"Festa con Gioia...!"

FOLLOW UP CON TEST VIRALE:

la gestione clinica del test virale

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ULSS 20 - Verona

PREVENZIONE SECONDARIA DEL CERVICOCARCINOMA

Perché ricercare l'HPV?

Come ricercare l'HPV?

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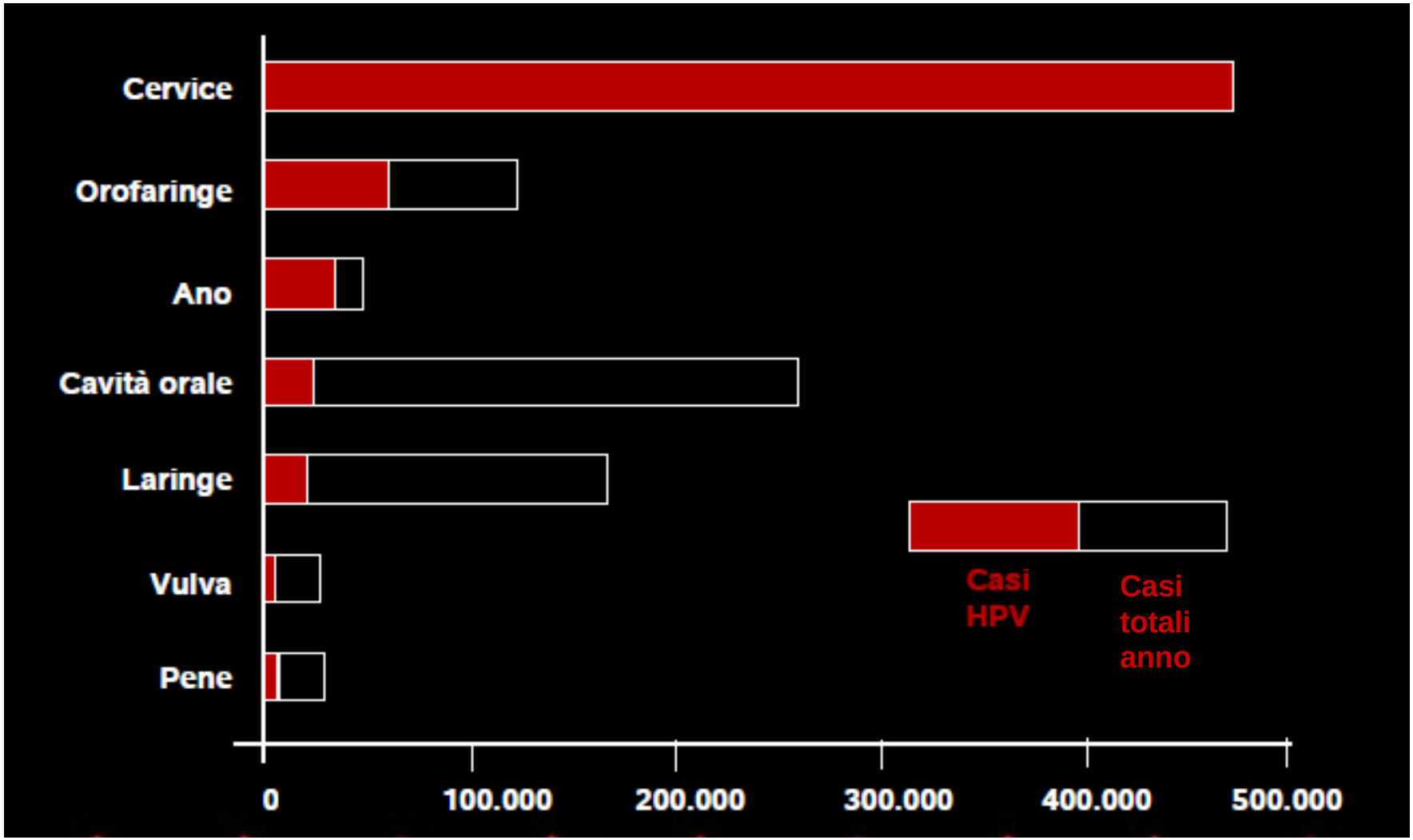
HPV e tumori



Come ricercare l'HPV?

Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors

2012 ASCCP Consensus Guidelines Conference

''HPV testing'' refers only to testing for **high-risk (oncogenic) HPV types**. Testing for **low-risk** (nononcogenic) HPV types has no role in the evaluation of women with abnormal cervical cytologic results.

These guidelines are intended for use **only with HPV tests that have been analytically and clinically validated** with proven
- acceptable reproducibility,
- clinical sensitivity, specificity,
- positive and negative predictive values for cervical cancer and verified precancer (CIN 2+), as documented by U.S. Food and Drug Administration (FDA) licensing and approval or publication in peerreviewed scientific literature

… che riescano ad individuare le lesioni CIN2+

SENSIBILITA'

- **ANALITICA**: % campioni POSITIVI sul totale dei campioni che contengono l'analita
- **CLINICA**: probabilità che il test sia POSITIVO in individui affetti

SPECIFICITA'

- **ANALITICA**: % campioni NEGATIVI sul totale dei campioni che NON contengono l'analita
- **CLINICA**: probabilità che il test sia NEGATIVO in individui NON affetti

2012: Caratteristiche degli HPV DNA test per l'utilizzo clinico

- dovrebbero essere **validati da studi clinici** attendibili

- dovrebbero essere **approvati dalla FDA** e **utilizzati in accordo alle specifiche indicazioni** fornite dall'ente

- dovrebbero **rispettare i criteri di performance** e di adeguatezza clinica (criteri di Stoler 2007 e di Meijer 2009)

CAP TODAY

Approved assays for detecting HPV

design, indications, and validation

All commercially available HPV tests are designed for the detection of HPV nucleic acids in clinical specimens.

Although many in-house HPV nucleic acid detection methods have been used successfully in research laboratories worldwide for more than two decades, **most of them are not approved by the FDA for clinical use.**

Currently, there are **five FDA-approved assays** that can be used to detect high-risk HPV. These include:

- Hybrid Capture 2 HPV DNA test
- Cervista HPV HR test
- Cervista HPV 16/18 test
- Cobas 4800
- Aptima HPV assay for the detection of E6 and E7 mRNA

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GENERAL CONSIDERATIONS

- **Risk cannot be reduced to zero** with currently available strategies, and attempts to achieve zero risk may result in unbalanced harms, including overtreatment.

- Adopted management strategies provide what **participants considered an acceptable level of risk of failing** to detect high-grade neoplasia or cancer in a given clinical situation.

- **Guidelines cannot be developed for all situations**. Clinical judgment should always be applied when applying guidelines to individual patients. This is especially true for guidelines based on less robust evidence.

L'HC2 È IL TEST COMMERCIALE PIÙ DIFFUSO

- Procedura standardizzata di semplice applicazione e costo non troppo elevato.

- Meno suscettibile a problemi di contaminazione e inibizione della PCR con la stessa sensibilità

- Estesa validazione clinica (post trattamento, endocervice….)

HC2: falsi negativi

- errori di prelievo
- integrazione del DNA virale nel genoma ospite: degradazione tratto DNA target
- tipo di virus la cui sonda non è compresa nel pool di sonde fornite nel kit
- tipo di virus non ancora identificato

