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## Cervical Cancer Prevention: An Update on New Screening and Risk-Based Management Guidelines

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## Disclosures

Advisory Board:  
Astellas  
Speakers Bureau:  
Astellas

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## Objectives

1. Describe the role of persistent oncogenic HPV in the development of pre-cancer and cancer of the cervix
  2. List two different uses of HPV testing in cervical cancer screening including co-testing and HPV testing as primary stand-alone screening
  3. Understand how HPV epidemiology drives risk-based cancer prevention
  4. Understand why risk-based management represents an improvement in care
  5. Learn fundamentals of risk-based guidelines for managing patients
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## Goal of Cervical Cancer Screening

- Prevent morbidity and mortality from cervical cancer by:
  - Identifying and treating high-grade cervical cancer precursors
  - Avoiding unnecessary and potentially hazardous evaluations and treatment
  - Minimizing costs to healthcare system

*Increase benefit and decrease harm!*

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Seastrom D, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. J Low Genit Tract Dis. 2012;16(3):175-204.

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## Key Facts In the Natural History of HPV

For management and counseling

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## HPV and Cervical Cancer

**Virtually all cervical cancers are associated with persistent infection with high-risk HPV types**

- Data from a variety of studies have confirmed that certain HPV types are associated with cervical cancer: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
- Others are probably associated: 26, 53, 66, 68, 73, 82

**Oncogenic HPV is a necessary cause of cervical cancer!**

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IARC. Monographs on the Evaluation of Carcinogenic Risks to Humans. (in press);  
Munoz N. Vaccine. 2006.

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## Role of Persistent Infection

- **Persistent infection with high-risk types of HPV is necessary for the progression of high-grade lesions to invasive cancer**
- Average episode lasts 4-20 months
- <50% of women have same type 1 year later
- Type 16 has a greater risk of persistence

Most HPV infection will go away in a short period of time.

McClure W. et al. Persistent genital human papillomavirus infection as a risk factor for persistent cervical dysplasia. *J Natl Cancer Inst.* 1995;87(10):1305-1371.  
Trotter H. Vaccine. 2006.

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## HPV-Associated Disease

- Anogenital cancers
- Cervical
- Anal
- Vulvar and vaginal
- Penile
- Other cancers
- Oral cavity, pharynx, larynx
- Skin
- Conjunctiva
- External genital warts
- Laryngeal papillomatosis

Munoz N. Vaccine. 2006; Lacey CJN. Vaccine. 2006.

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## High Lifetime Risk of HPV Infection

- 6.2 million new infections
- NHANES 2003-2004 reports a prevalence rate of 26.8% in US females age 14 -59
- Approximately 75% lifetime risk for sexually active individuals

Most everyone who is sexually active will be infected by HPV at some point!

Cates W. *Sex Transm Dis.* 1999; Weinstock H. *Perspect Sex Reprod Health.* 2004; Koutsky L. *Am J Med* 1997; Dunne EF. *J Infect Dis.* 2006; Dunne EF. *JAMA.* 2007.

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## CLINICAL EXPRESSIONS OF HPV

Subclinical and Active Disease  
Benign and Neoplastic Disease

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## Condylomata Acuminata: Male



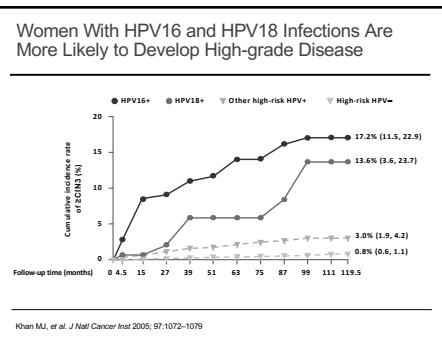
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## Risk Factors for Persistent HPV Infection and/or Neoplastic Progression

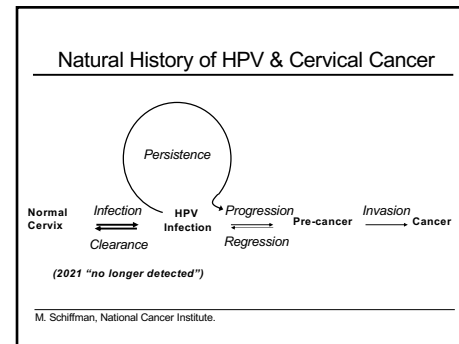
- Smoking
- HPV type
- Increasing age
- Lack of condom use
- Immunodeficiency (eg, HIV)
- Possibly OC use
- Possibly other STIs, such as chlamydia

Moscicki A.B. Vaccine. 2006; Moscicki A.B. *J Infect Dis.* 2004; Hogewoning CJ. *Int J Cancer.* 2003.

