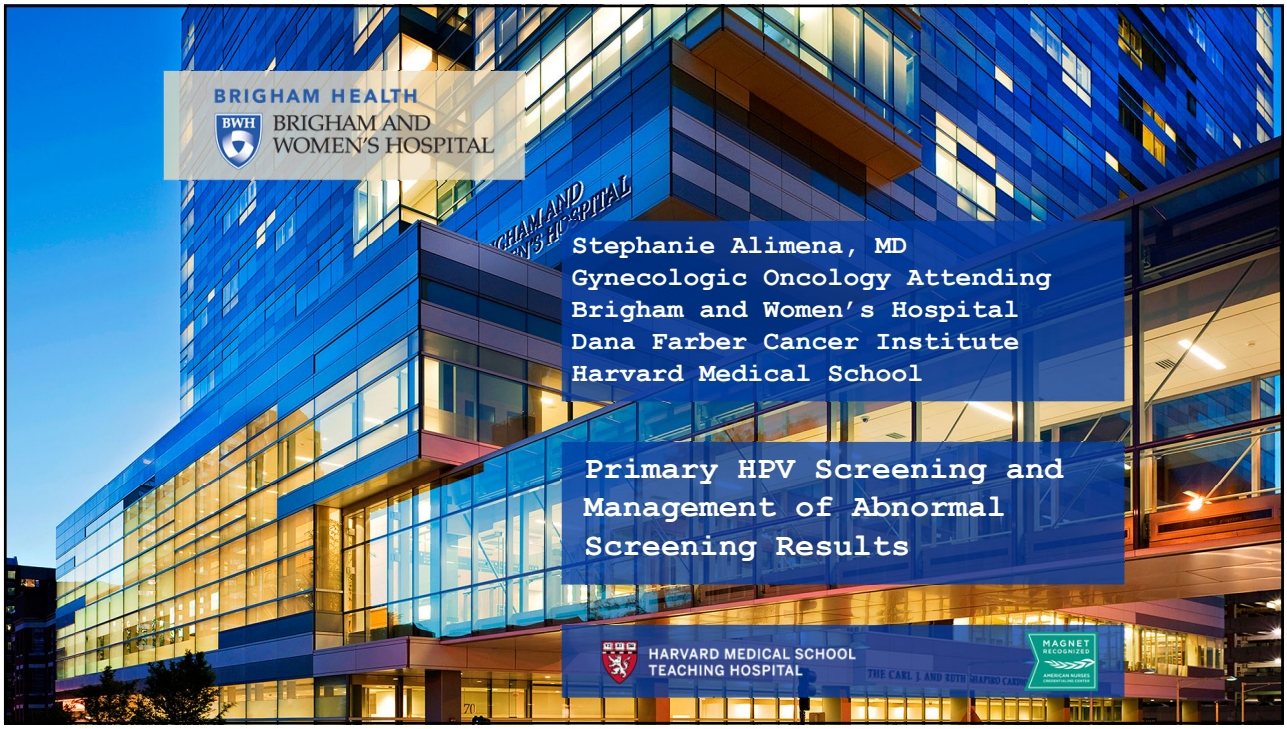

Disclosures: None

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Objectives

1) To review the rationale behind the transition to primary HPV screening.
2) To review which patients are candidates for primary HPV screening.
3) To review experiences in other countries who performed a nation-wide roll out of primary HPV screening.
4) To review data on self-collection of primary HPV testing and current FDA approvals for self-testing.
5) To review how clinicians manage results of primary HPV testing (whether clinician-collected or self-collected).
6) Bonus discussion: screening cessation criteria and limited data around AHCC for persistent HPV positivity.

Background

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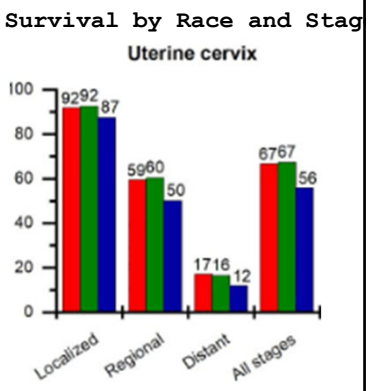
Background

- Cervical cancer is the fourth most common cancer in women and presents a significant risk to all people with a cervix.
- Cervical cancer is caused by persistent infection with high-risk human papillomavirus (HPV) types, in the vast majority of cases.
- In 2023, 13,960 women in the United States were diagnosed with cervical cancer, and 4,310 died from the disease.
- Black and Hispanic women have the highest incidence of and mortality from cervical cancer in the U.S.



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Background

WHO Publication: Global strategy to accelerate the elimination of cervical cancer as a public health problem (Nov 17, 2020)

- A vision of a world where cervical cancer is eliminated as a public health problem
- **90-70-90 targets by 2030:**
  - 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 precancer treated, and 90% of women with invasive cancer managed).

Why Primary HPV Screening?

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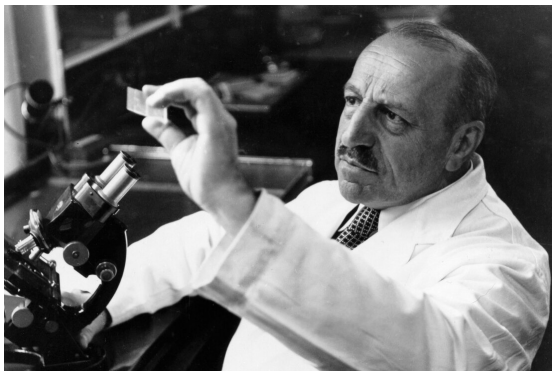
Where it started…

- George Papanicolaou first described the Pap smear in 1928, while working at New York University and Cornell University Medical College.
- Papanicolaou's findings were not widely accepted by the medical community until 1941.
- In 1983, Harald zur Hausen identified the human papillomavirus (HPV) as the cause of cervical dysplasia.



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Where we are right now…

TABLE Summary of screening recommendations

	US Preventive Services Task Force (USPSTF), 2024	American Cancer Society (ACS), 2020[11]
Age to start screening, years	21	25
Age to end screening, years	65	65
Screening test options and intervals	Ages 21–29: Cytology alone every 3 years Ages 30–65: cotesting every 5 years or Ages 21–29: Cytology alone every 3 years Ages 30–65: HPV testing alone every 5 years	HPV testing alone every 5 years or cotesting every 5 years or Cytology alone every 3 years

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Where it's going…

- In 2020, the WHO recommended HPV DNA testing as the primary screening method starting at the age of 30.
- Currently, primary HPV has been adopted in multiple countries, including Australia, the Netherlands, Turkey, England, and Argentina.

