Primary HPV Screening for Cervical Cancer: *Why and How?*

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Disclosures

This resource was developed by the Provider Workgroup as a part of the American Cancer Society National Roundtable on Cervical Cancer's Primary HPV Screening Initiative which aims to support the transition to and implementation of primary HPV screening across the United States.

Speaker's Disclosures:

I am an author and peer editor at Uptodate

Objectives

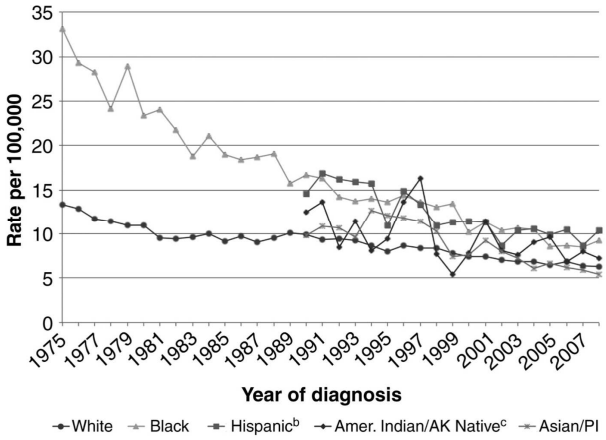
- Describe primary HPV screening, the preferred approach to cervical cancer screening per the American Cancer Society
- Review the pros and cons of this approach
- List three options for managing abnormal screening results
- Review new developments in cervical cancer screening and management

Cervical Cancer Prevention

Screening, Progress, and Elimination

Screening Prevents Cervical Cancer

Since screening has been introduced in the United States, the rate of cervical cancer has decreased by 80%.



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Peto J, et al. The cervical cancer epidemic that screening has prevented in the UK. *Lancet.* 2004;364(9430):249-56.

Screening vs. Surveillance: An Important Distinction

Screening is testing for disease among patients with no symptoms and ALL normal prior results.

Surveillance is interval testing among women and people with a cervix who have a prior abnormal test result or have received treatment.

Elimination

2030 Targets to Accelerate Elimination

90% of girls fully vaccinated with HPV vaccine by age 15 years

70% of women are screened with a high-performance test by 35 years of age and again by 45 years of age

90% of women identified with cervical disease receive treatment
90% of women with pre-cancer treated, and
90% of women with invasive cancer managed

Screening for Cervical Cancer in the United States

Guidelines

Comparison of Current Screening Guidelines & Recommendations for Average-risk Individuals

	American College of Obstetricians and Gynecologists (ACOG), 2020	US Preventive Services Task Force (USPSTF), 2018	American Cancer Society (ACS), 2020
Age to start screening	**21**		**25**
Screening test options and intervals	**Ages 21-65:** Cytology alone every 3 years *OR* **Ages 21-29:** Cytology alone every 3 years **Ages 30-65:** Cytology plus HPV testing every 5 years *OR* **Ages 21-29:** Cytology alone every 3 years **Ages 30-65:** HPV testing alone every 5 years		**Ages 25-65+ Preferred:** HPV testing alone every 5 years *OR* **Acceptable:** Either Cytology plus HPV testing every 5 years *OR* Cytology alone every 3 years
Age to end screening	**65** if 3 consecutive negative Pap tests OR 2 negative cytology plus HPV tests OR 2 negative HPV tests AND no abnormal tests within the prior 10 years		

What is Primary HPV Screening?

- Primary HPV screening is testing for HPV first, followed by a triage test such as cytology and/or HPV genotyping if the initial test is positive.
- The presence of a high-risk HPV type indicates a risk for developing a cervical pre-cancer or cancer—especially if the HPV test remains positive over time (years)
- There are only two HPV tests that are currently FDA approved for primary screening.
- *Historically cervical cancer screening was done with either Pap testing (cytology) or Pap plus HPV test (cotesting)*

Benefits of Primary HPV Screening

Advantages of Primary HPV Screening

- •Improved sensitivity for CIN3+ over cytology alone (↑detection by 50%)
  - Minimal loss of sensitivity over cotesting for CIN 3+. Difference is not statistically significant for cancer diagnosis*.
- •More efficient than cotesting
  - Similar reduction in cancer but requires far fewer tests overall
- •Potential for self-sampling
- •Improve access

