



Educate the Educators Program

Spring 2009 Literature Review



HPV Detection Methods

FDA-approved high-risk tests:

- Hybrid Capture 2 is a solution hybridization method that detects 13 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68)
- Cervista HPV HR uses an isothermal enzymatic DNA amplification process to detect 14 high-risk HPV types (*includes 66 in addition to other 13 high-risk types*)



HPV Genotyping Methods

Detection of HPV 16 and 18:

- Cervista HPV 16/18 was approved by the FDA in March 2009.
- This test is designed to detect HPV 16 and 18
- Approved for *adjunctive use when screening women \geq 30 yrs with HR HPV and cytology*
- Approved to *identify specific high-risk types of HPV in women with ASC-US*

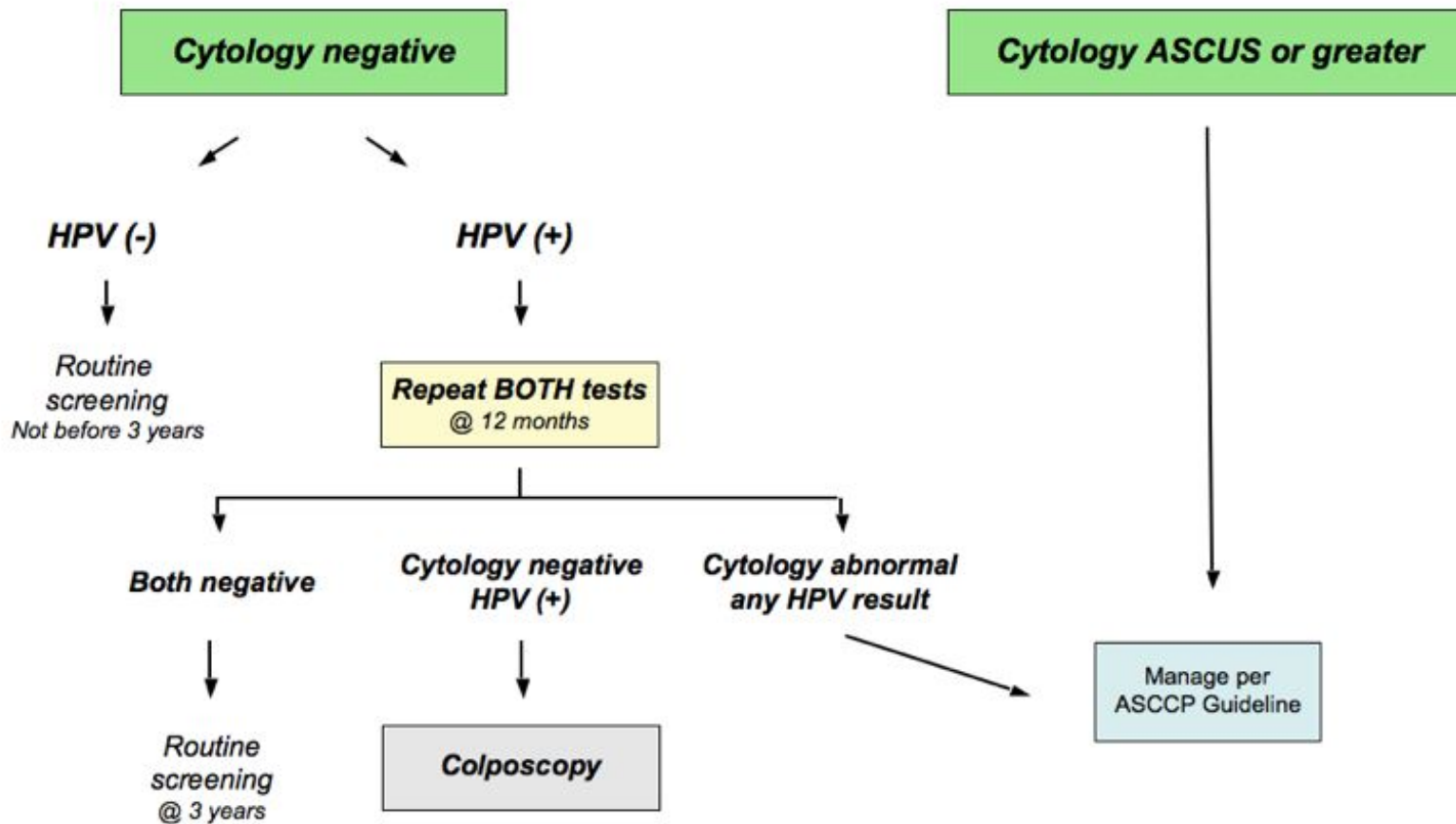


HPV (+) / Pap (-) Women

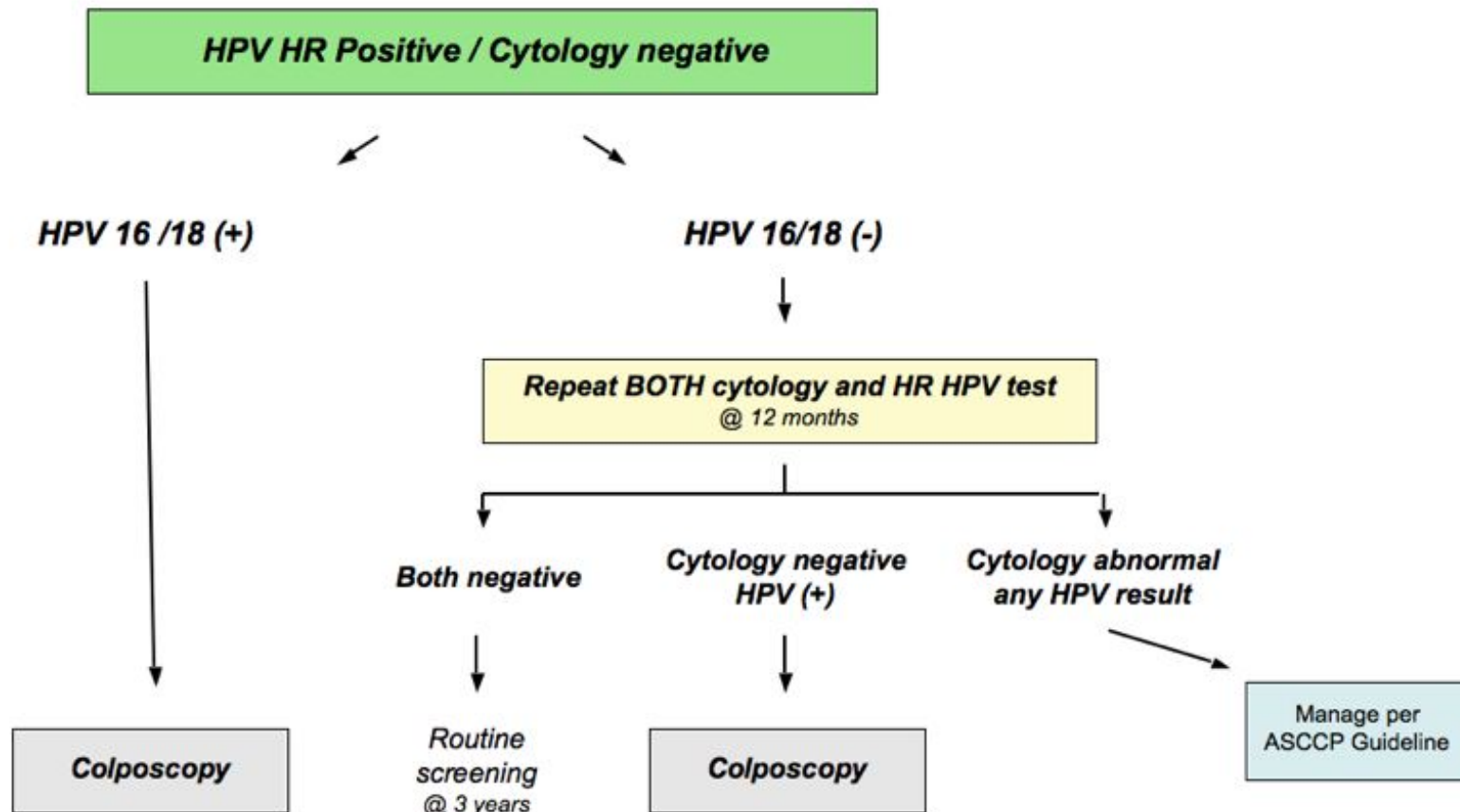
Management approaches:

- 2006 Consensus Guidelines identified two acceptable approaches for management
- Perform BOTH cytology and high-risk HPV testing at 12 months
- Use a HPV genotyping assay to determine which women have HPV 16 or 18

Use of HPV DNA Testing * as an Adjunct to Cytology for Cervical Cancer Screening in Women 30 Years and Older



Use of HPV Genotyping to Manage HPV HR * Positive / Cytology Negative Women 30 Years and Older





Women with ASC-US

What is the role of genotyping?

