Cytologic screening of the uterine cervix has resulted in a marked decline in the incidence of cervical cancer in the United States. Since the introduction of the Papanicolaou (Pap) test in 1941, incidence and mortality rates have declined to the 2005 estimate of 8.3 cases of invasive cervical cancer per 100,000 women. This rate translates into 10,520 cases per year among U.S. women and approximately 3900 deaths. Many, if not the majority, of deaths are among women who do not receive appropriate screening [1].

Clinical decision making for women with an abnormal Pap test has recently become more informed due to research involving the human papillomavirus (HPV) and the introduction of cervical cytology triage decision rules. There are 4 major developments. First, the 2001 revision of the Bethesda System redefined the terminology used to describe abnormal Pap test results. This revision classifies cervical cytologic abnormalities into 4 main categories: atypical squamous cells (ASC), low-grade squamous intraepithelial neoplasia (LSIL), high-grade squamous intraepithelial neoplasia (HSIL), and atypical glandular cells (AGC). ASC contains a subcategory designated as ASC-H (ASC, cannot rule out HSIL) [2,3].

The second development was the approval by the U.S. Food and Drug Administration (FDA) of the Hybrid Capture 2 (HC2) HPV DNA test (Digene Corporation, Gaithersburg, MD) for identification of high-risk HPV subtypes, both for triage of ASC cytology results and for primary screening, in conjunction with a Pap, of women 30 years and older. The HC2 test uses a ribonucleic acid probe to bind to high- and intermediate-risk HPV DNA types 16, 18, 31, 33, 39, 45, 51, 52, 56, 58, 59, and 68. Antibodies are then added that have a chemiluminescent marker, resulting in the identification as well as semiquantitation of high-risk types HPV subtypes. This method allows for detection of high-risk HPV subtypes at concentrations as low as 1 pg/mL. There is currently no rationale for identification of low-risk HPV subtypes. The HC2 test has been the subject of a large number of studies evaluating its sensitivity for predicting cervical intraepithelial neoplasia grade 3 (CIN 3) as compared with...
liquid phase and conventional Pap tests. The HC2 has consistently showed a sensitivity of 90% to 100% in detection of CIN 3 as compared with 50% to 75% for conventional Pap tests and approximately 85% to 88% for liquid phase [4–7]. The use of the combined cytology and HPV DNA test in cervical cancer screening will improve sensitivity for detecting both CIN 3 and adenocarcinoma in situ (AIS). The British experience with the combined screening (HPV DNA with Pap) demonstrated an improved sensitivity compared with Pap alone, with an increase from 76.6% to 97.1% and with a minimal loss of specificity (93.3% down from 95.8%).

The third development was the consensus conference sponsored by the American Society for Colposcopy and Cervical Pathology. The conference, held in 2001, brought together representatives multiple organizations, including the National Cancer Institute, American College of Obstetricians and Gynecologists, American Society of Cervical Cytology and Pathology, and the American Cancer Society. Their consensus guidelines for the management of women with abnormal cervical cytology and cervical histology were published and widely distributed [8–10].

And lastly, there will soon be available HPV type-specific testing, which will be able to more accurately assess individual risk based on type-specific HPV persistence. The 13 cancer-associated HPV types do not carry the same risk, and a positive HC2 test does not tell the individual that serial results are due to the same infection. A recent study by Castle et al [11] evaluated participants in the Atypical Squamous Cells of Undetermined Significance/Low-grade Squamous Intraepithelial Lesion Triage Study (ALTS) who had low-grade cytology abnormalities for risk of developing CIN 3 or greater over a 2-year period, comparing women infected with HPV 16 with those infected with any other high-risk subtype. This study demonstrated that patients with ASC or LSIL cytology who were HPV 16 DNA–positive at baseline had 2-year cumulative absolute risks for ≥CIN 3 of 32.5% and 39.1%, respectively. This is in comparison with patients with either ASC or LSIL and any other high-risk HPV subtype, who had an 8.4% and 99% risk for ≥CIN 3. This risk was no different than that observed in women with ASC or LSIL for whom HPV status was unknown [11]. Khan et al [12] reinforced these data with the report from Kaiser showing that women without any history of abnormal cervical cytology with HPV 16 in their cervix have a 10-year risk of CIN 3 of 17.3% as compared with 13.6% for HPV 18, 3% for all other HC2-positive patients combined, and a 0.8% risk in those who were originally HC2-negative.

