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!

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.

4

Key Facts In the Natural History of HPV

For management and counseling

5

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!

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

6

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.

Ho GY, et al. Persistent genital human papillomavirus infection as a risk factor for persistent cervical dysplasia. *J Nat Cancer Inst.* 1995;87(18):1365-1371.
Trottier 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.

8

High Lifetime Risk of HPV Infection

- HPV infections are very common. Nearly everyone will get HPV at some point in their lives.
- More than 42 million Americans are infected with types of HPV that are known to cause disease.
- About 13 million Americans, including teens, become infected each year.

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

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, National Center for Immunization and Respiratory Diseases, National Center for Chronic Disease Prevention and Health Promotion; last reviewed 2/9/24

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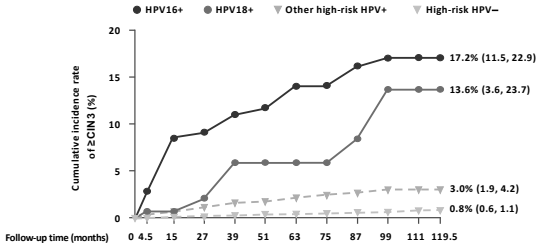
Risk Factors for *Persistent* HPV Infection and/or Neoplastic Progression

- 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.

10

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

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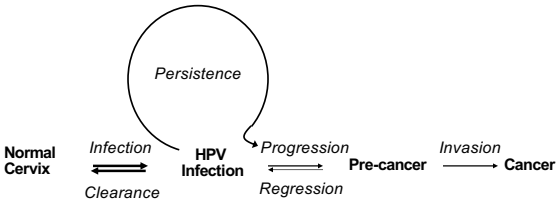
Natural History of HPV & Cervical Cancer



(2021 "no longer detected")

M. Schiffman, National Cancer Institute.

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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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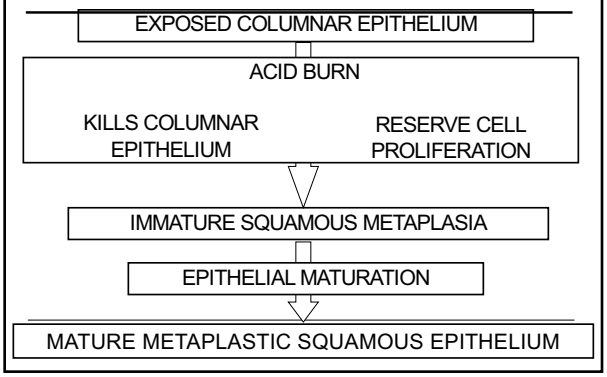
Events In Physiologic Metaplasia



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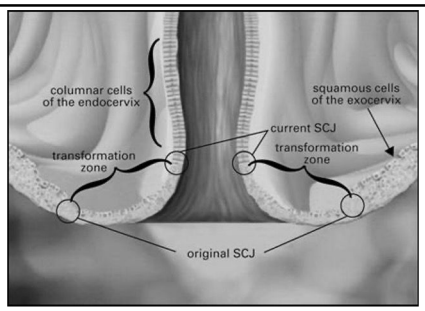
Cervical Transformation Zone



Source: http://www.merckmedicus.com/ppdocs/us/hcp/diseasemodules/hpvd/images/figure25.jpg

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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

Fontham ETH, Wolf AMD, Church TR, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. *CA Cancer J Clin*. 2020;70(5):321-346.
Advisory AP. Updated Cervical Cancer Screening Guidelines. https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2021/04/updated-cervical-cancer-screening-guidelines. Published 2021. Accessed Sept 29, 2021.
Curry SJ, Krist AH, Owens DK, et al. Screening for Cervical Cancer: US Preventive Services Task Force Recommendation Statement. *Jama*. 2018;320(7):674-686.

