

## Educate the Educators Literature Update

The ASCCP is expanding our *Educate the Educators* program by initiating a series of quarterly literature updates for our membership. This will include PDFs of the articles, as well as a commentary prepared by the *Educate the Educators* editorial committee. The commentary not only provides a synopsis of the key findings, but also attempts to put them into context. We are also making available for download PowerPoint slides documenting what we believe to be the key messages from these articles. These PowerPoint slides are designed so you can incorporate them into the *Educate the Educators* slide set. From time to time there also will be news items of general interest to our readership and we will cover these in a “What’s New?” section.

In this quarter’s *Educate the Educators* literature update we are sending you four articles that we think you will find interesting. Two of these articles, the one by Naucler *et al.* and one by Dillner *et al.*, present data from large European cervical cancer screening studies. The Naucler study uses the Swedescreen data to evaluate how cervical cancer screening strategies combining different variations of high-risk HPV DNA testing, HPV genotyping, and cervical cytology might work. They conclude that a cervical cancer screening program based on using high-risk HPV DNA testing alone as the primary screen with “reflex” cervical cytology reserved for HPV DNA positive women is an attractive screening option for women in their 30s and older. The Dillner article combines data from 7 different European cervical cancer screening trials that followed women for up to 72 months. This review concludes that because of the high

negative predictive value (NPV) of HPV DNA testing, it is safe to screen no more frequently than every 6 years when HPV DNA testing is used.

The third article comes from the NCI’s HPV research group which is continuing to analyze the data from ALTS. This article provides an in-depth look at the rates of regression of CIN 2 versus CIN 3 in ALTS. Castle *et al.* conclude that over a two year period of time, approximately 40% of CIN 2 lesions will undergo regression. The last article is a meta-analysis by De Vuyst *et al.* that assesses the association of HPV with vulvar, vaginal, and anal intraepithelial carcinomas and invasive cancers. This is a very nice summary for those of us who want to be able to reference these associations, or to counsel patients with these conditions.

### ETE Editorial Committee

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## Efficacy of HPV DNA testing with cytology triage and/or repeat HPV DNA testing in primary cervical cancer screening

Naucler *et al.* JNCI. 2009;101:88-99

Although cervical cytology continues to be the mainstay for cervical cancer prevention efforts globally, the newest HPV molecular diagnostic tests are so sensitive for identifying women at risk for CIN 3+ that some experts, and even some national screening programs, are reassessing the role that cytology plays in cervical cancer prevention. Perhaps because Europe has been much slower to adopt liquid-based cytology than North America, Europe is much further along in this reassessment. In addition, European health systems often have organized cervical cancer prevention systems, allowing for later initiation of screening and less frequent screening, both of which make HPV testing more attractive.

The recent article by Naucler *et al.* provides data from the Swedescreen study on how HPV DNA testing alone might be used for cervical cancer screening with cytology reserved for determining which HPV positive women need colposcopy.<sup>4</sup> Swedescreen is a population-based randomized controlled trial of HPV DNA testing that was carried out in women 32-38 years of age participating in the Swedish organized screening program between 1997 and 2005. One arm of Swedescreen received conventional cytology; the

other arm received both a conventional Pap test and HPV DNA testing. The HPV test that was used was a consensus PCR method (GP5+/6+) with type-specific probes for 14 high risk types of HPV. This article provides information on the 6,257 women in the arm that were screened using both cytology and HPV DNA testing. Women with abnormal cytology results were followed up according to regional practice. Women with normal cytology who were high-risk HPV positive underwent a second round of cytology and HPV DNA testing at least 12 months after enrollment and were referred to colposcopy if they tested persistently positive for the same type of HPV as found at enrollment. Follow-up was obtained by using data from the regional cytology and pathology registries, as well as the national cytology registry. These registries contain data on all cervical cytology and biopsies obtained in Sweden.

At enrollment, 2.3% of women had an abnormal cytology result and another 5.4% of cytology negative women were HPV DNA positive. This low rate of HPV positives is not unexpected since enrollment was limited to women 32-38 years old. As expected, the sensitivity of HPV DNA testing for either CIN 2+ or

CIN 3+ was significantly higher than that of cytology, but the specificity was lower, **Table 1**.