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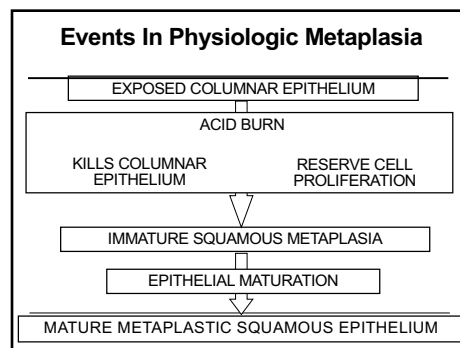
### Why Is the Cervix At Risk

#### Understanding Transformation Zones

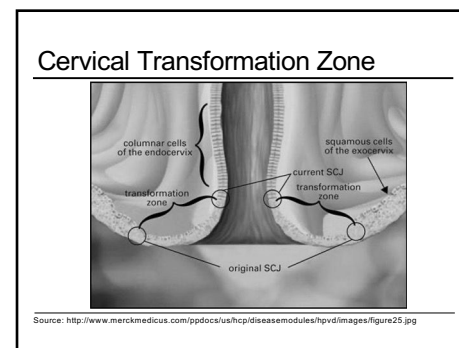
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- ### Transformation Zones and HPV Infection
- Area where one type of epithelium contacts and gradually replaces another through process of metaplasia
  - Present in cervix, anus, tonsils
  - Areas of HPV-related carcinogenesis
- Moscicki AB. Vaccine. 2006.

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## New Screening and Risk-Based Management Guidelines

- Increased knowledge of the natural history of HPV infection has allowed the evolution of screening and management guidelines.
- The role of HPV testing has increased in screening and management.
- There is a paradigm shift from results-based management to risk-based management.
- The management guidelines are available through a phone-based app for purchase or a free web version.

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## Current Approach to Cervical Cancer Prevention

Requires four separate but linked components:

- HPV vaccination
- Screening
  - Cytology with or without HPV testing
  - Stand alone HPV testing: Primary HPV Screening
- Evaluation of screen-positive women using colposcopy and cervical biopsy
- Treatment of women with biopsy-confirmed high-grade cervical cancer precursors
  - Expedited treatment of the highest risk women

Adapted from: "New HPV Test" [Article]. The New York Times. 2014. Available from: <http://www.nytimes.com/2014/01/16/health/new-hpv-test.html>. Accessed Jan 16, 2014.

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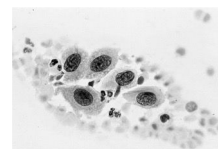
## Change Has Come!

*New 2020 American Cancer Society Screening Guidelines Have Changed From 2012!*

Current ASCCP, ACP and USPSTF Guidelines for Screening Remain the Same

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## 2012 ACS/ASCCP/ASCP Cervical Cancer Screening Guidelines



Saidin D, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. J Low Genit Tract Dis. 2012;16(3):175-204.

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## Factors Indicating Need for More Frequent Screening

- HIV infection
- Immunosuppression
- DES exposure in utero
- Previous treatment for CIN 2, CIN 3, or cancer

ACOG Practice Bulletin #109. 2009

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## Age to Start Cervical Cancer Screening

Factors to consider:

- HPV infections are common in young women
- Cervical cancer is rare in adolescents/young women
- Evaluation of minor cytological abnormalities:
  - Is expensive
  - Causes anxiety
  - Can lead to unnecessary treatments

ACOG Committee on Gynecologic Practice. Obstet Gynecol. 2006.

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## Current Cervical Cancer Screening Strategies From the USPSTF and ACS

Patient population	USPSTF (2018)	ACS (2020)
<21 y old	No screening	No screening
21–25 y old	Cytology alone every 3 y	<b>Preferred:</b> • Primary HPV * test every 5 y
25–29 y old		Acceptable: † • Cytology alone every 3 y
30–65 y old	• Cytology alone every 3 y • Cytology + HPV * every 5 y • Primary HPV * test every 5 y	• Cytology alone every 3 y
>65 y old	No screening necessary after adequate negative prior screening ‡	
Prior total hysterectomy	No screening necessary in those without a history of high-grade cervical dysplasia or cervical cancer	No screening necessary in those without a history of CIN 2+ or a more severe diagnosis in the past 25 y or cervical cancer ever
Prior HPV vaccination	Follow age-specific recommendations	

Table 1. Current Cervical Cancer Screening Strategies From the USPSTF and ACS  
Screening and management recommendations are based on:  
 \*Screening in cytology and HPV testing.  
 †Screening in cytology and HPV testing is not available.  
 ‡Adequate negative prior screening is defined as 1 consecutive negative primary HPV tests, 2 negative cytology tests, or 3 negative cytology tests within the last 10 years, and the most recent in the past 5 years.

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## The ASCCP Cervical Cancer Screening Task Force Endorsement and Opinion on the American Cancer Society Updated Cervical Cancer Screening Guidelines

- The ASCCP recognizes the need **to move toward primary HPV-based cervical cancer screening**
- Acknowledges that it will take time to transition clinical and laboratory workflow and operations.
- **The ASCCP no longer endorses its 2012 cervical cancer screening guidelines screening that do not include primary HPV**
- The combination of abnormal results that occur from either guidance should be managed using the **2019 ASCCP Risk-Based Management Consensus Guidelines**.

