

Southern California CSU DNP Consortium

California State University, Fullerton  
California State University, Long Beach  
California State University, Los Angeles

ESSENTIAL CHANGES TO THE MANAGEMENT OF ABNORMAL CERVICAL  
CYTOLOGY RESULTS

A DOCTORAL PROJECT

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DOCTOR OF NURSING PRACTICE

By

Zoila Argentina Paz

Doctoral Project Committee Approval:

Penny Weismuller, DrPH, RN, Project Chair  
Cindy Greenberg, DNSc, RN, PNP-BC, FAAN, Committee Member

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## ABSTRACT

In the United States, 3.5 million Pap smears show abnormal cytology and require additional follow-up. Early detection of abnormal cervical cytology improves successful treatment and can prevent early cervical changes from becoming cancerous. The new guidelines issued by the American Society for Colposcopy and Cervical Pathology provide recommendations for managing women with abnormal cervical cancer screening tests and cancer precursors following adoption of cervical cancer screening guidelines incorporating longer screening intervals and co-testing. The recommended conservative management is worrisome to providers who do not understand the evidence supporting cautious intervention. The purpose of this project was to develop a poster and a manuscript to disseminate to clinicians the science supporting the latest management guidelines for abnormal cervical cytological test results.

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## **BACKGROUND**

Cervical cancer, once the second most common cancer in women in both incidence and mortality, is now no greater than 11th in incidence and 13th in mortality in the United States, due to well-established cervical cancer screening and management programs (Mayeaux & Cox, 2012). Despite these measures, the American Cancer Society estimated that 4,030 deaths of invasive cervical cancer would occur in 2013, and approximately 12,340 cases were expected to be diagnosed (American Cancer Society [ACS], 2013). In the United States, each year between 50 and 60 million Pap smears are performed; of these, 3.5 million (7%) are read as abnormal, requiring additional follow-up or evaluation (Mahdavi & Monk, 2005). Appropriate management of women with histopathologically diagnosed cervical precancer is a key component of cervical cancer prevention programs. Early detection greatly improves the chances of successful treatment and prevents any early cervical changes from becoming cancerous.

Guidelines for the management of women with abnormal cervical cytology were updated by the American Society for Colposcopy and Cervical Pathology (ASCCP) in 2012 and published in 2013. The guidelines are stratified by a woman's age; cytologic diagnosis; infection with one or more oncogenic HPV types; and infection with HPV-16, HPV-18, or both (Sawaya, 2013). Algorithms for management of initial abnormalities and for subsequent follow-up are described as well.

### **Problem Statement**

New guidelines for disease management of abnormal Pap smears changed greatly from previous ASCCP guidelines. The newly recommended conservative management is worrisome to providers who do not understand the evidence supporting cautious

intervention. Due to the higher prevalence of transient HPV infections and regressive cervical abnormalities, less intensive management of young women with minimally abnormal cytology reports is recommended. Conservative management reduces the potential harms, such as cervical incompetency following colposcopy, from aggressively managing abnormalities likely to resolve spontaneously. For women 30-64 years of age, HPV/cytology co-testing is the preferred method for cervical cancer screening. HPV testing, either alone or in combination with cervical cytology, is more sensitive than cervical cytology alone in detecting high- or low-grade cervical histopathology. However, for women with precancerous findings the risk for cancer remains high, requiring more intensive follow-up than previously recommended.

### **Purpose Statement**

The aim of this project is to help providers understand the evidence supporting the essential changes from prior management guidelines and integrate them into practice through use of decision reminders. In order to achieve this aim, two dissemination vehicles have been developed to present the research supporting the key changes to the latest ASCCP guidelines. These dissemination vehicles include a manuscript to be submitted to *The Journal for Nurse Practitioners* and a poster presentation given at the Sigma Theta Tau International, Upsilon Beta chapter annual research day.

### **Supporting Framework**

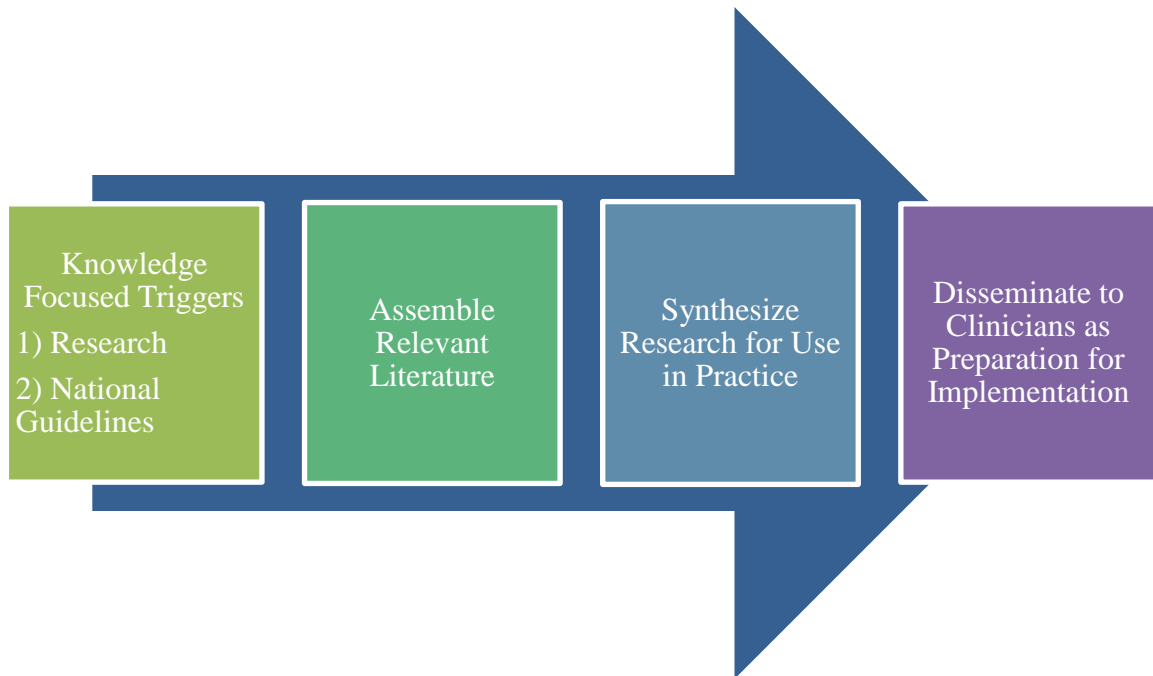
Numerous frameworks illustrate the process of applying research findings to practice, some of which are specific to nursing. Though the frameworks differ in terminology and structure, they contain similar innovation adoption processes and identify comparable explanatory variables. For this project the Iowa model will be used

to illustrate the steps involved in changing practice for follow-up of abnormal cervical screening test results based on the latest recommendations from ASCCP.

The Iowa Model of Evidence-Based Practice to Promote Quality Care is a practice model with the primary purpose of guiding clinicians in the use of evidence to improve healthcare outcomes. The model provides a good framework for research utilization and facilitating change toward evidence-based practice. It supports practice change through the systematic review of research and other evidence to create a culture of research conduct and research utilization (Zaccagnini & White, 2011).

Inquiry begins with problem and knowledge-focused triggers about clinical and operational efficiency and effectiveness regarding scientific knowledge for use in decision making in the advanced practice role (Titler et al., 2001). Updated ASCCP 2012 consensus guidelines for managing abnormal cervical cancer screening tests and cancer precursors are the source for stimulating questioning of current practice and whether patient care can be improved through the use of research findings.

The Iowa model recommends assembling relevant research and related literature on the topic. Titler et al. (2001) advises that the data be from evidence-based guidelines, systematic reviews, meta-analysis, and clinical studies on the topic to provide the best evidence possible from which to make practice decisions. Once the literature is gathered, the next step is critiquing and synthesizing the research for use in practice. After the literature is critiqued, a decision is made regarding the sufficiency of the evidence to guide practice.



*Figure 1.* Adaptation of Iowa Model for dissemination of evidence and guidelines.

Nationally, the ASCCP guidelines represent a decision to use the relevant research for the care of women; however, the evidence must be disseminated for clinicians to fully embrace the new guidelines. Figure 1 portrays the process of gathering, synthesizing and disseminating evidence and guidelines to prepare clinicians to adopt the recommendation.

### **Goals**

The goals of this project are to:

1. Assist clinicians in understanding the evidence supporting the essential changes from prior management guidelines for follow-up of abnormal cervical cancer screening tests.
2. Aid clinicians in the management of abnormal cervical cytology results by the integration of guidelines into practice through applicable and relevant evidence.

## **Objectives**

The objectives of this project are to:

1. Inform clinicians of the essential changes from prior management guidelines for the follow-up of abnormal cervical cancer screening tests.
2. Disseminate the evidence to update clinicians of essential modifications from ASCCP recommendations through conference presentations and a manuscript.
3. Promote communication about important guideline changes to enhance knowledge generation, translation, and utilization.

## **REVIEW OF LITERATURE**

### **Cytology and Histology Findings and Interpretation**

The 2001 Bethesda System defines terminology for reporting the results of cervical cytology, providing clear guidance for clinical management utilizing a uniform system of terminology (Solomon et al., 2002). The 2012 updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors uses this system to describe the categories of epithelial cell abnormalities. The categories include atypical squamous cells (ASC), low-grade or high-grade squamous intraepithelial lesions (LSIL or HSIL), and glandular cell abnormalities, including atypical glandular cells (AGC) and adenocarcinoma in situ (AIS). Cervical intraepithelial neoplasia (CIN) grades 1-3 are used to describe histologic abnormalities. Abbreviations and definitions for each epithelial and histologic abnormality and for infections important in cancer progression are found in Appendix A.

