
# HPV test: luci e ombre

**Carlo A. Liverani**

*Oncologia Ginecologica Preventiva*
*Dipartimento della Donna, del Bambino e del Neonato*
*Clinica "L. Mangiagalli" – Università di Milano*

Fondazione IRCCS Ca' Granda
Ospedale Maggiore Policlinico

Sistema Socio Sanitario
Regione Lombardia

# Disclosure

I have no actual or potential conflict of interest in relation to this presentation

# SCREENING:

# DIAGNOSI PRECOCE

PREVENZIONE DEL CANCRO INVASIVO

**NON** DELLE LESIONI PRENEOPLASTICHE

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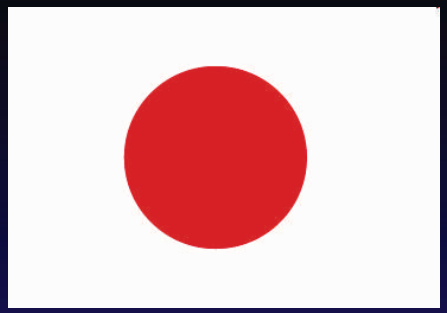
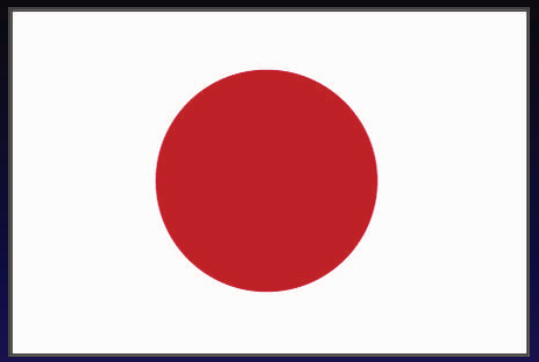


2010

Cervical cancer screening using either HPV test alone or co-testing (HPV + cytology) is not recommended for population-based screening due to insufficient evidence demonstrating an effect on cervical cancer related mortality

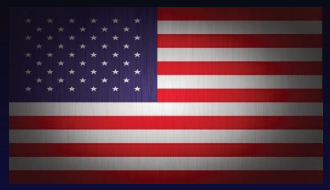
Hamashima C, Aoki D, Miyagi E, et al. The Japanese guideline for cervical cancer screening. *Jpn J Clin Oncol* 2010;40(6):485-502.



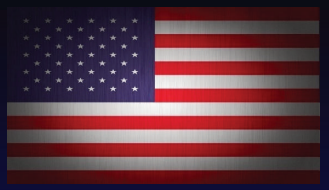
| Età | Metodo e intervalli |
|---|---|
| 20-40 anni | Pap test ogni 2 anni |
| 40-59 anni | Pap test ogni 2-3 anni |
| ≥ 60 anni | Pap test ogni 5 anni |

Hamashima C, Aoki D, Miyagi E, et al. The Japanese guideline for cervical cancer screening. *Jpn J Clin Oncol* 2010;40(6):485-502.

| Età | Metodo |
|---|---|
| < 21 anni<br>(Grado D) | No screening (in caso di esito Pap test ASC-US: non fare HPV test) |
| 21-29 anni<br>(Grado A) | Pap test ogni 3 anni<br>*Attenzione:*<br>- Se ASC-US HPV positivo o Pap ≥ LSIL: inviare a colposcopia (tranne che fra 21 e 24 anni, dove è raccomandato Pap test dopo 1 anno)<br>- Se Pap negativo o ASC-US HPV negativo: ripetere Pap test dopo 3 anni |
| 30-65 anni<br>in donne che desiderano meno controlli<br>(Grado A) | Co-test (cioè Pap test + HPV DNA test) ogni 5 anni<br>*Attenzione:*<br>- Se ASC-US HPV negativo: ripetere co-test dopo 3 anni<br>- Se ASC-US HPV positivo o Pap ≥ LSIL: inviare a colposcopia<br>- Se HPV positivo con Pap negativo: co-test dopo 1 anno; se dopo 1 anno<br>  - co-test negativo: ripetere co-test dopo 3 anni<br>  - Pap ≥ ASC-US o HPV positivo: inviare a colposcopia<br>*In alternativa*: genotipizzazione per HPV 16 o 16/18 (se negativi ripetere co-test dopo 1 anno; se positivi inviare a colposcopia)<br>- Se co-test negativo: ripetere co-test dopo 5 anni |
| 30-65 anni<br>nelle donne che preferiscono più controlli<br>(Grado A) | Pap test ogni 3 anni<br>*Attenzione:*<br>- Se ASC-US HPV positivo o Pap ≥ LSIL: inviare a colposcopia<br>- Se Pap negativo o ASC-US HPV negativo: ripetere Pap test dopo 3 anni |
| > 65 anni<br>(Grado D) | No screening, in presenza di pregresso screening adeguato (cioè almeno due risultati negativi negli ultimi 10 anni, con almeno uno negli ultimi 5)<br>Nelle donne con anamnesi positiva per lesioni CIN 2 o peggiori: continuare screening di routine per almeno 20 anni |
| Dopo isterectomia totale<br>(Grado D) | No screening<br>(si deve intendere: donne senza cervice uterina e senza una storia di lesioni CIN 2 o peggiori negli ultimi 20 anni, o senza storia di cancro da sempre) |
| Dopo vaccinazione anti-HPV | Raccomandazioni in base all'età<br>(per adesso esattamente come nelle donne non vaccinate) |



# Cervical cancer screening
# Women ages 21 to 65 years



The USPSTF recommends screening every 3 years with PAP TEST alone in women ages 21 to 29 years

The USPSTF recommends either screening every 3 years with PAP TEST alone, or every 5 years with hrHPV testing alone in women ages 30 to 65 years

U.S. Preventive Services
TASK FORCE

# EUROPA

- Inizio screening tra i 20-25 anni e i 30 anni
- Fine screening a 60-65 anni
- Citologia ogni 3-5 anni (a seconda delle risorse)
- HPV DNA test come "**unico test** di screening" a partire dai 30-35 anni (ad intervalli di 5 anni, fino a 10 anni dopo i 40)

von Karsa L, Arbyn M, DeVuyst H et al. European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination. Second edition – Supplements (September 2015)

# L'HPV test **NON** è raccomandato al di fuori dei programmi organizzati

von Karsa L, Arbyn M, DeVuyst H et al. European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination. Second edition – Supplements (September 2015)

# HPV test NOT recommended

- routine screening in women aged < 30 yrs
- more often than every 5 yrs for women > 30 yrs
- adolescents/young adults (< 25 yrs) with any abnormality
- initial triage or management of LSIL < 30 yrs
- initial triage of ASC-H, HSIL, AGC/AIS
- testing for low-risk HPV types

Davey DD et al. 2013 Statement on Human Papillomavirus DNA Test Utilization on behalf of the Cytopathology Education and Technology Consortium (CETC).
*Cancer Cytopathol* 2014;122(2):83-86. & *Am J Clin Pathol* 2014;141(4):459-61.

# HPV testing

L'uso inappropriato dei test HPV aumenta i costi senza offrire benefici e potenzialmente espone le donne a sovratrattamenti inutili se non dannosi


**Solomon D et al.** Statement on HPV DNA Test Utilization.

- *Arch Pathol Lab Med* 2009;133(8):1276-7.
- *J Low Genit Tract Dis* 2009;13(3):135-6.
- *Acta Cytol* 2009;53(3):247-48 (discussion: 249-52)
- *Am J Clin Pathol* 2009;131(6):768-9.
- *Diagn Cytopathol* 2009;37(7):542-3.
- *Cancer Cytopathol* 2009;117(3):154-6.

Nearly 30% of young women initiating first sexual activity test HPV positive within 1 year of first intercourse with a first male sex partner, and by 3 years almost half test positive

The cumulative transition probability from an HPV DNA negative state to an HPV 16 DNA positive state is greater than 30% after 24 months of first sexual exposure

Winer RL et al. Risk of female human papillomavirus acquisition associated with first male sex partner. *J Infect Dis* 2008;197(2):279-82.

L'HPV è talmente comune che praticamente quasi tutte le donne e gli uomini sessualmente attivi lo contraggono in qualche momento della propria vita

Oltre il 90% delle nuove infezioni da HPV, comprese quelle con i tipi ad alto rischio, regrediscono o non sono più rilevabili entro 12-36 mesi

*CDC Atlanta* - MMWR Recomm Rep 2015;64(No. RR-3):84-93.

# PAP TEST

Pap ripetuti ogni 3 anni → 90% dei cancri cervicali

Pap annuale fra 20 e 29 anni → rischio mancare lesione < 0,2%

10 Pap fra 30 e 50 anni → rischio mancare lesione < 0,001%

Massad LS. Assessing new technologies for cervical cancer screening: beyond sensitivity. *J Low Genit Tract Dis* 2008;12(4):311-5.