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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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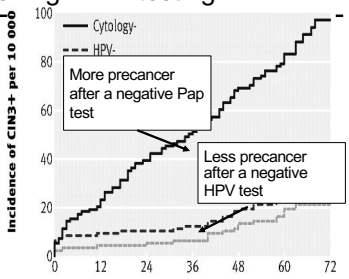
Evolution in screening: HPV testing

- HPV testing detects >90% of precancer
- Pap testing detects <70%
- Screening moving towards HPV testing
- Co-testing and HPV primary testing are fairly equivalent
- HPV self-collection can expand screening
- FDA approved May 15, 2024



Dillner, BMJ 2008

With permission: Rebecca B. Perkins MD, MSc
Boston University School of Medicine/ Boston Medical Center

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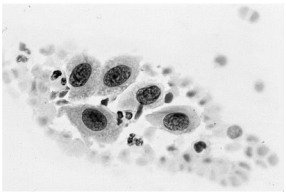
2012 ACS/ASCCP/ASCP Cervical Cancer Screening Guidelines



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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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	
21–25 y old	Cytology alone every 3 y	**No screening**
25–29 y old		**Preferred:**
30–65 y old	• Cytology alone every 3 y • Cotesting [b] every 5 y • Primary HPV [a] test every 5 y	**• Primary HPV [a] test every 5 y** Acceptable: [c] • Cotesting [b] every 5 y • Cytology alone every 3 y
>65 y old	No screening necessary after adequate negative prior screening [d]	
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
[a]Food and Drug Administration–approved test.
[b]Cotesting is cytology and hrHPV testing.
[c]Acceptable where access to primary HPV testing is not available.
[d]Adequate negative prior screening is defined as 2 consecutive negative primary HPV tests, 2 negative cotests, or 3 negative cytology tests within the last 10 years, and the most recent in the past 3–5 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.**

Marcus, Jenna Z. MD[1]; Cason, Patty RN, MS, FNP-BC[2]; Downs, Levi S. Jr. MD, MS[3]; Einstein, Mark H. MD, MS[1]; Flowers, Lisa MD[4] The ASCCP Cervical Cancer Screening Task Force Endorsement and Opinion on the American Cancer Society Updated Cervical Cancer Screening Guidelines, Journal of Lower Genital Tract Disease: July 2021 - Volume 25 - Issue 3 - p 187-191 doi: 10.1097/LGT.0000000000000614

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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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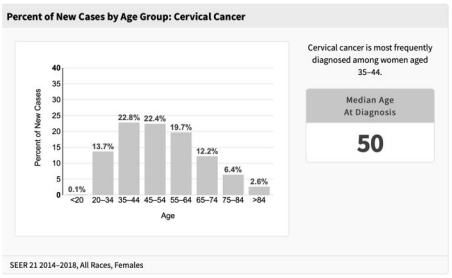
Cervical Cancer by Age Group



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Role of All Professionals….

Advocate for evidenced based guidelines!

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Avoid "OVER*PAP*ULATION" Follow Guidelines!

Neil Lonky ASCCP Biennial Meeting 2008

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HPV Testing

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Why Test for HPV?

- 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.

32

HPV Testing for Screening: Stratifies Risk

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

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

33

HPV Detection with FDA-Approved Tests

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

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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, 45, 51, 52 Grouped(33, 58, 35, 39, 68
Alinity (Approved 11/2/23)	High risk	56, 59, 66) Yes 16,18, 45, (31/33/52/58), (35/39/51/56/59/66/68)

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

With permission: ASCCP

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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[1]
- Follow-up after cervical treatment

1. Massad 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*. 2013;121(4):829-846. 1998;338(7):423-428.

37

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.

39

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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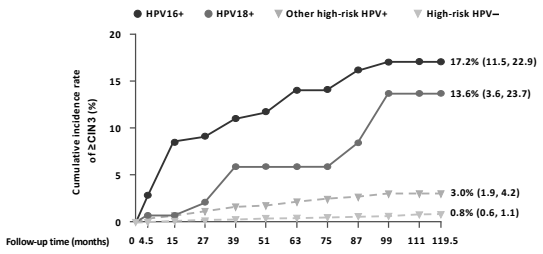
ACS/ASCCP/ASCP

"…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.

