Cervical cancer prevention:
Advances in primary screening and triage system

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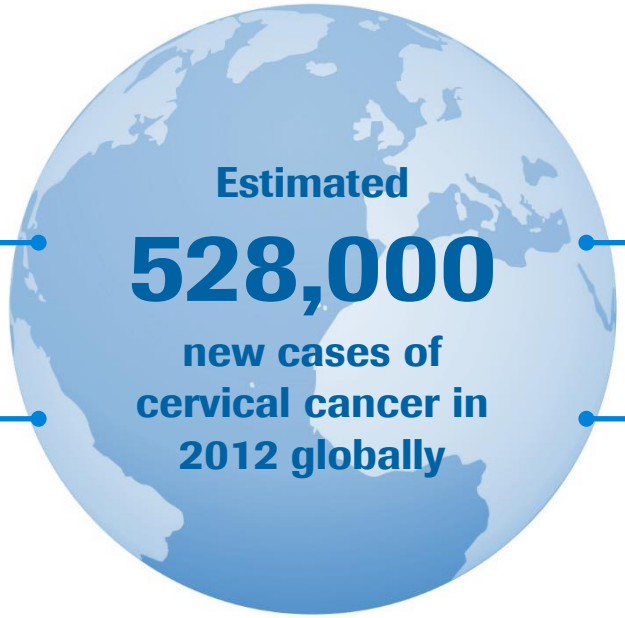
Cervical cancer is highly preventable through vaccination and organised screening program

7.5%
of all female cancer deaths

85%
of cervical cancer occurred in less developed region

i.e. Southeast Asia



Estimated
266,000 deaths
from cervical cancer worldwide in 2012

Where organised screening programmes are utilised, cervical cancer is estimated to comprise only **5%** of cancers in women

J. Ferlay, *et al*. 2012.

Cervical cancer is caused by infection with certain types of human papillomaviruses (HPV)

2 MAIN TYPES OF CERVICAL CANCER

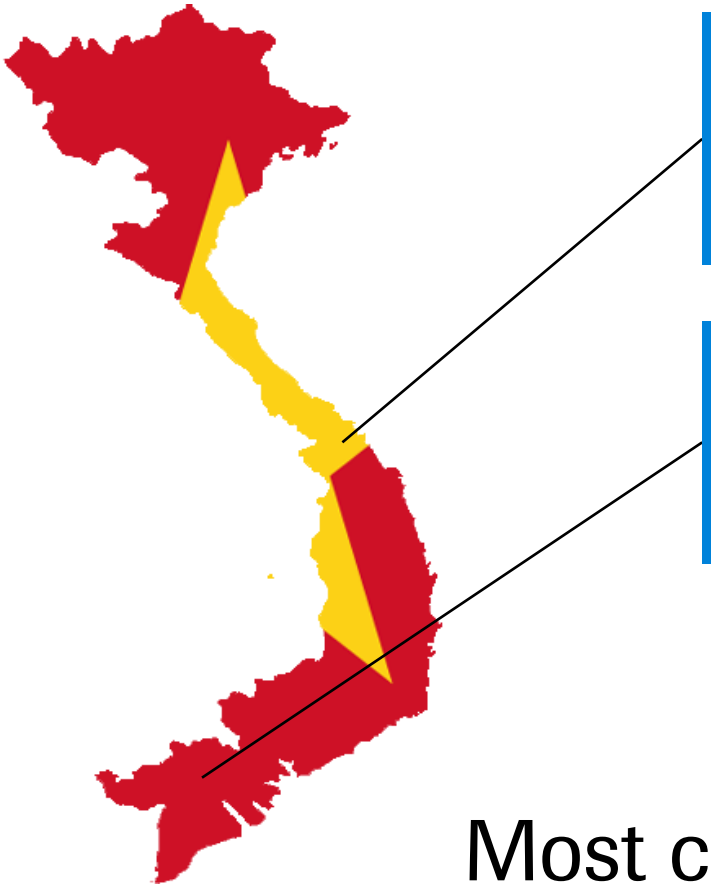
- squamous cell carcinoma
- adenocarcinoma

HPV16 and HPV18 are the most prevalent oncogenic HPV genotypes

- HPV infection is present in almost all cases of cervical cancer and its immediate precursor lesion, cervical intraepithelial neoplasia (CIN) grade 3 (CIN3)
- Persistent infection with one of 14 genotypes of high-risk HPV (hrHPV) causes greater than 99% of all cases of cervical cancer

1. Herzog *et al*. 2007 **2**. Saslow D *et al*. 2012 **3**. Schiffman *et al*. 2007

HPV infected 1 in 10 Vietnamese women



9.5% women infected with high risk HPV[1]

200 women from the Hai Chau district and 200 from the Son Tra district, Da Nang

9.7% women infected with **any** HPV[1]

1,550 women in Ho Chi Minh – cross-sectional study

Most common genotypes: 16 & 18[1,2]

1. Van SN et al. Anticancer Res. 2017 Mar;37(3):1243-1247.
2. Ly Thi-Hai Tran et al. Tran et al. BMC Women's Health (2015) 15:16

Population			
Women at risk for cervical cancer (Female population aged >=15 years)			37.7 million
Burden of cervical cancer and other HPV-related cancers			
Annual number of cervical cancer cases			5,146
Annual number of cervical cancer deaths			2,423
Crude incidence rates per 100,000 and year:		Male	Female
	Cervical cancer	-	11.3
	Anal cancer ‡	0.1-0.4	0.1-0.4
	Vulvar cancer ‡	-	0.4-0.9
	Vaginal cancer ‡	-	0.1-0.2
	Penile cancer ‡	0.9-1.7	-
	Pharynx cancer (excluding nasopharynx)	2.6	0.5
Burden of cervical HPV infection			
Prevalence (%) of HPV 16 and/or HPV 18 among women with:			
	Normal cytology		2.1
	Low-grade cervical lesions (LSIL/CIN-1)		27.4†
	High-grade cervical lesions (HSIL/CIN-2/CIN-3/CIS)		37.4
	Cervical cancer		82.8
Other factors contributing to cervical cancer			
Smoking prevalence (%), women			1.3
Total fertility rate (live births per women)			2.0
Oral contraceptive use (%) among women			12.3
HIV prevalence (%), adults (15-49 years)			0.5 [0.4 - 0.5]
Sexual behaviour			
Percentage of 15-year-old who have had sexual intercourse (men/women)			0 / 0
Range of median age at first sexual intercourse (men/women)			23.1-24.2 / 21.0-21.5
Cervical screening practices and recommendations			
Cervical cancer screening coverage, % (age and screening interval, reference)	6.5% (All women aged 25-64 screened every 3y, WHS 2003 Viet Nam)		
Screening ages (years)			-
Screening interval (years) or frequency of screens			-
HPV vaccine			
HPV vaccine introduction			
	HPV vaccination programme		Pilot program
	Date of HPV vaccination routine immunization programme start		-
	HPV vaccination target age for routine immunization		-
	Full course HPV vaccination coverage for routine immunization: % (calendar year)		-

‡Please see the specific sections for more information.
† The data is the subregion South-Eastern Asia

special article

Primary Prevention of Cervical Cancer: American Society of Clinical Oncology Resource-Stratified Guideline

In limited resource settings:

For which cohorts is routine vaccination recommended in limited resource settings?

- **Recommendation B1a**

  Public health authorities, ministries of health, and primary care providers should vaccinate girls as early as possible, starting at 9 through 14 years of age (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).

Should catch-up for those outside the priority age groups for vaccination be offered for prevention of HPV infection in maximal and enhanced resource settings?

- **Recommendation A3**

  For females who have received one dose and are age > 14 years, public health authorities may provide additional doses or complete the series up to 26 years of age (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

special article

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

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

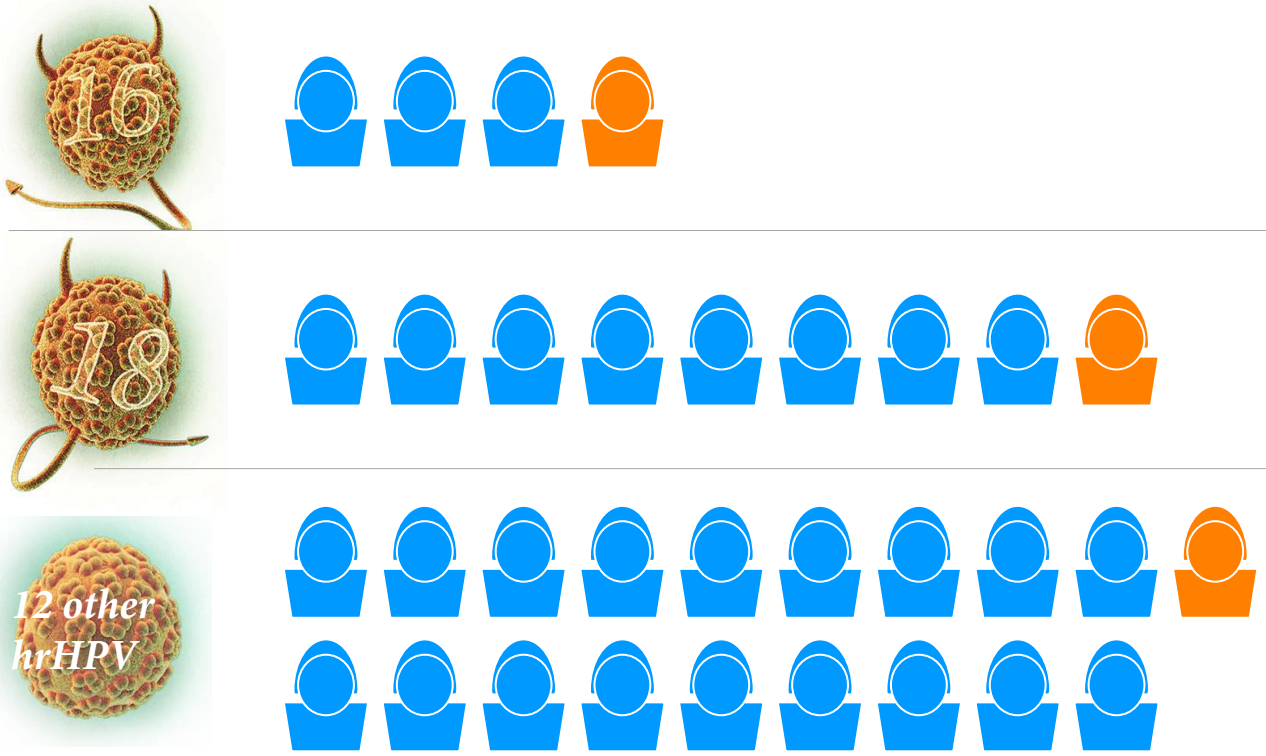
Exiting Screening

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

Jeronimo J et al. J Oncol Pract. 2016 Nov 15

Genotyping identifies women at highest risk

Risk of developing CIN3+ within 3 years



1 in 4

1 in 9

1 in 19

Source: Wright et al., *Gynecologic Oncology*, 2015

American Society of Clinical Oncology

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.

Jeronimo J et al. J Oncol Pract. 2016 Nov 15

Cervical Cancer Professional Guidelines

Implementation of HPV test

HKCOG – Guidelines for Cervical Cancer Prevention and Screening 2016

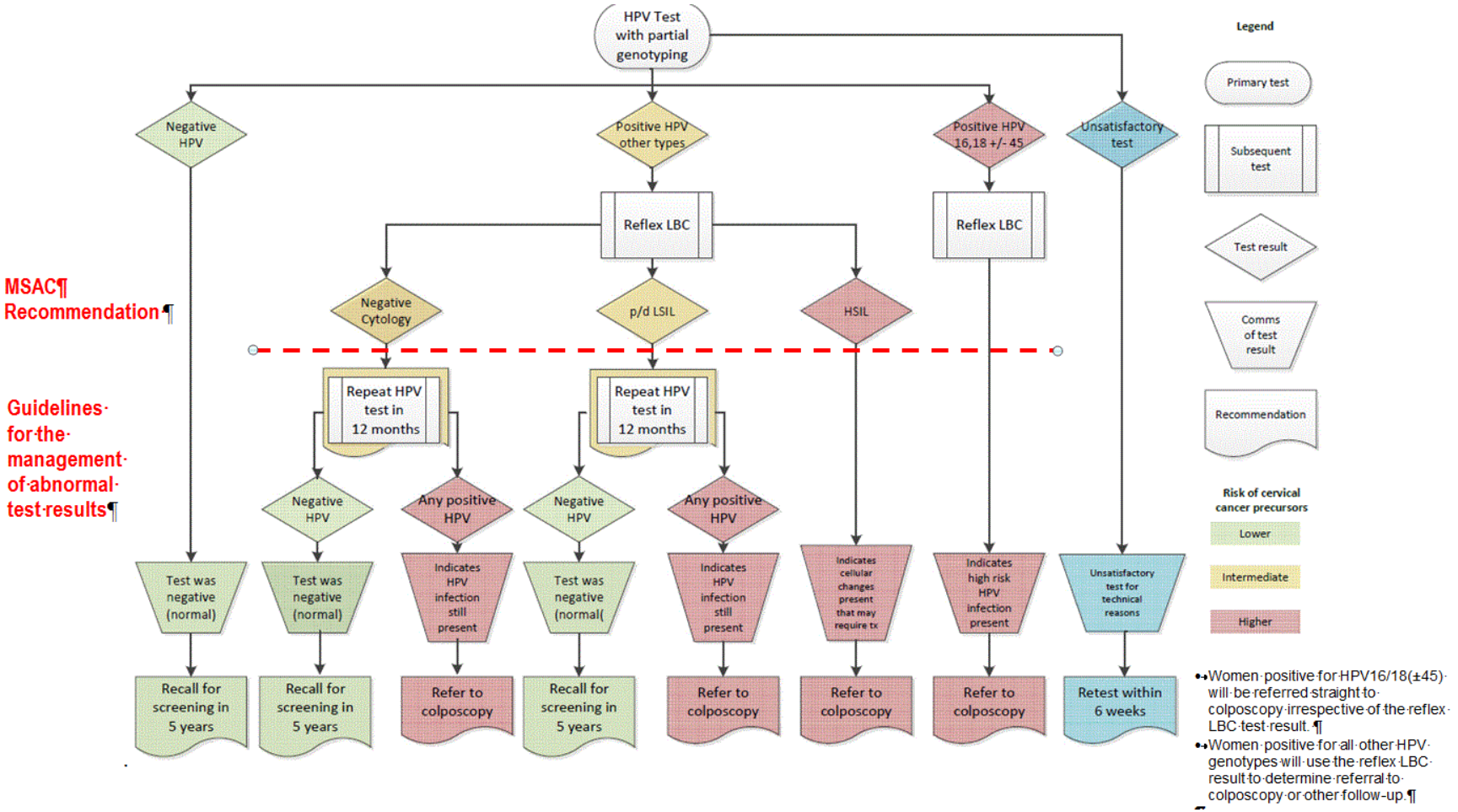
- Cervical cancer screening is still relevant to vaccines as current vaccines cannot offer full protection.
- The target population encompasses all women from age 25 or the time of commencing sexual activity (whichever is later) until the age of 64.
- HPV testing should only target at high-risk oncogenic HPV types.
- **A 5-year screening interval** is recommended after a negative co-test. Either repeat co-testing in 12 months or immediate HPV genotyping for HPV 16 alone or HPV 16/18 is acceptable.