*Gage JC et al *J Natl Cancer Inst.*2014;106(8)

See additional references in speaker notes and at the end of the presentation

Disadvantages of Primary HPV Screening

- •Lack of specificity
- •Requires integrated infrastructure to assure appropriate follow-up of positive HPV results
- •Only two tests are FDA approved for primary HPV screening
  - Not all HPV tests are approved for primary HPV screening

*See references in speaker notes and at the end of the presentation

Sensitivity of Screening Modalities

Pap Test

Low sensitivity

(high false negative)

HPV Test

High sensitivity

(low false negative)

***of a single pap test vs. a single HPV test**

Primary HPV Screening Compared to Cotesting

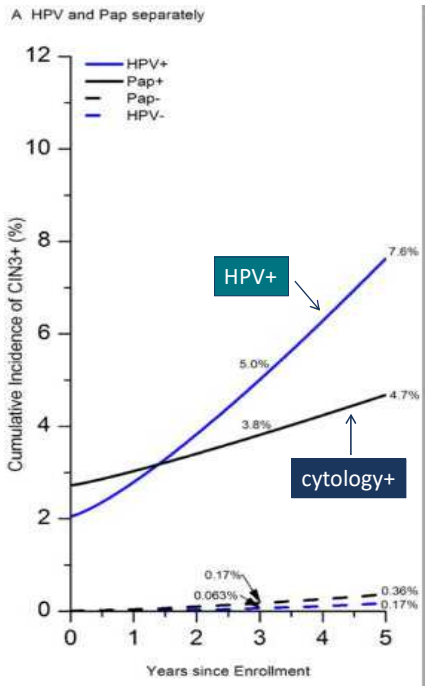
Primary HPV screening results in similar reduction in cancer rates compared to cotesting, with far fewer tests.

Strategy	Total Tests	Colpos	CIN 2,3	Cancer Cases	Cancer Deaths
No screening	0	0	0	18.86	8.34
Cyto q 3 y age 25-65	13,313	564	142	2.60	0.86
Cyto q 3 y from age 21 then Co-test q 5 y age 30-65	19,806	1,630	201	1.08	0.30
HPV q5 y age 25-65	10,954	1,775	195	0.94	0.28

*Per 1,000 persons with a cervix, screened over a lifetime

Fontham ETH, 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.

HPV Screening Alone Predicts Future Risk Better than Cytology



Katki et al. Benchmarking CIN3+ risk as the basis for incorporating HPV and Pap cotesting into cervical screening and management guideline. *J Low Genit Tract Dis.* 2013 Apr; 17(5 0 1): S28-S35

Far Fewer Cases of CIN3+ over 6 Years in Women Screened with HPV-based Tests than Cytology

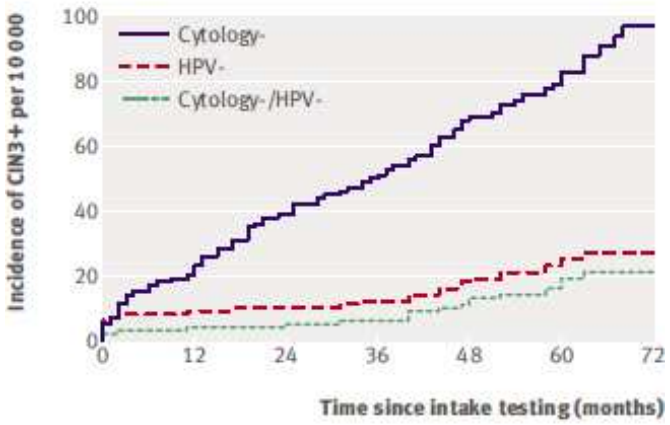


Fig 2 | Kaplan-Meier plots of cumulative incidence rate for CIN3+ for women according to baseline test results in first 72 months of follow-up, excluding Denmark and Tübingen

Dillner J, et al. Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: Joint European cohort study. *BMJ.* 2008;337:a1754.

