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CERVICAL CANCER SCREENING GUIDELINES:

Analyzing the Evolving Evidence

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Introduction: Current Cervical Cancer Screening Guidelines

New technologies and data emerge continually, and this toolkit provides a review of cervical cancer screening guidelines today. Included is a discussion of the benefits of co-testing and Pap testing, as well as important considerations and recommendations for the future of screening.

- The American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), American Society for Clinical Pathology (ASCP), and American College of Obstetricians and Gynecologists (ACOG) recommend that:[1,2]
  - Women should begin cervical cancer screening at 21 years of age.
  - Women 21 to 29 years old should be screened with Pap testing alone every 3 years.
  - Women age 30 to 65 years should be screened with Pap testing plus human papillomavirus (HPV) testing (co-testing) every 5 years, HPV testing alone every 5 years, or Pap testing alone every 3 years.
  - Women with adequate negative prior screening should discontinue screening after age 65.
- In August 2018, the US Preventive Services Task Force (USPSTF) published an "A"-level recommendation advising that women age 30 to 65 years may be screened with HPV testing alone, also referred to as HPV alone* in this document, every 5 years.[3] All other society guidelines remain unchanged.

Major professional societies agree:
Pap plus HPV together (co-testing) is the preferred cervical cancer screening method for women 30 to 65 years old.

AGE GROUP	RECOMMENDATIONS
< 21 Years	No routine speculum exam or cytology regardless of age of onset of intercourse or other risk factors. STD testing and counseling on safe sex and contraception as needed.
21–29 Years	Screening with cytology alone every 3 years.
30–65 Years	Cytology and high-risk HPV testing (co-testing) every 5 years (preferred per ASCCP), or high-risk HPV alone every 5 years, or cytology alone every 3 years.
> 65 Years	Discontinue screening after age 65 following adequate prior screening. However, women with a history of CIN2 or a more severe diagnosis should continue screening for at least 20 years.

*A positive HPV screening result may lead to further evaluation with cytology and/or colposcopy.

Benefits of Co-Testing

Benefit:
Better Detection of CIN3+ at Baseline

- Co-testing detects more precancerous lesions (severe cervical intraepithelial neoplasia or worse) than screening with HPV alone.[4,5]
- Studies have consistently shown that screening with HPV alone misses more cases of cervical cancer than screening with co-testing.[4,6-11]

RECOMMENDATION:
Screening with Pap plus HPV together (co-testing) should remain the preferred method of screening for women 30 to 65 years of age.

- A study of over a million women in the Kaiser Permanente Health System found that among 405 cases of cervical cancer detected during the study, 18.8% were HPV negative compared with 12.3% that were co-test negative.[4]
- Investigation of screening results from over 250,000 women in the Quest Diagnostics Health Trends study found that among 526 women with cancer, 18.6% tested negative for HPV less than 1 year prior to cancer detection, while only 5.5% were co-test negative less than 1 year before diagnosis (Figure 1).[6]
- Several studies have reported similar results, with HPV testing alone failing to detect between 9% and 31% of cervical cancer cases (Figure 2).[4,6-11]
- For precancers (AIS and CIN3), co-testing detected 93.9% (any+), HPV alone detected 86.7% (HPV+), and Pap detected 91.0% (Pap+) (Figures 3 and 4).[5]

Figure 1. Number of cases of cervical cancer < 1 year prior to diagnosis[6]

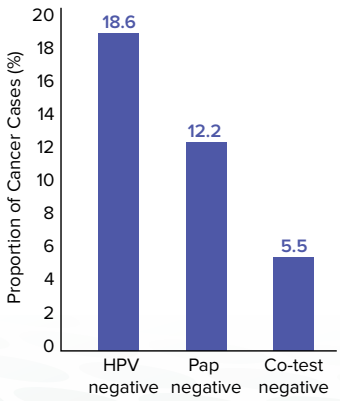
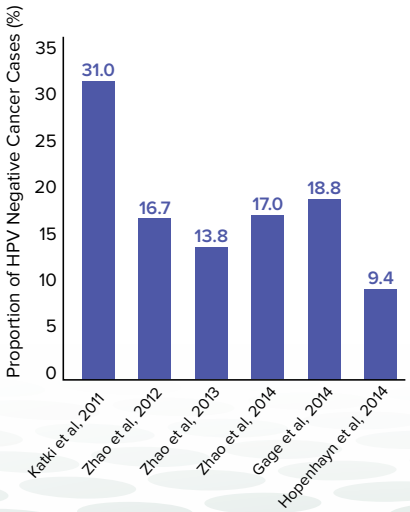


