

Hot Topics In Medicine Webinar

Cervical Cancer Screening Update

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Overview

- History of cervical cancer screening and natural history of HPV infection
- Describing the benefits and harms of cervical cancer screening program
- Review of current national society guidelines and the supporting evidence
- Update to risk-based management from result-based
- Health disparities in screening, prevention and treatment

Learning Objectives

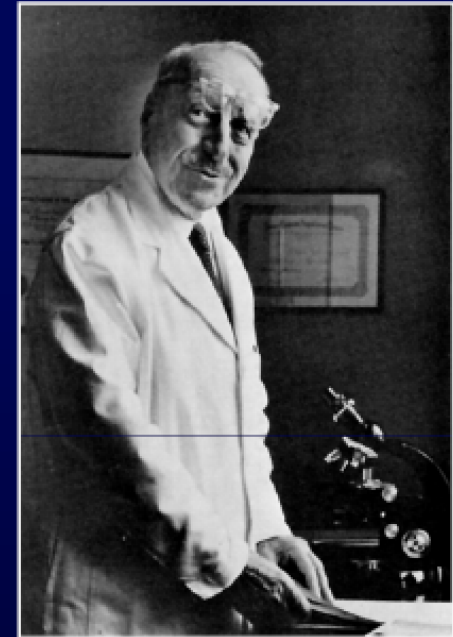
- Describe the rationale for moving from result-based management of abnormal results to risk-based management.
- Discuss criteria for discontinuation of cervical cancer screening.
- Review web and application-based tools to guide management of abnormal results.

Cervical cancer prevention:

Where have we been and where are we going?

Widespread introduction of the Pap begins

1955-1992
CA incidence ↓ by 60%



Conventional Pap smear

Liquid based cytology

HPV testing

Markers

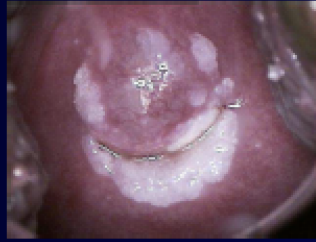
Vaccine
2006, 2014

1949

1996

2000's

Natural History of Cervical Cancer



CIN 1



CIN 2,3

Invasive CA



**HPV
infection**



**Avg. 6-
24 mo**

Avg. 10-13 yrs

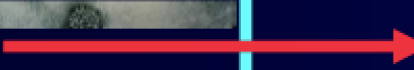
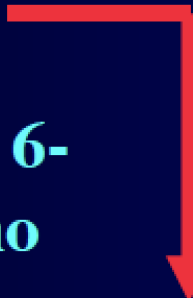
1-5%