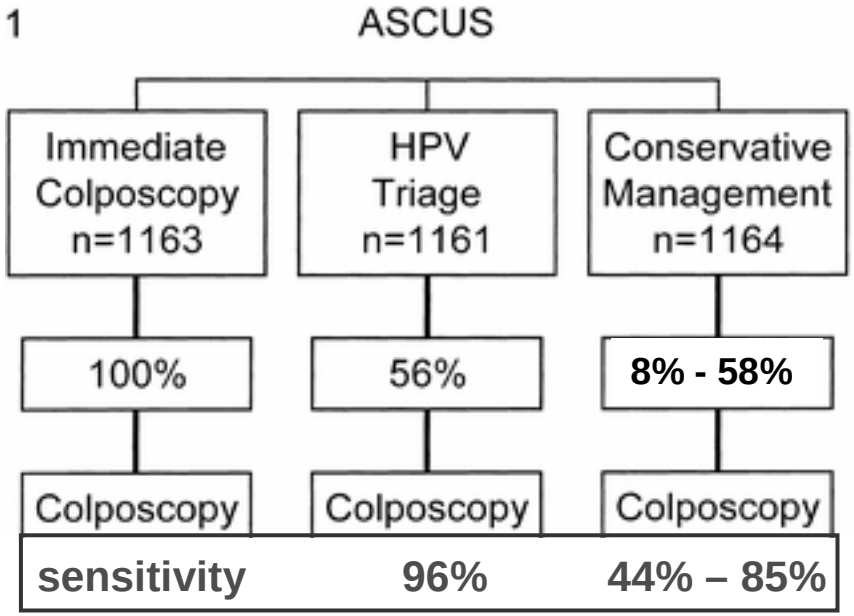
Quando ricercare l'HPV?

INDICAZIONI CONSOLIDATE

GESTIONE DEL PAP TEST "BORDERLINE"

ASCUS-LSIL Traige Study (ALTS) Group
Results of a randomized trial on the management of cytology interpretations of atypical squamous cells of undetermined significance**.**
Am J Obstet Gynecol. 2003 Jun;188(6):1381-2

3488 donne con diagnosi di ASC US - 5,1% CIN3 - FU 2 anni (sem.)



Consistent evidence is available indicating that **HPV-triage with HC2 is more accurate** (significantly higher sensitivity, similar specificity) than repeat cytology to triage women with Ascus

Marc Arbyn, Frank Buntinx, Marc Van Ranst, Evangelos Paraskevaidis, Pierre Martin-Hirsch, Joakim Dillner
Virologic Versus Cytologic Triage of Women With Equivocal Pap Smears: A Meta analysis of the Accuracy To Detect High-Grade Intraepithelial Neoplasia
JNCI Journal of the National Cancer Institute 2004 96(4):280-293;

15 studies

	Sensitivity	Specificity
HPV testing	94,8%	67,3%
Repeat cytology	81,8%	57,6%

***Conclusion**:* The published literature indicates that the **Hybrid Capture II assay has improved accuracy** (higher sensitivity, similar specificity) than the repeat Pap smear using the threshold of ASCUS for an outcome of CIN2+ among women with equivocal cytologic results.

Quando ricercare l'HPV?

INDICAZIONI CONSOLIDATE

FOLLOW-UP DELLE PAZIENTI TRATTATE PER CIN2-3 e AIS

FATTORI INFLUENZANTI IL RISCHIO di PERSISTENZA/RECIDIVA DOPO TRATTAMENTO della CIN

- FATTORI LEGATI ALLA CIN
- FATTORI LEGATI ALLA PAZIENTE
- FATTORI LEGATI AL TRATTAMENTO

…. MA IL **FATTORE DI RISCHIO** PIU' IMPORTANTE PER LA RECIDIVA della CIN è la:

PERSISTENZA dell' INFEZIONE da HPV

Jain S.: Gynec Oncology, 2001

Lin G.T.: Am J Obst gyn, 2001

Nobbenhuis M.A.: Br J Cancer, 2001

Paraskevaidis E.: Obst Gyn, 2001

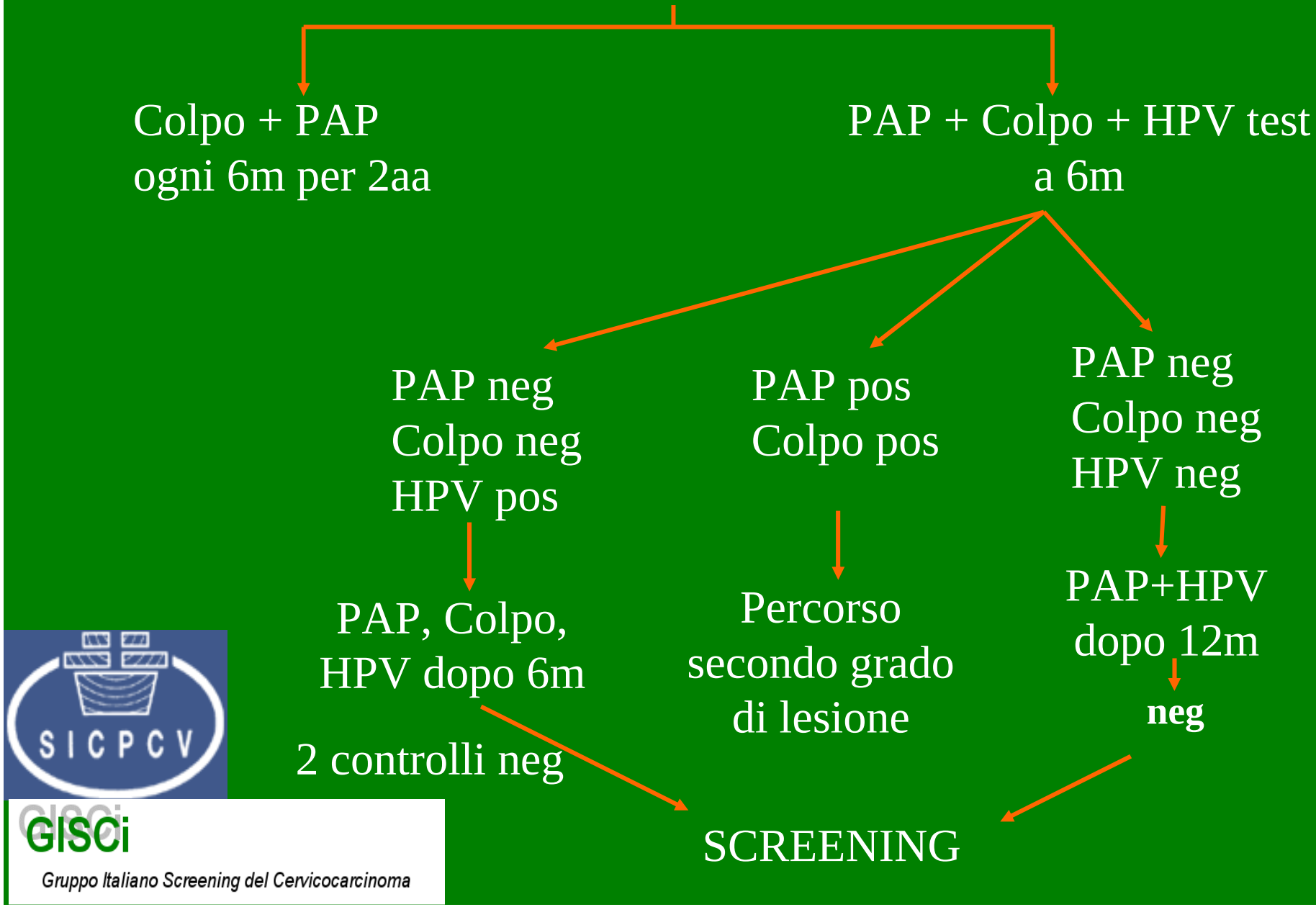
Europ. Net. Cer. Canc. Screen, 2006

CONCLUSION

Sufficient evidence exists **to recommend HPV testing** in triage of woman in surveillance **after treatment of CIN**

Arbyn M. et al.
Human papillomavirus testing and liquid-based cytology: results at recruitment from the new technologies for cervical cancer randomized controlled trial.
J Natl Cancer Inst. 2006 Jun 7;98(11):765-74

