Making Strides Towards Cervical Cancer Elimination: Updates on Prevention, Screening and Management

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An ineligible company is any entity whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Commercial support was not received for this CME/CE activity.

Learning Objectives

At the completion of the CME / CE activity, learners can:

Identify at least three (3) symptoms of cervical cancer.

Identify patients eligible for HPV vaccination.

Review current guidelines for cervical cancer screening.

Distinguish the different HPV tests (primary, cotest, reflex and genotyping).

List at least three (3) effective interventions to reduce disparities in cervical cancer screening.

Recent road trip





Outline

Manage Yourself	Habit 1 Be Proactive [®] The Habit of choice	 See alternatives, not roadblocks Focus on what you can influence I am free to choose and am responsible for my choices
	Habit 2 Begin with the End in Mind [®] The Habit of Vision	 Mental creation precedes physical creation Define practical outcomes
	Habit 3 Put First Things First [®] The Habit of Integrity and Execution	 Focus on the important, not just the urgent Effectiveness requires the integrity to act on your priorities Plan weekly, act daily
Lead Others	Habit 4 Think Win/Win [®] The Habit of Mutual Benefit	 Effective long-term relationships require mutual respect and mutual benefit Build trust with co-workers
	Habit 5 Seek First to Understand, then to be Understood [®] The Habit of Mutual Understanding	 To communicate effectively, we must first understand each other Practice empathic listening Give honest, accurate feedback
	Habit 6 Synergize [®] The Habit of Creative Cooperation	 The whole is greater than the sum of its parts Synergize to arrive at new and better alternatives
Unleash Potential	Habit 7 Sharpen the Saw [®] The Habit of Renewal	 To maintain and increase effectiveness, we must renew ourselves in body, heart, mind and soul

Call to action: addressing the other global pandemic

Cervical Cancer 101

HPV 101

Updates on Prevention Strategies

Screening updates and HPV based testing options

Updates on cancer therapeutics

What we can do moving forward

Habit #1: Be Proactive

- ▶ Third most common gyn cancer in U.S.
 - ▶ 14,000 new cases/year in the U.S
 - ▶ **4,000** death/year
 - Histologic subtypes
 - squamous (70%)
 - adenocarcinoma (25%)
 - Adenosquamous
 - ▶ clear cell (<5%)



Stats on other HPV related cancers



Figure 8

Numbers of HPV-Associated Cancers in Less Developed and More Developed Regions



Note: Global estimates of genital warts and RRP incidence are not available.

Source: de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol. 2012;13(6):607-15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22575588

The Other Global Pandemic

Age-Standardized Rate (World) per 100 000, Incidence, Females, in 2022 Cervix uteri



2022 worldwide

8th most common cancer 660,000 new cases 350,00 deaths

United States

14,000 cases 4000 deaths

GLOBOCAN 2022

Cervical Cancer is Preventable!

ORIGINAL ARTICLE

HPV Vaccination and the Risk of Invasive Cervical Cancer

Jiayao Lei, Ph.D., Alexander Ploner, Ph.D., K. Miriam Elfström, Ph.D., Jiangrong Wang, Ph.D., Adam Roth, M.D., Ph.D., Fang Fang, M.D., Ph.D., Karin Sundström, M.D., Ph.D., Joakim Dillner, M.D., Ph.D., and Pär Sparén, Ph.D.





HPV VACCINATION CAN PREVENT MOST OF THESE CANCERS.

And Preventable for other HPV cancers



	Level of Prevention	Strategies
	Primary	HPV vaccination, safe sex practices
	Secondary	HPV based screening and Colposcopy
V	Tertiary	Surgery, Chemo-radiation, immunotherapy

Habit 2: Begin with the End in Mind



Linda Eckert MD

Stop for a minute. Take that in: "a preventable cancer." Just think how rare it is to have those two words, *preventable* and *cancer*, together in one phrase. What does that mean?

Well, it means that medical providers know what causes cervical cancer, how to treat it and cure it if it's found early enough, and how to prevent it. Cervical cancer is a cancer that could be eliminated, that need not exist at all. Yet, this preventable cancer kills a woman somewhere in the world every two minutes. That translates to 360 women dying a day.

My Journey toward "Enough"

I've finally reached a place in my personal and professional life where I can no longer stand by and witness so much suffering. I need to shout out to the world from the rooftops: *Enough! Enough Marias. Enough unnecessary death and suffering.*

Evaluation of a patient with cervical cancer

- Most patients present to the ER or Urgent Care
- H&P, Assessment of medical comorbidities and social needs
 - Smoking cessation
 - Fertility desires
- ► Exam
 - Pelvic exam for clinical staging
 - Biopsy for tissue diagnosis
 - ▶ Labs: CBC, CMP (renal and liver function), HIV
- Imaging: PET CT preferred

Early Stage Disease



American Pregnancy Association

Stage	Description	5 year survival
Stage I	Confirmed to cervix	80-93%
1A1 1A2	Measured stromal invasion of <3.0 mm in depth Measured stromal invasion of ≥3.0 mm and <5.0 mm	
IB1 1B2 1B3	≥5mm stroma and <2cm greatest dimension ≥2cm and <4cm greatest dimension ≥4cm greatest dimension	
Stage II	Invades beyond uterus, not to pelvic wall to lower third of vagina	58-63%
IIA IIA1 IIA2	Without parametrial invasion <4.0 cm in greatest dimension ≥4.0 cm in greatest dimension	