**Avg. 6-
12 mo.**

HPV

disappearance

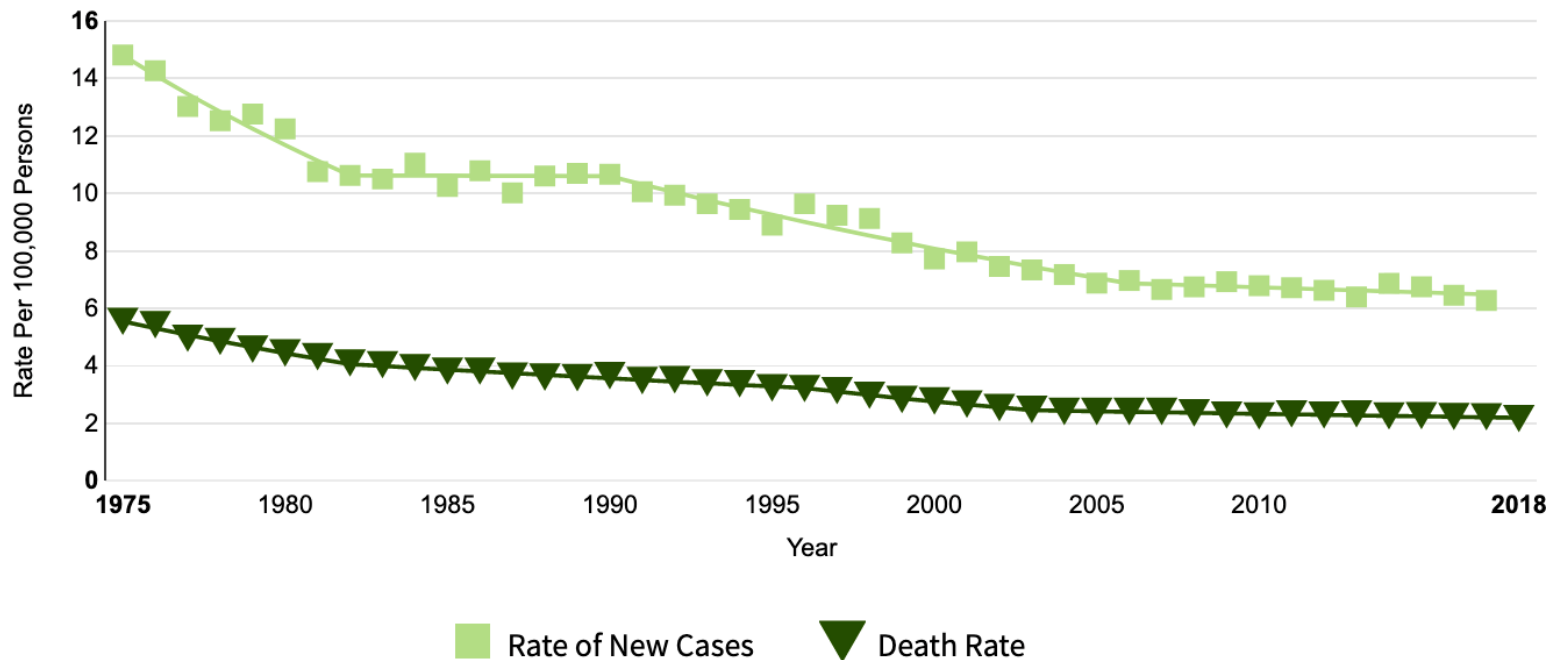
90%



Cervical Cancer, 1975-2018

Age-adjusted rates for new cases

Age-adjusted death rates



New cases come from SEER 9. Deaths come from U.S. Mortality.

All Races, Females. Rates are Age-Adjusted.

Modeled trend lines were calculated from the underlying rates using the [Joinpoint Trend Analysis Software](#).

<https://seer.cancer.gov/statfacts/html/cervix.html>

Cervical Cancer: The Present

Represents 0.8% of all new cancer cases in the U.S.

Cancer Type	Estimated New Cases 2020	Estimated Deaths 2020
1. Female Breast	276,480	42,170
2. Lung & Bronchus	228,820	135,720
3. Prostate	191,930	33,330
4. Colorectal	147,950	53,200
5. Melanoma	100,350	6,850
6. Bladder	81,400	17,980
7. Non-Hodgkin Lymphoma	77,240	19,940
8. Kidney & Renal Pelvis	73,750	14,830
9. Uterine	65,620	12,590
10. Leukemia	60,530	23,100
--		
20. Cervix	13,800	4,290

SEER Cancer Stat Facts: Cervical Cancer. National Cancer Institute. Bethesda, MD,
<https://seer.cancer.gov/statfacts/html/cervix.html>

Cervical Cancer Screening Program Objectives

1. Prevent the morbidity and mortality from cancer
2. Prevent over-management and over-treatment of precursor ***lesions that are most likely transient*** for which risks/harms of management/treatment outweigh benefits
3. Recognize that it is unrealistic to prevent all cancers

True Objectives of Screening

- Determine which lesions will progress
- Place emphasis on
 - Persistent HPV infection
 - CIN3
 - CIN2 in older women
 - Persistent CIN2 and CIN2/3 in non-adolescent younger women

Assumptions: Screening Intervals

- Risk of developing cancer prior to the next screening test should be unlikely
- Earlier detection of CIN3 is beneficial

Process Assumptions: Harms

- Recognize possible harms of screening
 - Anxiety over positive test
 - Stigma of having STI
 - Pain, bleeding, cost associated with procedure
 - Treatment related pregnancy complications
- Number of colposcopies done is a marker