Figure 2. Summary of cervical cancer cases that tested negative for HPV over several recent studies[4,6-11]



Study
The clinical studies represented within these sources were conducted using different study designs and various assays. Products included hc2, cob as 4800, ThinPrep®, SurePath, Linear Array, INNO-LiPA Genotype test.

Benefits of Co-Testing

Figure 3. Twice as many women with cervical cancer would be missed with HPV-alone screening versus co-testing[5]

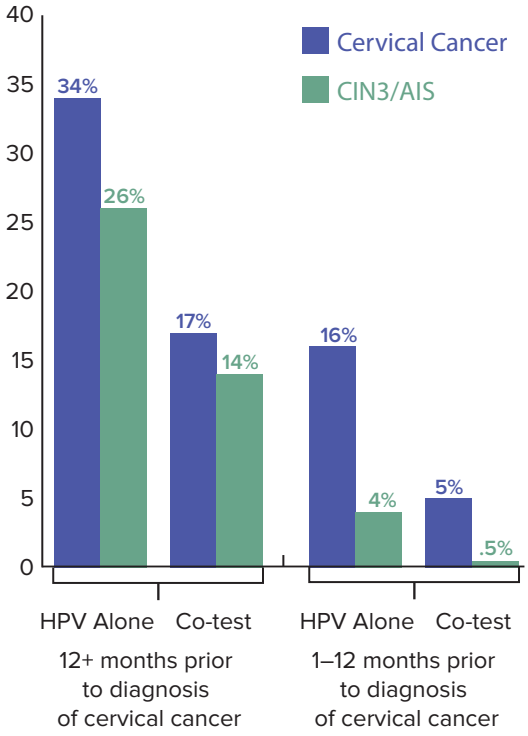
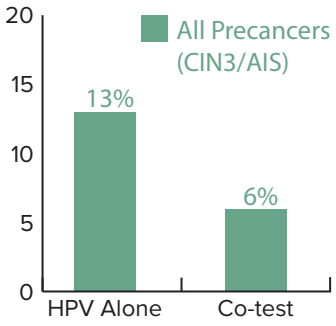


Figure 4. Among 1,000 women, proportion of all precancer cases (CIN3, AIS) that would be missed by HPV-alone screening versus co-testing[5]



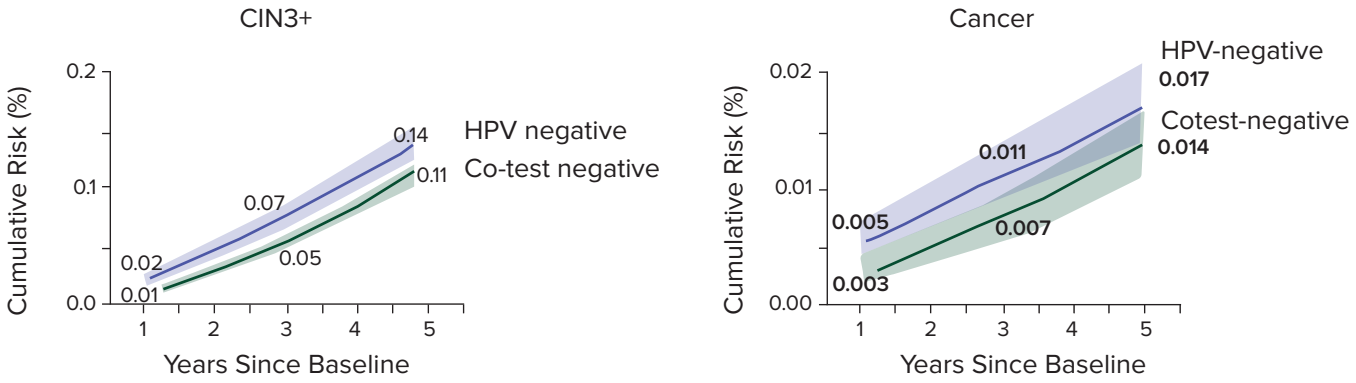
Benefits of Co-Testing

Benefit:
Reassurance Against CIN3+

- In a study of more than a million women, the risk of developing CIN3+ within 3 years of screening was 29% lower in women who were co-test negative versus women who tested HPV negative (Figure 5).[4]
- In seven European studies, 24% fewer women who were co-test negative at baseline developed CIN3+ over a 6-year period compared with women who were only HPV negative at baseline.[12]

Screening with Pap plus HPV together (co-testing) provides greater reassurance against cervical cancer than screening with HPV alone.

