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Five-year risk of CIN3+ and cervical cancer for women who test Pap-negative, but are HPV-positive

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Abstract

Objective—Current US guidelines for cotesting recommend that the large numbers of women who test Pap-negative, but HPV-positive, return in 1 year, and those who remain HPV-positive or have LSIL (or worse) Pap be referred for colposcopy. However, the performance of these guidelines in routine clinical practice has not been evaluated.

Methods—We estimated cumulative 5-year risks of CIN3+ for 32,374 women aged 30–64 with HPV-positive/Pap-negative cotest results at Kaiser Permanente Northern California during 2003–2010.

Results—The 5-year CIN3+ risk following an HPV-positive/Pap-negative cotest result, which was found in 3.6% of women, was 4.5% (95% CI 4.2%–4.8%). The 5-year cancer risk was 0.34% (95% CI 0.26% to 0.45%) and half of the cases were adenocarcinoma. Overall, 47% of the women remained HPV-positive upon return (median 415 days after baseline), a percentage that varied little over ages 30–64. At the return following a baseline HPV-positive/Pap-negative result, almost every repeat cotest result predicted greater subsequent 5-year CIN3+ risk than the same cotest result had at baseline (HPV-positive/LSIL: 9.2% vs. 6.1%, $p=0.01$; HPV-positive/ASC-US: 7.9% vs. 6.8%, $p=0.2$; HPV-positive/Pap-negative: 7.4% vs. 4.5%, $p<0.0001$; HPV-negative/LSIL:

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Conflicts of Interest: Dr. Schiffman and Dr. Gage report working with Qiagen, Inc. on independent evaluations of non-commercial uses of Care HPV (a low-cost HPV test for low-resource regions) for which they have received research reagents and technical aid from Qiagen for free. They have received HPV testing for research at no cost from Roche. Dr. Castle has received compensation for serving as a member of a Data and Safety Monitoring Board for HPV vaccines for Merck. Dr. Castle has received HPV tests and testing for research at a reduced or no cost from Qiagen, Roche, MTM, and Norchip. Dr. Castle is a paid consultant for BD, GE Healthcare, and Cepheid, and has received a speaker honorarium from Roche. No other authors report any conflicts of interest.

1.7% vs. 2.0%, $p=0.8$; HPV-negative/ASC-US: 2.9% vs. 0.43%, $p=0.0005$; HPV-negative/Pap-negative: 0.93% vs. 0.08%, $p<0.0001$).

Conclusions—Using the principle of “equal management of equal risks”, HPV-positive/Pap-negative women had subsequent CIN3+ risk consistent with risk thresholds for a 1-year return. However, upon returning in approximately 1 year, about one-half of women will be referred for colposcopy due to continued HPV positivity or Pap abnormality. Clinicians should keep in mind that cotest results at the return following a baseline HPV-positive/Pap-negative finding are riskier than the same baseline cotest results in the general population, supporting intensified clinical management of return cotests.

Keywords

Human Papillomavirus (HPV); cancer prevention; Pap; cervical intraepithelial neoplasia (CIN); Hybrid Capture 2 (HC2); prospective cohort

Introduction

Greater use of HPV and Pap cotesting in cervical screening is motivated primarily by the very low risk of cervical cancer among the great majority of women who test HPV-negative/Pap-negative. The main limitation of HPV testing is that benign infections likely to clear are common enough to lead to low predictive value of a single positive test. In other words, a large group of women will be HPV-positive but cytologically negative (Pap-negative); 90% or more of those women will never develop cancer or even its precursor, cervical intraepithelial neoplasia grade 3 (CIN3) (1–3).

The optimal clinical management of women who are HPV-positive/Pap negative is not firmly established. Immediate colposcopic referral of all could easily triple referral rates and would represent excessive intervention given the low risk of immediate CIN or cancer (CIN3+) in the group. However, the cumulative risk of eventual CIN3+ following a HPV-positive/Pap-negative cotest is considerably higher than a Pap-negative result alone. Therefore, the new US cotesting guidelines suggest following women who are HPV-positive/Pap-negative at 1 year, with a repeat cotest(4). Women testing positive for either the HPV or cytologic component of the re-screen are then referred to colposcopy; women testing HPV-negative/Pap-negative or HPV-negative/ASC-US at the return test subsequently are returned to standard screening intervals, because the infection is judged to have cleared.