Screening Strategies

Cytology alone every 3 years

Co-testing every 5 years

Primary HPV testing every 5 years

CA: A Cancer Journal for Clinicians

Article |  Free Access |

Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society

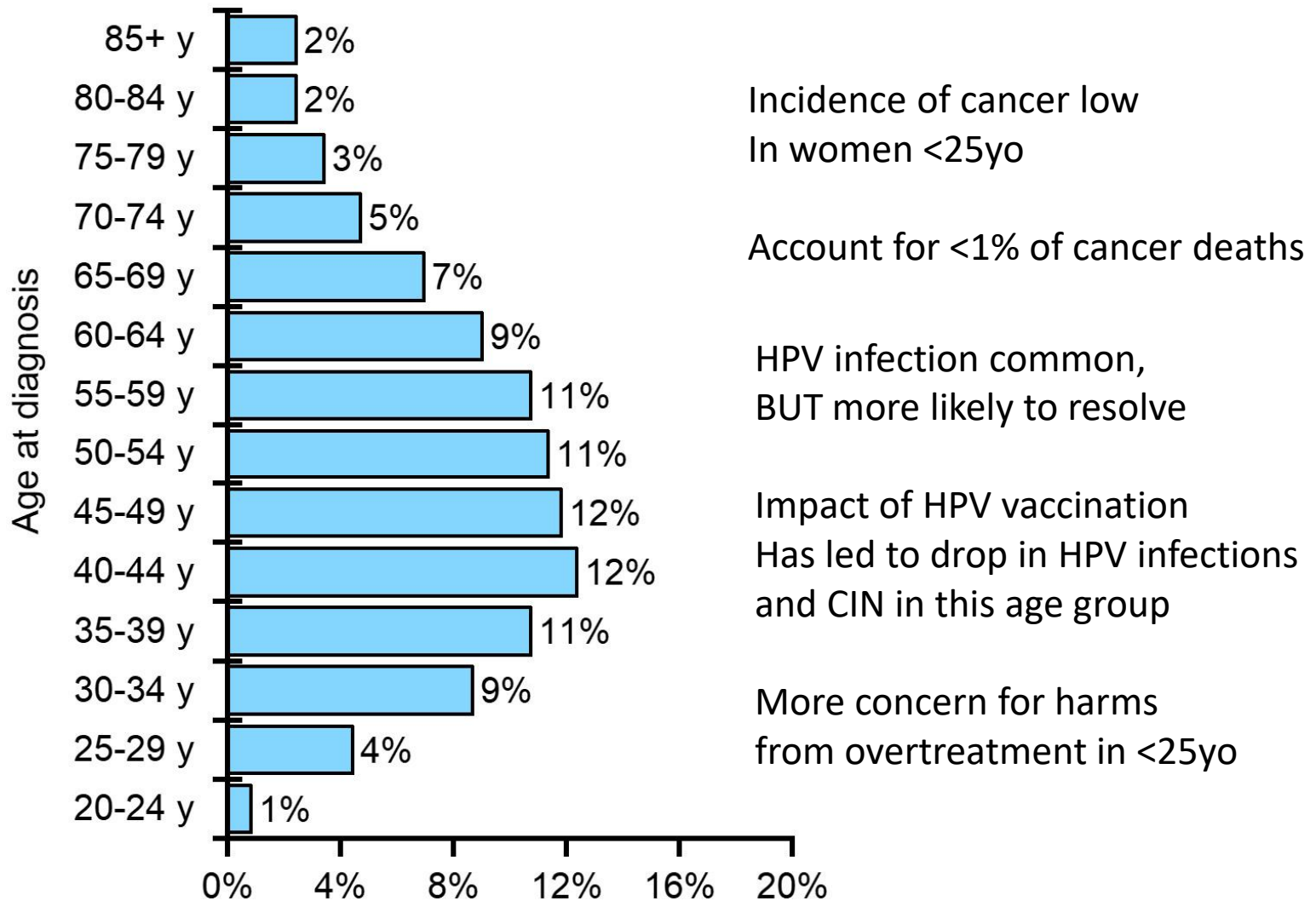
Elizabeth T. H. Fontham MPH, DrPH, Andrew M. D. Wolf MD, Timothy R. Church PhD, Ruth Etzioni PhD, Christopher R. Flowers MD, MS, Abbe Herzig PhD, Carmen E. Guerra MD ... [See all authors](#) ▾

First published: 30 July 2020 | <https://doi.org/10.3322/caac.21628> | Citations: 13

Age	2020 ACS*	2021 ACOG	2021 USPSTF
21-24	No screening		Cytology Q3
25-29	Preferred: HPV Q5 Acceptable: Co-test Q5 OR Cytology Q3		Cytology Q3 Can consider HPV Q5
30-65	Preferred: HPV Q5 Acceptable: Co-test Q5 OR Cytology Q3		Cytology Q3 OR HPV Q5 OR Co-test Q5
65+	NO screening after adequate prior negative screening		
Hysterectomy with cervix removal	No screening for those who do NOT have a history of CIN2+, ACIS or cancer in the 25 years leading up to hysterectomy		

Guidelines apply to all persons with a cervix, regardless of vaccination status

Distribution of Cervical Cancer Cases by Age at Diagnosis, United States, 2012 to 2016



Data Source: North American Association of Central Cancer Registries Incidence Data-Cancer in North America Analytic File.

CA: A Cancer Journal for Clinicians, Volume: 70, Issue: 5, Pages: 321-346, First published: 30 July 2020, DOI: (10.3322/caac.21628)

Co-testing disadvantages

- Doubles the number of screening tests (2 for each patient)
- Interpretation of 2 tests more complicated than single test
- Detects minor changes that have low risk for cancer → on a population basis = additional effort and cost w/o any more benefit compared to primary HPV

Supporting evidence from other studies

- Many European studies
 - co-testing offers minimal increased protection against subsequent development of CIN2+ compared to Primary HPV screening
- Kaiser N. California 1,011,092 women aged 30-64
 - Primary HPV test negative at 3-year intervals as good as co-test Q5

Test	CIN3+	Cancer
Co-test Q5	0.11%	0.014%
Cytology Q3	0.19%	0.020%
Primary HPV Q3	0.069%	0.011%

