GISCi

Gruppo Italiano Screening del Cervicocarcinoma

Workshop precongressuale 2015

Definizione del percorso di screening nelle donne vaccinate contro l'HPV: verso una Consensus Conference

Mercoledì 20 Maggio 2015

Complesso monumentale di Santa Caterina

Quale Test nelle vaccinate

Dott. Massimo Confortini

ispo ISTITUTO PER LO STUDIO E LA PREVENZIONE ONCOLOGICA

ITT Istituto Toscano Tumori

SST Servizio Sanitario della Toscana

- Quale test di screening nelle donne vaccinate

- Quale test di screening nelle donne non vaccinate

Donne non vaccinate

- Pap test fino a 30-34 anni
- HPV DNA 30/34-64 con citologia di triage

	Pop. Bersaglio 25-29	Pop. Bersaglio 30-33
Massa Carrara	5178	5016,8
Lucca	5621	5761,6
Pistoia	7717	7996
Prato	6891	6884
Pisa	8873	9223,2
Livorno	8465	8763,2
Siena	7223	7084
Arezzo	9780	9234,4
Grosseto	5495	5496
Firenze	20131	20152,8
Empoli	6434	6421,6
Viareggio	4169	4152
Stima Pap Screening	**5000**	**4000**

Quale test di screening nelle donne vaccinate

- Test HPV DNA primario +citologia di triage in tutte le fasce di età
- NO Pap di screening nella fascia 25-30/34

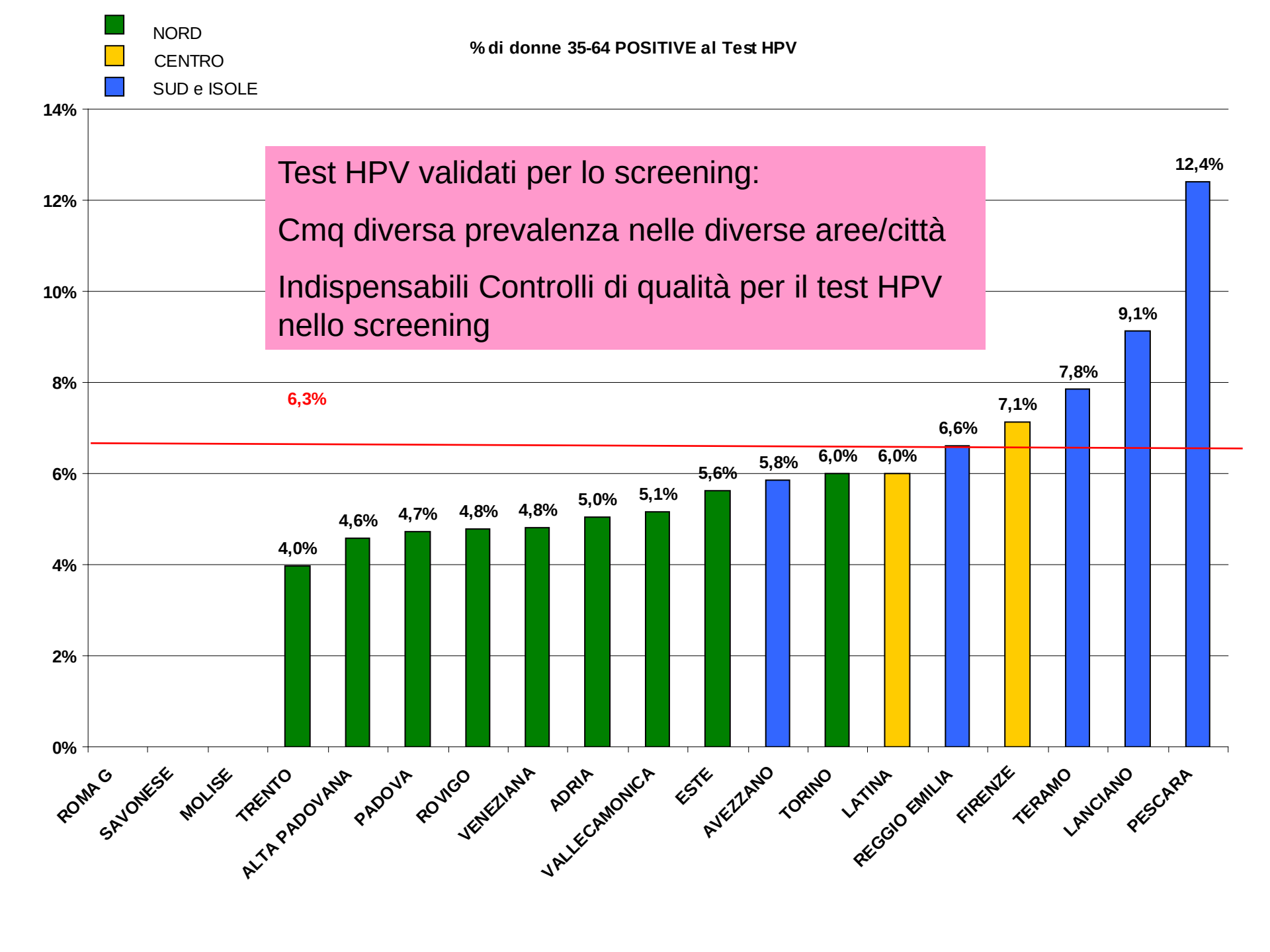
Which high-risk HPV assays fulfil criteria for use in primary cervical cancer screening?

Arbyn M, Snijders PJ, Meijer CJ, Berkhof H, Cuschieri K, Kocjan BJ, Poljak M.

Clin Microbiol Infect. 2015 Apr 30.