The choice of 1 year for the follow-up interval was somewhat arbitrary; it was based on natural history data showing that roughly half or more of prevalent HPV infections will clear within a year of detection (5–8). A 6-month interval would be more cautious but many women whose infections are destined to clear will still be HPV-positive at six months. A 2-year interval would permit a substantially larger fraction of infections to clear, leaving only those at greatest risk of associated cervical intraepithelial neoplasia grade 3 or worse (CIN3+). But, women and their providers might be unwilling to wait that long to assess whether infection is persistent, the cancer risk would increase modestly, and loss-to-follow-up might be higher with longer follow-up intervals.

Moving forward, it is useful to have data from routine clinical practice on the management of women with HPV-positive/Pap-negative results. We need more data on the percentage of HPV-positive/Pap-negative women who are still HPV positive, stratified by follow-up interval. Moreover, we wish to assess how increasing the interval for retesting affects the subsequent risk of diagnosing CIN3+. Finally, it is important to quantify the risks related to

various repeat cotest results obtained upon return after the baseline HPV-positive/Pap-negative screen.

Data from Kaiser Permanente Northern California (KPNC), which instituted Pap and HPV cotesting using Hybrid Capture 2 (HC2) for women 30 and older in 2003(9) can provide estimates of CIN3+ risk with varying retesting intervals from routine clinical practice. KPNC guidelines recommend retesting in 1 year for women with a baseline HPV-positive/Pap-negative screening result; however, in practice such women returned at varying intervals. We observed the proportions of repeat HPV positivity by retesting interval, and analyzed possible modification by age. We also examined the risk of finding CIN3+ as a surrogate of cancer risk by time to return testing, and by the results of the repeat cotest.

Methods

The design of our cohort study from KPNC has been described previously(9, 10); in this report we enlarged the dataset to include all women age 30–64 entering cotesting between 2006–2010. As a result of the data expansion, we were able to examine 965,360 women aged 30–64 screened from 2003 to 2010. For each woman, we considered as the baseline screen the first available cotest in the study period. Women were excluded only if they had no result available at their baseline test, or were outside of the age range. Of this group, 32,374 women had HPV-positive/Pap-negative cotest results at baseline. Follow-up pathology and diagnostic information was collected on all women through December 31, 2010. The Kaiser Permanente Northern California institutional review board (IRB) approved use of the data, and the National Institutes of Health Office of Human Subjects Research deemed this study exempt from IRB review.

Pap tests were performed at KPNC regional and facility labs. HPV tests were performed at the single regional lab. Conventional Pap slides were manually reviewed following processing by the BD FocalPoint Slide Profiler (BD Diagnostics, Burlington, NC, USA) primary screening and directed quality control system, in accordance with FDA-approved protocols. Starting in 2009, KPNC transitioned to liquid-based Pap using BD SurePath (BD Diagnostics, Burlington, NC, USA). Conventional or liquid-based Pap tests are reported according to the 2001 Bethesda System (11). Hybrid Capture 2 (HC2; Qiagen, Germantown, MD, USA) was used to test for high-risk HPV types according to manufacturer's instructions.

Women were followed according to routine local practice. The Permanente Medical Group (TPMG), which is the physician component of KPNC, develops Clinical Practice Guidelines for cervical cancer screening and management of abnormal tests in KPNC in partnership with the KP National Guideline Program, Care Management Institute, to support the clinical decisions of their providers. According to US national consensus guidelines, women with HPV-positive/ASC-US, or with LSIL or worse Pap, should undergo colposcopy(4). HPV-negative/ASC-US women should be re-tested in 1 year. From 2003–2005, HPV-positive/Pap-negative women at KPNC were generally monitored annually for cytologic evidence of disease. Since 2006, women with consecutive HPV-positive/Pap-negative results were offered colposcopy. At KPNC, cotesting is sometimes used in the management of abnormal results.

We calculated risk of CIN2+, CIN3+, and cancer for all women who tested HPV-positive/Pap-negative at their baseline screen. We also calculated risk for HPV-positive/Pap-negative women who returned for a repeat test, and calculated risk related to every repeat cotest combination starting at that test.

