Evaluation
and
Management
of Abnormal Pap Smears

A PRIMER FOR
PRIMARY CARE PROVIDERS

Prepared by
The Sage Screening Program
Health Promotion and Chronic Disease Division

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# Table of Contents

## INTRODUCTION

Cervical Cancer Screening

- **RATIONALE FOR SCREENING** ............................................................................................................................ 5
- **RISK FACTORS** ................................................................................................................................................... 5
  - Human Papillomavirus (HPV) .............................................................................................................................. 5
  - HVP Vaccines ...................................................................................................................................................... 6
- **SCREENING METHODS** ....................................................................................................................................... 7
  - Conventional Pap Smear Technique ................................................................................................................... 7
  - Liquid-based Cytology .......................................................................................................................................... 8
  - Automated Reading ........................................................................................................................................... 9
  - HPV Testing ...................................................................................................................................................... 9

## Screening, Diagnosis and Treatment

- **SCREENING GUIDELINES** .................................................................................................................................. 11
- **DIAGNOSTIC PROCEDURES** ........................................................................................................................... 11
  - Colposcopy ....................................................................................................................................................... 12
  - Diagnosis and Treatment during Pregnancy ...................................................................................................... 12
- **EVALUATION OF SPECIFIC SCREENING ABNORMALITIES** ........................................................................... 13
  - Specimen Adequacy .......................................................................................................................................... 13
  - Negative for Intraepithelial Lesion or Malignancy ............................................................................................ 13
  - Atypical Squamous Cells (ASC) .......................................................................................................................... 13
    - Undetermined Significance (ASC-US) .................................................................................................................. 14
    - Cannot Exclude HSIL (ASC-H) .......................................................................................................................... 14
  - Low-Grade Squamous Intraepithelial Lesion (LSIL) ........................................................................................... 14
  - High-Grade Squamous Intraepithelial Lesion (HSIL) .......................................................................................... 15
  - Atypical Glandular Cells (ACG, AIS) ................................................................................................................... 16

## Treatment Modalities

- **Ablative Techniques:** ......................................................................................................................................... 17
  - Cryotherapy ....................................................................................................................................................... 17
  - Laser ................................................................................................................................................................. 18
- **Excisional Techniques:** ...................................................................................................................................... 18
  - Loop Electrocautery Excision Procedure (LEEP) ............................................................................................. 18
  - Conization (Laser; Cold Knife) ........................................................................................................................ 18
  - Hysterectomy .................................................................................................................................................... 19

## Management of Biopsy-Confirmed Cervical Intraepithelial Neoplasia (CIN)

- **Low-Grade Lesions** ......................................................................................................................................... 19
  - CIN I (mild dysplasia, HPV) .............................................................................................................................. 19
- **High-Grade Lesions** ......................................................................................................................................... 20
  - CIN 2 (moderate dysplasia), CIN 3/CIS (severe dysplasia/carcinoma-in-situ) .................................................... 20

## Appendix

- Pap Smear Terminology: Bethesda System .............................................................................................................. 25
- Sage Program Standards for the Initial Management of an Abnormal Screening Pap ............................................. 26
- Algorithm ............................................................................................................................................................. 27
- Glossary ............................................................................................................................................................... 28
- References ........................................................................................................................................................... 29
Preface

This Primer presents the current recommended guidelines for the evaluation and management of abnormal Pap smears. These guidelines were developed by the American Society for Colposcopy and Cervical Pathology (ASCCP) and printed in JAMA, April 24, 2002. The purpose of this Primer is to have a quick and easy reference for health care providers and other health professionals who care for women with abnormal Pap smears. Through the use of this Primer, we hope to increase awareness of these guidelines among health care professionals.

Nearly 60 years ago, Dr. George Papanicolaou introduced the concept of sampling a small number of cervical cells and examining them under a microscope to yield information that could lead to the diagnosis of cancer. Widespread use of the Pap smear has identified women at risk for cancer and has led to a 75 percent reduction in cervical cancer deaths in the United States. This has remained a remarkable record in the history of public health. This Primer includes information on conventional Pap smears, liquid-based cytology, the role of human papillomavirus (HPV) testing in triaging of ASC-US Pap results, and information on studies of HPV vaccines. Hopefully, these newer techniques will also serve to reduce the numbers of cervical cancer deaths.