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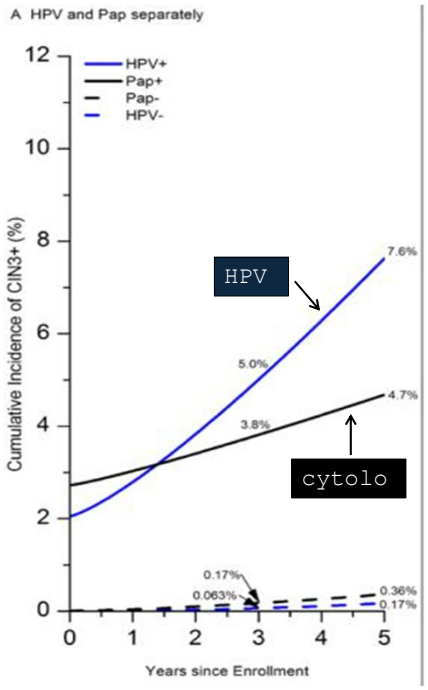
Why Primary HPV Testing?

- Primary HPV screening has been thoroughly tested in 13 population-based randomized controlled trials over 15 years of follow-up.
- All trials found that primary HPV screening is as effective at detecting incident CIN 3+ as cotesting, with fewer harms.
  - Shows improved sensitivity and a higher negative predictive value
  - Offers a **60% to 70% higher protection** against the development of cervical cancer compared to cytology

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

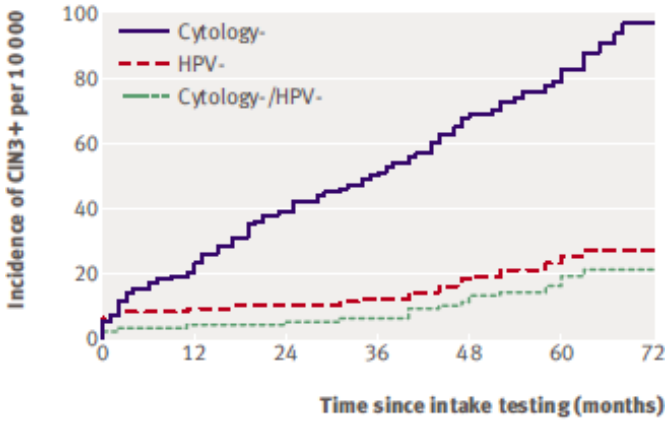


Fig 2 | Kaplan-Meier plots of cumulative incidence rate for CIN3+ for women according to baseline test results in first 72 months of follow-up, excluding Denmark and Tübingen

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.

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Test Characteristics of Screening Strategies for Detecting CIN 3+

	Primary cytology	**Co-testing**	**Primary HPV**
Sensitivity (%, 95 % CI)	90.7 (86.4, 93.8)	99.3 (97.1, 99.9)[§]	94.1 (90.3, 96.5)
Specificity (%, 95 % CI)	97.6 (97.5, 97.7)	97.6 (97.5, 97.7)	98.1 (98.1, 98.2)
PPV (%, 95 % CI)	9.6 (8.4, 10.8)	10.3 (9.1, 11.5)	12.1 (10.7, 13.6)
NPV (%, 95 % CI)	99.97 (99.96, 99.98)	100 (99.99, 100)	99.98 (99.97, 99.99)

4. Jin XW, Lipold L, Foucher J, Sikon A, Brainard J, Belinson J, Schramm S, Nottingham K, Hu B, Rothberg MB. 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 Nov;31(11):1338-1344. doi: 10.1007/s11606-016-3772-5. Epub 2016 Jul 14. PMID: 27418345; PMCID: PMC5071282.

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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 not statistically significant for cancer diagnosis
- •More efficient than co-testing
  - Similar reduction in cancer but requires far fewer tests overall
- •Potential for self-collection
- •Improved access

5. Wright TC, et al. The ATHENA human papillomavirus study: design, methods, and baseline results. *Am J Obstet Gynecol*. 2012;206(1):46.e1-46.e11.
6. 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):189-97.
7. Huh WK, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: Interim clinical guidance. *Obstet Gynecol*. 2015;125(2):330-337.
8. Castle PE, et al. Variable risk of cervical precancer and cancer after a human papillomavirus-positive test. *Obstet Gynecol*. 2011;117(3):650-656.
9. Gage JC, et al. Reassurance against future risk of precancer and cancer conferred by a negative human papillomavirus test. *J Natl Cancer Inst*. 2014;106(8);dju 153.
10. Fontham ETH, Wolf AMD, Church TR, Etzioni R, Flowers CR, Herzig A, Guerra CE, Oeffinger KC, Shih YT, Walter LC, Kim JJ, Andrews KS, DeSantis CE, Fedewa SA, Manassaram-Baptiste D, Saslow D, Wender RC, Smith RA. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. *CA Cancer J Clin*. 2020 Sep;70(5):321-346.

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Disadvantages of Primary HPV Screening

- •Lack of specificity
- •Requires integrated infrastructure
- •Only a few tests are FDA approved for primary HPV testing

1. Wright TC, et al. The ATHENA human papillomavirus study: design, methods, and baseline results. *Am J Obstet Gynecol*. 2012;206(1):46.e1-46.e11.
2. 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):189-97.
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Who is appropriate for primary HPV testing?

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Screening vs Surveillance vs Diagnostic Testing

- **Screening:** Testing for disease among patients with no symptoms and all normal prior results
- **Surveillance:** interval testing among patients who have an abnormal prior test result or prior treatments
  - An unknown history may fall in between routine screening and surveillance
  - If not actually documented –history is unknown and they may have an increased risk of disease
- **Diagnostic:** testing when a patient presents with a symptom such as bleeding, even if they are not "due" for screening (including in younger patients < age 21 and older women > age 65)

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Screening vs Surveillance vs Diagnostic Testing

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eTABLE A

Risk Stratification Options for Cervical Cancer Screening

Population	Recommendation
Low risk Patients who have had a hysterectomy (including the cervix) because of benign conditions Patients with a cervix but who have comorbidities and decreased life expectancy	No testing
Average risk Patients 25 to 65 years of age with a cervix	Primary HPV testing
High risk* Patients 30 to 65 years of age with a cervix and a high-risk condition (i.e., solid organ transplantation, chronic diseases managed by Janus kinase inhibitors or biologics, immunosuppressive drug treatment, HIV/AIDS, postcoital bleeding, or under surveillance for prior HPV-positive testing per American Society for Colposcopy and Cervical Pathology guidelines)	Cotesting

HPV = human papillomavirus.

*—High risk is not defined by smoking status, drug use, number of sex partners, or age (Demarco M, Egemen D, Hyun N, et al. Contribution of etiologic cofactors to CIN3+ risk among women with human papillomavirus-positive screening test results. *J Low Genit Tract Dis*. 2022;26(2):127-134).

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How is primary HPV testing going in other nations?

