Cervical Update 2016: What's New in Cervical Cancer Prevention

New Mexico Academy of Family Physicians
Taos
July 31, 2016

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I have no financial interests in any commercial entity related to this presentation.

Objectives

In this presentation I'll

- Compare the performance characteristics of cervical screening with HPV testing alone with cytology and cotesting.
- Discuss the potential added value of the 9-valent HPV vaccine.
- Outline a simple strategy for increasing the number of patients immunized against HPV.
- Discuss the limitations of colposcopy and how taking multiple biopsies can improve its efficacy.
- Review the scientific basis for the ASCCP Management Guidelines

ACS/ASCCP/ASCP 2012 Cervical Cancer Screening Recommendations

From age 30 – 65, co-testing with cytology and HPV testing every 5 years is preferred; screening with cytology alone every 3 years is acceptable.

Saslow et al. Ca Cancer J Clin 2012
Reissued in ACOG Practice Bulletin 167, January 2016

The Pap test has been successful for decades. Why add an HPV test?

If HPV causes cervical cancer, shouldn't HPV testing with or without cytology replace Pap testing as the standard of care?

- High risk HPV is the causative agent for cervical cancer.
  - RR for developing cervical cancer for woman HPV 16 + is 434 compared with HPV neg.

Benefits of Co-testing: Studies from U.S. and Europe

- Co-testing has higher sensitivity and NPV than Pap alone. (lower specificity)
- Co-testing leads to earlier diagnosis of CIN 3+ and Cancer
- Incorporating HPV finds more AIS than cytology alone
- Negative cytology plus negative HPV allows spacing screening beyond every three years.

Reduction in Cancer and Precancer with co-testing, POBASCAM Study

- 44,938 women randomized to co-testing or cytology
  - Two screening rounds 4-6 years apart

Diagnosis of Cancer			
	Co-testing	**Cytology**	**p value**
First round	**12 (0.06%)**	**6 (0.03%)**	**0.166**
2nd round	**4 (0.02%)**	**14 (0.07%)**	**0.031**

Diagnosis of CIN 2+ - 3+			
First Round	**Co-testing**	**Cytology**	**P Value**
CIN 2+	267 (1.34%)	215 (1.07%)	0.015
Second round	**Co-testing**	**Cytology**	**P Value**
CIN 3+	88 (0.45%)	122 (0.62%)	0.023

Rijkaart DC et al Lancet Oncol 2012;13:78-88

Pooled Analysis of 4 European RCTs of HPV Screening vs Cytology

Ronco G, Dillner J, Elfstrom KM et al. Lancet Nov 3, 2013

- Pooled data from Studies in UK, Italy, Sweden, Netherlands
  - Compared screening with cytology vs HPV (Mostly cotesting)
- 176,464 women aged 20-64 (median 35-41)
- 107 Invasive cancers diagnosed
  - No difference between groups first 2.5 years then significantly lower in HPV arm
- Overall 60% reduction in incidence

Positive HPV diagnoses more AIS and Adenocarcinoma than Cytology alone.

331,818 women enrolled in Kaiser N. Cal

Significantly more AIS and Adenoca diagnosed over 5 yrs if initial screen:

- HPV + vs Pap + (p<0.0001)
- HPV + / Pap – vs HPV -- / Pap + (p<0.0001)

	AIS	**Adenocarcinoma**
Total	70	27
Pap Negative	42 (60%)	23 (85%)
Pap Positive	28 (40%)	4 (15%)
HPV Positive	56 (80%)	21 (78%)
Pap -- / HPV +	31 (44%)	17 (63%)
Pap + / HPV --	3 (4%)	0

Katki, Kinney, et al Lancet oncol.2011;12:663-72

A negative HPV DNA test offers better protection after 6 years than a negative Pap does after 3 years.

