# Persisten High Risk HPV Genotiplemesi Pozitif ve Sitolojisi Negatif olan Kadınlarda High Grade CIN (CIN2+) Riski Nedir ?

Servikal Patolojiler ve Kolposkopi Derneği

TURKISH SOCIETY FOR COLPOSCOPY AND CERVICAL PATHOLOGY

**Prof. Dr. Ömer T. YALÇIN**

OSMANGAZİ ÜNİVERSİTESİ TIP FAKÜLTESİ KADIN HASTALIKLARI VE DOĞUM A B D

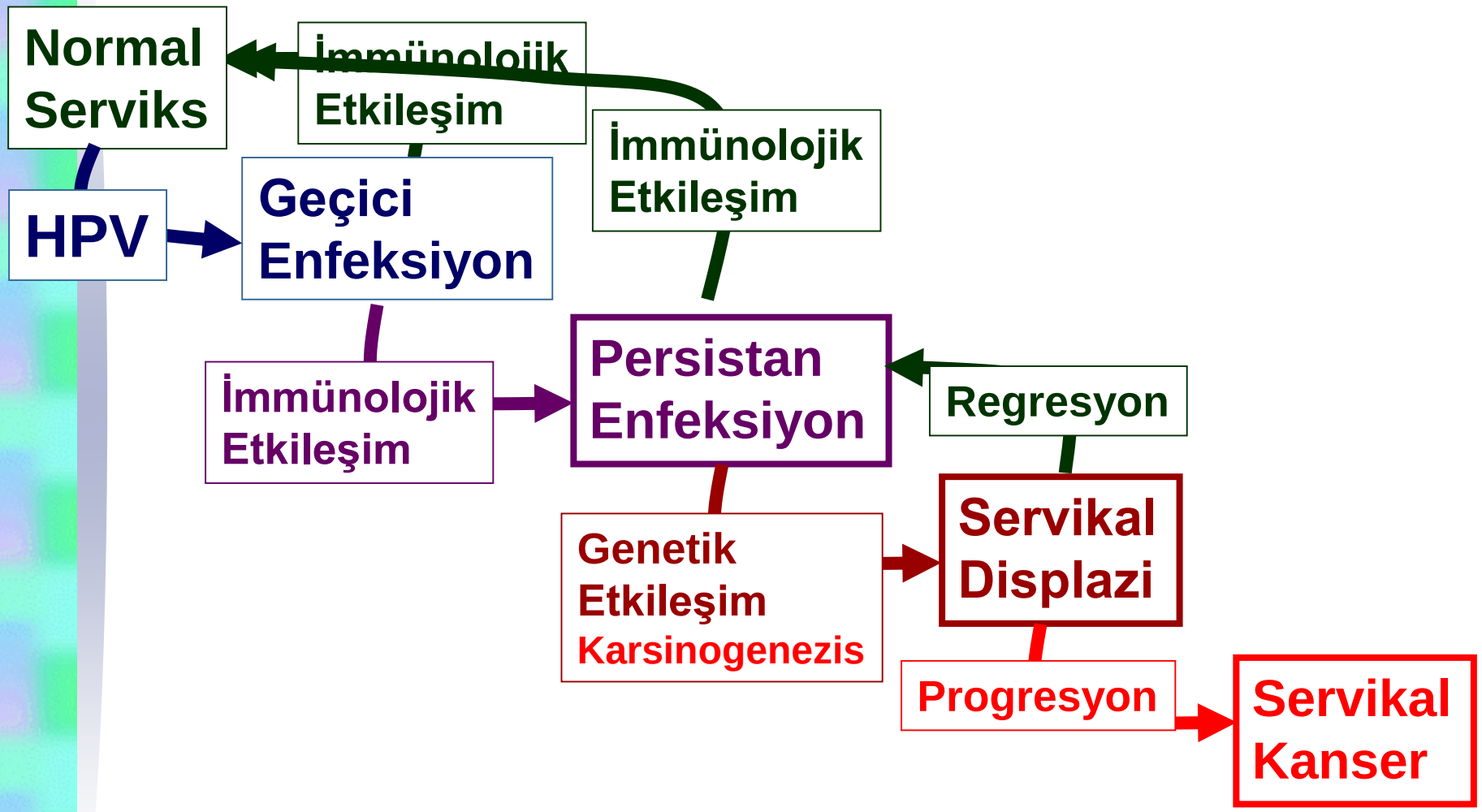
**Jinekolojik Onkoloji Bilim Dalı**

V. Ulusal Servikal Kongresi

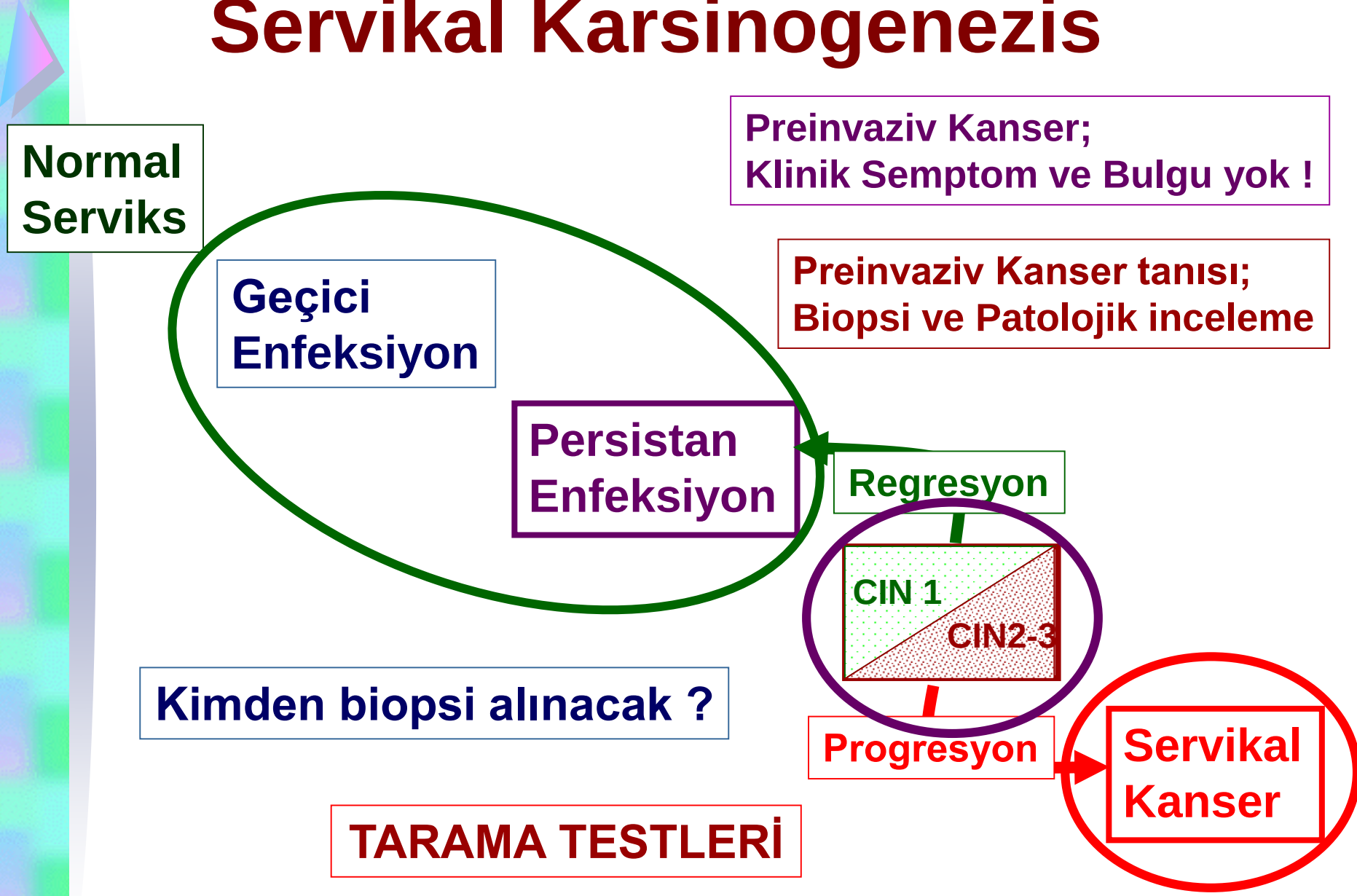
10 Aralık 2017

Wyndham Grand, İzmir

# Servikal Karsinogenezis



# Servikal Karsinogenezis



# KANSER TARAMA TESTLERİ

- Kesin tanı yöntemi değildir.
- Kesin tanı yöntemlerinin (Biopsi) uygulanacağı riskli grubu belirler
- Sempt. (-) ve Bulgu (-) olan hedef populasyona (Tüm kadınlara) yapılır
- Her yerde ve kolay uygulanmalıdır
- Hasta kabullenimi yüksek olmalıdır
- Ucuz olmalı, Fiyat - etkin olmalıdır;
  - Taranan hastalık prevalansı yüksek olmalı
  - Geç tanıda mortalite ve morbidite yüksek olmalı
  - Yöntemin tanısal etkinliği yüksek olmalı

➢ Hatalı Pozitif ve Hatalı Negatif Oranı düşük olmalı

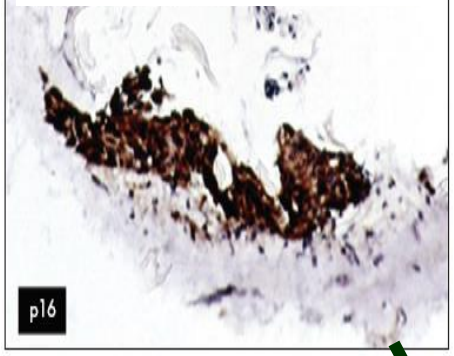
# Tarama Testleri

Normal Serviks

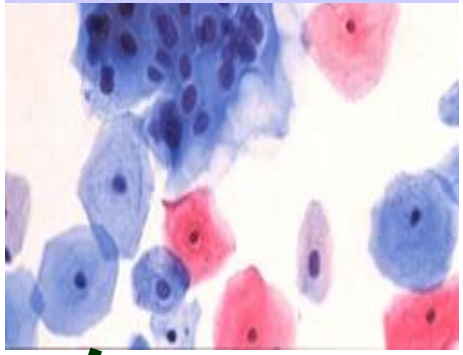
HPV (+)