With the apparent growing importance of HPV type-specific identification, new testing strategies are under development. The HC2 test identifies any of 13 HPV high-risk subtypes and may lead to a large number of false-positive tests for subtypes unlikely to progress to invasive cancer or CIN 3. For this reason, a more specific test is indicated. The use of DNA amplification methods based on polymerase chain reaction (PCR) is likely the next generation of HPV test. These methods have the advantage of being able to identify HPV by subtype. The sensitivity and specificity of the HC2 test as compared with PCR was evaluated via the ALTS trial. Twenty thousand samples were available for comparative evaluation of detection of the 13 high-risk HPV subtypes and detection of prevalent and incident CIN 3 or cancer. In this study, surprisingly, the HC2 test was found to have a higher sensitivity for detection of the high-risk HPV subtypes as well as a higher clinical sensitivity for the detection of cancer or CIN 3 [13]. There were multiple possible explanations for this finding. For example, the amount of liquid-based medium saved for the PCR testing was comparatively small to that used for HC2, and the majority of PCR tests (90%) were performed at 1 laboratory using 1 batch of line blots, so process standardization may have been an issue. The goal of PCR will be to maintain the current excellent sensitivity of the HC2 while improving specificity so as to limit false-positive test results.

**CASE STUDY**

**Initial Presentation**

A 29-year-old woman presents to a community health clinic for evaluation of an upper respiratory infection. She reports that she has no known medical problems, no allergies, and no history of surgery with the exception of a postpartum tubal ligation performed after the birth of her second child when she was 21. She is no longer married to the father of her children but is currently involved with a new partner for the past year. She smokes 1 pack of cigarettes per day. She denies any history of sexually transmitted diseases or abnormal Pap tests, has regular menses, and has no complaints of dyspareunia or dysmenorrhea. She reports more than 5 lifetime sexual partners. She has not had a pelvic examination since her tubal ligation because she “didn’t need birth control anymore.” She denies any gynecologic concerns.

- **What are the current guidelines for cervical cancer screening?**

Screening for cervical cancer via Pap test should begin 3 years after starting to have vaginal intercourse but not later than age 21 years. The American College of Obstetricians and Gynecologists recommends annual cytologic evaluation up to age 30. For women 30 years and older who have had 3 recent consecutive negative annual Pap tests and no history of CIN 2 or 3, immunocompromise, or diethylstilbestrol
exposure, Pap tests may be spaced every 2 to 3 years [14,15]. The safety of screening every 2 to 3 years in select women is confirmed by 2 large studies but could be compromised by a change in sexual partners and new recent exposures. Patient data from the National Breast and Cervical Cancer Early Detection Program were analyzed to evaluate the incidence of severe cytologic abnormalities following a normal Pap test. Age-adjusted rates for the development of severe cytology at 1, 2, and 3 years after a normal Pap test were 25/10,000, 29/10,000, and 33/10,000, respectively; these differences were not statistically significant [16,17]. The second study used a Markov model to estimate the rate at which dysplasia will progress to cervical cancer when stratified by the number of previously negative Pap tests. When evaluating women aged 30 to 64 years with a history of 3 or more negative Pap tests, the associated excess risk for developing cervical cancer is 3/100,000 [18].

Recognizing the excellent sensitivity of HPV testing and the fact that the misclassification of cervical cytology as atypical increases with age, HPV may be used in combination with cytology as primary screening in women 30 years and older. This indication for HPV testing recently gained approval from the FDA. If women undergo combined testing and both cytology and HPV test are negative, no further routine cervical screening is indicated for 3 years. In the instance of normal cytology and a positive test for HPV, the incidence of CIN 2–3 is much lower than the ASC/HPV combination, and these patients may be offered repeat cytology with HPV at 6 and 12 months, and if either are abnormal, colposcopy is indicated [19,20].