Abstract

Several countries are in the process of switching to hrHPV (high-risk human papillomavirus) testing for cervical cancer screening. Given the multitude of available tests, validated assays which assure high-quality screening need to be identified. A systematic review was conducted to answer the question which hrHPV tests fulfill the criteria defined by an international expert team in 2009, based on reproducibility and relative sensitivity and specificity compared to Hybrid Capture-2 or GP5+/6+ PCR-EIA. These hrHPV DNA assays were validated in large randomized trials and cohorts with follow-up of eight years or more. Eligible studies citing the 2009-guideline were retrieved from www.scopus.com and from a meta-analysis assessing the relative accuracy of new hrHPV assays versus the standard comparator tests to detect high-grade cervical intraepithelial neoplasia or cancer in primary screening. The cobas 4800 HPV Test and RealTime High Risk HPV test were consistently validated in two and three studies, respectively, whereas PapilloCheck HPV-screening test, BD Onclarity HPV assay and the HPV Risk Assay were validated each in one study. Other tests which partially fulfil the 2009-guidelines are: Cervista HPV HR Test, PCR-LMNX, a homebrew E6/E7 RT qPCR and MALDI-TOF. The APTIMA HPV assay targeting E6/E7 mRNA of hrHPV was also fully validated. However, the cross-sectional equivalency criteria of the 2009-guidelines were set up for HPV DNA assays. Demonstration of a low risk of CIN3+ after a negative APTIMA test over a longer period is waited for to inform about its utility in cervical cancer screening at five year or longer intervals.


NORD
CENTRO
SUD e ISOLE
% di donne 35-64 POSITIVE al Test HPV
Test HPV validati per lo screening:
Cmq diversa prevalenza nelle diverse aree/città
Indispensabili Controlli di qualità per il test HPV nello screening
14%
12%
10%
8%
6%
4%
2%
0%
6,3%
4,0%
4,6%
4,7%
4,8%
4,8%
5,0%
5,1%
5,6%
5,8%
6,0%
6,0%
6,6%
7,1%
7,8%
9,1%
12,4%
ROMA G
SAVONESE
MOLISE
TRENTO
ALTA PADOVANA
PADOVA
ROVIGO
VENEZIANA
ADRIA
VALLECAMONICA
ESTE
AVEZZANO
TORINO
LATINA
REGGIO EMILIA
FIRENZE
TERAMO
LANCIANO
PESCARA

Gruppo di I° livello

Il Test hr-HPV nei programmi di screening

Caratteristiche del test *hr-HPV*

a) I test HPV attualmente in uso si basano sulla rilevazione del DNA dei vari tipi HPV nei campioni clinici.

b) Nel contesto di protocolli di screening è ancora sufficiente testare il gruppo di HPV ad alto rischio "in toto"

c) Una nuova generazione di test combinano la ricerca di 13 HR-HPV con la genotipizzazione di HPV 16 e HPV 18

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DNA-based detection and genotyping assays

- HC2 Detect 13 HR-HPV genotypes collectively
- Cobas 4800 HPV test identifies separately HPV 16 and 18
- Abbott RealTime High Risk HPV assay identifies separately HPV 16 and 18
- BD HPV test detect separately 16,18,31,45,51 52 and 59.The remanaing types are grouped into two pools (33,56,58,66) and (35,39,68)
- Aptima HPV 16/18/45 genotype specifically detect 16,18 and45

uicc
global cancer control

IJC
International Journal of Cancer

HPV prevalence and accuracy of HPV testing to detect high-grade cervical intraepithelial neoplasia

Paolo Giorgi-Rossi[1], Silvia Franceschi[2] and Guglielmo Ronco[3]

Int. J. Cancer: **130**, 1387–1394 (2012) © 2011 UICC

Concern was raised on using testing for high-risk (HR) human papillomavirus (HPV) in cervical cancer screening in populations where HPV prevalence is high. The impact of HR HPV prevalence on the efficiency of HPV test-based screening has never been directly evaluated. A meta-regression of the relationship between HR HPV prevalence and the specificity and positive predictive value (PPV) of HPV DNA testing for the presence of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) was performed. Only studies that used Hybrid Capture 2 (HC2) were included. Country income (low–medium *vs.* high) was used as a proxy of previous screening. Twenty-six populations from 20 studies were included. For a 10% increase in HR HPV prevalence, HC2 specificity decreased by 8.41% [95% confidence interval (CI): 8.02–8.81], whereas PPV increased by 4.74% (95% CI: 2.45–7.03). HR HPV prevalence explained 98% of the variability in HC2 specificity and 38% of the variability in PPV. Country income did not affect specificity, but low–medium income was associated with higher PPV (3.81%; 95% CI: 1.53–6.10) after adjustment for HR HPV prevalence. When HR HPV prevalence is high, the specificity of HPV testing for CIN2+ decreases, but PPV does not decrease and it is high in inadequately screened populations. The number of HPV-positive women needing further assessment or treatment per CIN2+ case detected will therefore decrease and screening efficiency will improve. This is explained by the fact that HR HPV causes CIN2+: an increase in HR HPV prevalence is inevitably accompanied by an increase in CIN2+.

HPV prevalence and accuracy of HPV testing

Giorgi Rossi P,Franceschi S,Ronco G
IJC 2013

- The probability of finding CIN2+(Biological PPV) is substantially indipendent from HR HPV prevalence however **it is influenced by previous screening**

HPV prevalence and accuracy of HPV testing

Giorgi Rossi P,Franceschi S,Ronco G
IJC 2013

- The probability of progression from HR HPV infection to CIN2+ mainly depends on biological features of the virus that are not in function of HR HPV prevalence

- PPV will also decrease among **women who had been vaccinated against HPV 16 and 18** as these types confer a stronger risk of CIN2+

OXFORD

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Article

ARTICLE

Informed Cytology for Triaging HPV-Positive Women: Substudy Nested in the NTCC Randomized Controlled Trial

Christine Bergeron, Paolo Giorgi-Rossi, Frederic Cas, Maria Luisa Schiboni, Bruno Ghiringhello, Paolo Dalla Palma, Daria Minucci, Stefano Rosso, Manuel Zorzi, Carlo Naldoni, Nereo Segnan, Massimo Confortini, Guglielmo Ronco

Abstract

Background: Human papillomavirus (HPV)–based screening needs triage. In most randomized controlled trials (RCTs) on HPV testing with cytological triage, cytology interpretation has been blind to HPV status.