Enfeksiyon

Moleküler Değişim

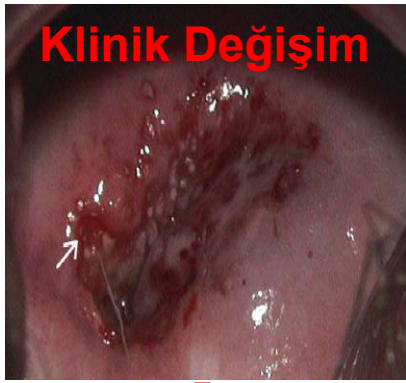



Hücresel Değişim

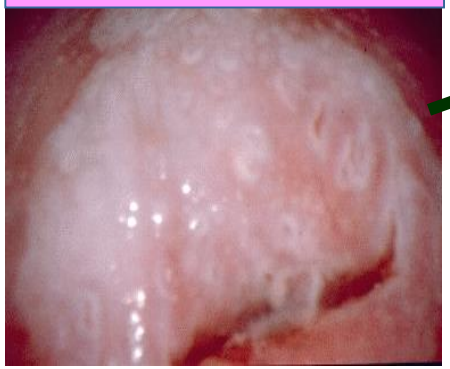


Persistan Enfeksiyon

Klinik Değişim



Dokusal Değişim



CIN 1

CIN2-3

Servikal Kanser

# PAP Smear; Sitolojik Değerlendirilmesi

| PAP Smear Grade | Displazi | CIN | Histolojik değişiklik | Bethesda |
|---|---|---|---|---|
| I | | Normal | Normal | Normal |
| II | | İnfilamasyon | İnfilamasyon | ASC<br>ASC-US<br>ASC-H |
| III | Hafif | CIN I | Bazal 1/3 | Low SIL |
| | Orta derecede | CIN II | <Bazal 2/3 | High SIL |
| | Şiddetli | CIN III | Tüm kalınlık | |
| IV | CIS | | | |
| V | SCC | SCC | SCC | SCC |

# Kolposkopi Endikasyonlar

- İnvasiv kanser şüphesi
- ASC-US (seçeneklerden biri olarak)
- ASC-H
- LGSIL
- HGSIL
- AGC ve AIS
- Persiste eden yetersiz smearler
- İlişki sırasında kanama, intermenstürel ve irregüler kanlı akıntı,hipertrofik T/Z

CANCER
CYTOPATHOLOGY

CANCER (CANCER CYTOPATHOLOGY) February 25, 2007 / Volume 111 / Number 1

# Human Papillomavirus Testing and Molecular Markers of Cervical Dysplasia and Carcinoma

**Donna Dehn,** PhD
**Kathleen C. Torkko,** PhD
**Kenneth R. Shroyer,** MD, PhD

Department of Pathology, University of Colorado at Denver and Health Sciences Center, Aurora, Colorado.

## TABLE 1
## Clinically Equivocal Cytologic Diagnostic Categories*

| Cytologic Diagnosis | Total Cases (Annual US Population)* | No Clinically Significant Lesion On Colposcopy |
|---|---|---|
| ASCUS | >2 million | 1.66–1.9 million |
| ASC-H | 0.20 million (estimated) | 0.001–0.15 million |
| LSIL | 1.65 million | 1.24 million |
| AGC | 0.31 million | 0.18–0.25 million |
| Total | >4.16 million | 2.66–3.54 million |

* Data summarized from references[20,122–129]

# >150 HPV types

## Mucosal
(tend to infect cells of the moist surface layers that line organs and cavities of the body)

## Cutaneous
(infect the skin and can cause warts there)

## "high-risk" types
(including types 16 & 18)

- ✓Low grade abnormalities of mucosal cells
- ✓High grade abnormalities/ pre-cancers in mucosal cells
- ✓Various cancers

## "low-risk" types
(including types 6 & 11)

- ✓Respiratory & laryngeal papillomas
- ✓Low grade abnormalities of mucosal cells
- ✓Genital warts (these rarely become cancer)

## "Common" warts
(hands & feet)

# HPV Testleri

- **Hybrid capture (HC II);**
  - **HrHPV taraması**
- **Polymerase Chain Reaction (PCR)**
  - **Yüksek riskli subtiplerin genotiplemesi**
- **Ayrı / aynı materyalden çalışılabilir**
- **Sitoteknisyen gerekmez**
- **Daha Objektif sonuç alınır**

# Identifying Women With Cervical Neoplasia

## Using Human Papillomavirus DNA Testing for Equivocal Papanicolaou Results

M. Michele Manos, PhD, MPH

JAMA, May 5, 1999—Vol 281, No. 17

**Kaiser Çalışması; 46.000 kadından Median yaş; 37**

**Pap smear sonrası HrHPV Triage;**

**ASCUS oranı %3.5**

**Table 3.** Predicted Outcomes of Triage Strategies*

| Strategy | Referred to Colposcopy† | Sensitivity for HSIL+ | Positive Predictive Value for HSIL+ | Negative Predictive Value for HSIL+ |
|---|---|---|---|---|
| Triage based on HPV test‡ | 39.5 (36.4-42.7) | 89.2 (78.4-95.2) | 15.1 (11.7-19.2) | 98.8 (97.4-99.5) |
| Triage based on repeat Pap test results§ | 38.9 (35.8-42.1) | 76.2 (63.5-85.7) | 12.9 (9.8-16.8) | 97.4 (95.7-98.5) |

further estimated that an HPV-based algorithm including the immediate colposcopy of HPV-positive women, and then repeat Pap testing of all others, would provide an overall sensitivity of 96.9% (95% CI, 88.3%-99.5%).

# Hr HPV Testi Klinik Kullanımı

- **Hr HPV Triage (Yönetim)**
  - **ASCUS, LGSIL, AGC**

# The ATHENA human papillomavirus study: design, methods, and baseline results

Thomas C. Wright Jr, MD; Mark H. Stoler, MD; Catherine M. Behrens, MD, PhD; Raymond Apple, PhD; Toniann Derion, PhD; Teresa L. Wright, MD

**STUDY DESIGN:** A total of 47,208 women aged 21 years or older undergoing routine screening were enrolled; liquid-based cytology and human papillomavirus (HPV) testing were performed. Women with abnormal cytology underwent colposcopy, as did high-risk HPV (hrHPV)–positive women and a random subset of women negative by both tests

**RESULTS:** The prevalence of cytologic abnormalities was 7.1%. hrHPV, HPV 16, and HPV 18 were detected using the cobas HPV Test in 12.6%, 2.8%, and 1.0% of women, respectively. Both cytologic abnormalities and hrHPV positivity declined with increasing age. The adjusted prevalence of cervical intraepithelial neoplasia grade 2 (CIN2) or greater in women aged 25-34 years was 2.3%, decreasing to 1.5% among older women.

# Age-Specific Evaluation of Primary Human Papillomavirus Screening vs Conventional Cytology in a Randomized Setting

J Natl Cancer Inst 2009;101:1612–1623

Maarit Leinonen, Pekka Nieminen, Laura Kotaniemi-Talonen, Nea Malila, Jussi Tarkkanen, Pekka Laurila, Ahti Anttila

## Conclusions

Primary HPV DNA screening with cytology triage is more sensitive than conventional screening. Among women aged 35 years or older, primary HPV DNA screening with cytology triage is also more specific than conventional screening and decreases colposcopy referrals and follow-up tests.

# Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial

*Dorien C Rijkaart, Johannes Berkhof, Lawrence Rozendaal, Folkert J van Kemenade, Nicole W J Bulkmans, Daniëlle A M Heideman, Gemma G Kenter, Jack Cuzick, Peter J F Snijders, Chris J L M Meijer*

**Lancet Oncol 2012; 13: 78–88**

worse in the second screening round relative to conventional cytology. Additionally, as was the case in the NTCC trial, the final POBASCAM data also show that HPV screening protects against cervical cancer better than does cytology alone. By contrast with other studies, CIN

**Interpretation** Implementation of HPV DNA testing in cervical screening leads to earlier detection of clinically relevant CIN grade 2 or worse, which when adequately treated, improves protection against CIN grade 3 or worse and cervical cancer. Early detection of high-grade cervical legions caused by HPV16 was a major component of this benefit. Our results lend support to the use of HPV DNA testing for all women aged 29 years and older.