Our goal must be to continue to reduce morbidity and mortality from cervical cancer. Improving the early detection of precancerous cervical lesions and assuring appropriate treatment will make achieving this goal a possibility. The most important way to improve the rates of early detection is for every woman to have regular Pap smears. Our hope is that this Primer will make a significant contribution to improving the health of all Minnesota women.

The Sage Screening Program
Minnesota Department of Health
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INTRODUCTION

Since the introduction of the Papanicolaou smear nearly 60 years ago, cervical cancer prevention and early detection has become one of the significant success stories in cancer control. In 1950, cervical cancer was the most common neoplasm diagnosed in women. Since then, deaths from cervical cancer have been reduced by nearly 75 percent. In 2006, it is estimated 9,710 women in the United States will be diagnosed with invasive cervical cancer and 3,700 will die from this disease. In Minnesota, between 1999-2003, about 175 women were diagnosed with invasive cervical cancer and 40 women died of this disease each year. During this same time frame, 1999-2003, women of color and American Indians were twice as likely to be diagnosed with invasive cervical cancer and three times more likely to die of this disease than non-Hispanic white women in Minnesota.

Early detection of high-grade lesions is the key to reducing morbidity and mortality from cervical cancer. Of women newly diagnosed with cervical cancer, 50 percent have never had a Pap smear, and another 10 percent have not had a Pap smear within the previous 5 years. Although precancerous cervical lesions are more commonly found in younger women, 44 percent of invasive cervical cancers are diagnosed in women over age 50. Thirty-seven percent of cervical cancer deaths occur in women age 65 and older (Seer data 1997-2002). In Minnesota, 40 percent of the invasive cervical cancer cases are diagnosed in women who are 50 years or older and 40 percent of cervical cancer deaths occur in women 65 years or older.

Histologically, 80 to 90 percent of cervical cancers are of squamous origin arising from rapidly dividing cells in the transformation zone near the squamo-columnar junction (SCJ). Adenocarcinoma arises from the mucous-producing cells of the endocervix and represents 10 to 20 percent of invasive cervical cancers. Adenocarcinoma poses a greater challenge to early diagnosis and treatment and represents a growing proportion of cancers, especially in women younger than 35 years of age.
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CERVICAL CANCER SCREENING

RATIONALE FOR SCREENING

The primary goal of cervical cancer screening is the early detection and treatment of precancerous lesions to prevent invasive cervical cancer. The majority of women with low-grade squamous intraepithelial lesions (LSIL) spontaneously regress without treatment. In the ALTS study, 83 percent of women referred for evaluation of LSIL tested positive for high-risk human papillomavirus (HPV) types. The progression of low-grade lesions (CIN 1/mild dysplasia) to high-grade (CIN 2–3/moderate and severe dysplasia/carcinoma-in-situ) occurs slowly. It takes an average of 9 years to progress from low-to high-grade lesions and from 3 months to 2 years for progression from high-grade lesions to invasive cancer. Currently studies are underway on the cellular immune system’s role in the progression from premalignancy to malignancy. As this becomes better understood, the parameters for long-term follow-up may become more defined.

RISK FACTORS

Human Papillomavirus (HPV)

There are over 100 known types of human papillomavirus (HPV), but only about 30-40 types infect the genital tract. Low-risk types or nononcogenic types of HPV include 6, 11, 40, 42, 43, 44, and 54. These are not associated with the development of cervical cancers. Type 6 and 11 are most commonly associated with external genital warts. Fifteen to twenty of the HPV types which infect the genital tract are high-risk or oncogenic types. Infection with high-risk oncogenic HPV types is the most significant risk factor in the development of precancerous lesions and the development of cervical cancer. Oncogenic HPV types may infect the cervix without causing symptoms. Oncogenic (high-risk) types 16 and 18 account for about two thirds of all cervical cancers. The next five most prevalent types (31, 33, 45, 52, 58) account for an additional 18 percent of cases. Other oncogenic HPV types include 35, 39, 51, and 56.
The human papillomavirus is primarily transmitted through genital contact. According to Centers for Disease Control and Prevention (CDC) estimates, at least 50 percent of sexually active men and women will acquire a genital HPV infection at some point in their lives. By age 50, at least 80 percent of women will have acquired a genital HPV infection. The peak prevalence of HPV infection occurs in women between the ages of 20-24 years and for men the peak prevalence rate occurs between 25-29 years. It is the most common sexually transmitted virus in the world.