It is estimated that 10-20% of women with an epithelial cell abnormality such as ASC have underlying CIN2 or 3 and that 1 in 1000 females may have invasive cancer (Solomon et al., 2002). Two categories of ASC exist: Atypical Squamous Cells of Undetermined Significance (ASC-US) and Atypical Cells, Cannot Exclude a High-Grade Squamous Intraepithelial Lesion (ASC-H). The term ASC-US denotes that the squamous epithelial cells are not normal and do not represent either benign cell changes or dysplasia (Mayeaux & Cox, 2012). ASC-H comprises roughly 5-10% of ASC cases overall and may indicate a greater potential for finding significant underlying cervical abnormalities (Mayeaux & Cox, 2012; Solomon et al., 2002). ASC-H is associated with a higher percentage of high-grade CIN and a higher prevalence of high risk (HR) HPV DNA when

compared to women with ASC-US (Mayeaux & Cox, 2012). See Tables 1 and 2 for risk of progression to cancer for these abnormalities based on a woman's age.

Table 1

*Five-year Risk of Premalignant or Malignant Disease with ASC-US Cytology*

Pap and HPV result	CIN2+	CIN3+	Cervical cancer
Women 21-24			
Cytology		3.0% <sup>1</sup>	0.032% <sup>1</sup>
HPV-positive		4.4% <sup>1</sup>	0.055% <sup>1</sup>
HPV-negative		0.57% <sup>1</sup>	0% <sup>1</sup>
Women 25-29			
Cytology		3.9% <sup>1</sup>	0.12% <sup>1</sup>
HPV-positive		7.1% <sup>1</sup>	0.16% <sup>1</sup>
HPV-negative		0.59% <sup>1</sup>	0.018% <sup>1</sup>
Women 30-64			
Cytology	6.9% <sup>2,3</sup>	2.6% <sup>2,3</sup>	0.18% <sup>2,3</sup>
HPV-positive	18% <sup>2,3</sup>	6.8% <sup>2,3</sup>	0.41% <sup>2,3</sup>
HPV-negative	1.1% <sup>2,3</sup>	0.43% <sup>2,3</sup>	0.05% <sup>2,3</sup>

*Note.* ASC-US = atypical squamous cells of undetermined significance; CIN = cervical intraepithelial neoplasia; HPV = human papilloma virus. From <sup>1</sup>Katki et al., 2013f; <sup>2</sup>Katki et al., 2013a; and <sup>3</sup>Katki et al., 2013e.

Table 2

*Five-year Risk of Premalignant or Malignant Disease with ASC-H Cytology*

Pap and HPV result	CIN2+	CIN3+	Cervical cancer
Women 21-24			
Cytology		16% <sup>1</sup>	0% <sup>1</sup>
Women 25-29			
Cytology		24% <sup>1</sup>	1.5% <sup>1</sup>
Women 30-64			
Cytology	35% <sup>2</sup>	18% <sup>2</sup>	2.6% <sup>2</sup>
HPV-positive	45% <sup>2</sup>	25% <sup>2</sup>	2.5% <sup>2</sup>
HPV-negative	12% <sup>2</sup>	3.5% <sup>2</sup>	2.1% <sup>2</sup>

*Note.* ASC-H = atypical squamous cells cannot exclude high grade intraepithelial lesion. CIN = cervical intraepithelial neoplasia; HPV = human papilloma virus. From <sup>1</sup>Katki et al., 2013f; and <sup>2</sup>Katki et al., 2013a.

Noninvasive squamous intraepithelial lesions are categorized by a two-tiered terminology, LSIL and HSIL, for reporting cervical abnormalities. LSIL is associated with a transient HPV infection, whereas HSIL is associated with viral persistence and higher risk for progression to cervical cancer precursors (Solomon et al., 2002). LSIL includes the categories of mild dysplasia, CIN1, and the presence of HPV. LSIL and CIN1 reveal the cytologic and pathologic effects of HPV. Most of these lesions will never progress to cancer. HSIL comprises the classifications of moderate and severe dysplasia, CIN2 and 3, and carcinoma in situ. Progression to cervical precancer in terms of histopathology, includes a diagnoses of CIN3, severe dysplasia, or carcinoma in situ (Schiffman, Castle, Jeronimo, Rodriguez, & Wacholder, 2007). See Tables 3 and 4 for risk of progression to cancer for these abnormalities based on a woman's age.

Table 3

*Five-year Risk of Premalignant or Malignant Disease with LSIL Cytology*

Pap and HPV result	CIN2+	CIN3+	Cervical Cancer
Women 21-24			
Cytology		3.0% <sup>1</sup>	0% <sup>1</sup>
Women 25-29			
Cytology		5.0% <sup>1</sup>	0% <sup>1</sup>
Women 30-64			
Cytology	16% <sup>2,3</sup>	5.2% <sup>2,3</sup>	0.16% <sup>2</sup>
HPV-positive	19% <sup>2,3</sup>	6.1% <sup>2,3</sup>	
HPV-negative	5.1% <sup>2,3</sup>	2.0% <sup>2,3</sup>	

*Note.* CIN = cervical intraepithelial neoplasia; HPV = human papilloma virus; LSIL = low-grade squamous intraepithelial lesion. From <sup>1</sup>Katki et al., 2013f; <sup>2</sup>Katki et al., 2013a; and <sup>3</sup>Katki et al., 2013b.



Table 4

*Five-year Risk of Premalignant or Malignant Disease with HSIL Cytology*

Pap and HPV result	CIN2+	CIN3+	Cervical Cancer
Women 21-24			
Cytology		28% <sup>1</sup>	0% <sup>1</sup>
Women 25-29			
Cytology		28% <sup>1</sup>	2.0% <sup>1</sup>
Women 30-64			
Cytology	69% <sup>2</sup>	47% <sup>2</sup>	7.3% <sup>2</sup>
HPV-positive	71% <sup>2</sup>	49% <sup>2</sup>	6.6% <sup>2</sup>
HPV-negative	49% <sup>2</sup>	30% <sup>2</sup>	6.8% <sup>2</sup>

*Note.* CIN = cervical intraepithelial neoplasia; HSIL = high-grade squamous intraepithelial lesion. From <sup>1</sup>Katki et al., 2013f; <sup>2</sup>Katki et al., 2013c.

### Natural History of Cervical Intraepithelial Neoplasia

A strong association exists between HPV infection and CIN (Schiffman et al., 1993); HPV status is closely related to the development, persistence, and progression of CIN lesions (Nobbenhuis et al., 1999). Central to the pathogenesis of most invasive cervical cancers and precancerous lesions is infection with specific oncogenic (or high risk) strains of HPV. HPV 16 is highly oncogenic, with an absolute risk of a premalignant diagnosis approaching 40% after 3-5 years of persistent infection. Persistent infections pose the greatest risk of precancer, comprising about 10% of the precancer diagnoses (Schiffman et al., 2007). HPV persistence with an oncogenic HPV genotype is necessary for the development of invasive cervical cancer (Hopman et al., 2000). Conversely, women who do not harbor an oncogenic HPV infection are at very low risk of acquiring cervical cancer.

Each year, an estimated 1.2 million women in the United States are diagnosed with CIN changes (Solomon et al., 2002). Low-grade CIN (CIN1) is associated with the presence of HPV and is not precancer; progression to cancer is rare, with 1% of CIN1

developing invasive carcinoma (Committee on Practice Bulletins-Gynecology, 2008; Jastreboff & Cymet, 2002). The significance of CIN2 is unclear. CIN2 has a greater possibility of progressing to CIN3 and cancer than CIN1; however, the cancer potential of CIN2 is uncertain (Committee on Practice Bulletins-Gynecology, 2008). CIN2 lesions regress without treatment. In one review, CIN2 progressed to cancer in 5% and to CIN3 in 20%, persisted in 40%, and regressed in 40% (Ostor, 1993). The occurrence of HR-HPV is an indicator for the risk of high-grade CIN (CIN2, CIN3). HR-HPV is necessary for development and maintenance of CIN3; the time course from CIN3 to invasive cervical cancer is approximately 8-12 years (Committee on Practice Bulletins-Gynecology, 2008; Nobbenhuis et al., 1999). CIN3 has a significant risk (>12%) of progressing to invasive carcinoma if left untreated (Jastreboff & Cymet, 2002).

### **Major Changes to the Management of Abnormal Screening Tests and Cancer**

#### **Precursors**

The ASCCP 2012 recommendations include essential changes from prior management guidelines, and include recommendations in the management of women with discordant co-test results (e.g., HPV-positive/Cytology negative, HPV-negative/Cytology worse than ASC-US). Follow-up visits are reduced with the integration of co-testing and longer screening intervals as part of the management guidelines. For women ages 21-29, Pap-only strategies are used without HPV testing, but co-testing in certain circumstances is expanded to women younger than 30 years. The guidelines differ somewhat for women in this age range for evaluations of cytologic and histologic abnormalities, which vary for women 21-24 years old compared with women ages 25 and older. This is based upon the increased risk of high-grade disease in women

25-29 years old compared with women 21-24 years old. Women 21-24 years are managed conservatively, especially for minor abnormalities, with the extension in adolescent management to women less than age 25 if inadvertently screened. Screening is no longer recommended for adolescents. The use of genotyping triages for HPV-positive/Cytology negative women with HPV-16 or HPV-18 to earlier colposcopy is recommended.