Methods: Women age 25 to 60 years enrolled in the New Technology in Cervical Cancer (NTCC) RCT comparing HPV testing with cytology were referred to colposcopy if HPV positive and, if no cervical intraepithelial neoplasia (CIN) was detected, followed up until HPV negativity. Cytological slides taken at the first colposcopy were retrieved and independently interpreted by an external laboratory, which was only aware of patients' HPV positivity. Sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values were computed for histologically proven CIN2+ with HPV status–informed cytology for women with a determination of atypical squamous cells of undetermined significance (ASCUS) or more severe. All statistical tests were two-sided.

Results: Among HPV-positive women, informed cytology had cross-sectional sensitivity, specificity, PPV and 1-NPV for CIN2+ of 85.6% (95% confidence interval [CI] = 76.6 to 92.1), 65.9% (95% CI = 63.1 to 68.6), 16.2% (95% CI = 13.0 to 19.8), and 1.7 (95% CI = 0.9 to 2.8), respectively. Cytology was also associated with subsequent risk of newly diagnosed CIN2+ and CIN3+. The cross-sectional relative sensitivity for CIN2+ vs blind cytology obtained by referring to colposcopy and following up only HPV positive women who had HPV status–informed cytology greater than or equal to ASCUS was 1.58 (95% CI = 1.22 to 2.01), while the corresponding relative referral to colposcopy was 0.95 (95% CI = 0.86 to 1.04).

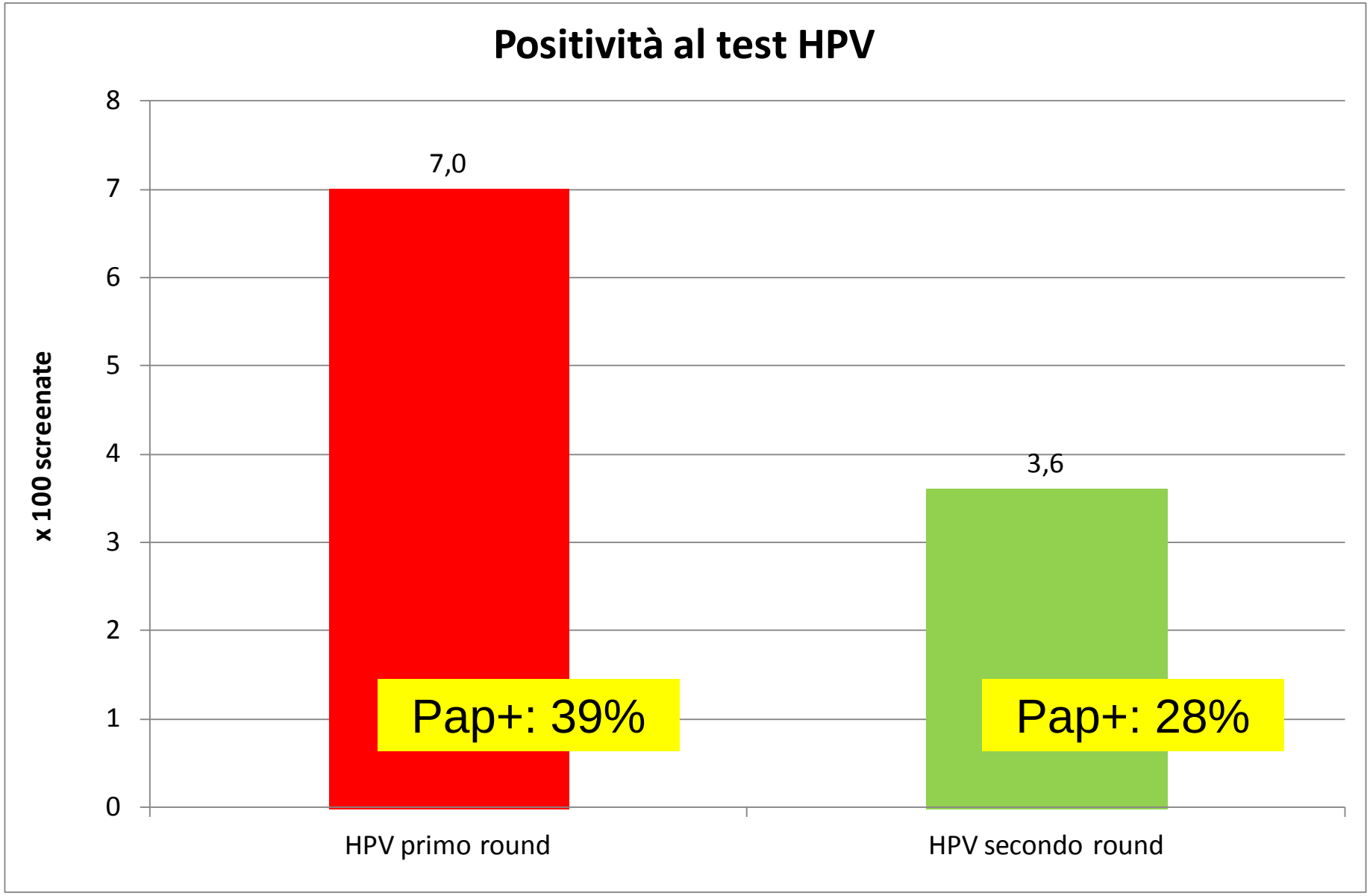
Conclusions: Cytology informed of HPV positivity is more sensitive than blind cytology and could allow longer intervals before retesting HPV-positive, cytology-negative women.