Primary HPV Screening

- **2014 FDA modified labeling for Cobas HPV test (Roche)** to include the additional indication for primary screening
- Addressing the Need for Advanced HPV Diagnostics trial (ATHENA)
 - Established that it is equivalent to superior
- **2015 ASCCP and SGO published interim guidance** for use of FDA-approved HPV test for primary screening

Primary HPV Screening Proposed Algorithm

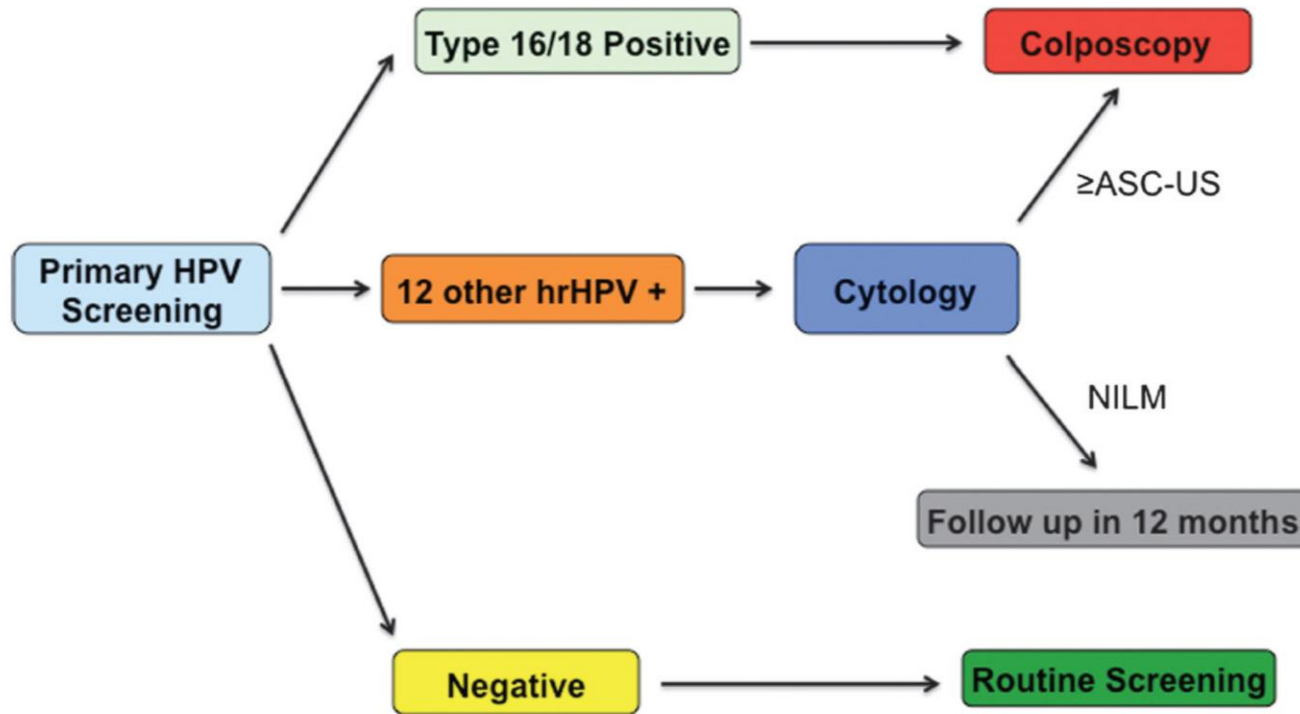


FIGURE 1. Recommended primary HPV screening algorithm. HPV, human papillomavirus; hrHPV, high-risk human papillomavirus; ASC-US, atypical squamous cells of undetermined significance; NILM, negative for intraepithelial lesion or malignancy.

*2020 ACS Guidelines Caveats

The recommendations **do not apply** to individuals at increased risk due to:

- History of solid organ or stem cell transplantation
- HIV infection
- Significant immunosuppression from other causes
- in utero exposure to diethylstilbestrol.

Primary HPV Screening Stipulations

- Only the Roche Cobas and Onclarity tests are FDA-approved for this purpose
- Do not use test in women <25 years old
- After a negative HPV screen, do NOT rescreen any sooner than 3 years

FDA-Approved Screening Tests

	FDA-approved Test	Genotyping
Primary HPV test	Cobas HPV (2014)	16, 18
	Onclarity HPV (2018)	16, 18, 45, 31, 51, 52, 33+58, 35+39+68, 56+59+66
Co-test	Digene HC2 (2003)	No
	Cervista HPV HR (2009)	No
	Cervista HPV 16/18 (2009)	HPV 16, 18
	Aptima HPV (2011)	No
	Aptima HPV16, 18/45 (2012)	HPV 16, 18/45
	Cobas HPV (2011)	HPV 16, 18
	Onclarity HPV (2018)	16, 18, 45, 31, 51, 52, 33+58, 35+39+68, 56+59+66

Criteria to Discontinue Screening

Age 65 with *adequate prior negative* screening

Within the past 10 years must have:

3 consecutive normal cytology results

OR

2 consecutive negative co-testing results

OR

2 consecutive negative Primary HPV results

Most recent test occurring within past 5 years

Screening should NOT resume for any reason

May be discontinued in individuals of any age with limited life expectancy.