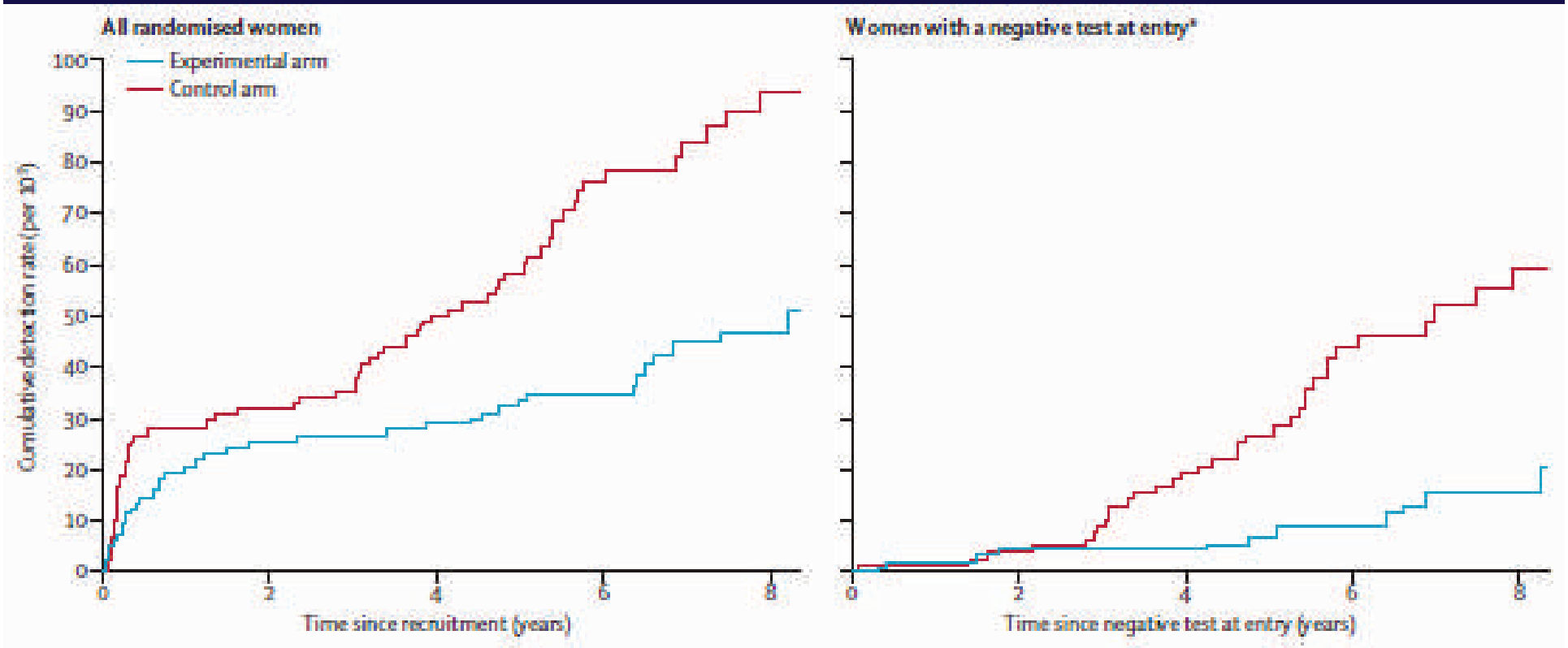
# Pap test / HPV test

Primary HPV screening with cytology triage finds more CIN lesions compared to conventional screening but mild lesions are overrepresented.

This is likely to result in overdiagnosis since most mild lesions are regressive.

Kotaniemi-Talonen L et al. Screening with a primary human papillomavirus test does not increase detection of cervical cancer and intraepithelial neoplasia 3.
*Eur J Cancer* 2008;44(4):565-71.

# Cumulative probability of developing cervical cancer in women allocated to Pap smear (red) or HPV testing/Pap smear (blue)




Ronco G et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet* 2014;383(9916):524-32.

Nessuno dei quattro trials ha portato dati sufficienti a dimostrare una reale riduzione nell'incidenza di cancro Quindi i dati sono stati uniti.

Ciononostante, i tassi di cancro cervicale non sono risultati diversi nel braccio HPV rispetto al braccio PAP nei primi 2,5 anni dall'arruolamento delle pazienti.

~~107~~

~~52 "prevalenti"~~

55

Austin RM. Can HPV primary screening reduce cervical cancer incidence and mortality? SCAN 2014;25(1):7-8.

- 19 cancri in 419.000 donne dopo HPV test
- 36 cancri in 358.656 donne dopo PAP test

portando alla conclusione di una protezione del 60-70% maggiore

**Tuttavia**

1) i dati sono dominati dallo studio italiano (40%), dove tutte le donne positive sono state immediatamente inviate a colposcopia, con oltre **il doppio di biopsie** effettuate rispetto al braccio PAP; nessuna riduzione dei cancri negli studi svedese ed inglese

2) solo 11 su 19 cancri rilevati dopo l'arruolamento erano inizialmente positivi all'HPV (58%)

Tasso di falsi negativi = **42%**
Studio ARTISTIC = **25%**
Kaiser Permanente = **31%**
Studio TOMBOLA = **23%**

Austin RM. Can HPV primary screening reduce cervical cancer incidence and mortality? SCAN 2014;25(1):7-8.

Nei casi presunti «prevalenti»
ben 4 su 25 erano HPV-negativi all'arruolamento (**16%**)

Austin RM. Can HPV primary screening reduce cervical cancer incidence and mortality? SCAN 2014;25(1):7-8.

Su 134 donne sottoposte a trattamento escissionale per CIN 2+, 19 casi erano risultati HPV-negativi (**14.2%**)

Liverani CA, *et al.* High risk HPV DNA subtypes and E6/E7 mRNA expression in a cohort of colposcopy patients from Northern Italy with high-grade histologically verified cervical lesions. Am J Transl Res 2012;4(4):452-457.

# A partire dal 2016 …

Screening primario con HPV test ad intervalli:

5 anni fino ai 40 anni di età

10 anni dopo i 40 anni di età

Vink MA et al. Primary human papillomavirus DNA screening for cervical cancer prevention: Can the screening interval be safely extended? Int J Cancer 2014 Dec 6. doi:10.1002/ijc.29381

2009

Over the two screening rounds combined, co-testing with HPV testing and cytology did not detect a higher rate of preneoplastic lesions than cytology alone

Kitchener HC et al. HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. *Lancet Oncol* 2009;10(7):672-82.

2010

Across all ages, 22% of women who had

CIN 2 or worse were HPV negative

Cotton S et al. Trial Of Management of Borderline and Other Low-grade Abnormal Smears Group. The role of human papillomavirus testing in the management of women with low-grade abnormalities: multicentre randomised controlled trial. *BJOG* 2010;117(6):645-59.

2013

Sensitivity of HPV testing was similar to that of Pap testing but caused more overdiagnosis

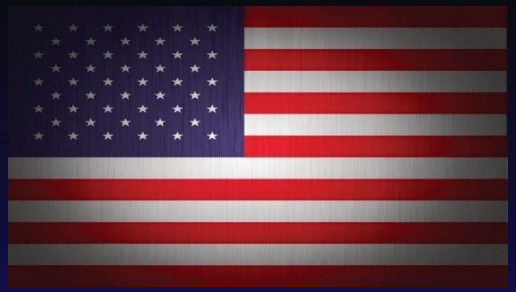
Therefore, implementation of HPV testing needs to be reconsidered especially in countries with well organised programmes

Malila N et al. The HPV test has similar sensitivity but more overdiagnosis than the Pap test – A randomised health services study on cervical cancer screening in Finland. *Int J Cancer* 2013;132(9):2141-7.

2014

Over long term follow-up (13 years!), the cumulative incidence of high grade lesions was the same for HPV screening and for cytology, implying that the increased sensitivity of HPV screening for high grade disease reflects earlier detection rather than overdiagnosis

Elfström KM et al. Long term duration of protective effect for HPV negative women: follow-up of primary HPV screening randomised controlled trial.
*BMJ* 2014;348:g130.



HOUSTON Methodist LEADING MEDICINE

2014

## Biopsies in 78 patients with HSIL

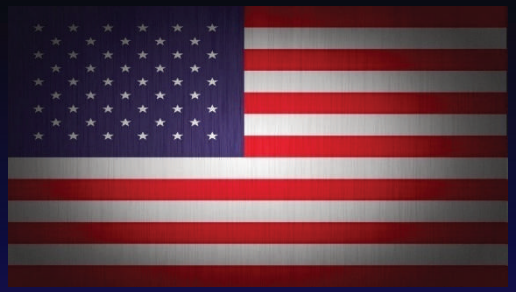
**13 of 34 biopsy-confirmed CIN 2-3 (38.2%) had negative Cobas HPV tests**

Zhou HS et al. The sensitivity of the Cobas HPV test in detecting biopsy-confirmed CIN2/3 cervical lesions: analysis of 33,857 cases with cytology and HPV co-testing. *J Amer Soc of Cytopath* 2014;3(5):S3.

In our study cohort, the false-negative rates of the Cobas HPV test were unacceptably high for detecting high-grade cervical lesions

If used as a primary screening test, the high false-negative rates of the Cobas HPV test will provide false assurance to physicians and patients, and will delay appropriate treatment

Zhou HS et al. The sensitivity of the Cobas HPV test in detecting biopsy-confirmed CIN2/3 cervical lesions: analysis of 33,857 cases with cytology and HPV co-testing. *J Amer Soc of Cytopath* 2014;3(5):S3.