Risk factors for acquiring an HPV infection include early age of first sexual intercourse, lifetime number of sexual partners and partners who have had multiple partners, uncircumcised male partner, smoking, and long-term use of oral contraceptives. Most HPV infections clear within 2 years presumably due to an effective immune response. A persistent infection with high-risk types of HPV is crucial for development of cervical precancerous lesions and cancer. Persistent HPV infection occurs when the same HPV type is detected two or more times over several months to 1 year. Currently, there is no cure for HPV. Early detection and removal of precancerous lesions is the only treatment. Yet, many women do not have Pap tests regularly. In one national health survey, a fifth of women aged 18 to 64 had not had a Pap test in the past three years.

**HPV Vaccines**

Currently there are two vaccines against HPV. Cervarix, a vaccine produced by GlaxoSmithKline, may be submitted for Federal Drug Administration (FDA) approval later this year. Gardasil has been approved and will be available fall 2006. Both vaccines would be given through a series of three injections over a six-month period. Gardasil protects against four types of HPV, two that cause most cervical cancers (types 16 and 18) and two that cause most genital warts (types 6, and 11). The Cervarix vaccine protects against HPV 16 and 18 that are responsible for the majority of cervical cancers. Both vaccines have been very effective in preventing infections from the targeted types of HPV and are 100 percent effective in preventing conditions caused by these HPV types. Studies so far have shown these vaccines to be effective anywhere from 2.5 to 4.5 years. Long-term effectiveness may not be known until after the vaccines are in use. These vaccines will not eliminate the need for Pap tests since they do not protect against all cancer-causing types of HPV, but they may decrease how often Pap smears are required. And the vaccines will not eliminate existing infections. Once these vaccines have FDA approval, they will be powerful additions to the disease prevention strategies in the fight to eliminate all deaths from cervical cancer.
SCREENING METHODS

The Pap smear has contributed greatly to the early detection of cervical cancer and has been credited with reducing cervical cancer mortality by 75 percent. There are limitations to its use. A technology assessment published in January 1999 by the Agency for Health Care Policy and Research (AHCPR) estimated the sensitivity of the conventional Pap smear to be 51 percent with a specificity of 98 percent. Despite these limitations, the conventional Pap smear remains the cornerstone of successful cervical cancer screening programs. Recent advances in slide preparation techniques and computer-assisted readings show promise for improving the accuracy of cervical cytology.

Limitations of the conventional Pap smears have led to the development of new technologies, most notably thin-layer and liquid-based screening. These methods are aimed at reducing the false-positive rate of conventional Pap smears and improving the quality of the sample since the specimen is placed directly into a liquid fixative providing immediate fixation. Sensitivity of the thin-layer Pap test was assessed in a study of 4,075 women and found to be 61 percent for detection of ≥ ASCUS after referral for colposcopy. In a review of 472,743 Pap smears, malignant cytology was identified in 36 smears obtained from liquid-based methods and in 32 by conventional Paps. False-positive results were obtained in 8.4 percent of liquid-based specimens and 12.5 percent of conventional specimens. Whether or not the thin-layer or liquid-based screening will reduce morbidity and mortality rates for cervical cancer remains undetermined.

