση (4)

- Μη ικανοποιητική κυτταρολογία (αίμα, φλεγμονή)

✓ Επανάληψη κυτταρολογίας σε 3 μήνες + κολποσκόπηση αν η κυτταρολογία εξακολουθεί να είναι μη ικανοποιητική

✓ Αν έχει γίνει HPV testing και είναι αρνητικό → επανάληψη κυτταρολογίας σε 3 μήνες

✓ Αν το HPV testing είναι θετικό → κολποσκόπηση ή επανάληψη κυτταρολογίας σε 3 μήνες

✓ Αν η ασθενής είναι θετική στους υπότυπους 16/18 → κολποσκόπηση άμεσα

- Σε άτυπα αδενικά κύτταρα (AGC) ή αδενοκαρκίνωμα in citu (AIS)

Κολποσκοπική διάγνωση CIN

- Πολλαπλές στοχευμένες βιοψίες (2-4) από τις λευκάζουζες (acetowhite) περιοχές

- Σε περίπτωση απουσίας acetowhite περιοχών ή άλλων αλλοιώσεων, οι τυφλές βιοψίες δεν συστήνονται


THIS WAY
THAT WAY

Αντιμετώπιση CIN μετά την κολποσκόπηση

- Θεραπεία σε περιπτώσεις CIN2+ ή επιμόνου CIN1 για τουλάχιστον 2 έτη
- Η θεραπεία δεν προτείνεται στις υπόλοιπες περιπτώσεις προς αποφυγή μαιευτικών επιπλοκών που σχετίζονται με τη θεραπεία
- Οι θεραπείες εκτομής (excision) προτιμώνται έναντι των θεραπειών εξάχνωσης (ablation)
- Απαραίτητη η ιστολογική εξέταση του κώνου (εστίες μικρο-διηθητικού καρκίνου, υγιή όρια)

≤ CIN1 (μετά από φυσιολογική/ASC-US/LSIL κυτταρολογία)

- < 25 ετών: επανάληψη κυτταρολογίας σε 1 χρόνο

✓ Σε περίπτωση φυσιολογικής, ASC-US ή LSIL κυτταρολογίας στον 1ο χρόνο→ επανάληψη κυτταρολογίας στον 2ο χρόνο και κολποσκόπηση (θεραπεία) αν η κυτταρολογία είναι ASC-US+ στον 2ο χρόνο

✓ Αν η κυτταρολογία είναι ASC-H/HSIL στον 1ο χρόνο → κολποσκόπηση άμεσα

- > 25 ετών: Επανάληψη κυτταρολογίας και HPV testing σε ένα χρόνο

✓ Σε περίπτωση ASC-US+ ή θετικού HPV testing → κολποσκόπηση και θεραπεία βάσει ευρημάτων

✓ Αν το co-testing είναι αρνητικό → screening

≤ CIN1 (μετά από ASC-H/HSIL κυτταρολογία)

- < 25 ετών: κυτταρολογία και κολποσκόπηση στους 12 και 24 μήνες και περαιτέρω αντιμετώπιση σύμφωνα με τα ευρήματα

- > 25 ετών: κυτταρολογία, HPV testing και κολποσκόπηση στους 12 και 24 μήνες και περαιτέρω αντιμετώπιση σύμφωνα με τα ευρήματα

- Σε κολποσκοπική/ιστολογική διάγνωση ≤ CIN1 μετά από HSIL κυτταρολογία είναι αποδεκτή και η άμεση διαγνωστική εκτομή της αλλοίωσης, χωρίς να προηγηθεί συντηρητική παρακολούθηση

CIN2

RESEARCH

OPEN ACCESS

Clinical course of untreated cervical intraepithelial neoplasia grade 2 under active surveillance: systematic review and meta-analysis

Karoliina Tainio,[1] Antonios Athanasiou,[2] Kari A O Tikkinen,[3] Riikka Aaltonen,[4] Jovita Cárdenas Hernándes,[5] Sivan Glazer-Livson,[1] Maija Jakobsson,[1] Kirsi Joronen,[4] Mari Kiviharju,[1] Karolina Louvanto,[1,6] Sanna Oksjoki,[4] Riikka Tähtinen,[7] Seppo Virtanen,[1] Pekka Nieminen,[1] Maria Kyrgiou,[8,9] Ilkka Kalliala[1,8]

- Συστήνεται θεραπεία
- Επίσης αποδεκτή η συντηρητική παρακολούθηση σε νεαρές γυναίκες που επιθυμούν τεκνοποίηση στο μέλλον, λόγω αυξημένης πιθανότητας υποστροφής, ειδικά σε γυναίκες < 30 ετών
- Αποδεκτός χρόνος συντηρητικής παρακολούθησης του CIN2 είναι μέχρι 2 χρόνια
- Αν υπάρχουν αμφιβολίες για τη συμμόρφωση της ασθενούς με το follow-up, η συντηρητική αντιμετώπιση δεν προτείνεται

Αναλυτικά…

- < 25 ετών: Θεραπεία ή συντηρητική παρακολούθηση με κολποσκόπηση και κυτταρολογία στους 6 και 12 μήνες

✓ Αν η κυτταρολογία → < ASC-H και η ιστολογία → < CIN2 και στις 2 επισκέψεις → κυτταρολογία στους 24 μήνες