Mancoske, Jenna Z. MD<sup>1</sup>, Cannon, Kelly R. MD, PhD, BC<sup>2</sup>, Dwyer, Levi S. Jr. MD, MS<sup>3</sup>, Edwards, Mark H. MD, MS<sup>4</sup>, Flowers, Lisa MD<sup>5</sup> The ASCCP Cervical Cancer Screening Task Force Endorsement and Opinion on the American Cancer Society Updated Cervical Cancer Screening Guidelines. Journal of Lower Gastrointestinal Disease. July 2021 - Volume 25 - Issue 3 - p 187-191 doi: 10.1097/LGI.000000000000014

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## American College of Obstetricians and Gynecologists (ACOG) Practice Advisory 4/21

Replaces Practice Bulletin No. 168, October 2016

- Adoption of the USPSTF guidelines which **expands** the recommended options for cervical cancer screening in average-risk individuals aged 30 years and older
- **Includes screening every 5 years with primary high-risk human papillomavirus (hrHPV) testing**
- Consistent with prior guidance, screening should begin at age 21 years
- Screening recommendations remain unchanged for average-risk individuals aged 21–29 years and those who are older than 65 years
- Management of abnormal cervical cancer screening results **should follow current ASCCP guidelines**

ACOG (2021). "Practice Advisory: Updated Cervical Cancer Screening Guidelines." from <https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2021/04/updated-cervical-cancer-screening-guidelines>

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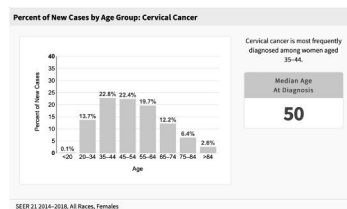
## American College of Obstetricians and Gynecologists (ACOG) Practice Advisory 4/21

Screening start age:

- Raising the screening start age to 25 years could:
  - Increase the already high rate of underscreening among individuals aged 25–29 years
  - Exacerbate existing health inequities in cervical cancer screening, incidence, morbidity, and mortality
- **ACOG, ASCCP, and SGO continue to recommend initiation of cervical cancer screening at age 21 years.**

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## Cervical Cancer by Age Group



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## Role of All Professionals...

Advocate for evidenced based guidelines!

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Avoid “OVERPAPULATION”  
Follow Guidelines!

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Neil Lomky ASCCP Biennial Meeting 2008

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## HPV Testing

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## Why Test for HPV?

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- Persistent high risk HPV is necessary for the development of cervical cancer
- An obvious corollary is that the absence of HPV means that the risk of cervical cancer is negligible

*The negative predictive value for combined HPV Testing and the Pap has been shown to be 99.21% for CIN3.*

Sherman ME, et al. J Nat Cancer Inst. 2003;95:46-52.

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## HPV Testing for Screening: Stratifies Risk

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- Allows for less frequent testing
- Identifies women who need increased surveillance

Wright TC. Obstet Gynecol. 2004. Katki HA et al. Lancet Oncol. 2011.

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## HPV Detection with FDA-Approved Tests

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- Five tests are currently FDA approved and commercially available in the US
- Two are approved for primary, stand-alone screening

*more...*

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## FDA Approved HPV Tests

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Available Tests	HPV Types Detected	Identifies HPV Type
Hybrid Capture 2	High and low risk panels (request high risk only)	No
Cervista HPV HR	High risk	No (add on test for 16 and 18)
cobas HPV Test	High risk	Yes for 16 and 18
APTIMA HPV mRNA assay	High risk	No (add on test for 16, 18, and 45)
Onclarity	High risk	Yes for 16, 18, 45

ASCCP. Educate the Educators: HPV and the HPV Vaccines. 2018

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## HPV Testing

FDA approved uses in screening:

- ASC-US Triage
  - Preferred age 25-65
  - Acceptable age 21-24 but does not change management if positive
  - Genotyping is not a factor in management
- Co-testing: Pap and HPV (age 30 and older)
  - Genotyping may be used to stratify management
- Primary HPV (Stand alone: age 25 and older)
  - FDA approved for only two HPV tests at this time
  - Genotyping is reported on all tests

Saslow D, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. J Low Genit Tract Dis. 2012;16(3):175-204.

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## HPV Testing

Other uses of HPV testing:

- Post abnormal screening and colposcopy follow-up
  - See guidelines<sup>1</sup>
- Follow-up after cervical treatment

1. Measured LS, EINSTEIN MH, Huh WK, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. Obstetrics and gynecology. 2012;121(5):829-846. 1988;33(7):423-429.

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## Co-Testing: Pap and HPV

Women 30 and Older

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## 2012 Guidelines: Screening for Women Ages 30-65

- Cytology + hrHPV testing (cotesting) every 5 years is preferred
- Cytology alone every 3 years is acceptable

Saslow D, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. J Low Genit Tract Dis. 2012;16(3):175-204.