The study then compared the performance of different screening strategies that used only HPV DNA testing to screen women for disease. These include HPV DNA testing with reflex cytology if HPV DNA positive, HPV DNA testing with genotyping for different combinations of high-risk HPV types if HPV positive, and combinations of cytology and genotyping. These are presented in depth in the article, but **Table 2** shows the relative performance of a strategy that was found to be the most feasible screening strategy. This strategy uses HPV DNA testing alone for screening followed by reflex cytology when women are found to be HPV DNA positive. With this strategy women who are negative on reflex cytology undergo repeat HPV DNA testing in 12 months whereas women with abnormal cytology undergo colposcopy.

A screening strategy of using HPV DNA testing only for screening, combined with reflex cytology for HPV positive women maintains a very high sensitivity for detection of disease while greatly improving the positive predictive value

**TABLE 1: SENSITIVITY AND SPECIFICITY OF CYTOLOGY AND HPV DNA TESTING IN SWEDESCREEN**

	CIN 2+		CIN 3+	
	SENS	SPEC	SENS	SPEC
HPV Testing	95%	94%	96%	94%
Cytology	71%	99%	74%	98%

**TABLE 2: PERFORMANCE OF DIFFERENT STRATEGIES TO DETECT CIN 2+ IN SWEDESCREEN**

SCREENING STRATEGY	SENS	PPV*	NO. TESTS PER CASE OF CIN 2+
Cytology only	71%	43%	101
HPV only	95%	19%	75
HPV and cytology in all women	100%	18%	143
HPV with reflex cytology	95%	38%	85

\* PPV is positive predictive value (e.g. what proportion of test positive women have CIN 2+)

(PPV) of the strategy. It also reduces the number of screening tests which are required to identify each case of CIN 2+ from 143 for a strategy that uses both HPV and cytology, to 85 tests per case.

European countries have historically been much more concerned about the costs of their cervical cancer screening programs than we have been in the United States. Most European countries initiate screening at a later age and have more extended screening intervals than is typical in the U.S. Because of its high sensitivity, HPV DNA testing is particularly attractive in countries where extended screening intervals are the norm. However, simply adding HPV DNA testing to their pre-existing cytology-based screening programs would cause a considerable increase in the costs of their programs, and some European countries are beginning to evaluate whether they could replace cytology with HPV DNA testing used alone as the screening test.<sup>5-7</sup> One of the greatest concerns with this approach is the lower specificity of HPV testing compared to cervical cytology. Even if HPV DNA testing was restricted to women in their late 30s and early 40s, using HPV DNA testing alone would greatly increase the number of women being referred to colposcopy. The results of the Swedescreen study suggest that one approach to reducing the number of unnecessary colposcopic examinations would be to perform

reflex cytology whenever a woman was found to be HPV DNA positive, much in the way we perform reflex HPV DNA testing for woman 21 years and older with ASCUS in the U.S. With this strategy, HPV DNA positive women with abnormal cytology results would receive colposcopy. Since HPV DNA positive women who are cytology negative on the reflex test will undergo repeat HPV DNA testing in 12 months and be sent to colposcopy only if they have a persistent HPV infection, the use of this strategy results in a screening program with both a high sensitivity and an acceptable specificity.

There is considerable U.S. interest in the results of this and similar trials (see discussion of the paper by Dillner *et al*). It should be noted, however, that this study, and most other European studies, have used conventional as opposed to liquid-based cytology and none have incorporated computer assisted cytology. In this study the rate of abnormal cytology (2.3%) was much lower than would be seen in the U.S. Therefore, the results obtained with these strategies in Europe might be different than what would be obtained in the U.S. At present the use of HPV testing alone without cervical cytology when screening women 30 years and older is neither FDA approved nor recommended by any professional organization.

## Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study

Dillner *et al.* *BMJ*. 2008;337:A1754

There is now a huge amount of data clearly demonstrating that HPV DNA testing is significantly more sensitive than cytology for identifying women 30 years and older with CIN 3+ and that combining HPV DNA testing together with cytology results in a very high negative predictive value (NPV) for CIN 2+<sup>5</sup>. However, even in women 30 years and older, a combination of HPV DNA testing and cytology is less specific than cytology alone. In the U.S., HPV DNA co-testing is currently utilized only about 25% of the time when screening women 30 years and older. The reasons that HPV testing is not being more widely utilized are many, but some of the most commonly expressed are that 1) although HPV DNA testing is clearly more sensitive than cytology in the short-term, the long-term impact of incorporating HPV DNA testing into screening programs is less clear; 2) the low incidence of cervical cancer in the U.S. makes HPV DNA testing unnecessary; 3) HPV DNA testing adds too much cost to the screening program; and finally, 4) the unnecessary anxiety that results when women with negative cytology results find out they are HPV DNA positive outweighs any potential benefit.

The recent article by Dillner *et al.* provides us with a glimpse into the long-term benefits of using HPV DNA testing when screening women 30 years and older.<sup>8</sup> The article combines data from seven primary screening trials in six European countries. These trials enrolled over 24,000 women who were screened using either cytology alone or a combination of cytology and HPV DNA testing and followed for differing lengths of time. During follow-up women had either at least one cervical cytology or a colposcopic/histopathologic examination. Thus, it allows a determination of the duration of protection against CIN 3+ associated with a negative HPV DNA test result. This is important for determining what the appropriate screening interval is for HPV DNA negative women.

All of the studies included in the Dillner article used cytology as currently practiced in each country. Five of the studies used the Hybrid Capture 2 (hc2) HPV DNA Assay and two used consensus PCR HPV assays. Several of the studies were

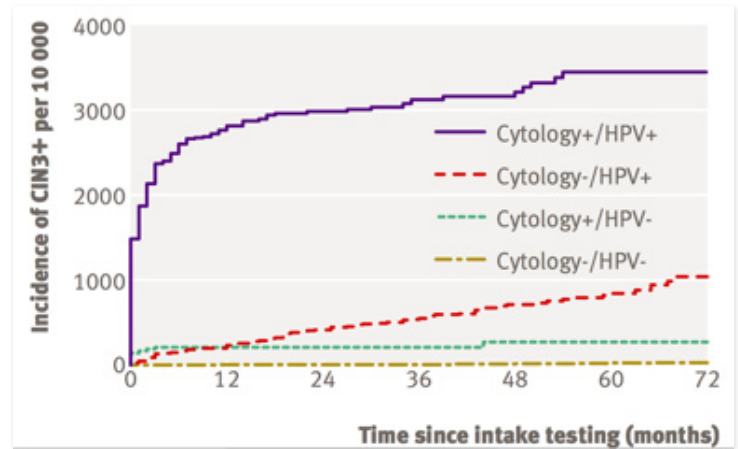


Figure 2: Cumulative incidence of CIN 3+ by combination of screening test results

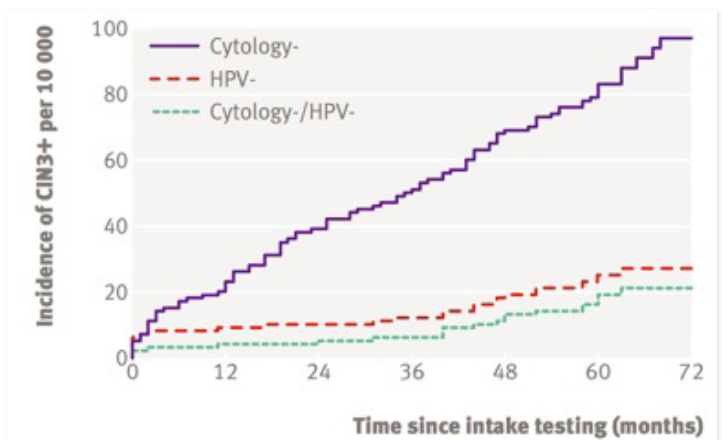


Figure 3: Cumulative incidence of CIN 3+ by cytology or HPV DNA testing

restricted to women at least 30 years of age, but some enrolled younger women. A major limitation to the study is that less than a third of the enrolled subjects remained in the study after 5 years of follow-up and this dropped to 20% at 6 years.