Surgical Management

- Treatment intent: CURATIVE
- Fertility Sparing
 - IA1: can do CKC or even LEEP vs simple trachelectomy
 - IA2-IB1 (<2cm lesion) radical trachelectomy with staging; Conception rates 50-70%
- Hysterectomy +/- bilateral salpingooophorectomy



Locally Advanced Disease



Stage	Description	5 year survival
Stage II	Invades beyond uterus, not to pelvic wall to lower third of vagina	58-63%
IIA IIA1 IIA2 IIB	Without parametrial invasion <4.0 cm in greatest dimension ≥4.0 cm in greatest dimension With parametrial invasion	
Stage III	Side wall extension, Iwoewr 1/3 vagina, hydronephrosis or involvement of pelvic/PA nodes.	32-35%
IIIA IIIB IIIC IIIC1 IIIC2	involves lower 1/3of the vagina,no extension to the pelvic wall Ext to the pelvic wall and/or hydronephrosis or non-functioning kidney Involves pelvic/PA LN (r&p notations) Pelvic LN PA LN	
Stage IV	Extends beyond true pelvis	15-19%
IVA	Spread to adjacent organs (Ex. Bladder, rectum)	

Chemo-radiation

- Treatment intent: Curative
- Primary chemo-radiation
 - External Beam Radiation
 - Brachytherapy
 - Cisplatin chemosensitization





Wikipedia

Mayo clinic

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Metastatic Disease



Stage	Description	5 year survival
Stage IVB	Spread to distant organs	<15-19%

Chao et al , Future Medicine 2014

Progression-free Survival

Systemic Treatment

- Goal: Palliative
- Chemotherapy: cis/carboplatin + paclitaxel
- GOG 240 (Tewari, NEJM 2014)
 - ▶ Adding bevacizumab increased ORR from 36 \rightarrow 48%
 - OS 16.8 vs 13.3 months (HR 0.77 (CI 0.62-0.95) (update Tewari, Lancet 2017)
- Keynote 826 (Colombo et al, NEJM 2021)
 - Adding pembrolizumab to PDL1 positive tumor improves PFS
 - PFS 10.4 vs 8.2 months (HR 0.65)
 - OS at 24 months (53 % vs 41.7% (HR 0.64))





Overall Survival

WHO 2030: Enough is enough – global mission to ERADICATE cervical cancer

Annually, it is

the annual number of new cases is projected

700 000

to INCREASE TO

MORE.

Few diseases reflect global inequities as much as cervical cancer. Cervical cancer is the fourth most common form of cancer among women worldwide.

More than SE AFFECTED ARE YOUNG

undereducated women who live in the world's poorest communities.

OF THE 20 HARDEST HIT COUNTRIES, **19 ARE IN AFRICA**



Even in high-income countries, the inequity of cervical cancer disproportionately afflicts women of color, minorities, and other marginalized communities.

middle-income

countries (LMICs)

Furthermore, The disease **KILLS MORE THAN** OF THE DEATHS occur in low- and

WOMEN EVERY YEAR. Unless we take action, this preventable tragedy will only worsen.

If we accept the status quo, BY 2030





DIAGNOSED IN OVER

vaccinated with the **HPV vaccine by** the age of 15;

90% of girls fully

- 70% of women screened using a highperformance test by the age of 35, and again by the age of 45;
- 90% of women with pre-cancer treated and 90% of women with invasive cancer managed.



Meeting and maintaining the 90-70-90 targets would yield significant returns in the coming century:

- the median cervical cancer incidence rate will fall by 42% by 2045, and by 97% by 2120, averting more than 74 million new cases of cervical cancer; and
- the median cumulative number of cervical cancer deaths averted will be 300 000 by 2030, over 14 million by 2070, and over 62 million by 2120.

Habit 3: First Things First





Human Papilloma Virus (HPV)



- Genital HPV is the most common STI in US
 - Incidence: 8-14 million persons infected each year
 - Prevalence: 80 million
 - Most are asymptomatic
 - Over 150 HPV types identified, over 40 affect genital area
 - Low risk: 6/11 cause genital warts, respiratory papillomatosis
 - High risk: oncogenic <u>16,18</u>, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, 73, and 82.

HPV Infection and Carcinogenesis



Woodman et al. Nature Reviews Cancer 2007

HPV Virology



E6/E7 expression allows for unregulated cell growth





HPV takes advantage of the differentiation pathway of keratinocytes that are destined to die naturally (anoikis). Since HPV is not cytolytic and does not cause viraemia, there is no inflammation and subsequent activation of the immune system. Infection of basal epithelial cells establishes a latent infection with low level replication of the viral episome and minimal viral protein expression. Following differentiation of the keratinocyte, early HPV genes are expressed and the viral episome is further amplified to higher copy numbers. Viral late protein expression and virus assembly occurs during terminal differentiation of the keratinocyte and virus are shed from the outermost layer of epithelial cells.