- Consensus Guidelines do not recommend HPV genotyping in women with ASC-US
- In ALTS the risk of CIN 2+ in HPV 16/18 positive ASC-US was approximately 40%
- However risk of CIN 2,3 in non-16/18 HPV high-risk positive ASC-US was about 20%
- ALL HPV (+) ASC-US require colposcopy

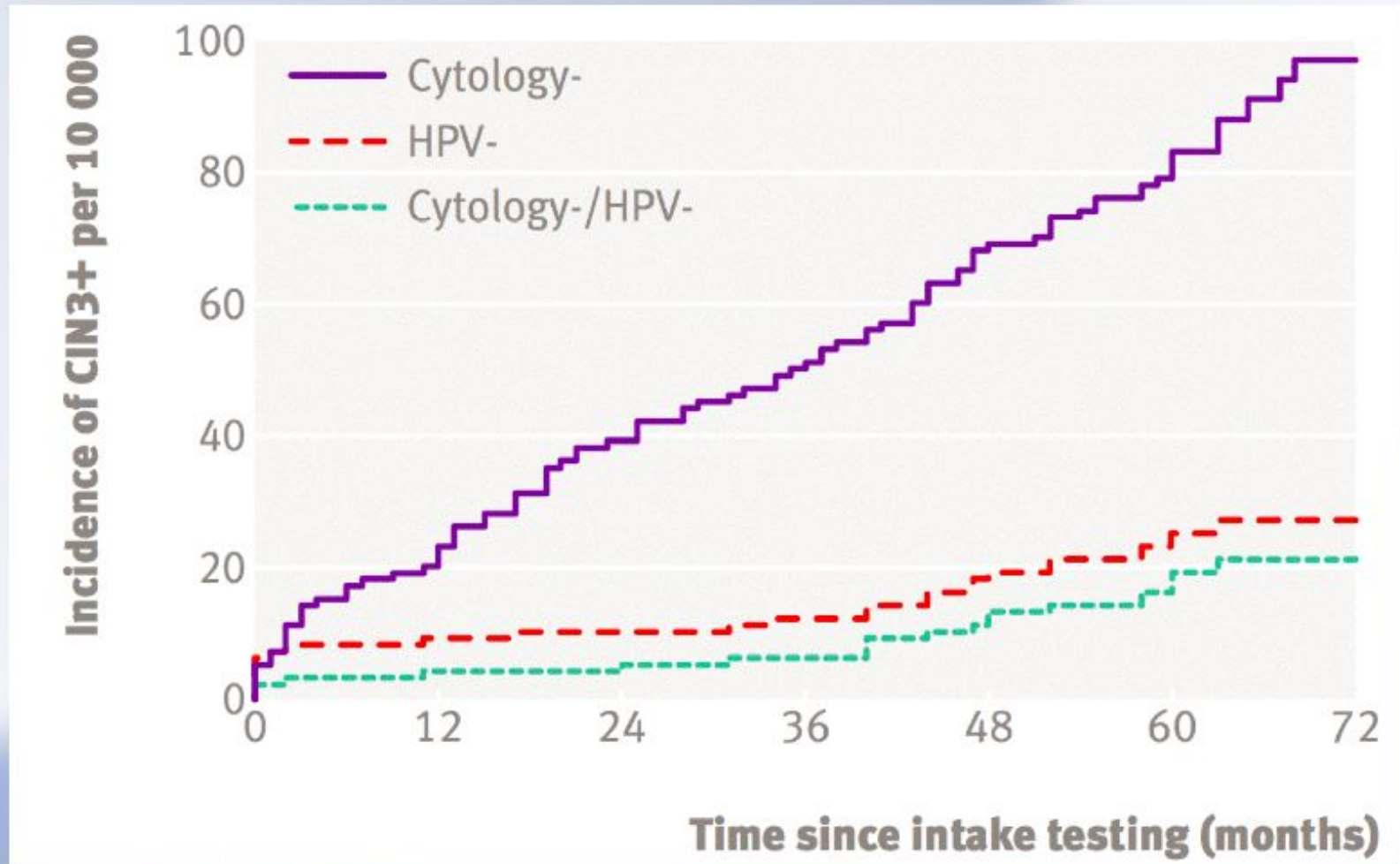


HPV Testing for Screening

Joint European cohort study

- Includes 24,295 women from 7 HPV screening trials in 6 European countries - age ranges varied between the trials
- Included only studies in which ≥ 1 Pap or histopathology exam during follow-up
- End-point; *cumulative incidence of CIN 3+*

Cumulative Incidence of CIN 3+





HPV Testing for Screening

Swedish randomized trial

12,527 women 32-38 yrs of age

Randomized to conventional cytology or cytology plus HPV (*PCR with GP5+/6+*)

HPV (+) / Pap (-) retested with BOTH at 12 mos - *colpo if persistently HPV (+)**

Follow-up by registry data for 4.1 yrs



Performance of HPV DNA Testing and Cytology in Swedescreen

	CIN 2		CIN 3+	
	Sens.	Spec.	Sens.	Spec.
<i>HPV testing</i>	95%	94%	96%	94%
<i>Cytology</i>	71%	99%	74%	98%



Performance of Different Strategies to Detect CIN 2+

Screening strategy	Sens.	PPV*	No. Tests per CIN2+
<i>Pap only</i>	71%	43%	101
<i>HPV only</i>	95%	19%	75
<i>HPV & Pap, all women</i>	100%	18%	143
<i>HPV with reflex Pap</i>	95%	38%	85

* PPV is positive predictive value (e.g. what proportion of test positive women have CIN 2+)