Histologically-confirmed CIN 3+ was identified during 6 years of follow-up in 381 (1.6%) of the 24,295 women. Positive predictive value (PPV) for CIN 3+ was greatest in

women who were both cytology positive (ASCUS or greater) and HPV DNA positive at enrollment; cumulative incidence of CIN 3+ was 34% in this group of women. Among women who had a negative enrollment cytology result but were HPV DNA positive, the cumulative incidence of CIN 3+ during 6 years of follow-up was 10%. The cumulative incidence dropped to 2.7% among women who were HPV DNA negative, but had a positive cytology result and was only 0.3% among women who were negative on both tests, **Figure 2**. It is also important to note that there was little difference in the cumulative incidence of CIN 3+ after 6 years among women who were negative by both cytology and HPV DNA testing and those who were negative by HPV DNA testing alone, **Figure 3** (note the different scale).

The results from the European screening trials are quite similar to those reported several years ago by Khan *et al.* who studied a cohort of approximately 20,000 women enrolled in the Kaiser Permanente health plan in Portland, Oregon.<sup>9</sup> In the U.S. Kaiser study, the cumulative incidence

rate of CIN 3+ at 10 years was 0.8% in women who were negative by both cytology and HPV DNA testing. Thus, both of the large cohort studies of the long-term protective effects of being HPV DNA negative have found that HPV DNA negative women have a low cumulative incidence of CIN 3+ for up to 10 years. Because of the durability of this protective effect, the authors concluded that it would be safe to extend the screening interval to 6 years in HPV DNA negative women. This is the direction in which several European countries are headed. It is also important to point out that these European studies demonstrate that once a woman is found to be HPV DNA negative, being doubly negative by both HPV and cytology provides minimal additional protection. This has led some to suggest that we may not need to use cytology for routine screening of older women. Instead, we might test using only a molecular HPV test and reserve cytology for HPV positive women. This concept is discussed in depth in the article by Naucner *et al.*<sup>4</sup>

## Evidence for frequent regression of cervical intraepithelial neoplasia Grade 2 (CIN 2)

Castle *et al.* *Obst. Gynecol.* 2009;113:18-25

The natural history of cervical intraepithelial neoplasia Grade 2 (CIN 2) has not been clearly defined and the debate of whether CIN 2 should be managed in the same fashion as a true cancer precursor (CIN 3) or as a lesion which is more likely to regress (CIN 1) continues on both sides of the Atlantic. Until we have better analytical tools that will allow us to precisely determine which individual CIN lesions will progress or persist and which will regress, any additional information regarding the regression rate of CIN 2 lesions or any insight into which lesions are more likely to regress can only benefit our ability to individualize patient care. Using data from the large NCI sponsored ASCUS/LSIL Triage Study (ALTS), Castle *et al.* evaluated the potential regression rate for CIN 2.<sup>10</sup> In addition, they looked at HPV genotyping data collected at enrollment into ALTS to determine if any trend could be identified that predicts which CIN 2 lesions are more likely to regress.

Patients were eligible for enrollment into ALTS if they had an ASCUS or LSIL result. At the time of enrollment, a gynecologic exam was performed that included a cervical cytology, HPV high-risk testing using Hybrid Capture 2 (hc2), and HPV genotyping by PCR. Patients were randomized to one of three arms, immediate colposcopy, colposcopy if HPV DNA positive by hc2, or repeat cytology, **Figure 4**. At enrollment all women had a repeat cytology and any woman with HSIL