Table 3. Sensitivity and immediate referral to colposcopy in studies applying cytological triage, according to knowledge of HPV status*

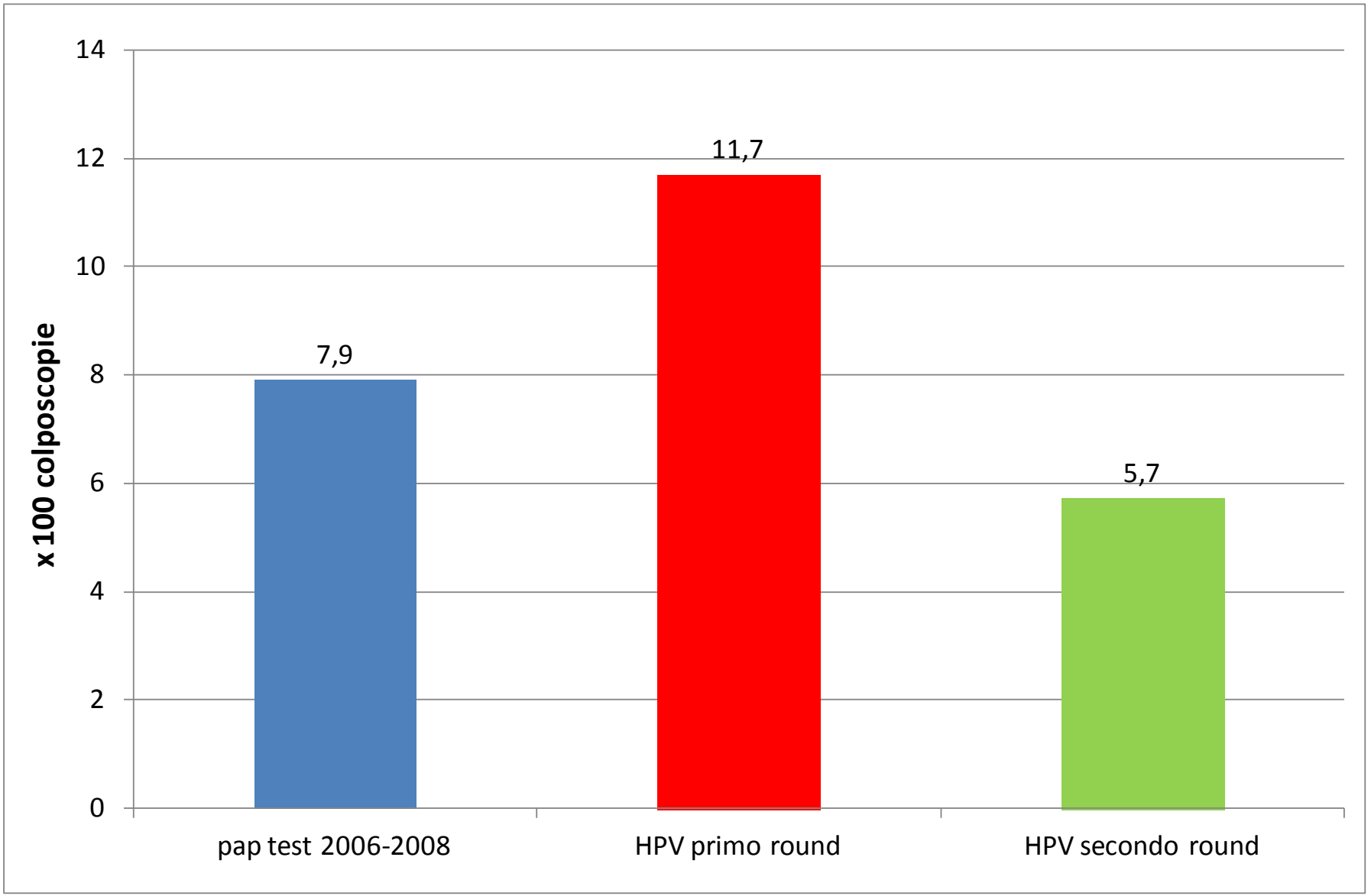
	Cross-sectional sensitivity†		Immediate referral to colposcopy ‡	
Study	Cin2+	Cin3+	Absolute	Relative to stand alone "blind" cytology
HPV status not known				
ATHENA (20)§	52.6% (200/380)	52.8% (133/252)	2.7%	0.42
CCCaST (21)‖§	59.9%	NA	1.1%	0.38
Swedescreen (6)	69.9% (58/83)	72.9% (35/48)	1.7%	NA
POBASCAM (7)	74.3% (179/241)	74.5% (187/251)	1.7%	0.47
NTCC Phase 1(10)¶	76.8% (96/125)	82.7% (43/52)	3.2%	0.83
ARTISTIC (7)#	92.4% (391/423)	95.6% (216/226)	6.4%	0.50
HPV status known				
This study	85.6% (77/90)	88.1% (37/42)	2.8%	0.99
Pilot Veneto Italy (22)**	77.4% (41/53)	NA	2.8%	1.07

Programma di screening cervicale con HPV nell'ULSS 17 Este (PD)

Risultati in donne al secondo round con test HPV


Positività al test HPV
x 100 screenate
8
7
6
5
4
3
2
1
0
7,0
3,6
Pap+: 39%
Pap+: 28%
HPV primo round
HPV secondo round