Effect of HPV in the United States



74% of infections occur among those aged 15-24

- Usually occurs shortly after sexual debut 38.9% by 24 months of first intercourse (Revzina 2005)
- Majority of HPV infections are transient and cause no clinical problems
 - Median time to seroconversion is 8months
 - > 70% of new HPV infections clear within 1 year
 - > 90% clear within 2 years
 - Persistent infection is most important risk factor for cervical ca (HPV 16 is most virulent) – progression to cancer is usually decades

Natural History of HPV and Cervical Cancer



Schiffman and Castle, NEJM 2005

Most HPV infections are transient



NIH cohort study in Guanacaste region of Costa Rica of 777 infections

85% of infections cleared over 3 years

By 6 years, 8% progressed to HSIL

PERSISTENT HPV infection

associated with risk for high grade dysplasia

Schiffman, Castle et al. Lancet. 2007.



Human papillomavirus is the **necessary (but not sufficient)** agent in the pathogenesis of cervical cancer

Time matters – takes years to progress to dysplasia **Type matters –** HPV 16

HPV 16 positive carries 434x high relative risk for cervical cancer compared to HPV negative

Persistence of HPV is a risk factor for CIN 3+



Kjaer JNCI 2010

"Unfortunate Experiment" – Cartwright Inquiry



Schiffman M, Rodríguez AC Lancet Oncol 2008; 9(5): 404 - 406

Additional Risk Factors for HPV Disease

Physiologic Risk Factors

- Persistent high risk HPV infection
- Increasing Age
- DES exposure
- Nutritional factors
- Immunosuppression/HIV infection
- Other STIs
- SMOKING (50% increase!)

Psycho-Social Risk Factors

- Low income
- Lack of insurance
- Poor health literacy
- Cultural beliefs
- Access
- Language barriers
- Discomfort with exam
- Pandemic driven closures

Pandemic effect

FIGURE 3

Cervical Cancer Screening Volumes



Troubling Cancer Screening Rates Still Seen Nearly Two Years Into the Pandemic (epicresearch.org)

HPV association with other cancers



Modified from: Saraiya M, et al. J Natl Cancer Inst. 2015;Apr 29:107(6). Criteri

Habit 4: Think Win/Win = Prevention



Google images



Google images


1943 – Diagnosis of Uterine Cancer by the Vaginal Smear by **Georgios Papanikolaou**

1983 – Harald zur Hausen (German Virologist) – makes first association between HPV16 virus and cervical cancer (awarded the 2008 Nobel Prize in Medicine)

1991 – Ian Frazer and Jian Zhou discovered VLPs

2003 – HPV test included in screening guidelines

2006 – HPV4 Gardasil introduced by Merck and Co

12/2014 – HPV9 Gardasil-9 introduced by Merck and Co





Primary Prevention: HPV Vaccine

Eligible persons	# Doses	Dosing Intervals
Persons 9-14 years Except immunocompromised	2	0, 6-12 months
Persons 15-26 years And immunocompromised 9-26 years *FDA expansion to age 45 10/2018	3	 0, 1-2, 6 months Minimum interval between 1st and 2nd dose is 4 weeks Minimum interval between 2nd and 3rd dose is 12 weeks Minimum interval between 1st and 3rd dose is 24 weeks

- Females with abnormal pap tests, positive HPV tests or genital warts can still receive the vaccine.
- Do not restart series if recipient is late for follow-up doses and resume vaccine series at regular dosing interval for remaining vaccines.
- ▶ If subsequent dose given too early, should be re-administered.
- Any available HPV vaccine product may be used to continue or complete series (interchangeable).

Who do we offer HPV vaccines to?

- Routine recommendation: ages 9-12
- "Shared decision making" for 27-45
 - Consider if at risk for new HPV strains = this is a PREVENTION vaccine
 - Consider costs to system and vaccine supply
- Immunocompromised
 - Will need 3 doses regardless of age
- Healthcare workers
 - ASCCP recommends vaccination with high exposure to HPV (gyn, FP, derm, OR)

How well are we vaccinating?

Estimated vaccination coverage with ≥1 HPV vaccine, 2020



Figure 6. HPV vaccine initiation and completion rates among 13-year-olds by urbanicity classification, 2018-2021 (Source: CAIR)



California HPV Vaccination Roundtable: "Using and Improving HPV Vaccination Data" Workgroup, 2023 Update

CA HPV RT

UPDATES on HPV vaccination

- Single dose recommendation
 - WHO Strategic Advisory Group of Experts on Immunization (SAGE) 2022.
 - one or two-dose schedule for the primary target of girls aged 9-14.
 - one or two-dose schedule for young women aged 15-20
 - immunocompromised individuals, including those with HIV, receive three doses if feasible, and if not at least two doses.
- Costa Rica HPV Vaccine trial (CVT) durability of single dose after year median followup shows vaccine efficacy at 80.2%





(Kreimer et al 2020)

Improving vaccination in US: Our Win-Win Strategies

Starting age 9: Earlier vaccination may improve compliance and meet goal for vaccination

Recommended Vaccination Schedule Guideline

Late AGES 13-14

2 Doses

6-12 months apar

On Time AGE 9-12

2 Doses

6-12 months apar

- CDC/ACIP says acceptable
- ACS, APA, National HPV vaccination roundtable recor
- AB 659: Cancer Prevention Act (Aguilar Curry)
 - Passed 10/13/2023
 - Recommend full HPV vaccination before admission to 8th grade at any private/public school
- SGO: Cervical cancer elimination taskforce

Habit 5: Seek First to Understand, then to be Understood



Screening guidelines?