Further changes from prior management guidelines include cytology at 12 months for ASC-US and then if negative cytology every 3 years; immediate colposcopy is no longer warranted. For women who receive HPV-positive and ASC-US cytology results, regardless of genotyping result, colposcopy is indicated. HPV-negative and ASC-US cytology results should be followed with co-testing at 3 years rather than 5 years, and are not sufficient to allow women 65 years of age or older exit to from screening. Unsatisfactory cytology reports require repeat testing, even if HPV-negative. Negative cytology reports with insufficient or absent endocervical cells can be managed without early repeat.

The updated ASCCP guidelines have made essential changes from previous management strategies based on analyses of data from more than one million women receiving care at Kaiser Permanente Northern California (KPNC) from 2003-2010. Guideline development was based on the concept of *benchmarking to implicit risk thresholds*. This means that risk estimates were calculated for each HPV and Pap co-test combination and matched (*benchmarked*) to the most similar risk based on Pap-alone (Katki et al., 2013a). In accordance with the principle of *equal management of equal risks*, the management option for the co-test result would be the same management option

for the Pap-alone result with the same level of risk for high-grade premalignant disease or cancer (Katki et al., 2013a). The rationale for each of the clinical management strategies provided by ASCCP is based upon benchmarking CIN3+ risks for co-test results to risk thresholds implicitly used on screening Pap tests. Acceptable risks were considered to be those approximating CIN3+ risk 3 years after negative cytology or 5 years after negative co-testing. In brief, the recommendations were based on the 5-year risk of CIN3+ in the KPNC cohort. The recommendations are as follows: (a) immediate colposcopy is recommended for risk exceeding 5%, (b) repeat testing in 6 to 12 months for risk of 2-5%, (c) repeat testing in 3 years for risk of 0.1-2%, and (d) repeat testing in 5 years for risk of 0.1% (similar to co-testing in women without a history of abnormality (Katki et al., 2013a; Massad et al., 2013).

### **Conservative Management for Women Aged 21-24 Years**

Invasive cervical cancer is rare among young women, accounting for 125 carcinomas per year (rate of 1.4 per 100,000 females) among women aged less than 25 years (Benard, Watson, Castle, & Saraiya, 2012). These low-risk women are at high risk for HPV exposure and HPV-associated lesions; therefore, the level of risk is high enough to warrant screening but is low enough to permit observation for minimal abnormalities (Massad et al., 2013). In a study conducted by Katki and colleagues (2013f), found that women aged 21-24 had a near zero cancer risk, and positive Pap test results predicted low CIN3+ risk. This observation was also found by Moscicki and colleagues (2008), who studied girls and women, aged 13-24 years. Moore et al. (2010) found a low risk of CIN3+ among this age group with HPV-positive ASC-US and LSIL smears. Based on the KPNC database, the 5-year risk of premalignant or malignant disease in women with

ASC-US cytology only irrespective of HR-HPV genotyping was 3.0% for CIN3+ and 0.032% for cervical cancer, while LSIL was 3.0% for CIN3+ and no cases identified for cervical cancer. Women aged 21-24 years with a cytology result of ASC-H have a low risk of CIN3+ despite ASC-H conferring a greater risk for CIN3+ over time than ASC-US or LSIL. This low risk is also true for young women with HSIL. Data from KPNC showed a cumulative 5-year risk of CIN3+ and cancer among women aged 21-24 with HSIL cytology of 28% and 0%, respectively (Katki et al., 2013f).

Based on the scientific evidence and in a move toward conservative management, ASCCP recommends less intensive management of young women with minimally abnormal cytology because the prevalence of transient HPV infections and regressive cervical abnormalities are higher (Benard, et al., 2012; Massad et al., 2013; Moscicki et al., 2001; Winer et al., 2003). Conservative management has led to less frequent testing and over treatment of young women, reducing the harm associated with diagnostic procedures including adverse birth outcomes and unnecessary follow-up interventions (Benard et al., 2012; Bruinsma & Quinn, 2011; Moyer, 2012). For example, ASCCP recommendations are less dependent upon HPV testing and guide clinicians to only refer for colposcopy if abnormal cytology results are severe or persistent, because women aged 21-24 have a lower risk of cervical cancer.

ASCCP recommendations related to young women have led to changes in the management of cytological abnormalities involving ASC-US or LSIL. Young women with LSIL and HPV-positive ASC-US are managed similarly, because the risk for CIN3+ is lower in women aged 21-24 (Katki et al., 2013f; Moore et al., 2010). Data from KPNC have shown that young women aged 21-24 have a 4.4% risk for CIN3+ and 0.055% for

cervical cancer with ASC-US/ HPV-positive cytology results, whereas ASC-US/HPV-negative results indicate a 0.57% risk for CIN3+ and no cases identified for cervical cancer (Katki et al., 2013f). Based on the data from KPNC, the new ASCCP guidelines prefer repeating the cytology alone at 12-month intervals and recommend returning to routine screening when two consecutive negative results are obtained. Immediate colposcopy is not warranted, unless repeat cytology at 12-month follow-up demonstrates cervical abnormalities for ASC-H, AGC, or HSIL. For women with ASC-US or worse at the 24-month follow-up, colposcopy is recommended. Reflex HPV testing is acceptable for ASC-US only, with routine screening recommended for HPV-negative results, and HPV-positive women should have a follow-up cytology annually for 2 years, with colposcopy after 1 year only if HSIL and after 2 years if ASC-US or LSIL persists.

Management of ASC-H or HSIL cytology is modified in women 21-24 years of age. ASC-H and HSIL have a greater risk for precancer than after ASC-US or LSIL. The 5-year CIN3+ risk is 16% after ASC-H and 28% after HSIL. The 5-year cancer risk for both ASC-H and HSIL is 0%; therefore, cancer is unlikely during extended observation (Katki et al., 2013f). Based on the KPNC data, ASCCP recommends colposcopy after ASC-H or HSIL cytology, but immediate treatment with loop electrosurgical excision procedure is unacceptable. Further recommends include observation with colposcopy and cytology every 6 months for up to 2 years for women with no CIN2 or CIN3 at colposcopy, until two consecutive negative Pap tests are reported and no high-grade colposcopic abnormality is observed. Repeat biopsies are indicated if ASC-H/HSIL fail to regress after 1 year, and diagnostic excision is recommended if HSIL cytology persists for 2 years.

Management of CIN1 in women 21-24 years of age depends on the antecedent cytology report, as risk for CIN3+ also depends on the cytology result (Massad et al., 2013). Observation with annual cytology is recommended if the prior Pap was ASC-US or LSIL because the risk of cervical cancer is low in this age group. Additionally, the rate of HPV infection is high and CIN lesions often regress spontaneously (Moscicki et al., 2001; Winer et al., 2003). For CIN1 preceded by ASC-H or HSIL, management depends on colposcopic findings, since ASC-H or HSIL are associated with an increased risk of subsequent high-grade disease. Diagnostic excision is recommended for an inadequate colposcopy. If the colposcopy is adequate, then acceptable alternatives include observation with Pap and colposcopy every 6 months, diagnostic excision, or review of Pap, colposcopy, or biopsies.

Women 21-24 years of age are less likely to have a high-grade CIN progress to cancer because a majority may regress on their own (Castle, Schiffman, Wheeler, & Solomon, 2009; McAllum et al., 2011; Moscicki et al., 2012). In a study by Nadim and Beckmann (2013), women younger than 25 years old with biopsy-proven HSIL (CIN2/3) had a higher likelihood that the histological specimen after an excisional biopsy of the cervix would be reported as CIN1 or no dysplasia. Likewise, in a prospective study with 95 females aged 13-24, 70% of CIN2 lesions regressed (Moscicki et al., 2010). For CIN3 among females aged 20-24, the estimated progression rate for CIN3 to cancer in 12 months was 0.5% (Matsumoto et al., 2011). Therefore, young women with CIN2, 3 are managed by ASCCP as follows: observation of CIN2 lesions is preferred but treatment is acceptable, treatment is recommended for CIN3, and when CIN2, 3 lesions are not otherwise differentiated observation or treatment is acceptable.

## **Risk Stratification of Women with Positive Human Papillomavirus and Negative Cytology**

HPV testing provides useful risk stratification in predicting a woman's long-term risk of cervical precancer (Castle et al., 2012). It is substantially more sensitive than cervical cytology for the detection of CIN2, 3 or cervical cancer. Women with cervical infections with carcinogenic HPV results are at greater risk for developing CIN3 and cervical cancer later than patients with HPV-negative tests (Katki et al., 2011). One study showed that among women who failed to clear their HR-HPV in 12 months, more than 10% had developed CIN3 (Naucler et al., 2009). The lag time between infection and appearance of the first microscopic evidence of precancer can be surprisingly short, often within 5 years; this is sufficient evidence to justify early return for retesting. However, the majority of HPV infections are cleared or suppressed by the immune system, greatly decreasing the risk of high-grade lesions; so observing women to allow for clearance is acceptable management by the ASCCP. High-risk HPV types that are found readily on screening are likely to clear quickly, with about half being undetectable within 6-12 months and most being undetectable by 2 years (Castle et al., 2009; Rodriguez et al., 2008).

ASCCP recommends repeat co-testing at 12 months for the management of women aged 30 or greater who are cytology negative, but HPV-positive. When both tests are negative, repeat co-testing at 3 years is recommended. KPNC data demonstrate that after many screening and diagnostic abnormalities, from HPV-positive and cytology negative co-testing to treated CIN3, risk for CIN3+ remains higher than after negative co-testing among women without prior abnormality. Therefore, ASCCP is suggesting that



women with abnormalities be followed with co-testing at 3-year intervals rather than at 5-year intervals (Massad et al., 2013). For women with ASC or worse or HPV-positive after the 12-month follow-up, colposcopy is recommended.