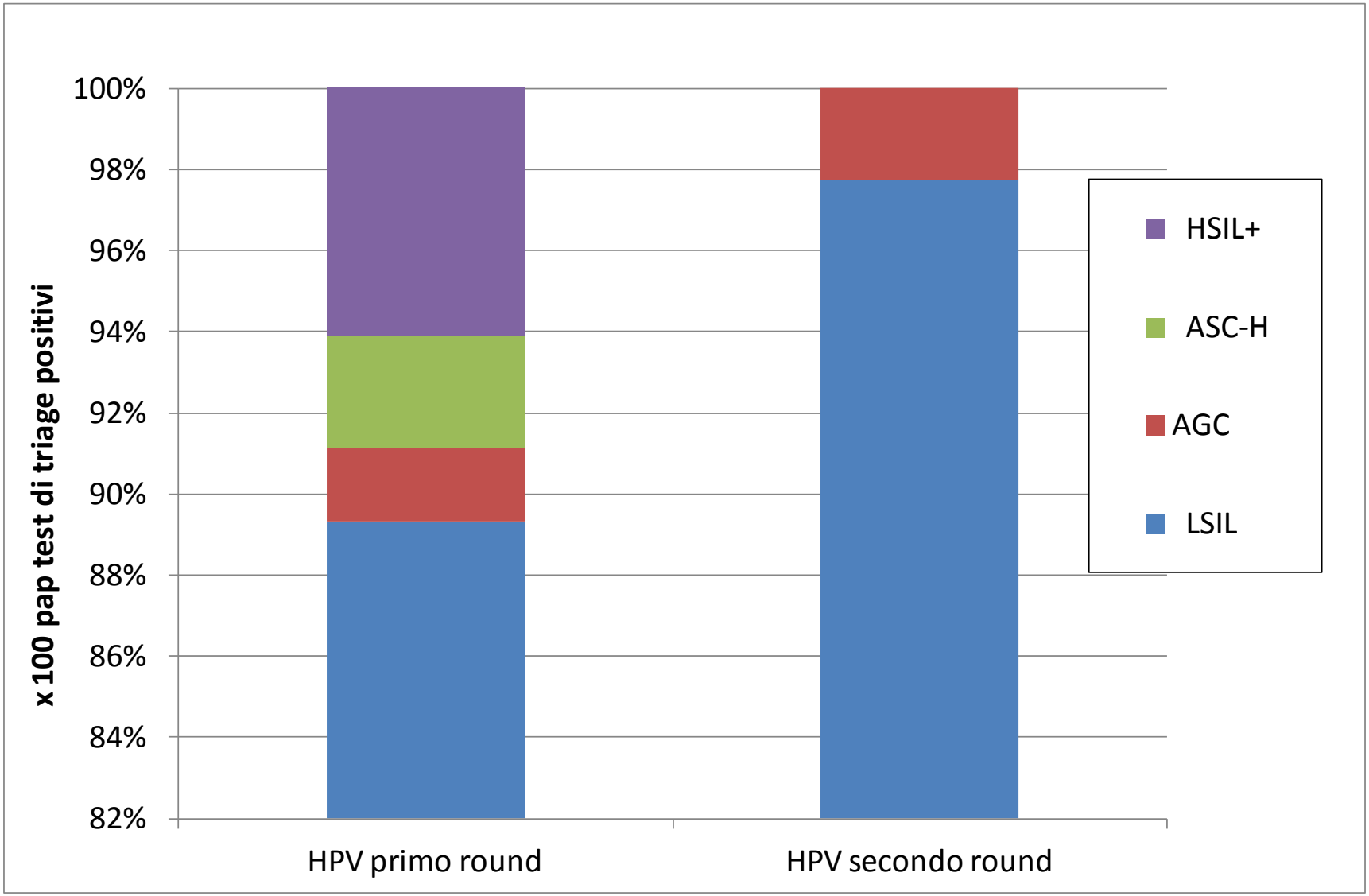
Valore Predittivo Positivo per CIN2+ alla colposcopia



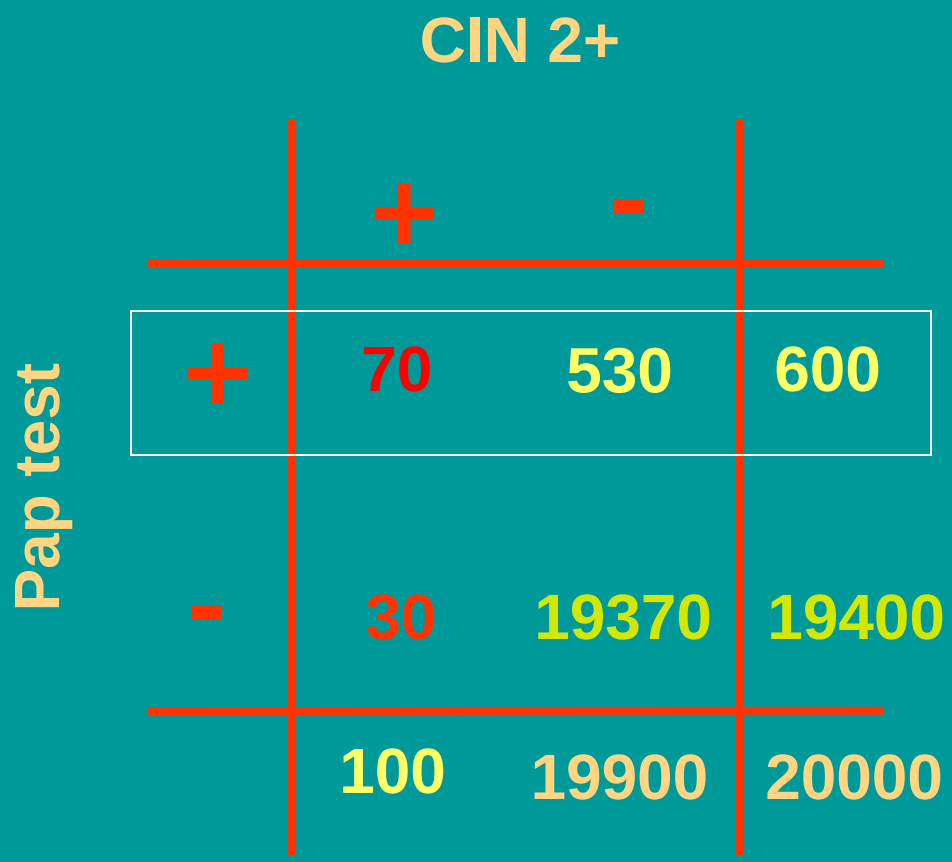
INDICATORI DI QUALITA' DELLA CITOLOGIA DI TRIAGE

