Primary HPV Screening – Current State of the Science - USA

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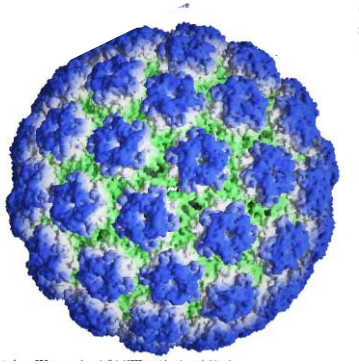
Financial Disclosure: Dr. Wright is a consultant to Roche and BD Diagnostics

Disclosures

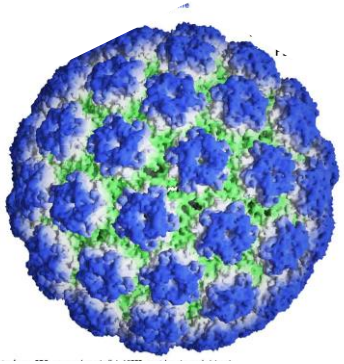
- Dr. Wright is a consultant and study pathologist for Roche and BD Diagnostics and receives payment for his services.
- Dr. Wright is a speaker for Roche and BD Diagnostics and receives payment for his services.



HPV for Primary Screening

FDA approval of cobas HPV test

- In April 2014 the FDA approved the use of the cobas HPV Test for primary cervical cancer screening
- Approval included a specific management algorithm
- Can begin screening with HPV at age 25 years



FDA Study - HPV Primary Screening

ATHENA trial – women ≥25 years old

- Cohort of 42,209 women ≥25 years from US
- Had gynecological exam, ThinPrep cytology test, HPV testing (and genotyping)
- All HPV (+) and/or cytology (+); and a subset of hrHPV (-) / WNL underwent colposcopy
- Patients with initial colposcopy were followed for 3 yrs and had exit colposcopy *(n=4063)*
- Total of 240 CIN 2 and 347 CIN 3 lesions

Wright et al. (2015) Gynecol Oncol

ATHENA: 3 Year CIR of CIN2+ or CIN3+

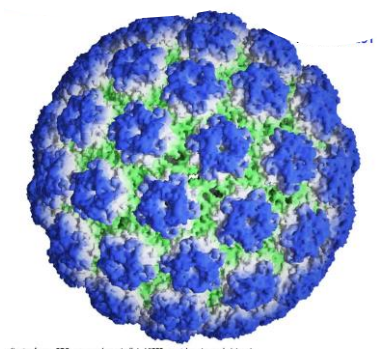
Stratified by screening test result at baseline

Test result	CIN2+	CIN3+
Cytology (-)	**1.7** (1.2-2.2)	**0.8** (0.5-1.1)
HPV (-)	**0.9** (0.5-1.5)	**0.3** (0.1-0.7)
Cytology & HPV (-)	**0.9** (0.4-1.4)	**0.3** (0.1-0.6)
Cytology (+)	**14.0** (12.5-15.5)	**9.2** (7.9-10.5)
HPV (+)	**15.5** (14.3-16.8)	**7.5** (6.7-8.3)

Wright *et al.* 2015 Gynecol Oncol

Primary HPV Screening - ≥25 yrs

HPV with 16/18 Genotyping and Reflex Cytology



HPV Testing

HPV−

Routine screening

12 other hrHPV+

Cytology

NILM

Follow up in 12 months

≥ ASC-US

COLPOSCOPY

HPV16/18+

COLPOSCOPY

Wright *et al.* (2015) Gynecol Oncol

Comparison of stratagies in ≥25 years

Tradeoffs between CIN3+ detected and colposcopy

Strategy	Screening Tests	CIN3+ Baseline	Total CIN3+	Colpos	Colpos to detect 1x CIN3+
Cytology only	45,166	143	179	1,934	10.8
Hybrid Strategy*	82,994	143	240	3,097	12.9
HPV Primary	52,651	197	294	3,769	12.8