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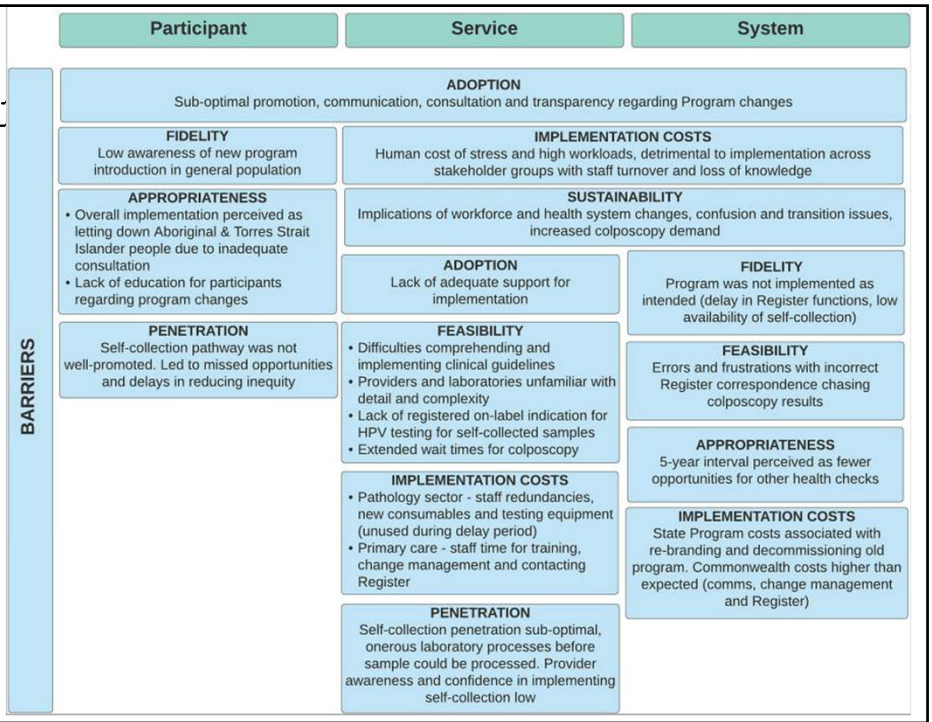
How it's going in other countries

- Several countries have implemented primary HPV-based organized screening programs, including Australia, the United Kingdom, and the Netherlands, including the use of self-sampling as a collection option
- However, program implementations have encountered challenges.
- Web-based petitions against primary HPV screening in Australia and Wales signed by members of the public before the launch (in response to increased screening intervals, later onset of screening, and concerns it was a purely cost-cutting measure)

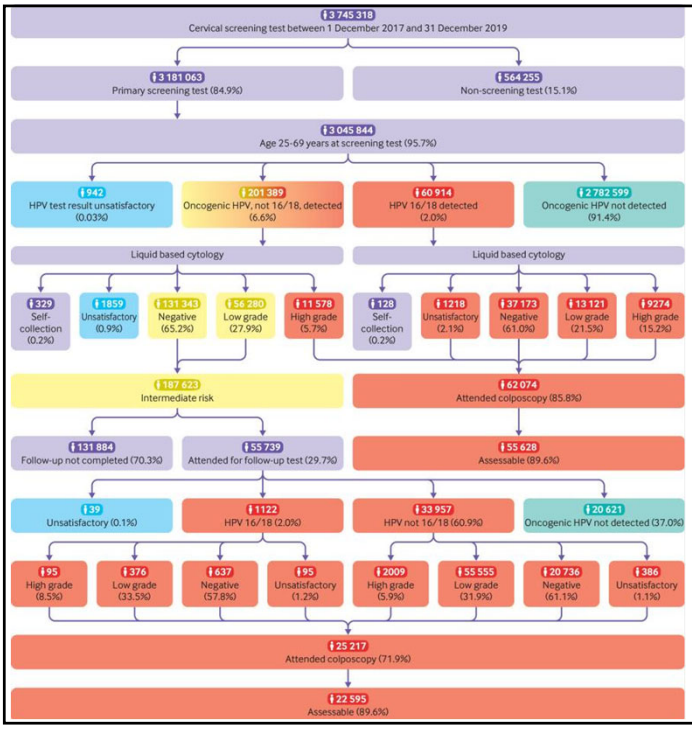
Australia

- In December 2017, the program changed from q2 year cytology for 20-69 year olds to q5 year HPV testing for patients 25-74 years old.
- Patients referred for colposcopy if HPV16/18 is detected OR both other HPV type (non 16/18) and the reflex cytology result showed a high-grade lesion (ASC-H) or worse or glandular abnormalities.
- Patients with HPV types besides 16/18 and negative or low-grade cytology results were referred for repeat HPV testing at 12 months
- The new program was predicted to be more effective and to cost less, with an expected further reduction in incidence and mortality from cervical cancer by 20-30%.

Australi



Brotherton et al, 2023
PMID: 37223565



Unsatisfactory | Low risk (routine screening) | Intermediate risk (12 month follow-up) | Higher risk (colposcopy)

Australia

- Dec 2017 to Dec 2019
- >3 million tests
- 4,522 patients had a self-collected sample (0.1% of patients)
- High colposcopy rates (around 75-80% of those considered high-risk)

Smith et al, 2022
PMID: 35354610

How about the American Cancer Society | National Roundtable on Cervical Cancer

- Despite the demonstrated efficacy and efficiency of primary hrHPV testing, uptake has been slow because of the limited availability of FDA-approved tests and the significant laboratory infrastructure changes required to switch to this screening platform.
- No national program or tracking like in other countries.

PRIMARY HPV SCREENING INITIATIVE AVAILABLE RESOURCES

Insurance Coverage/Payors Information

- Technical Guide for Billing and Coding for Primary HPV Screening
  - Audience: medical billers, providers, health plans, and administrative staff
- Insurance Coverage and Coding Overview One-Pager
  - Audience: medical billers, providers, health plans, and administrative staff

IT/EHR Information

- Provider Prompts and Patient Reminders One-Pager
  - Audience: IT/EHR administrators, clinical champions, others with an interest in optimizing their IT/EHR systems to support and advance the transition to primary HPV screening
- Test Orders and Results Codes Three-Pager
  - Audience: IT/EHR administrators, clinical champions, others with an interest in optimizing their IT/EHR systems to support and advance the transition to primary HPV screening
- Standardized Structured Data Two-Pager for Primary HPV Screening
  - Audience: IT/EHR administrators, clinical champions, others with an interest in optimizing their IT/EHR systems to support and advance the transition to primary HPV screening
- Results Tracking One-Pager
  - Audience: IT/EHR administrators, clinical champions, others with an interest in optimizing their IT/EHR systems to support and advance the transition to primary HPV screening

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 precancers earlier than cytology alone. Several studies have shown that for low risk women (those with all normal results) hpv screening works well. For higher risk patients/those in surveillance cotest may be more sensitive.