Primary HPV Screening is the Most Cost-Effective Approach

Screening Modality	Cases of CIN3+ Detected	Number of Colposcopies	Cost
Primary HPV Screening	294	2422	$3.47 M
Primary Cytology	285	2966	$4.80 M
Cotesting	308	2988	$5.85 M

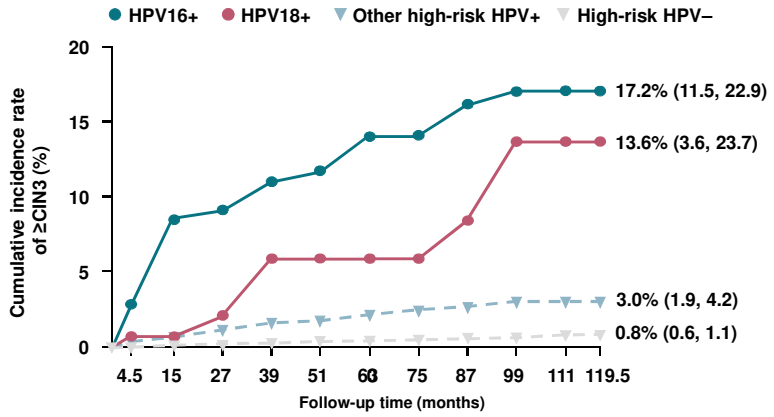
Modeling study based on 99,549 patients with cotesting followed over 3 years.

Jin XW, et al. Cost-effectiveness of primary HPV testing, cytology and co-testing as cervical cancer screening for women above age 30 years. *J Gen Intern Med.* 2016;31(11):1338-1344.

Important Considerations for Primary HPV Screening

Not All HPV Genotypes are the Same

Cumulative Risk of ≥CIN 3 Based on HPV Genotype at Baseline



At time zero, Pap negative or minimal abnormality

Khan MJ, et al. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. *J Natl Cancer Inst.* 2005;97:1072–1079.

Not all HPV Tests are the Same: Only TWO Tests are FDA approved for Primary HPV Screening in the United States

Assay	HC2	Aptima	cobas®*	Onclarity™*
Detection of…	HPV DNA	HPV E6/E7 mRNA	HPV DNA	HPV DNA
# of HPV types	13	14	14	14
Approved for primary screening	No	No	Yes	Yes
Assay type	RNA-DNA hybrids	E6, E7 mRNA	PCR	E6, E7 PCR
Internal control for specimen adequacy	No	No	Yes	Yes
HPV 16/18 genotyping results provided	No	No Can add 16, 18/45 11 others as an additional test	Yes 16, 18, 12 others	Yes 16, 18, 45, 31, 51, 52, [33,58], [56,69,66], [35,39,68]

**Approved for primary HPV screening*

How Many Visits are Needed for Primary HPV Screening?

- Both Roche cobas® and BD Onclarity™ have been validated for use with thin layer cytology samples
- That means that for clinician obtained samples the HPV can be checked and if positive, the cytology and genotyping can be performed on the same sample without an additional patient visit.
- This may require you to order “reflex cytology”—discuss with your lab.

Eventually we may be able to do “point of care” single visit HPV screening with self-sampling too.

Provider and Patient Concerns about Primary HPV Screening

Will we miss cancers?

Most cancers are caused by HPV, and HPV has been shown to be more sensitive and to pick up pre-cancers earlier than cytology alone.

Will colposcopies increase or decrease?

This is a bit unclear because as the percentage of younger women get vaccinated there should be many fewer younger women who test positive, but we will still be able to detect abnormalities among older women.

Will patients still see their providers?

There will still be many reasons for annual and other preventive health care visits and the frequency of primary HPV is not different from cotesting which has been well accepted.

Managing Positive HPV Test Results

What is Management?

Management guidelines refer to managing abnormal results and include guidance for ongoing surveillance of women after prior abnormal results or treatment (ASCCP).

What Happens After a Positive HPV Test?

- Partial Genotyping (16/18/Other)
- Extended Genotyping
- Cytology
- Dual-stain p16/Ki-67

Primary HPV Screening: Management with Partial Genotyping

- The currently FDA approved tests report HPV genotypes like this: HPV16 and HPV18 (Roche cobas®) or HPV16 and HPV18 plus several other individual and pooled high-risk genotypes (BD Onclarity™)
- HPV16 is the most carcinogenic, and is associated with approximately 60% of all cervical cancers, while HPV18 accounts for approximately 10% to 15% of cervical cancers
- Currently, the ASCCP Management Guidelines only use information from HPV16/18 genotyping and the pooled result.