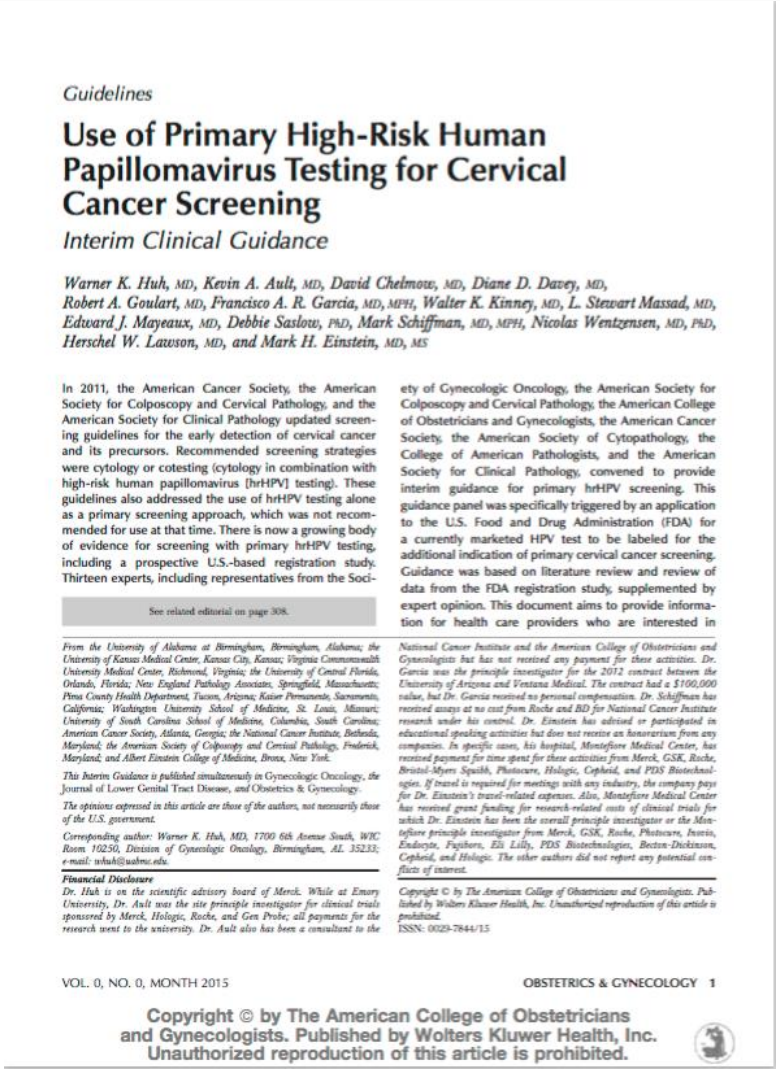
**Cytology for women ≤30 yrs and cotesting (without genotyping) for women 30 yrs and older*

Wright, T.C. *et al.* (2015) Gyn Oncol

Crude estimates in women 25 years and older

Total # women with ≥CIN3 = 347

2015 Interim Guidance - HPV Primary Screening: *ASCCP and SGO*



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

In 2011, the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology updated screening guidelines for the early detection of cervical cancer and its precursors. Recommended screening strategies were cytology or cotesting (cytology in combination with high-risk human papillomavirus [hrHPV] testing). These guidelines also addressed the use of hrHPV testing alone as a primary screening approach, which was not recommended for use at that time. There is now a growing body of evidence for screening with primary hrHPV testing, including a prospective U.S.-based registration study. Thirteen experts, including representatives from the Society of Gynecologic Oncology, the American Society for Colposcopy and Cervical Pathology, the American College of Obstetricians and Gynecologists, the American Cancer Society, the American Society of Cytopathology, the College of American Pathologists, and the American Society for Clinical Pathology, convened to provide interim guidance for primary hrHPV screening. This guidance panel was specifically triggered by an application to the U.S. Food and Drug Administration (FDA) for a currently marketed HPV test to be labeled for the additional indication of primary cervical cancer screening. Guidance was based on literature review and review of data from the FDA registration study, supplemented by expert opinion. This document aims to provide information for health care providers who are interested in

See related editorial on page 308.

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This Interim Guidance is published simultaneously in Gynecologic Oncology, *the* Journal of Lower Genital Tract Disease, *and* Obstetrics & Gynecology.