- Joint European Cohort Study compared HPV testing with conventional Pap in 6 countries
- N=24,295

Rate of CIN 3+ after baseline negative test				
	3 yrs	4 yrs	5yrs	6yrs
Pap –	0.51%	0.69%	0.83%	0.97%
HPV-	0.12%	0.19%	0.25%	0.27%

Dillner, J. et al. BMJ 2008;337:a1754

Kaiser Permanente Northern California

- 1.4 million women followed with cotesting
- Pap negative at baseline
  - 5 year Risk of CIN 3+ 0.26%
- Pap and HPV both negative at baseline
  - 5 year Risk of CIN 3+ 0.08%

Katki et al J Lower Genital Tract Dis 2013;17(5):S28-35
Katki et al. J Lower Genital Tract Dis 2013; 17(5):S64-68

Cumulative Incidence of ≥CIN3 after a Single Test for High-Risk HPV

30 Years and Older, Cytologically Normal Women

10 year risk of CIN 3 or worse <1% if HPV negative
10 year risk of CIN 3 or worse about 4% if HPV positive

Sherman *et al.*, JNCI, 2003


The New York Times

Friday, April 25, 2014 Today's Paper Personalize Your Weather

BUSINESS DAY

Alternative to Pap Test Is Approved by F.D.A.

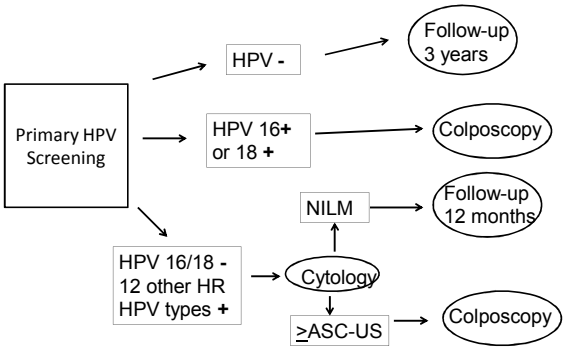
By ANDREW POLLACK APRIL 24, 2014

The Food and Drug Administration on Thursday approved the first alternative to the long-used Pap test as a primary screening method for cervical cancer, in the face of opposition from some women's groups and health organizations.

On April 24, 2014 the FDA approved extended indications for the Roche COBAS HPV test to include primary screening in women aged ≥25 *using a limited, defined protocol*

Algorithm for Primary HPV Screening

Modified from SGO / ASCCP Interim Guidance
Huh et al Gynecol Oncol 2015



Cumulative Incidence of ≥CIN3 - Risk if HPV16 or HPV18 is positive

30 Years and Older, Cytology Neg, ASCUS,LSIL

If HPV 16 positive at baseline, risk of CIN 3 or worse reaches 10% in a year
If HPV 18 positive at baseline, risk of CIN 3 or worse reaches 10% within 3 years.

Khan *et al.*, JNCI, 2005

Performance of Primary HPV Screening: The ATHENA Study

Wright, Stoler, Beherens, et al. Gynecol Oncol 2014

- 40, 901 women aged ≥25 followed for 3 years
- Compared three screening regimens
  - primary HPV screening with Cobas algorithm
  - cytology based screening with reflex HPV for ASC-US
  - "hybrid strategy" that approximates current screening with reflex HPV at age 25 and cotesting age ≥30

	Sens	Spec	PPV	NPV
Primary HPV	76.1	93.5	12.9	99.7
Cytology	47.8	97.1	17.0	99.3
Hybrid	61.7	94.6	12.6	99.5

Performance for diagnosis of CIN 3+ in women aged ≥25.
Primary HPV vs Cytology vs Hybrid (U.S. co-test based strategy)

Performance of Primary HPV Screening: The ATHENA Study

Wright, Stoler, Beherens, et al. Gynecol Oncol 2014

Number of Colposcopies Required by Each Screening Strategy

	Colposcopies		**Colposcopies to detect one case of CIN 3+**	
	Age ≥25 / Age ≥30		Age ≥25 / Age ≥30	
1^0 HPV	3769 **	2522**	12.8 *	13.1*
Cytology	1934	1294	10.8	10.1
Hybrid	3097	2457	12.9	13.0

*Sig. higher than cytology
** Sig. higher than both other strategies

On May 1, 2017, Australia will roll out a national screening program based on HPV testing (with Pap triage of positives) every 5 years for women aged 25-74.