The persistence of HR-HPV in normal cervical smears is associated with a significantly increased risk of developing abnormal cytologic results (Castle et al., 2009; Hildesheim et al., 1994; Hopman et al., 2000; Katki et al., 2013c). For example, in a study of over 32,000 women, 4.5% of study participants with a single HPV-positive and cytology negative result had a 5-year risk of CIN3+; this risk increased to 7.4% in women who were again HPV-positive, cytology negative one year later. HPV infection is transient in most patients, but some patients have persistent infection. Katki (2013c) found that women with HPV-positive and cytology negative results, 48% of women remained HPV-positive after 1 year, and 12% continued to be positive at 5 years (Katki et al., 2013c). Among 8656 women ages 20 to 29 with two HPV tests 2 years apart, researchers found a 5-year risk of CIN3+ of approximately 2% in women with a single HPV-positive test compared with 8% in those with two HPV-positive tests (Kjaer, Frederiksen, Munk, & Iftner, 2010).

When tracking for viral persistence, DNA testing for genotypes of specific HPV infections is useful in targeting the most carcinogenic genotypes. Separate detection of HPV 16 and 18 in women aged 30 and older with normal cytology is helpful in the differentiation of women at risk for CIN3 and cancer or CIN2+ (Castle et al., 2009). Women with normal cytology plus HPV-positive for HPV 16/18 have an 18-21% 10-year risk of developing CIN3, while women with non-16/18 high-risk types have a risk as low as 1.5% (Khan et al., 2005; Schlecht et al., 2001). ASCCP recommends colposcopy for

HPV-16 or HPV-18 positive tests, while those who test negative for both could wait a year before being screened again. ASCCP guidelines state that HPV-16/HPV-18 genotyping would be clinically beneficial in conjunction with cytology in HR-HPV positive women aged 30 or older (Einstein et al., 2010).

### **Follow-up for Atypical Squamous Cell Cytology Dependent on Human Papillomavirus Testing Results**

Cervical cytology interpretations of ASC-US are the most commonly reported cytologic abnormalities (Gage, Schiffman, Solomon, Wheeler, & Castle, 2010). Risk for invasive cervical cancer is low in women with ASC-US, because one to two-thirds of cases are not associated with HR-HPV infections (ASC-US-LSIL Triage Study Group [ALTS Group], 2003; Katki et al., 2013e). Testing for high-risk types of HPV in women can effectively triage women with ASC-US cytology, improving the detection of cervical neoplasia and permitting additional risk stratification. The risks for ASC-US are based on two evaluation strategies: cervical cytology alone and cervical cytology with HPV triage (testing for HR-HPV subtypes). HPV-negative ASC-US women are at very low risk for cervical precancerous lesions (CIN2+ 1.1%, CIN3+ 0.43%; Katki et al., 2013e). Additionally, the rate of CIN3 or worse over 2 years is 1.4% for women with HPV-negative ASC-US cytology (Safaeian, Solomon, Wacholder, Schiffman, & Castle, 2007). HPV-positive ASC-US interpretations are associated with an 18% risk for CIN2+, 6.8% risk for CIN3+, and 0.41% risk for cervical cancer. The risk for precancerous lesions or cancer for cervical cytology only, regardless of HPV status, is 6.9% for CIN2+, 2.6% for CIN3+, and 0.18% for cervical cancer (Katki et al., 2013e).

ASC-US plus HR-HPV types in women with initial negative colposcopy is associated with a 12% risk of CIN2 or CIN3 within 2 years. The ASC-US-LSIL Triage Study Group (ALTS Group, 2003) determined that HPV triage in the management of cytology interpretations of ASC-US is as sensitive as immediate colposcopy in the identification of CIN grade 3, while reducing the number of women referred for colposcopy by half. HPV testing leads to significantly less follow-up visits and colposcopic examinations when compared to repeat cytology with colposcopic referral. Several studies have investigated the sensitivity of HR-HPV testing in detecting CIN2+ or CIN3+ in women with ASC-US cytology. Their findings support the clinical use of HR-HPV testing to detect HR-HPV types in conjunction with cervical cytology for use in triage of women with ASC-US cytology (Einstein et al., 2010; Gage et al., 2010; Stoler et al., 2011).

Katki et al. (2013a) estimated the 5-year risk of CIN3+ or cancer among women aged 30 to 64 years testing HPV-negative/ASC-US and women testing Pap-negative alone. The findings indicate that women with HPV-negative/ASC-US (0.43%) had a similar risk for CIN3+ and cervical cancer as women testing Pap-negative alone (0.26%), regardless of HPV testing, but had a higher risk than women testing HPV-negative/Pap-negative (0.08%). In addition, the results show that cancer risks at ages 60 years and older may be higher for women testing HPV-negative/ASC-US (0.26%) versus testing negative Pap-alone (0.035%) (Katki et al., 2013a). Consequently, the authors do not recommend exiting these women from screening, and they should be re-evaluated in 1 year given the higher risk of cervical cancer. Furthermore, based on the KPNC data, the risk for CIN3+ and cancer in HPV-negative/ASC-US results are substantially higher than

negative Pap-alone results, suggesting HPV-negative/ASC-US results be followed with co-testing at 3-year intervals rather than at 5-year intervals (Massad et al., 2013).

Women with ASC-US and detected HPV-16 or HPV-18 have a greater absolute risk of CIN2 or worse compared with high-risk HPV-positive /HPV-negative women with results other than HPV-16/18 (Einstein et al., 2010; Gage et al., 2010; Stoler et al., 2011). KPNC noted that the risk for CIN3+ in both groups exceeded the threshold for colposcopy. Based on KPNC's findings, ASCCP recommends colposcopy regardless of genotyping results and does not advocate for HPV-16/18 genotyping in HPV-positive women with ASC-US since it did not lead to different management of these women (Katki et al., 2013e; Massad et al., 2013). Therefore, ASCCP prefers HPV testing with ASC-US, but accepts repeat cytology at 12 months for the management of women with ASC-US on cytology. Negative cytology results after 1 year and routine screening with cytology in 3 years is recommended. For women with ASC or worse on cytology after the 12-month follow-up, ASCCP recommends colposcopy.

### **Management Strategies for Low-grade Squamous Intraepithelial Lesions**

LSIL and HPV-positive ASC-US are clinically equivalent for risk of CIN grade 2 or 3 based on the ASCUS-LSIL Triage study (Cox, Schiffman, & Solomon, 2003). These data suggest that women with LSIL and HPV-positive ASC-US be managed similarly. For women aged 30-64 years, the new ASCCP guidelines recommend co-testing. This recommendation will increase the number of LSIL Pap results with HPV testing. HPV testing is not usually performed on LSIL Pap results since most cases of LSIL are HPV-positive. Currently ASCCP does not recommend reflex HPV testing because it does not efficiently select women for colposcopy, due to the high rate of HPV positivity.

However, when co-testing is performed in women 30 years of age or older, some women are found to be HPV-negative.

In the KPNC cohort, the risk of CIN3+ in HPV-negative/LSIL (2.0%) women was similar to that for women with ASC-US Pap test results (2.6%), without knowledge of HPV test results. HPV-negative/LSIL poses a lower risk than other Pap results; therefore, current ASCCP guidelines recommend repeat co-testing at 1 year.

Additionally, the risks of CIN2+ and CIN3+ among women aged 30-64 years testing HPV-positive/LSIL (18% CIN2+ and 6.8% CIN3+) were higher than those among women testing HPV-negative/LSIL (1.1% CIN2+ and 0.43% CIN3+) (Katki et al., 2013b). Also, very few cases of cancer were observed in women with LSIL Pap results testing HPV-positive or HPV-negative in the KPNC dataset. It is interesting that LSIL is not a frequent preceding Pap test result for overtly invasive cervical cancer.

For women with LSIL (or ASC-US plus HR-HPV types), with negative colposcopy, HPV testing at 1 year and repeat cytology at 2 years appears adequate (compared to previous strategy of frequent serial cytology). LSIL in women with negative initial colposcopy is associated with a 12% risk of CIN2 or CIN3 within 2 years based on a cohort of 864 women in the ALTS Group (2003) Study. Of 273 women with LSIL in the same study, 25 (9.2%) had CIN3 during follow-up. Based on a 2-year prospective cohort study, 1,132 women with HPV plus ASC-US and 852 with LSIL were evaluated. HPV testing at 12 months had 92% sensitivity for CIN2 or 3 with 55% repeat colposcopy rate. In contrast, repeat cytology every 6 months had 88% sensitivity with 64% repeat colposcopy rate (Guido, Schiffman, Solomon, & Burke, 2003). ASCCP prefers repeat co-testing at 12 months for the management of women with LSIL with a

negative HPV test, but colposcopy is acceptable. If follow-up co-testing at 12 months is cytology negative and HPV-negative, repeat co-testing at 3 years is recommended. If all tests are negative at that time, routine screening is recommended. For cytology results with ASC or higher or HPV positive, colposcopy is suggested. For LSIL with no HPV test or LSIL with positive HPV test, colposcopy is recommended.

### **Management of Women with Atypical Squamous Cells cannot Exclude High Grade Intraepithelial Lesions**

ASC-H confers a higher risk for CIN3+ over time than ASC-US or LSIL based on the data from KPNC (Massad, et al., 2013). ASC-H has a 5-year CIN3+ risk of 18% among women ages 30-64. The high rate of HPV detection in women with ASC-H makes reflex HPV testing relatively inefficient and is not recommended by ASCCP. The 5-year CIN3+ risk for women 30-64 years of age with HPV-negative/ASC-H is 3.5%, and for HPV-positive/ASC-H results the risk is 25% (Katki et al., 2013a). Therefore, if ASC-H exists, colposcopy is the choice of follow-up whatever the HPV result is.