Figure 5. Risk of women developing CIN 3+ *(left)* and cancer *(right)* following screening with HPV alone versus co-testing at 1-, 3-, and 5-year intervals[4]



Additional Benefits of Pap Testing

- HPV DNA levels change as cancer progresses. Some advanced cancers may test negative for HPV DNA and would be missed by HPV only screening. Alternatively, screening by detection of HPV DNA may pick up latent infections that are unlikely to become clinically relevant, causing unnecessary colposcopies and patient anxiety.[13]

Detecting adenocarcinoma and providing additional reassurance are among the additional benefits conferred by Pap plus HPV testing together.[6,13]

- In the Quest Diagnostics Health Trends study, among 169 adenocarcinomas detected, 26.6% were HPV negative less than 1 year prior to diagnosis compared with 8.3% that were co-test negative.[6]
- Collecting one Pap test sample can yield multiple test results, including detection of glandular disease and STIs such as *Chlamydia trachomatis* and *Trichomonas vaginalis* (Figure 6).

Figure 6. Multiple tests from one vial

Multifaceted Functionality	ThinPrep® Pap Test[a]
FDA Approval	1996
Improved Specimen Adequacy (compared to conventional Pap)	✓
Improved HSIL Detection (compared to conventional Pap)	✓
Glandular Disease Detection Labeling	✓
FDA Approved for Adjunctive HPV Tests	Aptima® HPV Assay Cervista® HPV Assays cobas HPV Test HC2 Assay
Adjunctive STI Approval/Clearance	Aptima Combo 2® CT/NG Assays Aptima® Trichomonas vaginalis Assay ProbeTec CT Q^{x} Assay
Shelf-life: Aptima HPV assays[b] Cervista HPV assays[c] Qiagen HC2 assay[d] cobas HPV assay[e]	 15 weeks 24 weeks 12 weeks 24 weeks

a. ThinPrep 2000 System [package insert]. MAN-02585-001 Rev. 007. Marlborough, MA: Hologic Inc.; 2017.
b. Aptima HPV Assays [product insert]. AW-11141-001. Rev 003. San Diego, CA. Hologic Inc.; 2015.
c. Cervista [package insert]15-3100. Rev 105. Marlborough, MA: Hologic Inc.; 2016.
d. Hc2 high risk HPV DNA test [package insert]. Gathenburg, MD, Qiagen; 2008.
e. cobas 4800 HPV test [package insert]. 05641225001-14 EN. Rev 12.0 Branchburg, NJ. Roche Molecular Systems, Inc. 2015.

Screening Intervals

- Cervical cancer is associated with persistent HPV infections. In young women who have recently become sexually active, the rate of HPV infection is high, but the large majority of those infections clear on their own (Figure 7).[14,15]
- Ronco et al.[16] found that screening with HPV alone resulted in overdiagnosis of cervical lesions in women 25 to 34 years old.

RECOMMENDATION:
Pap testing every 3 years should remain the primary screening strategy for women 21 to 29 years of age.