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 co-testing which has been well accepted.

American Cancer Society | NATIONAL ROUNDTABLE ON CERVICAL CANCER

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Initiative Workgroup Structure

Screening for HPV

Cervical cancer was once one of the most common causes of cancer death for American women. **Thanks to the development of cervical cancer screening tests**, this is no longer the case. Rates of cervical cancer and deaths from the disease have dropped significantly.

A screening test is used to find potential health problems early, before a person has any symptoms of disease.

The Pap test was the first test available to screen for cervical cancer. This test helps find cells on the cervix that are not normal and could develop into cancer. Infection with certain types of HPV can cause these cell changes.

HPV screening can identify if a person has one of these types of HPV before changes in the cells occur. Having one of these cancer-causing HPV types does not mean a person will surely get cancer, it just means they should be checked carefully to prevent cancer from developing.

We know that specific types of HPV cause cancer. Having a test that can find whether a person has one of these types is a great step forward in preventing cancer.

After Screening

Be Sure to Follow Up. Talking with your provider to learn about your results is very important.

If the test is negative...

- Low chance of cancer developing in the next 5 years
- You won't need screening again for 5 years (unless you've previously had an abnormal Pap or positive HPV test).

If the test is positive for any of the HPV types that can cause cancer...

- More testing will be needed
- A healthcare provider may need to take a closer look at your cervix and another HPV test may be needed sooner.

A positive result is an opportunity to prevent cancer, but only if you follow up with your provider!

It is so important to talk to your healthcare provider to get the extra care and testing needed to help prevent cancer.

American Cancer Society | NATIONAL ROUNDTABLE ON CERVICAL CANCER

Test Orders and Results Codes:
Transition to Primary HPV Screening

American Cancer Society | NATIONAL ROUNDTABLE ON CERVICAL CANCER

It's important to consider a unique test order and result code for primary HPV screening to ensure appropriate ordering, decision support alerts, and reporting metrics. Review the following steps for more information.

1. Prepare your reference lab to see if they offer FDA-approved primary HPV screening platforms:

Roche cobas®, BD Onclarity™, and Abbott Alinity m HR HPV are the only three FDA-approved manufacturers for primary HPV tests.

They also supply cotesting on the same assay with the same collection method.

- cobas® details
- Onclarity™ details
- Alinity m HR HPV details

You will need the lab information system's order code, CPT code, and results codes ideally with linked LOINC codes.

2. Prepare your EHR to differentiate test orders and results codes:

National CPT codes (87623, 87624, 87625) do not differentiate between HPV collected for primary screening, cytology with reflex HPV, or cotesting.

National LOINC codes (86658-2 Value Set) do not differentiate between HPV collected for primary screening, cytology with reflex HPV, or cotesting.

With the transition to primary HPV screening, creating unique test orders and results codes and labeling them clearly - primary HPV, cytology, and cotesting - that are linked to the resulting agency and processed through the HL7 interface:

- will guide clinicians to order the appropriate test,
- ensure the lab performs the appropriate test,
- and facilitate the monitoring of clinician screening practices.

American Cancer Society | NATIONAL ROUNDTABLE ON CERVICAL CANCER

3. Optimize preventive care tracking tools to differentiate test orders and results codes:

EHR preventive care reminders typically look for a group of codes (test order or result codes) to satisfy a certain screening protocol (primary HPV, cytology alone, cotesting).

While there may be several options available in your system, only one test order is appropriate for primary HPV screening. Therefore, a unique test order and result code for primary HPV screening ensures appropriate ordering, decision support alerts, and reporting metrics.

- For instance, you would not want a "reflex HPV test" that was added because of an ASCUS cytology to automatically satisfy your primary HPV screening reminders because if the "reflex HPV" was negative, the health care maintenance alert would incorrectly prompt a primary HPV test in 5 years.
  - Cytology abnormalities may be present that needed an alternative follow up plan.

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What about self-collection of primary HPV testing?

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.

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Is Self-Sampling Safe?

Diagnostic Accuracy for Detection of Cervical Precancer (CIN2+) of Clinician-Collected Cervical Cytology, HPV Testing Based on Clinician-Collected Cervical Specimens (Clinician HPV), and HPV Testing Using Self-Collected Vaginal Specimens (Self-HPV)

	Pooled sensitivity	Pooled specificity
Cytology	80.4 (95% CI = 73.2–86.1)	78.5 (95% CI = 69.8–85.2)
Self-HPV (PCR)	89.7 (95% CI = 84.2–93.5)	64.7 (95% CI = 44.6–80.7)
Clinician-HPV (PCR)	92.9 (95% CI = 88.6–95.5)	61.2 (95% CI = 41.2–78.1)

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Is Self-Sampling Safe?

	Rohner (2020)		Latsuzbaia (2022)		Martinelli (2023)	
Onclarity channel, HPV type	***n***	**% agreement**	***n***	**% agreement**	***n***	**% agreement**
Any hrHPV	220	83	278	89.3	188	89.5
16	62	89	73	98.1	72	95.1
18	15	97	18	98.1	7	97.9
31	21	97	55	96.9	39	94.8
45	16	97	18	98.4	9	99.0
33/58	20	98	44	96.9	23	97.9
35/39/68	37	94	50	95.7	30	95.5
51	19	99	36	97.1	13	98.3
52	30	97	42	96.1	22	97.9
56/59/66	57	97	79	94.9	50	94.4

Clinical Scenarios for Which Self-Collection Cannot be Used as HPV Testing Alone Is Not Currently Recommended

Clinical scenario	Current recommended screening test	Reference
People living with HIV	Cytology with or without HPV testing, depending on age	Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. CDC. Published online August 18, 2021. https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/
In utero diethylstilbestrol exposure	Cytology	ASCCP Clinical Consensus: Screening Recommendations for Clear Cell Adenocarcinomas in People Exposed to DES In Utero. Marcus J, Nelson E. Linder, M et al. Journal of Lower Genital Tract Disease 28(4):p 351–355, October 2024.
Surveillance after colposcopy for atypical glandular cells in which no CIN2+ found	Cytology with HPV testing (cotesting)	2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Consensus Guidelines Committee. J Low Genit Tract Dis. 2020 Apr;24(2):102–131.
Surveillance after diagnosis of adenocarcinoma in situ*	Cytology with HPV testing (cotesting)	2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Consensus Guidelines Committee. J Low Genit Tract Dis. 2020 Apr;24(2):102–131.