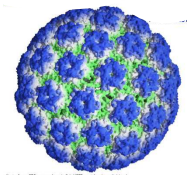
ASCCP 2019 Risk-Based Management Consensus Guidelines Key Points

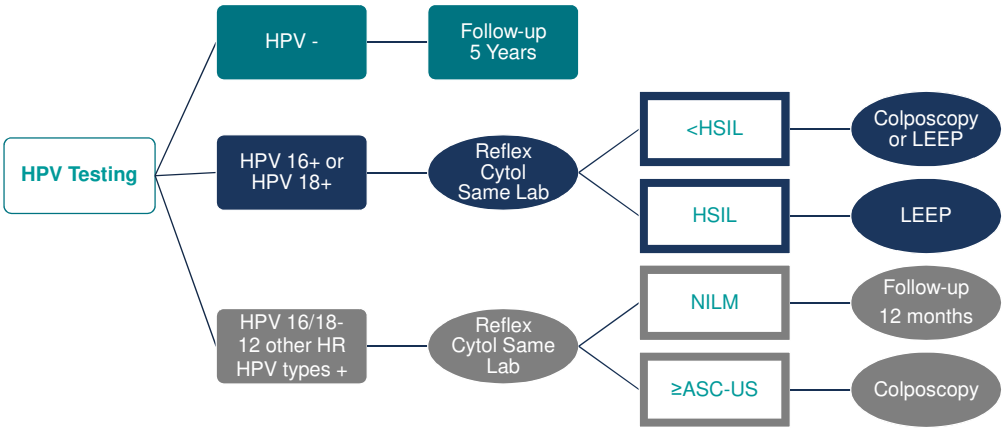
Persistent HPV is high risk compared to new HPV infection

- Prior HPV test result is an important risk modifier (negative, positive or unknown)

Individual patient risk estimates determine management

Algorithm for Primary HPV Screening





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Perkins RB, 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(2):102-131.

Primary HPV Screening Internationally

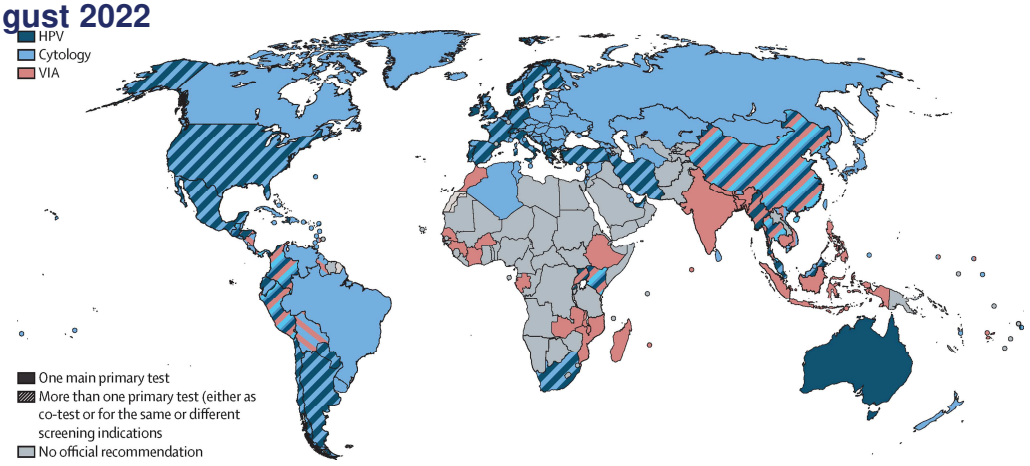
Studies on Primary HPV Screening Effectiveness in Different Countries

Multiple studies in different countries support the effectiveness of primary HPV screening for cervical cancer screening

- POBASCAM (Netherlands)
- ARTISTIC (United Kingdom)
- SWEDESCAN (Sweden)
- HPV Focal (British Columbia)
- Compass (Australia)
- ATHENA (United States)

Countries that Recommend Primary HPV Screening

48/139 countries (35%) recommend primary HPV screening as of August 2022



Bruni L, et al. Cervical cancer screening programmes and age-specific coverage estimates for 202 countries and territories worldwide: a review and synthetic analysis. *Lancet Global Health.* 2022;10(8):E11