### **Management of Women with High Grade Intraepithelial Lesions**

HSIL cytology results identify women at substantial risk. The peak incidence for HSIL is found in women ages 20-29 years. Cancer risk rises with age and is low in young women aged 21-24, even with follow-up. HSIL has a 5-year CIN3+ risk of 47% and a cancer risk of seven percent for women ages 30-64, which is why immediate excision is justified (Katki et al., 2013d). Risks are modified by HPV test results, HPV-negative HSIL results carry a 5-year risk of CIN3+ of 30%, while the 5-year cancer risk is seven percent. This is why there is no role for HPV triage in HSIL cytology results. In the KPNC cohort, the risk of CIN3+ in women 30-64 years of age testing HPV-positive

HSIL was 49%, while seven percent developed cancer (Katki et al., 2013d). Management of HSIL when HPV results are known from co-testing does not guide the choice between immediate diagnostic excision and colposcopy. For women with HSIL cytology, ASCCP recommends immediate loop electrosurgical excision or colposcopy as acceptable management strategies. Triage using either a program of repeat cytology alone or reflex HPV testing is unacceptable.

### **Management of Women with Unsatisfactory Cytology Results**

Unsatisfactory reporting rates for cytology results are 1.1% or less for both liquid-based preparations (SurePath and ThinPrep) and conventional Papanicolaou tests (Moriarty et al., 2009). Unsatisfactory cytology results usually stem from insufficient squamous cells or obscuring blood, inflammation, or other processes (Davey et al., 2008). Unsatisfactory results are unreliable for identifying epithelial abnormalities, and women with unsatisfactory results may be at significant risk for disease (Hock et al., 2003; Ransdell, Davey, & Zaleski, 1997). In a study examining outcomes of women with inadequate cervical smears for over 5 years, 2.2% of women developed histologically confirmed high grade CIN, although the difference was not significant at the 95% level of confidence (Hock et al., 2003). A 7-year prospective study found an unsatisfactory Pap smear indicated a 1.6-4.0 times higher risk of harboring a CIN2/3 or invasive cervical cancer compared to women with a normal Pap smear (Nygard, Sauer, Nygard, Skare, & Thoresen, 2004). The unsatisfactory Pap tests in these studies were performed using conventional smears. The majority of Pap tests in the United States are done using liquid-based media, which controls for most obscuring factors. The advantage of this method is an increased ability to detect abnormal cells, thereby significantly reducing the

number of unsatisfactory rates compared with conventional Papanicolaou tests (Holton, Smith, Terry, Madgwick, & Levine, 2008; Siebers et al., 2008). Liquid-based cytology demonstrates an almost complete elimination of most causes for unsatisfactory conventional Papanicolaou tests (Siebers, Klinkhamer, Vedder, Arbyn, & Bulten, 2012).

The rising use of HPV testing has raised new issues regarding the degree of cellularity, specimen adequacy, and reliability of results for both Pap and HPV testing (Davey et al., 2008). Sufficient evidence does not exist regarding the management of women with unsatisfactory cytology with co-testing, although the risk for high-grade disease with negative HPV values is low. In a study with 304 patients with unsatisfactory cytology results and HPV testing, 11 tested HPV-positive, with five (45%) patients having detectible low-grade squamous intraepithelial/CIN1 (Zhao & Austin, 2009). The remaining 293 women were HPV-negative, and only one case of CIN1 was identified, indicating a high negative predictive value associated with HR-HPV-negative results with an unsatisfactory cytology. It is important to mention that the currently available HPV tests lack a control for epithelial cellularity; therefore, a negative HPV test may not be reliable because of an insufficient sample (Massad et al., 2013).

For women with unsatisfactory cytology reports and unknown or negative HPV status, ASCCP recommends repeating the cytology in 2-4 months. Triage using reflex HPV testing is not indicated. Women 30 years old or older with unsatisfactory cytology and positive for HPV, acceptable options include either repeat cytology in 2-4 months or colposcopy. The repeat cytology approach in all women with unsatisfactory cytology involves colposcopy for two consecutive unsatisfactory results, resumption of routine



screening in cases of cytology negative and HPV-negative or HPV status unknown, and co-testing at 1 year is indicated in cases of cytology negative and HPV-positive.

### **Cytology Negative with Absent or Insufficient Endocervical/Transformation Zone**

Samplings of the Endocervical/Transformation Zone (EC/TZ) are regarded as indicators for quality in cervical screening programs; however, the importance of an EC/TZ sample in helping disease detection continues to be a matter of controversy (Zhao & Austin, 2007). A negative cytology report with an absent or insufficient EC/TZ component has sufficient cells for interpretation but lacks endocervical or metaplastic cells, denoting an inadequate sample of the squamocolumnar junction (Massad et al., 2013), raising the concern for missed disease. Zhao and Austin (2007) found that Pap-negative women with no EC/TZ showed no increased discovery of previously occult disease on follow-up relative to women whose Pap tests did have an EC/TZ. Huang, Quinn, and Tan (2000) concluded that the lack of an endocervical component was not statistically significantly associated with a higher incidence of either high-grade or low-grade abnormalities.

Previous guidelines recommended early repeat cytology, which is not the case with the present guidelines (Davey et al., 2002, 2008). Several studies do not support early repeat testing for women whose smears lack a sample from the transformation zone, unless abnormality is suspected or there are risk factors for cervical dysplasia. If there are no risk factors, testing at regular screening intervals is indicated (Elumir-Tanner & Doraty, 2011). A study by Mitchell (2001) demonstrated that early repeat testing of women whose Pap smears were negative but lacked an endocervical component was not justified because no higher rate of histologic high-grade abnormality was evident on

longitudinal follow-up, even when later smears included an endocervical component. Many longitudinal studies of Pap-negative women with no EC/TZ have failed to find increased disease on follow-up or that EC/TZ sampling reduces false negative rates (Mitchell, 2001; Mitchell & Medley, 1991; Zhao & Austin, 2007).

Currently, ASCCP management of cytology negative with absent or insufficient EC/TZ varies by age. For women 21-29 years of age, routine screening with cytology in 3 years is recommended and HPV testing is unacceptable. For women 30 years of age or older, the HPV result guides management. Zhao and Austin (2007) found that HPV DNA detection is independent of cytologic sampling of the TZ, providing objective risk assessment of patients with no EC/TZ. A study of 7,990 participants investigated the effect of the presence of an adequate EC/TZ component on the detection of HR-HPV DNA. The researchers found that liquid-based Pap tests (LBPT) with and without a TZ had similar rates of HR-HPV detection. Additionally, LBPT with and without TZ had similar follow-up biopsy diagnoses (Navina et al., 2006). However, adequate evidence is not available on the relationship between EC/TZ sampling and HPV DNA test results. ASCCP recommends HPV testing for women 30-64 years of age, stating that this offers an additional margin of safety for women cytology negative with absent or insufficient EC/TZ. Based on HPV status, ASCCP recommends that in women who are HPV-negative, routine screening with co-testing in 5 years is indicated. For women who are HPV-positive, acceptable options include either co-testing in 1 year or genotyping. If the HPV type is 16 or 18, colposcopy is performed. If HPV is not type 16 or 18, repeat co-testing in 12 months is indicated. If no HPV testing done, then HPV testing is preferred,

with management guided by results, but repeat cytology in 3 years is acceptable according to the ASCCP.

## METHODS

A literature search was performed using the key terms cervical cytology, cervical intraepithelial neoplasia, cervical cancer, and cervical dysplasia using online databases including CINAHL Plus, MEDLINE, OVID, and PubMed. The review of literature was structured by the areas of essential changes from prior ASCCP management guidelines. Research articles were selected if they published in peer-reviewed journals and addressed one or more of the following: management strategies of abnormal cytology results based on age, risk stratification (distinguishing the few women at risk from the many who are not at risk) in identifying women among whom CIN3+ is more likely, management of women with discordant co-testing results, the use and interpretation of HPV genotyping, and how results affect management. Sixty-two studies were identified, of which 32 were applicable to this project. The quality of the articles selected varied and include randomized, controlled trials, clinical trials without randomization (from cohort or case-controlled analytic studies), multiple time-series studies, epidemiologic studies, and evidence from opinions of respected authorities based on clinical experience, descriptive studies, and reports of expert committees.

## Results

The products produced as part of this project include a manuscript, titled *Essential Changes to the Management of Abnormal Cervical Cytology Results*, submitted to *The Journal for Nurse Practitioners* (Appendix B) and a poster presentation. Author guidelines for *The Journal for Nurse Practitioners* are found in Appendix C. A peer reviewed poster presentation was given at the Sigma Theta Tau

International, Upsilon Beta Chapter, annual poster session and induction in Anaheim, California, April, 2014 (Appendix D).

## DISCUSSION

The evidence behind the changes from the updated ASCCP management strategies is substantial. The guidelines have made essential changes from previous recommendations based on the review of the literature and analyses from the KPNC database. The KPNC data provides evidence on cervical cancer risk after abnormal tests, providing longitudinal data on nearly every Pap, HPV test, biopsy, and treatment conducted, and with more than 400 cancers, 4,000 CIN3+, and 10,000 CIN2+ having been diagnosed. It is also one of the longest and largest clinical experiences with HPV and cytology co-testing. Furthermore, the rationale for each of the clinical management options provided by ASCCP is based upon benchmarking CIN3+ risks from the KPNC cohort. The updated management guidelines are based on implicit risk thresholds developed in prior guideline processes. The concept of *equal management of equal risks* ensures simplified, consistent management for a variety of different test result combinations.