Cumulative risks of CIN2+, CIN3+ (including AIS), or cervical cancer for each cotest result were calculated as the sum of risk at baseline test (plotted at time zero on each figure) and the risk after baseline. Risk at the baseline screen was the risk of CIN2+, CIN3+, or cancer for Pap alone or cotest results where women were referred, without further screening, to colposcopy and was estimated using logistic regression on 5-year age groups 25–29, 30–34, ..., 60–64, separately for each Pap or cotest result. We used Weibull survival models (12) to estimate risks over time strictly after the baseline test, among women for whom CIN2+ was not found at the baseline test. Weibull models can make smoother and more accurate risk estimates than non-parametric methods analogous to Kaplan-Meier (13), and naturally handle interval-censoring of disease outcomes between screening tests. Separate Weibull models were fit for each Pap or cotest result, with age group as a covariate. When risk was calculated for a cytology result without regard to HPV testing, we refer to those risks as “Pap-alone”.

We focused primarily on risk of CIN3+ or cancer rather than CIN2+ because CIN2 is unreliably determined by pathologists(14, 15), often regresses spontaneously (16, 17), and may simply reflect uncertainty related to distinguishing acute HPV infection (CIN1) from CIN3(2).

We also calculated the risk of repeat HC2 positivity over time (this is not type-specific HPV persistence because HPV typing information was not available) using a non-parametric survival estimate analogous to Kaplan-Meier (13). Because the vast majority of HC2 positivity is observed to become negative, non-parametric estimates are accurate and smooth, making Weibull modeling unnecessary for HC2 positivity.

Results

Among women 30–64 at KPNC who had a cotest from 2003–2010, 3.6% had a baseline HPV-positive/Pap-negative result. Table 1 shows the distribution of the worst cumulative histologic findings through 2010 for these 32,374 HPV-positive/Pap-negative women, both overall and after the repeat cotest at the return test. Approximately 75% of them had a repeat co-test, at a median of 415 days after baseline. At that repeat co-test, 47.4% of women were HPV-positive; 30.2% of women with a follow-up co-test were again HPV-positive/Pap-negative. Among women with a repeat cotest, the vast majority of CIN2, CIN3/AIS, and cancer was found in those who again were HPV-positive. We compared the HPV prevalence of women 1 year after HPV+/Pap– results with the HPV prevalence with the same cytologic results at baseline. HPV prevalence was higher with every cytologic result at the repeat cotest versus the same cytologic results at baseline (Pap-negative: 38% vs. 3.7% at baseline; ASCUS: 86% vs. 38%; LSIL: 95% vs. 81%; AGC: 87% vs. 25%; ASC-H: 97% vs. 71%; and HSIL+: 98% vs. 94%).

About half of the total cancers among women with HPV-positive/Pap-negative baseline results were adenocarcinoma (32/60), a much higher percentage than seen at KPNC overall. Also, in women with a repeat cotest, 45% (10/22) of the subsequent adenocarcinoma cases were found in women with repeat HPV-positive/Pap-negative results at the return test.

Figure 1 presents risks of CIN2+, CIN3+, and cancer following HPV-positive/Pap-negative results and the percentage of repeat HC2 positivity (HC2 persistence) over time. For example, at 1-year after baseline, the CIN2+/CIN3+/Cancer risks were 2.8%/1.1%/0.11%. A total of 56% of women remained HPV-positive. At 2 years, the risks were 4.8%/2.0%/0.17% but only 37% of women remained HPV-positive. Over 5 years, the CIN3+ risk was 4.5% (95% CI 4.2%–4.8%), which is just below the 5.2% risk threshold required for immediate colposcopy if LSIL is considered to be at the threshold(10).

Figure 2 presents 5-year risks of CIN2+, CIN3+, and cancer following HPV-positive/Pap-negative results with the percentage of repeat HC2 positivity at the repeat cotest, by 5-year age groups. HC2 positivity at 1 year after baseline was between 55%–60% for all age groups from 30–64. Women age 30–44 had higher CIN2+/CIN3+ risk than women aged 45–64 (CIN2+: 11% vs. 7.6%, $p<0.0001$; CIN3+: 5.2% vs. 3.1%, $p<0.0001$); however, cancer risks were similar for both age groups (0.33% vs. 0.37%, $p=0.7$).