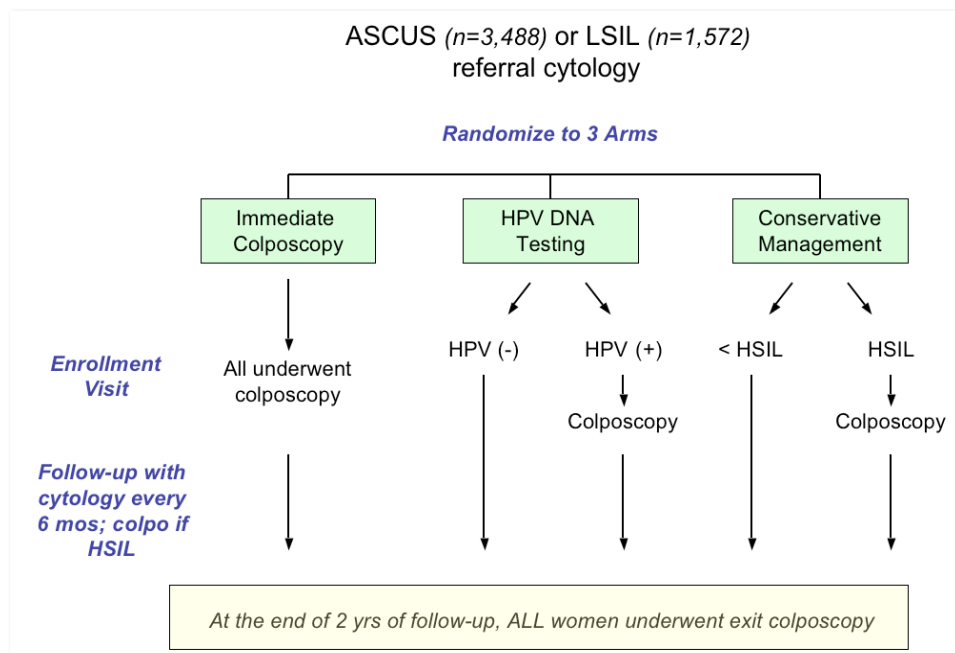


Figure 4: Design of ALTS

was referred to colposcopy, irrespective of the arm they were randomized to. Women were then followed for 2 years with cytology screening every 6 months and referred to colposcopy only if the repeat cytology was HSIL or greater. At the end of the study, all women underwent colposcopy.

After 2 years of follow-up, the three arms of the ALTS trial had a similar cumulative percentage of women diagnosed with CIN 3+, **Table 3**. In contrast, the cumulative percentage of women with CIN 2 after 2 years of follow-up varied significantly between the arms. In the immediate colposcopy arm the cumulative percentage of women diagnosed with CIN 2 by the end of the study (2 years) was 10.7%. In

contrast, in the HPV DNA testing arm the cumulative percentage of CIN 2 by the end of the study was 8.1% and in the conservative management arm it was only 6.0%. The difference in proportion of CIN 2 diagnosed in the conservative management arm compared with the immediate colposcopy arm was less pronounced in women aged 30 years and older (4.2% in the conservative management arm versus 5.5% in the immediate colposcopy arm) than in women aged younger than 30 years (6.4% in the conservative management arm versus 11.7% in the immediate colposcopy arm), but this age-specific effect did not reach statistical significance.

The data analysis compared the cumulative number of CIN 2 cases with the cumulative number of CIN 3+ cases across the three study arms. In the immediate colposcopy arm the CIN 2:CIN 3+ ratio after 2 years of follow-up was 1.1 whereas in the conservative management arm it was 0.57. This difference is interpreted as indicating that a significant proportion of CIN 2 lesions spontaneously regressed in the conservative management arm during follow-up whereas few CIN 3+ lesions regressed. The estimated regression rate for CIN 2 over the 2-year period was about 40% and CIN 2 caused by HPV 16 was less likely to regress than CIN 2 associated with other HPV types.

As practicing clinicians we should ask where does this information fit with our previous knowledge, what are the limitations of the study, and what implications does it have for clinical practice? This new analysis gives additional support to the fact that a substantial portion of CIN 2 lesions represent transient infections/reversible lesions and are not true precancers. These findings confirm what previous follow-up studies have found. Several years ago Mitchell *et al.* performed a systematic review of the different studies investigating the natural history of untreated biopsy-confirmed CIN, most of which were conducted in the 1970's and 1980's, **Table 4.**<sup>11</sup> Their meta-analysis found that 43% of CIN 2 lesions regress, which is almost identical to the 40% estimated regression in ALTS. The meta-analysis also found that 22% of CIN 2 lesions progress to carcinoma *in situ*. Since the cumulative prevalence of CIN 3+ in the three arms of ALTS was almost identical, progression appears to either take more than two years to occur, or is balanced out by the regression of an equivalent number of CIN 3+ lesions.