With greater understanding into the scientific evidence behind the latest guideline changes clinicians will be better equipped to make clinical decisions involving the management of abnormal Pap results. Clinicians utilizing the 2012 ASCCP recommendations will have at their disposal up-to-date guidelines substantiated on sound clinical evidence. This in turn will help clinicians educate patients about the revised guidelines, including age-related management strategies and the reduced follow-up visits with the integration of co-testing and longer screening intervals as part of the management recommendations, alleviating patient fears and reducing unnecessary worries. Clinician adherence to guideline recommendations, optimal follow-up, patient

education, appropriate referrals, and effective management of abnormal results are essential in the initial detection and successful treatment of early cervical changes.

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**APPENDIX A****GLOSSARY OF ABBREVIATIONS AND TERMS****Glossary of Abbreviations and Terms**

*Atypical squamous cells (ASC)*: cytologic changes suggestive of squamous intraepithelial lesions that are quantitatively or qualitatively insufficient for a definitive interpretation. Subdivided into two categories:

*Atypical squamous cells of undetermined significance (ASC-US)*: squamous epithelial cells are not normal and do not represent either benign cell changes or dysplasia.

*Atypical squamous cells cannot exclude high grade intraepithelial lesion (ASC-H)*: indicates a greater potential for finding significant underlying cervical abnormalities.

*Cervical intraepithelial neoplasia (CIN)*: describes many intraepithelial changes that can occur before cells become invasive cervical cancer cells. They include:

*CIN1*: mild dysplasia

*CIN2*: moderate dysplasia

*CIN3*: severe dysplasia

*CIN2+*: cervical intraepithelial neoplasia grade 2 or worse (CIN3+ and CIN2)

*CIN3+*: cervical intraepithelial neoplasia grade 3 or worse (CIN3, carcinoma in situ, and cancer)

*Endocervical (EC)*: within the uterine cervix.

*High risk human papillomavirus (HR-HPV)*: the various HPV genotypes associated with the potential to progress to cervical cancer.

*Human papillomavirus (HPV)*: most common sexually transmitted infection that may cause genital warts and cervical cancer.

*Squamous intraepithelial lesions (SIL)*: is the abnormal growth of squamous cells on the surface of the cervix. They include:

*Low-grade squamous intraepithelial lesion (LSIL)*: cells in these lesions are early in the process of changing in size, shape, and number on the surface of the cervix. In these low-grade lesions, the cells have only a few abnormal characteristics, but are still somewhat similar to the normal cells. Other common names for this low-grade SIL are mild dysplasia or CIN1.

*High-grade squamous intraepithelial lesion (HSIL):* the cells look very abnormal. However, these cells are still only on the surface of the cervix. They are not invading the deepest parts of the cervix yet. These lesions are also called moderate or severe dysplasia, CIN II or II or carcinoma in situ.

*Transformation zone (TZ):* area of the cervix where abnormal cells or dysplasia occur.



**APPENDIX B**

**MANUSCRIPT SUBMITTED TO *THE JOURNAL FOR NURSE PRACTITIONERS***

**Essential Changes to the Management of Abnormal Cervical Cytology**

Zoila Paz, MSN, WHNP-BC

Penny Weismuller, DrPH, RN

3900 E. Pacific Coast Hwy, Long Beach, CA 90804

310-612-0713 Cell

562-986-2454 Work

424-217-2704 Fax

**Abstract**

New guidelines for disease management of abnormal Pap smears changed greatly from former guidelines. Clinicians need strong evidence for understanding the major guideline changes for the management of abnormal cytological smears. This article summarizes the evidence supporting the essential changes.

## **Essential Changes to the Management of Abnormal Cervical Cytology Results**

Guidelines for the management of women with abnormal cervical cytology were updated in 2012 by the American Society for Colposcopy and Cervical Pathology (ASCCP). The guidelines are stratified by a woman's age, cytologic diagnosis, infection with HPV types.<sup>1</sup> Algorithms for management of initial abnormalities and for subsequent follow-up are described as well. The updated ASCCP guidelines are based on analyses of data from more than one million women receiving care at Kaiser Permanente Northern California (KPNC). Guideline development was based on the concept of *benchmarking to implicit risk thresholds*. This means that risk estimates were calculated for each HPV and Pap co-test combination and matched (*benchmarked*) to the most similar risk based on Pap-alone. In accordance with the principle of *equal management of equal risks*, the management option for the co-test result would be the same management option for the Pap-alone result with the same level of risk for high-grade premalignant disease or cancer.<sup>2</sup> The aim of this article is to help providers understand the evidence supporting the essential changes from prior management guidelines and integrate them into practice.

### **Cytology and Histology Findings and Interpretation**

The 2001 Bethesda System defines terminology for reporting the results of cervical cytology providing clear guidance for clinical management utilizing a uniform system of terminology.<sup>3</sup> The 2012 updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors uses this system to describe the categories of epithelial cell abnormalities. The categories include atypical squamous cells (ASC) and low-grade or high-grade squamous intraepithelial lesions

(LSIL or HSIL). To describe histologic abnormalities cervical intraepithelial neoplasia (CIN) grades 1-3 are used (see Table 1).

### **Major Changes to the Management of Abnormal Screening Tests**

The ASCCP 2012 recommendations include essential changes from prior management guidelines, and include recommendations in the management of women with discordant co-test results (e.g., HPV-positive/Cytology negative, HPV-negative/Cytology worse than ASC-US). Follow-up visits are reduced with the integration of co-testing and longer screening intervals as part of the management guidelines. Women ages 21 to 29, Pap-only strategies are used, without use of HPV testing, but co-testing in certain circumstances is expanded to women younger than 30 years. Women aged 21-24 years are managed conservatively, especially for minor abnormalities. The use of genotyping triages for HPV-positive/Cytology negative women with HPV-16 or HPV-18 to earlier colposcopy is recommended.

Further changes from prior management guidelines include cytology at 12 months for ASC-US and then if negative cytology every 3 years; immediate colposcopy is no longer an option. For women with HPV-positive and ASC-US on cytology, regardless of genotyping result, colposcopy is indicated. HPV-negative and ASC-US cytology results should be followed with co-testing at 3 years rather than 5 years, and are not sufficient to allow women 65 years of age or older exit from screening.

### **Conservative Management for Women Aged 21-24 Years**

Invasive cervical cancer is rare among young women, accounting for 125 carcinomas per year among women aged less than 25 years.<sup>4</sup> These low-risk women are at high risk for HPV exposure and HPV-associated lesions; therefore, the level of risk is

high enough to warrant screening but is low enough to permit observation for minimal abnormalities.<sup>5</sup> In a study conducted by Katki et al. (2013), women aged 21 to 24 had a near zero cancer risk, and positive Pap test results predicted low CIN3+ risk.<sup>6</sup> Based on the KPNC database the 5-year risk of premalignant or malignant disease in young women with ASC-US cytology only irrespective of HR-HPV genotyping was 3.0% for CIN3+ and 0.032% for cervical cancer, while LSIL was 3.0% for CIN3+ and no cases identified for cervical cancer.<sup>6,7</sup> Women aged 21-24 years with a cytology result of ASC-H have a low risk of CIN3+ despite ASC-H conferring a greater risk for CIN3+ over time than ASC-US or LSIL (see Table 2). This low risk is also true for young women with HSIL. Data from KPNC showed a cumulative 5-year risk of CIN3+ and cancer among women aged 21 to 24 with HSIL cytology of 28% and 0% respectively<sup>6</sup> (see Tables 3 and 4).

ASCCP recommendations of young women have led to changes in the management of cytological abnormalities involving ASC-US or LSIL. Young women with LSIL and HPV-positive ASC-US are managed similarly, because the risk for CIN3+ is lower in women aged 21 to 24.<sup>6,8</sup> Data from KPNC has shown young women aged 21-24 have a 4.4% risk for CIN3+ and 0.055% for cervical cancer with ASC-US/ HPV-positive cytology results, while ASC-US/HPV-negative results indicate a 0.57% risk for CIN3+ and no cases identified for cervical cancer.<sup>6</sup> Based on the data from KPNC, the new ASCCP guidelines prefer repeating the cytology alone at 12-month intervals and recommend return to routine screening when two consecutive negative results are obtained. Immediate colposcopy is not warranted, unless repeat cytology at 12-month follow-up demonstrates cervical abnormalities for ASC-H, AGC, or HSIL. For women with ASC-US or worse at the 24-month follow-up, colposcopy is recommended. Reflex

HPV testing is acceptable for ASC-US only, with routine screening recommended for HPV-negative results, and HPV-positive women should have a follow-up cytology annually for 2 years, with colposcopy after 1 year only if HSIL and after 2 years if ASC-US or LSIL persist.

Management of ASC-H or HSIL cytology is modified in women 21-24 years of age. Colposcopy is recommended after ASC-H or HSIL cytology, but immediate treatment with loop electrosurgical excision procedure is unacceptable. ASCCP recommends observation with colposcopy and cytology every 6 months for up to 2 years for women with no CIN2, 3 at colposcopy, until two consecutive negative Pap tests are reported and no high-grade colposcopic abnormality is observed. Repeat biopsies are indicated if ASC-H/HSIL fail to regress after one year, and diagnostic excision is recommended if HSIL cytology persists for 2 years.

