Is HPV Screening Safe Enough? CON

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Disclosures

- No financial relationships or conflict of interest to disclose

- ACOG, ASCCP, and SGO agree with the USPTF's enthusiasm for the promise of primary hrHPV screening and have previously provided interim guidance for its use.

But

- Is HPV screening safe enough to be the only extended interval screening for women ages 30 to 65 years?

USPSTF Draft Recommendations

Population	Recommendation	Grade
Women ages 21 to 65 years	The USPSTF recommends screening for cervical cancer every 3 years with cervical cytology alone in women ages 21 to 29 years. The USPSTF recommends either screening every 3 years with cervical cytology alone or every 5 years with high-risk human papillomavirus (hrHPV) testing alone in women ages 30 to 65 years	A
Women >65 years	The USPSTF recommends against screening for cervical cancer in women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer.	D
Women < 21 years	The USPSTF recommends against screening for cervical cancer in women younger than age 21 years.	D
Women with hyster-ectomy	The USPSTF recommends against screening for cervical cancer in women who have had a hysterectomy with removal of the cervix and do not have a history of a high-grade precancerous lesion (i.e., cervical intraepithelial neoplasia [CIN] grade 2 or 3) or cervical cancer.	D

https://www.uspreventiveservicestaskforce.org/Page/Document/draft-recommendation-statement/cervical-cancer-screening2

USPSTF Draft Recommendations

Population	Recommendation	Grade
	th cervical either gh-risk	A
	n older than wise at high	D
	n younger	D
nyster-ectomy	n who have y of a high-grade precancerous lesion (i.e., cervical intraepithelial neoplasia [CIN] grade 2 or 3) or cervical cancer.	D

USPSTF recommends either screening every 3 years with cervical cytology alone or every 5 years with high-risk human papillomavirus (hrHPV) testing alone in women ages 30 to 65 years

HrHPV testing replaces Cotesting

https://www.uspreventiveservicestaskforce.org/Page/Document/draft-recommendation-statement/cervical-cancer-screening2

Availability of FDA-Approved hrHPV Tests for Primary Screening

- Different HPV tests have different test characteristics
- Primary screening should be restricted to tests that have been validated through rigorous clinical trials for this use
- Currently, there is only one test is USFDA approved for primary hrHPV screening (Roche Cobas 4800)
  - It is available only in a limited number of laboratories and institutions
  - BD has applied for FDA approval of a new hrHPV screening test
- Many institutions would need to purchase new equipment or to use 3-year cytology, which has decreased sensitivity

Compliance Issues

- Many providers continue to perform routine annual cervical cancer screening, screen women younger than age 21 years, and screen women after hysterectomy —long after recommendations were made to end these practices
- Preserving cotesting as an alternative option and adding primary hrHPV screening will be less confusing to providers and patients
- Allows time for providers and patients to move to the new recommendations
  - Otherwise, they may cling to outdated habits with worse outcomes