- Women under age 30 are unlikely to develop cervical cancer (Figure 8),[17] and overtreatment of precancerous abnormalities associated with transient HPV infection can potentially cause complications in pregnancy.[18,19]
- Positive HPV results have been associated with increased anxiety shortly after testing[20] and can result in women reporting worse feelings about their previous and future sexual relationships.[21]
- In 2012, the ACS, ASCCP, and ASCP recommended that "because of the high prevalence of HPV in women under the age of 30, HPV testing should not be used to screen women in this age group due to the potential harms."[1]

Figure 7. Clearance of high-risk HPV infections over 30 months in women age 21 to 29 years[14]

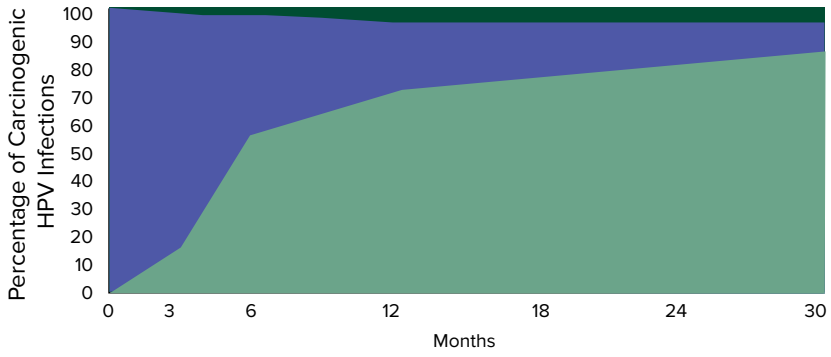
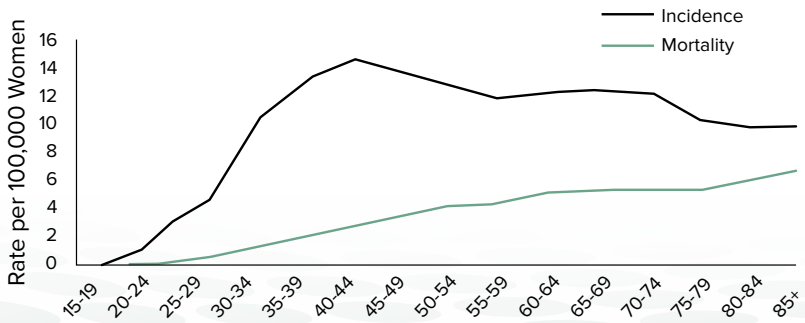


Figure 8. Cancer of the cervix uteri (invasive) incidence and mortality per 100,000 women by age in the United States[22]

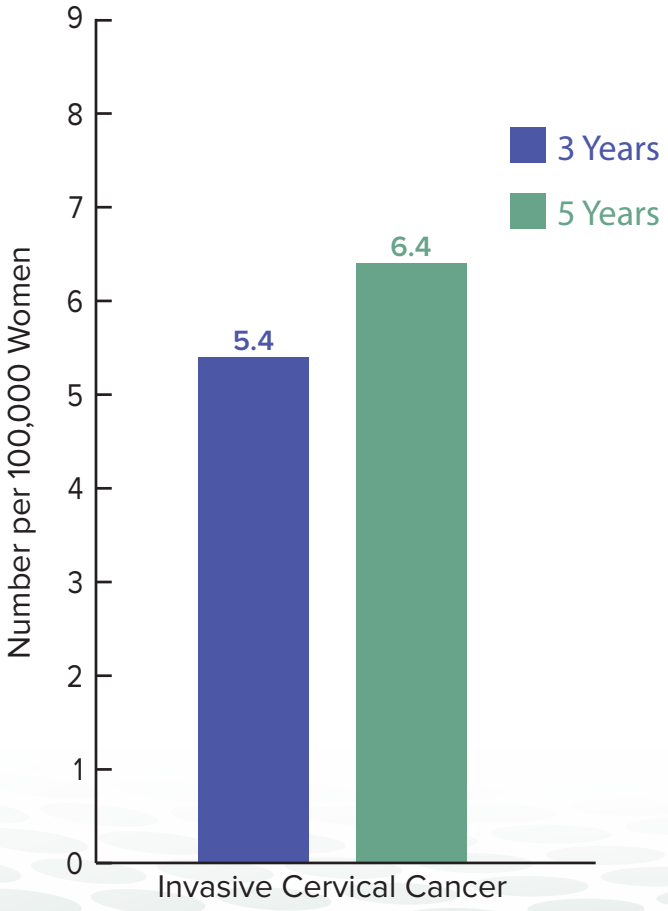


Screening Intervals

- A model of the outcomes associated with various cervical cancer screening strategies published by the USPSTF in 2013 found that lengthened screening intervals may result in appreciable increases in cervical cancer cases.[23]
- Castle et al.[24] found that for every co-testing round, the risk of CIN3+ was greater at 5 years than at 3 years (Figure 9):
  - Round 1 (no previous negative co-test): 0.070% (3 years) versus 0.098% (5 years)
  - Round 2 (1 previous negative co-test): 0.036% (3 years) versus 0.052% (5 years)
  - Round 3 (2 previous negative co-tests): 0.020% (3 years) versus 0.035% (5 years)

RECOMMENDATION:
The interval for screening women over 30 with Pap plus HPV together (co-testing) should be changed from 5 years to 3 years.