**256.648 donne 30-65 aa.**

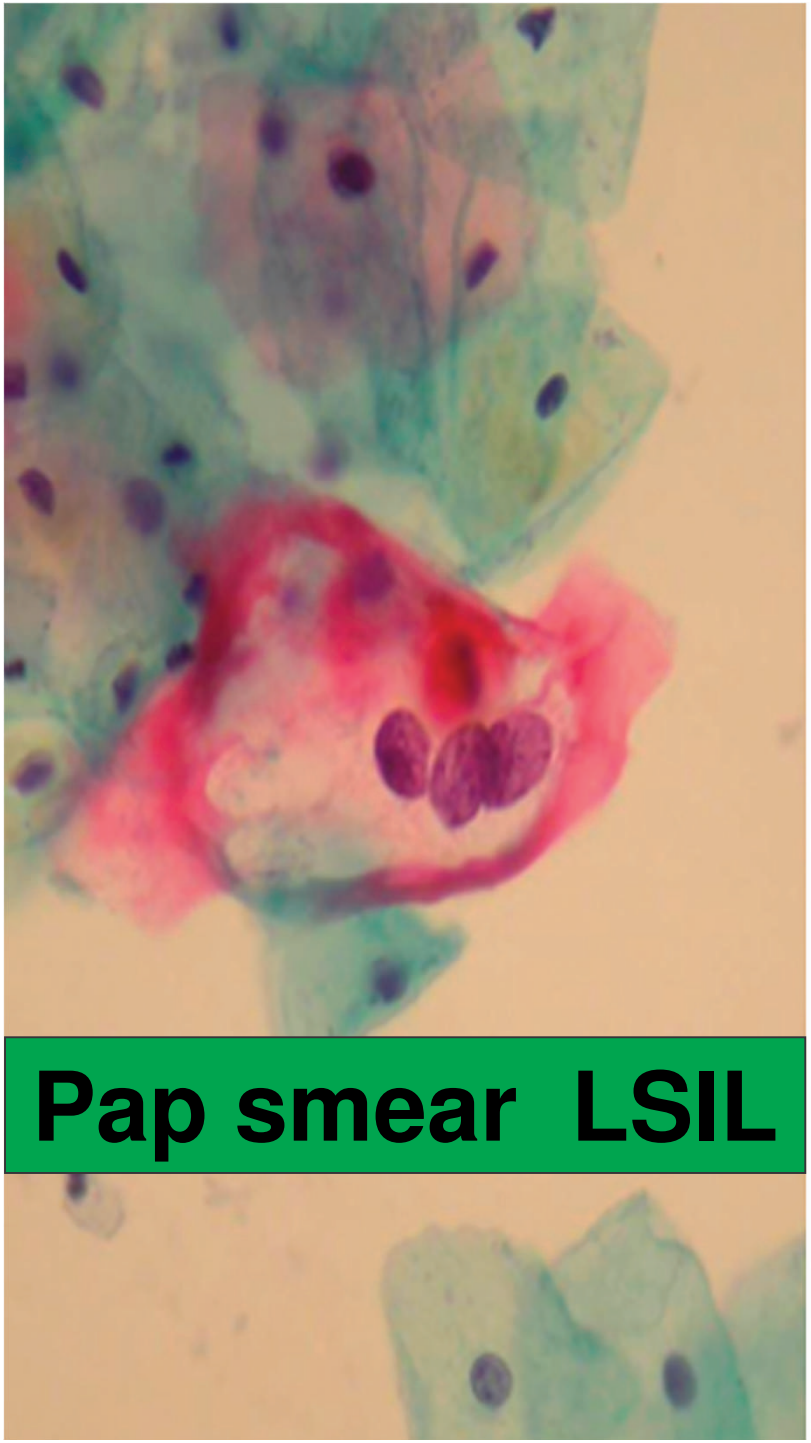
**(cotest e biopsia)**

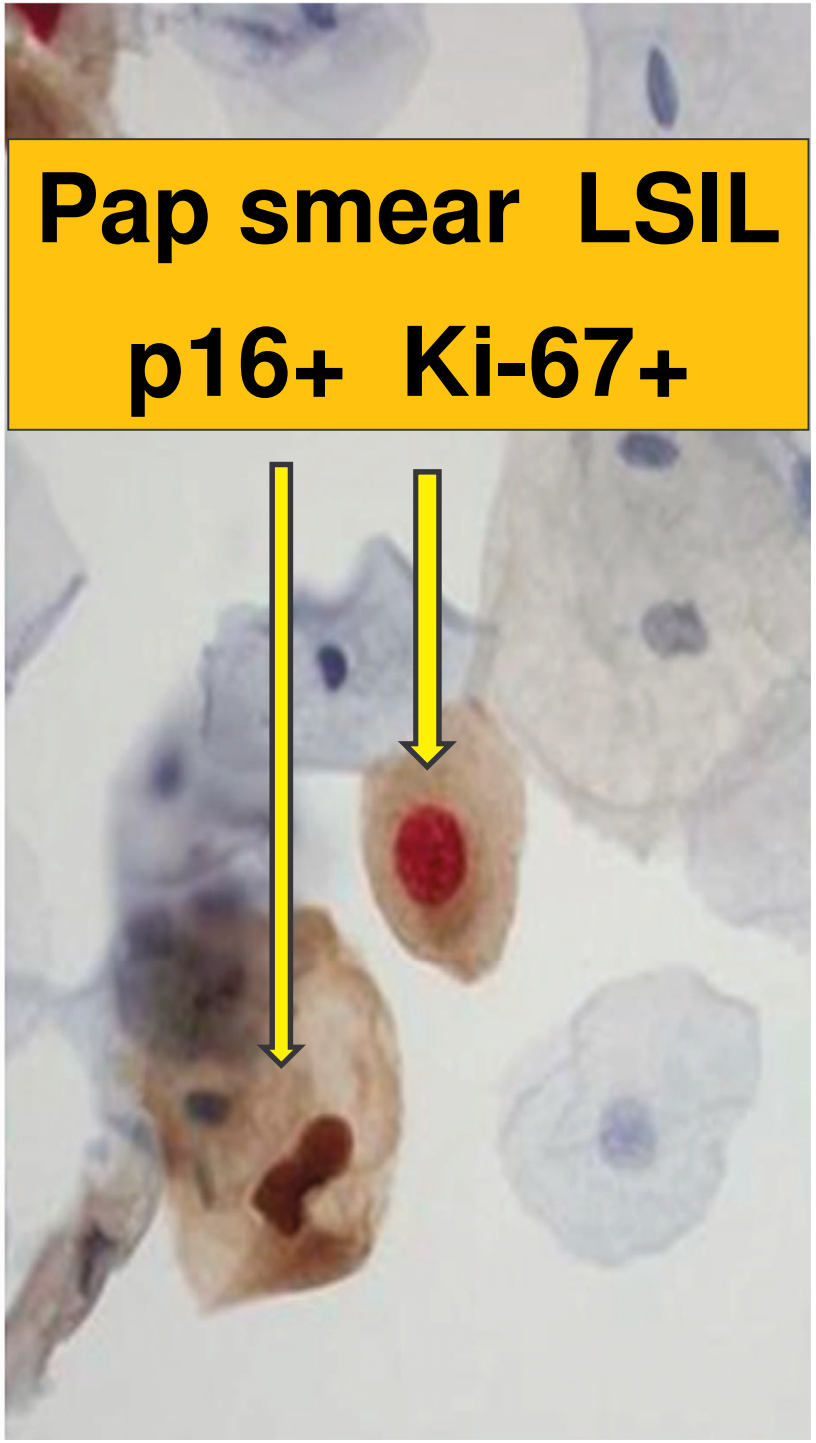
**2015**

| | HPV | Cito | cotest |
|---|---|---|---|
| 526 cancri cervicali | 19% | 12% | 5.5% |

| | HPV | Cito | cotest |
|---|---|---|---|
| 169 adenoca. cervicali | 26.6% | 20.7% | 8.3% |

Blatt AJ et al. Comparison of cervical cancer screening results among 256,648 women in multiple clinical practices. *Cancer Cytopathol* 2015;123(5):282-8.


Pap smear LSIL


Pap smear LSIL
p16+ Ki-67+

| Cases | Cytology | HR HPV + | p16/Ki-67 + |
|---|---|---|---|
| **515** | 301 ASC-US | 42.2% | 17.9% |
| | 169 LSIL | 76.3% | 43.2% |
| | 29 ASC-H | 69.0% | 65.5% |
| | 16 HSIL | 93.8% | 93.8% |
| | ***Sensitivity*** *for CIN 2-3* | **91.4%** | **94.3%** |
| | ***Specificity*** *for CIN 2-3* | **14.7%** | **61.9%** |

Killeen JL et al. Improved abnormal Pap smear triage using cervical cancer biomarkers. *J Low Genit Tract Dis* 2014;18(1):1-7.

# HPV DNA positive woman with a negative smear

- Infection with an oncogenic virus
- “High Risk” type
- NO lesions
- NO cure
- Sexually transmitted

## What many health professionals actually do

- Non validated tests
- Women under 30-35 yrs
- Re-screen every 2-3 yrs
- Test for low risk HPV types
- Genotyping
- Anal, vulvar, penile, oral sites
- Test for both low grade and high grade lesions
- Test male partner
- Test to screen for STD

- Treat HPV with surgery, laser, interferon, 5-FU, etc.

Liverani CA et al. 'What is and what should never be': use and misuse of HPV testing in cervical cancer prevention strategies. *Curr Womens' Health Rev* 2014;10(2):113-19.