Isn't it best to prevent HPV infections in the first place?

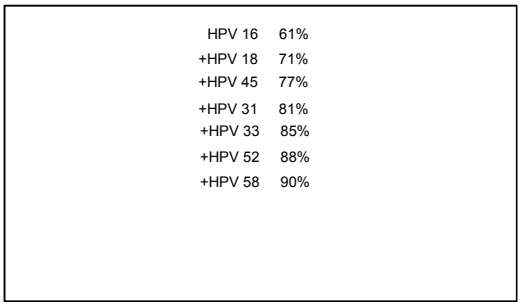
AGW

FDA News Release

FDA approves Gardasil 9 for prevention of certain cancers caused by five additional types of HPV

For Immediate Release
December 10, 2014

HPV Types Covered in HPV 9 Vaccine and increment of cervical cancers caused worldwide



Distribution of HPV Types Cx Ca- International

de Sanjose S, et al. Lancet Oncol. 2010 Nov;11(11):1048-56.

Cancer Caused by the HPV Types Covered in HPV 9 Vaccine in the U.S.

- HPV associated cancers (all sites): 74%
  - HPV 16 or HPV 18: 64% (~21,300 cases annually)
    - 65% females
    - 63% males
  - HPV 31,33, 45, 52, 58: 10% (~3,400 cases annually)
    - 14% females
    - 4% males
- Cervical cancer : 81%
  - HPV 16, 18: 66%
  - HPV 31, 33, 45, 52, 58: 15%

MMWR Mar 27, 2015/ 64(11)300-304

Guardasil 9: Phase III Efficacy Trial

- 14,000 females ages 16 through 26
- 96.7% efficacy
  - Against CIN 2+, VIN 2,3, VaIN 2,3 caused by HPV 31, 33, 45, 52, 58
  - Per protocol population
  - Immunogenicity against HPV 16, 18 was non-inferior to Guardasil 4
- > 99% Seroconversion both males and females for all HPV types

MMWR Mar 27, 2015/ 64(11)300-304

Fewer than 3-dose regimen for HPV vaccine

- Multiple studies show immunogenicity equivalence between three doses and 2 doses of the bivalent vaccine with dosing at 0 and 6 months
- WHO and European Medicines Agency recommends 2 dose regimen in females if first dose <15 y.o.
  - 2 doses standard in Mexico
  - ACIP Considering
- Duration of protection unknown
- One dose has been proposed.

Can we improve vaccine coverage

Compilation thanks to Basil Donovan

	Australia	New Zealand	Denmark	Sweden	USA	Germany
Type of Program (start year)	School- and clinic-based (2007)	School- and clinic-based (2008)	Clinic-based (2008-2009)	Clinic-based (2006-2007)	Clinic-based (2006)	Clinic-based (2007)
Coverage (youngest females)	83%	52%	85%	32%	32%	40%
Decline in GW in youngest females	93%	63%	90%	41%	35%	47%
Decline in CIN 2/3	Y	-	Y	-	-	-
Decline in target HPV prevalence	67%	-	49%	-	56%	53%
Herd protection for males	+++	++	Too early	+	+	-

Why don't mothers get their teenage daughters immunized against HPV?

- 2012 NIS Teen surveyed parents not intending to vaccinate their daughters in the next 12 months.
  - Vaccine not needed 19.1%
  - Vaccine not recommended 14.2%
  - Vaccine safety concerns 13.1%
  - Lack of knowledge about vaccine or disease 12.6%
  - Daughter not sexually active 10.1%

MMWR July 26, 2013 . 62(29);591-595

Recommendations to Improve Vaccination Coverage in Children, Adolescents & Adults

- Reminder/recall systems
- Immunization registries
- Standing orders
- Staff education
- Minimize patient out-of-pocket expense
  - Providers should enroll in Vaccines for Children (VFC) program
    - "MVPAP' *http://www.merck.com/merckhelps/vaccines/home.html*
- Identify barriers to immunization in your setting-
  - Hours of availability

Pickering, et al. *Clin Infect Dis.* 2009.
http://www.cdc.gov/vaccines/programs/vfc/providers/questions/qa-join.html

Colposcopy with biopsy is considered the foundation of cervical diagnosis. How *solid* is it?