Conventional Pap Smear Technique

Cytological abnormalities and severe dysplasia are more easily detected when endocervical cells are present in the specimen. Cervical sampling should be done by gently scraping the ectocervix with a curved spatula followed by the insertion and rotation of an endocervical brush. Tools used include a speculum, slides, spatula, endocervical brush, and fixative. The use of a cytobrush and an extended tip spatula maximizes the harvesting of endocervical cells and the detection of abnormalities. A broom should not be used for a conventional Pap smear as it does not collect an adequate sample. Warm water should be the only lubricant used on the speculum. The use of lubricating jelly can obscure cellular detail. The speculum should be the appropriate size for the patient’s comfort but must allow for adequate visualization of the vaginal walls and cervix. Since the vast majority of cancers arise from the transformation zone near squamo-columnar junction (SCJ), it is essential to sample from this area. (GRAPHIC 1)

In reproductive-age women, the squamo-columnar junction (SCJ) is commonly seen on
the ectocervix near the cervical os. In postmenopausal women, the SCJ presents higher in the endocervical canal. This may preclude direct visualization of the SCJ in these women (GRAPHIC 2). When performing a conventional Pap smear, the ectocervical

**Liquid-Based Cytology**

Liquid-based cytology uses a cervical brush/spatula or broom to collect the specimen which provides almost twice as many epithelial cells as other collection devices. The

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**GRAPHIC 1: The Squamo-Columnar Junction (SCJ)**

**GRAPHIC 2: Common Changes in the Squamo-Columnar Junction (SCJ) as the Woman Ages**

sample is collected first using a cervical spatula. The spatula is smeared over the slide. Then a brush is inserted into the endocervical canal and rotated no more than 1 to 2 revolutions. The brush is then rolled over the slide. Fixation of the slide occurs immediately to avoid drying. Cells are immediately rinsed from the collection device into a vial of preservative solution thereby better preserving cell structure. The vial is sent to the laboratory where a processor disperses the cell sample and spreads a monolayer on a slide ensuring a representative
sample of cells. This technique can be accompanied by a method of automated interpretation. The greater efficacy of liquid-based cytology can be attributed to the inclusion of the entire sample of cells in the collection fluid enabling the preparation of a slide more representative of all the cells collected. In addition, this technique eliminates air-drying artifact and the obscuring effects of blood, inflammation, and overlapping of cells. The fluid remaining after the slide preparation can also be used for HPV testing.

**Automated Reading**

Automated reading systems can be used for initial screening and/or for re-screening performed for quality control programs in cytology laboratories. A high-resolution digital scanner with a high-speed video microscope provides images taken from the laboratory slide. The slide is ranked on a scale from 0 (most likely to be normal) to 1.0 (more likely to contain abnormal cells). This type of system has been shown to improve detection of cytologic abnormalities and to decrease diagnostic variability. In independent trials, the accuracy of the automated reading was confirmed by biopsy data.

**HPV Testing**

As part of the 2001 consensus guidelines, high-risk HPV testing (HR HPV) is one of the three recommended management strategies for women with an ASC-US Pap report. If the HPV test is negative, she will not need a Pap smear for one year. If a women tests positive for HPV, she is immediately referred for colposcopy. If the colposcopy is negative (no CIN is found), she will need to return for repeat Pap tests at 6-12 month intervals or repeat HR HPV testing at 12 months.

When liquid-based cytology is used or when co-collection for HR HPV testing can be done at the initial screening visit, reflex HR HPV testing can be done if an ASC-US result is obtained on the Pap. These methods eliminate the need for the women to return for an additional exam. Reflex HR HPV testing is the preferred approach and is a cost-effective method to identify and triage women with an ASC-US result.

HR HPV testing is also a recommended follow-up for many cytological and histological cervical abnormalities. HR HPV testing can be helpful in determining further follow-up.
SCREENING, DIAGNOSIS, AND TREATMENT

SCREENING GUIDELINES

Pap smears should begin 3 years after a woman becomes sexually active or reaches 21 years of age, whichever comes first. Ideally an appointment with a clinic providing reproductive health services should occur before sexual activity begins. Screening for cervical cancer should occur annually for woman less than 30 years of age. Taking into account the risk status of the woman, after 3 annual, consecutive, normal Pap smears and no dysplasia in the last five years, screening may be done less often at the discretion of the health care provider and the patient. A woman, after discussion with her health care provider, may discontinue Pap screening between 65 and 70 years of age provided she has had adequate recent screening with normal Pap smears and is not otherwise at high risk for cervical cancer. **Within three years of having a new sexual partner, a woman over age 65 should resume cervical cancer screening.**