Self-Sampling Efforts

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NCI Cervical Cancer 'Last Mile' Initiative

Goal: *Overcome barrier of lack of FDA approval for self-collection approaches for HPV testing-based cervical cancer screening*

Approach: *Engage public and private sector stakeholders to facilitate regulatory approvals for self-collection*

Outcome: *Increase screening access and reduce cervical cancer incidence in underserved and high-burden populations*

https://prevention.cancer.gov/lastmile

Self-Sampling Efforts

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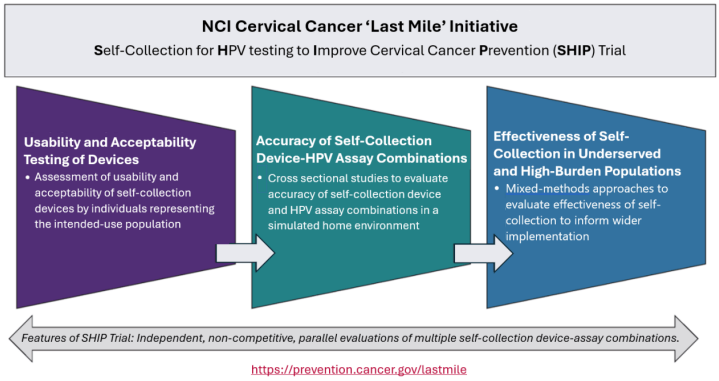
SHIP trial

- 25 clinical sites, covering a wide range of health system settings nationwide.
- Goal: Examine the accuracy of vaginal self-collection in a simulated home environment offered during a clinic visit vs collected by a health care provider during the same visit



Self-Sampling Approvals

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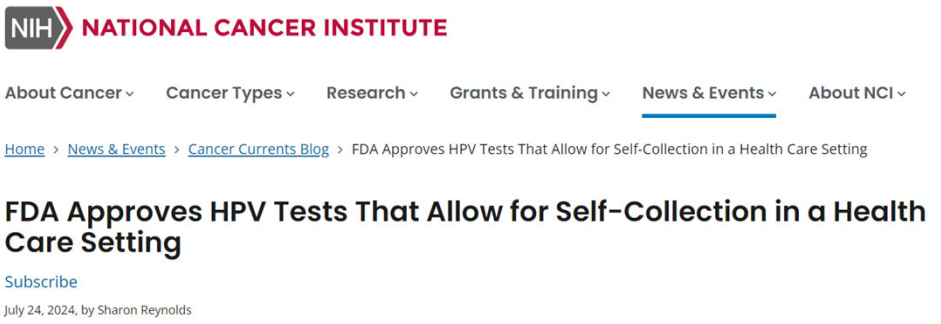

The tests included in the approvals are **BD Onclarity HPV**, made by Becton, Dickinson and Company (BD), and **Cobas HPV**, made by Roche Molecular Systems (both DNA based tests).

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YOUR HEALTH

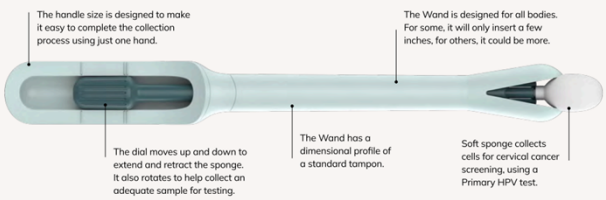
The FDA approves first U.S. at-home tool as a Pap-smear alternative

MAY 10, 2025 · 2:03 PM ET

Jennifer Ludden

Screening At-Home with the Teal Wand

The Teal Wand is purposefully designed to allow for easy at-home self-collection.



Teal Wand Highlights

- Unique, soft sponge is comfortable and maximizes sample collection
- One-handed use
- Accommodates different body sizes
- Familiar dimensions, similar to a tampon
- Atraumatic insertion profile to enhance comfort

The Teal screening box is mailed – it contains everything a woman needs to easily and comfortably collect her sample from the privacy of her home and mail the sample to the lab. At the lab, the sample is tested for high-risk HPV (human papillomavirus), which is the cause of nearly all cervical cancers. Results are shared via a secure patient portal, and medical providers are available virtually to discuss results and support with any follow-up care according to established medical guidelines[1].

[1]https://journals.lww.com/jlgtd/fulltext/2025/04000/self_collected_vaginal_specimens_for_hpv_testing_.6.aspx

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Uses Cobas test

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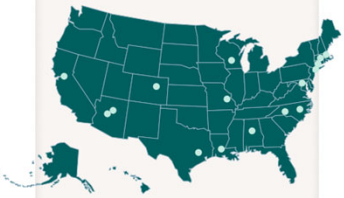
SELF-CERV Study

SELF-CERV study

16 study sites

600+ participants representing US population demographics



Exceeded all endpoints

95% Positive Percent Agreement

Equivalent to Clinician-Collection

Study Design

1 Self-collected sample with Teal Wand
Participant collects a sample using the Teal Wand and places in empty vial.

2 Clinician-collected sample
Clinician speculum exam (and visual inspection) then collects sample, per standard of care.

3 Surveys
Participant completes surveys to provide feedback on self-collection usability and both collection experiences.

- Both samples processed on Roche cobas Primary HPV assay
- Safety evaluated acutely and up to 2 weeks following

No serious or unanticipated adverse events, no device malfunctions

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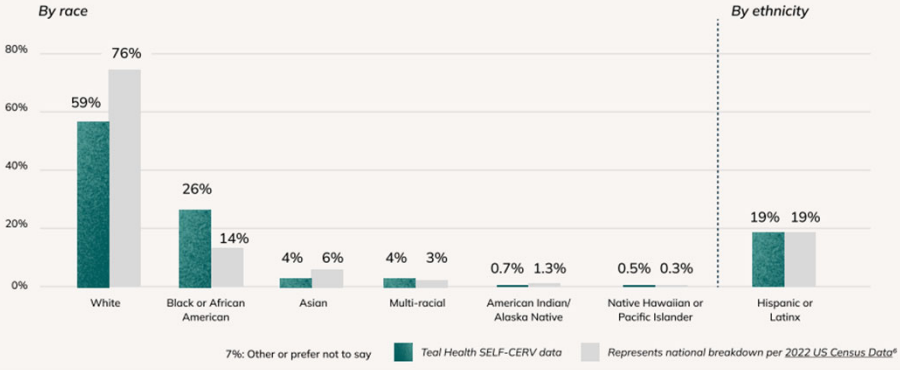
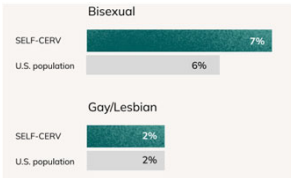
SELF-CERV Study

PART 1

Study Demographics and Overall Participation

The SELF-CERV study, which included more than 600 participants representing different ages, races, ethnicities, education levels, socioeconomic statuses, and sexual orientations, collected a comprehensive range of perspectives and health experiences, enabling conclusions that are widely applicable.