Sensitivity of Colposcopy with Biopsy

ALTS Group. Am J Obstet Gynecol 2003;188:1383-92

- Sensitivity for CIN 3+ = 53.6% (43.2-63.8)
  - Cases of CIN 3+ per QC Pathologists, detected on immediate colposcopy as percentage of cumulative cases found by end of study.

Colposcopy Dogma, 1975

A good colposcopist identifies and biopsies the single worst appearing lesion!

Number of biopsies taken that lead to ultimate diagnosis of CIN 3+

Gage et.al. Obstet Gynecol 2006;108:264-72

- 2675 women in ALTS with adequate colposcopy on enrollment
- Success in diagnosing CIN 2 or worse over the course of the study
  - 68.3% (142 / 208) when one biopsy taken
  - 81.8% (108 /132) when two biopsies taken
  - 83.3% (35 / 42) when three or more biopsies taken

P<.01 for 1 bx vs ≥2 bx

Does training predict expertise in colposcopy?

Gage et.al. Obstet Gynecol 2006;108:264-72

- Diagnosis of CIN 2+ on enrollment colposcopy
  - Correlated with number of biopsies (≥2)
  - Was independent of colposcopic impression
  - Was independent of training of colposcopist
    - General gynecologists, Nurse practitioners, Gynecologic oncologists, Gynecologic oncology fellows

Does colposcopy identify the worst lesion?

Pretorius et al Am J Obstet Gynecol 2004;191:430-434

- 364 of 8497 women in Shanxi province China with CIN 2,3, or cancer and satisfactory colposcopy

Diagnosis made by	
• Colposcopically directed biopsy	208 (57.1%)
• Random biopsy	136 (37.4%)
• Positive ECC only	20 (5.5%)

- CIN found on random bx involved fewer quadrants and of lower grade than colposcopically detected

What does a random biopsy add if there are no acetowhite areas?

Huh et al Obstet Gynecol 2014;124:670-8

- In ATHENA trial, 2839 women with abnormal Pap or +HPV test had satisfactory colposcopy and no lesion seen – had one random biopsy.
  - Histology CIN 2: 36 (1.3%) / CIN 3+: 45 (1.5%)
- Overall, random biopsy diagnosed 20.9% of the total CIN 2+ cases and 18.9% of CIN 3+.
- The yield of CIN 2+ was significantly higher if the HPV type was 16 or 18 vs 12 other high risk types.
  - CIN 3+ was diagnosed in 8.2% of women HPV 16 or 18+ vs 1.7% of those positive for 12 other high risk types

Should each distinct acetowhite lesion be biopsied?

Wentzensenn et al J Clin Oncol 2015. 33(1):83-9

- 690 women with abnormal cytology
  - 252 with HSIL on biopsy
- Each distinct acetowhite lesion biopsied, up to 4 biopsies
  - Random biopsy taken if <4 directed biopsies taken a random biopsy of a non-acetowhite area taken

Number of Targeted Biopsies	Cumulative sensitivity HSIL
1	60.6%
1-2	85.6%
1-3	95.6%
1-4	100%

How much does a random biopsy add?

Wentzensenn et al J Clin Oncol 2015. 33(1):83-9

- Non-directed biopsy of normal appearing area taken if <4 directed biopsies were taken
  - 446 (65%) of 690 women had <4 biopsies
  - 2% of HSIL detected from biopsy of normal appearing areas

Yield of HSIL: Targeted Biopsies

Targeted Biopsies	Pts.	Number HSILs
None	30	NA
1	90	11 (12.2%)
2	181	34 (18.8%)
3	145	68 (46.9%)

Additional yield of biopsy of normal appearing area

Number HSIL s
1 (3.3 %)
3 (3.3%)
4 (2.2%)
2 (1.4%)

Colposcopy Dogma 2015:

Take more biopsies!

Where should we biopsy?