Timing for discontinuation of cervical screening is still controversial. The American Cancer Society allows for discontinuation of cervical cytology in women older than 70 years as long as they have a preceding 10-year period of normal screening [15]. The American Geriatrics Society recommends regular cervical cytology at 1- to 3-year intervals until age 70 [21], while the U.S. Preventive Services Task Force allows for discontinuation at age 65 [22]. The most conservative position is offered by the American College of Obstetricians and Gynecologists, which advocates individualization of appropriate cytologic screening intervals and discontinuation in the context of annual pelvic examination and risk assessment [14].

A Missed Opportunity?

Even for women with access to preventive care, compliance with recommended cervical screening is unacceptably low. The Permanente Medical Group in California reviewed the history of members who developed invasive cervical cancer. Of the 642 women who developed cervical cancer, 60% had not had a Pap test in the past 36 months. This was true even though over 60% of the unscreened population had been insured for over 30 months at the time of their cancer diagnosis. Further, 70% of the women diagnosed with cervical cancer had seen either an internist or family practitioner at least once during the 36 months preceding diagnosis and 42% had been seen 3 or more times [23]. Similar results were seen in a review of preventive care within a Veterans Administration primary care clinic in which the Pap test compliance was 50% [24]. Women without access to insurance or other regular health care services have even less opportunity obtain timely screening services.

Urgent care clinics are an untapped resource for providing appropriate cervical cancer screening to women who otherwise might not seek preventive health care. One study assigned women presenting to an urgent care clinic with a complaint warranting a pelvic examination to a routine Pap test or encouraged them to schedule an appointment in the gynecology clinic at a later date. They found that of 111 women enrolled in the Pap test arm, 84.7% received the test as compared with only 29% of the 89 women who were referred to the clinic. Follow-up of abnormal Pap tests was an issue, with only 5/21 (24%) of women in the immediate-Pap group receiving follow-up as compared with 6/10 (60%) in the self-referral group. Overall rates of abnormal Pap test results were similar between the 2 groups (22.3% and 20%) [25]. In a later, larger study from this same clinic, 673 Pap tests were performed over a 1-year period. Almost half of these tests (48.2%) were performed for women who accessed care primarily through the urgent care center, while the remainder had an identified primary care provider. Roughly 60% of these women had no history of Pap test screening. The authors found that when women who accessed urgent care were compared with women who identified a primary care provider, rates of CIN were identical as were rates of follow-up, with over 50% of patients presenting for follow-up care [26]. Given this information, women who present for care at urgent care centers should be offered Pap test screening. This should certainly be done in the instance of a pelvic examination, and we would suggest it should be offered regardless of the complaint. Putting this idea into action is a challenge even in the most motivated of situations. In a series of studies, a cancer screening office system was introduced into 8 primary care clinics serving disadvantaged populations in Florida. This noncomputerized system aimed to change the practice paradigm of the clinics and increase the percentage of patients who were offered and up-to-date on Pap tests, mammograms, and fecal occult blood tests. Over 24 months, the cancer screening office system increased the odds of patients being up-to-date on mammography, but unfortunately there was no significant effect on Pap test compliance [27]. There should also be an established referral pattern should the Pap test return with an abnormality to optimize patient follow-up.
Follow-up Appointment

The patient schedules an appointment for a routine pelvic examination. After 2 missed appointments, she finally presents with a complaint of vaginal discharge and pruritus. The bimanual examination reveals a normally sized, mobile uterus and adnexa. The speculum examination reveals a cervix without gross visual lesions. Yeast is noted on potassium hydroxide wet preparation. A Pap is obtained via liquid phase cytology as well as routine cultures for gonorrhea and chlamydia. The patient is offered an HIV test but declines this after counseling. The patient is treated with a topical antifungal cream for her vaginal candidiasis and discharged from the clinic.

Cervical Cytology Results

The cytology report is received at the clinic 1 week later and reads, “Satisfactory specimen; atypical squamous cells of undetermined significance.”

- What is the next step in management for a patient with ASC?