FOLLOW UP POST TRATTAMENTO



SICPCV

GISCi

Gruppo Italiano Screening del Cervicocarcinoma

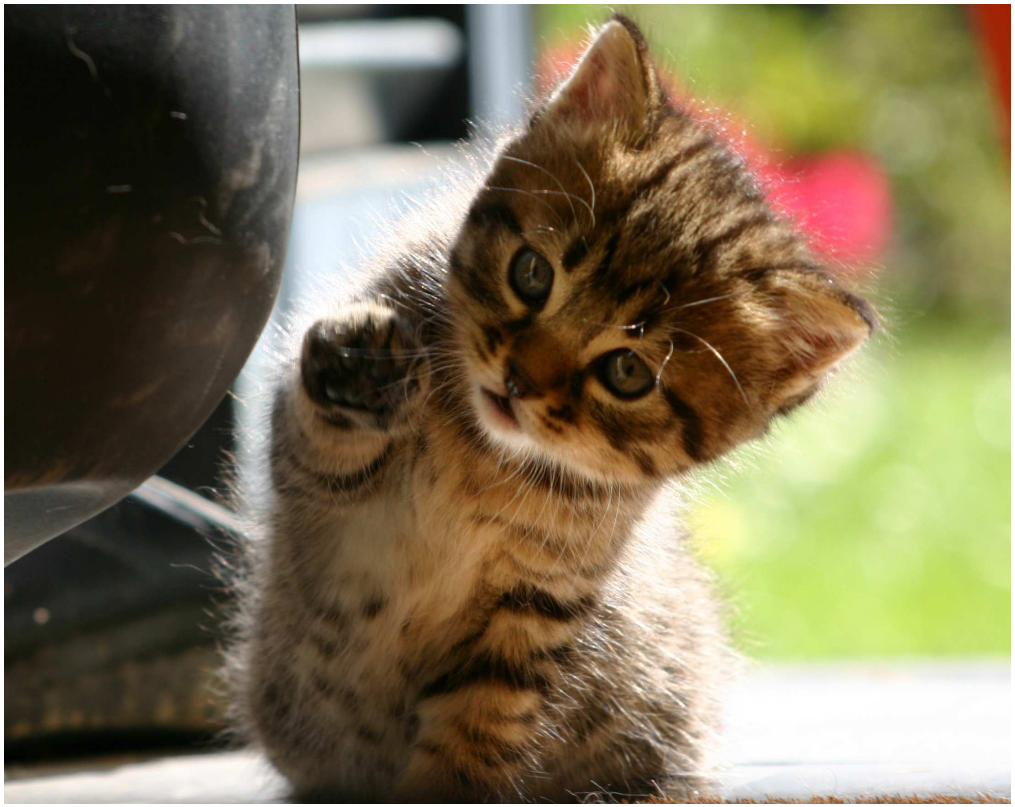
AIS TRATTATI: NECESSITA’ DI FOLLOW UP ?

Incremento assoluto e relativo dell’incidenza dell’adenocarcinoma
- diffusione sempre più capillare degli screening citologici
- aumentata incidenza dell’infezione da HPV, rilevato nell’88-94% delle forme invasive e nell’86,6-100% delle forme preinvasive.

Difficoltà di diagnosi
- sede e topografia delle lesioni
- difficoltà diagnostiche della componente ghiandolare

Frequenze delle recidive
- 50 – 80% in margini positivi
- 20 – 40% in margini negativi

Difficoltà terapeutiche
- isterectomia extrafasciale
- tecniche conservative



Gynecol Oncol. 2007 Jul;106(1):170-6. Epub 2007 May 4.

Human papillomavirus (HPV) test and PAP smear as predictors of outcome in conservatively treated adenocarcinoma in situ (AIS) of the uterine cervix.

Costa S, Negri G, Sideri M, Santini D, Martinelli G, Venturoli S, Pelusi C, Syrjanen S, Syrjanen K, Pelusi G

42 women (mean age 40.5 years; range 27-63 years) underwent conservative (cone) treatment of AIS.

Were prospectively **followed up for a mean of 40 months** (median 42 months), using colposcopy, PAP smear, biopsy and HPV testing (with hybrid capture II) repeated at 6-month intervals

Persistent or recurrent disease was observed in 17 (40.4%) cases,

19% in patients with free margins

65% among those with involved margins on the first conization.