- Percentuale di Pap test positivi
- **VPP di HPV+/Cito+**
- Tasso di identificazione di lesioni istologiche CIN 2+ al reclutamento
- Intervallo fra prelievo e data di invio del richiamo ad un anno

Distribuzione delle diagnosi dei pap test di triage positivi



Valore predittivo positivo: popolazione non vaccinata



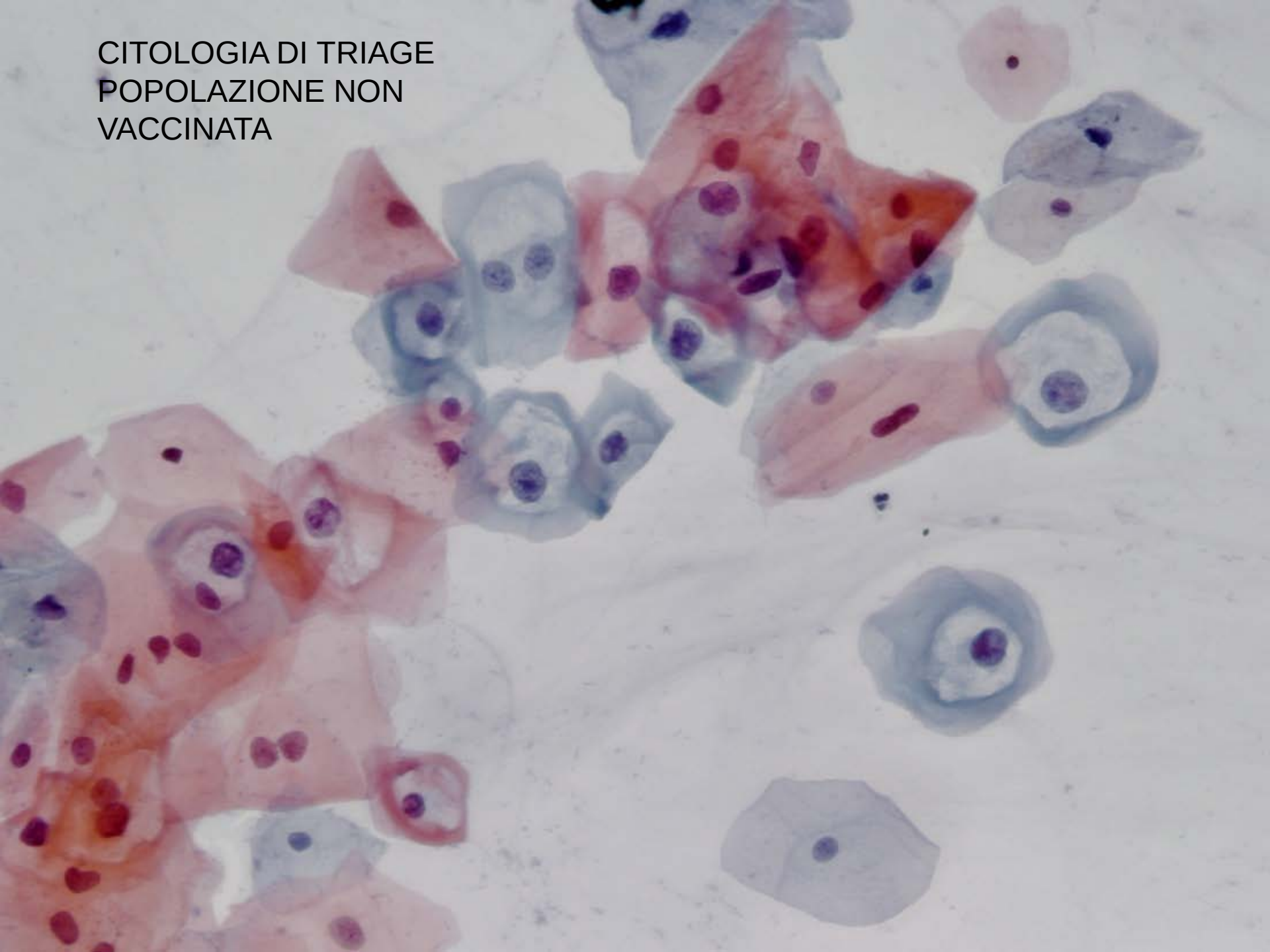
Specificity = 95%

Referral to colpo 3%

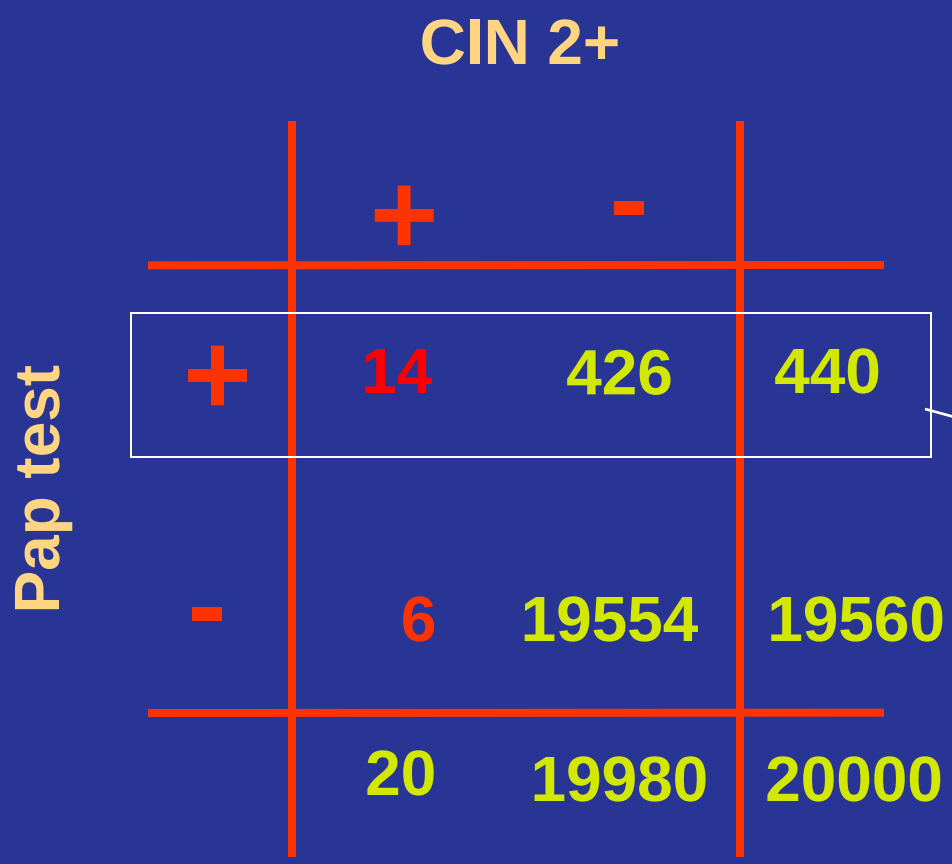
PPV 12%

Sensitivity = 70%

Prevalence of CIN2+ = 0.3%


CITOLOGIA DI TRIAGE
POPOLAZIONE NON