#### **Women with Positive Human Papillomavirus and Negative Cytology**

HPV testing provides useful risk stratification in predicting a woman's long-term risk of cervical precancers.<sup>9</sup> Women with cervical infections with carcinogenic HPV results are at greater risk for developing CIN3 and cervical cancer later than patients with HPV-negative tests.<sup>2</sup> One study showed that among women who failed to clear their HR-HPV in 12 months, more than 10% had developed CIN3.<sup>10</sup> The lag time between infection and appearance of the first microscopic evidence of precancer can be surprisingly short, often within 5 years; this is sufficient to justify early return for retesting. However, the majority of HPV infections are cleared or suppressed by the immune system, greatly decreasing the risk of high grade lesions; so observing women to allow for clearance is acceptable management by the ASCCP.

ASCCP recommends repeat co-testing at 12 months for the management of women aged 30 or greater who are cytology negative, but HPV-positive. When both tests are negative, repeat co-testing at 3 years is recommended. Based on the KPNC data demonstrating that after many screening and diagnostic abnormalities, from HPV-positive and cytology negative co-testing to treated CIN3, risk for CIN3+ remains higher than after negative co-testing among women without prior abnormality; therefore, ASCCP is suggesting women with abnormalities be followed with co-testing at 3-year intervals rather than at 5 years.<sup>5</sup> For women with ASC or worse or HPV-positive after the 12-month follow-up, colposcopy is recommended.

The persistence of HR-HPV in normal cervical smears is associated with a significantly increased risk of developing abnormal cytologic results.<sup>2,11,12,13</sup> As an example, in a study of over 32,000 women, 4.5% of study participants with a single HPV-positive and cytology negative result had a 5-year risk of CIN3+, this risk increased to 7.4% in women who were again HPV-positive, cytology negative 1 year later.<sup>14</sup> Among 8,656 women ages 20-29 with two HPV tests two years apart, researchers found a 5-year risk of CIN3+ of approximately two percent in women with a single HPV-positive test compared with 8% in those with two HPV-positive tests.<sup>15</sup>

When tracking for viral persistence, DNA testing for genotypes of specific HPV infections is useful in targeting the most carcinogenic genotypes.<sup>11</sup> Separate detection of HPV- 16/18 in women aged 30 and older with normal cytology is helpful in the differentiation of women at risk for CIN3+ or CIN2+.<sup>11</sup> Women with normal cytology plus HPV-positive for HPV-16/18 have an 18-21% 10-year risk of developing CIN3, while women with non-16/18 high-risk types have a risk as low as 1.5%.<sup>16,17</sup> ASCCP

recommends colposcopy for HPV-16 or HPV-18 positive tests, while those who test negative for both could wait a year before being screened again. ASCCP guidelines state that HPV-16/HPV-18 genotyping would be clinically beneficial in conjunction with cytology in HR-HPV positive women aged 30 or above.<sup>18</sup>

### **Management of Atypical Squamous Cell Cytology**

Cervical cytology interpretations of ASC-US are the most commonly reported cytologic abnormalities.<sup>19</sup> Risk for invasive cervical cancer is low in women with ASC-US, because one- to two-thirds of cases are not associated with HR-HPV infections.<sup>20, 21</sup> Testing for high-risk types of HPV in women can effectively triage women with ASC-US cytology, improving the detection of cervical neoplasia and permitting additional risk stratification. The risks for ASC-US are based on two evaluation strategies, cervical cytology alone and cervical cytology with HPV triage. HPV-negative ASC-US women are at very low risk for cervical precancerous lesions (CIN2+ 1.1%, CIN3+ 0.43%).<sup>21</sup> Additionally, the rate of CIN3+ over 2 years is 1.4% for women with HPV-negative ASC-US cytology.<sup>22</sup> HPV-positive ASC-US interpretations are associated with an 18% risk for CIN2+, 6.8% risk for CIN3+, and 0.41% risk for cervical cancer.<sup>21</sup> The risk for precancerous lesions or cancer for cervical cytology only regardless of HPV status is 6.9% for CIN2+, 2.6% for CIN3+, and 0.18% for cervical cancer.<sup>21</sup>

Katki et al. (2013) estimated the 5-year risk of CIN3+ or cancer among women aged 30 to 64 years testing HPV-negative/ASC-US and women testing Pap-negative alone.<sup>21</sup> The findings indicate that women with HPV-negative/ASC-US (0.43%) had a similar risk for CIN3+ and cervical cancer as women testing Pap-negative alone (0.26%), regardless of HPV testing, but had a higher risk than women testing HPV-negative/Pap-



negative (0.08%). In addition, the results show that cancer risks at ages 60 years and older may be higher for women testing HPV-negative/ASC-US (0.26%) versus testing negative Pap-alone (0.035%).<sup>2</sup> Consequently, the authors do not recommend exiting these women from screening, and they should be re-evaluated in 1 year given the higher risk of cervical cancer. Furthermore, based on the KPNC data, the risk for CIN3+ and cancer in HPV-negative/ASC-US results are substantially higher than negative Pap-alone results, suggesting HPV-negative/ASC-US results be followed with co-testing at 3-year intervals rather than at 5 years.<sup>5</sup>

Women with ASC-US and detected HPV-16 or HPV-18 have a greater absolute risk of CIN2+ compared with high-risk HPV-positive/HPV-negative women with results other than HPV-16/18.<sup>18, 19, 23</sup> KPNC study noted the risk for CIN3+ in both groups exceeded the threshold for colposcopy. Based on KPNC findings ASCCP recommends colposcopy regardless of genotyping results and does not advocate for HPV- 16/18 genotyping in HPV-positive women with ASC-US since it did not lead to different management of these women.<sup>5, 21</sup> Therefore, ASCCP prefers HPV testing with ASC-US, but accepts repeat cytology at 12 months for the management of women with ASC-US on cytology. Negative cytology results after one year, routine screening with cytology in 3 years is recommended. For women with ASC or worse on cytology after the 12-month follow-up, ASCCP recommends colposcopy.

### **Management of Low-grade Squamous Intraepithelial Lesions**

LSIL and HPV-positive ASC-US are clinically equivalent for risk of CIN2/3 based on the ASCUS-LSIL Triage study. This data suggests that women with LSIL and HPV-positive ASC-US be managed similarly. For women aged 30 to 64 years, the new

ASCCP guidelines recommend co-testing. This recommendation will increase the number of LSIL Pap results with HPV testing. HPV testing is not usually performed on LSIL Pap results since most cases of LSIL are HPV-positive. Currently ASCCP does not recommend reflex HPV testing, because it does not efficiently select women for colposcopy, owing to the high rate of HPV positivity. However, when co-testing is performed in women 30 years of age or older, some women have HPV-negative.

In the KPNC cohort, the risk of CIN3+ in HPV-negative/LSIL (2.0%) women was similar to that for women with ASC-US Pap test results (2.6%) without knowledge of HPV test results.<sup>7</sup> HPV-negative/LSIL poses a lower risk than other Pap results; therefore current ASCCP guidelines recommend for repeat co-testing at 1 year.

Additionally, the risks of CIN2+ and CIN3+ among women aged 30 to 64 years testing HPV-positive/LSIL (18% CIN2+ and 6.8% CIN3+) were higher than those among women testing HPV-negative/LSIL (1.1% CIN2+ and 0.43% CIN3+<sup>7</sup> (see Table 3).

For women with LSIL with negative colposcopy, HPV testing at one year and repeat cytology at two years appears adequate (compared to previous strategy of frequent serial cytology). ASCCP prefers repeat co-testing at 12 months for the management of women with LSIL with a negative HPV test, but colposcopy is acceptable. If follow-up co-testing at 12 months is cytology negative and HPV-negative, repeat co-testing at 3 years is recommended. If all tests are negative at that time, routine screening is recommended. Cytology results with ASC or higher or HPV-positive, colposcopy is suggested. LSIL with no HPV test or LSIL with positive HPV test, colposcopy is recommended.

## **Management of Atypical Squamous Cells cannot Exclude High Grade Intraepithelial Lesions**

ASC-H confers a higher risk for CIN3+ over time than ASC-US or LSIL based on the data from KPNC.<sup>5</sup> ASC-H has a 5-year CIN3+ risk of 18% among women ages 30-64. The high rate of HPV detection in women with ASC-H makes reflex HPV testing relatively inefficient and is not recommended by ASCCP. The 5-year CIN3+ risk for women 30-64 years of age with HPV-negative/ASC-H is 3.5%, and for HPV-positive/ASC-H results the risk is 25%.<sup>2</sup> Therefore, if ASC-H exists, colposcopy is the choice of follow-up whatever the HPV result is.

### **Management of High Grade Intraepithelial Lesions**

HSIL cytology results identify women at substantial risk. The peak incidence for HSIL is found in women ages 20-29 years. Cancer risk rises with age and is low in young women aged 21-24, even with follow-up. HSIL has a 5-year CIN3+ risk of 47% and a cancer risk of 7% for women ages 30-64, which is why immediate excision is justified.<sup>24</sup> Risks are modified by HPV test results, HPV-negative HSIL results carry a 5-year risk of CIN3+ of 30%, while the 5-year cancer risk is 7%. This is why there is no role for HPV triage in HSIL cytology results. In the KPNC cohort, the risk of CIN3+ in women 30-64 years of age testing HPV-positive HSIL was 49%, while 7% developed cancer<sup>24</sup> (see Table 2). Management of HSIL when HPV results are known from co-testing does not guide the choice between immediate diagnostic excision and colposcopy. For women with HSIL cytology, ASCCP recommends immediate loop electrosurgical excision or colposcopy as acceptable management strategies. Triage using either a program of repeat cytology alone or reflex HPV testing is unacceptable.