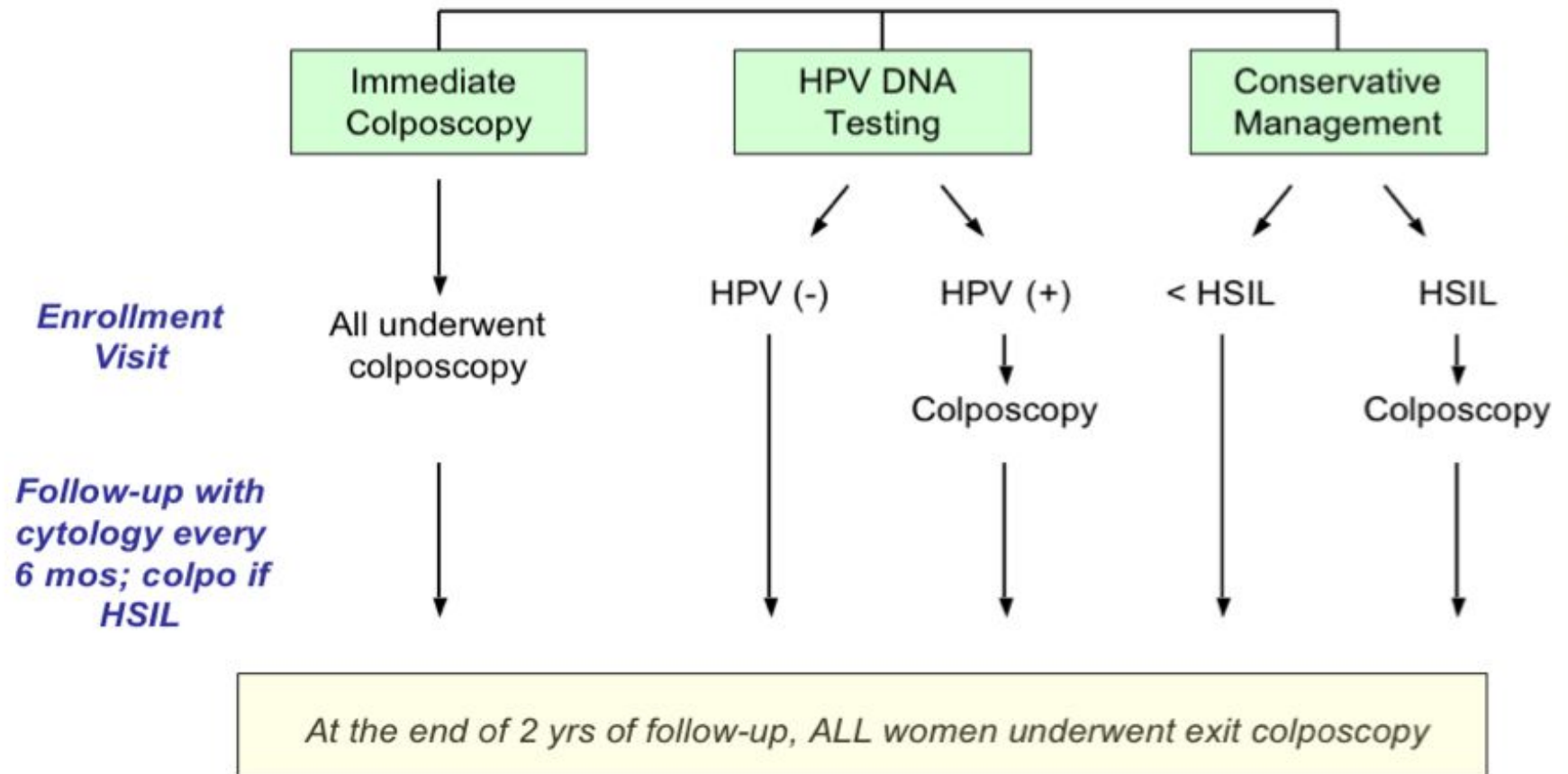
Natural History of CIN 2

Data from ALTS

- ALTS was a three armed clinical trial:
immediate colposcopy, HPV DNA testing, and cytological follow-up only
- Women without CIN 2+ at enrollment were followed for 2 yrs with Paps every 6 mos
- At the end of the trial ALL women underwent colposcopy and many had LEEPs

ASCUS ($n=3,488$) or LSIL ($n=1,572$)
referral cytology

Randomize to 3 Arms





Detection of CIN 2 and CIN 3+ in ALTS

<i>Arm</i>	<i>% Diagnosed with</i>	
	CIN 2	CIN3+
Immediate colposcopy		
<i>at enrollment</i>	8.2%	6.7%
<i>cumulative at end of study</i>	10.7%	10.2%
HPV DNA Testing		
<i>at enrollment</i>	5.6%	7.5%
<i>cumulative at end of study</i>	8.1%	10.1%
Conservative management		
<i>at enrollment</i>	1.8%	4.3%
<i>cumulative at end of study</i>	6.0%	10.6%



Natural history of CIN lesions

Lesion Grade	% of lesions that		