The opinions expressed in this article are those of the authors, not necessarily those of the U.S. government.

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Financial Disclosure

Dr. Huh is on the scientific advisory board of Merck. While at Emory University, Dr. Ault was the site principle investigator for clinical trials sponsored by Merck, Hologic, Roche, and Gen Probe; all payments for the research went to the university. Dr. Ault also has been a consultant to the National Cancer Institute and the American College of Obstetricians and Gynecologists but has not received any payment for these activities. Dr. Garcia was the principle investigator for the 2012 contract between the University of Arizona and Ventana Medical. The contract had a $100,000 value, but Dr. Garcia received no personal compensation. Dr. Schiffman has received assays at no cost from Roche and BD for National Cancer Institute research under his control. Dr. Einstein has advised or participated in educational speaking activities but does not receive an honorarium from any companies. In specific cases, his hospital, Montefiore Medical Center, has received payment for time spent for these activities from Merck, GSK, Roche, Bristol-Myers Squibb, Photocure, Hologic, Cepheid, and PDS Biotechnologies. If travel is required for meetings with any industry, the company pays for Dr. Einstein's travel-related expenses. Also, Montefiore Medical Center has received grant funding for research-related costs of clinical trials for which Dr. Einstein has been the overall principle investigator or the Montefiore principle investigator from Merck, GSK, Roche, Photocure, Inovis, Endocyte, Fujifilm, Eli Lilly, PDS Biotechnologies, Becton-Dickinson, Cepheid, and Hologic. The other authors did not report any potential conflicts of interest.

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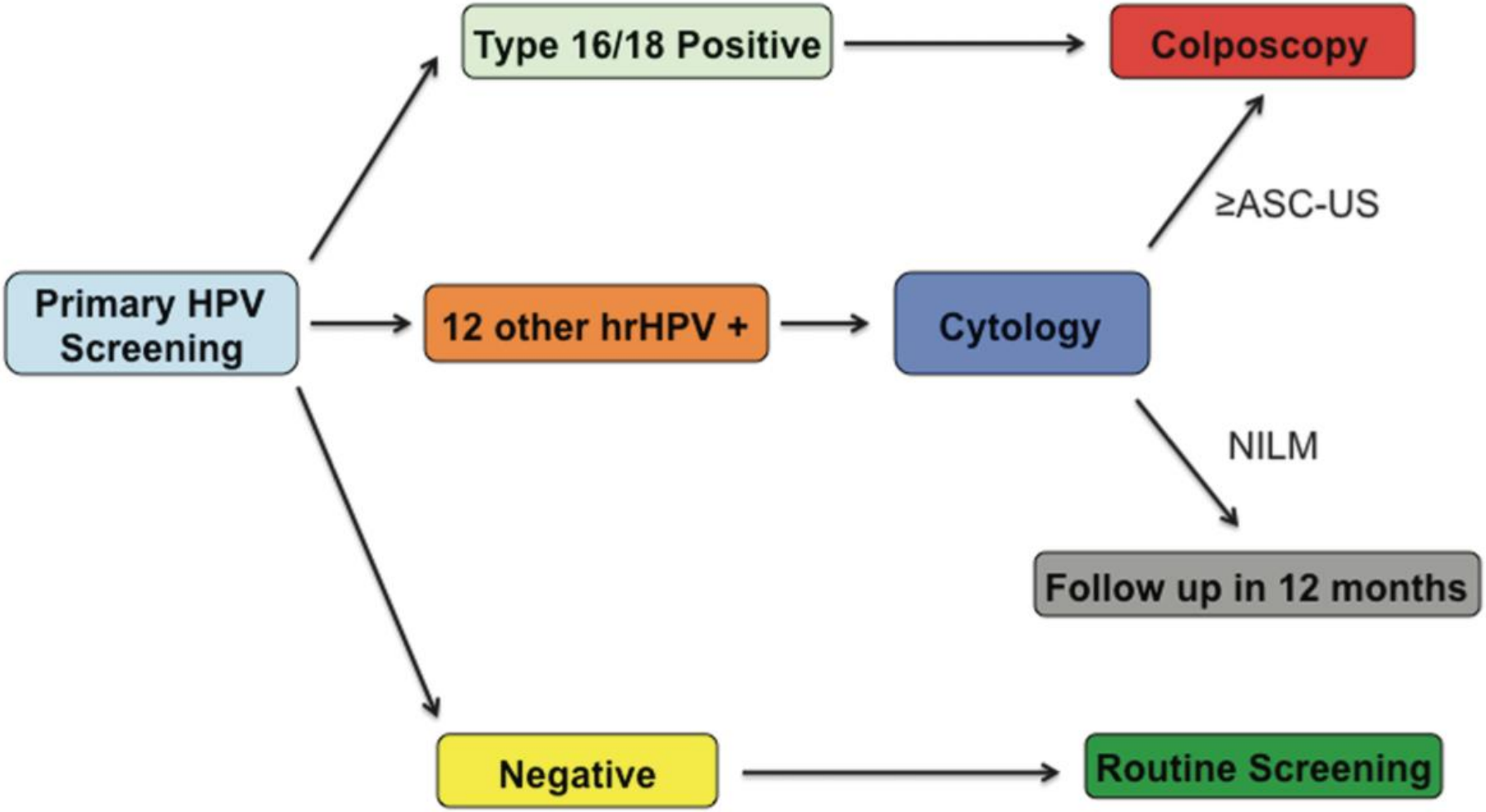
Key Findings:

- *A negative hrHPV test provides greater reassurance of low CIN3+ risk than a negative cytology result*
- *Because of equivalent or superior effectiveness, primary hrHPV screening can be considered an alternative to current US cytology-based cervical cancer screening methods*
- *Based on limited data, triage of hrHPV (+) women using combination of 16/18 genotyping and reflex cytology appears reasonable*

Huh, W.. *et al.* (2015) Obst Gynecol

2015 Interim Guidance - HPV Primary Screening: *ASCCP and SGO*



Huh, W.. *et al.* (2015) Obst Gynecol

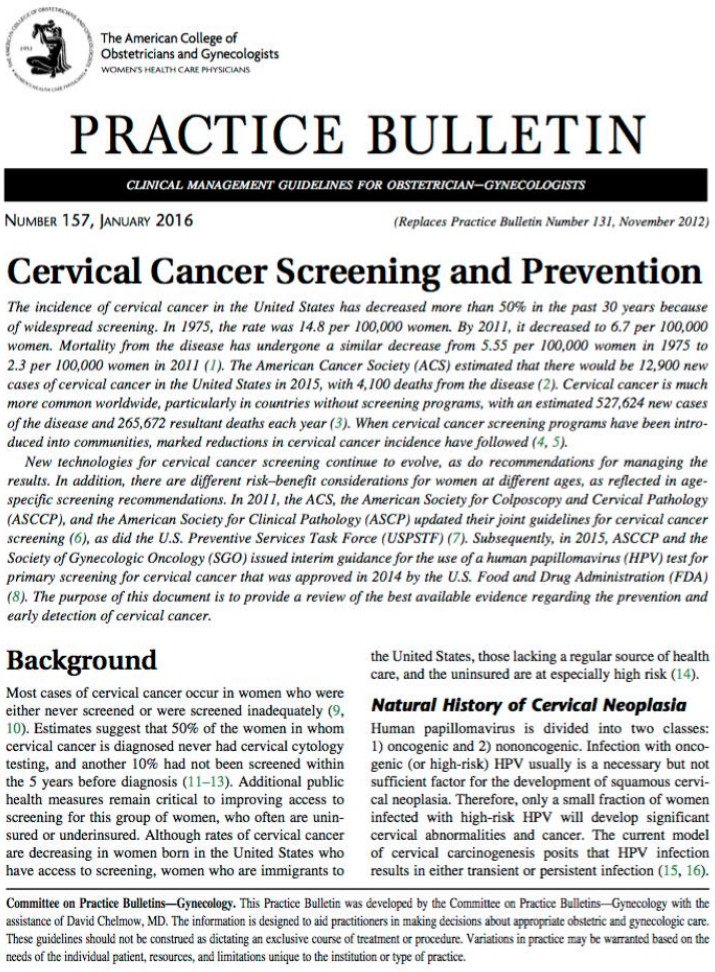
Interim Guidance - HPV Primary Screening: *SGO and ASCCP*

