

# HPV Primary Screening

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# Disclosures

I have no financial disclosures

Thanks to Warner Huh, MD  
for the use of his slides in this talk

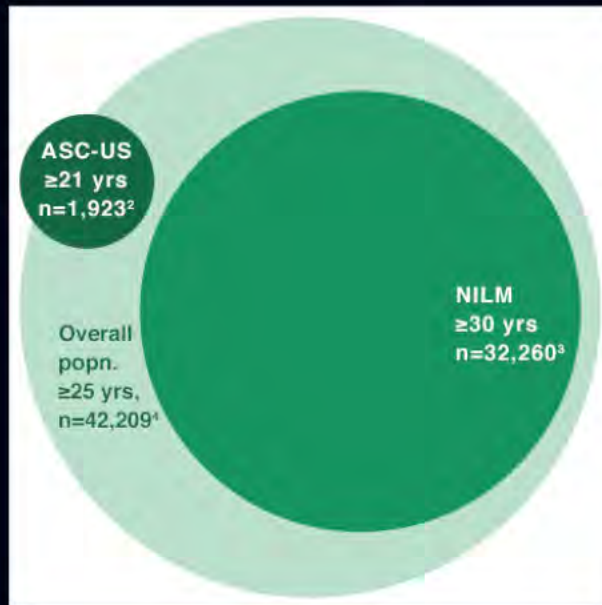
# 2012 Screening Guidelines

HPV testing alone as a screening strategy was not recommended as an alternative to cytology alone or co-testing, although it “appears promising”.

Since then, findings from the ATHENA study have led to:

- FDA approval of one HPV test for primary HPV screening
- Published guidance for the clinical use of primary HPV screening

# Addressing the Need for Advanced HPV Diagnostics (ATHENA trial)



- 47,000 women enrolled
- Roche Cobas 4800: FDA approval for ASC-US triage and cotesting
- Unanimous approval for candidate primary HPV screening algorithm (13-0) on March 12, 2014



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# FDA NEWS RELEASE

**For Immediate Release:** April 24, 2014

**Media Inquiries:** Susan Laine, 301-796-5349, [susan.laine@fda.hhs.gov](mailto:susan.laine@fda.hhs.gov)

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## FDA approves first human papillomavirus test for primary cervical cancer screening

The U.S. Food and Drug Administration today approved the first FDA-approved HPV DNA test for women 25 and older that can be used alone to help a health care professional assess the need for a woman to undergo additional diagnostic testing for cervical cancer. The test also can provide information about the patient's risk for developing cervical cancer in the future.

*Guidelines*

# Use of Primary High Risk Human Papillomavirus Testing for Cervical Cancer Screening

*Interim Clinical Guidance*

*Warner K. Huh, MD, Kevin A. Ault, MD, David Chelmow, MD, Diane D. Davey, MD, Robert A. Goulart, MD, Francisco A. R. Garcia, MD, MPH, Walter K. Kinney, MD, L. Stewart Massad, MD, Edward J. Mayeaux, MD, Debbie Saslow, PhD, Mark Schiffman, MD, MPH, Nicolas Wentzensen, MD, PhD, Herschel W. Lawson, MD, and Mark H. Einstein, MD, MS*

# RCTs of HPV testing in screening

- POBASCAM study: The Netherlands (Meijer et al., Int J Cancer 2004; Bulkman et al, Lancet 2007)
- Indian Trial (Osmanabad) (Sankaranarayanan et al. NEJM 2009)
- ARTISTIC trial: UK (Kitchener et al. Lancet Oncol 2009)
- NTCC Italian Study (Ronco et al., Lancet Oncol, 2006; JNCI 2006)
- SWEDESCREEN: Swedish trial (Elfgren et al. AJOG 2005; Naucier et al., NEJM 2007; JNCI 2009)
- Finnish RCT (Kotaniemi et al., BJC 2005; Eur J Cancer 2008; IJC 2008; Leinonen et al., JNCI 2009)
- CCCaST study: Canada (Mayrand et al., IJC 2006; NEJM 2007)
- BC RCT (HPV FOCAL): Canada (Ogilvie et al, BJC 2012)
- ATHENA Trial: United States