Figure 9. Cumulative detection of (risk for) cervical cancer at 3 and 5 years after screening, by HPV testing and cytologic evaluation based on screening history (not preceded by a negative co-test)[24]

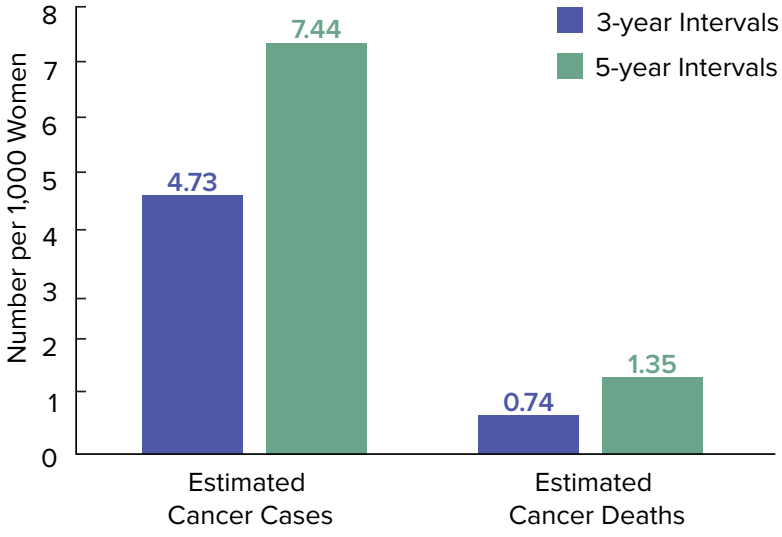


Screening Intervals

- Gage et al.[25] found that for women age 30 to 64, the 3-year risk in the New Mexico Human Papillomavirus Pap Registry (NMHPVPR) cohort was 0.39% and the 5-year risk was 0.54%. These data may be more reflective of real-world screening practices than the managed care setting studied by Castle et al.,[24] however, the trends in screening intervals are consistent across practice settings.

Lengthening screening intervals from 3 years to 5 years is estimated to double cervical cancer cases (Figure 10), with an additional 1 in 369 women in the United States being diagnosed with cervical cancer using a 5-year interval.[23,26]

Figure 10. Estimated cancer cases and deaths per 1,000 women over a lifetime for a screening strategy beginning with Pap testing over 3 years at age 21, then co-testing at 3- versus 5-year intervals beginning at age 30[26]