41

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

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Primary HPV Screening

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

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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	(33, 58, 35, 39, 68 56, 59, 66)
Alinity	2023	16,18, 45	(31/33/52/58), (35/39/51/56/59/66/68)

With permission: ASCCP

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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

45

Why HPV Primary Screening?

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

Cox 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.

46

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):578-586.

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

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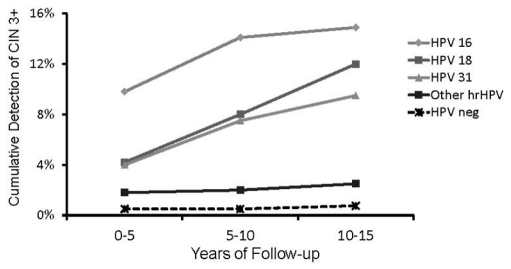
Predictive Value of HPV Genotyping

15-y risk of CIN 3+ in Kaiser Northwest cohort



Educate the Educator: ASCCP 2016

48

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.* 2012;206(1):46.e41-46.e11.

49

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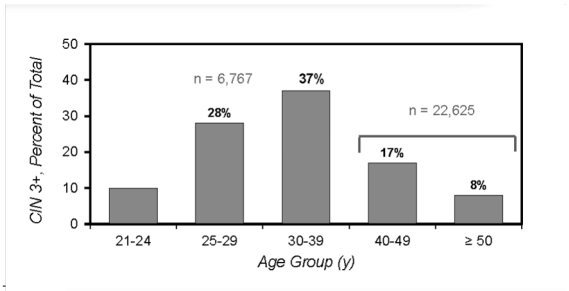
Proportion of CIN3 by Age Group Athena Trial: Why Start Primary Screening at Age 25



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

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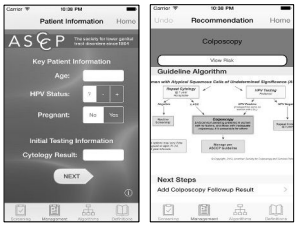
Original ASCCP Application



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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):102-131

54

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

Risk of CIN3+

61-100%
5-60%
1-4% ⇦
0.05%
0.02%
<0.01%

Presentation given by Dr. Richard Guido 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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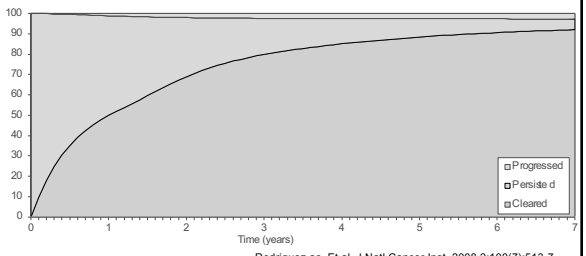
Most HPV Infections Become Undetectable in 1-3 years: Those That Persist Cause CIN3+ Over Time

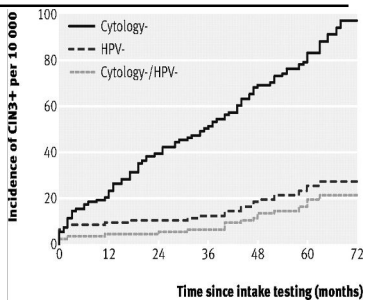


Rodriguez ac. Et al J Natl Cancer Inst. 2008 2;100(7):513-7

60

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



Dillner, BMJ 2008 Oct 13;337:a1754

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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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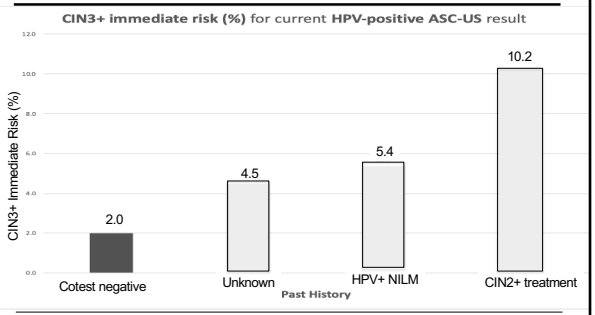
Past History Influences Current Risk