# Issues to Consider with Cytology

- Duke Report (Nanda et al., 2000): sensitivity 51%, specificity: 98%
- Highly subjective test: substantial inter-laboratory (as well as intra-laboratory) variability and limited reproducibility
- Unable to identify those women who are at future risk of developing cervical cancer precursors
- Unclear how cytology will perform as HPV vaccination rates increase in the US



# Primary HPV Screening:

- A negative hrHPV test provides greater reassurance of low CIN3+ risk than a negative pap (cytology) result.
- Because of equivalent or superior effectiveness, primary hrHPV screening can be considered as an alternative to cytology based cervical cancer screening.

# Case 1

Your practice has decided to use primary HPV screening for cervical cancer. You tell this to a 45 y.o. new patient who says she has “always” had a yearly Pap test and doesn’t understand why she isn’t getting a Pap this visit.

# Case 1

You reply:

- A. It's more effective to do the most sensitive test first
- B. HPV testing is more sensitive for risk of future disease
- C. HPV testing is more sensitive and reproducible than cytology alone
- D. All of the above

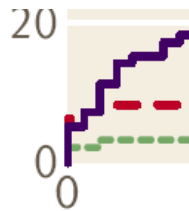
# Case 1

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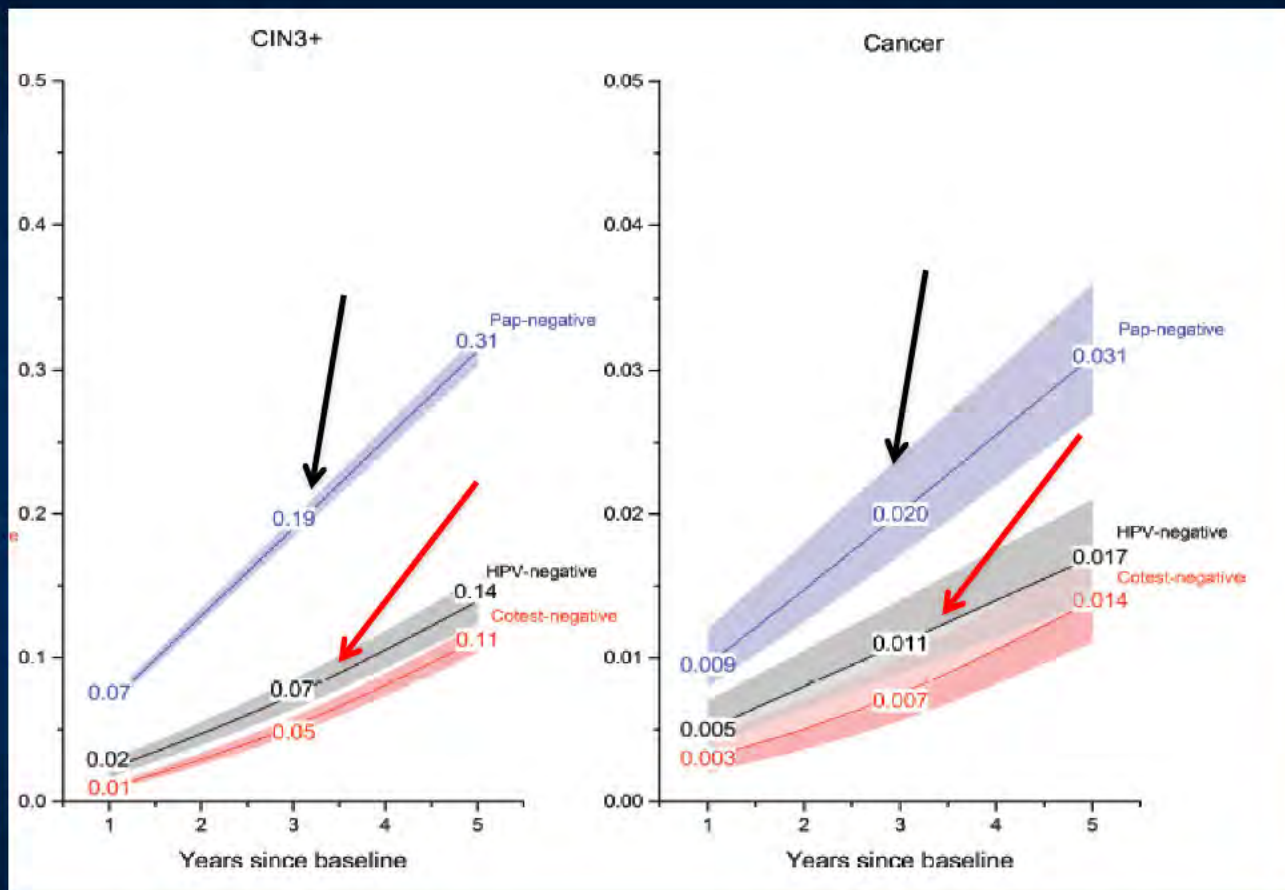
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## Cumulative incidence of CIN3+ according to baseline test results in European sites (excluding Denmark and Tübingen)