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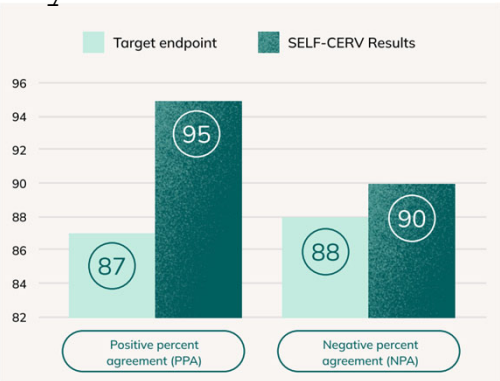
SELF-CERV Study

- 96% sensitivity



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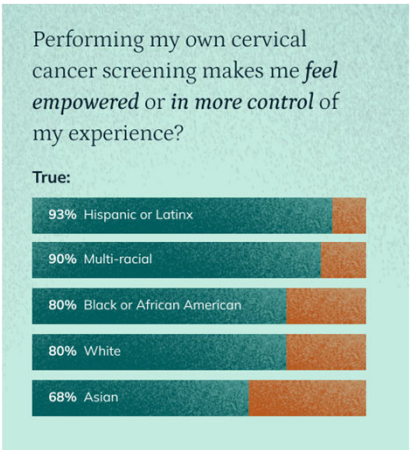
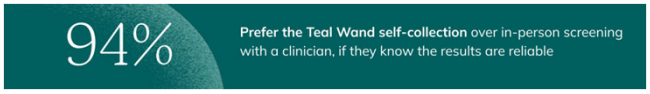
SELF-CERV Study





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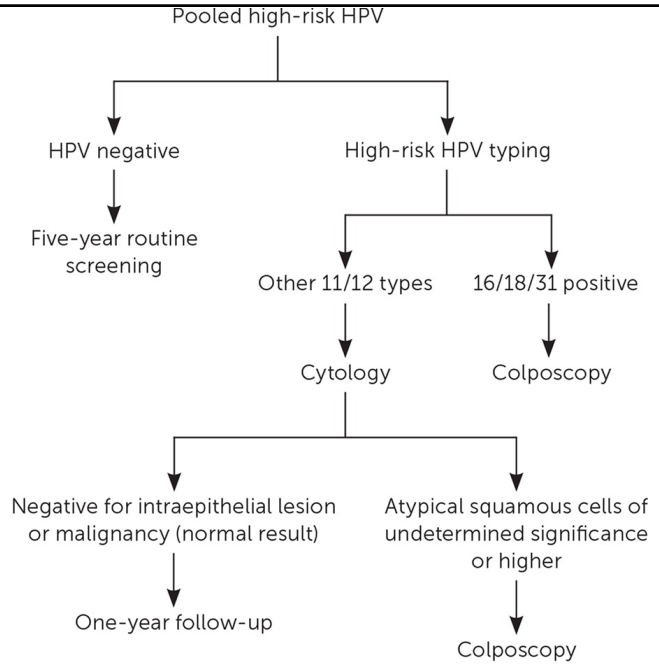
How do clinicians manage abnormal primary HPV tests?

Management of Abnormal Results



HPV = human papillomavirus.

HPV test result	Management of clinician- vs. self-collected collected specimens	Current HPV test result	Current cytology result	Past history	Management
HPV 16/18	Clinician-collected: Laboratory performs cotest or reflex cytology. Self-collected: Colposcopy recommended. Collect cytology at colposcopy.	16	HSIL	Noncontributory	Treatment preferred; colposcopy acceptable
		16	ASC-H	Noncontributory	Treatment or colposcopy
		16	NILM, ASC-US, LSIL, AGC, or no cytology	Noncontributory	Colposcopy[1]
		18	HSIL	Noncontributory	Treatment or colposcopy
		18	NILM, ASC-US, LSIL, ASC-H, AGC, or no cytology	Noncontributory	Colposcopy[1,2]
HPV 45, 33/58, 31, 52, 35/39/68, 51 Untyped or "other" types when 16 and 18 are not present	Clinician-collected: Laboratory performs cotest or reflex cytology. Self-collected: Patient returns for collection of cytology unless current test is 2nd consecutive HPV+ in which case colposcopy recommended.	45, 33/58, 31, 52, 35/39/68, 51 or untyped/other	HSIL, ASC-H, AGC	Noncontributory	Colposcopy[1,2]
		45, 33/58, 31, 52, 35/39/68, 51	ASC-US, LSIL	Noncontributory	Colposcopy
		Other/untyped	ASC-US, LSIL	Documented HPV negative screen in past 5 years or colposcopy <CIN2 within past 1 year	Repeat HPV test in 1 year
		Other/untyped	ASC-US, LSIL	Any history other than above	Colposcopy
		45, 33/58, 31, 52, 35/39/68, 51 or untyped/other	NILM	Normal[3] or colposcopy <CIN2 within past 1 year	Repeat HPV test in 1 year
		45, 33/58, 31, 52, 35/39/68, 51 or untyped/other	Not available	HPV+ without colposcopy (i.e. current test is 2nd consecutive HPV+)	Colposcopy
HPV 59/56/66	Clinician- collected: No additional immediate testing needed. Laboratory may run cytology if cotesting is performed.[4] Self-collected: No additional immediate testing needed	59/56/66	ASC-H, AGC, or HSIL	Noncontributory	Colposcopy[1,2]
		59/56/66	No cytology or NILM, ASC-US, LSIL	Normal or colposcopy <CIN2 within past 1 year	Repeat HPV test in 1 year
		59/56/66	Not available	HPV+ without colposcopy (i.e., current test is 2nd consecutive HPV+)	Colposcopy

Primary HPV Screening Barriers

- We need a better tracking system for results – ideally national tracking, like Australia and other countries.
- We need systems in place before implementing – coordinate with key stakeholders in the lab, clinics, administration.
- Educate patients about new system BEFORE launch.
- Educate providers about new system, new orders, interpretation of results, and referral pathways for colposcopy.
- How do we ensure that abnormal self collection tests are followed up with an in person exam appropriately?

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Bonus Slides

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Screening Cessation

Screening Cessation

- While rates of cervical cancer have been declining over the past several decades, approximately 20% of cervical cancer cases in the U.S. occur in people older than age 65.
- Current guidelines recommend discontinuing cervical cancer testing at age 65 for individuals at average risk:
  - at least three consecutive negative cytology tests or two consecutive negative HPV tests or co-tests in the prior 10 years
  - never diagnosed with cervical cancer or with a high-grade precancerous lesion in the past 25 years
  - not immunosuppressed (e.g., HIV)

Screening Cessation

- Current guidelines for exiting screening are based on the rarity of cervical cancer diagnosed over age 65 among patients who had regular screening with multiple negative cytology and HPV tests.
- However, the feasibility of implementing these guidelines in clinical practice is relatively unknown.