GENERAL GYNECOLOGY

# A systematic review of randomized trials assessing human papillomavirus testing in cervical cancer screening

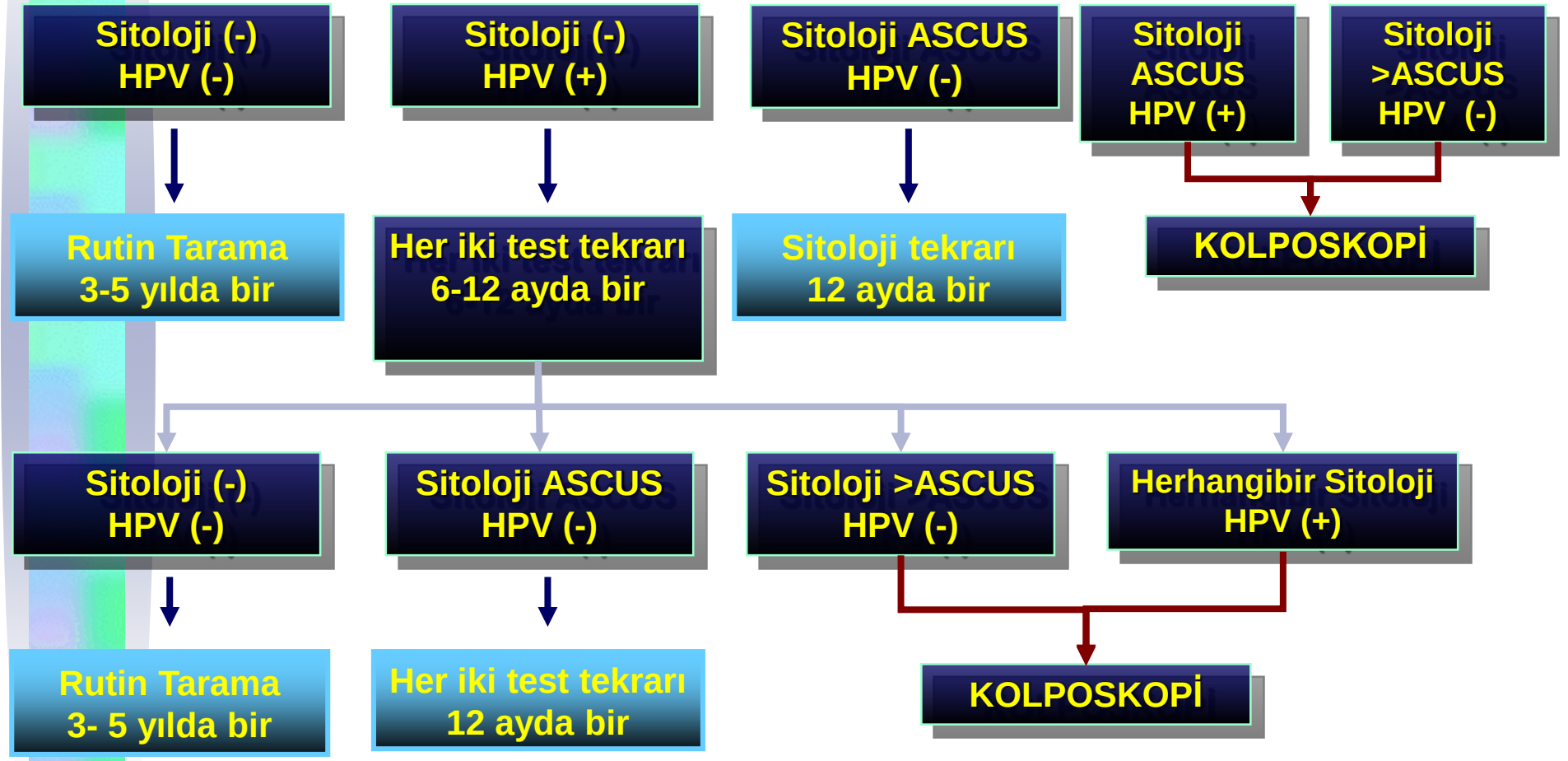
Insiyyah Y. Patanwala, MD; Heidi M. Bauer, MD, MS, MPH; Justin Miyamoto, MD; Ina U. Park, MD, MS; Megan J. Huchko, MD, MPH; Karen K. Smith-McCune, MD, PhD

articles. Six studies met inclusion criteria. Relative sensitivities for detecting CIN3 or greater of HPV testing-based strategies vs cytology ranged from 0.8 to 2.1. The main limitation of our study was that testing methodologies and screening/management protocols were highly variable across studies. Screening strategies in which a single initial HPV-positive test led to colposcopy were more sensitive than cytology but resulted in higher colposcopy rates. These results have implications for cotesting with HPV and cytology as recommended in the United States.

# Hr HPV Testi Klinik Kullanımı

- **Hr HPV Triage (Yönetim)**
  - ASCUS, LGSIL, AGC
- **Hr HPV Tarama**
  - Hr HPV + Pap test kombinasyonu

# Taramada Sitoloji ve Hr HPV Testi Kombinasyonu



# Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials

Lancet 2014; 383: 524–32

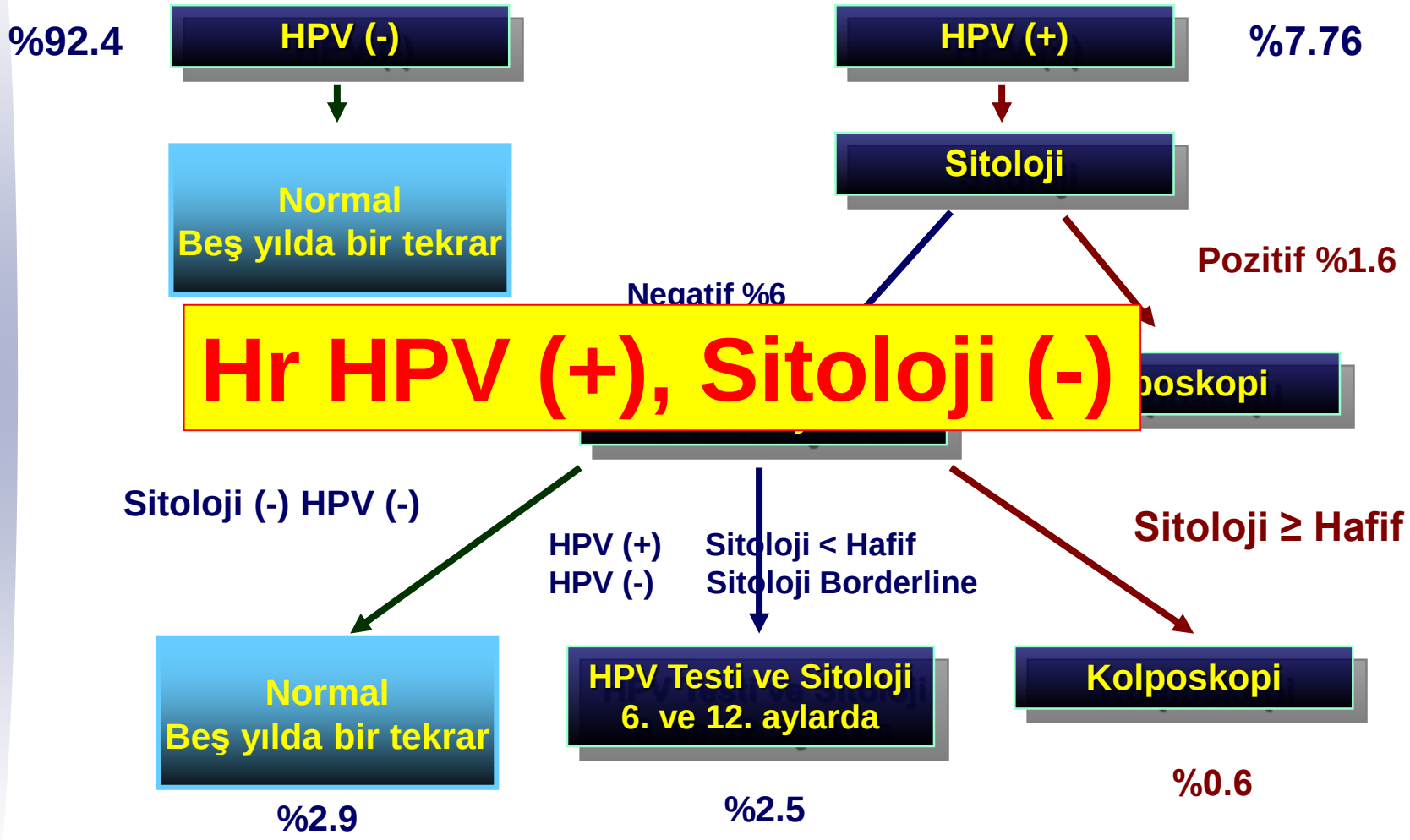
*Guglielmo Ronco, Joakim Dillner, K Miriam Elfström, Sara Tunesi, Peter J F Snijders, Marc Arbyn, Henry Kitchener, Nereo Segnan, Clare Gilham, Paolo Giorgi-Rossi, Johannes Berkhof, Julian Peto, Chris J L M Meijer, and the International HPV screening working group**

**Interpretation** HPV-based screening provides 60–70% greater protection against invasive cervical carcinomas compared with cytology. Data of large-scale randomised trials support initiation of HPV-based screening from age 30 years and extension of screening intervals to at least 5 years.

# Hr HPV Testi Klinik Kullanımı

- **Hr HPV Triage (Yönetim)**
  - **ASCUS, LGSIL, AGC**
- **Hr HPV Tarama**
  - **Hr HPV + Pap test kombinasyonu**
  - **Hr HPV Primer Tarama**
    - **Sitoloji Triage**

# Primer Taramada Hr HPV




*"Proposed New Screening Algoritm - Percentages Based on HART Population Aged 30-60"*

# Cervical cancer screening by high risk HPV testing in routine practice: results at one year recall of high risk HPV-positive and cytology-negative women

*J Med Screen*
2014, Vol. 21(1) 30–37

Annarosa Del Mistro[1], Helena Frayle[1], Antonio Ferro[2], Susanna Callegaro[3], Annamaria Del Sole[4], Anna Stomeo[5], Emanuela Cirillo[6], Chiara Fedato[7], Silvana Pagni[8], Luisa Barzon[8] and Manuel Zorzi[7], on behalf of the Veneto HPV-screening Working Group

**Results:** Of 46,694 women screened by HPV testing up to December 2011, 3,211 (6.9%) tested hrHPV positive; 45% of these had a positive triage cytology. Those with negative cytology were invited for 1-yr repeat testing. Compliance with invitation was 61.6% at baseline and 85.3% at 1-yr repeat. Rate of persistent hrHPV positivity was 58% (830/1,435). Colposcopy performed in women with a positive hrHPV test at 1-yr repeat accounted for 36% of all colposcopies performed within the screening programmes. Cumulatively, a histological high-grade lesion was detected in 276 women (5.9‰ detection rate), 234 at baseline (85%), and 42 (15%) at 1-yr repeat.