ASC is the term used to describe cellular abnormalities that are more than can be attributed to reactive changes alone but not severe enough to warrant a diagnosis of LSIL [3]. The ASC category accounts for 2 million of the 3.5 million abnormal Pap test results in the United States each year, making it the most common cytologic abnormality reported. The overall risk of finding CIN 2 or 3 is between 6.4% and 11.9%, and the risk of finding invasive cancer is 0.1% to 0.2% [27-31]. Although the overall risk of finding CIN 2 or 3 or invasive cancer is low, because of the large numbers of abnormal Pap tests read as ASC there are more women with CIN 3 and cancer in this population than in the HSIL or LSIL groups. For this reason, vigilance must be paid to this diagnosis, with care to avoid being too aggressive with initial management and to arrange appropriate evaluation and follow-up.

The management of this patient may follow 3 paths. Option 1: if HC2 is available, the liquid cytology medium may undergo reflex testing for high-risk types of HPV. If HPV is identified, the patient should be referred for colposcopic examination with directed biopsies. If HPV is not identified, the patient may be returned to routine screening in 1 year. Option 2: if HC2 is not available or the initial Pap was a smear, repeat the Pap test in 4 to 6 months. If the second Pap test is ASC or greater, the patient should be referred for colposcopic examination and directed biopsies. If the second Pap test is normal, the patient should undergo a third Pap test in another 4 to 6 months with the results of this test dictating either return to yearly screening or referral to colposcopic examination (in the case of ASC or greater) (Figure 1). Option 3 is to refer the patient to immediate colposcopy at the time of abnormal Pap test.

These strategies were studied in the ALTS trial [32]. In this study, patients with ASC cytology were randomized to undergo immediate colposcopy after 1 abnormal ASC Pap, triage to colposcopy via a positive HC2 for HPV, or conservative management with repeat Pap tests every 6 months. In each study arm, the overall incidence of CIN 3 was 8% to
The use of HC2 HPV triage improves the sensitivity of detecting CIN 3 by selecting only those patients with positive HPV for colposcopic examination. Sensitivity is 95.7% versus 87% for referral with 2 abnormal Pap tests. The use of HPV triage also reduced the number of women unnecessarily sent for colposcopy seen with the repeat cytology strategy. In the ALTS trial, 55.6% of women with ASC were referred for colposcopy after HPV testing as compared with 67.1% referred based on repeat abnormal cytology.

A cost-effectiveness analysis based on 2 years of data from the ALTS trial [33] compared the direct medical costs of immediate colposcopy, HPV DNA testing, and conservative management with up to 3 cytology examinations. Effectiveness for this analysis was modeled on the histologic diagnosis of CIN 3 or greater. A key assumption for this model was that HPV DNA testing was not a reflex test and required an additional office visit. HPV triage remains the most cost-effective and sensitive strategy when modeling on years of life saved from cervical cancer as well as detection of CIN 3 [34].

![Figure 2. Algorithm for management of low-grade squamous intraepithelial lesion (LSIL). Management options may vary if the woman is pregnant, postmenopausal, or an adolescent. ASCCP = American Society for Colposcopy and Cervical Pathology. (Adapted with permission from reference 10.)](image)

The initial management for patients with either LSIL or HSIL results on Pap test is immediate referral for colposcopy. The reason for this is twofold. First, between 83% and 94% of women with LSIL will test positive for high-risk types of HPV. This statistic is especially true in women younger than 25 [32,35]. As a result, the use of HC2 to triage these women to colposcopy or repeat cytology in 12 months is less cost-effective. Second, the underlying prevalence of CIN 2 or 3 in patients with LSIL cytology ranges from 15% to 30% [32]. Therefore, patients with LSIL are at high risk for moderate (CIN 2) to severe (CIN 3) dysplasia on biopsy and warrant thorough colposcopic evaluation; the same is true for patients with ASC-H. An HSIL result on Pap test must be evaluated by careful colposcopic examination. These patients have a 2% risk of invasive cervical cancer at the time of initial examination [8] and a 20% risk of progression to invasive cervical cancer if CIN 3 is present and not treated [36] (Figure 2 and Figure 3).