VACCINATA

Valore predittivo positivo: popolazione vaccinata



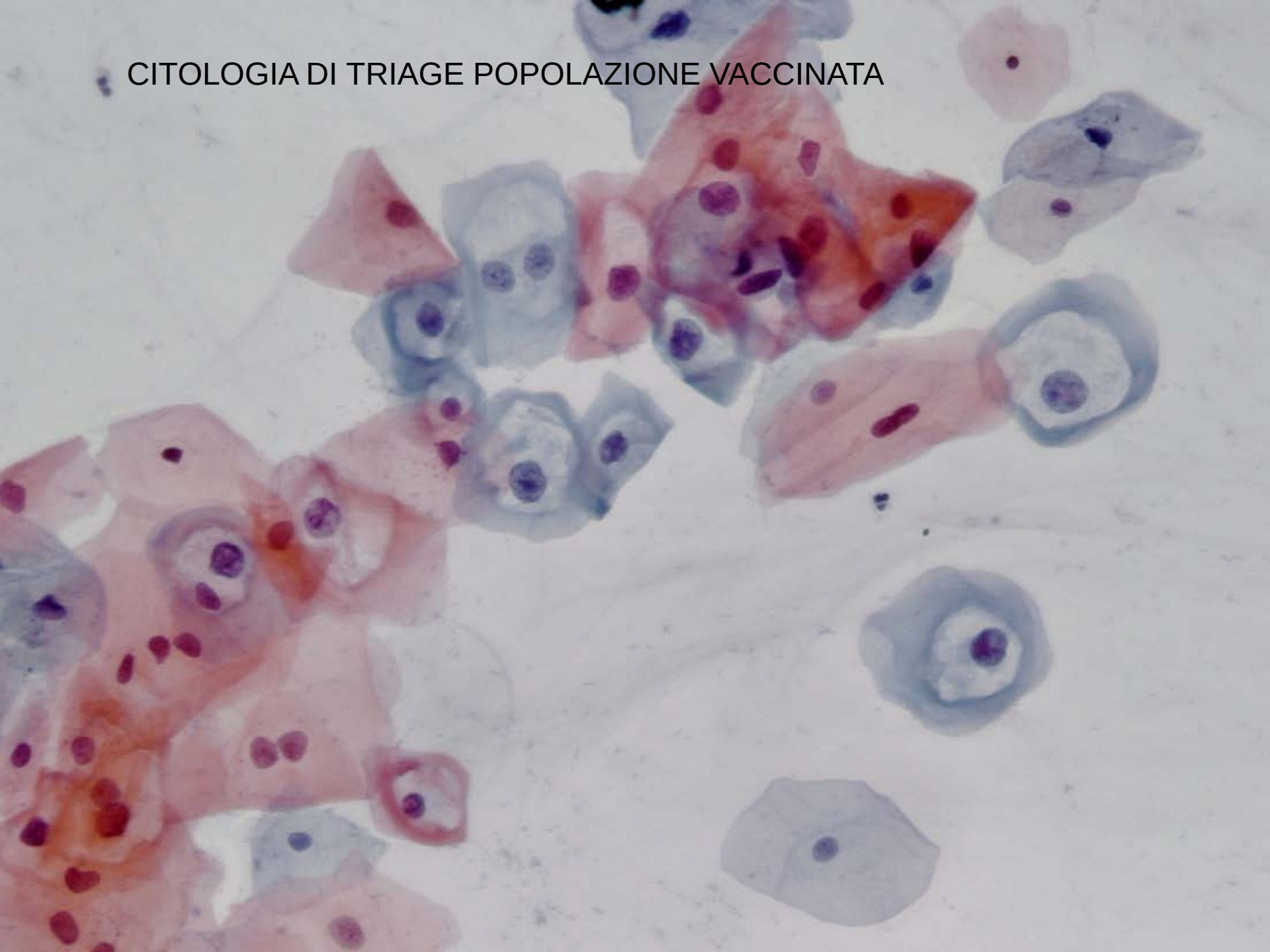
Specificity = 95%

Referral to colpo 2.2%
PPV 3%

Sensitivity = 70%

Prevalence of CIN2+ = 0.1%

CITOLOGIA DI TRIAGE POPOLAZIONE VACCINATA



Quale test di screening nelle donne vaccinate

- Il Valore Predittivo Positivo della citologia di triage basato su un cut-off LSIL+ diminuirà in modo importante nelle donne vaccinate in quanto la stragrande maggioranza delle diagnosi di LSIL corrisponderanno lesioni istologiche CIN1.