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## Rationale for Cotesting Ages 30-64

- Increased detection of prevalent CIN3
- Decreased CIN3 in subsequent screening rounds
- Achieves risk of CIN3 equal to cytology alone @ 1-3 year intervals
- Enhances detection of adenocarcinoma/AIS
- Minimizes the increased number of colposcopies, thus it reduces harms.

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## ACS/ASCCP/ASCP

"...health care providers can rely on the negative predictive value of the HPV test to assure women who cotest negative that they are at very low risk for CIN3 and cancer for at least 5 years after negative cotesting."

Saslow D, et al. Ca J Clin. 2012.

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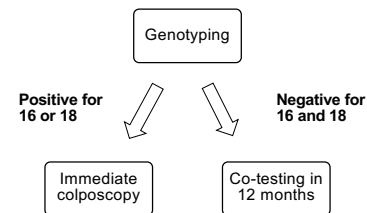
### Screening Interval for Combined Pap and HPV Testing in Women 30 and Older: Co-Testing

HPV Result	Cytology	Recommended Management
Negative	Negative	Cotest in 5 years
Negative	ASC-US	Cotest in 3 years
Positive	ASC-US	Colposcopy
Negative	LSIL	Repeat cotesting in 1 year preferred; colposcopy acceptable
Positive	Pap ≥ LSIL	Colposcopy
Any	HSIL	Colposcopy or immediate loop electrosurgical excision
Positive	Negative	Option 1: Cotest in 12 months Option 2: Reflex to genotyping for HPV 16/18. If positive, colposcopy. If negative, cotest in 12 months

Massad LS, et al. *J Low Genit Tract Dis*. 2013; Saslow D. *CA Cancer J Clin* 2012.

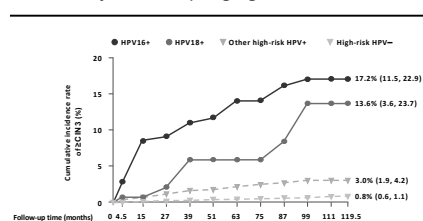
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### Genotyping to Triage Women ≥30 with Pap-/HPV+ Results



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### Women With HPV16 and HPV18 Infections Are More Likely to Develop High-grade Disease



Khan MJ, et al. *J Natl Cancer Inst* 2005; 97:1072-1079

45

### Management of Repeat Testing After HPV +, Cytology - Results

HPV Result	Cytology	Recommended Management
Negative	Negative	Repeat cotesting in 3 years
Positive	Negative	Perform colposcopy
Any	Pap ≥ ASC-US	Perform colposcopy

Massad LS, et al. *J Low Genit Tract Dis*. 2013; Saslow D. *CA Cancer J Clin* 2012.

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### Primary HPV Screening

Stand-alone HPV test  
FDA Approved in 2014 for 25 years and older

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### FDA Approved HPV Tests

Available Tests	HPV Types Detected	Identifies HPV Type
Hybrid Capture 2	High and low risk panels (request high risk only)	No
Cervista HPV HR	High risk	No (add on test for 16 and 18)
cobas HPV Test	High risk	Yes for 16 and 18
APTIMA HPV mRNA assay	High risk	No (add on test for 16, 18, and 45)
Onclarity	High risk	Yes for 16, 18, 31, 45, 51, 52

ASCCP. *Educate the Educators: HPV and the HPV Vaccines*. 2018

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## Primary HPV: Available Testing Platforms

Primary HPV test	Year FDA approved	Individual genotypes reported	Pooled genotypes reported
cobas HPV	2014	16, 18	31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68
Onclarity HPV	2018	16, 18, 31, 45, 51, 52	Grouped results: 33, 58, 35, 39, 68, 56, 59, 66

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## 2014 FDA Approval for Primary HPV Testing for Cervical Cancer Screening

### Rationale

- More sensitive and reproducible than cytology
- Assesses current and future risk
- More cost-effective for large-volume screening
- May be more useful in women vaccinated against HPV

Educate the Educator: ASCCP 2016

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## Why HPV Primary Screening?

Co-testing (Pap and HPV testing) is only marginally better than HPV testing alone!

Cao JT, et al. Comparison of cervical cancer screening strategies incorporating different combinations of cytology, HPV testing, and genotyping for HPV 16/18: results from the ATHENA HPV study. *Am J Obstet Gynecol*. 2013;208(3):184 e181-184 e111.

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## Importance of Genotyping for HPV 16 & 18

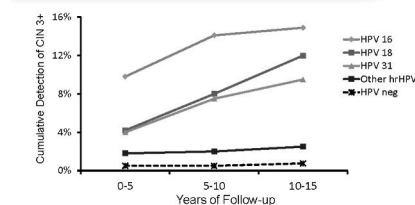
- Over two thirds of cervical cancers in the United States are caused by HPV 16 & 18
- Other individual high-risk HPV genotypes are associated with far fewer cancers
- Persistent HPV 16 infection confers a very high risk for CIN 3+, as shown in multiple long-term studies

Wright TC Jr, et al. Evaluation of HPV-16 and HPV-18 genotyping for the triage of women with high-risk HPV+ cytology-negative results. *Am J Clin Pathol*. 2011;136(4):576-586.