**5.064** pazienti
(95% screening primario 23-65 anni):

Quattro HPV test:

| | |
|---|---|
| HC-II (Qiagen) | 20,4% **+** |
| Cobas (Roche) | 26,8% **+** |
| CLART (Genomica) | 25,1% **+** |
| APTIMA (Hologic) | 16,7% **+** |

*Citologia anormale = 7%*

Rebolj M et al. Disagreement between human papillomavirus assays: an unexpected challenge for the choice of an assay in primary cervical screening. PLoS One 2014 Jan 20;9(1):e86835. doi: 10.1371

**5.064** pazienti
(95% screening primario 23-65 anni):

1.679 (**33%**) POSITIVE ad almeno un test:

- 41% concordanza tutti e quattro i test
- 30% concordanza donne ≥ 30 anni
- **29%** concordanza screening primario
- 22% concordanza con citologia normale

*Citologia anormale = 7%*

Rebolj M et al. Disagreement between human papillomavirus assays: an unexpected challenge for the choice of an assay in primary cervical screening. PLoS One 2014 Jan 20;9(1):e86835. doi: 10.1371

1) Citologia nel triage HPV POS:

- 68% tutti e quattro i test positivi: invio in colposcopia
- 32% l'invio a colposcopia dipende dal test impiegato

2) Casi HPV POS / Cito NEG:

- sono pazienti a più elevato rischio, quindi non è consigliabile re-screening ad intervalli allungati

- re-test dopo 6-12 mesi porta a controlli ravvicinati molte donne tutto sommato a rischio relativamente basso (che sarebbero risultate negative impiegando un altro test HPV)

Rebolj M et al. Disagreement between human papillomavirus assays: an unexpected challenge for the choice of an assay in primary cervical screening. PLoS One 2014 Jan 20;9(1):e86835. doi: 10.1371

# *Conclusioni*

Nello screening primario in donne ≥ 30 anni

la discordanza fra i test rende problematico

accettare HPV test come benefico

Rebolj M et al. Disagreement between human papillomavirus assays: an unexpected challenge for the choice of an assay in primary cervical screening. PLoS One 2014 Jan 20;9(1):e86835. doi: 10.1371

In the case of the ACS / ASCCP / ASCP, approximately 25% of committee members reported financial associations with companies that make HPV tests

Smith-McCune K. Choosing a screening method for cervical cancer: Papanicolaou testing alone or with Human Papillomavirus testing. *JAMA Intern Med* 2014;174(7):1027-8.

**Conflitti d'interesse** Huh WK et al. Use of Primary High-Risk Human Papillomavirus Testing for Cervical Cancer Screening: Interim Clinical Guidance. *Obstet Gynecol* 2015;125(2):330-7, *Gynecol Oncol* 2015;136(2):178-82, *J Low Genit Tract Dis* 2015;19(2):91-6.
Merck, GSK, Hologic, Roche, Gen Probe, Becton-Dickinson, Cepheid

**Conflitti d'interesse** Wright TC et al. Primary cervical cancer screening with human papillomavirus: End of study results from the ATHENA study using HPV as the first-line screening test. *Gynecol Oncol* 2015;136(2):189-97.
Roche, BD Diagnostics, GenProbe-Hologic, Cepheid, Genentech

**Funding / support**
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**Role of the sponsor**
Roche Molecular Systems was involved in all aspects of the design and conduct of the study; collection, management, analysis, and interpretation of the data. Catherine Behrens and Abha Sharma who are Roche employees were integral to the preparation of the manuscript and the sponsor reviewed the final manuscript

# A toxic combination of vested interest and good intentions

Heath I. Overdiagnosis: when good intentions meet vested interests. *BMJ* 2013;347:f6361.

# L'HPV test NON deve essere eseguito:

- decidere se vaccinare o meno contro HPV
- screening per STD
- pazienti affette da condilomatosi florida anogenitale
- screening per cervicocarcinoma come unico test
- donne al di sotto dei 30 anni di età
- sedi diverse dalla cervice uterina (anale, orale, etc.)

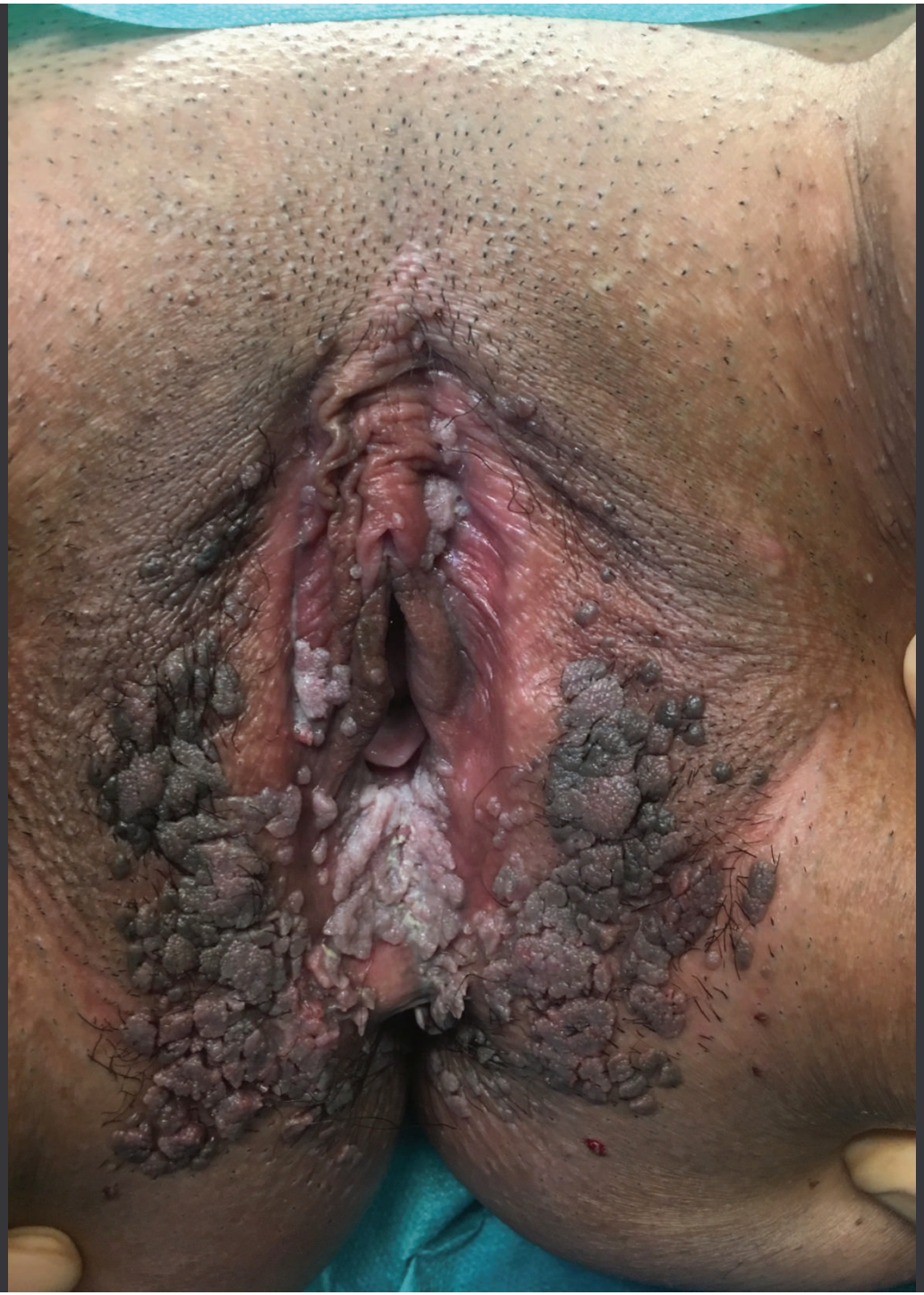
*CDC Atlanta* - MMWR Recomm Rep 2015;64(No. RR-3):84-93.

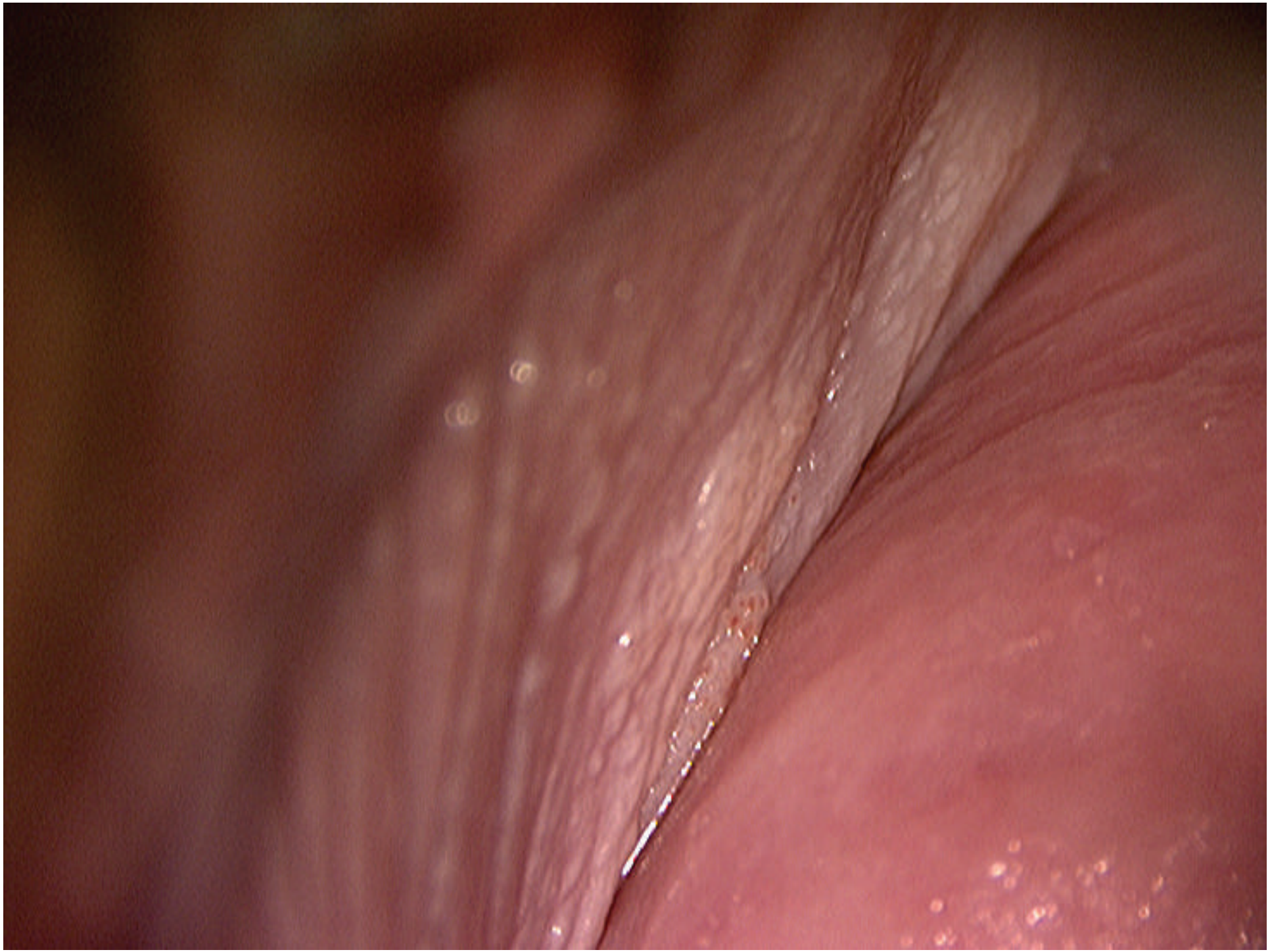
# EUROPA

- Inizio screening tra i 20-25 anni e i 30 anni
- Fine screening a 60-65 anni
- Citologia ogni 3-5 anni (a seconda delle risorse)
- HPV DNA test come **unico** test di screening a partire dai 30-35 anni (ad intervalli di 5 anni, fino a 10 anni dopo i 40)