History of Cervical Cancer Cases

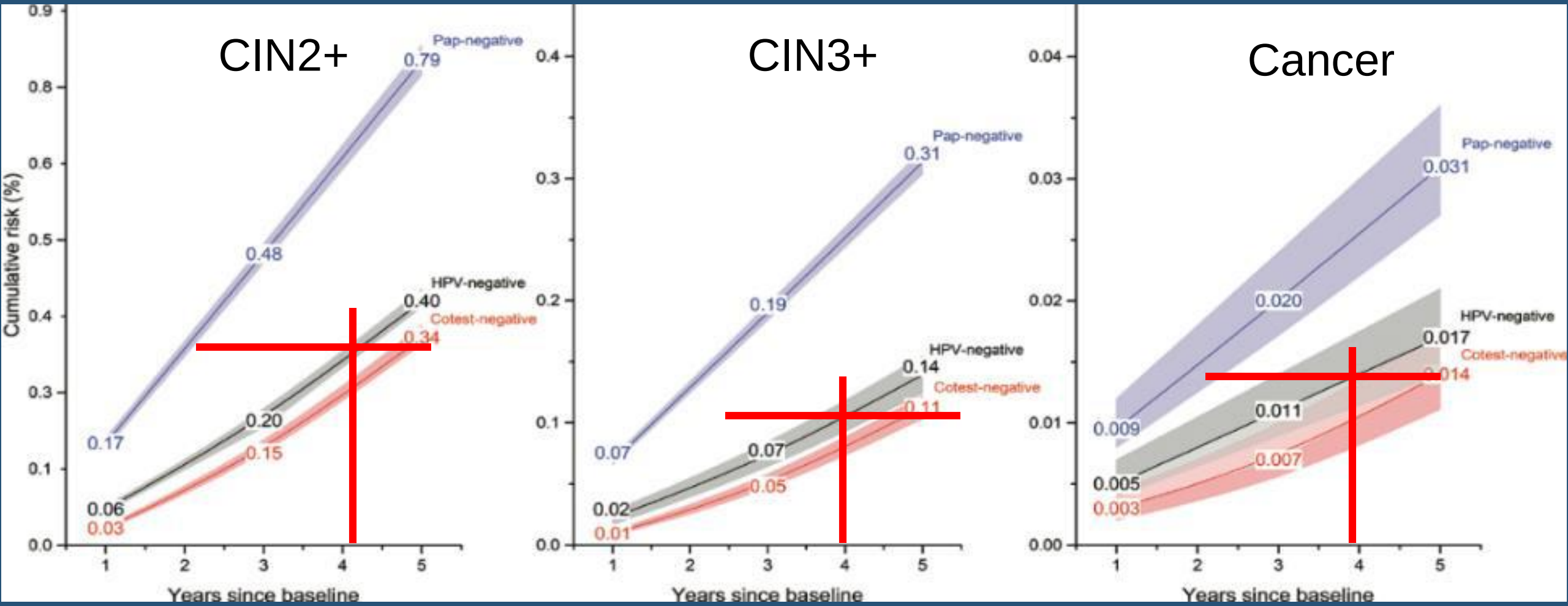
Cause	Kaiser (US)	Sweden
No recent screen	56%	64%
Cytology detection failure	32%	24%
Failure of follow-up	13%	11%

Leyden WA, et al. J Natl Cancer Inst. 2005 May 4;97(9):675-83.
Andrae B, et al.. J Natl Cancer Inst. 2008 May 7;100(9):622-9.

Decreased Detection Compared with Cotesting

- Cotesting provides highest sensitivity for detection of CIN3+
  - HrHPV testing provides most of the sensitivity in contesting
- There is added detection with cervical cytology
  - In a NCI analysis of U.S. data from Kaiser Permanente Northern California, the risk of CIN 3 and cancer appeared roughly equivalent between 4-year primary hrHPV screening and 5-year cotesting

Gage J, et al. J Natl Cancer Inst 2014;106:1–4.



Cumulative risks of CIN 2+, CIN3+ and cancer among women aged 30 to 64 years at Kaiser Permanente Northern California by enrollment Pap and HPV test result, 2003 to 2012.

Supporting Data and U.S. Population

- The draft guideline cites mostly international studies for the move to HPV primary screening every 5 years
- These countries generally have organized screening programs with and high rates of HPV vaccination
- Screening in the USA is opportunistic and many women do not receive sufficient screening
- U.S. HPV vaccination uptake has lagged behind that in other developed countries
- It is unclear how these differences will affect the efficacy of primary HPV screening – more US data is needed

Availability of FDA Approved HPV Testing Methodology and False Negative Results

- Laboratory quality control and ongoing proficiency testing are extremely important
- Several HPV tests do not provide an internal specimen adequacy control to ensure that cervical epithelial cells have been sampled
  - When co-testing is utilized, the laboratory is able to provide a visual check of specimen adequacy
- There is a risk of false negative HPV results without co-testing
- There is very little data regarding interfering substances such as lubricants and blood

HPV Negative Cervical Cancer

- The prevalence of HR-HPV types varies with demographic populations
- The current U.S. population is very diverse, in contrast to the patient populations in the prior European trials
- As with any laboratory test, the sensitivity of high risk HPV testing is not 100%
- A subset of carcinomas may not be detected by HPV testing alone