Other Interim Guidance

- Re-screening after a negative primary hrHPV screen should occur *no sooner* than every 3 years
- Primary hrHPV screening should not be initiated before 25 years of age
- Cytology alone and cotesting remain the screening options specifically recommended in major guidelines

Huh, W.. *et al.* (2015) Obst Gynecol

2016 Cervical Cancer Screening and Prevention Practice Bulletin: *ACOG*



The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

PRACTICE BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN–GYNECOLOGISTS

NUMBER 157, JANUARY 2016 (Replaces Practice Bulletin Number 131, November 2012)

Cervical Cancer Screening and Prevention

The incidence of cervical cancer in the United States has decreased more than 50% in the past 30 years because of widespread screening. In 1975, the rate was 14.8 per 100,000 women. By 2011, it decreased to 6.7 per 100,000 women. Mortality from the disease has undergone a similar decrease from 5.55 per 100,000 women in 1975 to 2.3 per 100,000 women in 2011 (1). The American Cancer Society (ACS) estimated that there would be 12,900 new cases of cervical cancer in the United States in 2015, with 4,100 deaths from the disease (2). Cervical cancer is much more common worldwide, particularly in countries without screening programs, with an estimated 527,624 new cases of the disease and 265,672 resultant deaths each year (3). When cervical cancer screening programs have been introduced into communities, marked reductions in cervical cancer incidence have followed (4, 5).

New technologies for cervical cancer screening continue to evolve, as do recommendations for managing the results. In addition, there are different risk–benefit considerations for women at different ages, as reflected in age-specific screening recommendations. In 2011, the ACS, the American Society for Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology (ASCP) updated their joint guidelines for cervical cancer screening (6), as did the U.S. Preventive Services Task Force (USPSTF) (7). Subsequently, in 2015, ASCCP and the Society of Gynecologic Oncology (SGO) issued interim guidance for the use of a human papillomavirus (HPV) test for primary screening for cervical cancer that was approved in 2014 by the U.S. Food and Drug Administration (FDA) (8). The purpose of this document is to provide a review of the best available evidence regarding the prevention and early detection of cervical cancer.

Background

Most cases of cervical cancer occur in women who were either never screened or were screened inadequately (9, 10). Estimates suggest that 50% of the women in whom cervical cancer is diagnosed never had cervical cytology testing, and another 10% had not been screened within the 5 years before diagnosis (11–13). Additional public health measures remain critical to improving access to screening for this group of women, who often are uninsured or underinsured. Although rates of cervical cancer are decreasing in women born in the United States who have access to screening, women who are immigrants to the United States, those lacking a regular source of health care, and the uninsured are at especially high risk (14).

Natural History of Cervical Neoplasia

Human papillomavirus is divided into two classes: 1) oncogenic and 2) nononcogenic. Infection with oncogenic (or high-risk) HPV usually is a necessary but not sufficient factor for the development of squamous cervical neoplasia. Therefore, only a small fraction of women infected with high-risk HPV will develop significant cervical abnormalities and cancer. The current model of cervical carcinogenesis posits that HPV infection results in either transient or persistent infection (15, 16).