Two of the limitations to the study with respect to integrating the results into clinical management are: 1) the histopathological diagnosis of CIN 2 is not consistent among pathologists and shows a very high rate of inter- and intraobserver variation; and 2) many laboratories in the U.S. no longer report cervical biopsies as CIN 2 or CIN 3, but instead combine them into CIN 2,3.<sup>12</sup>

**TABLE 3: DETECTION OF CIN 2 AND CIN 3+ IN ALTS \***

ARM	% OF WOMEN DIAGNOSED WITH	
	CIN 2	CIN 3+
<b>Immediate colposcopy</b>		
at enrollment	8.2%	6.7%
cumulative at end of study	10.7%	10.2%
<b>HPV DNA testing</b>		
at enrollment	5.6%	7.5%
cumulative at end of study	8.1%	10.1%
<b>Conservative management</b>		
at enrollment	1.8%	4.3%
cumulative at end of study	6.0%	10.6%

\* Note: Data is derived from Figure 1 of the article

**TABLE 4: NATURAL HISTORY OF CIN LESIONS**

LESION GRADE	% OF LESIONS THAT		
	REGRESS	PERSIST	PROGRESS*
CIN 1	57%	32%	11%
CIN 2	43%	35%	22%
CIN 3	32%	56%	12%

\* progression to carcinoma *in situ*, modified from reference 11

## Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: A meta-analysis

De Vuyst *et al.* *Int. J. Cancer.* 2009;124:1626–1636

The prevalence of HPV types found in cervical carcinoma and its precursors has been well characterized. Less information is known about the types and frequencies of HPV found in vulvar, vaginal, and anal neoplasia. In this meta-analysis, De Vuyst and colleagues searched available literature databases to find articles that reported HPV typing in non-cervical, lower genital tract lesions.<sup>13</sup> To be selected, the articles had to use clearly described PCR primers in a minimum of 4 cases of carcinoma or intraepithelial neoplasia. In all, a total of 63 studies of vulvar, 14 of vaginal, and 29 of anal lesions identified from MEDLINE were included. The vast majority of information on HPV in anal intraepithelial neoplasia (AIN) was obtained from studies of HIV-positive men who have sex with men (MSM).

The overall prevalence of HPV in VIN was 84%. It was highest (85%) in high-grade vulvar intraepithelial neoplasia (VIN 2,3) and lowest (40%) in vulvar cancer, **Table 5**. In comparison, HPV 16 was least commonly detected in VIN 1 and most commonly detected in VIN 2,3. Infection with multiple types of HPV was uncommon; 13% in VIN 1 and 3% in vulvar cancer (not shown in Tables). HPV prevalence varied depending on patient demographics and the histological type of vulvar cancer. HPV prevalence was significantly higher in North American studies than in studies from elsewhere. It was also higher in younger women (OR 3.6, 95% CI: 2.4–5.5 for women aged ≤60 versus women aged ≥71 years). HPV prevalence was

**TABLE 5: PREVALENCE OF HPV IN NON-CERVICAL LOWER GENITAL TRACT LESIONS**

LESION	NO.	ANY HPV	HPV 16	HPV6 / 11
<b>Vulva</b>				
VIN	1197	84%		
VIN 1		68%	10%	31%
VIN 2,3		85%	72%	~5%
VULVAR CANCER	1873	40%	32%	~2%
<b>Vagina</b>				
VAIN	298	94%		
VAIN 1		100%	23%	0
VAIN 2,3		90%	58%	~5%
VAGINAL CANCER	136	70%	54%	~2%
<b>Anal</b>				
AIN	1280	93%		
AIN 1		92%	37%	54%
AIN 2,3		94%	60%	~10%
ANAL CANCER	955	84%	73%	~2%

69% in carcinomas of the warty-basaloid type compared to 13% in keratinized carcinomas (OR 13.5, 95% CI: 9.4-19.4).

A higher prevalence of HPV infection was observed in cases of vaginal and anal intraepithelial neoplasia and carcinoma. The overall HPV prevalence in vaginal intraepithelial neoplasia (VAIN) was 94%, varying from 100% in VAIN 1 to 90% in VAIN 2,3, and 70% in vaginal carcinomas. The prevalence of infection with multiple HPV types again decreased from 10% in VAIN 1 to 3% in vaginal carcinoma. For AIN, the overall

prevalence of HPV was 93%. Infection with multiple HPV types was much more prevalent in cases of AIN, occurring in 54% of AIN 1 and 7% of anal carcinoma. HPV prevalence was unrelated to histological type of anal carcinoma, but was more frequent in women than men (OR 3.5, 95% CI: 2.3–5.3). Among individuals with AIN 2,3, HIV-positive individuals were more likely to be infected with HPV than HIV-negative ones (97% vs. 90%;  $p=0.0075$ ), and multiple HPV types were more common in HIV-positive individuals. Finally, HPV 16 was significantly under-

represented and most other HPV types significantly over-represented in AIN 2,3 in HIV-positive, compared to HIV-negative individuals.