Egemen D, Cheung 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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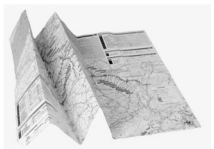
Paradigm Shift



Results-based guidelines are like a map (static)

Risk-based guidelines are like a GPS (dynamic)

With permission: ASCCP

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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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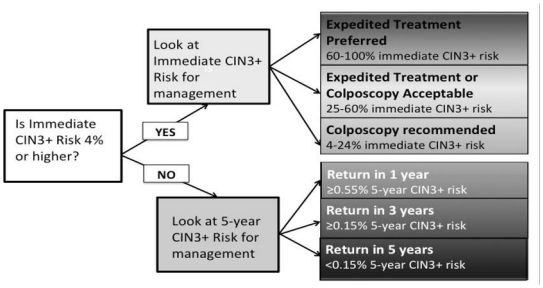
Patients Stratified Into Risk Levels



Perkins RB et al. J Low Genit Tract Dis. 2020;24(2):102-131.

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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 for 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 ≥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 (≥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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The Length of Intensive Surveillance Depends on the Abnormality

- Low-grade abnormalities:
  HPV test or cotest at 1 year
  Extend to 3 year intervals if negative
  Continue for at least 10 years
- CIN2/3 after treatment
  HPV test or cotest at 6 months, 18 months, 30 months
  Extend to 3 year intervals if all tests negative
  Repeat colposcopy for any HPV-positive result

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After Initial Surveillance:

Screening resumes at 3-year intervals using HPV testing or contesting or annual intervals if using Pap alone

- Surveillance should continue for at least 25 years after treatment for CIN2/2
- Even if patient undergoes hysterectomy
- Even if patient is over 65
- Screening may continue past age 65 if the patient is in good health

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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: A*ccommodates 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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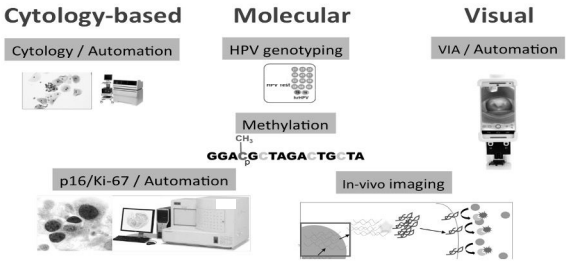
*Enduring: A*ccommodates New Tests in Development



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Dual Stain

- Identifies abnormal cells through biomarker staining of cervical cells collected during routine screening
- Biomarkers: p16 and Ki-67 when both are positive signal changes at the cellular level that indicate a transforming HPV infection
  - P16 overexpression is caused by increased E7 oncoprotein activity (correlated with persistent HPV infection)
  - Ki-67 is a marker of tumor proliferation
- HPV positive women with a negative dual stain could wait 3 years before repeat screening
- HPV positive women with a positive dual stain require colposcopy

"For HPV-Positive Women, Test Can Guide Cervical Cancer Screening Follow-Up", NCI

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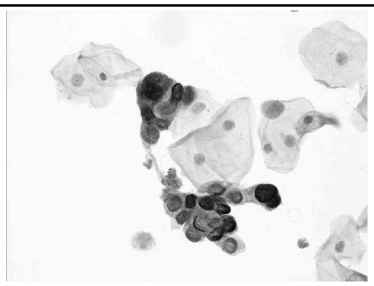
Dual Stain