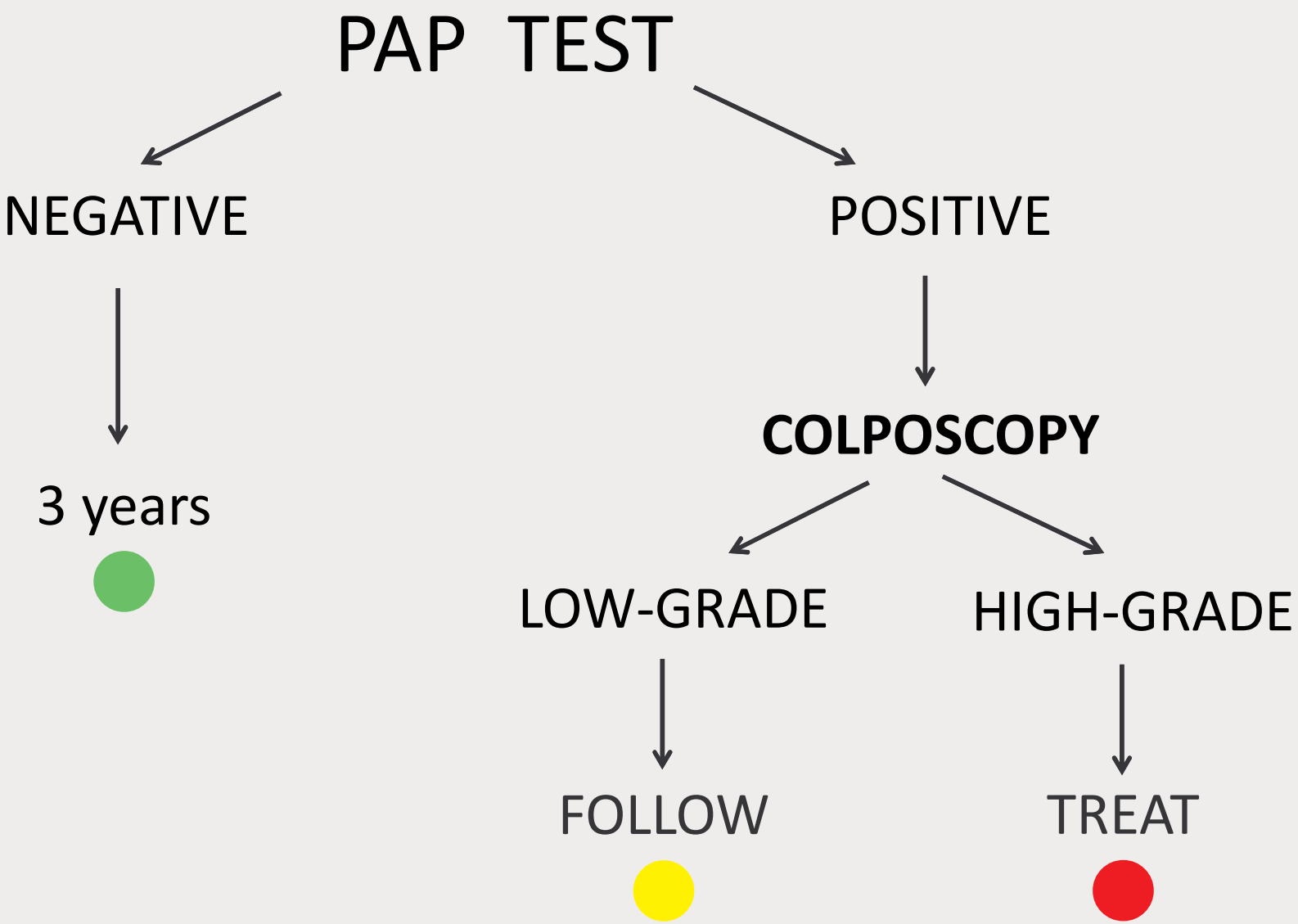
# L'HPV test **NON** è raccomandato al di fuori dei programmi organizzati

von Karsa L, Arbyn M, DeVuyst H et al. European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination. Second edition – Supplements (September 2015)

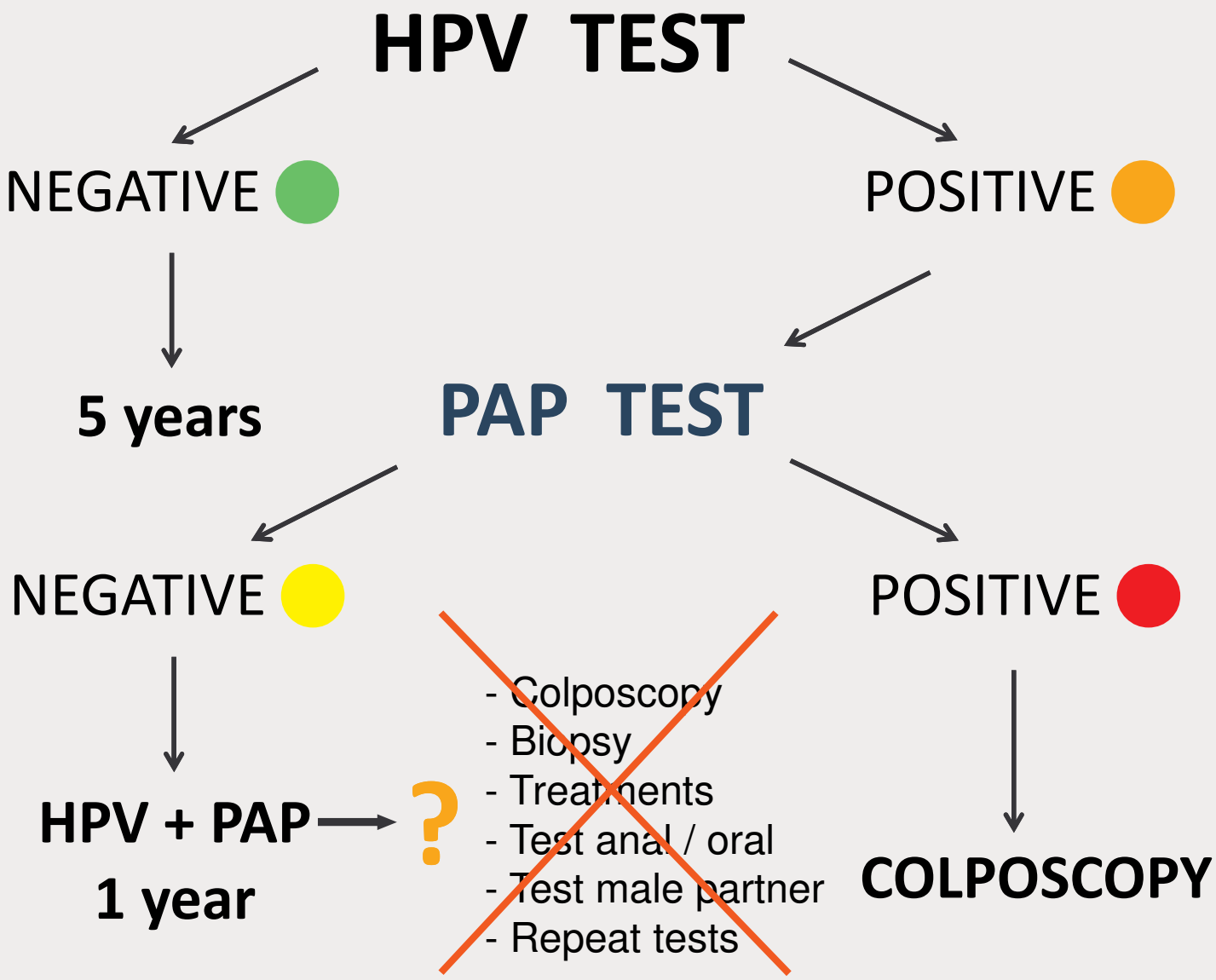




# Primary Cervical Screening - Cyto



# Primary Cervical Screening - HPV

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I.F.C.P.C.