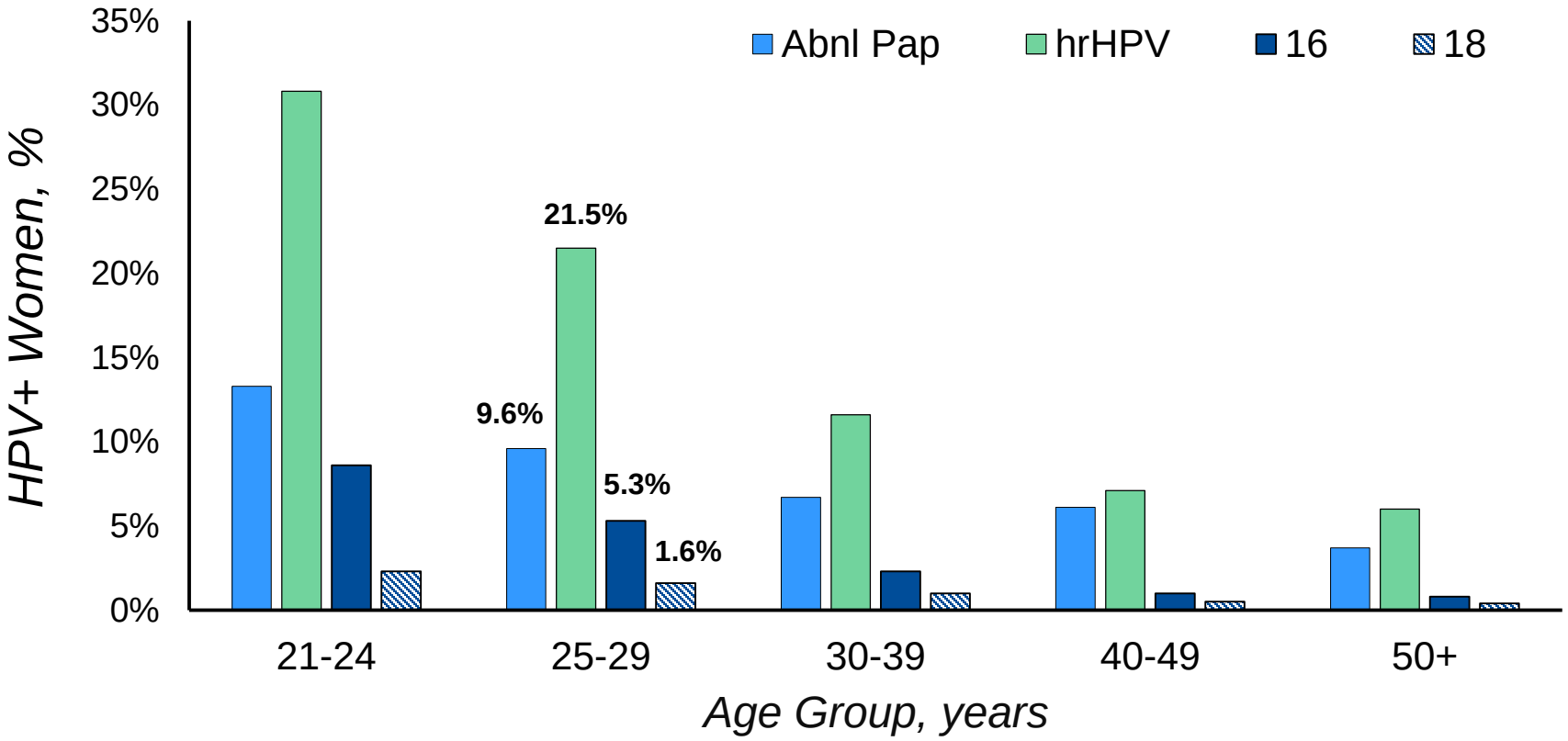
Committee on Practice Bulletins—Gynecology. This Practice Bulletin was developed by the Committee on Practice Bulletins—Gynecology with the assistance of David Chelmow, MD. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

Key Findings:

- *If screening with primary HPV testing is used, it should be performed as per the ASCCP and SGO interim guidance.*
- *Screening should stop at 65 yrs if negative screening history*
- *Should not be used in women who no longer have a cervix*
- *Cotesting is reasonable to perform at 1 yr in HPV (+) women with negative genotyping and cytology*
- *Only use the FDA-approved test*