SCCPS – Scientific Committee Position Paper on Primary HPV Screening for Cervical Cancer Prevention

- Primary HPV screening should employ the use of a polymerase chain reaction (PCR) based assay to detect HPV DNA.
- While the SCCPS Scientific Committee cannot endorse one particular test over another, it is noteworthy that at the time of publication of this paper, **only the cobas® HPV test from Roche Molecular Diagnostics, is FDA approved for primary HPV screening.**
- The use of **primary HPV testing** as a screening tool for CIN3+ has been shown to be **more cost effective than co-testing (HPV + cytology).**

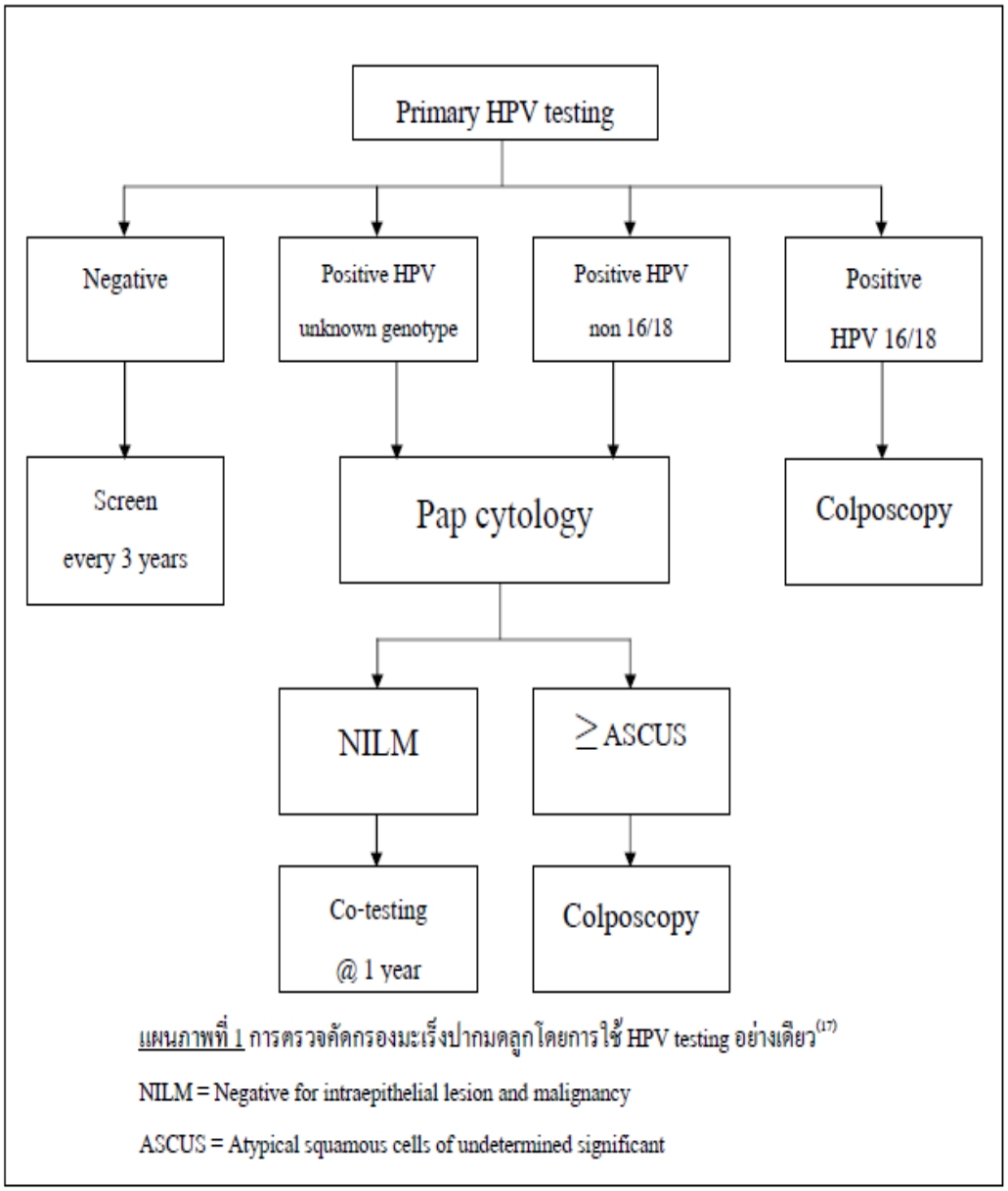
Australian National Primary Screening Program

Commencing on 1 Dec 2017



Initial screen at age 25, 5 year intervals, exit screen between 70 and 74

Thailand HPV Primary Screening Guidelines



แผนภาพที่ 1 การตรวจคัดกรองมะเร็งปากมดลูกโดยการใช้ HPV testing อย่างเดียว[17]

NILM = Negative for intraepithelial lesion and malignancy

ASCUS = Atypical squamous cells of undetermined significant

Vietnam has a similar national guideline – recommended in Tier 3 hospitals

Cervical Cancer Professional Guidelines

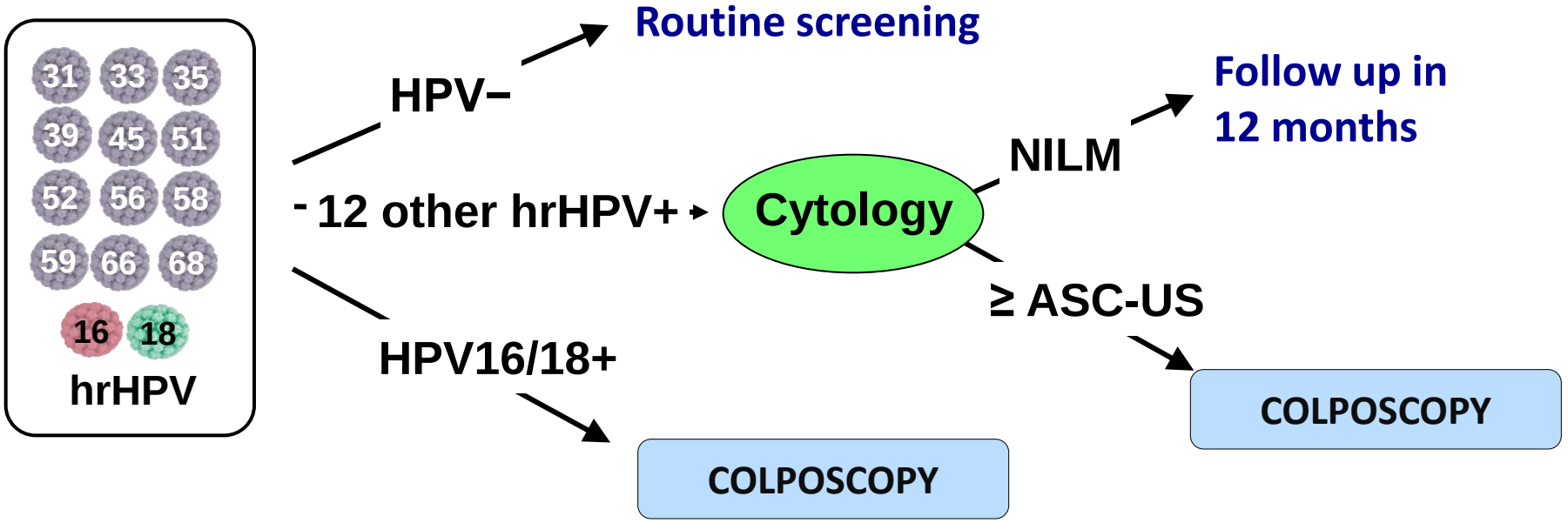
Implementation of HPV test

Primary screening with HPV DNA test has been recommended in the following guidelines:




World Health Organization

US HPV Primary Screening Guidelines – 2015



For women aged 25+

hrHPV, high risk HPV

Cervical cancer screening has contributed significantly to a decline in cervical cancer incidence and death

Pap cytology and HPV tests are the main tests used for routine cervical cancer screening

Pap cytology	HPV testing
IDENTIFIES CELLULAR CHANGES associated with cervical disease and infection	**IDENTIFIES** the presence of the viral **CAUSE OF DISEASE**

PATIENT MANAGEMENT GOAL

To prevent the development of cervical cancer or detect it at early treatable stages

1. Naucler *et al*. 2009 **2.** Chemlow *et al*. 2012 **3.** International Agency for Research on Cancer, 2005

Comparison of different strategies

TABLE 2
Clinical outcomes of different strategies for detection of CIN2 or more severe

Strategy number and name		Tests performed, n	Colposcopies performed, n	Colposcopies to detect 1 CIN2 or more severe, n	CIN2 or more severe cases identified, n	Cases identified for 12 month follow-up (estimated), n	Sensitivity, %	Sensitivity relative to ASC-US triage	False-positive rate, %	Specificity relative to ASC-US triage
1	Cytology with reflex HPV (ASC-US triage)	35,546	816	5.7	144	0	51.4	1.00	12.0	1.00
2	Cytology alone	34,254	1644	11.0	149	0	53.2	1.03	26.6	0.83
3	Cotesting with reflex for ASC-US	68,508	816	5.7	144	109	51.4	1.00	12.0	1.00
4	Cotesting with genotyping and cytology triage: HPV 16/HPV 18 and ASC-US HPV-positive threshold	68,508	1202	6.4	189	64	67.5	1.31	18.0	0.93
5	Cotesting with genotyping and cytology triage: HPV 16/HPV 18 and LSIL threshold	68,508	1030	6.0	173	80	61.8	1.20	15.2	0.96
6	HPV alone	34,254	2341	9.7	242	0	86.4	1.68	37.3	0.71
7	HPV with reflex to cytology	37,126	596	4.5	133	109	47.5	0.92	8.2	1.04
8	HPV with genotyping	34,254	580	4.8	122	120	43.6	0.85	8.1	1.04
9	HPV with genotyping and reflex cytology: ASC-US threshold	36,423	982	5.5	178	64	63.6	1.24	14.3	0.97
10	HPV with genotyping and reflex cytology: LSIL threshold	36,423	810	5.0	162	80	57.9	1.13	11.5	1.00

ASC-US, atypical squamous cells of undetermined significance; *CIN*, cervical intraepithelial neoplasia; *HPV*, human papillomavirus; *LSIL*, low-grade squamous intraepithelial lesion.

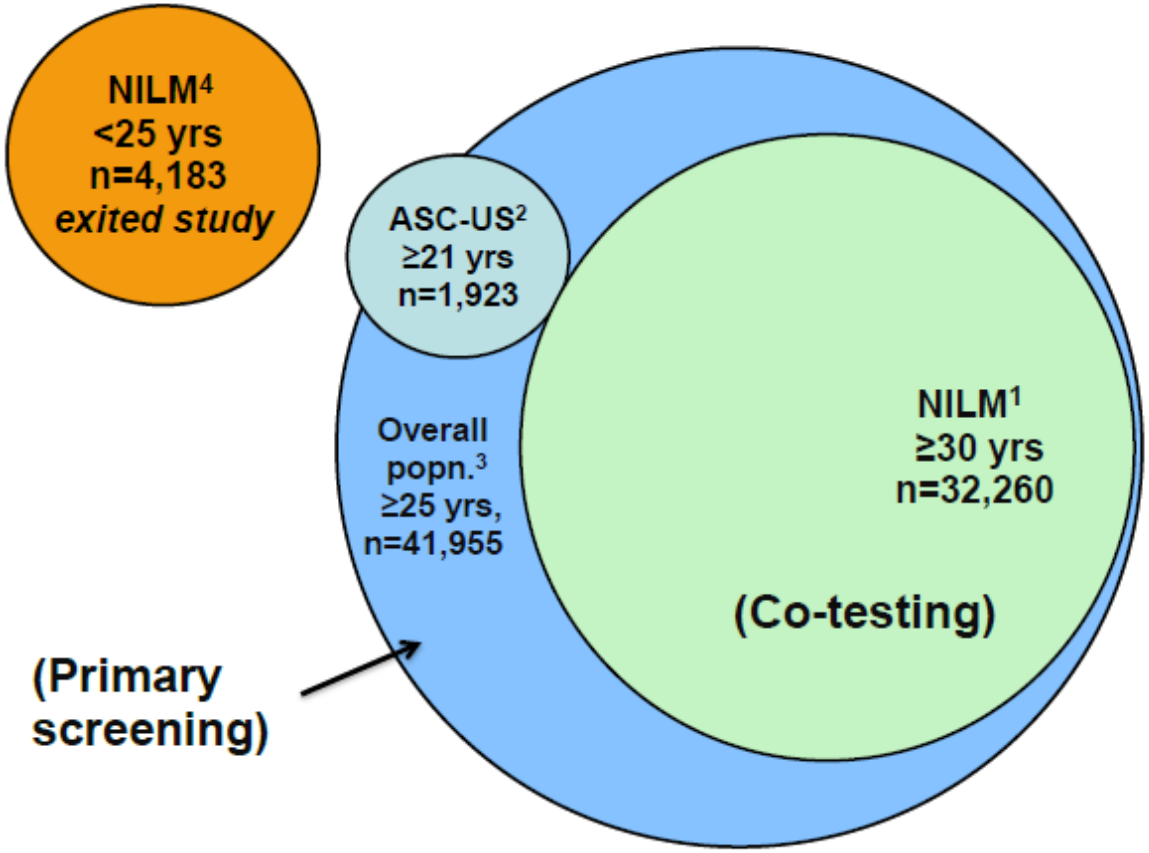
Cox. Cervical cancer screening strategies: evaluation of results from the ATHENA HPV study. Am J Obstet Gynecol 2013.