Cumulative incidence of CIN3+  
(per 10,000)



Time since initial testing (mos.)



Gage J *et al*, JNCI, 2014

## Case 2

A 24 y.o. graduate student with limited student insurance has read about primary HPV screening. She would like to be screened with HPV alone. You are unsure if your lab uses the FDA-approved test for HPV primary screening.

## Case 2

You reply:

- A. Yes, this is a good test for someone in your financial circumstances
- B. Yes, our lab does HPV testing so it must be able to do HPV primary screening
- C. No, you are not a candidate for this test
- D. No, I prefer co-testing for cervical cancer screening



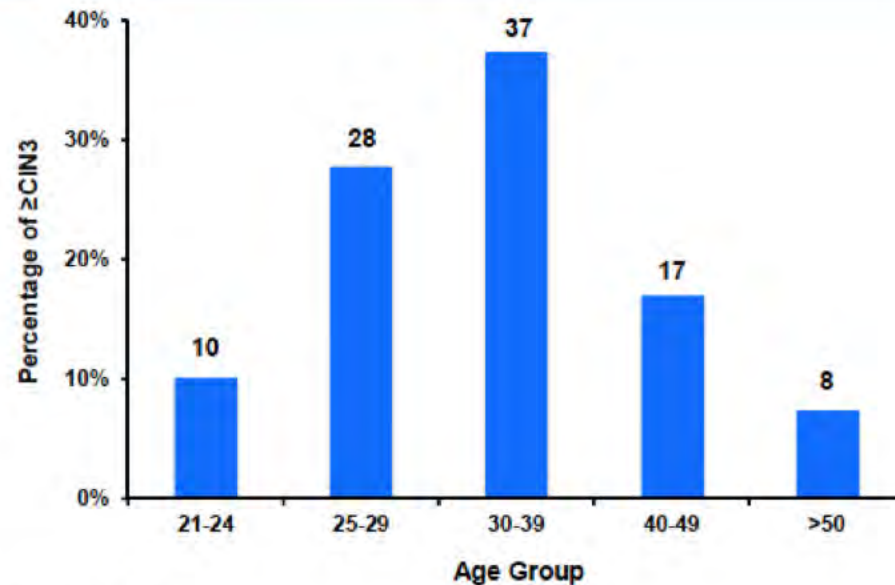
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# Why Start at 25 years of Age?

## ≥CIN3 by Age Group ATHENA



Data not reviewed by FDA  
Wright et al. *Am J Obst Gynecol*, 2011.

CC-28

From 3/12/2014 FDA Panel Materials

# Age To Initiate Primary HPV Screening

Primary HPV screening should not be initiated prior to age 25.