Table 2 presents the risks for each repeat cotest result (following HPV-positive/Pap-negative at baseline), compared with the risk of that same cotest when it was found at baseline. After a baseline HPV-positive/Pap-negative result, almost every repeat cotest result had greater subsequent 5-year CIN3+ risk than that same cotest result had overall at baseline (HPV-positive/LSIL: 9.2% vs. 6.1%, $p=0.01$; HPV-positive/ASC-US: 7.9% vs. 6.8%, $p=0.2$; repeat HPV-positive/Pap-negative compared to the baseline one: 7.4% vs. 4.5%, $p<0.0001$; HPV-negative/LSIL: 1.7% vs. 2.0%, $p=0.8$; HPV-negative/ASC-US: 2.9% vs. 0.43%, $p=0.0005$; HPV-negative/Pap-negative: 0.93% vs. 0.08%, $p<0.0001$). Notably, the cancer risk of an HPV-negative/Pap-negative result was increased if it was preceded by an HPV-positive/Pap-negative result (0.13% for the repeat test vs. 0.011% for the baseline test, $p=0.002$).

Table 3 benchmarks the risks following selected cotest results at the repeat cotest following HPV-positive/Pap-negative to the implicit CIN3+ risk thresholds that currently trigger each management option according to current US guidelines (3).

- The 5-year CIN3+ risk for repeat HPV-positive/Pap-negative at the return cotest following baseline HPV-positive/Pap-negative was 7.4%, which exceeds the risk threshold for colposcopy of 5.2% based on LSIL diagnosed at baseline.
- The 5-year CIN3+ risk for HPV-negative/ASC-US at the return cotest following HPV-positive/Pap-negative (2.9%) places it in the equivalent risk range of ASCUS and a 1-year follow-up cotest recommendation.
- The 5-year CIN3+ risk for HPV-negative/Pap-negative at the return test following HPV-positive/Pap-negative (0.93%) places it in the equivalent risk range of Pap-negative alone and a 3-year repeat cotest.
- The 5-year CIN3+ risk for HPV-negative/LSIL at the return cotest following HPV-positive/Pap-negative (1.7%) places it in the equivalent risk range of LSIL and immediate colposcopy, in spite of having a low 5-year CIN3+ risk, because the immediate CIN3+ risk was also 1.7% (all CIN3+ for these women was diagnosed immediately) which is comparable to the immediate CIN3+ risk for LSIL of 2.5%(10).

Discussion

“HPV-positive/Pap-negative” results are the most common positive screening result obtained from cotesting. At KPNC among women aged 30–64 at study entry, 3.6% of women received this baseline result. Because so many women are affected, the proper management of HPV-positive/Pap-negative results is essential to the overall success of cotesting as a cervical screening strategy.

In our population, 5-year risk of CIN3+ in women with HPV-positive/Pap-negative results was 4.5%, only slightly lower than the threshold for immediate colposcopic referral implicitly set by the risk of cytologically-evident HPV infections, viz., LSIL (5.2% in KPNC) and HPV-positive/ASC-US (6.8%). It could be argued, based on the principle of “equal management of equal risks,” that all women with HPV-positive/Pap-negative results be immediately referred to colposcopy. However, this would double colposcopic referrals.

Moreover, at the time of colposcopy, many early lesions found by this approach would be colposcopically inapparent and/or likely to regress. Therefore, the threshold for colposcopic referral at baseline can effectively be drawn between the LSIL and HPV-positive/Pap-negative categories.

If immediate colposcopic referral is not recommended, the question then becomes “when should HPV-positive/Pap-negative women return?” A 1-year return is currently recommended per national guidelines(4); a 2-year return would permit substantially more HPV clearance to occur, and thus substantially reduce unnecessary colposcopic examinations, but that would raise the risk of cancer. Specifically, based on KPNC data, if all women with repeat HPV positivity were referred to colposcopy, a 2-year return would lead to 1,900 fewer colposcopies per 10,000 HPV-positive/Pap-negative women than a 1-year return (56% prevalence at 1 year minus 37% at 2 years), but at the estimated potential cost of 6 more cancers per 10,000 women (0.17%–0.11%, Figure 1). Consequently, a longer return interval is unlikely to be adopted in the US.

A slight majority of cancers that we observed in 5-year follow-up among HPV-positive/Pap-negative women were adenocarcinoma, more than would be expected based on the overall KPNC data (28% adenocarcinoma). Because 46% of adenocarcinoma occurred in women who were Pap-negative at baseline (as compared to 21% for squamous carcinoma), Pap screening was less effective at detecting the precursors of adenocarcinoma. The greater sensitivity of HPV/Pap cotesting might increase the effectiveness of screening for adenocarcinoma, as suggested by data from other prospective analyses(1, 18).