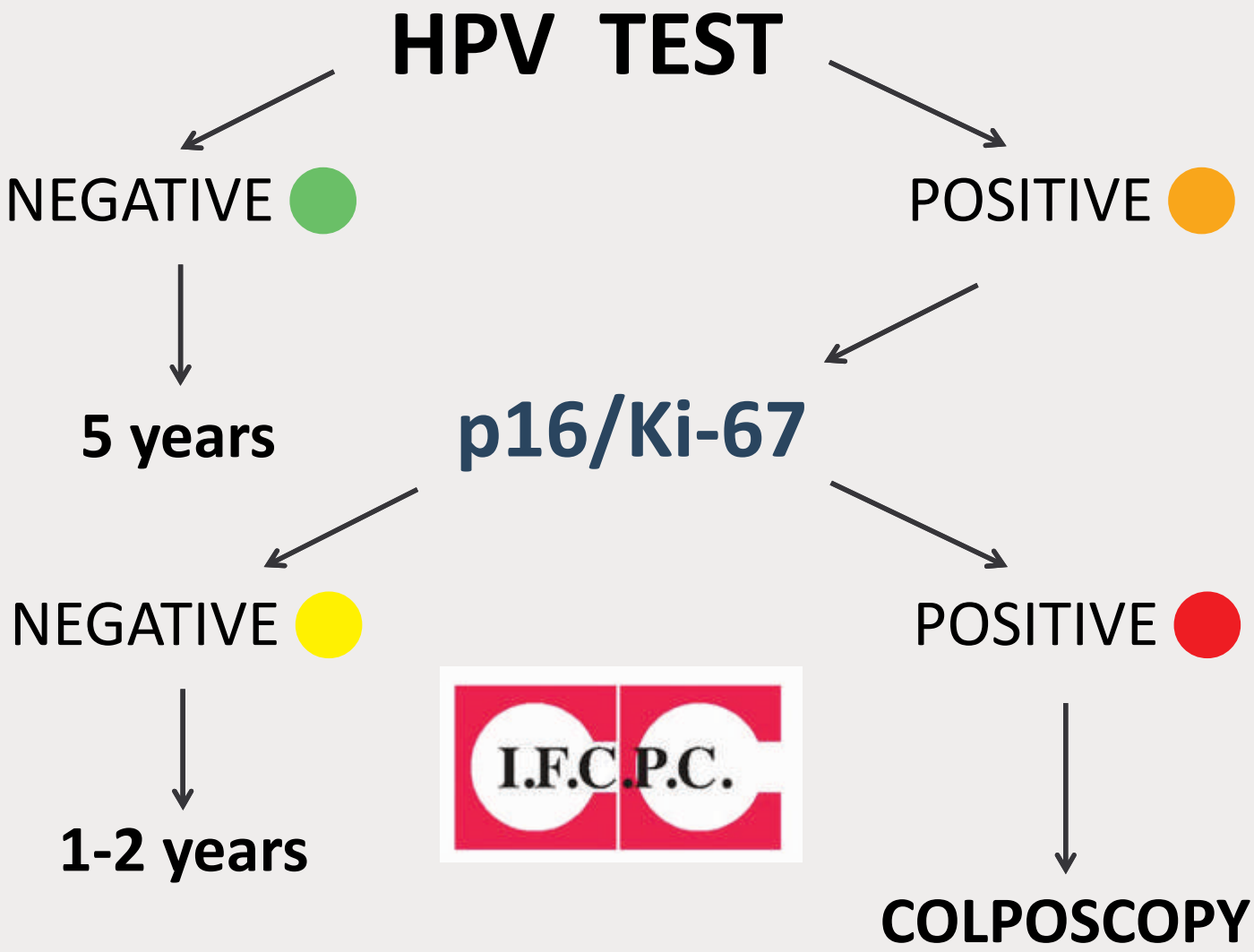
# NEGATIVE co-test

Risk of CIN 3 in 5 years = **8:10.000**

(reasonable risk)