- Biopsy the most abnormal looking area.
  - Then biopsy other areas that have even a minimally abnormal colposcopic appearance.
  - In the U.S. some colposcopists are also taking random biopsies if no lesion is seen.
- The ASCCP Guidelines have safeguards to find CIN that may be missed on colposcopy.
  - Close follow-up with a low threshold for repeat colposcopy or excision
  - Requires good patient follow-up.

OK! Let's get to the ASCCP Management Guidelines.
This seems like a classic example of the product of a committee.

ASCCP Guidelines Based on Principle of Equal Management for Equal Risk

5 year cumulative risk of CIN 3+ in Kaiser Permanente Northern Cal. Database

		5 year risk of CIN 3+
LSIL	Colposcopy	5.2%
	Observe	

LSIL cytology has long been the agreed upon threshold for colposcopy.
In KPNC Database, if cytology was LSIL, the 5 year risk of CIN 3+ was 5.2%

Katki et al. Lower Genital Tract Dis 2013; 17(5):S28-35

Management Benchmarked to 5 year risk of CIN 3+

		5 year risk of CIN 3+
LSIL	Colposcopy	5.2%
ASC-US / no HPV	Repeat in 6-12 months	2.6%

If Pap is ASC-US and no HPV done, ASCCP 2006 guidelines called for repeat in 6-12 months.

Katki et al. Lower Genital Tract Dis 2013; 17(5):S28-35

Management Benchmarked to 5 year risk of CIN 3+

		5 year risk of CIN 3+
LSIL	Colposcopy	5.2%
ASC-US / no HPV	Repeat in 6-12 months	2.6%
Pap Negative	Repeat in 3 years	0.26%

Screening guidelines for negative cytology alone call for repeat screening in 3 years.

Katki et al. J Lower Genital Tract Dis 2013; 17(5):S28-35

Management Benchmarked to 5 year risk of CIN 3+

		5 year risk of CIN 3+
LSIL	Colposcopy	5.2%
ASC-US / no HPV	Repeat in 6-12 months	2.6%
Pap Negative	Repeat in 3 years	0.26%
Pap Neg/ HPV Neg	Repeat in 5 years	0.08%

Screening guidelines for negative cytology and negative HPV call for repeat screening in 5 years.

Katki et al. J Lower Genital Tract Dis 2013; 17(5):S28-35

Here are a few examples of how the Guidelines use this principle.

A 23 y.o. G1 P1 has LSIL on her Pap. Since she's under age 30, HPV test was not done.

What is the next step in her management?

A. Colposcopy

B. HPV test

C. Cytology in one year

D. Co-testing in 5 years

The ASCCP Guidelines set the threshold for colposcopy at a level of risk equivalent to LSIL.

The 5 year cumulative risk for CIN 3+ in women aged 21-24 fell below that threshold. The recommendation, therefore was follow-up, not colposcopy for ASC-US and LSIL in this age group.

% 5 year risk of CIN 3+ based on cytology -KPNC 2003- 10

N =	21 – 24 133,947	25 – 29 135,382	30 – 64 165,360
LSIL	**3.0***		(5.2) Colposcopy threshold
ASC-US HPV+	**4.4***		
ASC-US HPV-	0.57	0.59	0.43
Negative	0.2	0.36	0.26

*= Sig different from 25-29 or 30-64

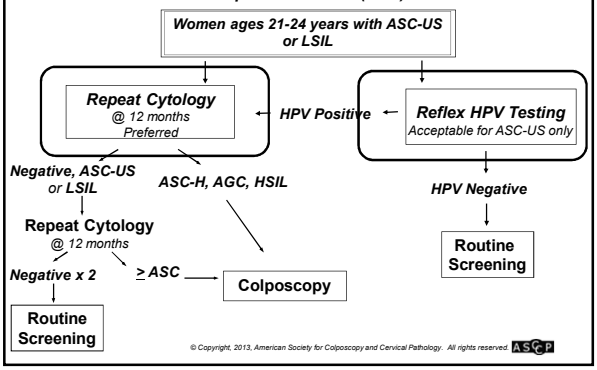
Katki et al. J Lower Genital Tract Dis 2013; 17(5):S64-68