Rationale for discontinuing at age 65

- CIN2+ rare after age 65
 - Most abnormal screens are false+, do NOT reflect pre-cancer
- HPV risk remains 5-10%
- Colposcopy, biopsy and treatment more difficult → harms of screening amplified
- Incident HPV infection is unlikely to lead to cancer within remaining lifetime

Cervical cancer in women >age 65

- 14.1% of US population
- Have 19.6% of the new cases of cancer
- Most cases occur in unscreened or inadequately screened women
- Modeling studies show continued screening would prevent VERY FEW cases
 - If screening continued to age 90: Would prevent 1.6 cases of cancer and 0.5 cancer-related deaths in 1000 women
 - Slight gain BUT significant cost of increasing colposcopies
 - Low risk of progression with newly acquired HPV infection, NO need to resume screening

When to continue after age 65

HIV/immune compromise

Personal history of CIN2+ or AIS

Continue routine screening for at least 25 years after treatment, even if extends past age 65

Inadequate or unknown
screening history

Stop after hysterectomy if...

Cervix was removed

AND no history of CIN2+

Evidence of adequate prior negative screening
NOT required

Rationale for stopping after hysterectomy

- Vaginal cancer RARE (7/1,000,000/yr)
- 663 tests needed to find 1 vaginal dysplasia
- 2066 women followed after hyst for average 89 months
 - 3% had vaginal dysplasia and **NONE** had cancer
- Risk of abnormal pap after hyst ~1%
 - Compares w/risk of breast CA in men

Special Circumstances--HIV

- Cytology alone w/in 1 year of onset of sexual activity or if already active w/in 1 year of diagnosis, but no later than age 21.
- Under age 30 – annual X3, then Q3 years w/cytology alone.
- Age 30+ – can co-test or do cytology alone, Co-test Q3 years if initial annual testing X3 normal
- Continue regular Q3 year intervals beyond age 65

Special circumstances – Immune compromise, DES exposure

- *No consensus guidelines for women w/immune compromise due to cause other than HIV.*
- Traditionally annual cytology has been done, but reasonable to apply HIV guidelines to this group
- DES exposure – reasonable to do annual cytology

Health Disparities in Cervical Cancer Screening, Prevention & Treatment

- 4th most common cancer among women globally
 - 604,000 new cases, 342,000 deaths in 2020.
 - ~90% of new cases and deaths worldwide occurred in low- and middle-income countries.
- HPV-16 and 18 account for ~ 50% of high-grade cervical pre-cancers
- Those with HIV 6X more likely to develop cervical cancer than HIV neg
- HPV vaccination, screening and treatment of pre-cancerous lesions is cost-effective in preventing cervical cancer.
- Cervical cancer can be cured if diagnosed at early stage and treated promptly.
- Comprehensive cervical cancer control
 - primary prevention (vaccination against HPV),
 - secondary prevention (screening and treatment of pre-cancerous lesions),
 - tertiary prevention (diagnosis and treatment of invasive cervical cancer)
 - palliative care.

Global Efforts

- The World Health Assembly: global strategy to accelerate the elimination of cervical cancer.
 - GOAL = reach the threshold < 4 cases of cervical cancer per 100, 000 women/yr
 - WHO has set “90-70-90” targets to be reached by 2030 and to be maintained
 - 90% of girls fully vaccinated with HPV vaccine by age 15;
 - 70% of women screened with a high-performance test by age 35, and again by 45 yo; and
 - 90% of women identified with cervical disease receive treatment (90% of women with pre-cancer treated; 90% of women with invasive cancer managed).

Self-collection HPV test

- Promising strategy to improve screening uptake
- PCR-based self collection tests have similar sensitivity for HPV detection compared to clinician collected samples
- ACOG Practice Advisory April 2021
 - ***“Although HPV self-sampling has the potential to greatly improve access to cervical cancer screening, and there is an increasing body of evidence to support its efficacy and utility, it is still investigational in the United States.”***

American Society for Colposcopy and Cervical Pathology

Easy to use App Includes:

- Screening Guidelines
- Management of Abnormal Results
- Available in Spanish



\$10



Clinical Example #1

28yo G0 with screening results – ASCUS, HPV-

The screenshot displays the ASCP (American Society for Clinical Pathology) interface. At the top, the ASCP logo is visible. Below it, there are four tabs: Screening, Management, Publications, and Definition. A progress bar shows three steps: Clinical Situation, Testing, and Recommendation. The 'Testing' step is currently active. Under the 'Current testing' section, there are two main categories: HPV and Cytology. The HPV section has four options: None, Negative (selected), Positive (untyped), and Positive (genotyped). The Cytology section has four options: None, Normal, ASC-US (selected), and LSIL. Below the test results, there is a question: 'Does the patient have previous screening test results taken after the age of 25?' with 'Yes' and 'No' buttons. At the bottom, there are 'Back' and 'Next' navigation buttons.