Screening Cessation

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Results

- Included a total of 42,393 patients who turned age 66 during the study period (2010-2019).
- About three-quarters of the cohort (75.7%) were ineligible to exit screening at age 66.

Screening Cessation

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Screen Exit Eligibility on 66th Birthday	N (%)
Ineligible	**32,094 (75.7)**
Under Surveillance	2,740 (6.5)
Prior Cervical Cancer Diagnosis	333 (12.2)
Hysterectomy & Abnormality (40-65 years old)	424 (15.5)
High-Grade Result (40-65 years old)	209 (7.6)
Low-Grade Result (55-65 years old)	1,681 (61.4)
HIV-positive	93 (3.4)
Insufficient Screening History	29,354 (69.2)
Hysterectomy & No Tests	1,884 (6.4)

Even among the 4,037 patients (9.5% of the cohort) who remained in the healthcare system for at least 10 years, 61% remained ineligible to exit screening, predominantly due to insufficient screening history (50%).

Screening Cessation

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Results – Testing After Age 65

- Among people ineligible to exit due to needing surveillance
  - Most (60.4%) had no subsequent evaluation after their 66th birthday
  - Of the 39.6% who were evaluated, **76 (7.0%) of women were diagnosed with cancer or high-grade precancerous lesion,** including seven (0.7%) cervical cancers
- Among those ineligible to exit due to insufficient screening history
  - 83.7% were not subsequently screened
  - Of the 16.3% who were screened, **90 (1.9%) women were diagnosed with cancer or high-grade precancerous lesions,** including 34 (0.7%) diagnosed with cervical cancer.

Screening Cessation

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Results – Testing After Age 65

- Among those eligible to exit with a sufficient screening history
  - 34.3% had at least one subsequent cytology and/or pathology result
  - **High-grade precancerous lesions or cervical cancer were diagnosed in 0.6%** (n=16; N=6 [0.2%] were cancer).

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Screening Cessation

Conclusions

- In two large healthcare systems, we found that 75.7% of patients may not be eligible to exit cervical cancer screening at age 66.
- Most of these ineligible patients lacked sufficient documentation to meet guideline recommendations to stop testing due to too few cervical cancer tests prior to their 66th birthday (91.5% of them).
- There were over three times as many cases of cervical cancer and high-grade dysplasia detected among people ineligible for screening exit due to insufficient history versus those eligible for screening exit following sufficient history.

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Screening Cessation

Conclusions

- Overall, relying on the EHR to make these important clinical decisions may be neither feasible nor practical, and that this complexity may harm patients.
- Life expectancy is increasing, and hysterectomy rates are declining, meaning that we expect to see an increase in the size of the population over age 65 who remain at risk for cervical cancer in the coming years. Additionally, the proportion of non-white women over age 65 is expected to increase due to changing racial demographics in the U.S.
- If we do not carefully evaluate our current system for exiting cervical cancer screening, this could result in worsening age-related and race-related disparities in cervical cancer rates and outcomes.

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Screening Cessation

Conclusions

- We could instead devise a different model for screening cessation while awaiting a change in national tracking of results.
- Another proposal may involve increasing the cut-off age to one that accounts for estimated life expectancy, similar to breast and colorectal cancer screening guidelines and similar to age cut-offs used in other countries (such as Finland).

Potential Targeted Treatments for HPV

Reminder: no stake in the game, all investigational use (not FDA approved)

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AHCC/LEM

- AHCC® (Amino Up, Ltd., Sapporo, Japan) is a standardized extract of cultured **lentinula edodes mycelia (LEM)** that was developed in Japan in 1992.
- It is composed of dried powder extracted from shiitake mushrooms, and primarily made of up α-glucan components.
- Several animal and human studies have reported a variety of therapeutic effects, including potential activity against infection and potential anti-tumor activity.

SUGGESTED USE: Take 2-4 vegicaps daily before meals or as directed by your healthcare professional.

Supplement Facts

Serving Size: 2 vegicaps
Servings Per Container: 30

Amount Per Serving	% Daily Value
AHCC® proprietary blend	1.5 g †
Mycelia extract of basidiomycetes (*Lentinula edodes*) mushrooms (with acylated alpha-glucans), carnauba plant wax, dextrin (tapioca), cellulose (plant), alpha-cyclodextrin (vegetable)	

† Daily value not established.

Other ingredients: vegetable cellulose, leucine.

AHCC® is a registered trademark of Amino Up Company Ltd

WARNING: DO NOT USE IF SEAL IS BROKEN OR MISSING. Keep out of reach of children. Store at room temperature. Consult a doctor before use if you are pregnant or lactating, have or had a medical condition, or are taking prescription drugs.

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AHCC/LEM Mechanism

- Immune cell activation is essential for cancer rejection.
- However, the tumor microenvironment leads to deterioration of immune function, which enables cancer cells to survive and proliferate.
- LEM can activate the immune system by binding to toll-like receptors (TLRs) and inducing the activation of dendritic cells, natural killer cells, macrophages, and T cells to help fight infection and cancer.

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AHCC/LEM in HPV infection

Only ONE randomized study and includes only 50 patients.

- Smith JA, Gaikwad AA, Mathew L, et al. AHCC® Supplementation to Support Immune Function to Clear Persistent Human Papillomavirus Infections. *Front Oncol.* 2022;12:881902. Published 2022 Jun 22. doi:10.3389/fonc.2022.881902

- Phase II randomized, double-blind, placebo controlled study

AHCC® Supplementation to Support Immune Function to Clear Persistent Human Papillomavirus Infections

HARVARD MEDICAL SCHOOL AND BRIGHAM AND WOMEN'S HOSPITAL

Judith A. Smith[1,2], Anjali A. Gaikwad[1], Lata Mathew[1], Barbara Rech[3], Jonathan P. Faro[4], Joseph A. Lucci III[1,2], Yu Bai[5], Randall J. Olsen[6] and Teresa T. Byrd[1]*

[1] Department of Obstetrics, Gynecology and Reproductive Sciences, UT Health McGovern Medical School, Houston, TX, United States, [2] Department of Pharmacy, UT Heath-Memorial Hermann Cancer Center, Houston, TX, United States, [3] UT Physicians Women's Center, Houston, TX, United States, [4] Specialists in Obstetrics & Gynecology, Houston, TX, United States, [5] Department of Pathology, UT Health McGovern Medical School, Houston, TX, United States, [6] Department of Molecular Pathology, Houston Methodist Research Institute, Houston, TX, United States

- Included women ≥ age 30 with persistent high-risk HPV infections for > 2 years.
- AHCC 3 g once daily x 6 months vs

Inclusion criteria:

- Women over 30 years of age who have an HPV positive test and normal/negative cytology, atypical cells, ASCUS, or CIN1 or CIN2 cervical dysplasia within 3 months of study entry. This minimized potential confounders such as immune modulation that may possibly clear the infection, which is common in women under the age of 26.
- Women must have had 2 other HPV-positive tests with normal/negative cytology, atypical cells, ASCUS, or CIN1 or CIN2 cervical dysplasia
  - 1 greater than 6 months and no more than 18 months prior to study entry and
  - 1 greater than 24 months prior to study entry. (This is to help establish persistent HPV infection.)