Ronco G, et al. HPV16 and HPV18 genotyping in cervical cancer screening. *Lancet Oncol*. 2011;12(9):831-832.

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## Predictive Value of HPV Genotyping 15-y risk of CIN 3+ in Kaiser Northwest cohort



Educate the Educator: ASCCP 2016

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## ATHENA: Addressing the Need for Advanced HPV Diagnostics

- Prospective, multicenter, US-based study of 47,208 women aged 21 and older
- Recruited at time of routine screening
- 2.6% had been vaccinated against HPV
- Screened by liquid based cytology and HPV test

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):189-197.

Wright TC, Jr, et al. The ATHENA human papillomavirus study: design, methods, and baseline results. *Am J Obstet Gynecol*. 2015;208(1):60.e1-46.e11.

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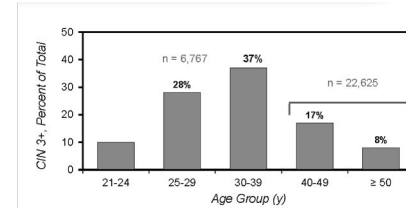
### Absolute Risk of CIN in Cytology: Negative Women ≥ 30 years, Athena Study

HPV Status	CIN 2+	CIN 3+
High-risk HPV-	0.9%	0.3%
High-risk HPV+ (pooled)	6.3%	4.1%
High-risk HPV 16/18+	11.7%	9.9%
Other 12 High-risk HPV+	4.7%	2.5%

Wright TC, Stoler MH, Behrens CM, 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):189-197. Educate the Educator ASCCP 2016

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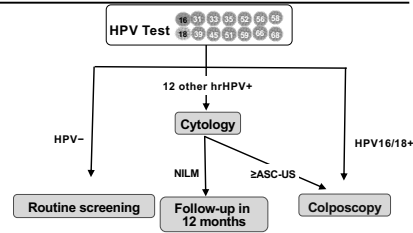
### Proportion of CIN3 by Age Group Athena Trial: Why Start Primary Screening at Age 25



Wright TC, Stoler MH, Behrens CM, 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):189-197. Educate the Educator ASCCP 2016

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### 2015 The HPV Primary Screening Algorithm: Published when only the cobas test was approved for primary screening



\*\*\*\*\* 2019 All positive HPV tests, regardless of genotype, should have additional reflex triage testing performed from the same laboratory specimen (e.g., reflex cytology).

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### 2019 ASCCP Risk-Based Management Consensus Guidelines For Abnormal Cervical Cancer Screening Tests

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### Original ASCCP Application



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### Risk-Based Management Guidelines

Goals are to increase accuracy and reduce complexity for providers and patients

Development of Guidelines by 19 Participating Organizations

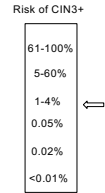
The 2019 guidelines are designed to be enduring, unlike prior versions which required major updates every 5-10 years to adjust for new technologies and emerging evidence.

Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Guidelines for abnormal cervical cancer screening tests and cancer pre-cursors. *J Low Genit Tract Dis*. 2020;24(2):102-121

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### New Risk-Based Algorithm: Should improve cancer prevention AND decrease unnecessary testing

- Provider enters woman's current test results and past history
- Risk matrix is used to calculate her risk of CIN2/3
- Computer algorithm generates risk score



Presentation given by Dr. Richard Gade at the April 2018 ASCCP Annual Meeting in Las Vegas, NV

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### What Data Were Used/ How Do We Know They Are Representative?

Kaiser Permanente Northern California Data (KPNC)

- Largest/longest real clinical experience with HPV-based screening in the world
- Over 1.5 million women with routine cotesting from 2003-2017
- HPV genotyping for ~19,000 patients
- Provides risk-based evidence for most of the common decision points that occur in screening
- Long length of follow-up allows use of past-history for more personalized management

Cheung LC et al J Low Genit Tract Dis 2020;24(2):90-101.

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### Which Risk Factors Influence Pre-Cancer Development?

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### HPV Vaccination: Important But NOT Included (yet)!