Dual-stain testing on Pap test samples identifies the presence of two proteins: p16 (brown) and Ki-67 (red).
Credit: National Cancer Institute

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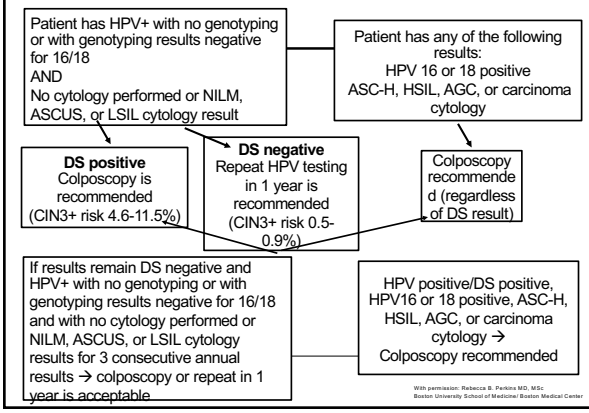
Algorithm for Dual Stain Results



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Boston University School of Medicine/ Boston Medical Center

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Extended Genotyping

- 2 FDA approved tests:
  - Onclarity channel configuration
    - HPV 16, 18, 45, 33/58, 31, 52, 35/39/68, 51
  - Alinity channel configuration
    - HPV 16,18, 45, 31/33/52/58, 35/39/51/56/59/66/68
- Currently, extended genotyping is being evaluated on whether it will be included into the risk-based management guidelines
  - It is only considering the Onclarity test
  - Data for approval was collected with the Onclarity test
  - The Alinity test groups the HPV types differently

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Self-Collection: HPV Test

5/15/24 FDA approved self-collected primary HPV testing in a health-care setting

- Patient uses a collection kit to take a vaginal sample
- This provides a vaginal HPV test
  - 2 tests were approved
    - Cobas HPV test
    - Onclarity HPV test
- This sample does not allow for cytology or dual stain testing

American Cancer Society Statement: FDA Approval of HPV Self-Collection for Cervical Cancer Screening
May 15, 2024

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Rationale for HPV Self-Collection

- Increase the number of individuals screened
  - >50% of cancers occur in unscreened/under-screened
- Reduce barriers to clinician-collected screening
  - Patients may gain access to testing in settings that do not perform speculum exams
  - Discomfort with pelvic exams (mobility, trauma, pain, gender identity)
- Successful implementation has been seen in programs in The Netherlands, Australia and other sites

American Cancer Society Statement: FDA Approval of HPV Self-Collection for Cervical Cancer Screening
May 15, 2024

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What does self-collection mean for patients, clinicians, and healthcare systems?

- **Note, vaginal (self-collected) samples are managed differently than cervical (clinician-collected) samples*
- **HPV-positive vaginal (self-) samples require speculum exam and Pap collection for evaluation.*

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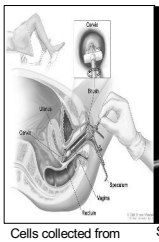
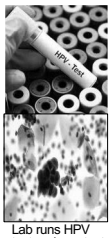
Clinician-collected cervical sample (Pap/HPV co-test)



Cells collected from cervix


Sample placed into appropriate medium



Lab runs HPV test and pap test

- POSITIVE results need colposcopy. Expedited treatment, or 1-year follow-up per 2019 ASCCP management guidelines

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Patient-collected vaginal sample (HPV test with second visit for Pap)


Swab collected from vagina **in the clinic**

Not yet approved for home use


Sample placed into medium. HPV test run in lab.