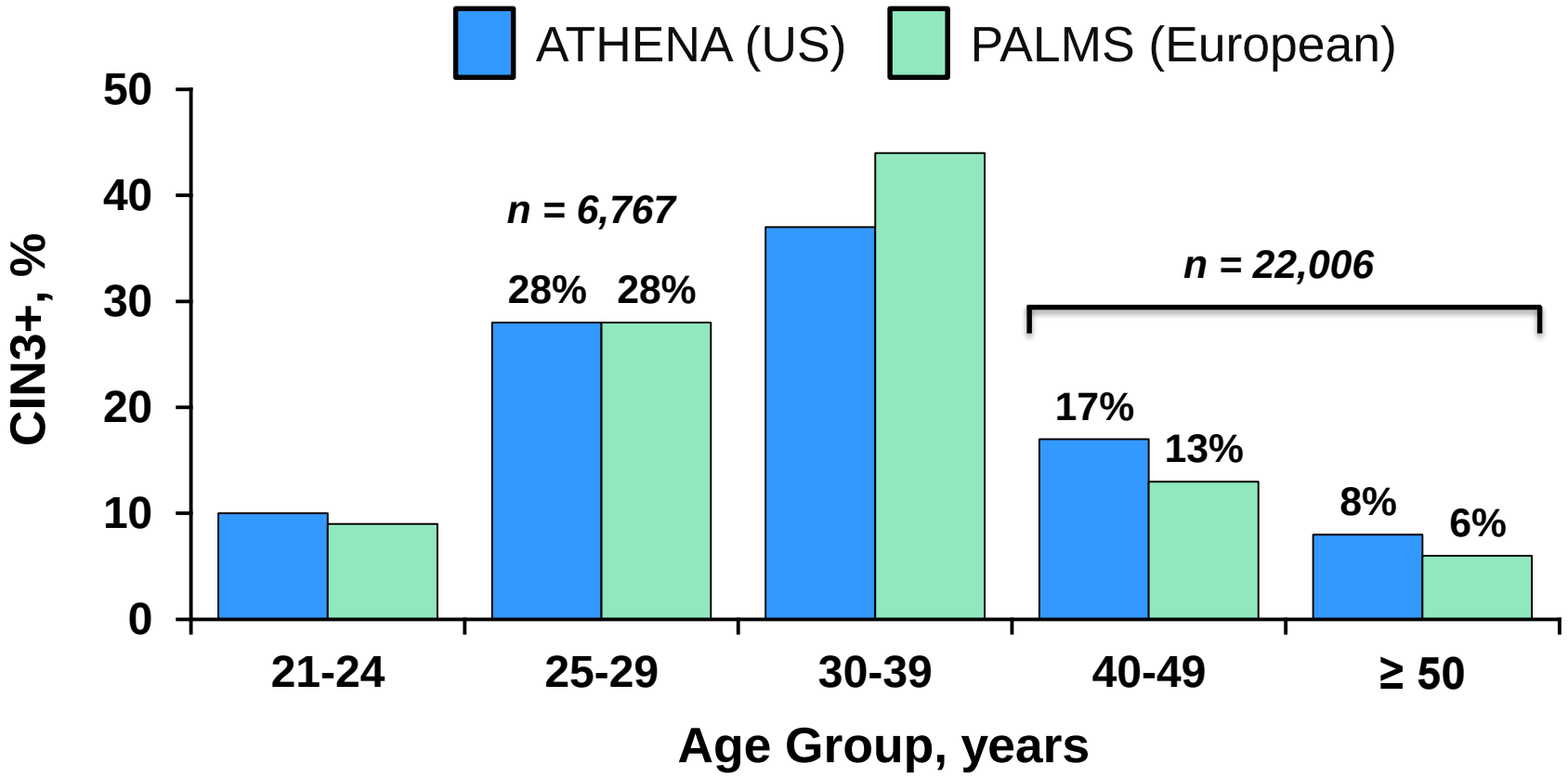
Screening Women 25-29 Years

Prevalence of hrHPV by age group - ATHENA



Wright TC Jr, et al. *Am J Obstet Gynecol*. 2011.