	Regress	Persist	Progress*
CIN 1	57%	32%	11%
CIN 2	43%	35%	22%
CIN 3	32%	56%	12%

* progression to carcinoma in situ

Mitchell et al. *JNCI Monogr* 1996;21:17-25



HPV in Non-cervical lesions

Data from meta-analysis:

- Meta-analysis of associations of HPV and vulvar, vaginal, and anal lesions
- To be included had to:
 - Utilize clearly described PCR assay***
 - Include minimum of 4 cases of cancer or intraepithelial neoplasia***
- 64 studies of vulvar; 14 of vaginal; 29 of anal



HPV in Non-cervical Lesions

	ANY HPV	HPV 16
Vulva		
<i>VIN - all grades</i>	84%	
<i>VIN 1</i>	68%	10%
<i>VIN 2,3</i>	85%	72%
<i>Vulvar cancer</i>	40%	32%
Vagina		
<i>VAIN - all grades</i>	94%	
<i>VAIN 1</i>	100%	23%
<i>VAIN 2,3</i>	90%	58%
<i>Vaginal cancer</i>	70%	54%



HPV in Non-cervical Lesions

	ANY HPV	HPV 16
Anus		
<i>AIN - all grades</i>	93%	
<i>AIN 1</i>	92%	37%
<i>AIN 2,3</i>	94%	60%
<i>Anal cancer</i>	84%	73%