Cox JT et al. Am J Obstet Gynecol. 2013 Mar;208(3):184.e1-184.e11

ATHENA – Use of HPV Test for Primary Screening

3 different populations

47,208 women enrolled



Liquid-based cytology
+
HPV test

ASC-US Triage

Co-testing

Primary screening

1. Stoler MH, et al. Am J Clin Pathol 2011; 135: 468–475; 2. Wright TC, Jr, et al. Am J Obstet Gynecol, 2011; 136: 578–586; 3. Castle PE, et al. Lancet Oncol 2011; 12:880–890; 4. Roche Molecular Systems. Data on file. 2011.

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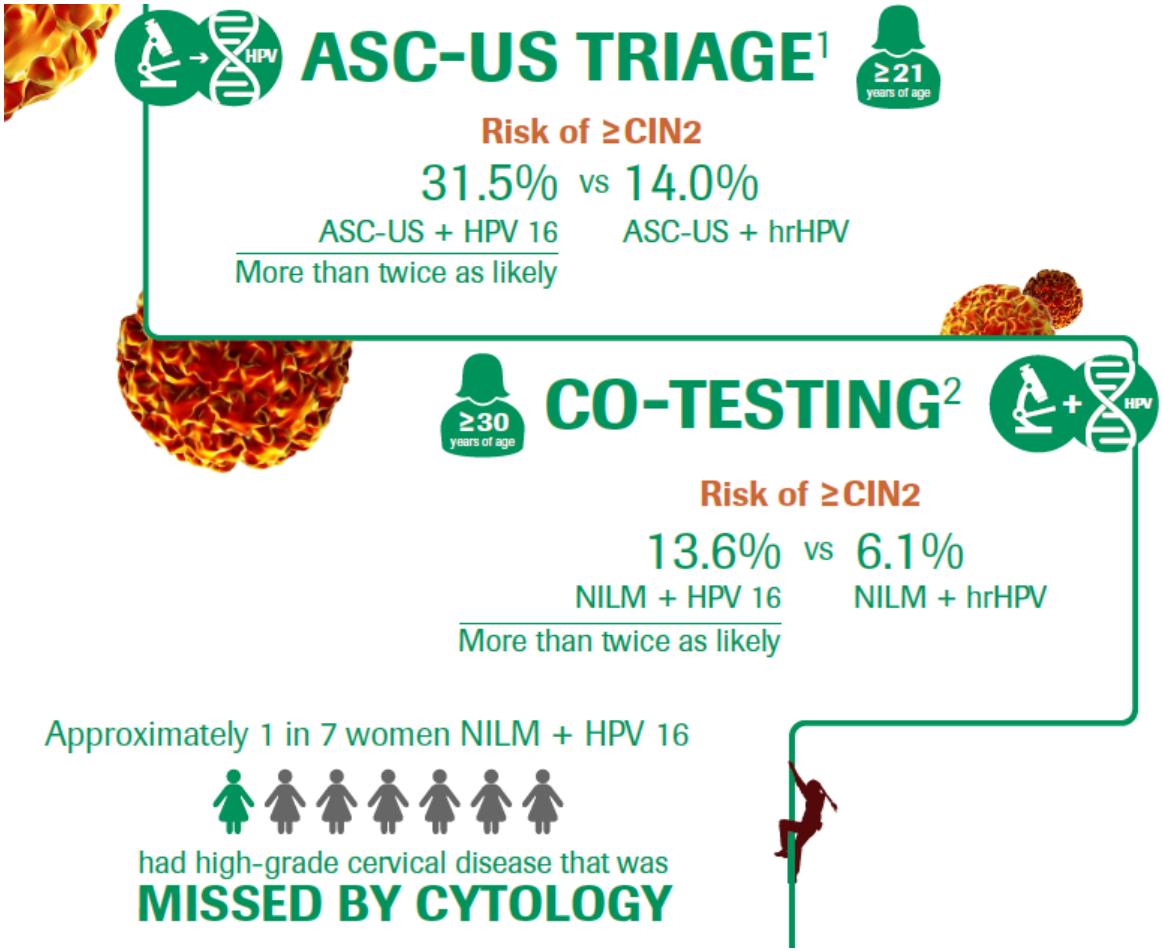

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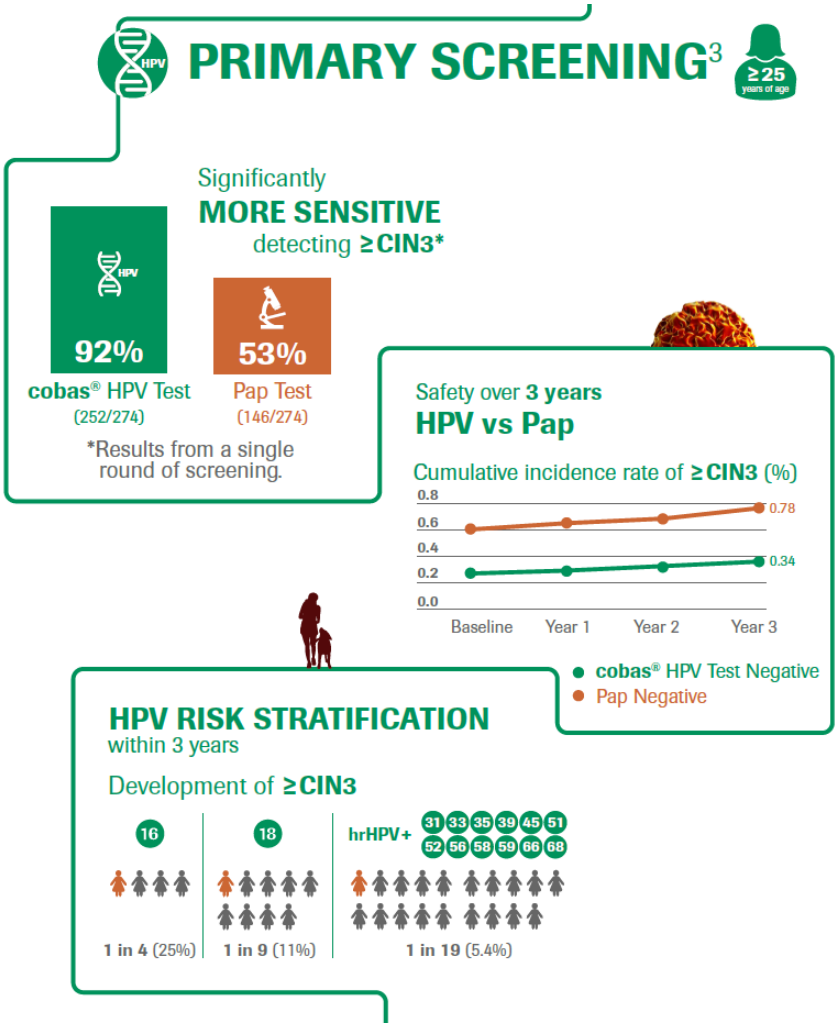

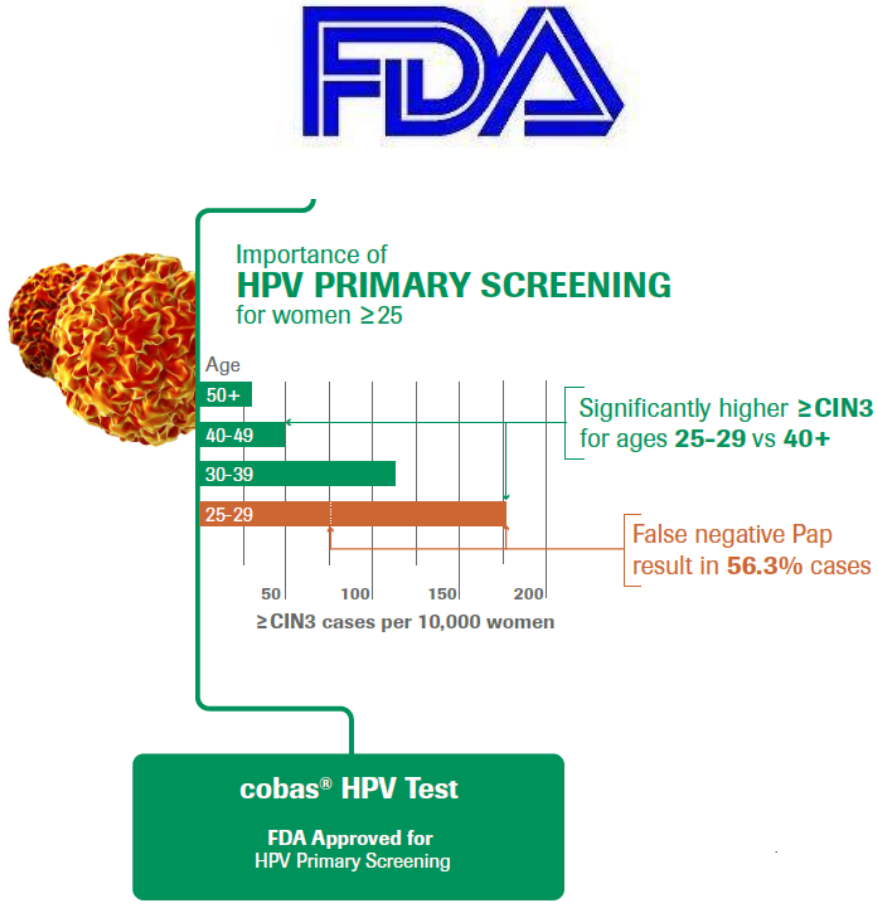

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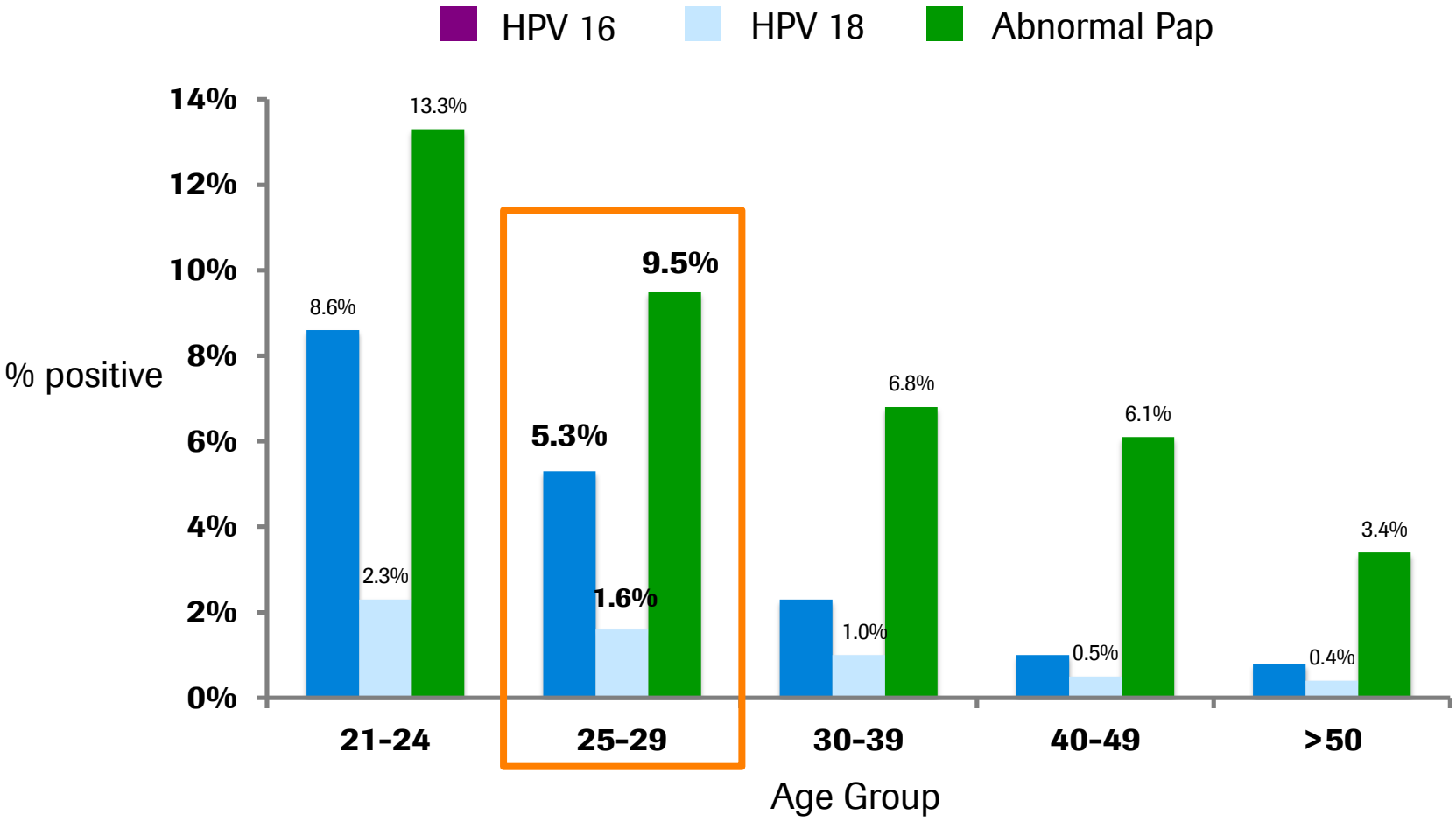
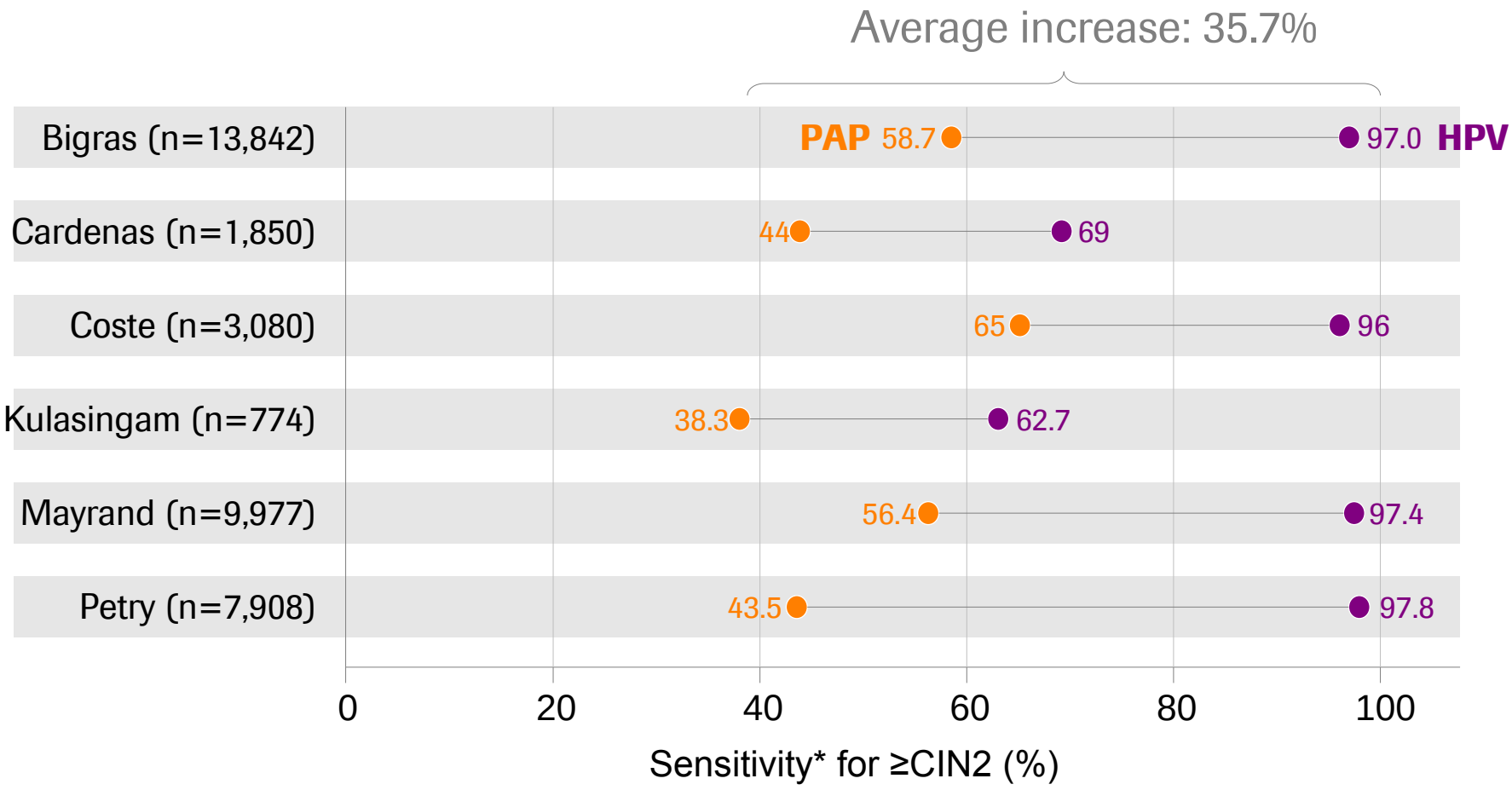
HPV 16/18 Genotyping Triages Fewer Women to Colposcopy than ≥ASCUS Cytology