*C. Redman* IFCPC 2017

# Primary Cervical Screening - Dual Staining



# HPV TEST

NEGATIVE

POSITIVE

**5 years**

HPV 16/18

NEGATIVE

POSITIVE

p16/Ki-67

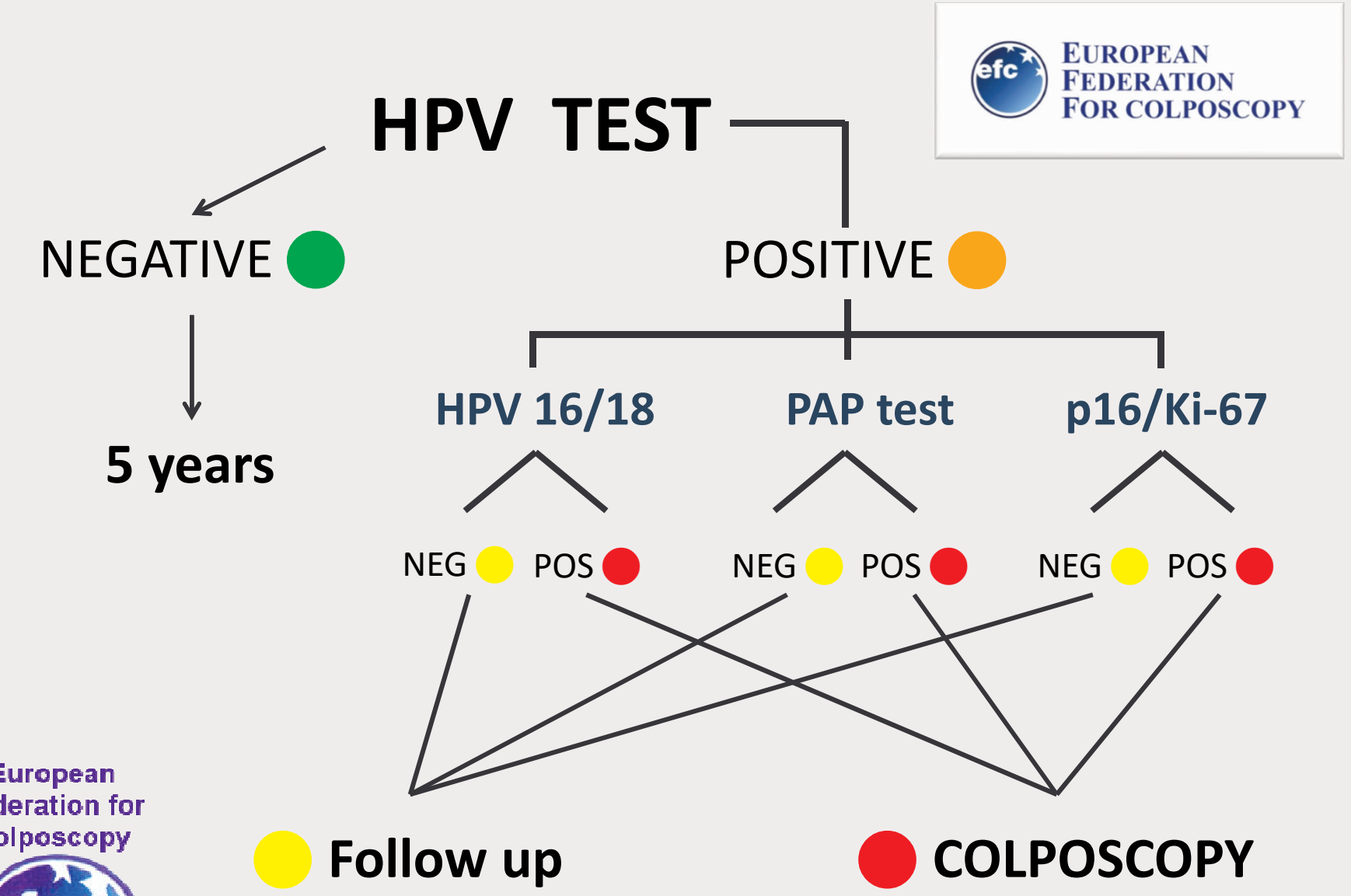
NEGATIVE

POSITIVE

**COLPOSCOPY**

**1-2 years**

N. Wentzensen – IFCPC 2017

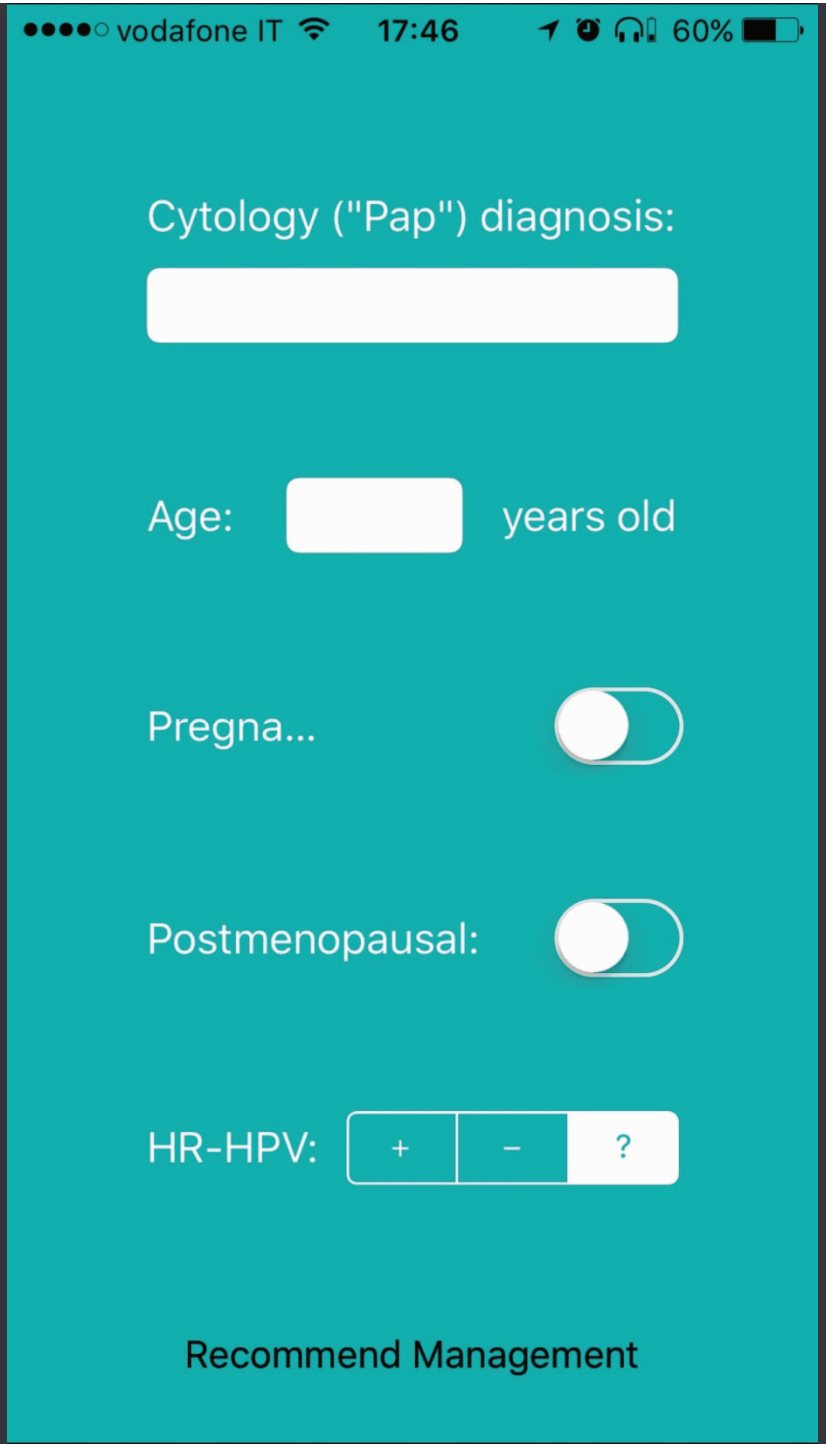


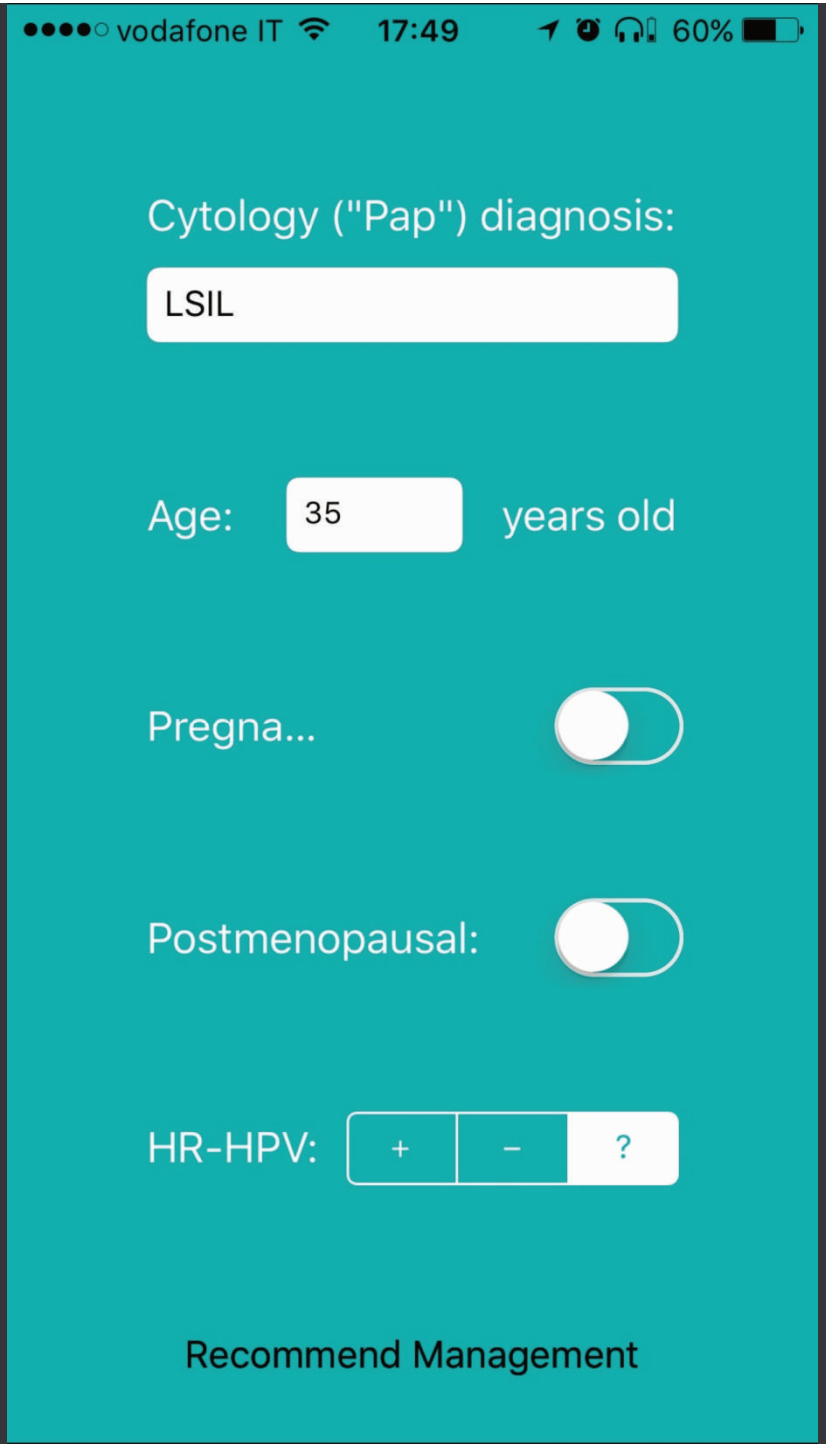

EUROPEAN FEDERATION FOR COLPOSCOPY

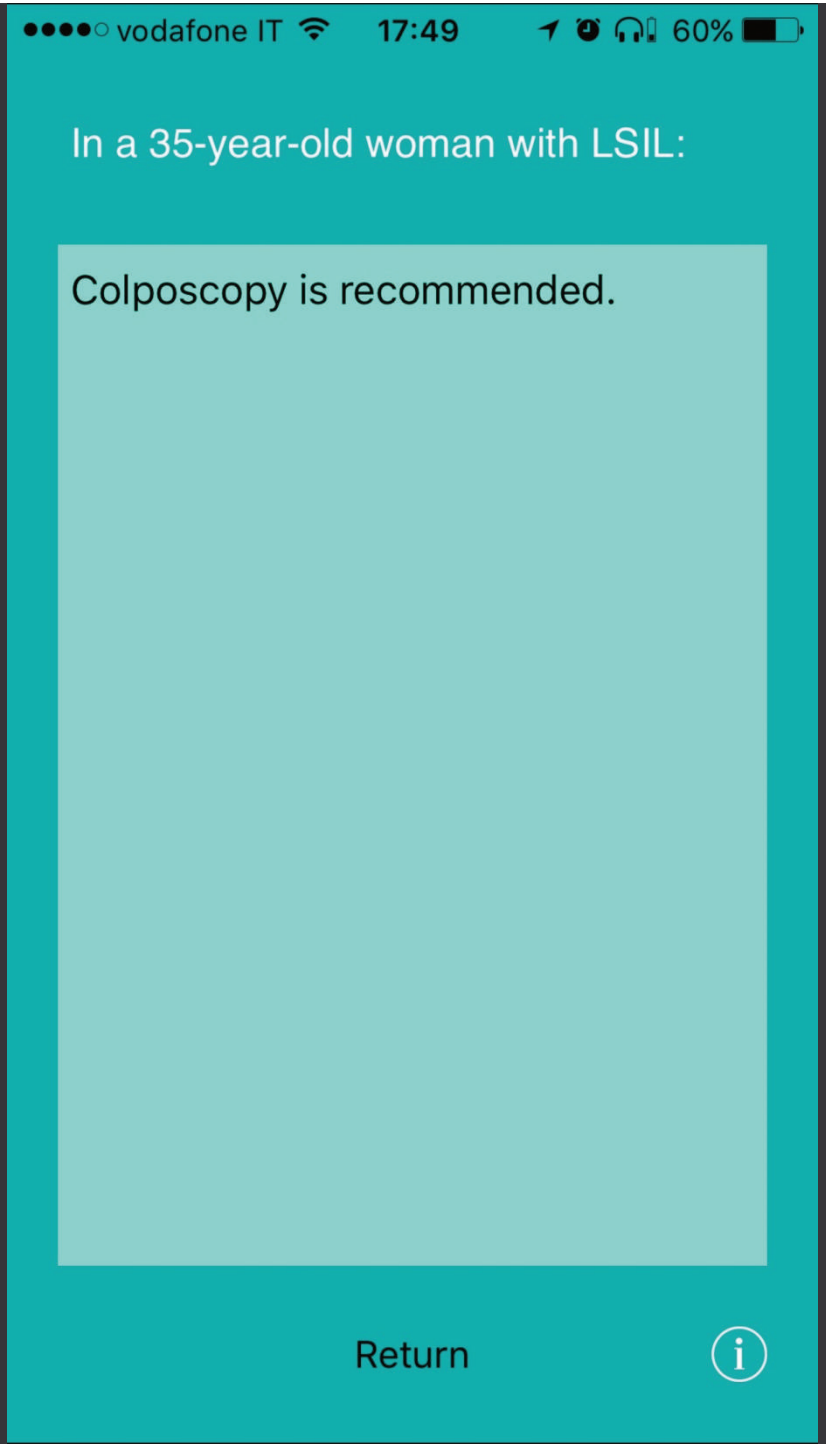
European Federation for Colposcopy

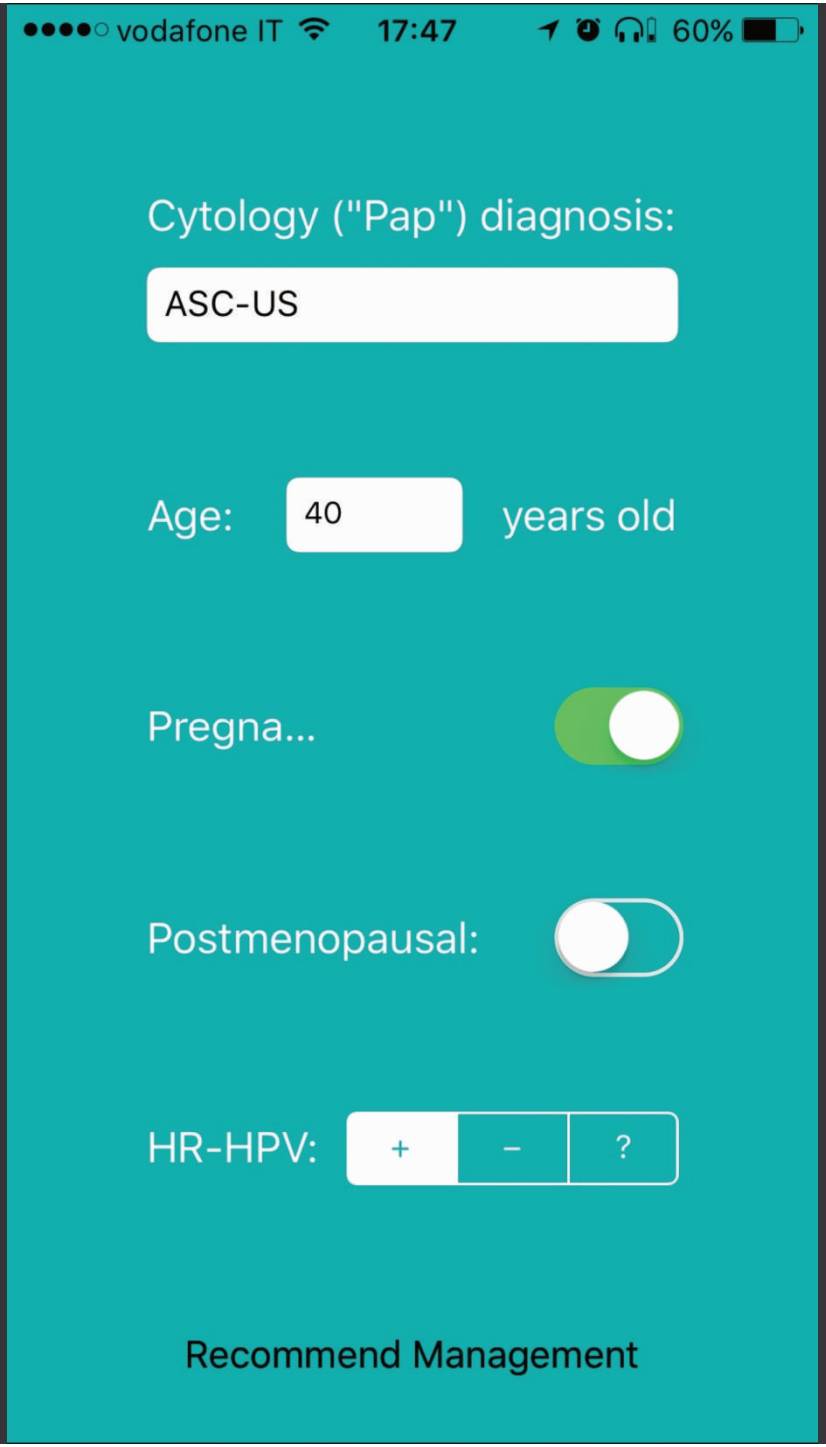
C. Bergeron – EFC 2017

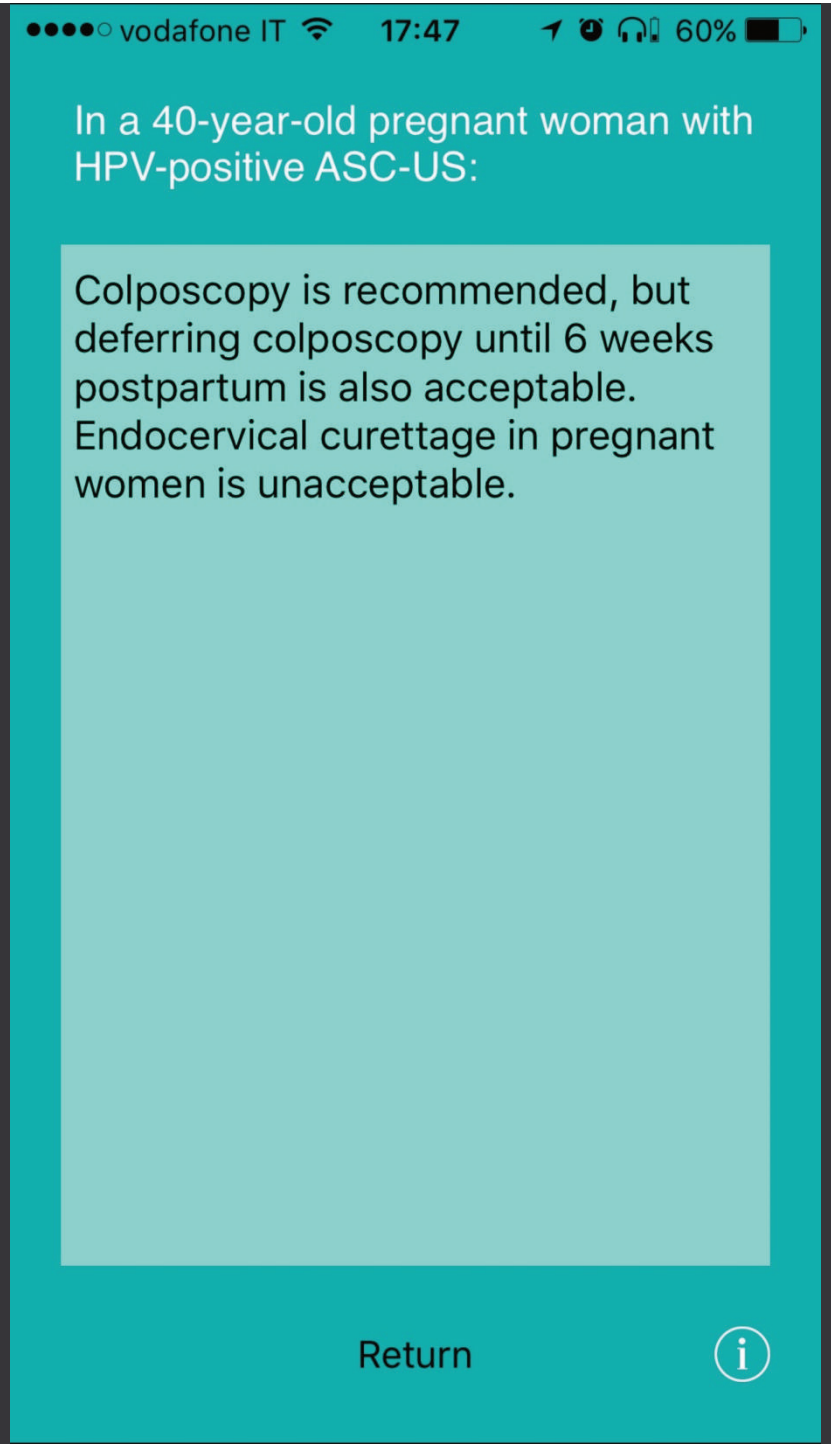
| App Name | Apple iTunes | Google Play | Price |
|---|---|---|---|
| ASCCP Mobile  | X | X | $9.99 |
| Pap App  | | X | $1.99 |
| Pap Reader  | X | | Free |


vodafone IT
17:46
60%
Cytology ("Pap") diagnosis:
Age:
years old
Pregna...
Postmenopausal:
HR-HPV:
+
–
?
Recommend Management


vodafone IT
17:49
60%
Cytology ("Pap") diagnosis:
LSIL
Age:
35
years old
Pregna...
Postmenopausal:
HR-HPV:
+
−
?
Recommend Management


vodafone IT
17:49
60%
In a 35-year-old woman with LSIL:
Colposcopy is recommended.
Return


vodafone IT
17:47
60%
Cytology ("Pap") diagnosis:
ASC-US
Age:
40
years old
Pregna...
Postmenopausal:
HR-HPV:
+
–
?
Recommend Management


vodafone IT
17:47
60%
In a 40-year-old pregnant woman with HPV-positive ASC-US:
Colposcopy is recommended, but deferring colposcopy until 6 weeks postpartum is also acceptable. Endocervical curettage in pregnant women is unacceptable.
Return


Carlo
Carlo Liverani
Milano, Italy
Guglielmo

# Screening

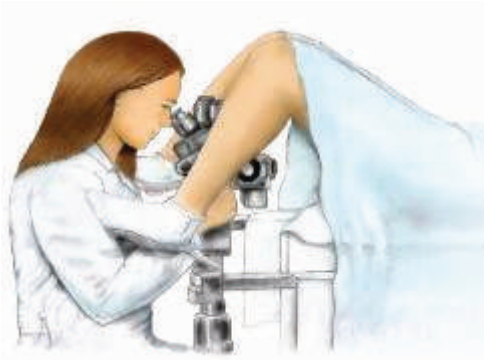
HPV TEST

HPV 16/18

p16/Ki-67

# Gynecologist

PAP TEST



- Counseling
- STD
- Vax
- Contraception
- Colposcopy:
- Treat / Follow

APPS

?

“Not everything that can be counted counts, and not everything that counts can be counted”

(*W.B. Cameron*)

# Grazie