Exclusion criteria:

- History of myocardial infarction within past 6 months, unstable angina, CHF, or uncontrolled hypertension (>140/90).
- Women with a current or prior diagnosis of cancer.
- Women with a current diagnosis of CIN3 cervical dysplasia.
- Women who are pregnant or breastfeeding.
- Women with a history of hepatitis (autoimmune, A, B, or C) or antigen positive.
- Patients with history of significant psychiatric disorders (schizophrenia, bipolar, and psychosis) or uncontrolled seizures.
- Patients with significant medical comorbidities at the discretion of the primary gynecologist. Including immunosuppressive conditions (i.e., HIV+ and rheumatoid arthritis) or taking immune modulation mediations (i.e., immunosuppressants).
- Women who have taken commercial supply of AHCC within the past 6 months on their own. Those who have been participating in the AHCC 1 g day pilot study are eligible to enroll in this study.
- Women currently taking other immune-modulating nutritional supplements.

AHCC® Supplementation to Support Immune Function to Clear Persistent Human Papillomavirus Infections

HARVARD MEDICAL SCHOOL AND BRIGHAM AND WOMEN'S HOSPITAL

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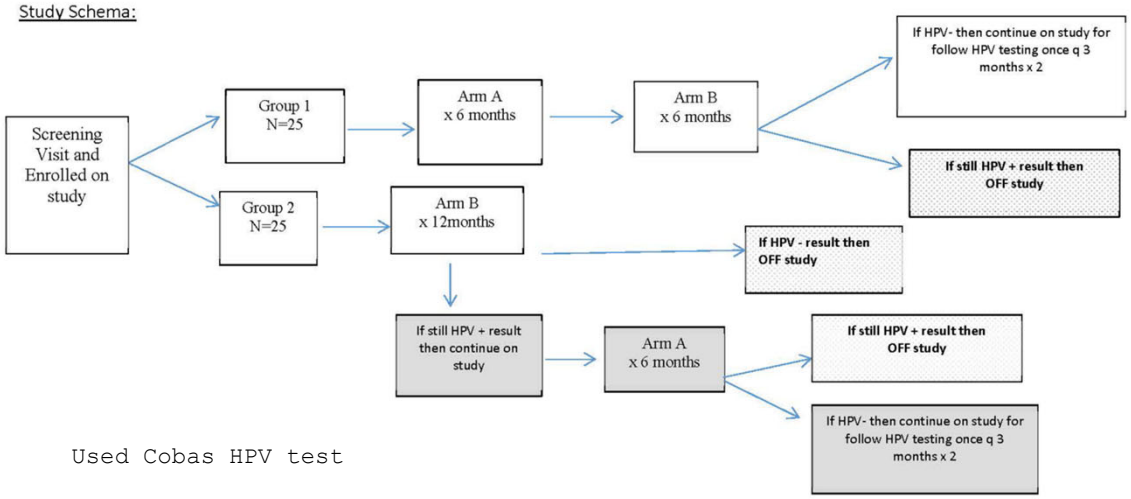
Study Schema:



Used Cobas HPV test

AHCC® Supplementation to Support Immune Function to Clear Persistent Human Papillomavirus Infections

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TABLE 2 | Summary of patient demographics.

	Placebo (N = 19) Mean (SD)	AHCC (N = 22) Mean (SD)
Age	46.4 (± 13.5)	42.8 (± 8.9)
Race	15 White 3 Black 1 Asian	19 White 1 American Indian 1 Black 1 Other
BMI (kg/m^2)	23.8 (± 13.4)	21 (± 11)
Number of sexual partners	6.3 (± 7.9)	7.8 (± 6.4)
Number of partners in last year	1 (± 1)	1 (± 1)

TABLE 3 | Summary of the HPV response.

Outcome	Placebo arm (N = 19)	Blinded AHCC arm (N = 22)	Placebo patients who went onto unblinded AHCC (N = 12)	All AHCC patients (N = 34)
Overall response rate	10.5% (2)	63.6 (14)	50% (6)	58.8% (20)
CR (complete response: HPV negative after 12 months of stopping AHCC)	10.5% (2)	40.9% (9)	50% (6)	44.1% (15)
PR (partial response)	NA	22.7% (5)	NA	22.7% (5)
NR (no response)	89.5% (17)	36.3% (8)	50% (6)	41.1 (14)

Partial response: initially HPV negative after 6 months of AHCC, but then HPV positive again after 6 months off AHCC

AHCC® Supplementation to Support Immune Function to Clear Persistent Human Papillomavirus Infections

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TABLE 4 | Summary of adverse events reported in the study.

	Placebo (N = 25)	AHCC (N = 25)
Nausea	2 (8%)	1 (4%)
Bloating	1 (4%)	1(4%)
Heartburn	0	1 (4%)
fatigue	0	1 (4%)

AHCC® Supplementation to Support Immune Function to Clear Persistent Human Papillomavirus Infections

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Conclusions

- The results from this phase II study demonstrated that AHCC 3 g once daily for 6 months was effective to support the host immune system to clear persistent HPV infections and was well tolerated with no significant adverse side effects reported.
- The duration of AHCC supplementation required beyond the first negative result needs more evaluation to optimize durable outcomes

AHCC® Supplementation to Support Immune Function to Clear Persistent Human Papillomavirus Infections

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Limitations and Cautions Against Routinely Recommending

- No data on HPV subtyping (16 or 18) provided
- No data concerning rates of regression of CIN2
- Only 41 patients completed treatment and follow up.
- 22% partial response rate (HPV+ again within a few months of stopping AHCC)
- Potentially costly for patients ($50-75 for one month supply).
- Different doses of active ingredient across different supplements – difficult for patients to verify they are actually receiving the studied 3g daily dose.
- Not FDA approved or regulated. May interact with letrozole (decreased effectiveness in breast cancer mouse model) and drugs broken down by cytochrome P450. No data on drug interactions among patients on trial.
- Unclear whether safe in pregnancy or breastfeeding (excluded these patients)
- Allergic reactions in those with allergy to mushrooms.

AHCC® Supplementation to Support Immune Function to Clear Persistent Human Papillomavirus Infections

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The Encouraging Stuff

- Approximately 44% complete response rate (HPV negative and stayed negative)
- Crossover design helped with validity of trial drug
- Low rate of adverse events

In Our Practice

- We have not started routinely recommending. Rather we discuss these pros/cons in healthy patients over age 30 with persistent HPV for over 2 years