Wright T. et al. *Am J Obst Gynecol*. 2011;205:1e1-1e11

HPV screening superior to Pap cytology across multiple studies



Source: Whitlock et al., *Ann Intern Med.,* 2011

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Treatment of Women With Precursor Lesions

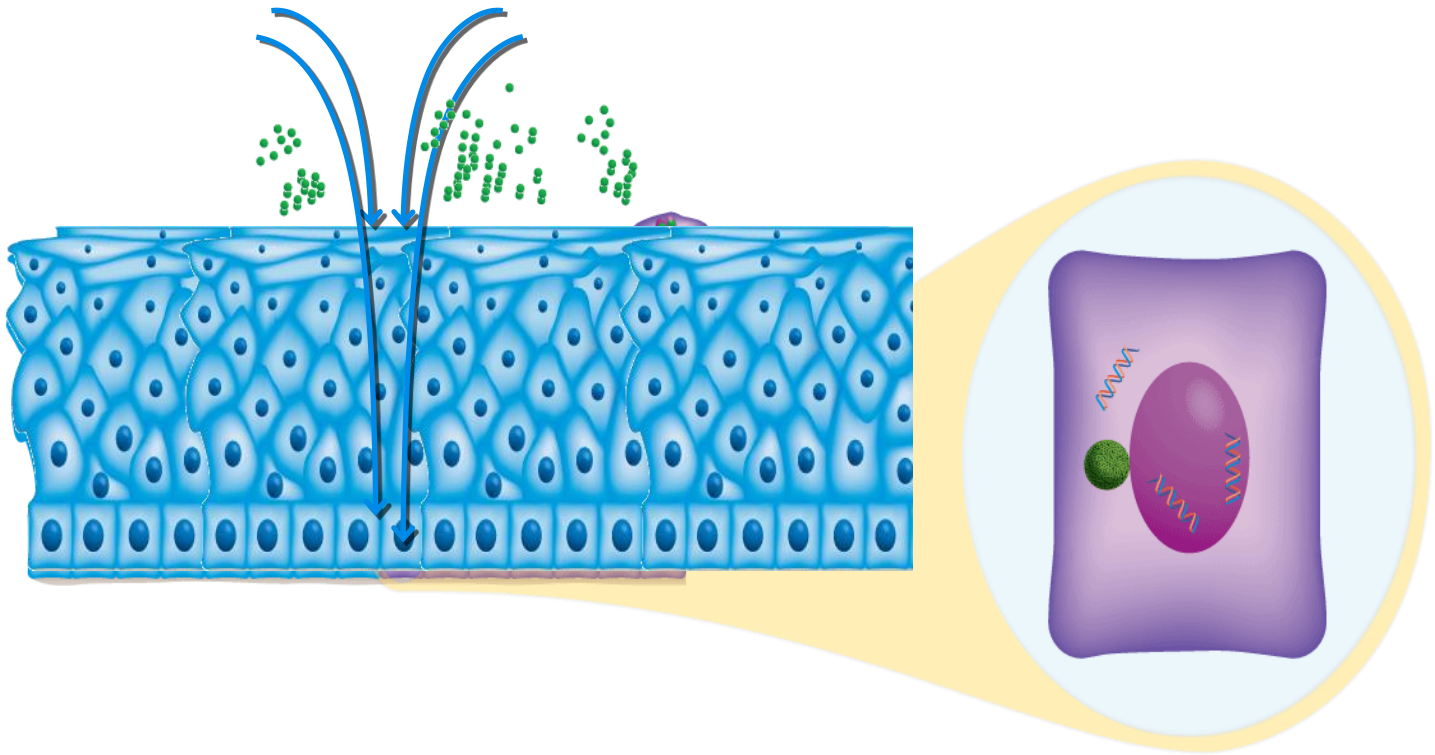
- In basic settings, treatment options are cryotherapy or loop electrosurgical excision procedure (LEEP).
- In other settings, LEEP (if high level of quality assurance) or ablation (if medical contraindication to LEEP) is recommended.
- Twelve-month post-treatment follow-up is recommended for all settings.

Special Populations

- Women who are HIV positive or immunosuppressed for other reasons should be screened with HPV as soon as diagnosed and screened twice as many times in a lifetime as the general population.
- The management of abnormal screening results for women with HIV and positive results of triage is the same as in the general population
- Women should be offered primary screening 6 weeks postpartum in basic settings and 6 months postpartum in other settings.
- Screening may be discontinued in women who have received a total hysterectomy for benign causes with no history of cervical dysplasia or HPV. Women who have received a subtotal hysterectomy (with an intact cervix) should continue receiving routine screening.

Jeronimo J et al. J Oncol Pract. 2016 Nov 15

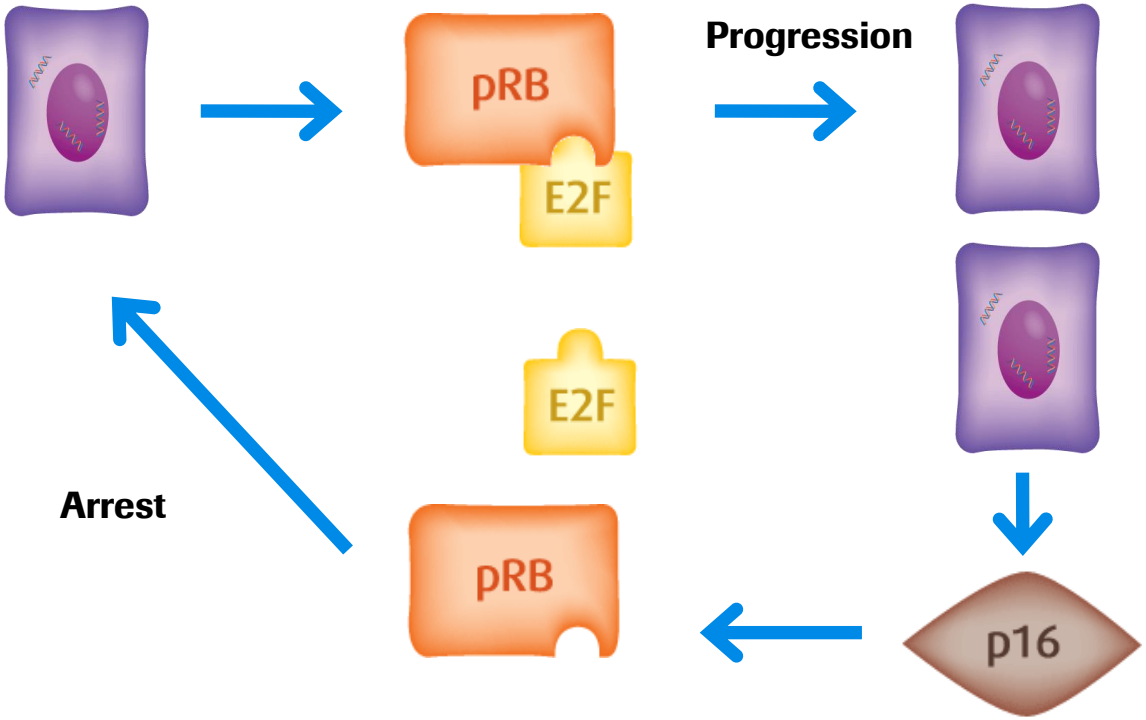
Why triaging hrHPV positive?



- The onset of HPV-mediated cervical disease occurs when HR-HPV types infect the basal cells of the epithelium.
- The vast majority of HPV infections are transient and clear within 6-12 months.

Bergeron C, et al. Cancer Cytopathol. 2015 Jun;123(6):373-81.

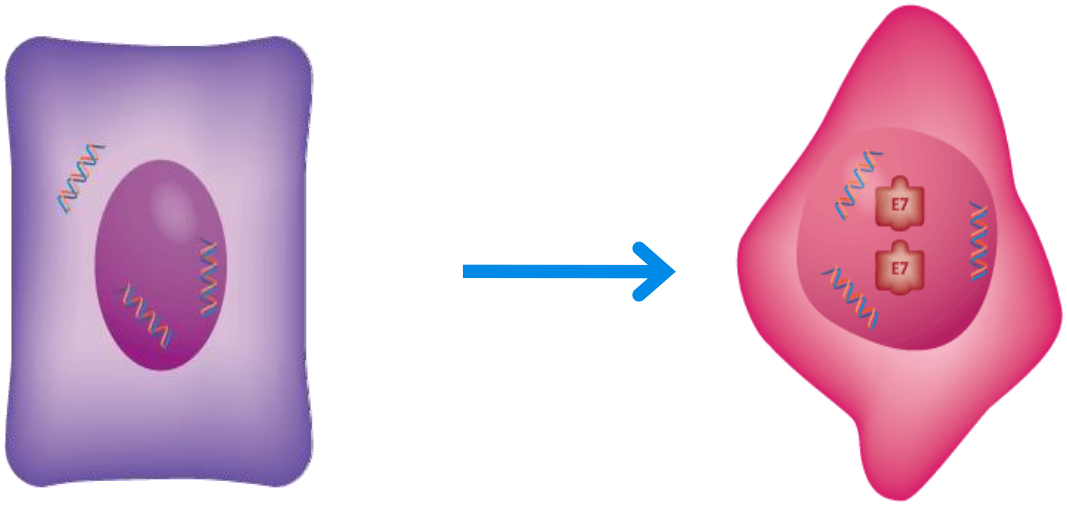
Transient HPV Infection



Although transient HPV infection may result in increased cell proliferation, these infections do not disrupt the balance between pRB and E2F or the control of p16 expression.

Bergeron C, et al. Cancer Cytopathol. 2015 Jun;123(6):373-81.

Transforming HPV Infection



Some HR-HPV infections persist and produce levels of viral E6 and E7 oncoproteins that can mediate oncogenic transformation by disrupting the cell cycle regulatory mechanism.

Bergeron C, et al. Cancer Cytopathol. 2015 Jun;123(6):373-81.