As more information is gathered regarding vulvar, vaginal, and anal intraepithelial neoplasia, obvious comparisons to cervical neoplasia will arise. Although the prevalence of HPV was lower in vaginal (70%) and vulvar carcinoma (40%) than that reported with cervical carcinoma (87%), the prevalence found in anal carcinoma (84%) was similar.<sup>14</sup> This may not be all that surprising when one considers that both cervical and anal cancers are reported to arise in a squamocolumnar junction (i.e., the dentate line, between the anal canal and the rectum), unlike vulvar and vaginal carcinomas.<sup>15</sup>

Another important conclusion that can be drawn from this information is that, unlike cervical and anal carcinomas, which are almost universally HPV-related diseases, there appears to be two distinct subsets of vulvar and vaginal carcinoma. The high prevalence of HPV in high-grade precursor lesions in the vagina (90%) and the vulva (85%) are similar to that seen in CIN 2,3 (85%)<sup>14</sup>. These HPV-related lesions, when they progress, are responsible for the 70% of vaginal and the 40% of vulvar carcinomas that are associated with HPV. The remainder of vaginal and vulvar carcinomas appear to develop independently of HPV, and may result in different histologies, as seen in the variation of HPV prevalence found in warty-basaloid carcinoma (69%) and

keratinized carcinoma (13%) of the vulva. Although differences in histology are also seen with age at diagnosis (warty-basaloid carcinoma being diagnosed more often among younger women than the keratinized type), the prevalence of HPV is higher among younger women and may help to explain the trends seen in the number of vulvar cancers and their precursors found in different age groups.<sup>16</sup>

Finally, this analysis continues to support the importance of HPV 16 in anogenital neoplasia. HPV 16 was found in over three-quarters of HPV-positive anogenital carcinomas at all three sites which is even higher than the approximately half of cervical carcinomas attributed to HPV 16. The prevalence of HPV 16 is lower in high-grade intraepithelial neoplasia than in carcinomas at all three non-cervical sites, suggesting a greater potential of HPV 16 associated lesions to progress to carcinoma in comparison to other lesions. In the era of prophylactic HPV vaccines, no article attributing disease to HPV types would be complete without mention of the impact that an HPV 16/18 containing vaccine might have. The authors conclude that, based upon the results of their meta-analysis, ~40% of vulvar carcinoma, 60% of vaginal carcinoma and 80% of anal carcinoma may be avoided by prophylactic vaccines targeting HPV 16 and 18.

A similar proportion of high grade intraepithelial lesions of the vagina and anus, and an even higher proportion of VIN 2,3 (75%), may also be prevented.

## What's New?

### FDA Approves Another HPV Test

In March 2009 the FDA announced approval for clinical use in the U.S. of two new HPV DNA diagnostic tests (*FDA press release is included*): One of these tests is designed to identify the 14 high risk types of HPV that are associated with cervical cancer. This test will be marketed under the name Cervista HPV HR. The other test is designed to specifically detect HPV 16 and HPV 18 and will be marketed under the name Cervista HPV 16/18. Both tests utilize an isothermal enzymatic DNA amplification process with a fluorescent read out and are being sold by Hologic Inc. who also makes the ThinPrep Pap test.

**The FDA-approved clinical indications for Cervista HPV HR are similar to those of the Hybrid Capture 2 HPV DNA Assay. These are:**

1. To screen patients with ASC-US cervical cytology results to determine the need for referral to colposcopy.
2. Used adjunctively with cervical cytology to screen women 30 years and older to assess the presence or absence of high-risk HPV types.

**The approved clinical indications of the Cervista HPV 16/18 test are:**

1. In women 30 years and older the test may be used adjunctively with the Cervista HPV HR test in combination with cervical cytology to assess the presence or absence of specific high-risk HPV types.