HPV vaccination prior to age 18 reduces the CIN3+ risk by 50%

HOWEVER:

- Current cohort is 21-24 years, a group already conservatively managed.
- 50% age eligible female first dose vaccine population coverage achieved 2015
- Documentation of vaccination and age at which vaccine is necessary to apply this factor correctly—*historically guidelines have not included factors clinicians can't document*
- Management will likely change as vaccinated cohorts age

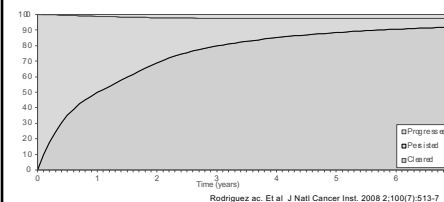
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### Fundamental Concept #1

- The longer an HPV infection has been present, the higher the risk of pre-cancer and cancer
- Time matters
- Type matters (HPV 16 most dangerous)
- Other patient factors don't matter if you know about HPV
- CLINICAL CORRELATE: Colposcopy is always needed following two consecutive positive HPV tests

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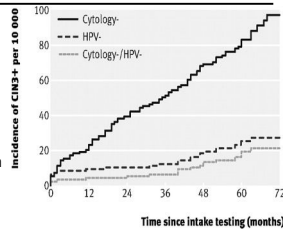
### Most HPV Infections Become Undetectable in 1-3 years: Those That Persist Cause CIN3+ Over Time



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## HPV-Based Screening Is Better Than Cytology Alone

- Cytology (Pap testing) is less sensitive than HPV testing
- Detects 50-70% of CIN3+ vs >90%
- Cytology alone does not confer long-term protection against CIN3+ following a negative test



Obstet. Gynecol. 2008 Oct 13;337:1754

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## HPV Testing is Necessary for Proper Management

- HPV infections cause nearly all cervical cancers
- HPV testing is a key component of care
- More precise management is possible when patients are tested

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## New Guidelines Prefer HPV Testing for Follow Up

- Surveillance with cytology alone is acceptable *only* if testing with HPV or cotesting is not feasible.
- Cytology is less sensitive than HPV testing for detection of precancer and is therefore recommended more often.
- **Cytology is recommended at 6-month intervals when HPV testing or cotesting is recommended annually.**
- **Cytology is recommended annually when 3-year intervals are recommended for HPV or cotesting.**

Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Guidelines for abnormal cervical cancer screening tests and cancer pre-cursors. J Low Genit Tract Dis. 2020;24(2):102-131

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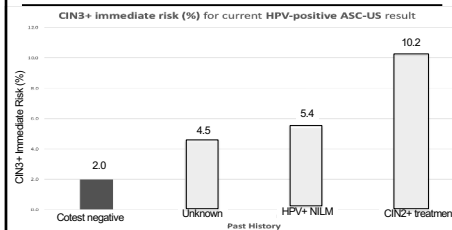
## Fundamental Concept #2: Management is Based on Risk, Not Results

- Recommendations of colposcopy, treatment, or surveillance are based on a patient's risk of CIN3+ determined by a combination of **current results** and **past history** (*including unknown history*).
- The same current test results may yield different management recommendations depending on the history of recent/past test results and other risk factors.

Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Guidelines for abnormal cervical cancer screening tests and cancer pre-cursors. J Low Genit Tract Dis. 2020;24(2):102-131

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## Past History Influences Current Risk



Eggen D, Chuang LC, et al. Risk Estimates Supporting the 2019 ASCCP Risk-Based Management Consensus Guidelines. J Low Genit Tract Dis. 2020;24(2):132-143

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## Risk Thresholds for CIN3 and Management

- **Recommendation for colposcopy, treatment, or surveillance is based on a patient's risk of having CIN3+**
- This risk is calculated within an algorithm with the patient's current results and any previous results that are available put into an app
- The algorithm is designed to provide the risk-based information with as much or as little previous history as known

Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Guidelines for abnormal cervical cancer screening tests and cancer pre-cursors. J Low Genit Tract Dis. 2020;24(2):102-131

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## Risk Thresholds for CIN3 and Management

- If the risk for CIN3 is 4% or higher, clinical actions will fall into the categories of colposcopy or expedited treatment
- For patients with a highest risk of 60% or higher, it is preferred to proceed directly to expedited excisional treatment without colposcopy
- Patients with risk between 25% and 59% can choose between expedited treatment or colposcopy

Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Guidelines for abnormal cervical cancer screening tests and cancer pre-cursors. J Low Genit Tract Dis. 2020;24(2):102-131

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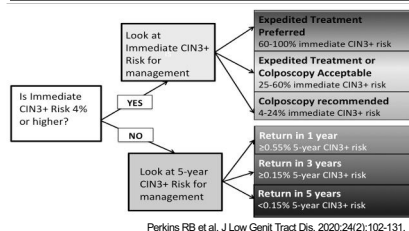
## Risk Thresholds for CIN3 and Management

- In patients with a 4% to 24% risk: colposcopy is preferred
- Patients with a risk below 4% are managed with surveillance: repeat HPV testing or cotesting at 1, 3, or 5 years that is determined by the estimated 5-year CIN3 risk

Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Guidelines for abnormal cervical cancer screening tests and cancer pre-cursors. J Low Genit Tract Dis. 2020;24(2):102-131

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## Patients Stratified Into Risk Levels



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## 2019 Management Guidelines Highest Risk Patients Receive Expedited Treatment

- High-grade cytology with HPV16 infections are highest risk
- Excisional treatment for patients at high risk of pre-cancer without requiring confirmatory biopsy

Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Guidelines for abnormal cervical cancer screening tests and cancer pre-cursors. J Low Genit Tract Dis. 2020;24(2):102-131

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## Changes to Follow-up After Treatment of CIN2/3

- HPV-based testing at 6 months, then annually for 3 years
- **Continued surveillance with HPV testing or co-testing at 3-year intervals for at least 25 years**
- Continued surveillance at 3-year intervals beyond 25 years is acceptable as long as the patient's life expectancy and ability to be screened are not significantly compromised by serious health issues.