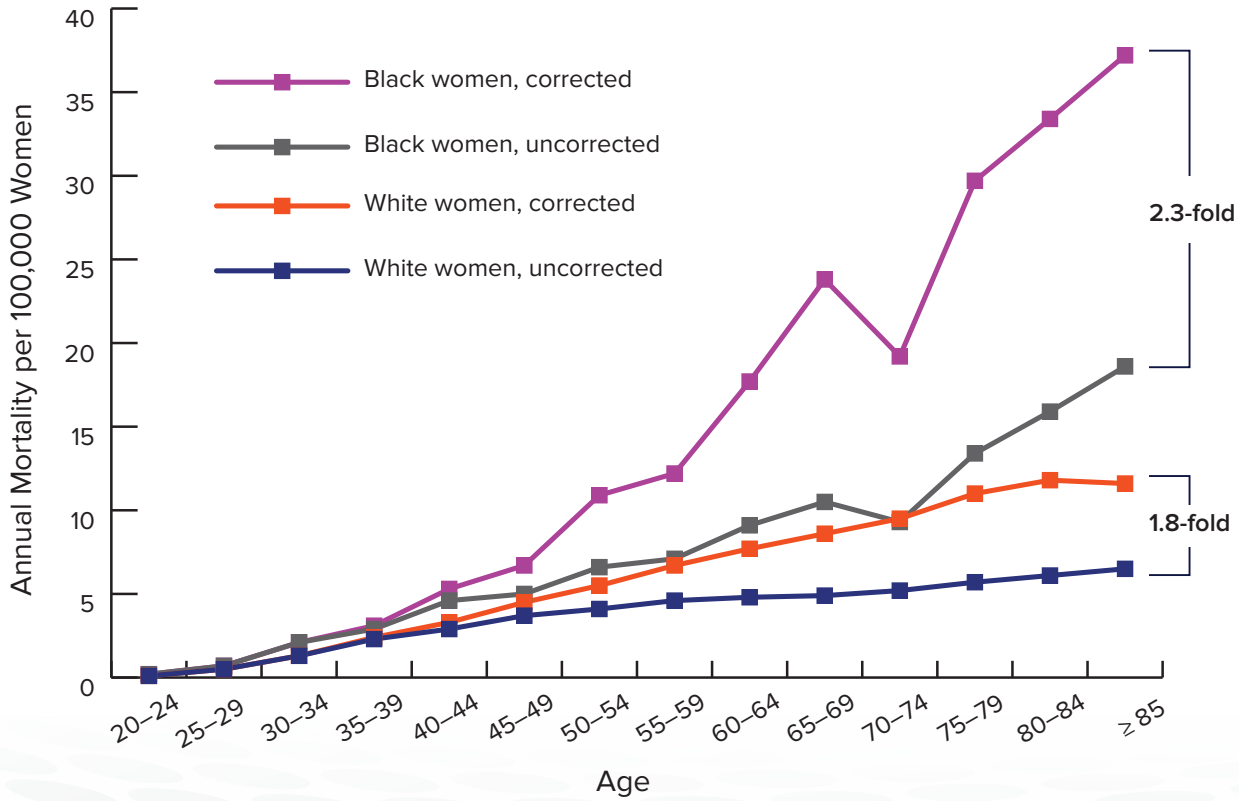
Screening in Women Over 65

The current recommendation is to stop screening at 65 because the risk of cervical cancer in women over this age is thought to be small. However, data suggest that this risk might be underestimated for several reasons:

RECOMMENDATION:
Continue screening in women over 65.

- **Underestimation of risk:** Previous studies have not accounted for the increased rates of hysterectomy in women over 65. Women without a cervix are not at risk for cervical cancer, so these previous studies likely underestimated the risk for cervical cancer in women over 65.[27]
- **Disparities in prevalence:** Cancer disparities in African American women may underestimate the risk of death from cervical cancer in women over 65 (Figure 11).[28]
- **Changing sexual practices:** Current risk assumptions for number of lifetime sexual partners and HPV exposure may not be accurate for current cohorts of women. Changing sexual practices mean that women have more partners, and later in life, leading to increased HPV exposure.[29]

Figure 11. Cervical cancer rates for women 65+ may underestimate the true prevalence[28]