2. Used adjunctively with the Cervista HPV HR test in patients with ASC-US cervical cytology results, to assess the presence or absence of specific high-risk HPV types. The results of this test are not intended to prevent women from proceeding to colposcopy.

It is important to note that at the 2006 ASCCP Consensus Conference the use of HPV genotyping assays was widely discussed.<sup>2,3</sup> Based on the data available from several studies it was determined that HPV genotyping assays that detect HPV 16 and 18 would be very useful for determining which cytology negative women 30 years and older who are HPV DNA positive (for any of the high-risk types of HPV) should be referred for immediate colposcopy and which can be followed-up with a repeat cervical cytology and high-risk HPV testing in 12

months, **Figure 1**. It should be stressed, however, that the use of HPV genotyping is but one option when using HPV DNA testing when screening women 30 years and older. The other option is to repeat both the cytology and high-risk HPV test at 12 months in HPV DNA positive / cytology negative women. It is also important to recognize that cytological screening without adjunctive HPV DNA testing remains a viable approach to screening women 30 years and older.

It is important to note that both the committee that handled atypical squamous cells and the committee that handled HPV DNA testing decided that HPV genotyping does not add clinical benefit to the management of women with ASC-US. This decision was based on data available as of 2006. Data from the

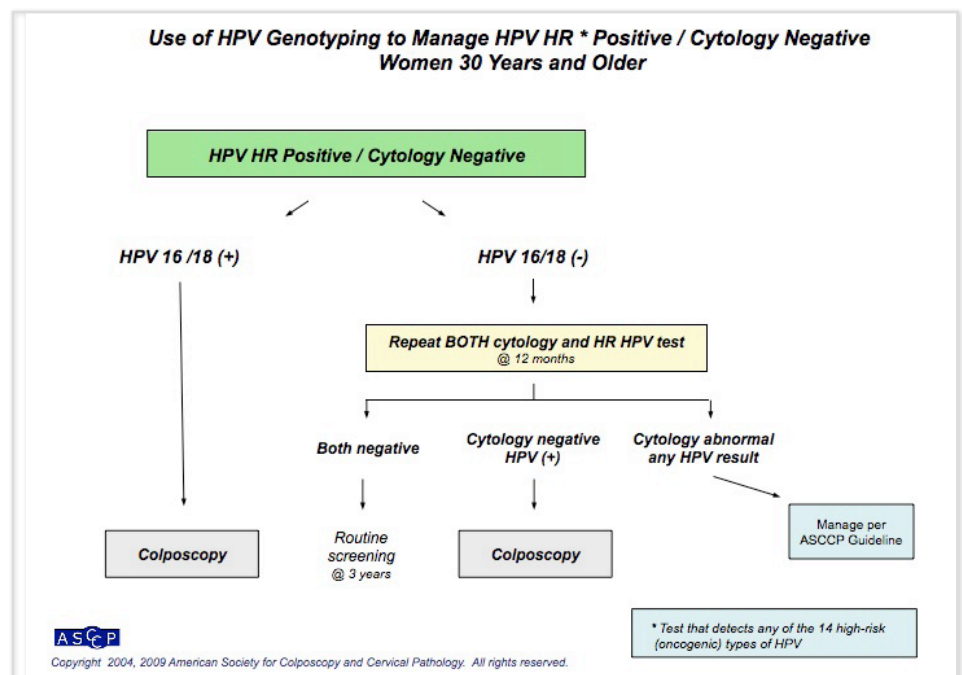


Figure 1: Algorithm for using HPV genotyping for HPV 16 and 18 to triage high-risk HPV positive / cytology negative women

pivotal trial of the new HPV genotyping assay that led to the FDA approved indication of using 16/18 genotyping in women with ASC-US has not yet been published. *Therefore at the current time the ASCCP Consensus Guidelines do NOT recommend the use of HPV genotyping in women with ASC-US.*

As HPV DNA testing becomes more widespread we need to remember that there are other situations where HPV DNA testing is NOT recommended. These include: 1) all adolescents

(irrespective of their cytology results), 2) when managing women in the general population with LSIL, 3) when managing women with ASC-H, and 4) more frequently than every three years in women 30 years and older who are negative by both cytology and high-risk HPV DNA typing. These may change in the future as more data become available, but for now HPV testing is not recommended in these situations.

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