ASCP

Screening Management Publications Definition

Clinical Situation Testing Recommendation

Current testing

HPV

None Negative Positive (untyped) Positive (genotyped)

Cytology

None Normal ASC-US LSIL

Does the patient have previous screening test results taken after the age of 25?

Yes No

← Back Next →

Screen 2: Confirmation of History

The screenshot shows the ASCEP app interface. At the top, the ASCEP logo is displayed. Below it, a navigation bar includes 'Screening', 'Management', 'Publications', and 'Definitive'. The 'Management' tab is selected and underlined. A progress indicator shows three steps: 'Clinical Situation' (active), 'Testing', and 'Recommendation'. The main content area is titled 'Confirmation' and includes the text 'Routine screening (within past 5 years)' and 'Age: 25 to 29'. A section labeled 'Current results' contains a bullet point: 'Cotest with negative HPV and abnormal cytology result of ASC-US'. At the bottom, there are two buttons: '← Back' and 'Next →'.

ASCEP

Screening Management Publications Definitive

Clinical Situation Testing Recommendation

Confirmation

Routine screening (within past 5 years)

Age: 25 to 29

Current results

- Cotest with negative HPV and abnormal cytology result of ASC-US

← Back Next →

Final Screen with Recommendation

ASCP

Screening Management Publications Definition

Clinical Situation Testing Recommendation

Recommendation

3-year follow-up¹

HPV-based screening at follow-up visit²

Risk

5 year risk of CIN3+ is 0.40%¹

Return Period	5-year CIN3+ Risk
5-YEAR RETURN	0.0%
3-YEAR RETURN	0.15%
1-YEAR RETURN	0.55%
5-year CIN3+ risk (Total)	9.0%

5 year risk of CIN3+ is **0.40%¹**

← Back Start Over

Clinical Example #2





55yo G0: 2023 – Normal cytology, HPV-16

ASCP




Screening Management Publications Definition

Current testing





⚙️ HPV

 None	 Negative	 Positive (untyped)	 Positive (genotyped)
---	---	--	---

HPV DNA

 HPV 16	 HPV 18	 HPV Other
---	---	---

🔬 Cytology

 None	 Normal	 ASC-US	 LSIL
---	---	--	---

Does the patient have previous screening test results? ⓘ

Yes No

Screen 3: Confirmation of History

Screening Management Publications Definition

Clinical Situation Testing Recommendation

Confirmation

Routine screening (within past 5 years)
Age: 30 to 65

Current results

- Cotest with a HPV16 positive result and normal cytology

← Back Next →

Final Screen with Recommendation

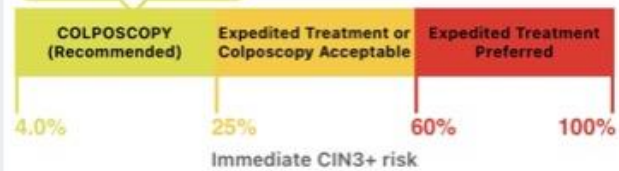
Screening Management Publications Definition

Recommendation

Colposcopy¹

Risk

Immediate risk of CIN3+ is 5.3%¹



Immediate risk of CIN3+ is 5.3%¹

← Back

Start Over

References

1. [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.](#)

Clinical Example #3: Follow-up after treatment

55yo G0: **2022 – LEEP conization for CIN3**

2023 – ASCUS, HPV-

ASceP

Screening Management Publications Definit

HPV

None Negative Positive (untyped) Positive (genotyped)

Cytology

None Normal ASC-US LSIL

Does the patient have previous results since treatment?