HPV 16/18+ →directly to colposcopy *(note there is no expedited treatment option)*

Other HPV+ → patient returns to office for Pap

Lab runs Pap


Positive Pap → colposcopy

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Boston University School of Medicine/ Boston Medical Center

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Implications for patient visits among HPV+

- In a clinician-collected co-testing scenario (our current practice)
- Results returned to clinicians have Pap and HPV results
- Need for colposcopy based on combination of HPV and Pap results
- In a patient-collected vaginal HPV screening scenario, patients with HPV16/18+ proceed directly to colposcopy, all other results require speculum exam for a Pap
- Pap collected at an additional visit with pelvic exam
  - Approximately 60-70% of HPV-positives
- Those with positive results require an additional visit for colposcopy
  - Approximately 35-40% of HPV-positives

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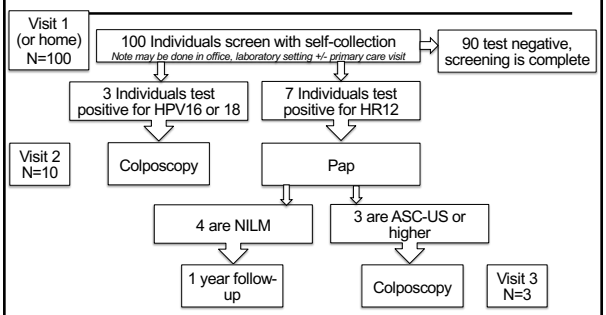
Hypothetical population of 100 individuals undergoing self-collection: screening population



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Summary of implications for screening population

- In a self-collection scenario, approximately 90% of patients will test negative, and 10% of patients will test positive and need a follow-up exam
- Among these, 3% go straight to colposcopy, 4% get a Pap test and do not need colposcopy, and 3% need a Pap test and then colposcopy
- Note that self-collection overcomes barriers to screening, but pelvic exams, Pap tests, colposcopy, and treatment are still necessary to prevent cancer

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New guidelines coming for self-collection: Focus of guidelines development

Data analysis:

- Sensitivity of HPV self-collection vs. HPV provider collection vs. cytology: Important for re-testing interval
- Evaluation of overall and type-specific agreement to inform whether extended genotyping recommendations can be applied to self-collected specimens
- Target population for HPV self-collection
- Management of HPV results from self-collected specimens

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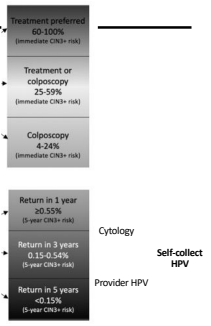
Diagnostic accuracy and return intervals

- Screening interval is determined by 5-year risk of CIN3+ among *test-negatives*
- High sensitivity ▸ low risk in *test-negatives*
  - **Cytology**
    Pooled sensitivity: 83.9% (95% CI 79.4-87.6)
  - **Self-HPV**
    Pooled sensitivity: 91.4% (95% CI 86.5 to 94.6)
  - **Clinician-HPV**
    Pooled sensitivity: 93.1% (95% CI 89.2 to 95.7)



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Putting the Risk-Based Guidelines to Use

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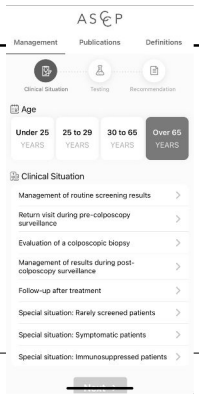
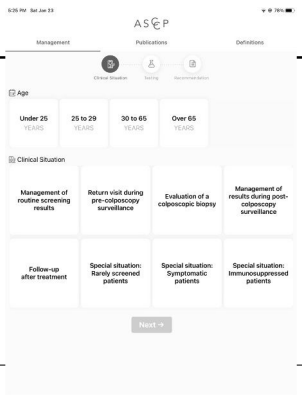
Phone App