Which HPV based test?

Goals of cervical cancer screening

- Evaluation of normal looking cervix for identifying high risk and persistent HPV infections (HPV test) or high grade dysplasia (cytology)
 - Transient infections do not lead to cervical cancer
 - Patients treated for high grade dysplasia will enter SURVEILLANCE, not screening

Cervical Cancer Workup



Asymptomatic



Screening Pap→ colposcopy and biopsies



Symptomatic

- Abnormal or postcoital vaginal bleeding
- Foul smelling discharge
- Pelvic pain/sciatic pain
- Trouble urinating
- Anemia



Pelvic exam and biopsies

Cervical Cancer Screening Guidelines

	Age to screen	Recommendation
USPTF 2018/ACOG/ASCCP	21-29	Cytology q3 years
	30-65	-Cytology q3 years OR -Cotesting q5 years OR -Primary HPV q5years (FDA approved tests: Roche cobas and BD clarity)
ACS 2020	25-65	- Primary HPV q5years (preferred) -Cotesting q5 years (alternate) - Cytology q3 years (alternate)

Why the change by ACS?

TABLE 4. Model-Estimated Benefits and Burdens of Cervical Cancer Screening Starting at Age 21 Versus 25 Years, per 1000 Screened Over a Lifetime

	PER 1000 WOMEN					
SCREENING STRATEGY ^a	TOTAL NO. OF TESTS ^b	NO. OF COLPOS	CIN2, CIN3 DETECTED	CANCER CASES	CANCER DEATHS	LYG
1. No screening	0	0	0	18.86	8.34	63,921.34
2. Cyto every 3 y from age 21 y/cotest every 5 y ages 30-65 y	19,806	1630	201	1.08	0.30	64,192.97
3. Cyto every 4 y from age 21 y/HPV every 3 y ages 25-65 y	17,067	2209	217	0.75	0.23	64,195.53
 Cyto every 4 y from age 21 y/HPV every 5 y ages 25-65 y 	12,042	1826	209	0.81	0.25	64,195.35
5. Cyto every 4 y from age 21 y/cotest every 5 y ages 25-65 y	20,859	2029	213	0.82	0.26	64,195.26
 Cyto every 3 y from age 25 y/HPV every 5 y ages 30-65 y 	10,671	1303	175	1.46	0.40	64,188.10
7. Cyto every 3 y ages 25-65 y	13,313	564	142	2.60	0.86	64,176.12
8. HPV every 5 y ages 25-65 y	10,954	1775	195	0.94	0.28	64,193.52

Abbreviations CIN, cervical intraepithelial neoplasia; COLPOS, colposcopies; Cotest, cytology and human papillomavirus test; Cyto, cytology; HPV, human papillomavirus test; LYG, life-years gained.

^aScenarios 1 through 5 were reported previously (see Kim 2018^{44,45}), whereas scenarios 6 through 8 were estimated as part of the supplementary modeling analysis. ^bValues indicate the total number of tests, irrespective of primary, triage, or surveillance context.

When to stop cervix cancer screening

At age 65

- Provider determines "adequate screening"
- ACS/ASCCP/ASCP guidelines define adequate prior screening as
 - ► 3 consecutive negative cytology results
 - or 2 consecutive negative HPV results
 - within 10 years before cessation of screening
 - most recent test occurring within 5 years"

- Continue beyond age 65 if:
- Adequacy cannot be assessed
- Assessment of lifetime risk

Special Circumstances

Heightened surveillance:

- Prior history of CIN 2/3, VAIN, VIN, PAIN, or cervical/vulvar/vaginal cancer – screen for at least 25 years after diagnosis
 - No colpo on LSIL lesion or less
- High risk patients: history of in utero DES exposure or immunosuppression (HIV, transplant patients, steroid use)
- Uterine didelphys pap both cervices!

No need to continue screening:

- Hysterectomy for benign indication (unless meets criteria above)
- Women with history of endometrial cancer



Screening in Immunocompromised Populations

TABLE 1. Summary of Cervical Cancer Screening and Vaccination Recommendations

	General-population cervical cancer screening	Increased screening ^a with immunosuppressant use	Increased screening ^a regardless of immunosuppressant use	HPV vaccination ^b
Solid organ transplant			Х	Х
End-stage renal disease			Х	Х
Hematopoietic stem cell transplant ^c			Х	Х
Systemic lupus erythematosus			Х	Х
Rheumatoid arthritis	X^d	Х		Х
Inflammatory bowel disease	X^d	Х		Х
Multiple sclerosis	X^d	Х		Х
Disease-modifying therapies or monoclonal antibodies	X^e	X^e		Х

Traditional Cytology

- Conventional Pap
- Majority of cells not captured use wood or plastic spatula
- Non-representative transfer of cells
- Clumping and overlapping of cells
- Obscuring material
- HPV testing requires separate swab

- Liquid based cytology (LBC)
- Virtually all of sample collected use plastic spatula
- Even distribution of cells
- Decrease in unsatisfactory results less likely to be affected by gel, blood, other contaminants
- Increased sensitivity for SIL
- Specimen available for HPV and other STD tests