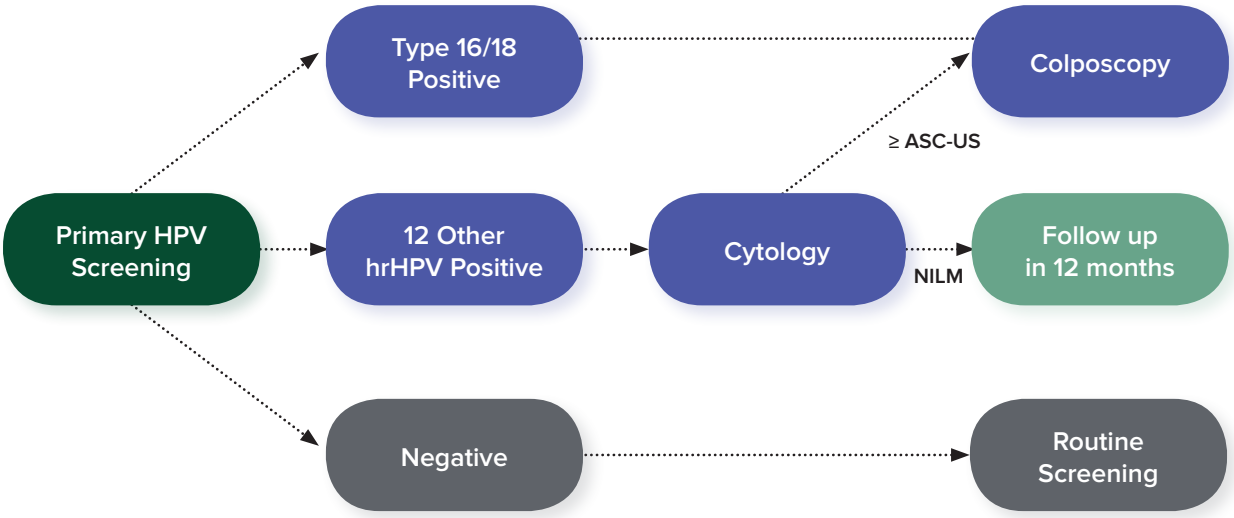
Correcting Common Misconceptions

- A common misconception is that HPV only is easier logistically. However:
  - **HPV testing and Pap testing involve the same procedure** for both provider and patient.
  - HPV and Pap testing use the **same collection device** and are performed on the **same sample**.
  - Both tests offer the **same level of patient comfort.**

MISCONCEPTION:
"Screening with HPV alone is easier."

- **Current interim guidance for screening with HPV alone is complex,** and adherence may be a challenge.
  - The screening algorithm put forth by the Interim Guidance published simultaneously in *Gynecologic Oncology*, the *Journal of Lower Genital Tract Disease,* and *Obstetrics & Gynecology* is complicated, requires additional provider and patient time and resources, and invites more risk of disease than screening with Pap plus HPV together (Figure 12).[30]

Figure 12. Recommended algorithm for screening with HPV alone[30]



Correcting Common Misconceptions

- A survey of women's perceptions of cervical screening practices found that the majority of women screened reported that they would prefer to continue to receive Pap testing, with approximately 40% reporting that they would be anxious if they received screening with HPV alone.[31]

MISCONCEPTION:
"Patients will be unaffected by additional changes in cervical cancer screening."

- Another study found that 68.4% of women surveyed were willing to attend cervical screening every 3 years, while only 25.2% were willing to adopt a 5-year screening interval.[32]
  - The stigma surrounding a positive HPV test has been found to affect anxiety, but cancer risk and the potential for cervical lesions are of greater concern.[33,34]
  - There is some evidence that HPV testing does not increase a woman's anxiety when it is combined with Pap testing.[35]
- Women may be resistant to changes in screening intervals and methodology associated with changes in cervical screening technology.

Screening with HPV alone and extended screening intervals cause patient anxiety.

Correcting Common Misconceptions

MISCONCEPTION:
"Screening with HPV alone is less expensive."

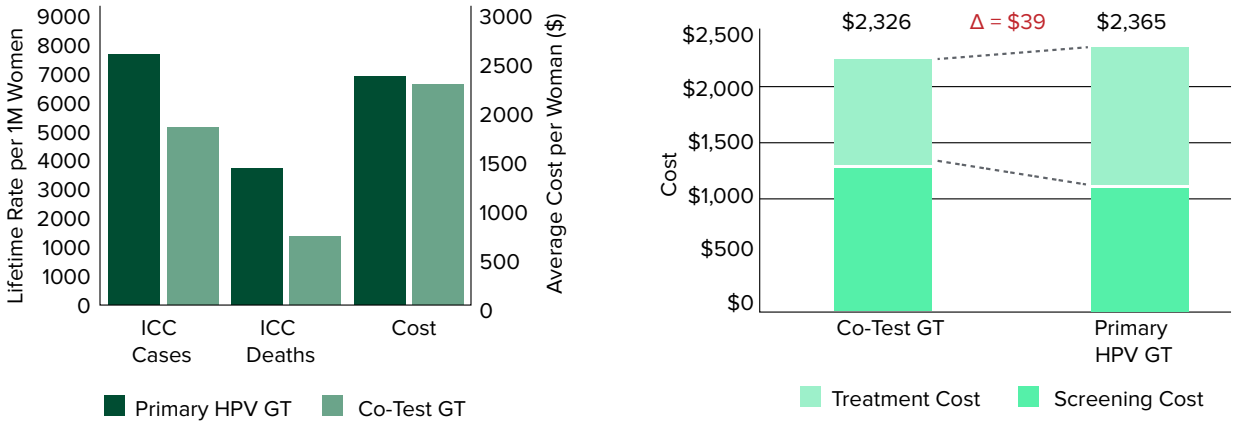
One screening test is not more cost-effective than two:

- Several factors affect the relative costs of screening with HPV alone versus with Pap plus HPV together (co-testing):
  - Test performance (sensitivity/specificity)
  - Test costs
  - Treatment costs
- A cost-effectiveness model comparing different cervical screening strategies found that an HPV-alone screening strategy that included genotyping for two high-risk strains, HPV 16/18, reduced costs with similar effectiveness to a co-testing strategy that did not include genotyping for HPV 16/18.[36]
- Further investigation of the cost-effectiveness of co-testing with HPV 16/18 genotyping compared with screening by HPV 16/18 genotyping alone found that co-testing provided greater clinical benefit at similar costs (Figure 13).[37]

Model assumptions:

- Co-testing at 3 years versus 5 years
- Screening with an mRNA-based HPV test and liquid-based cytology, compared to HPV alone screening with a DNA-based test

Figure 13. Lifetime cervical cancer incidence and mortality, and average cost per woman, for co-testing with HPV 16/18 genotyping *(left)* versus screening with HPV alone with HPV 16/18 genotyping *(right)*[37]



This data is intended for insurers.
1M: 1 million
HPV: Human papillomavirus
ICC: Invasive cervical cancer

Correcting Common Misconceptions

- Evidence shows that while all FDA-approved HPV tests are highly sensitive for detecting CIN2+, mRNA testing is the most specific for detecting biopsy-confirmed CIN3+ at baseline screening.
- Four separate peer-reviewed studies have demonstrated that testing with assays that detect HPV mRNA is equivalent to testing with DNA-based assays (Figure 14).[38-41]
  - Screening with HPV mRNA or DNA provides the same protection against detecting CIN2+ up to 7 years after initial screening[37]

MISCONCEPTION:
"Testing for HPV mRNA will miss precancers."

Figure 14. Summary of longitudinal studies comparing HPV DNA and mRNA-based tests

Study	Screening Population	# Years of Follow-up	Risk of CIN2+ Following Baseline HPV mRNA–	Risk of CIN2+ Following Baseline HPV DNA–	Statistically Significant Difference?
Reid et al.[38] CLEAR study	n = 10,509	3	0.23%	0.26%	No
Cook et al.[39] FOCAL study	n = 3,476	4	0.53%	0.56%	No
Iftner et al.[40] GAST study	n = 10,040	6	0.62%	0.47%	No
Forslund et al.[41]	n = 65,911	7	0.16% for CIN3+	0.12% for CIN3+	No

- In women with ASCUS or LSIL, screening with HPV mRNA achieved high long-term sensitivity in predicting future cervical dysplasia.[42]
  - –Johansson et al.[42] showed that 100% of CIN3+ detected 4.5 years after screening had been mRNA-positive at baseline.

RECOMMENDATION:
Risk-based guidelines should not distinguish between mRNA-based or DNA-based testing as evidence demonstrates that both assays provide **equivalent protection** against detecting CIN2+ up to 7 years later.

Summary of Recommendations

CERVICAL CANCER SCREENING:
The Future

These evidence-based recommendations are aimed at balancing harms and benefits in order to achieve optimal patient care:

- **Co-testing is preferred in women ≥ 30**: Maintain Pap plus HPV together (co-testing) as the preferred method for cervical cancer screening in women ≥ 30 years old.
- **Decrease the co-testing interval:** Change the interval for co-testing women ≥ 30 years old from every 5 years to every 3 years.
- **Pap testing should remain the preferred test for women < 30:** Recommend that women 21 years of age begin cervical cancer screening with Pap testing every 3 years and not begin HPV screening until ≥ 30 years old.
- **Continue screening women > 65:** Continue screening women over the age of 65 who have not undergone hysterectomy.
- **Risk-based guidelines should not distinguish between mRNA-based or DNA-based testing:** Evidence demonstrates that both assays provide equivalent protection against detecting CIN2+ up to 7 years later.

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