# Use of a high-risk human papillomavirus DNA test as the primary test in a cervical cancer

**Table 1.** Main results of the HPV test-based screening programme at baseline (women screened from April 2009 to April 2011) and at the 1-year repeat of women found to be HPV+/Pap− at baseline (up to April 2012)

| | Baseline | | 1-year repeat after HPV+/Pap− tests | |
|---|---|---|---|---|
| | *n* | % | *n* | % |
| **Women invited** | 23 368 | | 501 | |
| **Total women examined (% = crude compliance)** | 12 026* | 51.5 | 394 | 78.6 |
| **Proportion of positive HPV tests** | | | | |
| Overall | 829/11 895 | 7.0 | 223/394 | 56.6 |
| 25–29 years | 176/1102 | 16.0 | 52/86 | 60.5 |
| 30–34 years | 161/1221 | 13.2 | 46/78 | 59.0 |
| 35–64 years | 492/9573 | 5.1 | 125/230 | 54.3 |
| **Proportion of positive Pap tests among HPV+** | 328/829 | 39.6 | 48/223 | 21.5 |
| **Referral rate to immediate colposcopy** | 328/11 895 | 2.8 | 223/394 | 56.6 |
| **Compliance to immediate colposcopy** | 273/319** | 85.6 | 178/223 | 79.8 |
| **CIN2+ DR (%)** | | | | |
| Overall | 41/11 895 | 3.4 | 12/394 | 30.5 |
| 25–29 years | 4/1102 | 3.6 | 1/86 | 11.6 |
| 30–34 years | 10/1221 | 8.2 | 4/78 | 51.3 |
| 35–64 years | 27/9572 | 2.8 | 7/230 | 30.4 |
| **PPV for CIN2+ at first colposcopy** | 32/273 | 11.7 | 11/178 | 6.2 |
| **Referral rate to 1-year recall** | 501/11 895 | 4.2 | | |

# Five-Year Risks of CIN 3+ and Cervical Cancer Among Women Who Test Pap-Negative But Are HPV-Positive

Hormuzd A. Katki, PhD,[1] Mark Schiffman, MD, MPH,[1]
Philip E. Castle, PhD, MPH,[2] Barbara Fetterman, SCT (ASCP),[3]
Nancy E. Poitras, PMP,[3] Thomas Lorey, MD,[3] Li C. Cheung, MS,[4]
Tina Raine-Bennett, MD, MPH,[5] Julia C. Gage, PhD, MPH,[1]
and Walter K. Kinney, MD[6]

[1]*Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, DHHS, Bethesda, MD;* [2]*Albert Einstein College of Medicine, Bronx, NY;* [3]*Regional Laboratory, Kaiser Permanente Northern California, Berkeley, CA;* [4]*Information Management Services, Inc, Calverton, MD;* [5]*Women's Health Research Institute, Division of Research, Kaiser Permanente Northern California, Oakland, CA; and* [6]*Division of Gynecologic Oncology, Kaiser Permanente Medical Care Program, Oakland, CA*

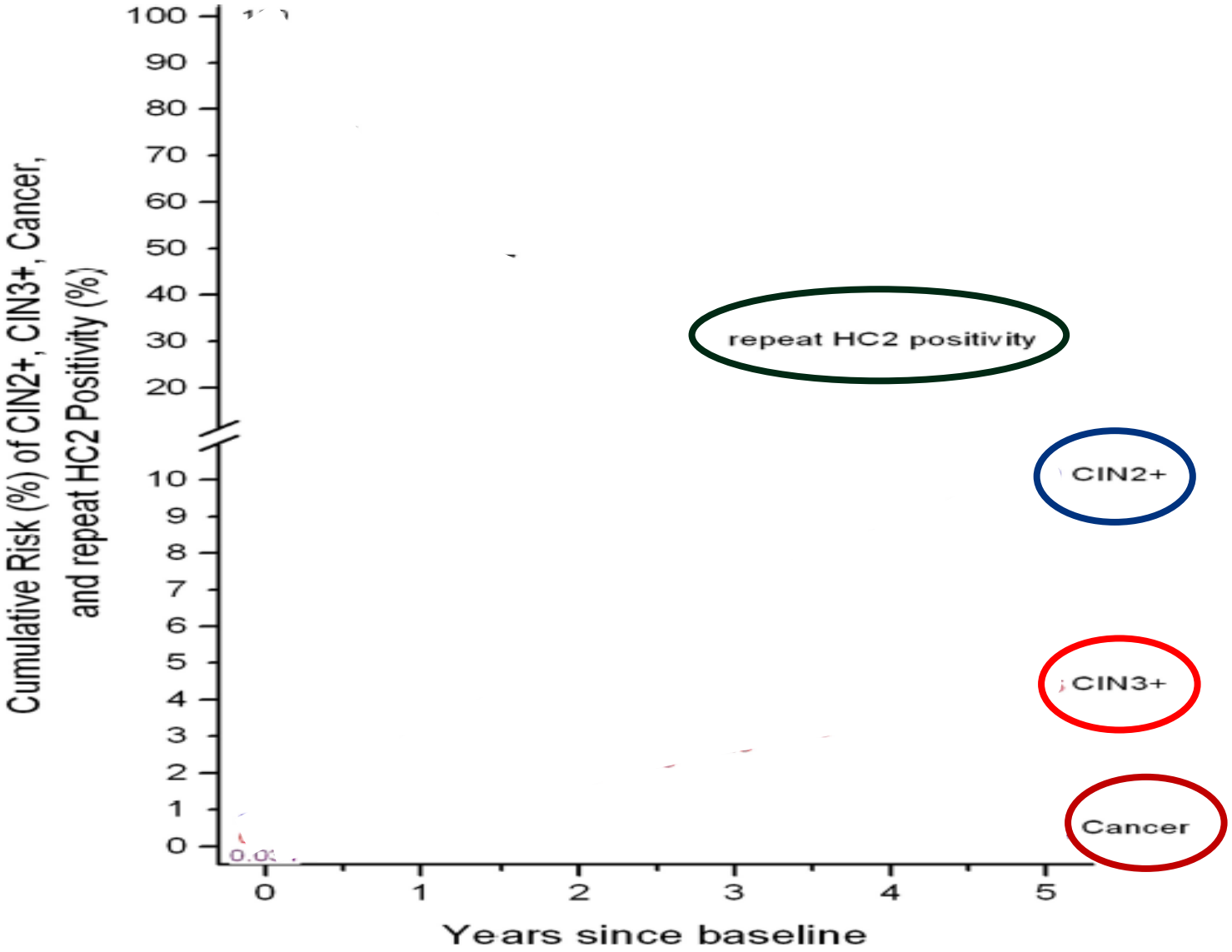



Figure 1. Decline of repeat HC2 positivity and cumulative risks of CIN 2+, CIN 3+, and cancer since baseline among women aged 30 to 64 years, testing HPV-positive/Pap-negative at baseline.

Table 2. Cumulative 5-Year Risks of CIN 2+, CIN 3+, and Cancer Among Women Aged 30 to 64 Years at Baseline Given Repeat Cotest Results (Excluding High-Grade Pap Tests) After HPV-Positive/Pap-Negative Compared to the Risk for Those Cotests at Baseline

| | CIN 2+ | | CIN 3+ | | Cancer | |
|---|---|---|---|---|---|---|
| Cotest result | 5-y risk at baseline, % | 5-y risk after repeat cotest following HPV-positive/ Pap-negative, % | 5-y risk at baseline, % | 5-y risk after repeat cotest following HPV-positive/ Pap-negative, % | 5-y risk at baseline, % | 5-y risk after repeat cotest following HPV-positive/ Pap-negative, % |
| HPV-positive/LSIL | 19 | 24 | 6.1 | 9.2 | 0.089 | 0.18 |
| HPV-positive/ASC-US | 18 | 22 | 6.8 | 7.9 | 0.41 | 0.405 |
| HPV-positive/Pap-negative | 10 | 16 | 4.5 | 7.4 | 0.34 | 0.46 |
| HPV-negative/LSIL | 5.1 | 6.8 | 2.0 | 1.7 | [a] | [b] |
| HPV-negative/ASC-US | 1.1 | 5.2 | 0.43 | 2.9 | [a] | [b] |
| HPV-negative/Pap-negative | 0.27 | 1.8 | 0.08 | 0.93 | 0.011 | 0.13 |

## Table 3. Benchmarking CIN 3+ Risks for Repeat Cotest Results After HPV-Positive/Pap-Negative to Risk Thresholds Implicitly Used to Determine Clinical Management Options Based on Screening Pap Tests

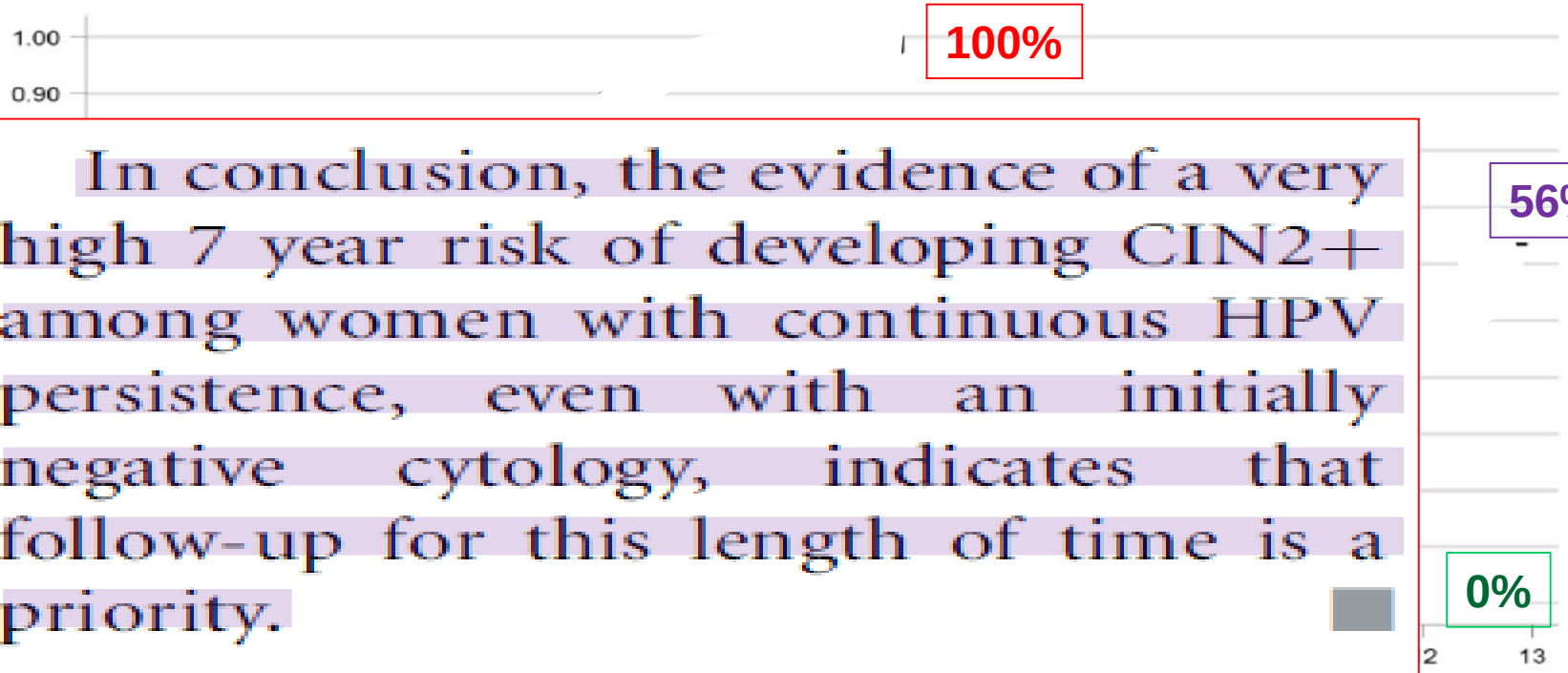
| | Implicit risk threshold: 5-y CIN 3+ risk by baseline Pap result alone (regardless of HPV result)[a] | | | 5-y CIN 3+ risk after given repeat cotest result after HPV+/Pap− | | |
|---|---|---|---|---|---|---|
| Current recommended management strategy based on Pap alone | Management-defining result | Frequency in women aged 30–64 y, % | CIN 3+ risk, % | Repeat cotest result after HPV+/Pap− | Frequency in women aged 30–64 y, % | CIN 3+ risk, % |
| Immediate colposcopy | LSIL | 0.97 | 5.2 | HPV+/Pap− | 0.75 | 7.4 |
| | | | | HPV−/LSIL | 0.006 | 1.7[b] |
| 1-y return | ASC-US | 2.8 | 2.6 | HPV−/ASC-US | 0.04 | 2.9 |
| 3-y return | Pap− | 95.6 | 0.26 | HPV−/Pap− | 1.3 | 0.93 |
| 5-y return | HPV−/Pap− | 92.0 | 0.08 | | | |