A Map to Success with the ThinPrep® Pap Test





Sensitivity of Pap Smear

	Sensitivity	Specificity
Pap smear	55 -80%	96.8%
HPV test	94.6%	94.1%

	CIN 2+	CIN3+	Cervical cancer
Neg cytology along	0.68%	0.26%	0.025%
Pap neg, HPV neg	0.27%	0.08%	0.011%
Pap neg, HPV pos	10%	4.5%	0.34%

Katki et al, JLGTD 2013

HPV Testing – how to order it

- Reflexive (RNA/DNA) done with ASCUS result
- Cotesting (RNA/DNA) done along with cytology every 5 years for age ≥30
- HPV genotyping (DNA)- specifically looking for 16/18 strains triage to colposcopy
- Primary HPV testing (DNA) preferred by ACS
- All HPV tests are FDA approved for co-testing
- Primary HPV testing limited to 3 vendors

Test	BD Onclarity™ HPV Assay	QIAGEN digene [®] HC2 High-Risk HPV DNA Test	HOLOGIC Aptima™ HPV Assay	HOLOGIC Cervista™ HPV HR	ROCHE cobas [®] HPV for 4800 System	ROCHE cobas® HPV for 6800/8800 Systems
Approved for HPV primary screening	~	×	×	×	\checkmark	\checkmark
Separate results for HPV 16 and 18	\checkmark	×	Separate assay runª	Separate assay run⁵	\checkmark	~
Genotyping beyond HPV 16 and 18	16, 18, 31, 45, 51, 52	×	18/45 combined®	×	×	×
Internal control for human genes	\checkmark	×	×	\checkmark	\checkmark	\checkmark
PCR-based DNA assay	\checkmark	X DNA, non-PCR	X RNA, non-PCR	X DNA, non-PCR	\checkmark	\checkmark
No cross-reactivity with low-risk HPV genotypes	\checkmark	×	×	×	\checkmark	\checkmark
E6/E7 target region	\checkmark	×	\checkmark	\checkmark	×	×
Manufacturer offers full cervical screening solution	Cytology and HPV	HPV only	Cytology and HPV	HPV only	Cytology and HPV	Cytology and HPV
Clinical trial	Onclarity trial	ASC-US/LSIL Triage Study (ALTS)	CLEAR trial	Cervista HPV HR trial	ATHENA trial	IMPACT trial

An overview of FDA-approved HPV assays¹⁻⁷

^a A separate test can be used to identify HPV 16 and 18/45 in women with positive results ^b A separate test can be used to identify HPV 16 and 18 in women with positive results.



2019 Clinical Action Thresholds



Perkins, Guido et al., JLGTD 2020, Egemen et al, JLGTD, 2022 Immediate risk – chance of having CIN3+ today

- 5-year risk chance of CIN3+ within 5 years from today
- 3-year risk chance of CIN3+ within 3 years from today

Highlights from 2024 ASCCP

- Enduring Guidelines
- Novel strategies
 - Primary HPV testing
 - Extended genotyping
 - Dual staining
 - Self collection



Primary HPV Testing



FDA-approved high-risk HPV tests

Assay	hc2	Cervista	cobas	Aptima	Onclarity		Alinity
Detection of	HPV DNA	HPV DNA	HPV DNA	HPV E6/E7 mRNA	HPV DNA		HPV DNA
# of HPV types	13	14	14	14	14		
Assay type	RNA-DNA hybrids	Invader technology	PCR	RNA amplification/ hybridization	PCR		PCR
Internal control for specimen adequacy	No	Yes	Yes App	_№ roved for pr	_{Yes} imary scre	ee	Yes ning
HPV 16/18 genotyping available	No	Yes	Yes Included	Yes + type 45	Extended genotyping		Extended genotyping

Enduring Guidelines Timeline



Dual Stain Recommendations



Dual stain (CINtec Plus) = cytology stain for 2 markers for "molecular triaging"

- p16 (tumor suppressor targeted by E7 gene product of HPV; brown)
- Ki-67 (proliferation marker; red)
- Positive result: at least one cell with both stains indicates presence of high grade dysplasia
- Proprietary: Roche Diagnostic, FDA approved 3/2020

Percentage of disease detected (≥CIN2, age 25-65)



Primary HPV Screening: <u>>25 years</u> Triage with 16/18 Genotyping and Dual Staining



Value based considerations

- PRO: When compared to cytology, DS requires fewer colposcopies and detects CIN 3 earlier.
- CON: However, DS is expensive and may be confusing to many providers

Test	Base Case	Low	High	Reference		
HPV Test	35.09	26.32	43.86	CMMS Fee Schedule 2021		
Cervical Cytology	26.61	19.96	33.26	CMMS Fee Schedule 2021		
Dual Stain Test	178.30	133.73	222.88	CMMS Fee Schedule 2021		
Colposcopy with Biopsies	387.31	201.07	502.02	CMMS Fee Schedule 2021		
DS MUCH MORE EXPENSIVE THAN CYTOLOGY Harper D Cancer Prev Res 2023						

Extended Genotyping

Carcinogenic HPV type	% of Cervical Cancers	9-year risk of progression to CIN3+ of incident HPV infection	Risk Group
16	60.3	6.3	16
18	10.5	3.0	18/45
45	6.1	2.2	18/45
33	3.7	4.5	16-related
31	3.6	2.2	16-related
52	2.7	2.2	16-related
58	2.2	1.9	16-related
35	2.0	2.8	16-related
39	1.6	1.1	Lower risk
51	1.2	1.1	Lower risk
59	1.1	0.9	Lower risk
56	0.9	0.8	Lower risk
68	0.6	1.0	Lower risk

Different risks for different HPV subtypes.