Yes No

Treated Histology

Histologic HSIL (CIN 2) Histologic HSIL (CIN 3) Histologic HSIL (unspecified)

← Back Next →



ASceP

Screening Management Publications Definit

Clinical Situation Testing Recommendation

Confirmation

Follow-up after treatment

Age: 30 to 65

Current results

Cotest with negative HPV and abnormal cytology result of ASC-US

Treatment

Treatment with a histologic result of CIN 3

← Back Next →



ASceP

Screening Management Publications Definit

Clinical Situation Testing Recommendation

Recommendation

1-year follow-up¹

HPV-based screening at follow-up visit²

Risk

5 year risk of CIN3+ is 3.8%¹

Return	5-YEAR RETURN	3-YEAR RETURN	1-YEAR RETURN
Risk	0.0%	0.15%	0.55%

5-year CIN3+ risk

5 year risk of CIN3+ is 3.8%¹

Figure

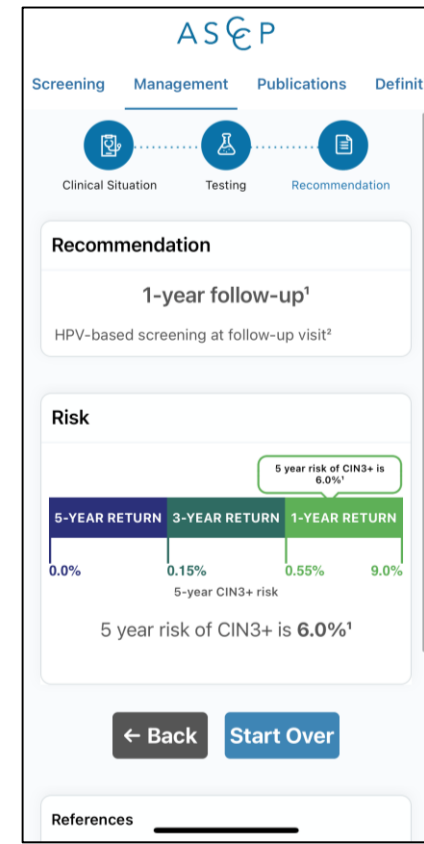
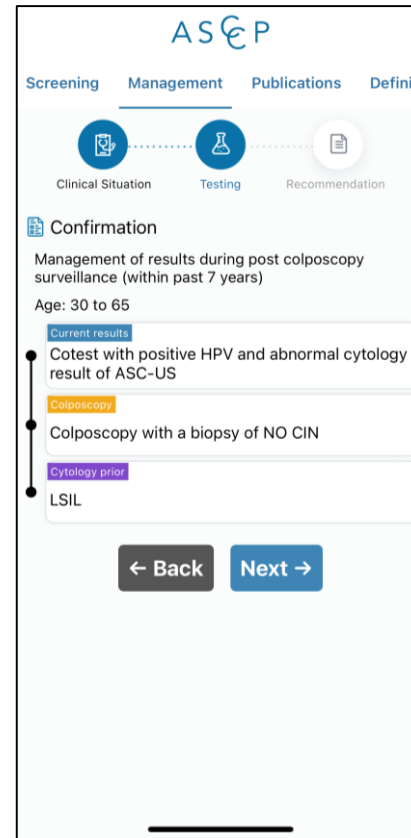
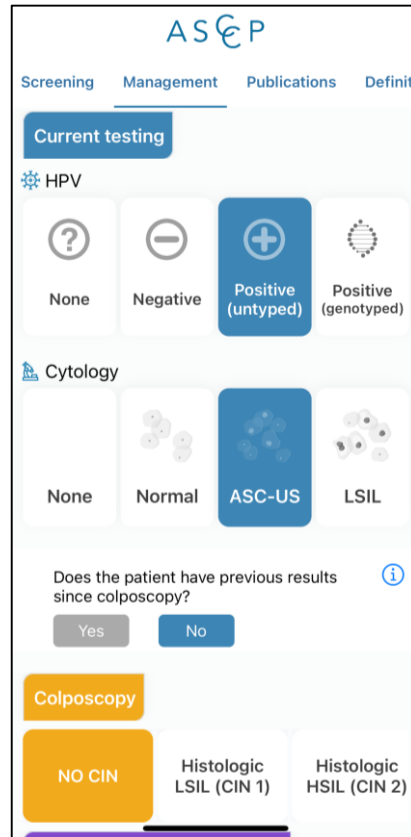
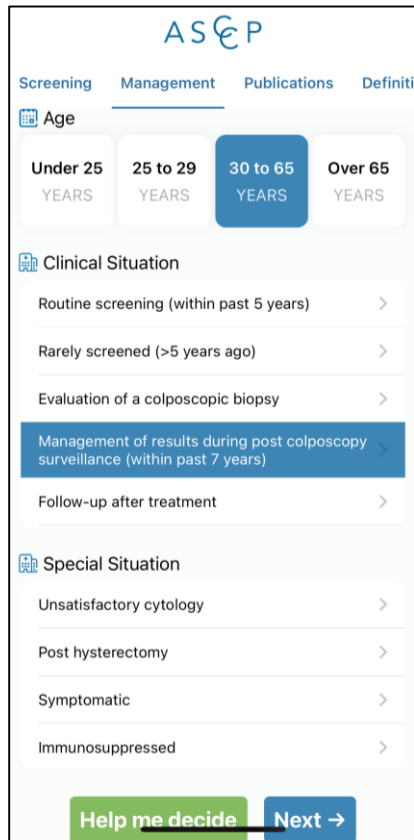
Figure 7: Management of Histologic HSIL (CIN2 or CIN3 or Not Further Specified)¹