Age modifies the risk of CIN3+ following an HPV-positive/Pap-negative result. Our analysis was restricted to women receiving routine cotesting at KPNC, i.e., those aged 30–64; thus, we did not study risks among younger women. Within the age range we examined, women aged 30–44 had significantly higher risk of CIN3+ than women aged 45–64. This is concordant with the broad peak of CIN3 that is centered approximately a decade following the peak of HPV acquisition. In the KPNC data, the differences were large enough that the benchmarking principle would suggest immediate colposcopy for the younger group alone. It is not clear, however, whether the added complexity of age-specific management of HPV-positive/Pap-negative results is worth the gain in individualizing care.

After an HPV-positive/Pap-negative result, we found that the 5-year risks following repeat cotests increased for almost all cotest combinations, compared with the same combinations at baseline, i.e., ignoring any previous history. Thus, it is a meaningful piece of past medical history to know that a woman has recently tested HPV-positive/Pap-negative. We did not expect this result for women whose repeat cotest was HPV-negative/Pap-negative. We expected that the negative cotest would signal the clearance of the previous infection, leaving the woman at extremely low risk. Instead, we observed some continued elevation in risk extending to an elevated risk even for subsequent cancer.

As a result of these findings, it seems justified to manage women with somewhat greater caution, for any cotest result that comes immediately after an HPV-positive/Pap-negative result. Specifically, our benchmarking of risks following key cotest results at the return test following HPV-positive/Pap-negative to the implicit CIN3+ risk (10) suggests that repeat HPV-positive/Pap-negative results at the return test, following baseline HPV-positive/Pap-negative, is sufficiently risky to merit immediate colposcopic referral. An HPV-negative/Pap-negative result at the return test following HPV-positive/Pap-negative has equivalent risk of a Pap-negative result alone without knowledge of HPV status suggesting 3-year return is warranted; the data did not support immediate return to routine, 5-year cotesting intervals. Current consensus guidelines (4) suggest that women with HPV-negative/ASC-US

at the cotest following HPV-positive/Pap-negative can return to routine screening. We observed that their 5-year CIN3+ risk was 2.9%, which would suggest instead a 1-year return. This affected very few women (0.04% of the total KPNC cohort that we analyzed had baseline HPV-positive/Pap-negative followed by HPV-negative/ASC-US). It might be worth simplifying the guidelines by referring this small group to colposcopy, along with the even smaller (0.006%) group of women with an HPV-positive/Pap-negative baseline result and a follow-up cotest of HPV-negative/LSIL.

The major limitation of this analysis is that it was conducted in a single, particular setting that might not be representative of other populations. Women aged 30–64 in KPNC constitute a well-screened, low-risk population, and their risk is similar to some (3) but lower than other prospective cohort studies (1). Of note, we cannot compare the risk estimates here directly to studies (19–23) in which all HPV-positive women were referred immediately to colposcopy because KPNC guidelines do not recommend referral of women with HPV-positive/Pap-negative results to colposcopy without evidence of persistence or progression on follow-up cotesting in 1 year.

In conclusion, the optimal management of the common finding of HPV-positive/Pap-negative cotest results is not simple. Improved management techniques and strategies for these women will affect many women, as we have shown for cytologic ASC-US (24). Like ASC-US, HPV-positive/Pap-negative women would likely benefit from a triage strategy to guide management, especially since the vast majority of these women do not have clinically important disease. HPV genotyping for HPV16 and HPV18 is an already-approved triage option that warrants more examination. Research into the use of p16/Ki-67 testing, to distinguish low-risk from high-risk in this large group of women comprises another high-priority for the coming years. A clinically-useful triage technique would have a major impact on the effectiveness of the cotesting strategy.

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Figure 1. Among women aged 30–64 testing HPV-positive/Pap-negative at baseline, decline of repeat HC2 positivity since baseline, and cumulative risks of CIN2+, CIN3+, and cancer since baseline.

Figure 2. Among women aged 30–64 testing HPV-positive/Pap-negative at baseline, 5-year cumulative risks of CIN2+, CIN3+, and cancer, and percent of women repeat HC2 positive, by age group

Table 1

Distribution of worst histologic diagnosis over 2003–2010 among women aged 30–64 who (A) tested HPV -positive/Pap-negative at baseline (32,374 women), and (B) had a repeat cotest (22,766 women).