✓ Αν η κυτταρολογία → ≥ ASC-H ή η ιστολογία ≥ CIN2 στους 6 ή 12 μήνες → κυτταρολογία και κολποσκόπηση στους 18 και 24 μήνες

- > 25 ετών: Η αντιμετώπιση είναι ίδια, αλλά προτείνεται το co-testing

CIN3 / AIS

- Συστήνεται θεραπεία

Follow-up

- HPV testing και κυτταρολογία στους 6 μήνες (test of cure), ανεξαρτήτως της κατάστασης των ορίων εκτομής
- Αν τα όρια εκτομής είναι θετικά για CIN2+ σε ασθενή < 25 ετών χωρίς προγραμματισμό τεκνοποίησης στο άμεσο μέλλον, μπορεί να πραγματοποιηθεί άμεσα επαναληπτική εκτομή
- Αν το co-testing στους 6 μήνες είναι αρνητικό → co-testing ετησίως για 3 χρόνια και στη συνέχεια κάθε 3 χρόνια για τουλάχιστον 25 χρόνια
- Ιστορικό θεραπείας CIN → αυξημένος κίνδυνος CaCx
- Αν η κυτταρολογία ή το HPV testing στους 6 μήνες είναι θετικό→ κολποσκόπηση και περαιτέρω αντιμετώπιση βάσει ευρημάτων

Συμπερασματικά

- Ανάγκη εξατομικευμένης αντιμετώπισης του HSIL
- Tailored treatment ανάλογα με την ασθενή, τα αποτελέσματα των εξετάσεων και το ιστορικό
- Η απόφαση για κολποσκόπηση, θεραπεία ή συντηρητική αντιμετώπιση βασίζεται στην πιθανότητα για CIN3+

Mobile App

The ASCCP Management Guidelines App is Now Available

Streamline navigation of the ASCCP Risk Based Management Consensus Guidelines with the **NEW** ASCCP Management Guidelines App

- Evidence-based management guidelines
- Simple navigation
- Uncomplicated guidance

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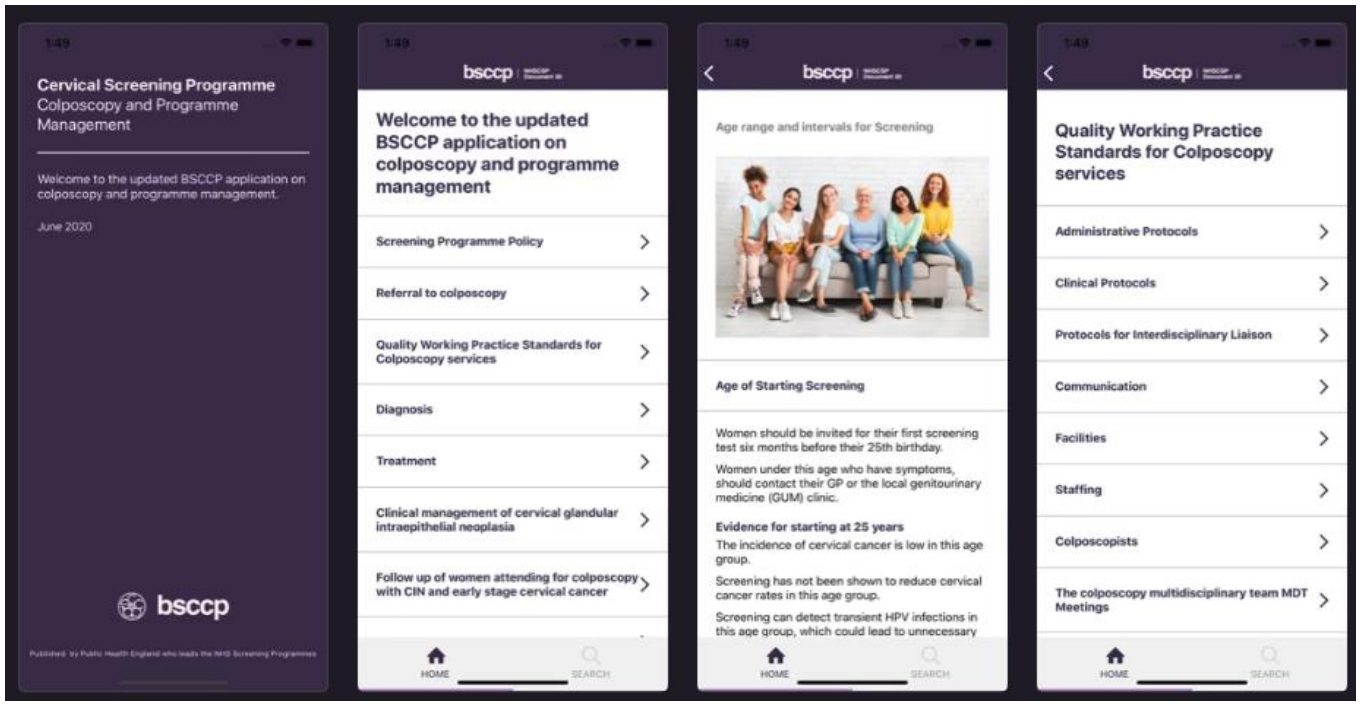


THANK YOU
AND MAY THE FORCE BE WITH YOU
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