HPV Negative Cervical Cancer

HPV types in invasive cervical cancers from 7 US cancer registries

	Total	HPV16	HPV18+, HPV16 -	Other HR types+	Other rare types +	HPV -	Odds Ratio	OR 95% CI
Total	777	395 (50.8)	122 (15.7)	162 (20.9)	25 (3.2)	73 (9.4)	-	-
White	409	213 (52.1)	64 (15.7)	72 (17.6)	12 (2.9)	48 (11.7)	2.53	1.0–6.41
Black	129	64 (49.6)	24 (18.6)	32 (24.8)	3 (2.3)	6 (4.7)	1.0	-
Hispanic	124	63 (50.8)	16 (12.9)	30 (24.2)	5 (4.0)	10 (8.1)	2.01	0.65–6.19
Asian, PI	93	40 (43.0)	16 (17.2)	24 (25.8)	5 (5.4)	8 (8.6)	1.97	0.62–6.89
All other	17	11 (64.7)	1 (5.9)	4 (23.5)	0 (0.0)	1 (5.9)	2.67	0.28–25.69
Squamous	570	317 (55.6)	61 (10.7)	141 (24.7	23 (4.0)	28 (5.0)	1.0	-
AdenoCa	179	65 (36.3)	58 (32.4)	19 (10.6)	1 (0.6)	36 (20.1)	5.10	2.88–9.04
All other	28	13 (46.4)	3 (10.7)	2 (7.1)	1 (3.6)	9 (32.1)	6.25	2.31–16.91

Hopenhayn C, et al. J Low Genit Tract Dis. 2014;18:182-189.

HPV Negative Cervical Cancer

70 US Invasive Cervical Carcinomas Diagnosed in 2012

Method[a]	HPV Results: Positive, No. (%)	HPV Results: Negative, No. (%)	*P* Value
HC2, n = 72	61 (85)	11 (15)	Reference value
Cervista, n = 12	11 (92)	1 (8)	.30
Cobas, n = 3	2 (67)	1 (33)	.24
Total, n = 87	**74** (85)	**13** (15)	

Cancer Type	HPV^+, No. (%)	HPV^-, No. (%)
Squamous cell carcinoma, n = 55	44 (80)	11 (20)
Adenocarcinoma, n = 13	11 (85)	2 (15)
Others (see text), n = 2	2 (100)	0 (0)

- 15% to 20% of cervical cancers were HRHPV negative
- Although not statistically significant, the rate of HPV negativity varied between tests

Zhao C, et al. Arch Pat hol Lab Med. 2015;139:184-188.

HPV Negative Cervical Cancer - Carcinoma

Comparison of Pap and HRHPV Results Within 1 Year of Diagnosis

Histologic Type	No.	Age, Average (Range), y	HPV-Positive, No.	HPV-Positive, %	HPV-Negative, %
SCC	364	45.9 (23-81)	346	95.0	5.0
ADC	56	43.4 (26-88)	42	75.0	25.0
ADSQ	5	43.2 (34-49)	5	100	0
Small cell carcinoma	2	58.5 (57-60)	2	100	0
Total	427	45.6 (23-81)	395	92.5	7.5

Retrospective study of 427 cases of invasive cervical carcinoma in Guangzhou, China

HPV testing was performed with HC2 in all but 5 SCC cases tested with the Tellgenplex 26 HPV genotyping panel

Zheng B, et al. Cancer Cytopathol. 2015;123:428-34.