Clinical Example #4: Post colposcopy surveillance

33yo G2P2: 2019 – Normal cytology

2022 – LSIL, HPV+ (untyped) → Colposcopy → NO CIN

2023 – ASCUS, HPV+ (untyped)



Clinical Example #5: ASC-H

33yo G2P2: 2019 – Normal cytology

2022 – ASC-H → Colposcopy → NO CIN

2023 – ASCUS, HPV+ (untyped)

ASceP

Screening Management Publications Definit

Age

Under 25 YEARS 25 to 29 YEARS 30 to 65 YEARS Over 65 YEARS

Clinical Situation

- Routine screening (within past 5 years) >
- Rarely screened (>5 years ago) >
- Evaluation of a colposcopic biopsy >
- Management of results during post colposcopy surveillance (within past 7 years) >
- Follow-up after treatment >

Special Situation

- Unsatisfactory cytology >
- Post hysterectomy >
- Symptomatic >
- Immunosuppressed >

Help me decide Next →

ASceP

Screening Management Publications Definit

Current testing

HPV

None Negative Positive (untyped) Positive (genotyped)

Cytology

None Normal ASC-US LSIL

Does the patient have previous results since colposcopy? Yes No

Colposcopy

NO CIN Histologic LSIL (CIN 1) Histologic HSIL (CIN 2)

ASceP

Screening Management Publications Definit

Clinical Situation Testing Recommendation

Confirmation

Management of results during post colposcopy surveillance (within past 7 years)

Age: 30 to 65

Current results

- Cotest with positive HPV and abnormal cytology result of ASC-US

Colposcopy

- Colposcopy with a biopsy of NO CIN

Cytology prior

- ASC-H

← Back Next →

ASceP

Screening Management Publications Definit

Clinical Situation Testing Recommendation

Recommendation

Colposcopy¹

Risk

Immediate risk of CIN3+ is 6.6%²

Management Option	Immediate CIN3+ risk
COLPOSCOPY (Recommended)	4.0%
Expedited Treatment or Colposcopy Accep...	25%
Expedited Treatment Preferred	60%
100%	100%

Immediate risk of CIN3+ is 6.6%²

Figure

Figure 10: Management of Histologic LSIL (CIN1) or Less Preceded by ASC-H Cytology

Clinical Example #6: HIV

33yo **HIV+** G1P1: 2022 – Normal cytology, HPV-
2023 – LSIL, HPV+

ASCP

Screening Management Publications Definit

Age

Under 25 YEARS 25 to 29 YEARS **30 to 65 YEARS** Over 65 YEARS

Clinical Situation

Routine screening (within past 5 years) >

Rarely screened (>5 years ago) >

Evaluation of a colposcopic biopsy >

Management of results during post colposcopy surveillance (within past 7 years) >

Follow-up after treatment >

Special Situation

Unsatisfactory cytology >

Post hysterectomy >

Symptomatic >

Immunosuppressed >

Help me decide Next →



Dismiss

Managing Patients With Immunosuppression.

Screening
Cervical cancer screening and abnormal result management recommendations for immunocompromised individuals without HIV use the guidelines developed for people living with HIV144:
• Cytology only screening should begin within 1 year of first insertional sexual activity
• Continue cytology
• Continue every 3 y years
• Cytology alone or 30 years for the pat

Management of Ab
In immunocomprom referral is recomme US or higher.
• If HPV testing is ne repeat cytology in 6 colposcopy referral
• For any result of A HPV positive, referre
• For all cytology res AGC, AIS, and HSIL) regardless of HPV te

[Perkins RB, Guido B based management cervical cancer scre Genit Tract Dis 202](#)

Management of Abnormal Results

In immunocompromised patients of any age, colposcopy referral is recommended for all results of HPV-positive ASC-US or higher.

- If HPV testing is not performed on ASC-US results, then repeat cytology in 6 to 12 months is recommended, with colposcopy referral for ASC-US or higher.
- For any result of ASC-US or higher on repeat cytology or if HPV positive, referral to colposcopy is recommended.
- For all cytology results of LSIL or worse (including ASC-H, AGC, AIS, and HSIL), referral to colposcopy is recommended regardless of HPV test result if done.

Summary

- For average risk patients, start screening at age 25 (cytology only age 21-24 acceptable)
- Primary HPV testing at 5-year intervals is the preferred screening strategy (co-testing Q5 years acceptable)
- Use genotyping to guide management of positive HPV test results
- **USE THE ASCCP APP** to guide management of abnormal results!