But, is it enough to change management?



configuration

configuration

Triaging based on extended genotyping

	Current HPV	Current cytology	Past results	Management
HPV 16/18	16	HSIL ¹	N/A ²	Treatment preferred; colposcopy acceptable
	16	ASC-H ³	N/A	Treatment or colposcopy
	16	NILM, ⁴ ASC-US, ⁵ LSIL, ⁶ AGC ⁷ , or no cytology	N/A	Coloscopy ⁸ Son plogy if not already done
	18	HSIL	N/A	porty
	18	NILM, ASCUS, LSIL, ASC-H, AGC, or no cytology	N/A	of cytology if not already done
HPV 45,33/58, 31, 52/35/39/68,	45,33/58, 31, 52/35/39/68, 51 or untyped/other	HSIL, ASC-H, AGC	NA	
51	45,33/58, 31, 52/35/39/68, 51	ASC-US or LSIL		
Untyped or "other" types when	Untyped/other	ASC-US or LSIL		1 year
16 and 18	Untyped/other	ASC-US or LSIL		
are not present	45,33/58, 31, 52/35/39/68, 51 or untyped/other	NILM		ar
	45,33/58, 31, 52/35/39/68, 51 or untyped/other	N/A	Hi curre HPV+)	
HPV 59/56/66	59/56/66	ASC-H, AGC, or HSIL ¹²	N/A	Supy ⁸
	59/56/66	NILM, ASC-US, LSIL or no cytology ¹²	Normal or colposcopy <cin2 within past 1 year</cin2 	Repeat HPV test in 1 year
	59/56/66	N/A	HPV+ without colposcopy (i.e. current test is 2 nd consecutive HPV+)	Colposcopy

Massad et JLGTD 2025

Self collection

Rationale for HPV self collection (also provider collected vaginal sample)

- >50% of cervical cancers occur in unscreened/underscreened populations
- Pandemic driven closures further reduced screening
- Patient discomfort with pelvic exams (mobility, trauma, pain, gender identity)

Data from other countries show improved screening (Netherlands, Australia)

Self collection testing is accurate

TABLE 2 - 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)

Pooled absolute sensitivity and specificity estimates based on 6 studies identified from the systematic literature search with available data on HPV vaginal selfcollection and provider-collected HPV and cytology data.

FDA Approves HPV Self Collection Test

FDA Approves HPV Tests That Allow for Self-Collection in a Health Care Setting

Subscribe

July 24, 2024, by Sharon Reynolds

On May 14, the Food and Drug Administration (FDA) expanded the approvals of two tests that detect cancercausing types of human papillomavirus (HPV) in the cervix. Both tests are used as part of screening for cervical cancer.

Under these expanded approvals, people can now be offered the option to collect a vaginal sample themselves for HPV testing if they cannot have or do not want a <u>pelvic</u> <u>exam</u>. However, the collection, which involves a swab or brush, must be done in a health care setting, such as primary care offices, urgent care, pharmacies, and mobile clinics.



For now, the option to selfcollect a vaginal sample for HPV testing must be done in a health care setting. Credit: iStock/SDI Productions

The tests included in the approvals are Onclarity HPV, made by Becton, Dickinson and Company (BD), and cobas HPV, made by Roche Molecular Systems.

ASCCP self collection recommendations

CLINICAL PRACTICE

OPEN

Self-Collected Vaginal Specimens for HPV Testing: Recommendations From the Enduring Consensus Cervical Cancer Screening and Management Guidelines Committee

Nicolas Wentzensen, MD, PhD,¹ L. Stewart Massad, MD,² Megan A. Clarke, PhD,¹ Francisco Garcia, MD, MPH,³ Robert Smith, PhD,⁴ Jeanne Murphy, PhD, CNM,⁵ Richard Guido, MD,⁶ Ana Reyes, MS,⁷ Sarah Phillips, MS,¹ Nancy Berman, MSN, ANP-BC, NCMP, FAANP,⁸ Jeffrey Quinlan, MD,⁹ Eileen Lind, NP,¹⁰ Rebecca B. Perkins, MD,¹¹ and Enduring Consensus Cervical Cancer Screening and Management Guidelines Committee

HPV test result	Management of clinician- vs. self-collected collected specimens	Current HPV test result	Current cytology result	Past history	Management
HPV 16/18	<u>Clinician-collected</u> : Laboratory performs cotest or reflex cytology <u>Self-collected:</u> Colposcopy recommended. <u>Collect cytology at colposcopy</u> .	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 2 nd 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 past<br="" within="">1 year</cin2>	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</cin2 	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 2 nd consecutive HPV+)	Colposcopy
HPV 59/56/66	Clinician- collected: No additional immediate testing needed. Laboratory may run cytology if cotesting is performed. ⁴ <u>Self-collected:</u> 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</cin2 	Repeat HPV test in 1 year
		59/56/66	Not available	HPV+ without colposcopy (i.e., current test is 2 nd consecutive HPV+)	Colposcopy

Newest update on screening

Announcements

FDA Approves Teal Health's Teal Wand[™]—The First and Only At-Home Self-Collection Device for Cervical Cancer Screening, Introducing a Comfortable Alternative to In-Person Screening

Women can now collect their own sample from the privacy of home, no speculum required, and mail it to a certified lab to be tested on the same test as the doctor's office, with the same accuracy.