Il VPP per le LSIL dovrebbe essere calcolato per CIN1+ ?

Quale test di screening nelle donne vaccinate

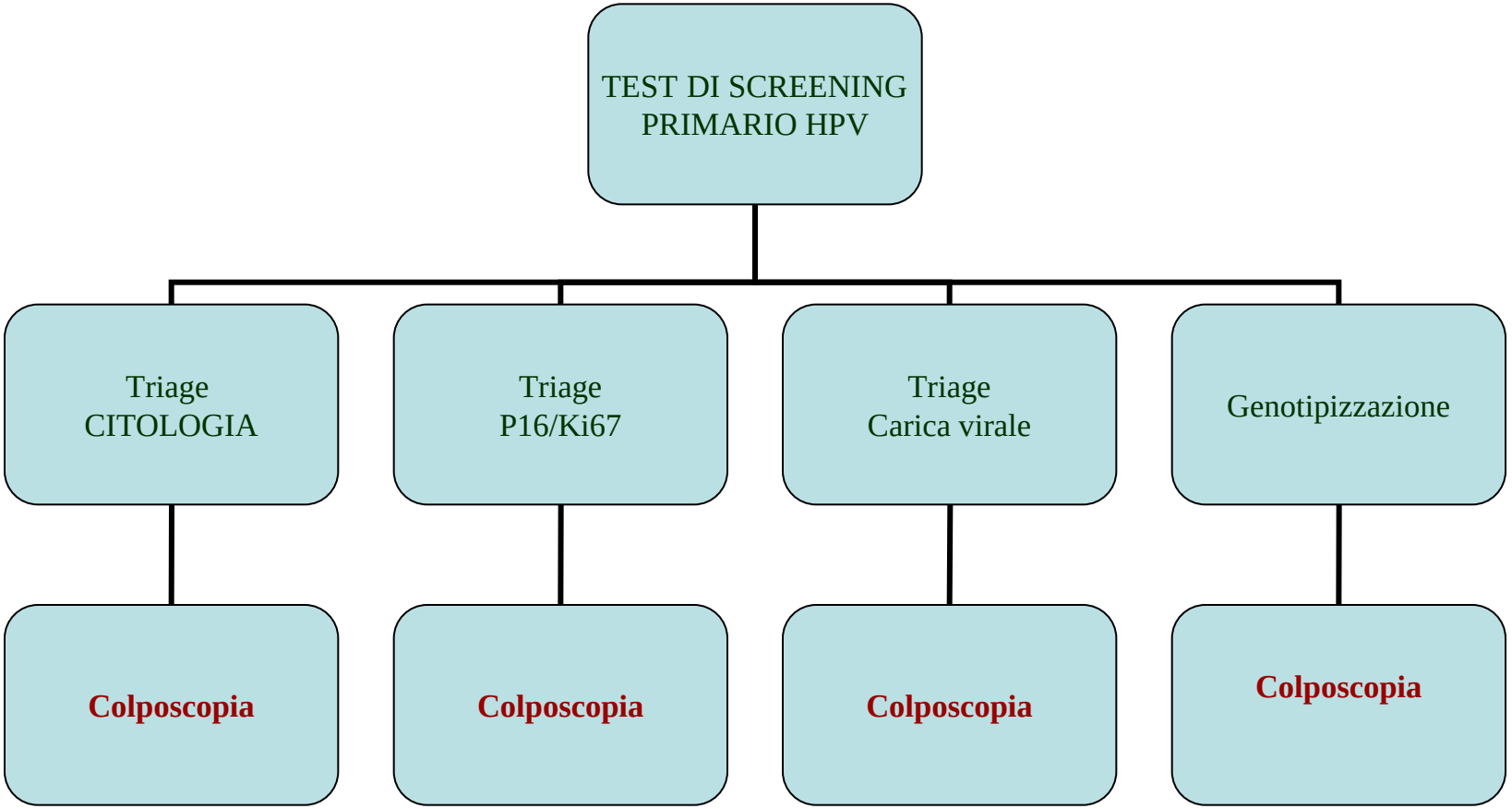
- Necessità quindi di rivalutare il cut-off della citologia di triage per l'invio in colposcopia ed assumeranno maggior importanza le diagnosi borderline di ASC-H e AGC

- IL VPP per CIN2+ della citologia di triage dovrebbe essere calcolato complessivamente per ASC-H/AGC e HSIL

- Ancora più problematico sarà capire le performance della citologia di triage HPV+ in donne vaccinate al secondo round di screening

FUTURO PROSSIMO

COORTI VACCINATE



Interobserver Reproducibility and Accuracy of p16/Ki-67 Dual-Stain Cytology in Cervical Cancer Screening

Nicolas Wentzensen, MD, PhD, MS[1]; Barbara Fetterman, SCT (ASCP)[2]; Diane Tokugawa, MD[2]; Mark Schiffman, MD[1]; Philip E. Castle, PhD, MPH[3]; Shannon N. Wood, MSc[1]; Eric Stiemerling, CT (ASCP)[2]; Nancy Poitras, PMP[2]; Thomas Lorey, MD[2]; and Walter Kinney, MD[4]