In **4** patients, an adenocarcinoma **(AdCa) stage IA1** was diagnosed during the follow-up.

The combination of PAP smear and HPV testing gives

- SE of 90.0%, SP 50.0%, PPV 52.9% and NPV 88.9% at first follow-up

- 100% SE and 100% NPV at the second follow-up visit.

Quando ricercare l'HPV?

NUOVE PROPOSTE CLINICHE

2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors

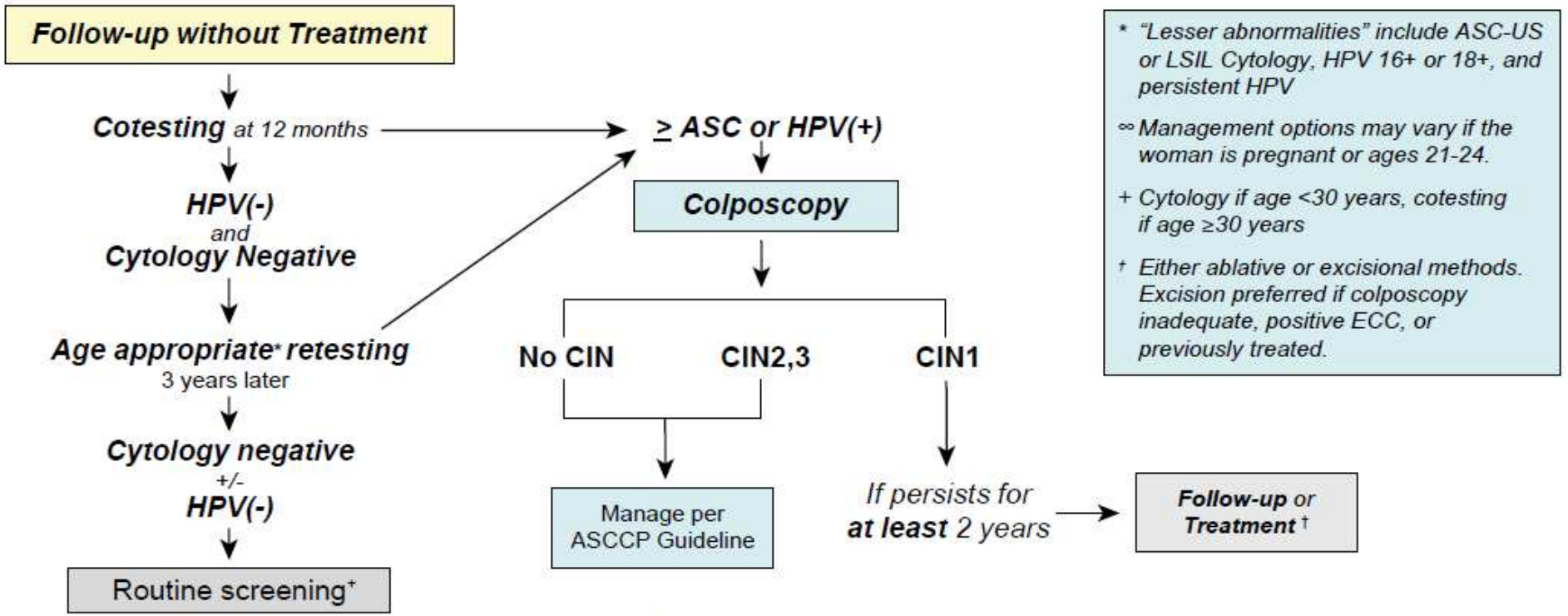
Previous guidelines remain valid, but knowledge has advanced.
Screening has changed.