HPV Negative Cervical Cancer - Adenocarcinoma

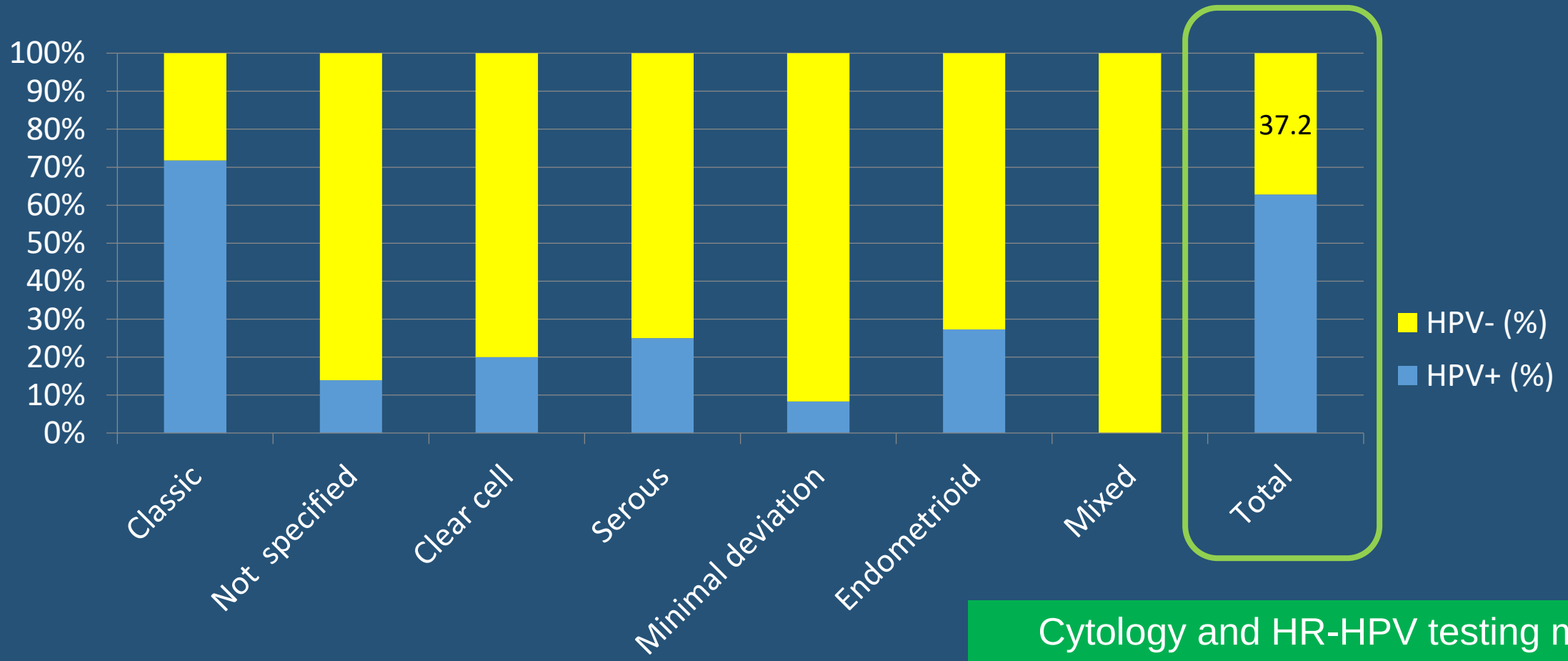
Comparison of Pap and HRHPV Results Within 1 Year of Diagnosis

Papanicolaou Test Result	HPV-Positive		HPV-Negative	
	No.	%	No.	%
Malignant	1	7.7	1	16.7
HSIL	2	15.4	0	0
ASC-H	1	7.7	0	0
AGC	6	46.2	5	8.3
ASCUS	1	7.7	0	0
NILM	1	8.3	0	0
Total	12	100	6	100

Zheng B, et al. Cancer Cytopathol. 2015;123:428-34.

HPV Negative Cervical Cancer - Adenocarcinoma

Worldwide analysis of 760 cases



Cytology and HR-HPV testing miss different sub-sets of invasive cancer

Pirog EC, et al. Mod Pathol. 2014;27:1559-1567.

Summary

- ACOG, SGO, ASCCP support of USPSTF's proposal to incorporate primary HPV testing into its guidelines, we urge the USPSTF to retain 5-year co-testing as a screening option for women aged 30–65 years

- Is it safe enough?

Perhaps

- Is primary HPV testing alone the best plan now?

Perhaps not