"New more specific biomarkers could be used to triage screen-positive women to help differentiate between benign hrHPV infections or related cytologic abnormalities and clinically important hrHPV infections that have caused or will cause ≥CIN3"

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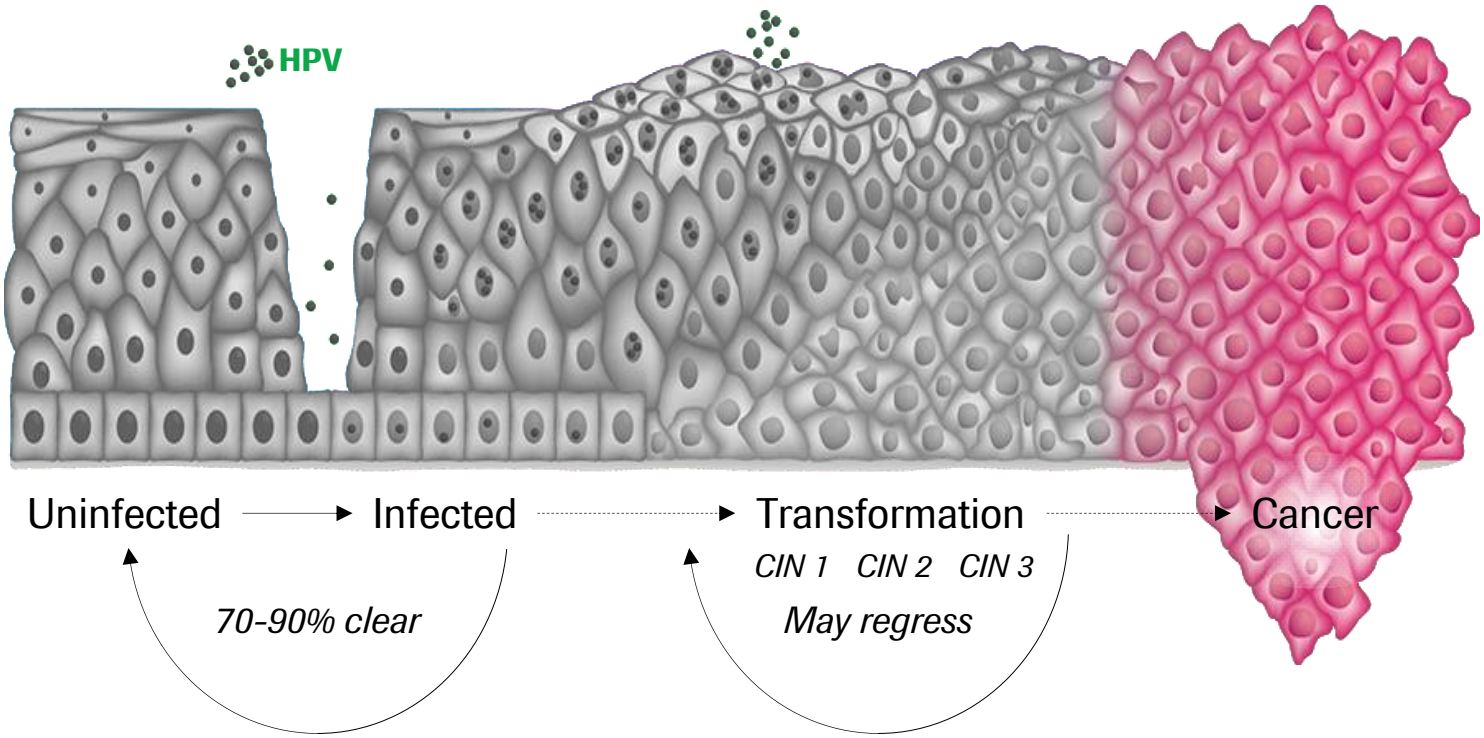
- ❑ p16/Ki-67 immunocytochemistry
- ❑ E6 oncoprotein detection
- ❑ HPV viral genome methylation

New Screening Technologies

Several new technologies are being investigated for all resource setting levels. They need to be tested and approved before use in any setting. These include a number of potentially promising new biomarkers that might achieve better performance as a triage for women with hrHPV-positive results than cytology and/or HPV genotyping. The most advanced of these next-generation biomarkers with respect to validation and readiness for introduction into routine practice is $p16^{INK4a}$ immunocytochemistry (p16 ICC). In a number of studies, p16 ICC has demonstrated high sensitivity and specificity that is similar to or better than cytology testing for ⩾ CIN2 and ⩾ CIN3 among women with hrHPV-positive results.[70,78,79] In addition, Ki-67, a cell proliferation marker, has been included with p16 ICC (p16/Ki-67 ICC) as a dual stain to create a morphology-independent test.[70]

Jeronimo J et al. J Oncol Pract. 2016 Nov 15

We span the spectrum of disease progression



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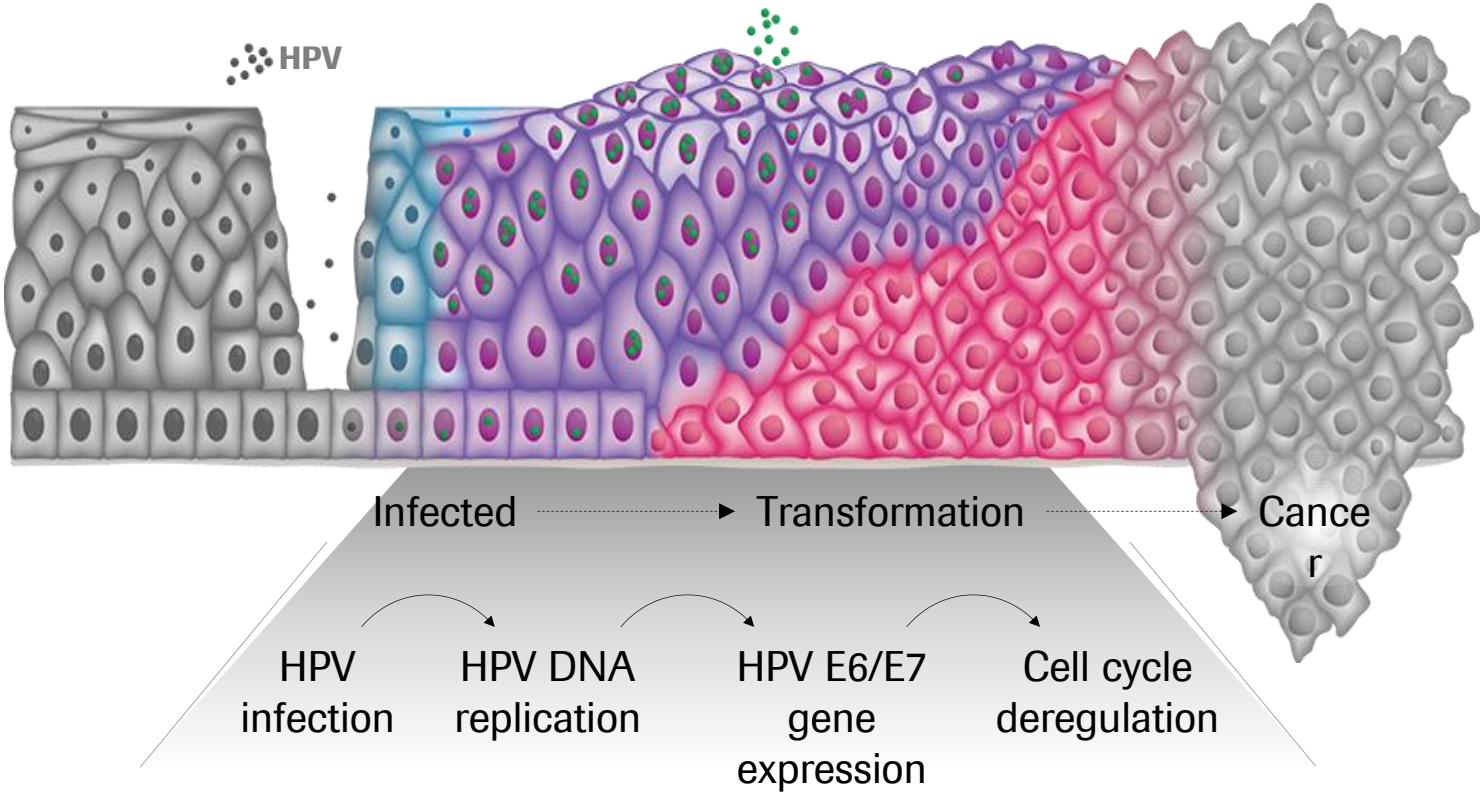

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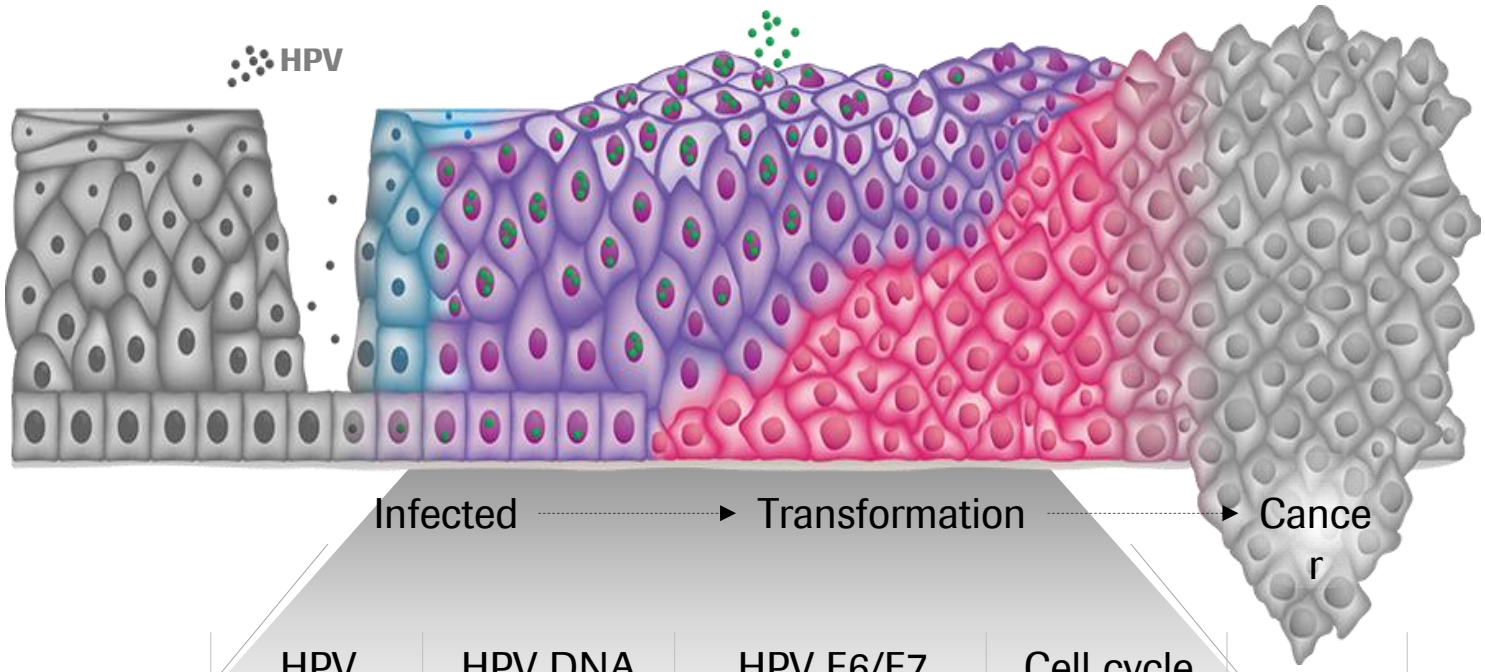
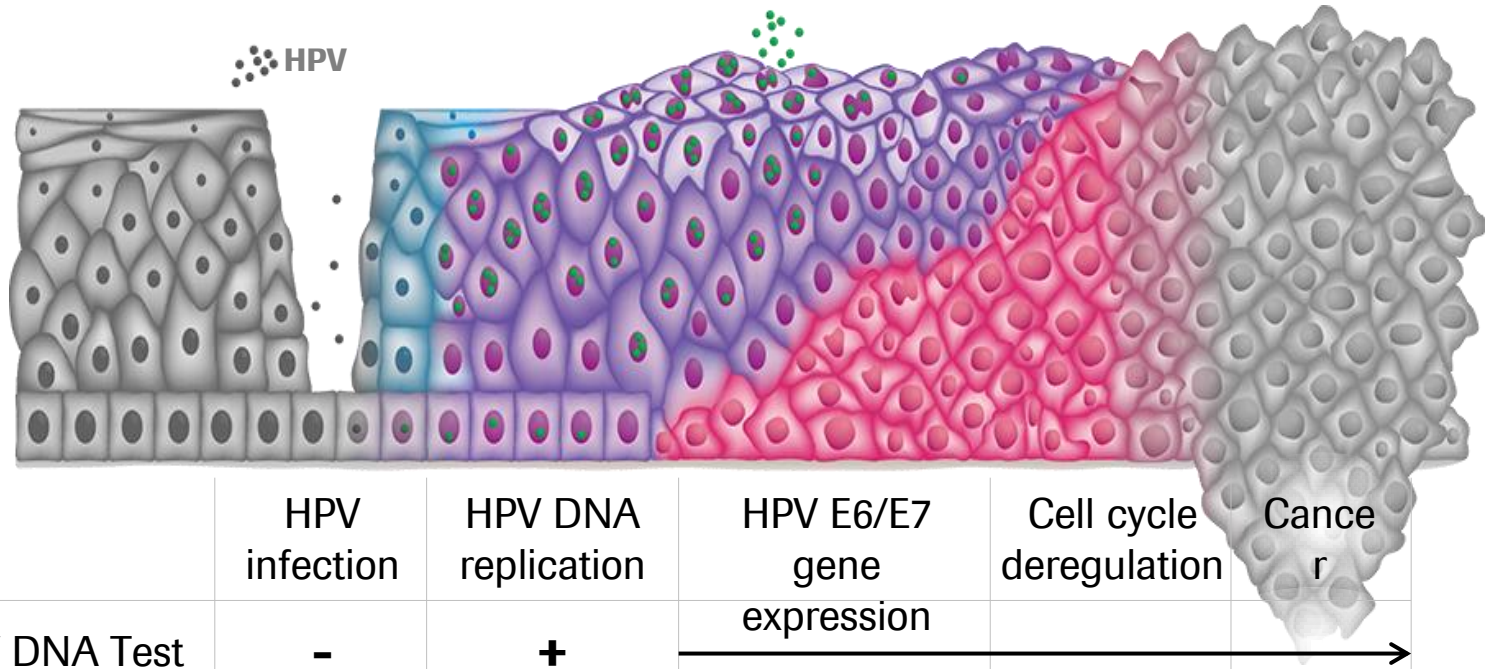