Starting at age 25, the number of colposcopies increased but found 54% more CIN 3

However, progression to cancer is uncommon in this age group and it is uncertain if identification of CIN 3 before age 30 will reduce cervical cancer

## Case 2

This patient is not age appropriate for primary HPV screening and the test the lab uses is not FDA approved for this indication.

Co-testing is recommended only for women 30 and older

## Case 3

A 30 y.o. comes in for contraception. Her last cervical cancer screen was cytology at age 28. She asks about screening at this visit. Your lab uses the FDA- approved test.

## Case 3

You reply:

- A. Yes, you are now 30 and due for co-testing
- B. Yes, we can offer you primary HPV screening
- C. No, you are not due for screening
- D. A or B

## Case 3

You reply:

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# Optimal Interval for Primary HPV Screening

Rescreening after a negative screen should occur  
no sooner than every 3 years

There are limited prospective US data to determine the best interval for Primary HPV Screening. In the ATHENA trial, the incidence of CIN 3 over 3 years was less than 1%. European trials have used 3 year screening intervals. Until further US data is available, screening no sooner than 3 years is recommended.



## Case 4

Your practice utilizes Primary HPV Screening. A 36 y.o. woman s/p BTL has a positive HPV 16 result. You call her to recommend:

## Case 4

- A. Perform co-testing
- B. Repeat HPV test one year
- C. Perform colposcopy
- D. Perform LEEP

## Case 4

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## Case 4

The risk of high grade disease with a positive HPV 16 test is too great to delay further testing and colposcopy is recommended, just as it is with co-testing when genotyping finds HPV 16 or 18.

However, treatment with any modality is not recommended unless high grade disease is found.

## Case 5

A 47 y.o. woman sees you for screening. She has just recently obtained health insurance and is trying to “catch up” on her preventive care. She thinks her last Pap was over 10 years ago and states that none have ever been abnormal. Your lab uses the FDA-approved HPV test for primary screening. Her result returns negative for 16 and 18 but positive for the other pooled high risk types.

What do you recommend?

## Case 5

What do you recommend?

- A. Perform co-testing now
- B. Perform cytology now
- C. Perform colposcopy now
- D. Perform co-testing at 12 months

## Case 5

What do you recommend?