Co-testing with cytology and HPV testing at 5-year intervals is now the **preferred or acceptable strategy** for cervical cancer screening for women aged 30-64 years

TABLE 1. Summary of Recommendations

POPULATION	PAGE NUMBER	RECOMMENDED SCREENING METHOD[a]	MANAGEMENT OF SCREEN RESULTS	COMMENTS
Aged < 21 y	153	No screening		HPV testing should not be used for screening or management of ASC-US in this age group
Aged 21-29 y	154-155	Cytology alone every 3 y	HPV-positive ASC-US[b] or cytology of LSIL or more severe: Refer to ASCCP guidelines[2]	HPV testing should not be used for screening in this age group
			Cytology negative or HPV-negative ASC-US[b]: Rescreen with cytology in 3 y	
Aged 30-65 y	155-162	HPV and cytology "cotesting" every 5 y (preferred)	HPV-positive ASC-US or cytology of LSIL or more severe: Refer to ASCCP guidelines[2]	Screening by HPV testing alone is not recommended for most clinical settings
			HPV positive, cytology negative: Option 1: 12-mo follow-up with cotesting Option 2: Test for HPV16 or HPV16/18 genotypes • If HPV16 or HPV16/18 positive: refer to colposcopy • If HPV16 or HPV16/18 negative: 12-mo follow-up with cotesting	
			Cotest negative or HPV-negative ASC-US: Rescreen with cotesting in 5 y	
		Cytology alone every 3 y (acceptable)	HPV-positive ASC-US[b] or cytology of LSIL or more severe: Refer to ASCCP guidelines [2]	
			Cytology negative or HPV-negative ASC-US[b]: Rescreen with cytology in 3 y	
Aged > 65 y	162-163	No screening following adequate negative prior screening		Women with a history of CIN2 or a more severe diagnosis should continue routine screening for at least 20 y
After hysterectomy	163-164	No screening		Applies to women without a cervix and without a history of CIN2 or a more severe diagnosis in the past 20 y or cervical cancer ever
HPV vaccinated	164-165	Follow age-specific recommendations (same as unvaccinated women)		

Management of Women with No Lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 1 (CIN1) Preceded by "Lesser Abnormalities"*∞



HPV test e counselling

NCSP Guidelines for Cervical Screening

HPV testing: smear taker responsibilities

The smear taker is responsible for **informing women about the role of high-risk human papillomavirus testing (HPV testing)** in the pathogenesis of cervical cancer and the use of HPV testing as an adjunctive test.

The smear taker is responsible **for explaining the meaning of a positive/negative HPV test result to the woman** (refer to HPV testing fact sheet). Women who test positive for high-risk types of HPV may experience anxiety about developing cancer despite being at very low risk.

The smear taker has to **help women to understand the results of their HPV test and to follow up with any ongoing management.**

CONCLUSIONI

L’HPV test è certamente il futuro

tuttavia è un test giovane

…….difficoltà organizzative, pressioni economiche e desiderio di novità…. ne forzano l’entrata in scena