**Follow-up**

The patient is tested for high-risk types of HPV with HC2. She tests positive for HPV and is referred for colposcopic examination. At the time of colposcopy, the impression of the physician is CIN 1. Several biopsies are obtained that confirm this impression.

- How does management change with LSIL or HSIL cytology?
A histologic diagnosis of CIN 1 is used to describe the patients with “mild dysplasia” or “HPV changes.” These patients have a risk between 11% and 13% for development of CIN 2 or 3 over a 2-year follow-up period [9,37]. For this reason, the current American Society for Colposcopy and Cervical Pathology guidelines for CIN 1 management recommend repeat cytology at 6 and 12 months with referral to repeat colposcopy in the event of an ASC or worse cytology. Once cytology has been normal for 3 consecutive cytologic evaluations done 6 months apart, the patient may resume yearly evaluation [9]. An alternative strategy is to evaluate for high-risk HPV at 12 months and refer back to colposcopy if there is evidence of persistent infection.

Immediate treatment may be offered to women for whom expectant management results in undue anxiety and may be performed via ablation or excision. Persistence of disease beyond 1 to 2 years may also prompt the physician to offer therapy, although there is no evidence demonstrating that it is unsafe to continue expectant management. Future guidelines may incorporate the identification of a specific HPV type or types as preliminary evidence would suggest that infection with HPV 16 or 18 constitutes a worse prognosis for the development and progression of CIN than infection of other types.

These lesions have a much higher rate of progression to invasive carcinoma and for this reason warrant treatment. Ablation (cryotherapy or laser vaporization) may be used for CIN 2 and 3 lesions if the lesion is not suspected to be invasive by colposcopic criteria, is confined to the ectocervix, the colposcopy is satisfactory and no portion of the lesion involves the endocervical canal, the entire lesion is visualized and endocervical curettage is negative. This is rarely done today due to the ease of office excisional therapy and the reassurance of histologic verification of the final diagnosis.

Excisional therapy may be performed via a loop electrosurgical procedure, cold-knife conization, or laser conization. Patients with CIN 2 or CIN 3 with unsatisfactory colposcopy, extension of the lesion into the endocervical canal, suspicion of microinvasion, or endocervical curettage positive for CIN 2–3 should undergo an excisional procedure. Finally, patients with a 2-step or greater discrepancy (cytology HSIL and no CIN 2–3 found at colposcopy) between the Pap test and colposcopic findings should undergo excisional therapy. Among patients with CIN 2, 43% will regress in the absence of treatment, 35% will persist, and 22% progress to CIN 3 or invasive cervical cancer. Patients with CIN 3 progress to invasive carcinoma 14% of the time [38].
A cytologic diagnosis of ASC-H has a higher association with underlying CIN 2–3, ie, 24% to 66% depending on the series. The variability of identification of high-risk histology is based in large part on the inability to standardize ASC-H cytologic diagnosis between communities [19,20]. Given the wide variability in identifying high-risk disease among ASC-H cytology and the apparent high risk its existence confers, the patient with ASC-H is best served by referral to immediate colposcopy. Patients with ASC-H, HPV-positive ASC, and LSIL are all managed the same way. If no lesion is identified or biopsies are consistent with CIN 1 or less, then the patient may undergo surveillance with cytology at 6 and 12 months or HPV evaluation at 12 months with referral to repeat colposcopy with ASC or greater. Loop electrosurgical procedure or other excisional therapy is not appropriate initial therapy for patients with ASC-H, as this cytology does not meet the criteria for HSIL.