Management Benchmarked to 5 year risk of CIN 3+

	Management	5 year risk of CIN 3+
LSIL	Colposcopy	5.2%
ASC-US / no HPV	Repeat in 6-12 months ☆	2.6%
Pap Negative	Repeat in 3 years	0.26%
Pap Neg/ HPV Neg	Repeat in 5 years	0.08%

Katki et al. J Lower Genital Tract Dis 2013; 17(5):S28-35

Management of Women Ages 21-24 years with either Atypical Squamous Cells of Undetermined Significance (ASC-US) or Low-grade Squamous Intraepithelial Lesion (LSIL)



A 32 y.o. has LSIL on cytology. Her colposcopy directed biopsy returns CIN 1. How should she be managed?

A. Repeat Pap in 6 and 12 months
B. Co-test in one year
C. Cryotherapy
D. Hysterectomy

When a colposcopy returns CIN 1 (or negative), what is the risk of CIN3+?

The level of risk is tied to the antecedent cytology.

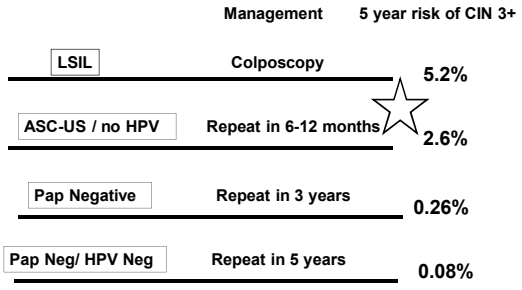
Cumulative 5 year risk of CIN 3+ after CIN 1 or negative colposcopy (Kaiser Northern Cal)

Kaiser Permanente Northern California Database, age 25+

Antecedent Cytology	N	% CIN 3+
HSIL+	549	15
ASC-H	1,189	7.8
LSIL/ HPV+ ASC-US	17,097	3.8

Katki et al. J Lower Genital Tract Dis 2013; 17(5):S69-77

Management Benchmarked to 5 year risk of CIN 3+



Our patient's risk of CIN 3+ = 3.8%. The guidelines recommend re-testing in one year – with cotesting.

But what if her cotest after CIN 1 had returned Pap negative, HPV +? The algorithm says repeat colposcopy, and the process starts all over. If her HPV doesn't clear, she could be stuck with annual colposcopies. How do we get patients off the colpo-go-round???

Managing the persistently minimally abnormal screening test with no evidence of CIN 2+

Sawaya GF, Smith-McCune K Obstet Gynecol 2016;127:459-67

- In ALTS, women with a normal colposcopic impression on second colposcopy had lower risk of CIN 3+ than if the impression was LSIL or HSIL
  - If second colposcopic impression was normal, risk = 2.7%
    - Similar to risk if HPV negative =2.0%
- Author's recommendation:
  - On second colposcopy, liberal use of biopsy, ECC, examination of vulva and vagina
    - If no evidence of CIN -> cotest in 3 years.

Finally, last September, the CDC and NIH published new guidelines for cervical screening women with HIV.

Screening in HIV infected Women

- If HIV+, regardless of mode of transmission, begin screening at onset of sexual activity or age 21, whichever is earlier
- Women younger than age 30: Screen with cytology
  - Cytology at time of diagnosis
  - Annual cytology until 3 consecutive negatives, then cytology every 3 years
- Women age ≥30: Screen with cytology or cotesting
  - Cytology screening:
    - annual cytology until 3 consecutive negative, then every 3 years
  - Screening with cotesting:
    - If both cytology and HPV are negative, every 3 years
- Continue screening through lifetime
- Manage abnormal results the same as the general population

NIH/CDC/ IDSA 2015

So that's where we are with cervical cancer prevention in Summer, 2016. What does the future hold?

As more young women get vaccinated, we can anticipate less cervical dysplasia. This translates to more false positive Pap tests with a lower positive predictive value.

As the Pap becomes less predictive, we will increasingly turn to screening with the HPV test alone possibly with triage of positives using cytology or perhaps another biomarker, and at still more extended intervals.
Stay tuned…