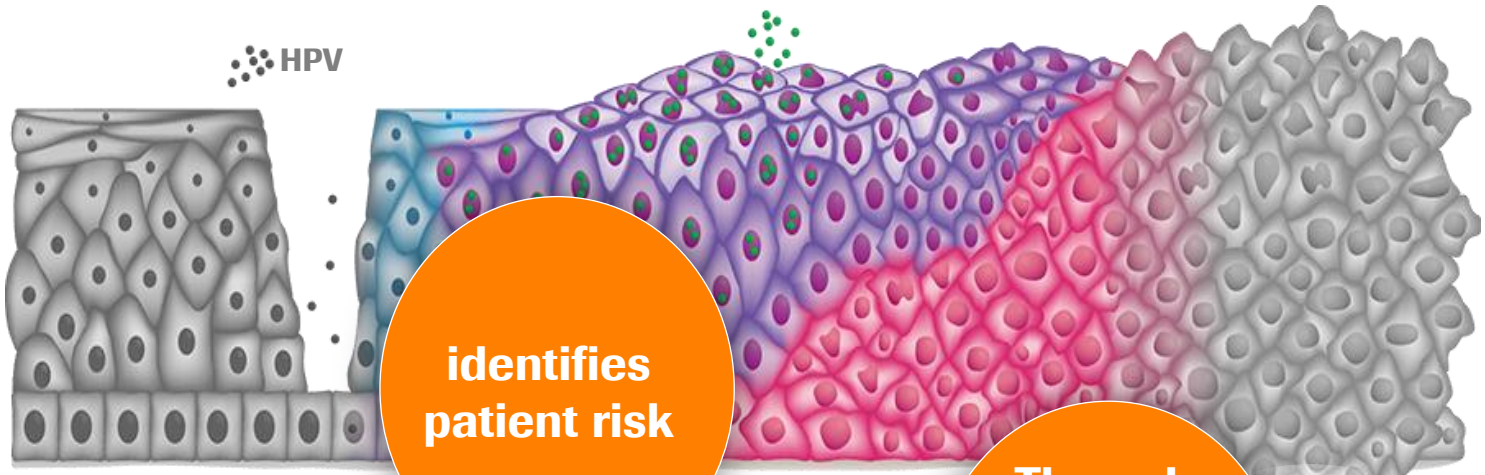
	HPV infection	HPV DNA replication	HPV E6/E7 gene expression	Cell cycle deregulation	
HPV DNA Test					

We span the spectrum of disease progression



	HPV infection	HPV DNA replication	HPV E6/E7 gene expression	Cell cycle deregulation	Cancer
HPV DNA Test	-	+	→	→	→
p16/Ki-67 Test	-	-	-	+	→

Our tests identify both risk & progression



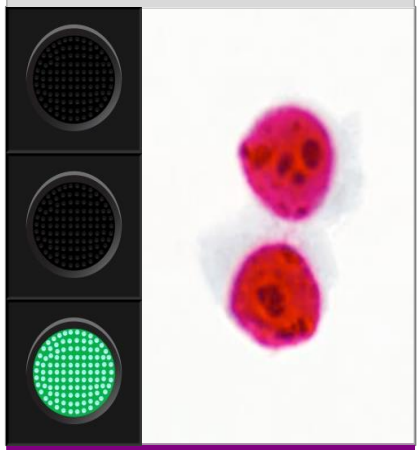
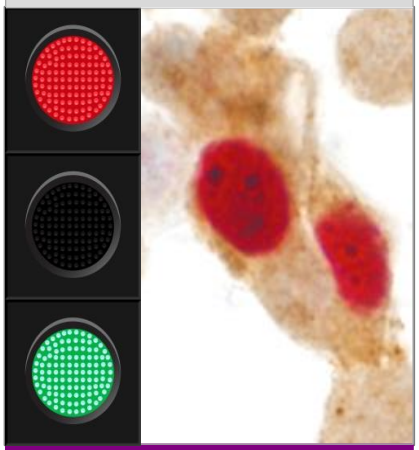
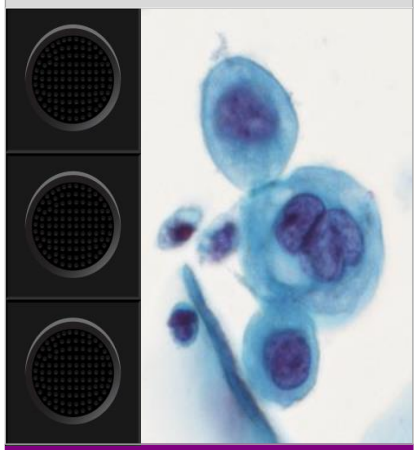
identifies patient risk

The only biomarkers to detect cell transformation

	HPV infection	rep…ion	HPV E6/E7 gene expression	Cance r
HPV DNA Test	-	+		
p16/Ki-67 Test	-	-	-	+

Objectives of p16/Ki-67 triage

In healthy cells, expression of p16 and Ki-67 is mutually exclusive

P16/Ki-67	P16/Ki-67	P16/Ki-67	Pap Cytology
			
Negative	**Negative**	**Disease**	**Subjective**
p16 expression	**Ki-67 expression**	Simultaneous **p16** and **Ki-67** expression	Regular Pap smear
Leads to cell cycle arrest in normal cells	Indicates cell cycle progression and cellular proliferation	Indicates cellular oncogenic transformation	Relies on subjective interpretation of morphology only

P16/Ki-67 Dual-stained Cytology as a Sensitive and Efficient Triage for Colposcopy of HPV-positive Women in Primary HPV Screening

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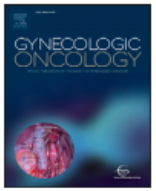


Triaging HPV-positive women with p16/Ki-67 dual-stained cytology: Results from a sub-study nested into the ATHENA trial

Thomas C. Wright Jr. [a,*], Catherine M. Behrens [b], James Ranger-Moore [c], Susanne Rehm [c,d], Abha Sharma [b], Mark H. Stoler [e], Ruediger Ridder [c,d]

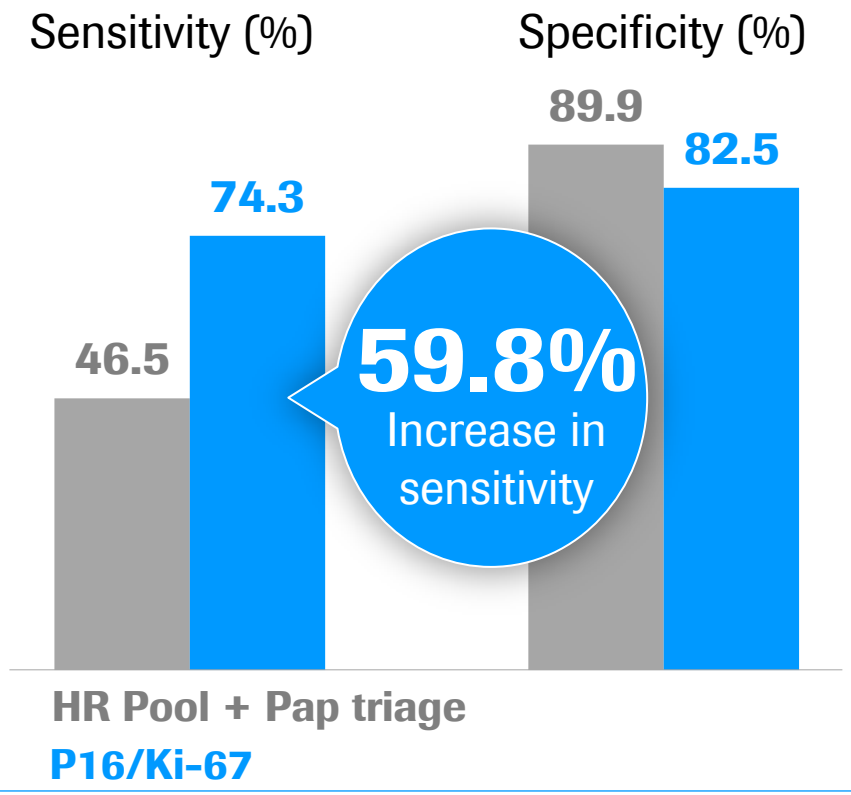
[a] Columbia University, New York City, NY, USA
[b] Roche Molecular Systems, Inc., Pleasanton, CA, USA
[c] Ventana Medical Systems, Inc., Tucson, AZ, USA
[d] Roche mtm laboratories AG, Mannheim, Germany
[e] University of Virginia, Charlottesville, VA, USA

HIGHLIGHTS

- Retrospective study in which residual cytology specimens were dual-stained with p16/Ki-67
- Dual-stained cytology had a higher sensitivity in HPV-positive women than did Pap cytology.
- Positive and negative predictive values were higher for dual-staining than Pap cytology.

The Roche portfolio delivers the optimal screening strategy

HPV DNA & p16/Ki-67

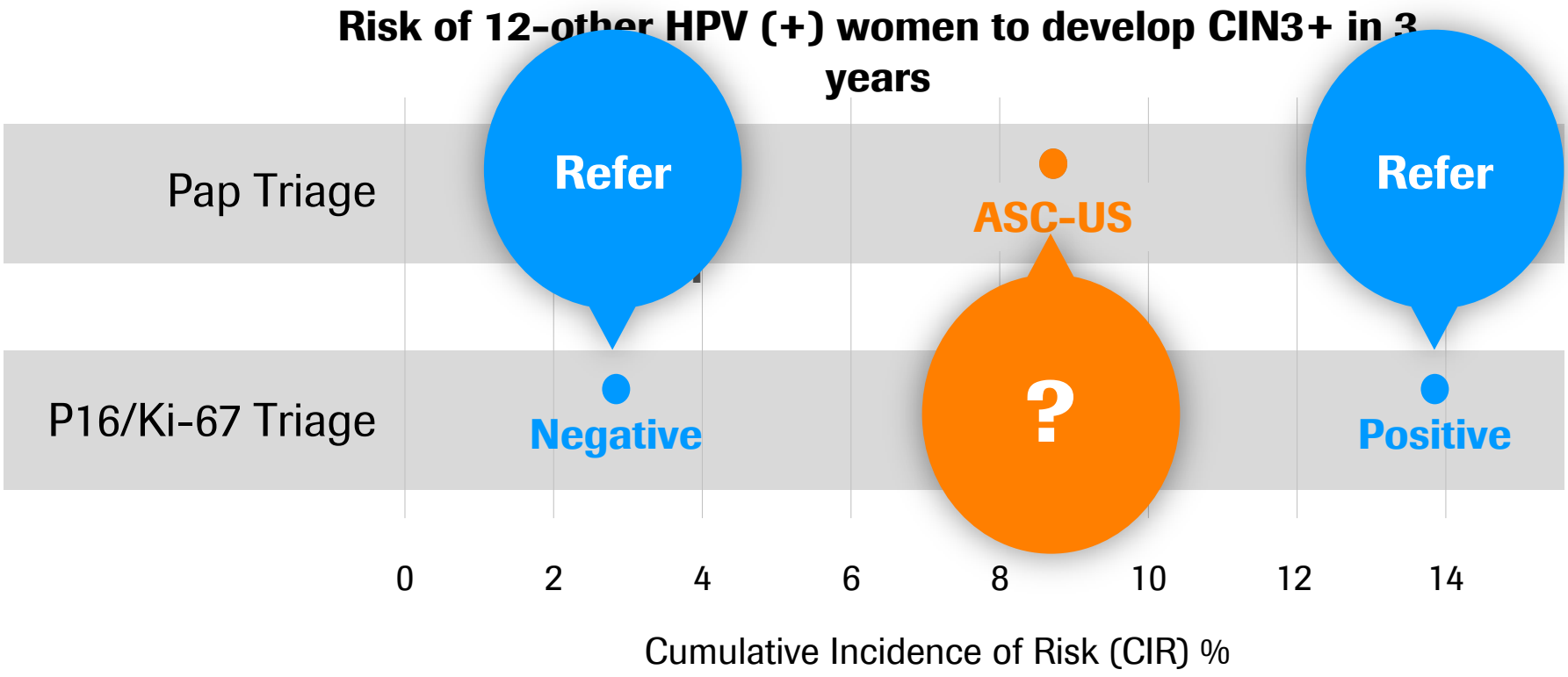


Study Design

- Retrospective study; end-point biopsy CIN2+
- ATHENA study sub-population of women 25 or older with cobas HPV positive result
- Comparison of HPV primary screening with LBC triage vs HPV primary screening with 16/18 genotyping and CINtec *PLUS* triage for 12 other hrHPV
- Testing performed on residual ATHENA samples in PreservCyt vials

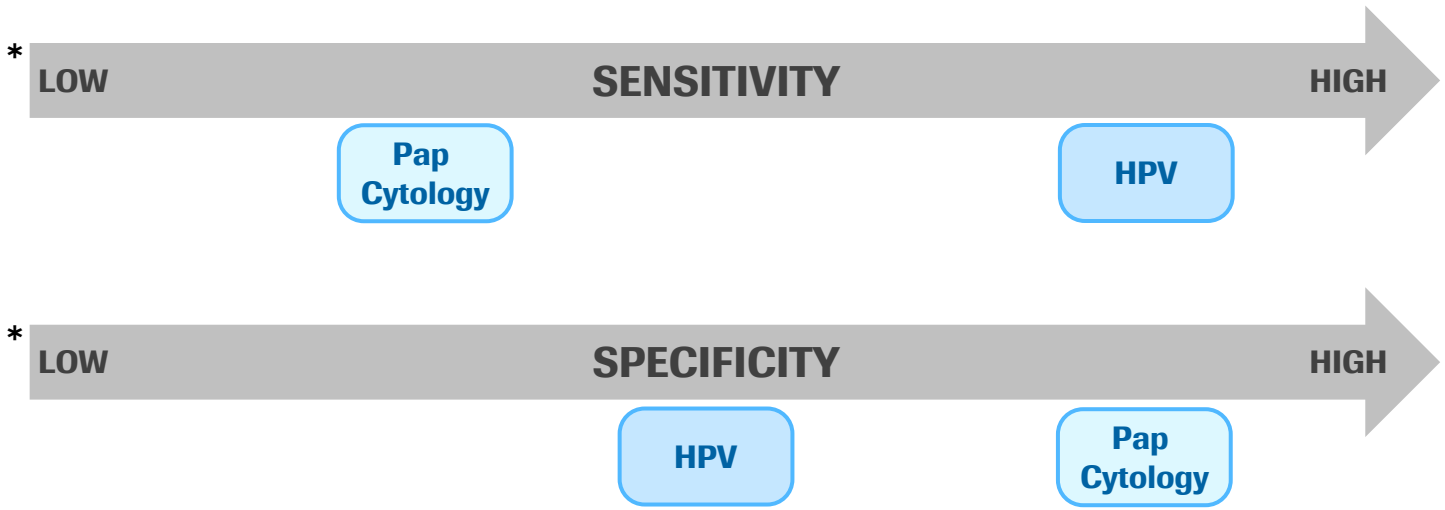
Wright et al. 2017

The role of p16/Ki-67 in triaging system



Source: Wright et al., IPV abstract, 2015

Cervical cancer screening programmes strive to identify disease and avoid false-positives