New Developments

Extended Genotyping, Dual Stain, Self-sampling

Potential Benefits of Extended Genotyping in Response to a Positive HPV Result

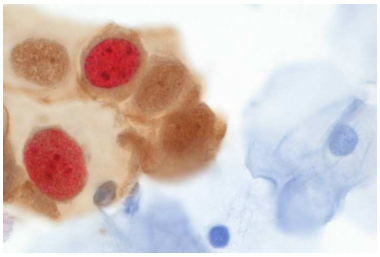
- Adds additional high-risk types, e.g. 31, to pool of high-risk genotypes (16/18) that may require immediate colposcopy
  - i.e. CIN3+ risk above colposcopy threshold.
- Identifies genotypes at very low risk that could possibly be followed at interval longer than one year
  - e.g. 56, 59, 66.
- By identifying individual genotypes, allows more precise identification of type-specific persistence, a higher risk condition than persistence of pooled HPV positivity.
- Additional studies needed to increase validity of HPV types in risk strata and assess clinical utility. Extended genotyping is not yet incorporated into the ASCCP guidelines.

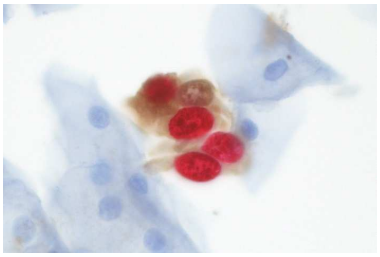
Stoler MH, et al. Stratified risk of high-grade cervical disease using Onclarity HPV extended genotyping in women, ≥25 years of age, with NILM cytology. *Gynecol Oncol.* 2019;153(1):26-33.

p16/Ki-67 Dual Stain

The positivity of p16/ki-67 strongly indicates the presence of high-grade dysplasia.

FDA approved 3/2020, but not yet incorporated into ASCCP algorithms





- Ki-67 is a marker of cell proliferation.
- P16 is a marker of loss of cell cycle regulation- a hallmark of neoplastic transformation.
- Under normal physiologic conditions, staining of p16 and Ki-67 should not show expression in the same cells.

Red nuclear stain: Ki-67
Brown cytoplasmic stain: p16

Slide modified from Teresa Darragh, MD

Clinical Advantage of Triage with Partial Genotyping plus Dual Stain

Fewer colposcopies

CIN3+ risk of 16/18 positive with negative dual stain falls below colposcopy threshold

These patients brought back for surveillance in one year

More patients returned to routine screening

Patients testing 16/18 negative plus dual stain negative

Fewer colpos per CIN3+ diagnosis

Greater efficiency

Wentzensen N, et al. Clinical evaluation of human papillomavirus screening with p16/Ki-67 dual stain triage in a large organized cervical cancer screening program. *JAMA Intern Med.* 2019;179(7):881–888.

Self-sampling

- Not yet FDA approved in US
- Multiple effectiveness studies and patient acceptability studies have shown that self-sampling is effective, is cost-effective and is acceptable to women, especially among under-screened populations
  - Sensitivity comparable to clinician-obtained samples with PCR-based HPV tests.
  - A positive test requires a physician collected specimen for triage

Arbyn M, et al. Detecting cervical precancer and reaching underscreened women by using HPV testing on self-samples: Updated meta-analyses. *BMJ*. 2018;363:k4823.

Performance of Self-sampling Compared to Clinician-collected Samples

- A randomized, paired screen-positive, non-inferiority trial
- RCT of women in the Netherlands
- 187,473 women invited to participate:
- 8,212 participants randomly allocated to the self-sampling group
- 8,198 randomly allocated to the clinician-based sampling group

HPV-positive cross-test results by study group and outcome

	Total	Self-sampling group	Clinician-based sampling group
CIN2 or worse	184/194 (95%)	106/110 (96%)	78/84 (93%)
CIN3 or worse	108/113 (96%)	69/72 (96%)	39/41 (95%)

Polman NJ, et al. Performance of human papillomavirus testing on self-collected versus clinician-collected samples for the detection of cervical intraepithelial neoplasia of grade 2 or worse: A randomised, paired screen-positive, non-inferiority trial. *Lancet Oncol.* 2019;20(2):229-238.

Thank you!

Questions?

References

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