AGC comprises only 0.10% to 0.27% [39–43] of all Pap test results. The rarity of this lesion has precluded its evaluation in relation to HPV on any large scale. One study performed within the Kaiser system in Oregon looked at 137 cases of AGC referred to colposcopy. The investigators performed HC2 HPV tests on all subjects and found that all cases of AIS (5/137) and 92% of cases of CIN 2–3 (12/137) were positive for HPV. This resulted in a positive predictive value and sensitivity for combined AIS and CIN 2–3 of 41% and 94%, respectively [41]. A second study correlated the presence of high-risk HPV in patients with AGC Pap smears with histologic findings. They report a sensitivity for finding significant cervical pathology of 83%, a specificity range of 78% to 82%, a positive predictive value of 57% to 61%, and a negative predictive value of 91% to 95% [42]. While these studies may direct us toward a new role for HPV in the triage of AGC, larger, prospective trials that support this use are required and currently ongoing by the National Cancer Institute–funded Gynecologic Oncology Group. Current recommendations from the American Society for Colposcopy and Cervical Pathology are referral for colposcopically directed biopsy and endocervical sampling and, in addition, women older than 35 years or with abnormal bleeding should undergo endometrial biopsy. Many women will be recommended to undergo cervical excisional procedures should no etiologic lesion be identified and review of cytology is concerning for an endocervical neoplastic process [44]. Many experts are currently using a negative HPV test for reassurance, allowing young nulliparous women to avoid an excisional cervical procedure, and following the patient every 6 months (Figure 4).

**Case Conclusion**

The patient returns to clinic for follow-up after her colposcopy. Her physician discusses the results of her biopsy and explains the current standard of care for management. The patient voices understanding that she will need to be seen for a repeat Pap test in 6 months and based on that result would either be referred back to colposcopy (should her Pap test reveal ASC or greater) or...
be followed with another repeat Pap test in 6 months if her results are normal. She receives counseling as to the etiology of her abnormal Pap test and understands that she cannot return to yearly screening until she has had 3 consecutively normal Pap tests, each approximately 6 months apart. After listening to the discussion of her results and recommended follow-up, the patient asks her physician about “that vaccine I heard about on TV that is supposed to cure HPV.” She wants to know if she can get vaccinated and avoid undergoing surveillance Pap tests and cytology.

The HPV Vaccine
Among sexually active women, the prevalence of HPV infection is between 26% and 64%, with adolescents comprising the population with the highest baseline prevalence [45,46]. The prevalence of HPV infection decreases after the age of 30, but persistent infection, especially with HPV 16, places these patients at high risk for CIN 3 or cancer [47]. HPV infection and its sequelae, both medical and financial, present an important public health issue. The ability to prevent or cure HPV infection would be an important step toward eliminating cervical dysplasia and cancer.

There have been 3 major studies evaluating the use of an HPV vaccine. The first was a randomized, double-blind study of 2392 women aged 16 to 23 years who were HPV-negative upon study entry. They were given either an HPV 16 virus particle vaccine or placebo and followed for a median of 17.4 months with an endpoint of persistent HPV 16 over 2 or more visits. The incidence of persistent disease was 0 per 100 woman-years at risk in the vaccine group and 3.8 per 100 woman-years in the placebo group [48]. The second trial evaluated a bivalent vaccine against HPV 16 and 18 in 1113 women randomly assigned to placebo or active vaccine. This study found the vaccine to be 95% effective at preventing persistent disease and 92% effective at preventing cytologic abnormalities [49]. The largest and most recent trial was a study of 12,167 women aged 16 to 26 years who tested negative for both HPV 16 and 18 on study entry. These women were randomized to receive either placebo or a vaccine against HPV 16 and 18. Patients were then followed over an average of 2 years. None of the patients who received the complete vaccine cycle (3 doses over 6 months) contracted HPV 16 or 18 [23].

While these results are exciting from a public health standpoint, 2 facts must be emphasized. First, these trials are directed against primary prevention, so this vaccine will be marked as a childhood immunization. Efficacy depends on immunization prior to first sexual activity and potential exposure to HPV. Second, these vaccines have not yet demonstrated efficacy for elimination of already acquired HPV infection or cytologic abnormality, although this is a future direction for research. HPV vaccines are not currently a therapeutic option for already infected patients.

SUMMARY
The most effective program for cervical cancer prevention would appropriately identify women at risk and initiate screening at a time interval that precedes disease onset but not so early as to incur undue patient inconvenience. Further, we would have tests that had a high sensitivity for identifying abnormal cytology, with a low false-positive rate.