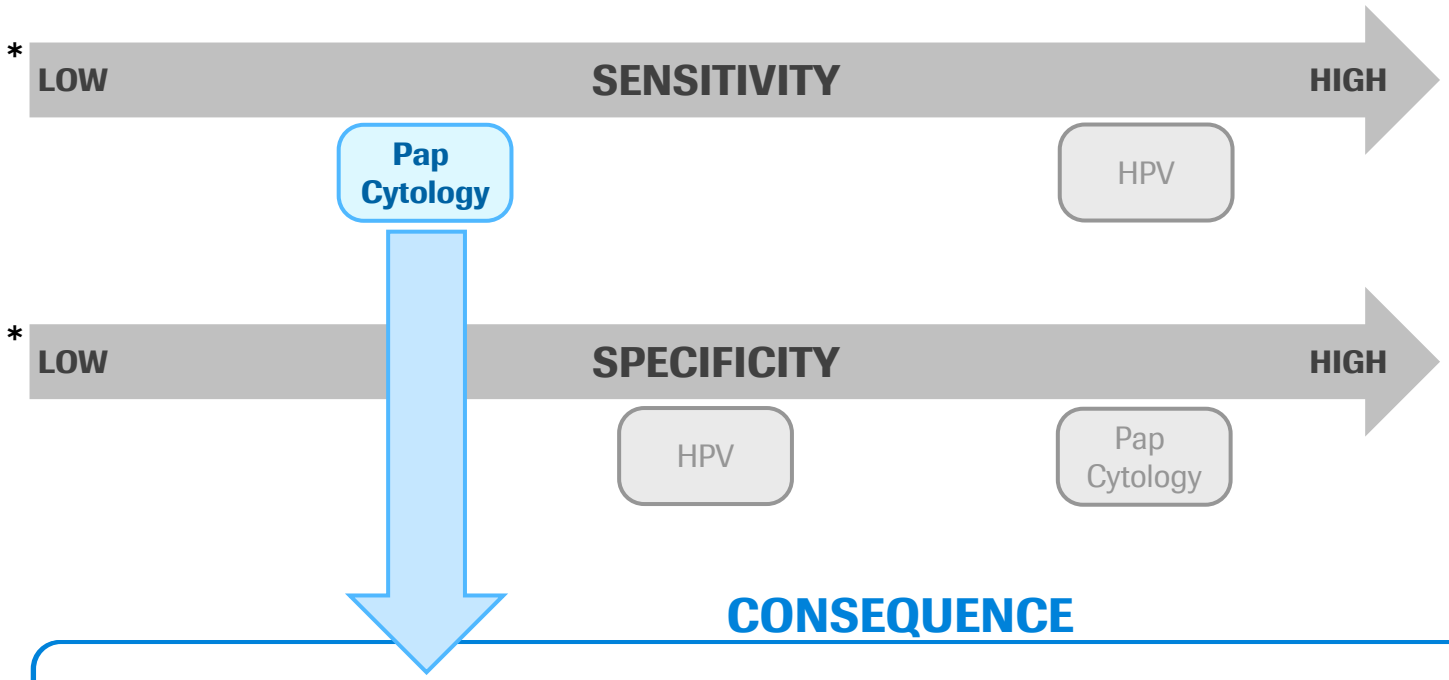
CONSEQUENCE

Without a meaningful triage test to add specificity and not sacrifice the sensitivity of the initial screening test, women are required to attend more frequent follow up visits or undergo unnecessary invasive procedures, leading to inefficiencies and financial burden on the healthcare system.

* Ranges account for varying results across age groups and screening thresholds

1.Castle *et al*. 2011. **2.** Killeen *et al*. 2014 **3.** Petry *et al*. 2011 **4**. Waldstrom *et al*. 2014

Even with perfect compliance to screening guidelines, a system based on Pap cytology misses disease



ISSUE

TESTS WITH LOW SENSITIVITY CAN MISS DISEASE

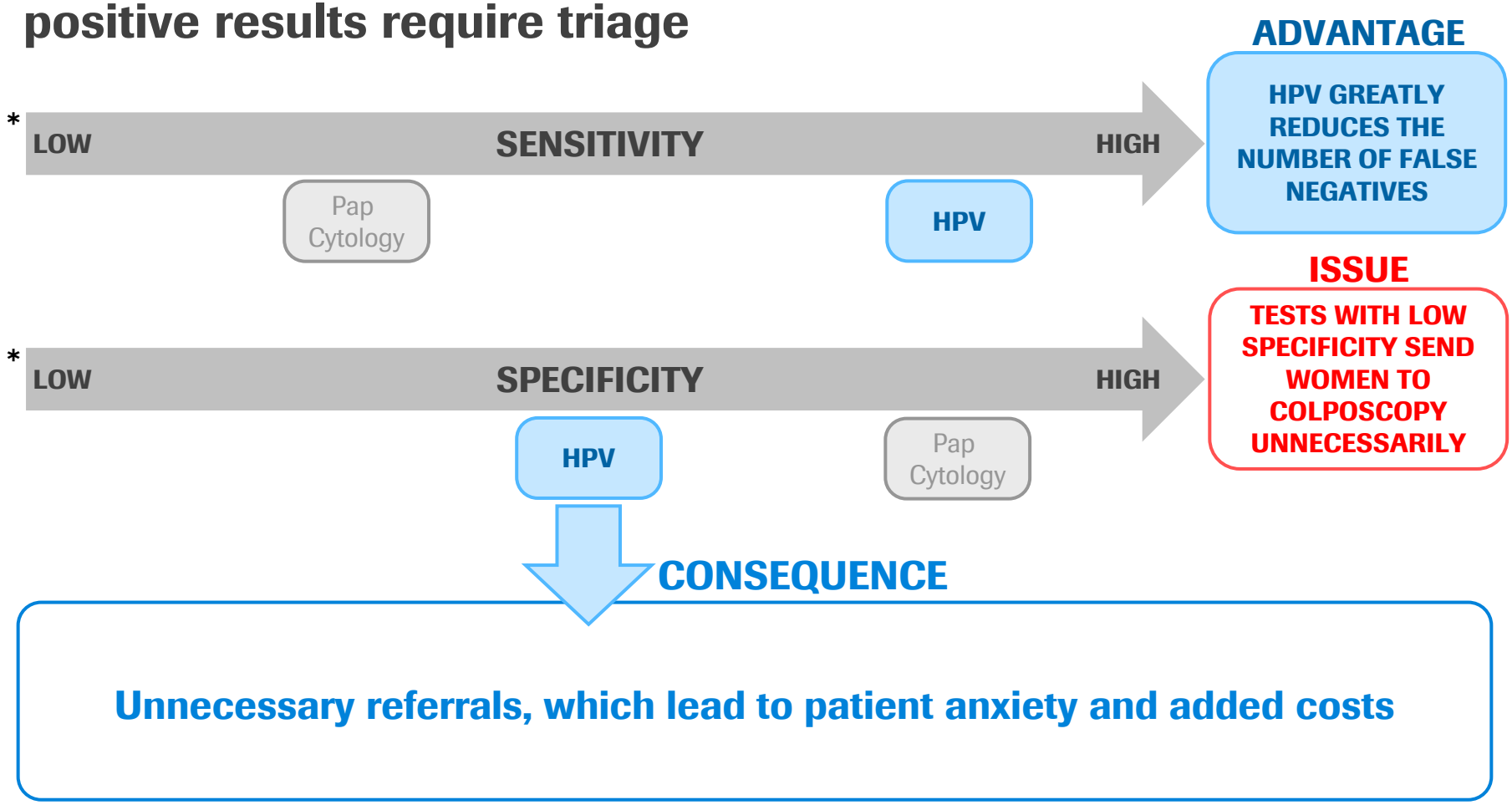
CONSEQUENCE

Available research demonstrates that many women have high-grade cervical precancers, and even cancers, despite an adequate Pap cytology screening history.

* Ranges account for varying results across age groups and screening thresholds

1. Castle *et al*. 2011 **2.** Sasieni *et al*. 1996 **3.** Sung *et al*. 2000

HPV DNA testing is the most sensitive screening method, but positive results require triage



* Ranges account for varying results across age groups and screening thresholds

1. Castle *et al*. 2011 **2**. Naucler P, *et al*. 2009 **3.** Mayrand M, *et al*. 2007

To address the limitations of primary screening tests, further tests are required

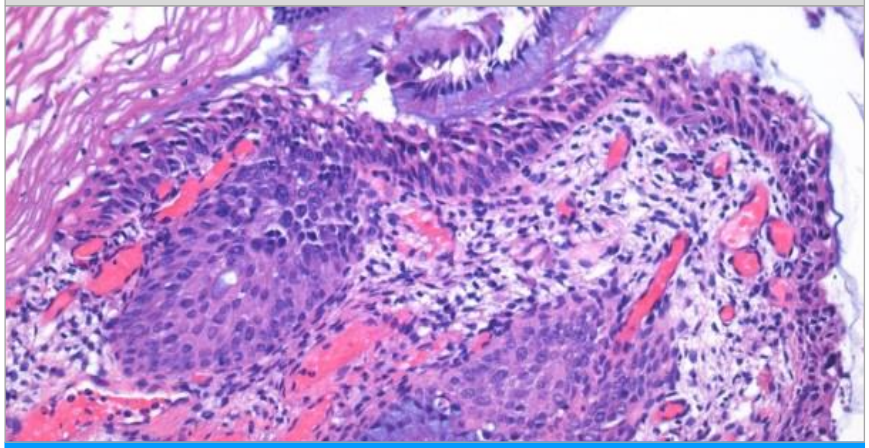
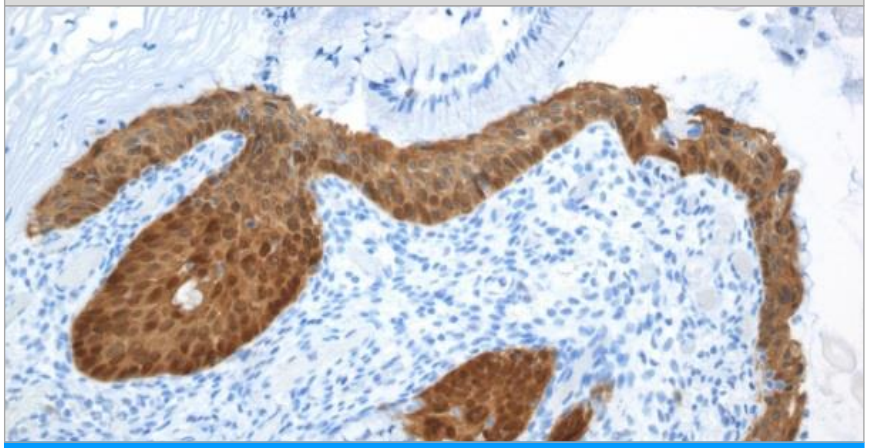
UNMET NEED

A triage test which **adds specificity without sacrificing** initial test **sensitivity**, reduces the number of follow up visits and unnecessary invasive procedures

The p16/Ki-67 test is the only triage test combining high specificity with high sensitivity to detect high-grade disease

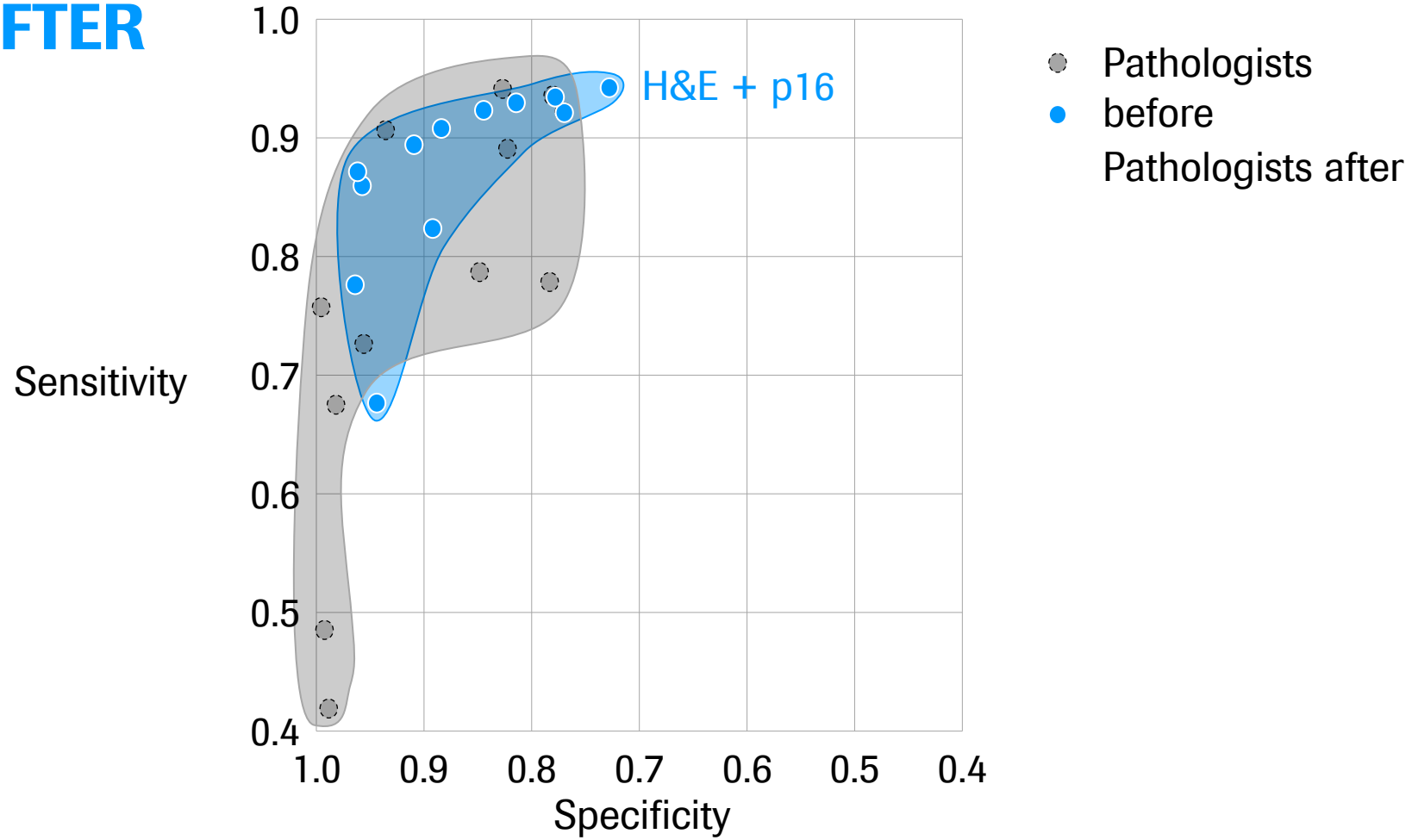
1. Castle *et al*. 2011 **2.** Schmidt *et al*. 2011 **3.** Sasieni *et al*. 1996 **4.** Sung *et al*. 2000 **5.** Leyden *et al*. 2000 **6.** Petry *et al*. 2011