*Note: 2012 guidelines recommended return to 5-yr screening intervals and did not specify when screening should cease. New evidence indicates that risk remains elevated for at least 25 yrs, with no evidence that treated patients ever return to risk levels compatible with 5-yr intervals.*

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## ASSUMPTION: Intervals for retesting should reflect underlying risk (equal management for equal risks)

The goal was to:

- Define surveillance intervals
- Define threshold to release patients back to general population screening
- Define risk thresholds for short interval follow up at 1 and 3 years
- Determine which tests to use for surveillance and at what intervals
- HPV alone, HPV/cytology cotesting, cytology (Pap) alone

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### 5-year Return Clinical Action Threshold

Guideline:

- When patients have an estimated 5-year CIN3+ risk of <0.15% based on past history and current test results:
  - Return to routine screening at 5-year intervals using HPV-based testing is recommended.
- *Note HPV-based testing is cotesting or primary HPV testing*

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### 3-year Return Clinical Action Threshold

Guideline:

- When patients have an estimated 5-year CIN3+ risk  $\geq 0.15\%$  but <0.55% based on past history and current test results:
  - Repeat testing in 3 years with HPV-based testing is recommended
- *Note HPV-based testing is cotesting or primary HPV testing*

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### 1-year Return Clinical Action Threshold

Guideline:

- When patients have an estimated risk of CIN3+ based on past history and current result that is below the threshold for immediate colposcopy (4.0% immediate risk) and above the 3-year follow-up threshold ( $\geq 0.55\%$  at 5 years):
  - Repeat testing in 1 year with HPV-based testing is recommended
- *Note HPV-based testing is cotesting or primary HPV testing*

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### Personalized Recommendations Improve Management

- Expedited diagnosis and treatment for *high-risk* patients
- Fewer invasive procedures on *low-risk* patients

Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis 2020;24:102-31.

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### Patients at High-Risk

- Should be referred for expedited treatment
- Specific combinations of test results are so high-risk that patients should proceed directly to a diagnostic excisional procedure (LEEP)
  - HPV 16+ HSIL
  - HPV-positive HSIL in patients who are underscreened (defined as no screening in more than 5 years)

Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis 2020;24:102-31.

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### Patients at Medium Risk Should be Referred for Colposcopy

- Patients who are HPV+ twice in a row
- Any HPV16 or HPV18 positive
- Any high-grade Pap result (ASC-H, AGC, HSIL)
  - Even if HPV results are negative
- Low-grade Pap results that are HPV positive (ASC-US or LSIL)
  - Unless preceded by a negative HPV screening test or co-test within 5 years or by a normal colposcopy within 1 year

Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis 2020;24:102-31.

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### Fundamental Concept #3

After an abnormal result, patients enter a surveillance period of close follow up

- All abnormalities require an initial period of intensive surveillance followed by a longer period of surveillance at 3 year intervals

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### For Individuals of Average Risk Who Have a Cervix

All positive HPV tests, regardless of genotype, should have additional reflex triage testing performed from the same laboratory specimen (e.g., reflex cytology).

- Additional testing from the same laboratory specimen is recommended because the findings may inform colposcopy practice.
- For example:
  - Those with HSIL cytology and concurrent positive testing for HPV genotype 16 qualify for expedited treatment.

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### Key changes to 2015 Primary HPV Testing Interim Guidance

- HPV 16 or 18 infections have the highest risk for CIN3 and occult cancer, so additional evaluation (e.g., colposcopy with biopsy) is necessary even when cytology results are negative.
- If HPV 16 and 18 testing is positive, and additional laboratory testing of the same sample is not feasible, the patient should proceed directly to colposcopy.

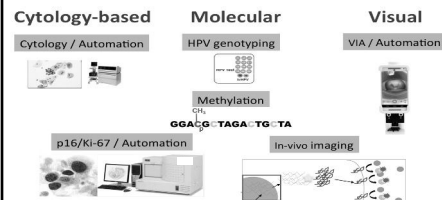
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### Enduring: Accommodates New Tests in Development

- Establishment of risk-based thresholds means that new tests can be evaluated against existing thresholds instead of making new algorithms for each new test
- Test characteristics will be objectively compared to existing Clinical Action Thresholds
- Standardized, transparent clinical guidance will logically follow from test characteristics and existing consensus thresholds
- Reduces the need for interim guidance and frequent consensus conferences