# Management of women with human papillomavirus persistence: long-term follow-up of a randomized clinical trial

American Journal of Obstetrics & Gynecology MARCH 2017

Kristina Elfgren, MD; K. Miriam Elfström, PhD; Pontus Naucler, MD; Lisen Arnheim-Dahlström, PhD; Joakim Dillner, MD

FIGURE 4
**Cumulative proportion of CIN2+ among women with type-specific persistence**




In conclusion, the evidence of a very high 7 year risk of developing CIN2+ among women with continuous HPV persistence, even with an initially negative cytology, indicates that follow-up for this length of time is a priority.

# Performance of carcinogenic human papillomavirus (HPV) testing and HPV16 or HPV18 genotyping for cervical cancer screening of women aged 25 years and older: a subanalysis of the ATHENA study

*Lancet Oncol* 2011; 12: 880–90

*Philip E Castle, Mark H Stoler, Thomas C Wright Jr, Abha Sharma, Teresa L Wright, Catherine M Behrens*

The management of HPV-positive women with negative cytology results remains a clinical dilemma.[43] Although some guidelines recommend rescreening of such women in 1 year,[15,44] this strategy has substantial drawbacks. First, some women will already have CIN3 or worse, which includes a small but appreciable number of women with invasive cervical cancer.[17] Second, loss to follow-up in this population can be high (about 50%)[16,45] and, as such, can offset the gain in sensitivity (but not NPV) of use of HPV testing for primary screening. In view of these issues, an immediate triage strategy is needed for this group.

# Performance of carcinogenic human papillomavirus (HPV) testing and HPV16 or HPV18 genotyping for cervical cancer screening of women aged 25 years and older: a subanalysis of the ATHENA study

*Lancet Oncol* 2011; 12: 880–90

*Philip E Castle, Mark H Stoler, Thomas C Wright Jr, Abha Sharma, Teresa L Wright, Catherine M Behrens*

ATHENA is the largest US registration trial to assess the performance of HPV DNA testing with individual genotyping for HPV16, HPV18, or both compared with liquid-based cytology for cervical cancer screening. Our findings show that HPV DNA testing has higher sensitivity than cytology; detection of HPV16, HPV18, or both alone has similar sensitivity to ASC-US or worse cytology; and detection of HPV16, HPV18, or both in combination with low-grade squamous intraepithelial lesion or worse cytology has better sensitivity than ASC-US or worse cytology. HPV testing with individual genotyping for HPV16, HPV18, or both could provide a more efficient strategy for cervical cancer screening than do existing programmes based on cytology.

# HPV16 and HPV18 genotyping in cervical cancer screening

against cervical cancer. For example, immediate referral of women who were HPV16-positive, HPV18-positive, or had ASC-US or worse (instead of only those with ASC-US or worse), allowed detection of about 25% of HPV-positive CIN3 or worse a year earlier

# HPV16/18 genotyping for the triage of HPV positive women in primary cervical cancer screening in Chile

*Infectious Agents and Cancer* (2015) 10:43

Marcela Lagos[1], Vanessa Van De Wyngard[2], Helena Poggi[1], Paz Cook[2], Paola Viviani[2], María Isabel Barriga[3], Martha Pruyas[4] and Catterina Ferreccio[2,5*]

**Results:** Among the 8,265 participants, 10.7 % were hrHPV positive, 1.7 % had ASCUS+ cytology, 1.2 % had CIN2+; 776 (88 %) hrHPV positive women had complete results, of whom 38.8 % were positive for HPV16 (24.0 %), HPV18 (9.7 %) or both (5.1 %). CIN2+ prevalence in HPV16/18 positive women (16.3 %, 95 % CI 12.3-20.9) was twice that of HPV16/18 negative women (8.0 %, 95 % CI 5.7-10.8). HPV16/18 genotyping identified 40.5 % of CIN2, 66.7 % of CIN3 and 75.0 % of cancers. Compared to hrHPV screening alone, HPV16/18 triage significantly reduced the referral rate (10.7 % vs 3.7 %) and the number of colposcopies required to detect one CIN2+ (9 vs 6). When HPV16/18 negative women with baseline ASCUS+ cytology were also colposcopied, an additional 14 % of CIN2+ was identified; referral increased slightly to 4.2 %.

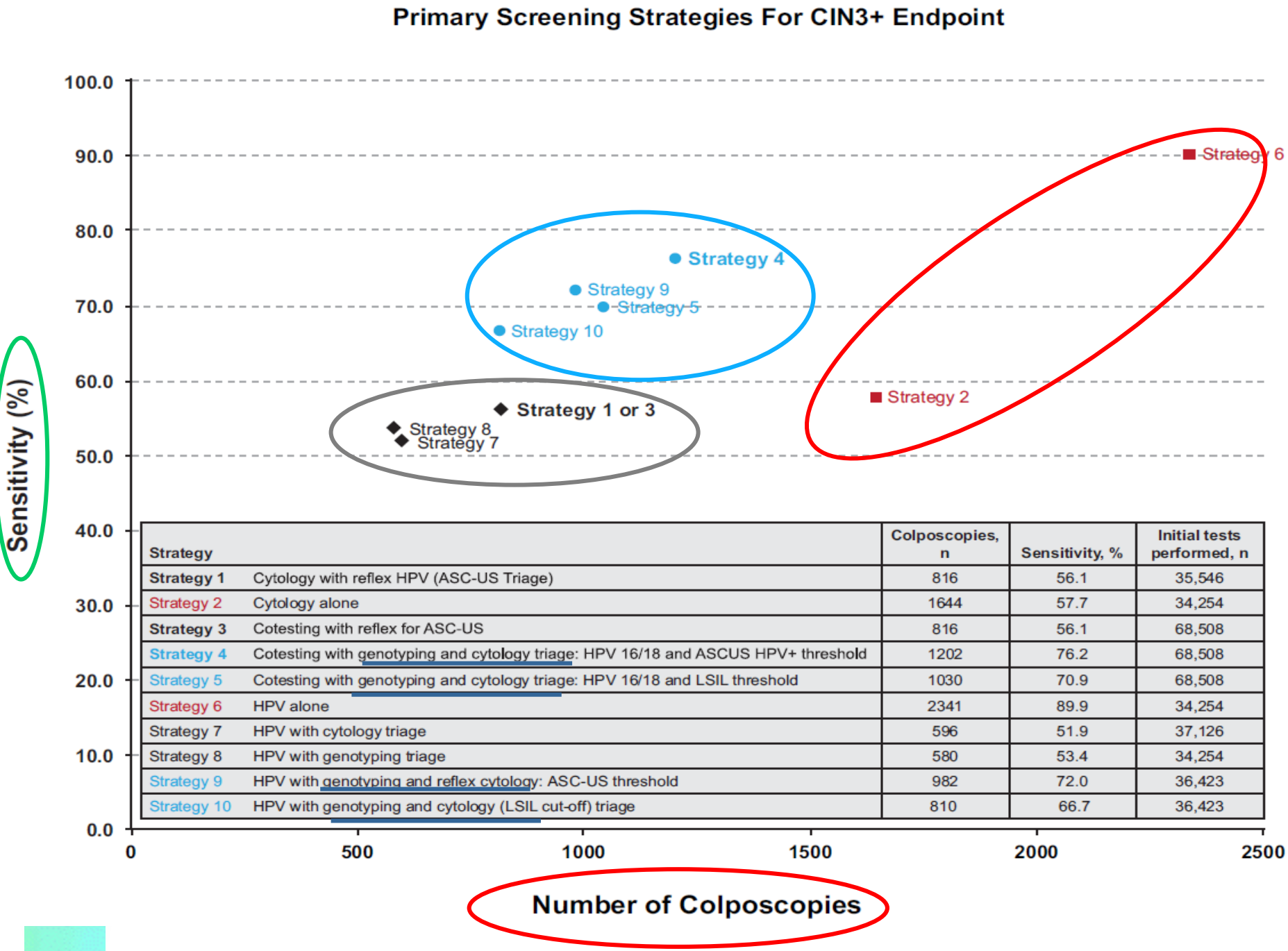
# Comparison of cervical cancer screening strategies incorporating different combinations of cytology, HPV testing, and genotyping for HPV 16/18: results from the ATHENA HPV study

J. Thomas Cox, MD; Phillip E. Castle, PhD, MPH; Catherine M. Behrens, MD, PhD; Abha Sharma, PhD; Thomas C. Wright Jr, MD; Jack Cuzick, PhD; and the Athena HPV Study Group

MARCH 2013 American Journal of Obstetrics & Gynecology

**CONCLUSION:** Strategies that maximize detection of women at greatest risk of cervical intraepithelial neoplasia grade 3 or greater by immediate referral to colposcopy, with follow-up testing of women at intermediate risk, maximize the benefits of cervical cancer screening while decreasing the potential harm. Incorporating screening with HPV and triage of HPV-positive women by a combination of genotyping for HPV16/18 and cytology provided a good balance between maximizing sensitivity (benefit) and specificity by limiting the number of colposcopies (potential harm).