Cotest result	Total	Worst histologic diagnosis during follow-up							Total CIN3 or AIS, n	Adeno-carcinoma, n	Total cancers, n
		<CIN1, n	CIN1, n	CIN2, n	CIN3, n	AIS, n	Squamous carcinoma, n				
(A) Women HPV-positive/Pap-negative at baseline											
Total	32,374	27,344	3,241	1,036	607	83	693	16	32	60	
(B) Women with repeat cotest											
Total	22,766	18,235	2,982	898	579	71	607	11	22	44	
HPV-negative/Pap-negative	11,388	11,059	268	31	22	4	26	1	2	4	
HPV-negative/ASCUS	374	329	35	4	5	1	6	0	0	0	
HPV-negative/LSIL	59	43	12	3	1	0	1	0	0	0	
HPV-positive/Pap-negative	6,866	4,918	1,345	341	217	33	245	2	10	17	
HPV-positive/ASCUS	2,258	1,116	785	243	103	8	106	2	2	8	
HPV-positive/LSIL	1,133	498	434	134	62	5	65	2	0	2	

Total cancers includes not only squamous cell carcinoma and adenocarcinoma but also adenosquamous carcinoma, and cervical cancer of unknown histology or histology unrelated to HPV infection. The category "Total CIN3 or AIS" also includes women with diagnoses that did not differentiate between CIN3 and AIS. "<CIN1" is included for completeness, and includes normal or metaplastic biopsy findings, no biopsy taken, and no record of colposcopy found.

Table 2

Cumulative 5-year risks of CIN2+, CIN3+, and cancer for women aged 30–64 at baseline given repeat cotest result (excluding high-grade Pap test) after HPV-positive/Pap-negative, compared to the risk for those cotests at baseline

Cotest result	CIN2+			CIN3+			Cancer	
	5-year risk at baseline (%)	5-year risk after HPV-positive/Pap-negative (%)	5-year risk after HPV-negative (%)	5-year risk at baseline (%)	5-year risk after HPV-positive/Pap-negative (%)	5-year risk after HPV-negative (%)	5-year risk at baseline (%)	5-year risk after HPV-positive/Pap-negative (%)
HPV-positive/LSIL	19	24		6.1	9.2		0.089	0.18
HPV-positive/ASC-US	18	22		6.8	7.9		0.41	0.405
HPV-positive/Pap-negative	10	16		4.5	7.4		0.34	0.46
HPV-negative/LSIL	5.1	6.8		2	1.7	*		*
HPV-negative/ASC-US	1.1	5.2		0.43	2.9	*		*
HPV-negative/Pap-negative	0.27	1.8		0.08	0.93		0.011	0.13

Benchmarking CIN3+ risks for repeat cotest result after HPV-positive/Pap-negative to risk thresholds implicitly used to determine clinical management options based on screening Pap tests

Table 3

Current recommended management strategy based on Pap-alone	Implicit risk threshold: 5-year CIN3+ risk by baseline Pap result alone (regardless of HPV result) ¹			5-year CIN3+ risk after given repeat cotest result following HPV +/- Pap-	
	Management-defining result	Frequency in women aged 30-64	CIN3+ risk	Repeat cotest result following HPV +/- Pap-	Frequency in women aged 30-64
Immediate Colposcopy	LSIL	0.97%	5.2%	HPV+/Pap- HPV-/LSIL	0.75% 0.006% 7.4% 1.7% *
1-year return	ASC-US	2.8%	2.6%	HPV-/ASC-US HPV-/Pap-	0.04% 1.3% 2.9% 0.93%
3-year return	Pap-	95.6%	0.26%		
5-year return	HPV-/Pap-	92.1%	0.08%		

* HPV-/LSIL was placed in the immediate colposcopy band because it has immediate CIN3+ risk of 1.7%, which is comparable to the immediate CIN3+ risk of 2.5% for LSIL (not shown in table) required for referral for immediate colposcopy. In contrast, the immediate CIN3+ risk for HPV-/ASCUS (0.27%) was not sufficiently high to justify referral for immediate colposcopy.

¹Data presented in: Katki HA, Schiffman M, Castle PE, Fetterman B, Poitras NE, Lorey T, et al. Benchmarking CIN3+ risk as the basis for incorporating HPV and Pap cotesting into cervical screening and management guidelines *J Low Genit Tract Dis* In press.