## **Conclusion**

With greater understanding into the scientific evidence behind the latest guideline changes clinicians will be better equipped to make clinical decisions involving the management of abnormal Pap results. Clinicians utilizing the 2012 ASCCP recommendations will have at their disposal up-to-date guidelines substantiated on sound clinical evidence. This in turn will help clinicians educate patients about the revised guidelines, including age-related management strategies and the reduced follow-up visits with the integration of co-testing and longer screening intervals as part of the management recommendations, alleviating patient fears and reducing unnecessary worries. Clinician adherence to guideline recommendations, optimal follow-up, patient education, appropriate referrals, and effective management of abnormal results are essential in the initial detection and successful treatment of early cervical changes.

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Table 1

*Glossary of Abbreviations and Terms*

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**Atypical squamous cells (ASC):** cytologic changes insufficient for a definitive interpretation. Subdivided into two categories:

Atypical squamous cells of undetermined significance (ASC-US): squamous epithelial cells are not normal and do not represent either benign cell changes or dysplasia.

Atypical squamous cells cannot exclude high grade intraepithelial lesion (ASC-H): indicates a greater potential for finding significant underlying cervical abnormalities.

**Cervical intraepithelial neoplasia (CIN):** describes intraepithelial changes that can occur before cells become invasive cervical cancer. They include:

CIN1: Mild dysplasia

CIN2: Moderate dysplasia

CIN3: Severe dysplasia

CIN2+: Cervical intraepithelial neoplasia grade 2 or worse

CIN3+: Cervical intraepithelial neoplasia grade 3 or worse

**High risk human papillomavirus (HR-HPV):** the various HPV genotypes associated with the potential to develop cervical cancer.

**Squamous intraepithelial lesions (SIL):** is the abnormal growth of squamous cells on the surface of the cervix. They include:

Low-grade squamous intraepithelial lesion (LSIL): these cells are early in the process of changing in size, shape, and number on the surface of the cervix.

High-grade squamous intraepithelial lesion (HSIL): these cells are a large number of precancerous cells.

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Table 2

*Five-Year Risk of Premalignant or Malignant Disease with ASC-US and ASC-H Cytology*

Pap and HPV result	CIN2+	CIN3+	Cervical Cancer
<b>ASC-US</b>			
Women 21- 24			
Cytology		3.0% <sup>6</sup>	0.032% <sup>6</sup>
HPV-positive		4.4% <sup>6</sup>	0.055% <sup>6</sup>
HPV-negative		0.57% <sup>6</sup>	0% <sup>6</sup>
Women 25-29			
Cytology		3.9% <sup>6</sup>	0.12% <sup>6</sup>
HPV-positive		7.1% <sup>6</sup>	0.16% <sup>6</sup>
HPV-negative		0.59% <sup>6</sup>	0.018% <sup>6</sup>
Women 30-64			
Cytology	6.9% <sup>2,21</sup>	2.6% <sup>2,21</sup>	0.18% <sup>2,21</sup>
HPV-positive	18% <sup>2,21</sup>	6.8% <sup>2,21</sup>	0.41% <sup>2,21</sup>
HPV-negative	1.1% <sup>2,21</sup>	0.43% <sup>2,21</sup>	0.05% <sup>2,21</sup>
<b>ASC-H</b>			
Women 21-24			
Cytology		16% <sup>6</sup>	0% <sup>6</sup>
Women 25-29			
Cytology		24% <sup>6</sup>	1.5% <sup>6</sup>
Women 30-64			
Cytology	35% <sup>2</sup>	18% <sup>2,6</sup>	2.6% <sup>2,6</sup>
HPV-positive	45% <sup>24</sup>	25% <sup>24</sup>	2.5% <sup>24</sup>
HPV-negative	12% <sup>24</sup>	3.5% <sup>24</sup>	2.1% <sup>24</sup>



Table 3

*Five-Year Risk of Premalignant or Malignant Disease with LSIL Cytology*

Pap and HPV Result	CIN2+	CIN3+	Cervical Cancer
Women 21-24			
Cytology		3.0% <sup>6</sup>	0% <sup>6</sup>
Women 25-29			
Cytology		5.0% <sup>6</sup>	0% <sup>6</sup>
Women 30-64			
Cytology	16% <sup>2,7</sup>	5.2% <sup>2,7</sup>	0.16% <sup>2</sup>
HPV-positive	19% <sup>2,7</sup>	6.1% <sup>2,7</sup>	
HPV-negative	5.1% <sup>2,7</sup>	2.0% <sup>2,7</sup>	

Table 4

*Five-Year Risk of Premalignant or Malignant Disease with HSIL Cytology*

Pap and HPV result	CIN2+	CIN3+	Cervical cancer
Women 21-24			
Cytology		28% <sup>6</sup>	0% <sup>6</sup>
Women 25-29			
Cytology		28% <sup>6</sup>	2.0% <sup>6</sup>
Women 30-64			
Cytology	69% <sup>24</sup>	47% <sup>24</sup>	7.3% <sup>24</sup>
HPV-positive	71% <sup>24</sup>	49% <sup>24</sup>	6.6% <sup>24</sup>
HPV-negative	49% <sup>24</sup>	30% <sup>24</sup>	6.8% <sup>24</sup>

## APPENDIX C

### AUTHOR GUIDELINES FOR THE JOURNAL FOR NURSE PRACTITIONERS

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- **Purpose**

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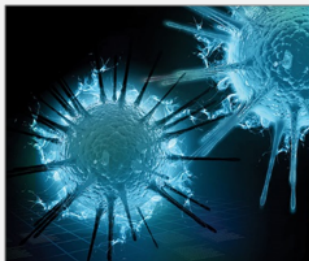
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## APPENDIX D

### POSTER PRESENTATION

#### BACKGROUND

- Annually, in the United States, 3.5 million Pap smears show abnormal cytology and require additional follow-up.
- Appropriate management of histopathologically diagnosed precancer is a key component of cervical cancer prevention.
- Early detection improves successful treatment and can prevent early cervical changes from becoming cancerous.
- Appropriate management could prevent nearly 12,000 new cases of cervical cancer each year.
- New guidelines dramatically changed following adoption of cervical cancer screening guidelines incorporating longer screening intervals and co-testing.
- New guidelines are worrisome to providers who do not understand the evidence supporting the management changes.



#### PURPOSE

- Clarify and disseminate evidence for the new cervical management guidelines to clinicians for easy understanding.

#### Evidence for Management of Abnormal Cervical Cytology

Zoila Paz, DNP, RN, WHNP-BC

and

Penny Weismuller, DrPH, RN

Southern California CSU DNP Consortium

#### Five-year Risk of Premalignant or Malignant Disease with ASC-US Cytology

Pap and HPV result	CIN2+	CIN3+	Cervical cancer
<b>Women 21-24</b>			
Cytology		3.0% <sup>1</sup>	0.032% <sup>1</sup>
HPV-positive		4.4% <sup>1</sup>	0.055% <sup>1</sup>
HPV-negative		0.57% <sup>1</sup>	0% <sup>1</sup>
<b>Women 25-29</b>			
Cytology		3.9% <sup>1</sup>	0.12% <sup>1</sup>
HPV-positive		7.1% <sup>1</sup>	0.16% <sup>1</sup>
HPV-negative		0.59% <sup>1</sup>	0.018% <sup>1</sup>
<b>Women 30-64</b>			
Cytology	6.9% <sup>2,3</sup>	2.6% <sup>2,3</sup>	0.18% <sup>2,3</sup>
HPV-positive	18% <sup>2,3</sup>	6.8% <sup>2,3</sup>	0.41% <sup>2,3</sup>
HPV-negative	1.1% <sup>2,3</sup>	0.43% <sup>2,3</sup>	0.05% <sup>2,3</sup>

<sup>1</sup>Katki et al., 2013f; <sup>2</sup>Katki et al., 2013a; and <sup>3</sup>Katki et al., 2013e.

#### CLINICAL SIGNIFICANCE AND RECOMMENDATIONS

- There is strong evidence for recommended screening and follow-up of abnormal cytology.
- Conservative management of young women 21 to 24 is based on history of transient HPV and regressive cervical abnormalities. This reduces potential harms, such as cervical incompetency following colposcopy.
- For women 25 and older with precancerous cervical findings (CIN 3+), risk for cancer is high and requires more intensive follow-up than previously recommended.
- Patients may be used to previous screening intervals and tests. Clear patient education about the revised guidelines is important.
- Providers should consider decision-support algorithms to assure that the new guidelines are firmly integrated into clinical decision-making.

#### CO-TESTING

- HPV is a causative agent for cervical cancer.
- Co-testing is the preferred method for cervical cancer screening in women 30-64.
- HPV testing required in younger women with abnormal cytology.

#### GUIDELINE CHANGES

- Pap only strategies for women 21-29.
- Conservative management for women 21-24.
- Early colposcopy for women with negative cytology only when genotyping is HPV 16/18 positive.
- Immediate colposcopy no longer warranted for ASC-US cytology. Repeat Pap smear in one year.
- Immediate colposcopy for ASC-US cytology with HPV positive result, regardless of genotyping.
- Co-testing (HPV/Pap) at three years for HPV negative/ASC-US cytology.
- Women over 65 with HPV-negative ASC-US are not sufficient to allow exit from screening.
- Cytology reported as unsatisfactory requires repeat even if HPV negative.
- Cytology reported as negative but lacking endocervical cells can be managed with early repeat.

For more information contact:  
zoila\_a\_paz@csu.fullerton.edu