## Sensitivity for CIN3 or more severe and number of colposcopies




| Strategy | | Colposcopies, n | Sensitivity, % | Initial tests performed, n |
|---|---|---|---|---|
| **Strategy 1** | Cytology with reflex HPV (ASC-US Triage) | 816 | 56.1 | 35,546 |
| Strategy 2 | Cytology alone | 1644 | 57.7 | 34,254 |
| **Strategy 3** | Cotesting with reflex for ASC-US | 816 | 56.1 | 68,508 |
| Strategy 4 | Cotesting with genotyping and cytology triage: HPV 16/18 and ASCUS HPV+ threshold | 1202 | 76.2 | 68,508 |
| Strategy 5 | Cotesting with genotyping and cytology triage: HPV 16/18 and LSIL threshold | 1030 | 70.9 | 68,508 |
| Strategy 6 | HPV alone | 2341 | 89.9 | 34,254 |
| Strategy 7 | HPV with cytology triage | 596 | 51.9 | 37,126 |
| Strategy 8 | HPV with genotyping triage | 580 | 53.4 | 34,254 |
| Strategy 9 | HPV with genotyping and reflex cytology: ASC-US threshold | 982 | 72.0 | 36,423 |
| Strategy 10 | HPV with genotyping and cytology (LSIL cut-off) triage | 810 | 66.7 | 36,423 |

# Triage of Women With Negative Cytology and Positive High-Risk HPV: An Analysis of Data From the SHENCCAST II/III Studies

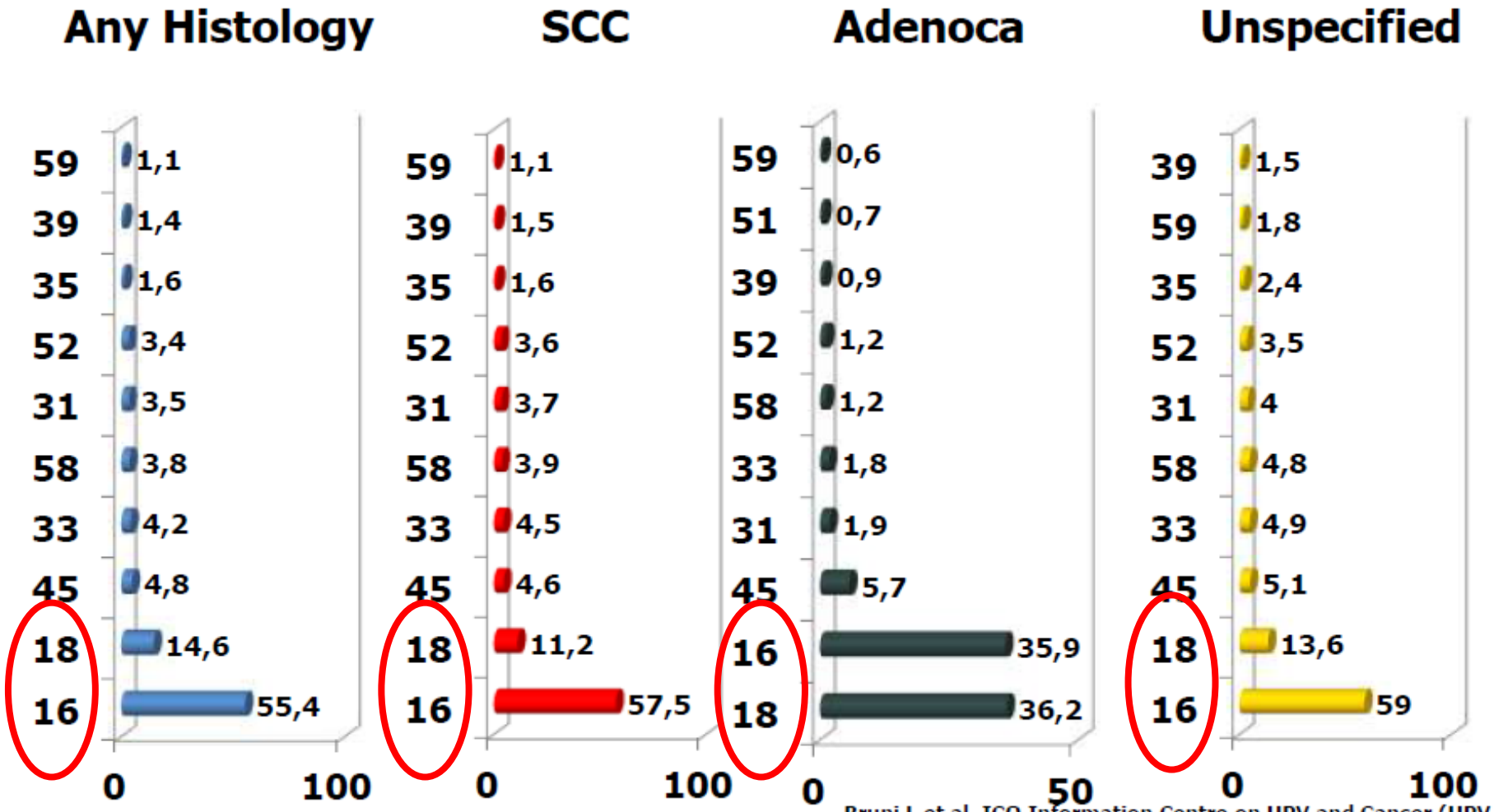
Sarah Kay Goodrich, MD,[1] Robert G. Pretorius, MD,[2] Hui Du, MD,[3] RuiFang Wu, MD,[3] and Jerome L. Belinson, MD[1,4]

[1]*Women's Health Institute, Department of Gynecology, Cleveland Clinic, Cleveland, OH;* [2]*Department of Obstetrics and Gynecology, S.C.P.M.G. Fontana, Fontana, CA;* [3]*Department of Obstetrics and Gynecology, Peking University Shenzhen Hospital, Shenzhen, China; and* [4]*Preventive Oncology International, Cleveland Heights, OH*

*Conclusions.* In the cytology-negative HR-HPV–positive population, Cervista 16/18 as the HPV detection method would refer 11.8% of women for colposcopy and diagnose 61.5% of the CIN 3+, while MALDI-TOF16/18 would refer 19.4% and diagnose 66.7% of the CIN 3+. Cervista HPV-16/18 seems to be the superior triage test. However, in resource-limited settings, an assay that includes 16/18 genotyping in the primary result (rather than a second test) may be more cost efficient. ■

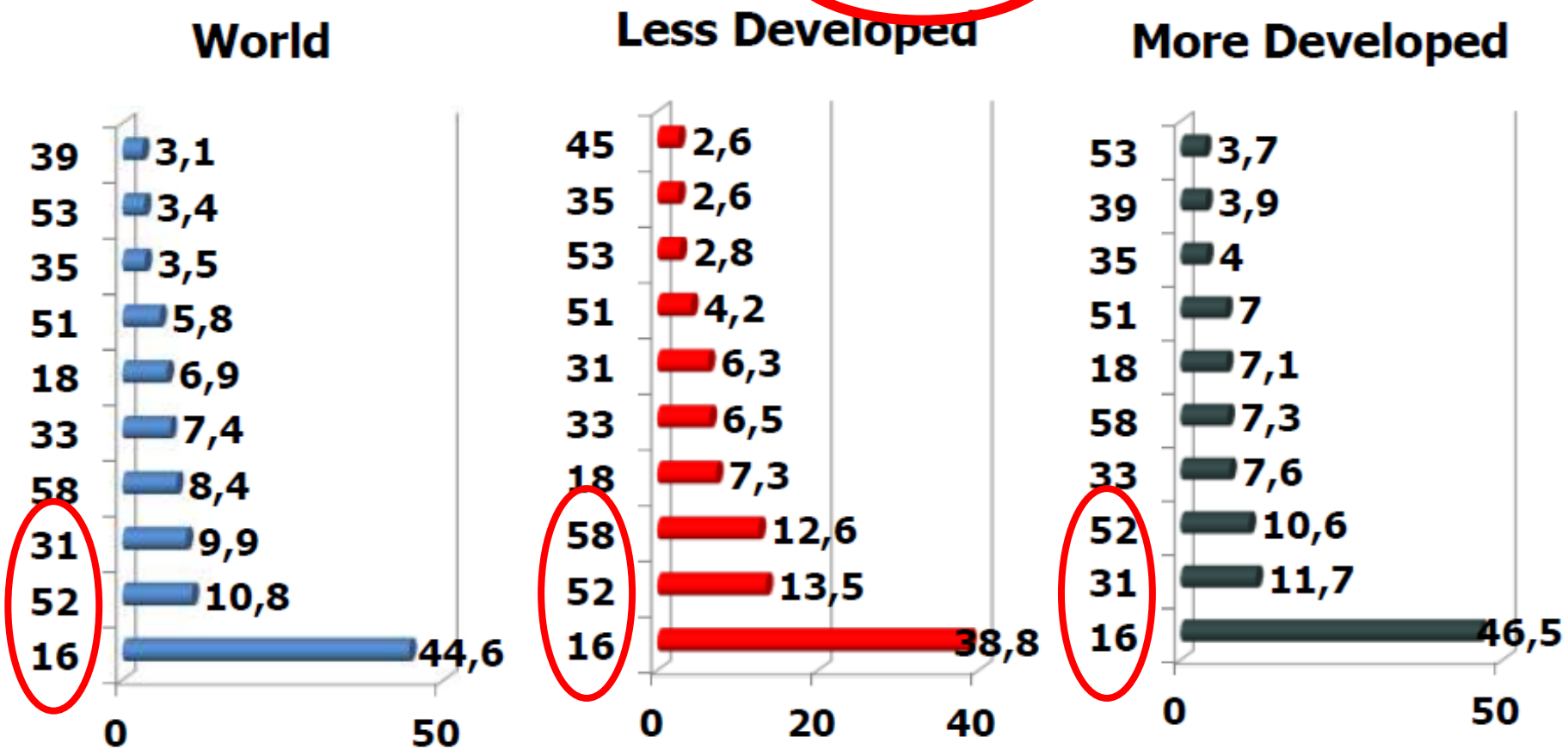
# Distribution of HPV types in ICC by Histologic Types

Prevalance %




Bruni L et al. ICO Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in theWorld. Summary Report 2016

# Top Ten Most Oncologic HPV Types in the World – H-SIL




Bruni L et al. ICO Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in theWorld. Summary Report 2016

# Prevalence of high-risk human papilloma virus genotypes and associated risk of cervical precancerous lesions in a large U.S. screening population: Data from the ATHENA trial

Gynecologic Oncology 137 (2015) 47–54

Joseph Monsonego [a,*], J. Thomas Cox [b,1], Catherine Behrens [c], Maria Sandri [d], Eduardo L. Franco [e], Poh-Sin Yap [c], Warner Huh [f]

overall population, HPV16 conferred the greatest absolute risk of ≥CIN3 both in women aged 25–29 and ≥30 years (14.2% and 15.1%, respectively) followed by HPV31 (8.0% and 7.9%), HPV52 (6.7% and 4.4%) and HPV18 (2.7% and 9.0%). Similar trends were seen in women with negative cytology. The percent positivity increased markedly with disease progression for HPV16 and HPV18 which were responsible for 45.6% and 8.4% of ≥CIN3, respectively. Of note, HPV 18 was responsible for 50% of adenocarcinoma in situ (AIS) and 50% of invasive cancer cases.