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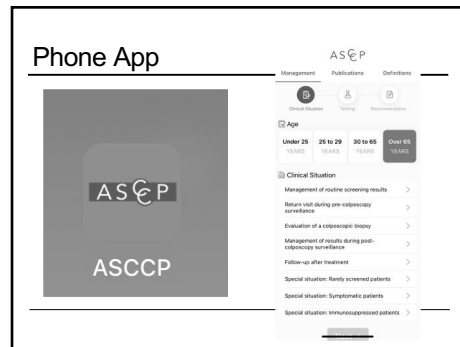
### Enduring: Accommodates New Tests in Development



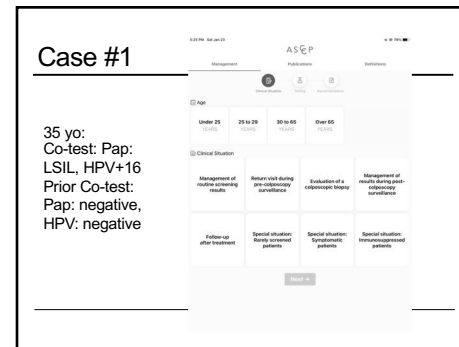
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### Putting the Risk Based Guidelines to Use

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### Case #2

41yo:  
Pap: ASC-US  
HPV+: Other  
(not 16/18)  
No previous  
screening results  
known.

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### Case #2

98

### Case #2

99

### Case #2

100

### Case #3

44yo:  
Pap: HSIL  
HPV+ 16

101

### Case #3

102



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### Summary

The new guidelines for cervical cancer prevention:

- More benefit with least harm (over screening)
- Identifies low risk women (HPV and Pap negative) and reassures them about safety of longer screening interval
- Identifies truly at-risk women *with persistent HPV* ... Follow them diligently
- FDA approval of HPV testing as a primary screen, April 2014
- 2019 Risk-based Guidelines: simplify management
- 2019 Risk-based Guidelines: enduring as new tests can be added over time

Never has education of patients and clinicians been more ~~important~~

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### Summary

- Majority of cervical cancer in U.S. occurs in women who have not been screened or infrequently screened

*Improving access to screening for these women will have a great impact on the prevention of cervical cancer!*

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### THANK YOU!

### QUESTIONS?

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### References

1. Cheung LC, Egemen D, Chen X, et al. 2019 ASCCP risk-based management consensus guidelines: methods for risk estimation, recommended management, and validation. J Low Genit Tract Dis 2020;24:90-101.
2. Demarco M, Egemen D, Raine-Bennett TR, Cheung LC, Befano B, Poltras NE, Lorey TS, Chen X, Gage JC, Castle PE, Wentzensen N, Perkins RB, Guido RS, Schiffman M. A Study of Partial Human Papillomavirus Genotyping in Support of the 2019 ASCCP Risk-Based Management Consensus Guidelines. J Low Genit Tract Dis. 2020;24(2):144-147.
3. Dillner J, Rebolj M, Birembaut P, ... stifter T. Joint European Cohort Study. Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study. BMJ. 2008 Oct 13;337:a 1764.
4. Egemen D, Cheung LC, Chen X, et al. Risk estimates supporting the 2019 ASCCP Risk-Based Management Consensus Guidelines. J Low Genit Tract Dis 2020;24:132-43.
5. Demarco M, Egemen D, Raine-Bennett TR, et al. A study of partial human papillomavirus genotyping in support of the 2019 ASCCP risk-based management consensus guidelines. J Low Genit Tract Dis 2020;24:144-7.

107

### References

6. Perkins RB, Fuzzell LN, Lake P, McIntyre M, Nayar R, Saraiya M, Loukissas J, Felder T, Guido RS, & Vadaparampil ST. Incorporating Stakeholder Feedback in Guideline Development for the Management of Abnormal Cervical Cancer Screening Tests. J Low Genit Tract Dis. 2020;24(2):167-177.
7. Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis 2020;24:102-31.
8. Pierce Campbell CM, Menezes LJ, Paskett ED, Giuliano AR. Prevention of Invasive Cervical Cancer in the United States: Past, Present, and Future Cancer Epidemiology and Prevention Biomarkers Sep 2012, 21 (9) 1402-1408
9. Risk Estimates Supporting the 2019 ASCCP Risk-Based Management Consensus Guidelines. <https://www.nclm.nih.gov/RiskTables/>
10. Huh WK, Ault KA, Chelmow D, et al. Use of Primary High-Risk Human Papillomavirus Testing for Cervical Cancer Screening: Interim Clinical Guidance. Obstet Gynecol. 2015;125(2):330-337.

108

## References

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10. Mesicki AB, Cox JT. *J Low Genit Tract Dis.* 2010. Saslow D, et al. *CA Cancer J Clin.* 2012; ACOG Committee on Practice Bulletins. *Obstet Gynecol.* 2012; USPSTF. Moyer VA on behalf of the USPSTF. *Ann Intern Med.* 2012.
12. Final Recommendation Statement: US Preventative Task Force *JAMA.* 2018;320(7):674-686. doi:10.1001/jama.2018.10897
13. 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):189-197.
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