Prevalence of CIN 3+ by Age
Results from ATHENA and PALMS



More CIN3+ disease in women aged 25 to 29 years than in women aged ≥ 40 years

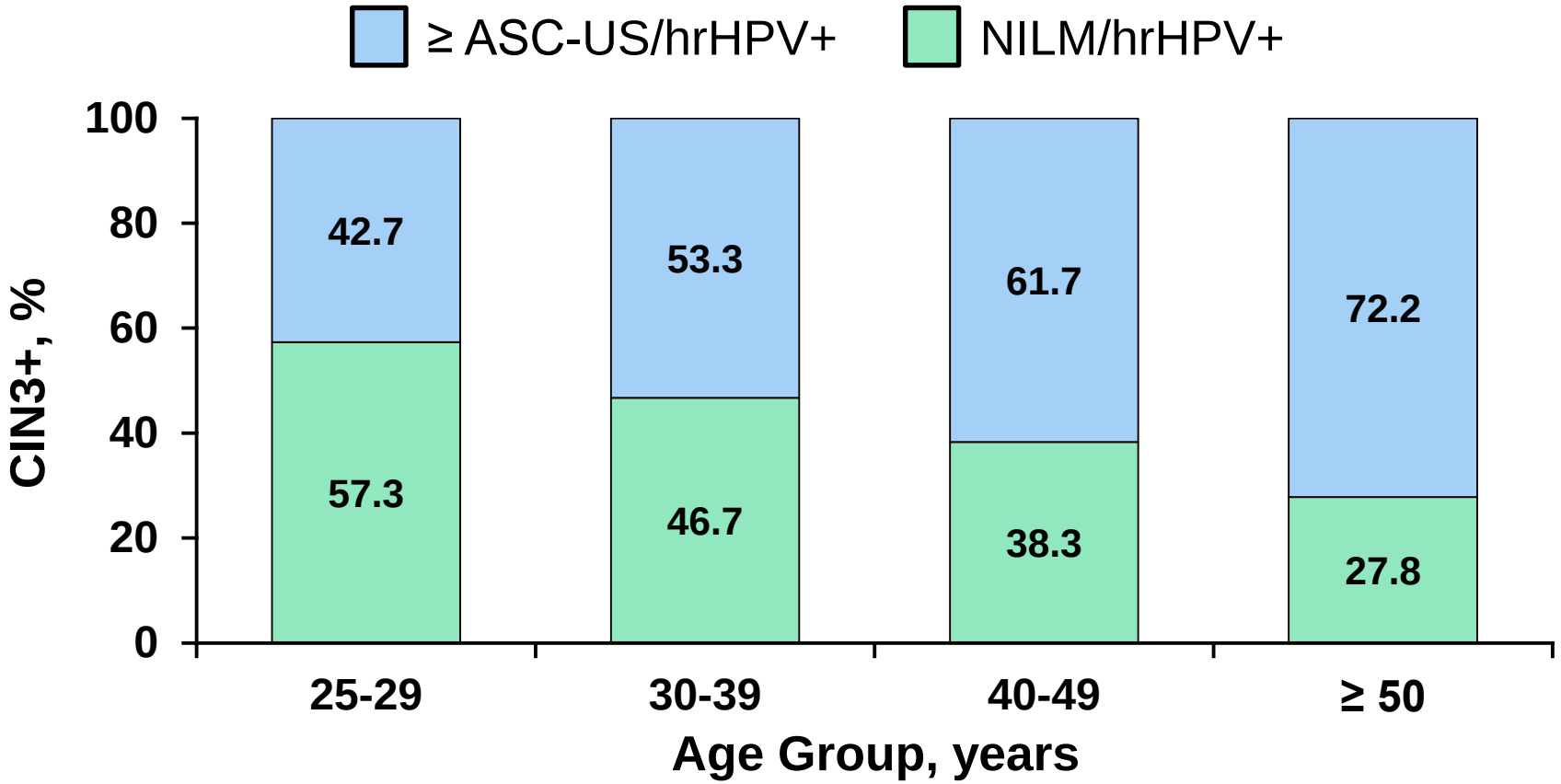
Aged 25 to 29: n = 6767 (ATHENA) and 3373 (PALMS).

Ventana, data on file.

Wright TC Jr, et al. *Am J Obstet Gynecol*. 2012;206:46.e1-46.e11.

Why Not Cytology for Women 25 -29 Yrs?

Results From ATHENA



More than half of the CIN3+ cases in the 25 - 29 age group had false-negative cytology

HPV for Primary Screening

How commonly is it being used in the U.S.?

- Adoption to date has been very slow
- There are a number of possible reasons

  No one group / agency has decision-making power on how to screen and the decision is left up to individual clinicians

  Many clinicians and patients are comfortable with cytology and do not see a reason to stop using it

  HPV primary screening not yet endorsed by USPSTF – with Affordable Care Act this is very important