In terms of screening initiation, current recommendations are to begin Pap tests after 3 years of vaginal intercourse and no later than age 21. Screening should continue yearly until age 30. The use of cytology and simultaneous HPV testing is not recommended for women younger than age 30 secondary to the high prevalence of HPV in this population. For women age 30 years and older, combined Pap and HPV testing are the preferred screening modality of both the American College of Obstetricians and Gynecologists as well as the American Society for Colposcopy and Cervical Pathology. Annual cytology is also an acceptable option with referral to colposcopy for 2 consecutive ASC results, ASC with positive HPV, ASC-H, AGC, LSIIL, and HSIL. If both the cytology and HPV are negative for abnormalities, screening may be performed at 3-year intervals. If the patient has normal cytology but a positive HPV test, repeat the cytology and HPV test in 6 to 12 months and triage to colposcopy if either are abnormal.

For all age-groups, ASC with positive HPV, ASC-H, LSIIL, and HSIL should be referred for colposcopy and directed biopsy. Patients with AGC should be referred for colposcopy with endocervical curettage and endometrial biopsy for women older than 35 years or if any abnormal bleeding is described.

Patients with histologically demonstrated CIN 1 should be offered repeat cytology at 6 and 12 months or HPV testing at 12 months, with referral to colposcopy for ASC or greater or positive HPV test. Patients for whom conservative management leads to unacceptable anxiety may be offered excisional or ablative therapy, but this has not proven to be a safer alternative to conservative follow-up.

Management of CIN 2 may be excisional or ablative. Ablation may only be used if the lesion is visualized in its entirety, does not involve the endocervical canal, and a negative endocervical curettage has been obtained. CIN 3 lesions are usually treated via excisional modalities, such as loop electrosurgical excisional procedure or cold knife conization. Follow-up after ablation or excision involves repeat Pap test at 6 month intervals or a HPV test at 6 months, with referral to repeat colposcopy for ASC or greater or positive HPV test.

In all instances, the treatment of women with abnormal Pap tests should involve full disclosure of the etiology and natural history of HPV infection and its relation to smoking and to sexual behavior. An informed patient is more apt to
participate and cooperate in the management of the abnormal Pap test, which often involves long-term surveillance and requires a strong relationship between provider and patient. Finally, HPV vaccination has demonstrated efficacy only for primary prevention of HPV acquisition and is not currently a therapeutic option for women already infected with high-risk HPV. While the ability to prevent disease initiation is an exciting prospect from a public health perspective, more research needs to be done before HPV vaccines will be available as a secondary prevention measure.

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References

CME EVALUATION: The Abnormal Pap Test: Evaluation, Treatment, and Monitoring

DIRECTIONS: Each of the questions below is followed by several possible answers. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. When should cervical cancer screening be initiated?
   (A) If infection with human papillomavirus (HPV) is suspected
   (B) Within 5 years of becoming sexually active
   (C) 3 years after beginning to have vaginal intercourse but no later than age 21 years
   (D) At age 25 years

2. The majority of women found to have a histologic diagnosis of cervical intraepithelial neoplasia (CIN) 2 or 3 will have a preceding Pap result of atypical squamous cells (ASC).
   (A) True
   (B) False

3. For patients with ASC on cervical cytology, the most appropriate follow-up evaluation is
   (A) Immediate referral to colposcopy
   (B) Reflex evaluation for the presence of high-risk HPV and referral to colposcopy if present
   (C) Repeat cytology within 6 months and referral to colposcopy if second abnormal cytology result
   (D) All of the above are appropriate depending on available resources

4. For a patient with CIN 1 on biopsy, which of the following management options is recommended?
   (A) Referral for excisional therapy
   (B) Repeat cytology in 6 months
   (C) Repeat cytology in 12 months
   (D) Repeat testing for HPV in 12 months
   (E) B & D

5. For patients with atypical glandular cells on cervical cytology, follow-up evaluation should include:
   (A) Immediate referral to colposcopy and endometrial biopsy
   (B) Repeat cytology in 6 months
   (C) Reflex testing for high-risk HPV
   (D) None of the above
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