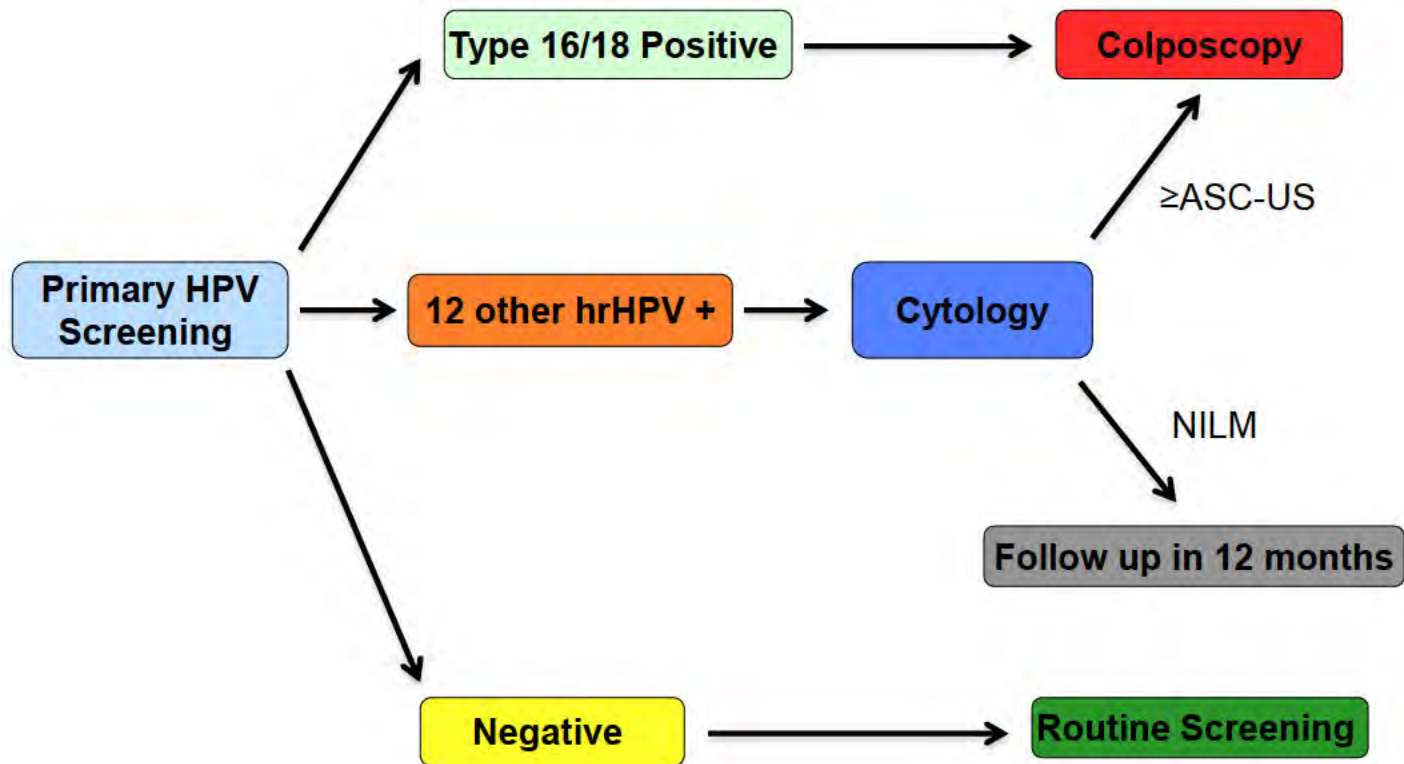
- A. Perform co-testing now
- B. Perform cytology now**
- C. Perform colposcopy now
- D. Perform co-testing at 12 months

## Case 5

According to the algorithm proposed in the Interim Clinical Guidance, “reflex” cytology can be performed and subsequently managed according to the appropriate ASCCP Guideline.

The best scenario is somewhat unknown for this situation but it puts it into the realm of co-testing, for which we do have data.





# Primary HPV Screening- Concerns

- ✓ Three screening options: more patient and provider confusion
- ✓ Unknown screening interval
- ✓ Comparison to co-testing?
- ✓ Over-treatment of women 25-29 years of age
- ✓ Missing cases where there is abnormal cytology yet a negative HPV result
- ✓ Currently only one test FDA- approved

# Comparison to Co-Testing

Retrospective study\* reported in 2015 looked at missed cases of CIN 3 or cancer

	CIN 3	Cancer
Cytology alone	8.7%	12.2%
HPV alone	6.0%	18.6%
Co-testing	1.2%	5.5%

\* Blatt et al. Cancer Cytopathol 2015; 123 (5): 282-288

# HPV Negative CIN 3 and Cancer

- KPNC data<sup>1</sup> ---2019 HSIL results in cohort of 965,360
  - 119 were HSIL HPV negative at baseline
    - 5 year risk of CIN 3 was 30% with HSIL HPV neg (20 pts)
    - 5 year risk of cancer was 6.8% with HSIL HPV neg (4 pts)
- 2012 report<sup>2</sup> of Pap and HPV results in 70 cancers
  - 13 HPV negative cancers
    - 9% (5 of 53) HPV test less than 1 year
    - 23% (6 of 26) HPV test 1-3 years
    - 25% (2 of 8) HPV test 3 to 5 years

<sup>1</sup>Katki et al. JLGTD 2013; 17 (5); S50-55

<sup>2</sup>Zhao et al. Arch Pathol Lab Med 2015; 139: 184-

# “Range of Reasonable Options”

Patient preference

Maximize benefits and minimize harms

Resource utilization.

Process of comparing new strategies with current approaches

Sawaya and Kupperman. Obstet and Gynecol 2015. 125 (2) :308-310