Habit #6: Synergize



Surgery, Chemotherapy, Radiation


Eras Tour of cervical cancer treatment

1999 Sis Platin

- Adding cisplatin to RT improves PFS/OS
- 2014 Best Bev-lieve
 - ▶ GOG 240: Improved OS if add bev (17mo vs 13.3mo)
- 2018 MIS-direction
 - ▶ LACC trial- final analysis OS at 4/5 years shows 90.6% vs 96.2%
- 2023 Synergize with Key:
 - ▶ Keynote 826: pembro to systemic chemo+/- bev improved OS (28.6 vs
 - Keynote A18 pembro to chemoRT improves PFS
- 2024 Interlace
 - GCIG Interlace induction chemo before chemoRT improves PFS and OS





Immunotherapy



PD-L1 on the tumor cells binds to PD-1 on the T-cell leading to inactivation of T-cells and inhibits killing of tumor cells



Blocking PD-1 or PD-L1 with immune checkpoint inhibitors (anti-PD-1 or anti-PD-L1) enables T-cells to recognize and kill tumor cells.



'Cause, baby, now we got bad blood You know it used to be mad love So take a look what you've done 'Cause baby, now we got bad blood (hey!)

Habit 7: Sharpen the Saw



Patients: Increase knowledge and awareness

Providers: Strong recommendations, decrease missed opportunities

Social Media: Reduce Stigma

Systems: Improve access, standardized workflows

How well are we preventing HPV cancers

FIGURE. Quadrivalent vaccine-type (4vHPV-type) prevalence among sexually experienced females aged 14–34 years, by age group, vaccination history,* and survey years — National Health and Nutrition Examination Survey, United States, 2003–2018^{†,§}



88% reduction!

1% Prevalence of HPV in age 14-19

Racial disparities in cervical cancer

Figure 1

Racial and Ethnic Disparities in Cervical Cancer

Cervical Cancer Incidence and Mortality Rates by Race/Ethnicity, 2014-2018



Incidence Mortality

NOTE: Data are age-adjusted rates per 100,000 women.

SOURCE: National Cancer Institute. SEER Stat Fact Sheets: Cervix Uteri Cancer. Accessed May 2021. • PNG



Emerging evidence for extending screening for certain populations



Figure 3. Age-specific cervical cancer mortality rates, uncorrected and corrected for the prevalence of hysterectomy, in (A) white and (B) black women.

How well are we doing?

- Assessment of USPSTF Screening Guideline Adherence 2005 and 2019
 - Reviewed cross sectional day from the National Health Interview Survey (n=20,557)
 - 2005: screening q3 years (21-65yo)
 - 2019: q3 year (21-29), cotest 5 years (30-65)





23%: Individuals without updated screening

B Reasons for not receiving screening



Reasons for underscreening ethnic



Reasons for underscreening – sexual orientation



Reasons for underscreening – location



Reasons for underscreening insurance



Reverse disparity



Review of 118 HPV vaccine studies in US (n=3mil)

Minorities were 6.1 more likely to initiate HPV vaccination compared to Whites

Minorities were 8.6% less likely to follow-up with full HPV vaccine series

Where are we now?

Cervical Cancer Incidence Rates by Race in the USA



Trauma Informed Care

TRAUMA: events or circumstances experienced by an individual as physically or emotionally harmful or life-threatening, which result in adverse effects on the individual's functioning and well-being (SAMHSA)



REALIZES the widespread impact of trauma and understands the potential paths to recovery.

RECOGNIZES signs and symptoms of trauma in clients, families, staff and others involved with the system.

RESPONDS by fully integrating knowledge about trauma into policies, procedures and practices

RESIST Re-Traumatization 4 Rs for Trauma Informed Approach

TIC during gynecologic exams

- During gynecologic exams
 - ▶ Ensure patient in safe space do they want another person present or not
 - Ask permission to start exam, have chaperone
 - Share steps of procedure before you do them
 - Use nonjudgemental objective language
 - Reinforce throughout the visit that the patient has control
 - Be flexible to patient needs and requests

Review abnormal findings and next steps – "no news is good news"

What are we doing at Harbor/DHS

Primary Prevention

- Vaccination: orchid prompt to offer starting age 9
- Secondary prevention
 - 2024: Launch primary HPV testing
 - DHS Expected practice
 - 2025: Launch self collection
- Tertiary Prevention
 - Incorporate immunotherapy into care of local advanced and advanced cervical cancer
 - Future roles for clinical trials

CA HPV Vaccination Roundtable



The California HPV Vaccination Roundtable invites you to attend a free training on

The Announcement Approach

for Increasing HPV Vaccination

Approved for 1 unit of AAFP Elective credits



This one hour, interactive online meeting will share strategies for recommending HPV vaccination to promote vaccine acceptance and save clinical time. Learn the latest on HPV vaccine research and guidelines, as well as brief, evidence-based communication strategies to increase vaccine uptake by your adolescent patients.