*Conclusions.* HPV16 played a major role in the development of ≥CIN3 irrespective of age, supporting the identification of HPV16 in primary screening for all women. Identification of HPV18 is also warranted, given its significant contribution to AIS and cancer. Identification of non-16/18 genotypes as a pool should provide sufficient information for screening.

Clinical Commentary

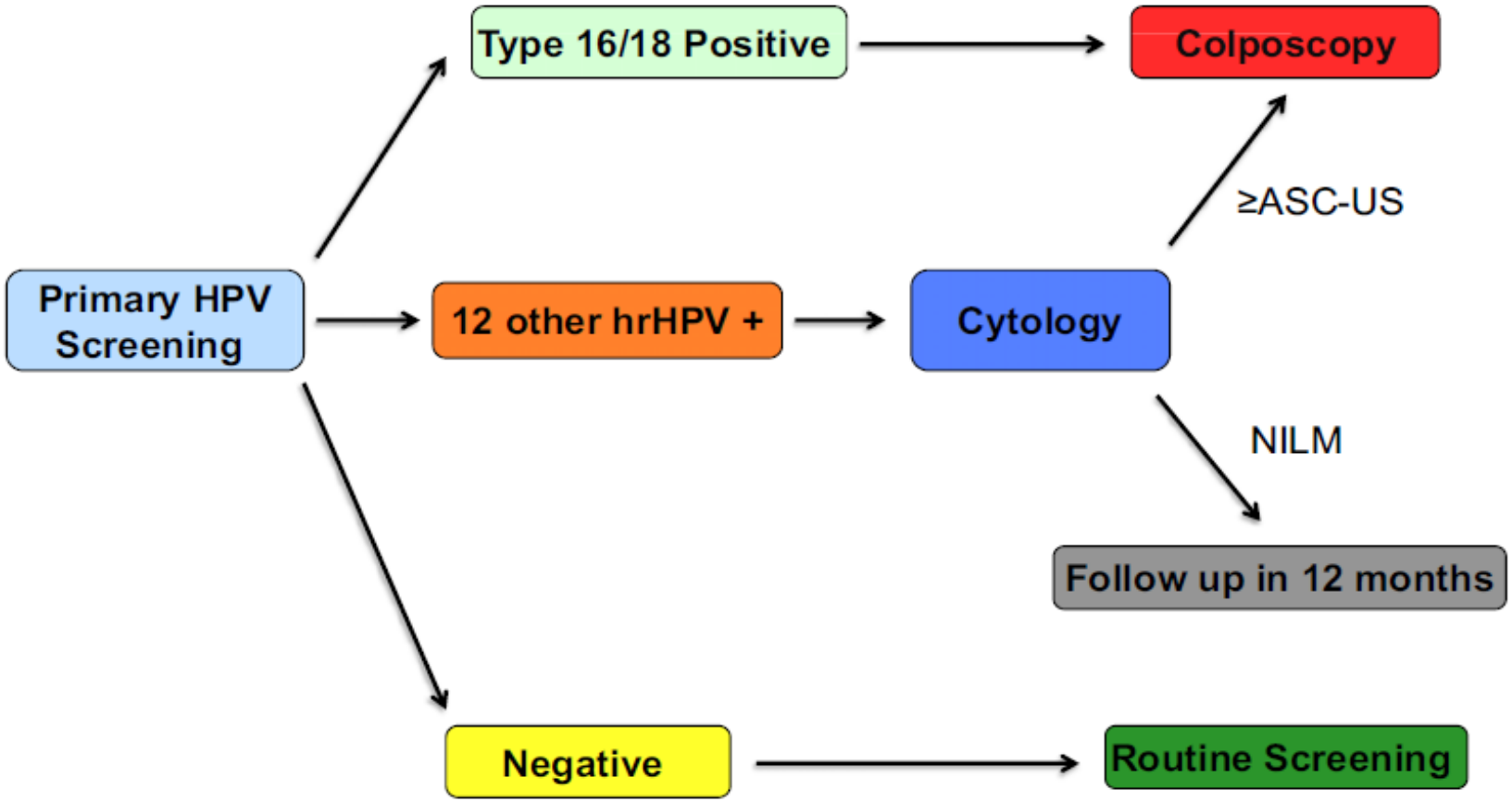
Gynecologic Oncology 136 (2015) 178–182

# Use of primary high-risk human papillomavirus testing for cervical cancer screening: Interim clinical guidance ☆

Warner K. Huh [a,*], Kevin A. Ault [b], David Chelmow [c], Diane D. Davey [d], Robert A. Goulart [e], Francisco A.R. Garcia [f], Walter K. Kinney [g], L. Stewart Massad [h], Edward J. Mayeaux [i], Debbie Saslow [j], Mark Schiffman [k,1], Nicolas Wentzensen [k,1], Herschel W. Lawson [l], Mark H. Einstein [m]

**A negative hrHPV test provides greater reassurance of low CIN3 + risk than a negative cytology result.**

**Based on limited data, triage of hrHPV-positive women using a combination of genotyping for HPV 16 and 18 and reflex cytology for women positive for the 12 other hrHPV genotypes appears to be a reasonable approach to managing hrHPV-positive women.**


Primary HPV Screening
Type 16/18 Positive
Colposcopy
≥ASC-US
12 other hrHPV +
Cytology
NILM
Follow up in 12 months
Negative
Routine Screening

# Hr HPV Testi Klinik Kullanımı

- **Hr HPV Triage (Yönetim)**
  - ASCUS, LGSIL, AGC
- **Hr HPV Tarama**
  - Hr HPV + Pap test kombinasyonu
  - Hr HPV Primer Tarama
    - Sitoloji
    - HPV 16-18 Genotiplemesi

Search

# ASCCP Updated Consensus Guidelines FAQs

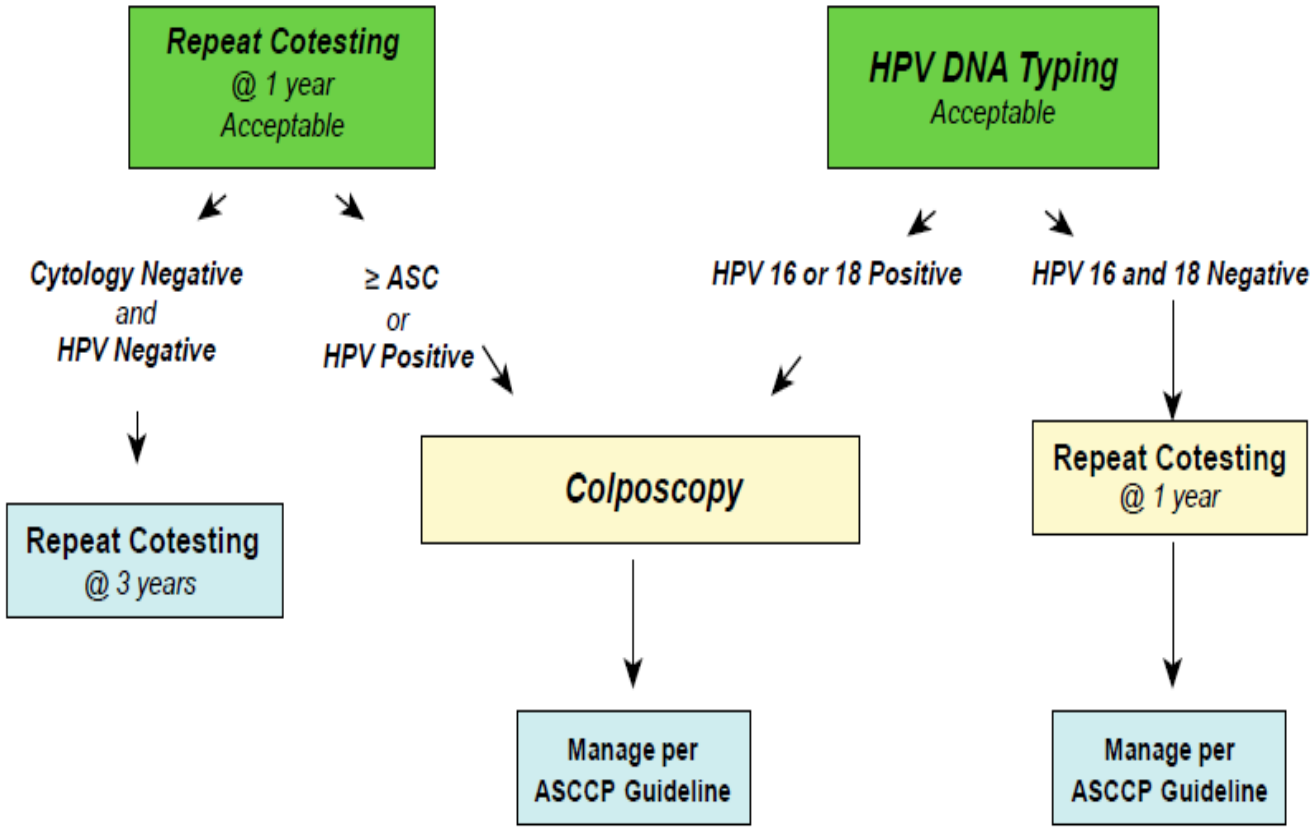
## – What's New?