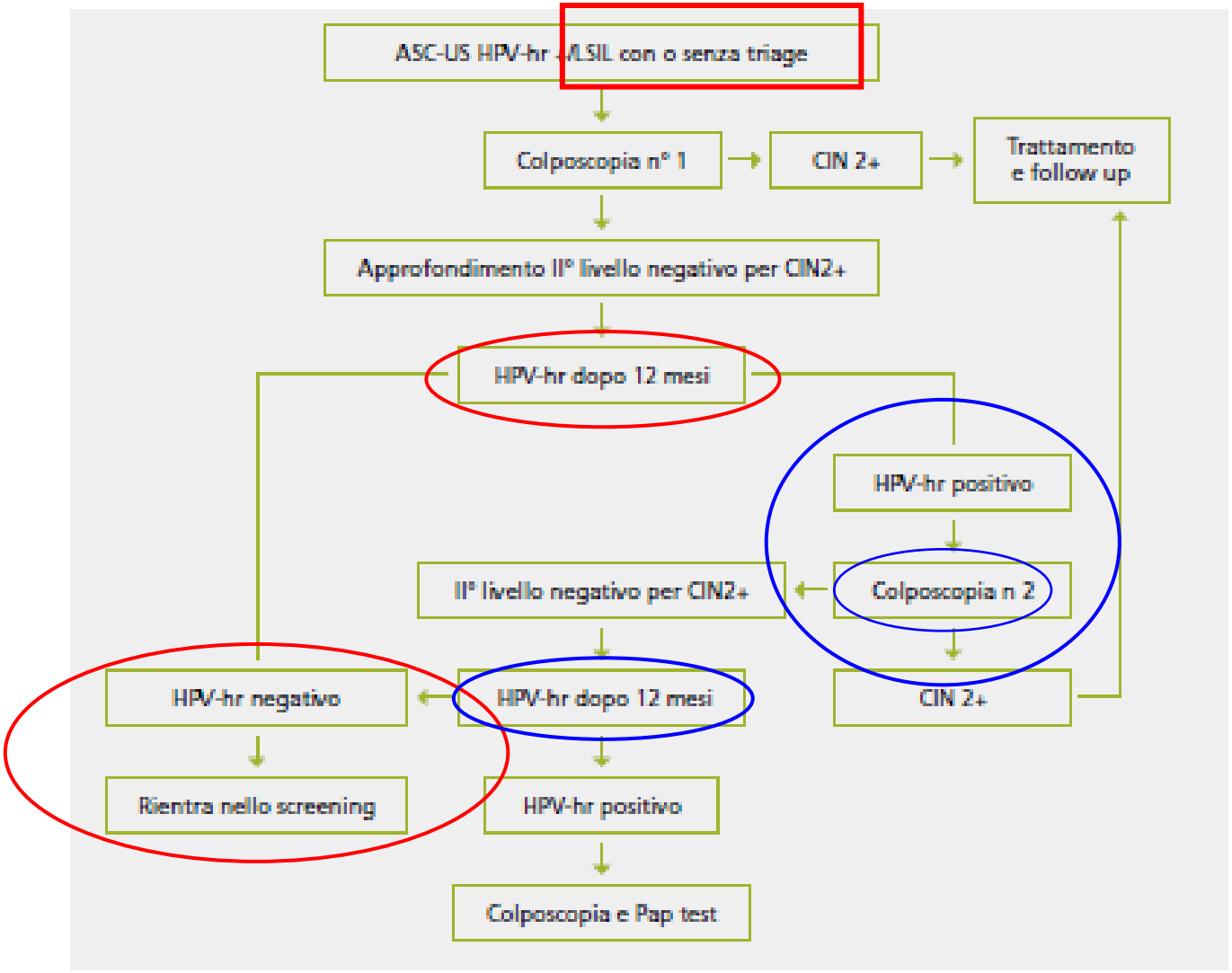
come in tutti gli avvicendamenti un periodo di affiancamento tra le 2 tecniche potrebbe essere opportuno

…… anche perché da noi il pap test ha dato ottimi risultati

e non sono completamente chiari gli effetti degli allungamenti dei tempi di controllo che l’introduzione di questa tecnica inevitabilmente comporta


Grazie


UTILIZZO DEL TEST HPV-HR
NEL TRIAGE DELLE ASC-US,
DELLE L-SIL IN DONNE CON PIU'
DI 35 ANNI, NEL FOLLOW-UP DELLE
DONNE CON CITOLOGIA ASC-US+
DOPO UN APPROFONDIMENTO
DI SECONDO LIVELLO NEGATIVO
PER CIN2+ E NEL FOLLOW-UP
DOPO TRATTAMENTO DELLE LESIONI
CIN2-3: AGGIORNAMENTO 2012


ASC-US HPV-hr +/LSIL con o senza triage
Colposcopia n° 1
CIN 2+
Trattamento e follow up
Approfondimento II° livello negativo per CIN2+
HPV-hr dopo 12 mesi
HPV-hr positivo
II° livello negativo per CIN2+
Colposcopia n 2
HPV-hr negativo
HPV-hr dopo 12 mesi
CIN 2+
Rientra nello screening
HPV-hr positivo
Colposcopia e Pap test