101

Case #1

35 yo:
Co-test: Pap: LSIL, HPV+16
Prior Co-test:
Pap: negative, HPV: negative



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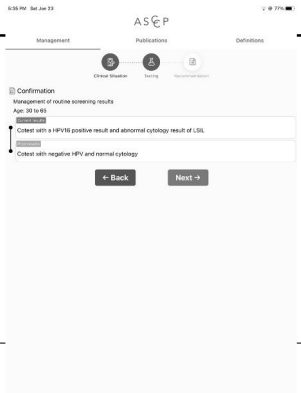
Case #1

103

Case #1

104

Case #1



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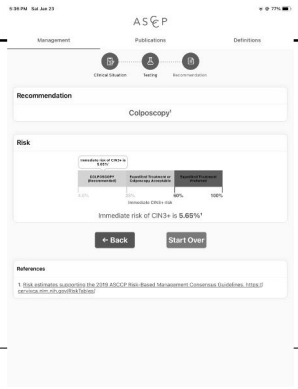
Case #1



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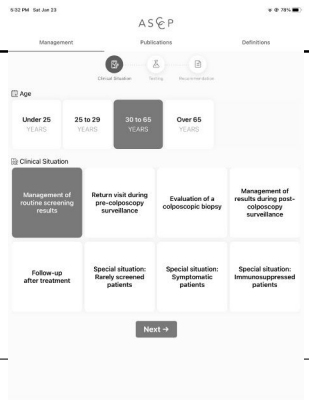
Case #2

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



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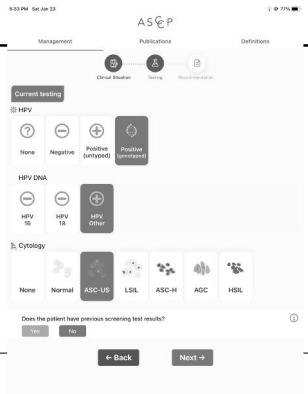
Case #2



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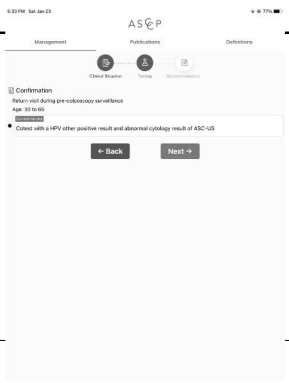
Case #2



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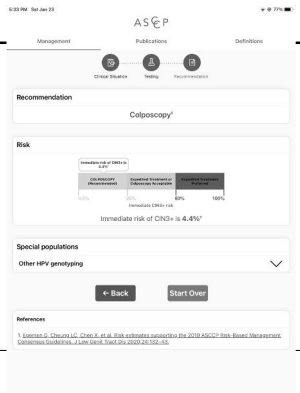
Case #2



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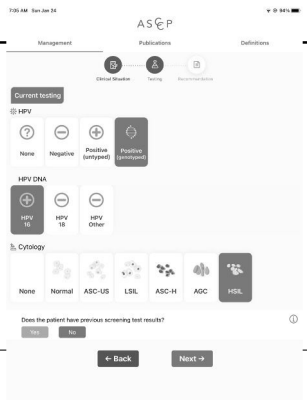
Case #3

44yo:
Pap: HSIL
HPV+ 16



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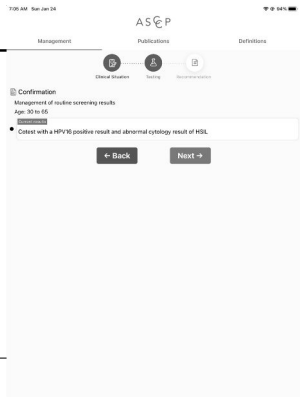
Case #3



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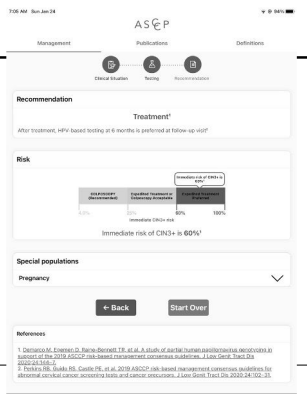
Case #3



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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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