BENEFITS

- Learn an evidence-based approach to increasing HPV vaccination endorsed by the National Cancer Institute.
- This approach saves clinical time and patients prefer it.
- Stay up-to-date on the latest in HPV vaccine research

Trainings are held virtually.

For more information and to schedule a training, contact Shauntay Davis-Patterson at Shauntay.davis@cdph.ca.gov

American Cancer Society

2025 Partner Opportunities to Prioritize HPV Vaccination

Register your organization to join us!

HPV Vaccination Health System Learning Community

Who:

Community health centers, pediatric practices, and family practice medical groups located in: CA, FL, GA, IL, MI, NJ, NY, NC, OH, PA, TX, and VA.

What

Learning community exploring quality improvement practices to close adolescent vaccination care gaps and improve clinical processes. Live CME/CNE credits available for all sessions after the info session.

When: Info session: April 24

Series: May 22, July 24, September 25, October 23, and December 11 from 2-3pm EST.

Where: Virtual via Zoom meeting. Registration required.

HPV Vaccination Promising Practices Series

Who:

Healthcare providers, health plans, public health professionals, and community partners.

What:

Informative quarterly series to learn about the latest evidence-based practices to improve on-time HPV vaccination rates among adolescents aged 9-13.

When:

March 26, June 25, August 27, and November 19 from 2-3pm EST.

Where:

Virtual via Zoom webinar. Registration is rolling so you can join anytime throughout the year!

Rural HPV Vaccination Learning Community

Healthcare providers, health plans, public health professionals, and community partners who serve rural communities.

What:

Learning community aimed at connecting partners and improving on-time HPV vaccination rates among adolescents aged 9-13. Live CME/CNE credits available.

When:

2nd Wednesday of every month (March-December) 2-3pm EST.

Where:

Virtual via Zoom meeting. Registration is rolling so you can join anytime throughout the year!



Register here

Register here!

Precision
This programming is supported by the Centers for Disease Control and Prevention of the U.S. Department of Health and Human Services
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Cetty
Wexs of, nor an endorsement. by CDC/HS, or the U.S. Government.





Arrester Oiler





WHO 2030: Enough is enough – global mission to ERADICATE cervical cancer

Few diseases reflect global inequities as much as cervical cancer. Cervical cancer is the fourth most common form of cancer among women worldwide.

More than SE AFFECTED ARE YOUNG

undereducated women who live in the world's poorest communities.

OF THE 20 HARDEST HIT COUNTRIES, **19 ARE IN AFRICA**



Even in high-income countries, the inequity of cervical cancer disproportionately afflicts women of color, minorities, and other marginalized communities.

middle-income

countries (LMICs)

Furthermore, The disease **KILLS MORE THAN** OF THE DEATHS occur in low- and

WOMEN EVERY YEAR.

Unless we take action, this preventable tragedy will only worsen. If we accept the status quo,

BY 2030

annual DEATHS WILL RISE TO 400 000 Annually, it is



the annual number of new cases is projected to INCREASE TO 700 000

- 90% of girls fully vaccinated with the **HPV vaccine by** the age of 15;
- 70% of women screened using a highperformance test by the age of 35, and again by the age of 45;
- 90% of women with pre-cancer treated and 90% of women with invasive cancer managed.



Meeting and maintaining the 90-70-90 targets would yield significant returns in the coming century:

- the median cervical cancer incidence rate will fall by 42% by 2045, and by 97% by 2120, averting more than 74 million new cases of cervical cancer; and
- the median cumulative number of cervical cancer deaths averted will be 300 000 by 2030, over 14 million by 2070, and over 62 million by 2120.

Closing Thoughts



But I must do my part, knowing it will take a far-reaching, global effort to conquer this cancer. I'm willing to spread the word to anyone who will hear it. That word, the word that pushes me to keep going, is the title of this book: *Enough*.

Enough, because cervical cancer can be stopped. Enough, because each of us can play a role in making it stop.

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Frequently Asked Questions (FAQs)

Q1: Should I still do a pap if I see a cervical mass on routine exam?

A: Maybe. Pap test is a screening test for a presumably normal looking cervix. If a mass or cancer is suspected, recommend biopsy or referral to gynecology for evaluation/biopsy as a pap test may not be diagnostic.

Q2: My patient completed the HPV vaccine series. Does she still need to get cervical cancer screening routinely?

A: Yes, current guidelines recommend same cervical cancer screening intervals regardless of prior HPV vaccination history

Frequently Asked Questions (FAQs)

Q3: My healthy 67yr old patient who transferred her care from another country is asking if she still needs a pap smear as she states that she never had an abnormal pap smear. Is it ok to stop?

A: Depends. If patient is not able to provide adequate screening over the preceding 10 years, would recommend ongoing screening until can document 3 consecutive negative liquid-based cytology test results or 2 consecutive negative primary HPV or co-tests (most recent test within 5 years).

Q4: I got an unsatisfactory pap test result but her HPV test was negative. Is it ok to just repeat it next year?

A: No, unsatisfactory cytology should be repeated in 2-4 months. Also consider cause for unsatisfactory cytology (i.e. Infection, vaginal atrophy) and treat underlying cause before repeat pap test.

Questions



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Thank you!