CINtec Histology: improved tissue diagnosis

H&E Only	H&E and CINtec Histology
	
Subjective	**Objective Biomarker: Disease**
Relies on interpretation of morphology only	Expression of p16 in tissue sections (brown) indicates abnormality

CINtec Histology improves H&E diagnosis

AFTER



Source: Bergeron et al. *Am J Clin Pathol*. 2010

LAST assessment and recommendation

WORKING GROUP	ASSESSED	SELECTION CRITERIA
cap ASCCP AMERICAN SOCIETY FOR COLPOSCOPY AND CERVICAL PATHOLOGY	p16 Ki-67 (Mib1) ProEx C L1 HPV 16/18 mRNA Telomerase/TERC HPV genotyping	**2,291** papers identified : met inclusion **72:** criteria **53:** papers on p16 Size of study: >100 subjects Clinical validation studies (e.g. established sensitivity/specificity, performance against histological standard) Cytology studies including histologic standards/true (3-way) adjudication may be included

Source: Darragh et al., *Arch Pathol Lab Med,* 2012

LAST assessment and recommendation

WORKING GROUP	ASSESSED	RECOMMENDATION
cap ASCCP AMERICAN SOCIETY FOR COLPOSCOPY AND CERVICAL PATHOLOGY	**p16** Ki-67 (Mib1) ProEx C L1 HPV 16/18 mRNA Telomerase/TERC HPV genotyping	"We concluded that **only p16,** a biomarker that is recognized in the context of HPV biology to reflect the activation of E6/E7 driven cell proliferation, **had sufficient evidence** on which to make recommendations regarding use in lower anogenital tract lesions."

Source: Darragh et al., *Arch Pathol Lab Med,* 2012

LAST assessment and recommendation

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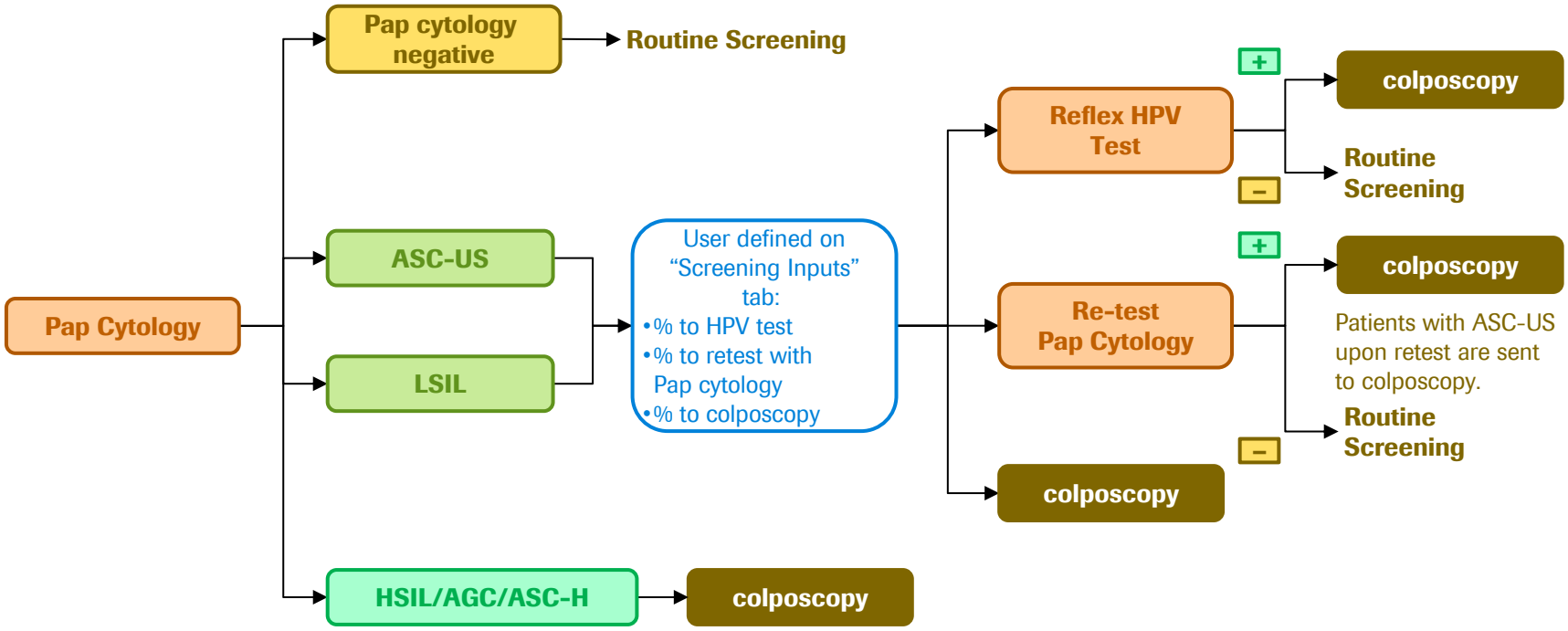
Source: Darragh et al., *Arch Pathol Lab Med,* 2012; Stoler et al. in *WHO Classification of Tumors of Female Reproductive Organs*, 2014

Cytology testing with reflex HPV testing

May miss positive >CIN2 findings

Current Strategy



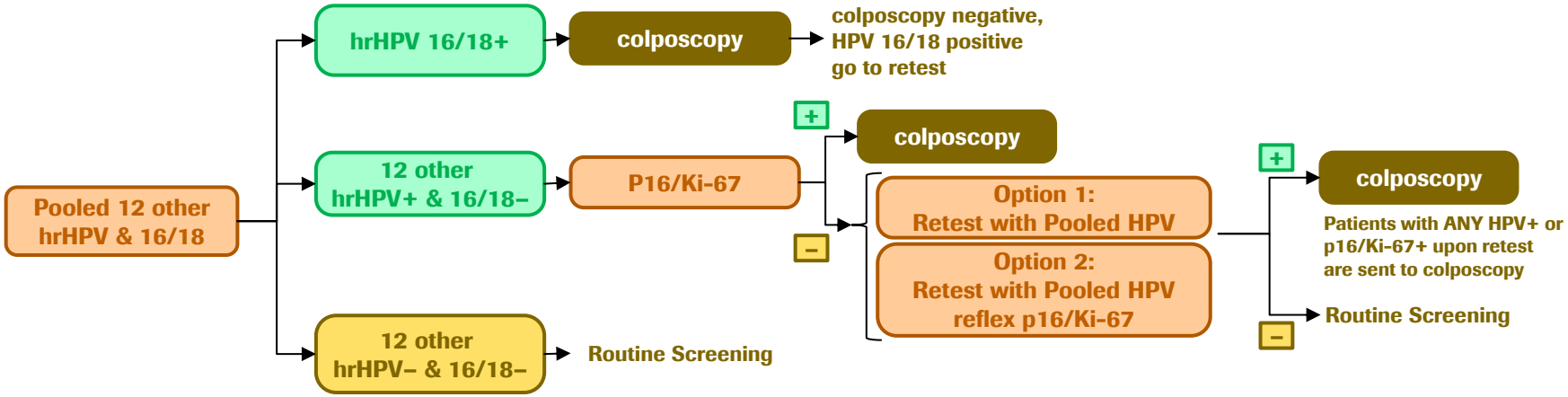
1. Wentzensen *et al.* 2007 **2.** Schmidt *et al.* 2011 **3.** Petry *et al.* 2011 **4.** Uijterwaal *et al.* 2014

The triage with p16/Ki-67 test identifies the women who need to immediately go to colposcopy

Primary screening with HPV and triage with p16/Ki-67 test demonstrates high sensitivity and specificity in detecting ≥CIN2 lesions avoiding unnecessary colposcopy

Possible strategy for optimal patient management:

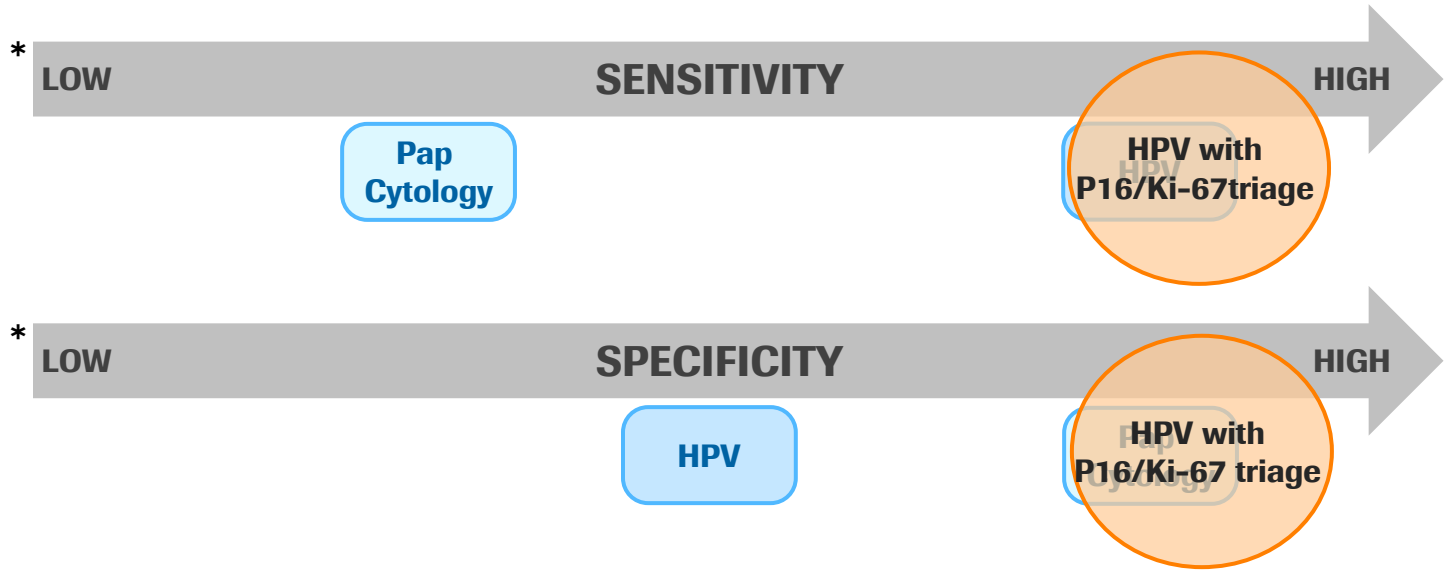
1. HPV primary screening with HPV 16/18 genotyping
2. Reflex 12 other hrHPV+ women to p16/Ki-67 testing



1. Wentzensen *et al.* 2007 **2.** Schmidt *et al.* 2011 **3.** Petry *et al.* 2011 **4.** Uijterwaal *et al.* 2014

The triage with p16/Ki-67 test is both highly sensitive and highly specific

- The test has the potential to capture more disease, which is missed due to the poor sensitivity of Pap cytology, and to significantly reduce the number of unnecessary colposcopies



Range in sensitivity and specificity reflect different populations covered in trials

1. Castle *et al*. 2011 **2.** Ikenberg *et al*. 2013 **3.** Wentzensen *et al*. 2012 **4.** Roche Data on File (ATHENA) **5.** Roche Data on File (PALMS)

Conclusions

- 2017 ASCO: Cervical cancer prevention:
  - Primary prevention: vaccination in 9 – 25 year old women
  - Secondary prevention: HPV DNA test in 25 – 50 year old women
- Vietnamese guidelines recommended primary screening with HPV DNA
- HPV DNA test is highly sensitive as primary screening tool
  - 92% vs 53% compared to regular Pap
- A triage tool is required to enhance specificity of HPV DNA test
  - p16/Ki-67 cytology-based test is an advanced triage system
- WHO guidelines described p16 histology as an aid for cervical cancer diagnosis

Doing now what patients need next

Does mRNA Provide Long-term Protection?

Baseline HPV in women ≥30 yrs with NILM (cotesting setting)

	APTIMA (CLEAR Study)		cobas HPV (ATHENA Trial)	
Baseline Visit	Number	Sensitivity	Number	Sensitivity
CIN 2+	20	70%		83%
CIN 3+	11	91%		90%
After 3 Years				
CIN 2+	47	55%		82%
CIN 3+	23	78%	95	88%

Significant loss in APTIMA sensitivity after 3 year interval

Should we trust negative mRNA /Pap negative result? Should we send women back to routine screening? Will they develop CIN3+ in the next 3 years time?

Data for performance of cobas on file with FDA (Roche)

Reid J. et al. 205 AJCP – APTIMA Performance