- Returning to 'routine' screening
- Managing women with discordant cotest results:
  - (HPV+ /Cytology -
  - HPV- /Cytology ≥ ASC-US
- Extending adolescent (age <21) management guidelines to women < age 25
- Treating CIN1 on ECC as + ECC or CIN1?
- Managing women with unsatisfactory cytology and specimens missing endocervical or transformation zone components

## – How should I manage women with discordant cotesting results?

- Use cotesting management recommendations only for women ≥30 years of age.
- HPV+/Pap- women can be managed in two ways:
  - Repeat cotesting in one year, with colposcopy if HPV+ or ASC-US+ (including HPV-/ASC-US) and repeat cotesting in 3 years if cotest results are negative.
  - Genotyping, with colposcopy if HPV16+ or18+ and repeat cotesting in 1 year if both HPV 16 and 18 are negative.

# Management of Women ≥ Age 30, who are Cytology Negative, but HPV Positive



# A model to evaluate the costs and clinical effectiveness of human papilloma virus screening compared with annual papanicolaou cytology in Germany

'European Journal of Obstetrics & Gynecology and Reproductive Biology 212 (2017) 132–139

Karl Ulrich Petry[a,*], Cordula Barth[b], Jürgen Wasem[b], Anja Neumann[b]

**Table 3**
Cost analysis of different scenarios. Data shown are average annual costs (costs incurred over 10 years divided by 10) and expressed in millions of Euros (€). Sums may not total precisely due to rounding.

| | Annual Pap | Scenario 1 HPV+ followed by Pap | Scenario 2 HPV+ followed by p16/Ki-67 dual-stained cytology | Scenario 3 HPV 16/18 followed by colposcopy | Scenario 4 HPV/Pap cotesting |
|---|---|---|---|---|---|
| Screening | 146.9 | 93.2 | 94.5 | 93.4 | 110.0 |
| Office visit | 93.7 | 35.0 | 34.0 | 34.2 | 34.2 |
| Pap cytology | 51.5 | 1.0 | <0.1 | <0.1 | 18.8 |
| HPV | 1.7 | 57.0 | 55.4 | 55.7 | 55.8 |
| Reflex genotyping | 0 | 0 | 0 | 0 | 0 |
| p16/Ki-67 dual-stained cytology | 0 | 0.2 | 5.0 | 3.5 | 0.9 |
| Diagnostic | 16.0 | 11.0 | 13.9 | 16.6 | 13.4 |
| Office visit | 0.8 | 0.7 | 1.0 | 1.4 | 1.0 |
| Colposcopy + biopsy | 5.6 | 5.1 | 7.1 | 9.4 | 7.1 |
| Surveillance | 9.6 | 5.2 | 5.8 | 5.8 | 5.3 |
| Treatment | 14.0 | 12.7 | 12.5 | 12.6 | 12.9 |
| CIN2 | 0 | 0 | 0 | 0 | 0 |
| CIN3 | 3.7 | 3.7 | 4.2 | 4.2 | 3.9 |
| Cervical cancer | 10.2 | 8.9 | 8.3 | 8.3 | 9.0 |
| Total annual cost | 176.9 | 117.0 | 120.9 | 122.6 | 135.9 |
| Difference HPV vs Pap | | −34% | −32% | −31% | −23% |

*Conclusion:* Screening strategies including primary HPV testing for high-risk subtypes (HPV-16/18) in conjunction with p16/Ki-67 dual-stained cytology can improve the detection of cervical cancer at a lower total annual cost than conventional Pap cytology screening.

# Servikal Kanser Tarama Testinde, Servikal Sitoloji Sonucu Normal Olarak Değerlendirilip HPV 16 ve/veya 18 ile HPV 16-18 dışı (Diğer) Yüksek Riskli HPV Tipleri Tespit Edilen Hastaların Kolposkopik Biyopsi Sonuçlarının Karşılaştırılması

**Patients groups:** Cytology(-), HR-HPV(+) **:677**

HPV 16 and/or 18 (+) **: 361**

Other than HPV-HR 16-18 (other) (+) **: 316**

# Grupların Karşılaştırılması

- Servikal sitoloji sonucu normal olarak değerlendirilip HPV 16-18 dışı (diğer) yüksek riskli HPV tipleri tespit edilen hastalarda ***kolposkopik değerlendirme dikkate alınması gereken bir durum gibi görünmekte***

| | | | |
|---|---|---|---|
| | | | P<0.001 |
| ≥HSIL | 85/361 (%23,5) | 18/316 (%5,7) | |
| Servikal Kanser | 4/361 (%1,1) | 2/316 (%0,6) | P=0,5 |

special article

# Secondary Prevention of Cervical Cancer: ASCO Resource-Stratified Clinical Practice Guideline



This ASCO guideline reinforces selected recommendations offered in the ACS/ASCCP/ASCP, ASCCP, CCO, WHO, von Karsa et al,[5] and Huh et al[6] guidelines and acknowledges the effort

resource level (ie, basic, limited, enhanced, maximal)

These guidelines were published between 2011 and 2015. Six were based completely or in part on systematic reviews.[5,24-29] The WHO guideline has the largest global constituency and makes recommendations for resource-constrained areas. All the other guidelines were developed in maximal resource–level settings. Various types and levels of

# Key Recommendations

## *Primary Screening*

- Human papillomavirus (HPV) DNA testing is recommended in all resource settings.
- Visual inspection with acetic acid may be used in basic settings.
- The recommended age ranges and frequencies in each setting are as follows:
  - Maximal: 25-65 years, every 5 years
  - Enhanced: 30-65 years, if two consecutive negative tests at 5-years intervals, then every 10 years
  - Limited: 30-49 years, every 10 years
  - Basic: 30-49 years, one to three times per lifetime

In basic settings without current mass screening, infrastructure for HPV testing, diagnosis, and treatment should be developed.

## *Exiting Screening*

- Maximal and enhanced: ≥ 65 years with consistently negative results during past ≥ 15 years
- Limited and basic: ≤ 49 years, resource-dependent; see specific recommendations

## *Triage*

- In basic settings, visual assessment for treatment may be used after positive HPV DNA testing results.
  - If visual inspection with acetic acid was used as primary screening with abnormal results, women should receive treatment.
- For other settings, HPV genotyping and/or cytology may be used.

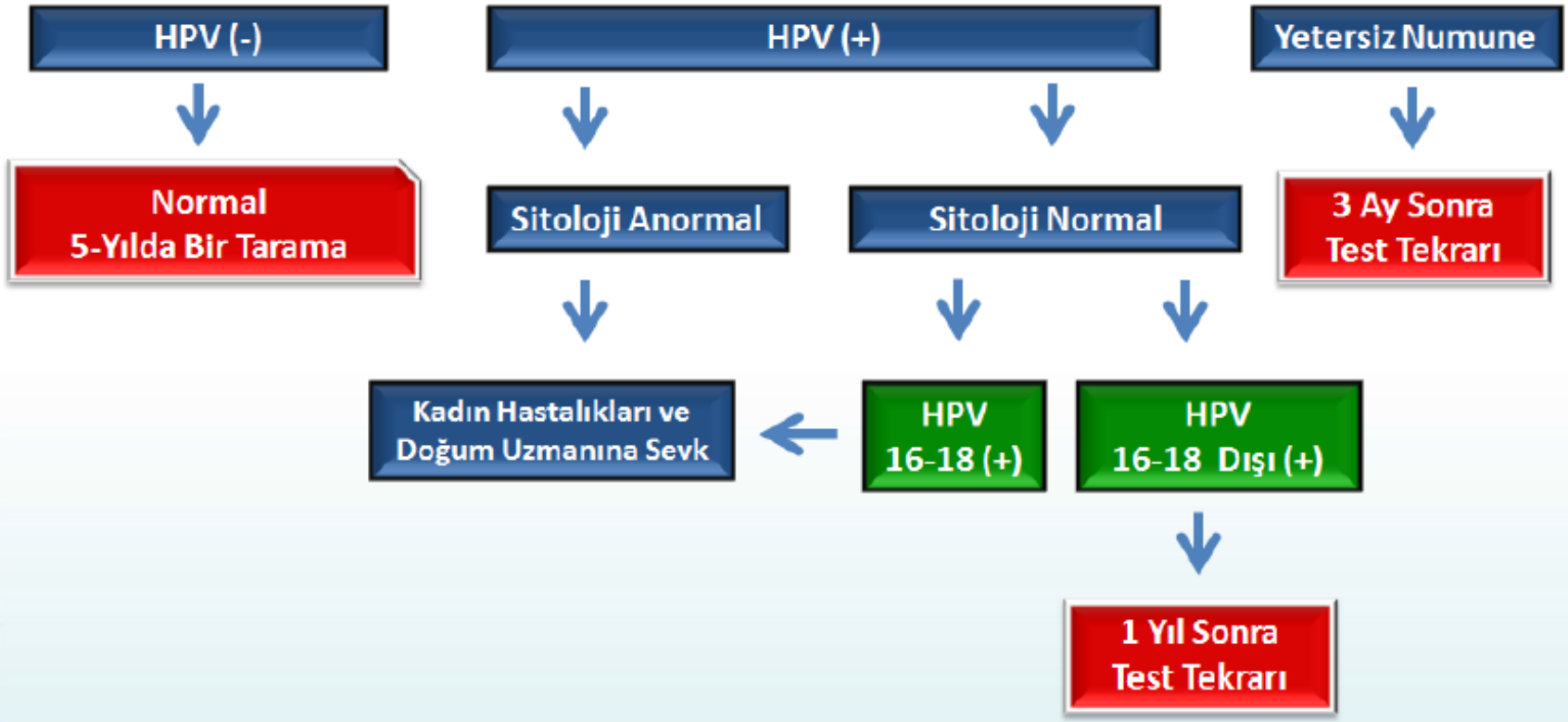
## *After Triage*

- Women with negative triage results should receive follow-up in 12 months.
- In basic settings, women should be treated if there are abnormal or positive triage results.
- In limited settings, women with abnormal results from triage should receive colposcopy, if available, or visual assessment for treatment, if colposcopy is not available.
- In maximal and enhanced settings, women with abnormal or positive results from triage should receive colposcopy.

T.C. Sağlık Bakanlığı
Türkiye Halk Sağlığı Kurumu

# HPV Bazlı Tarama Programı

"Yeni Tarama Algoritmi – 30-64 Yaş Kadınlar"



# DİKKATİNİZ İÇİN TEŞEKKÜRLER


***Prof. Dr. Ömer T. YALÇIN***

OSMANGAZİ ÜNİVERSİTESİ
TIP FAKÜLTESİ
KADIN HASTALIKLARI VE DOĞUM A B D

**Jinekolojik Onkoloji**
**Bilim Dalı**