Women of any age who are immunosuppressed, are infected with human immunodeficiency virus (HIV) or were exposed *in utero* to diethylstilbestrol (DES) may require more frequent screening. Women having a total hysterectomy with removal of the cervix for benign conditions no longer require Pap smears. Women having a hysterectomy for benign disease and a portion of the cervix remains should continue screening at the same intervals as before the hysterectomy. When a hysterectomy is done on a woman with a history of cervical dysplasia, vaginal or vulvar dysplasia, or cervical cancer, the health care provider should individualize the follow-up schedule. When a woman has had a hysterectomy with associated multiple-site disease, close individualized follow-up is essential postoperatively.

DIAGNOSTIC PROCEDURES

The Pap smear is a screening test used for the early detection and treatment of precancerous lesions to prevent invasive cervical cancer. It is not a diagnostic test. An abnormal Pap smear warrants further diagnostic evaluation and histologic confirmation of the cytologic finding. Colposcopy is the diagnostic test of choice. Additional workup is indicated if colposcopy fails to make a definitive diagnosis. Failure to adequately follow-up a Pap smear abnormality
represents a missed opportunity for cancer prevention and early detection, and becomes an area for potential litigation.

**Colposcopy**

Colposcopy with biopsy with or without endocervical curettage (ECC) is usually the first step in the evaluation of an abnormal Pap smear. Colposcopy provides a magnified view of the cervix, vagina, and vulva. Through the use of colposcopy, features that predict neoplasia including specific tissue characteristics and vascular patterns can be detected. After the application of a 3 to 5 percent acetic-acid solution for a minimum of 3 minutes, the cervix and upper vagina are evaluated for aceto-white areas and areas of mosaicism and punctuation. The most abnormal-appearing areas should be biopsied, with particular attention to those nearest the SCJ, where the most severe portions of dysplastic lesions tend to be located. High-grade abnormalities appear as thick, sharply demarcated aceto-white lesions, often with coarse vascular markings. Invasive cervical cancer has varying appearances and may be nodular, papillary, ulcerated, or friable with hemorrhage. If no abnormal areas are seen to biopsy, endocervical sampling should be performed.

Practitioners with adequate training and experience to thoroughly and effectively evaluate the cervix, vagina, and vulva should perform colposcopy. The colposcopist must be able to interpret the findings correctly and perform biopsies from the most suspicious areas. Most examinations will include cervical biopsies and endocervical sampling. There are occasions when further evaluation is deemed necessary by the colposcopist. These include inadequate visualization of the SCJ, incomplete visualization of cervical lesions, and a lack of correlation between cytologic abnormality and visual or biopsy findings. This may necessitate Loop Electrocautery Excision Procedure (LEEP), laser, or cold knife conization.

**Diagnosis and Treatment during Pregnancy**

Pregnant women with a high-grade squamous intraepithelial lesion needing colposcopy should be referred and followed by either an obstetrician-gynecologist or a gynecological oncologist with experience in the colposcopic changes occurring in pregnancy. Endocervical sampling is not acceptable in pregnant women if the colposcopy is unsatisfactory. A repeat exam should be done in 6-12 weeks because the results may become satisfactory as pregnancy progresses. If there is no invasive disease, lesions should be followed with additional colposcopic and cytologic exams. Biopsy should only be done if the lesion worsens or if invasive cancer is identified. Treatment is not recommended unless invasive disease is suspected.
**EVALUATION OF SPECIFIC SCREENING ABNORMALITIES**

**Specimen Adequacy**

This is an important quality assurance component of the Bethesda System. It categorizes specimens as: Satisfactory for evaluation (with a note for presence/absence of endocervical/ transformation zone components) or Unsatisfactory for evaluation (specify reason). The unsatisfactory category distinguishes between rejected/not processed specimens (i.e., unlabelled specimens) and those processed but determined to be unsatisfactory following microscopic examination. Specimens with more than 75 percent of epithelial cells obscured are “unsatisfactory.”

**Negative for Intraepithelial Lesion or Malignancy**

This term is used for specimens showing no epithelial abnormalities. Organisms or other non-neoplastic findings may be reported also in this section. (See page 25 for partial list of organisms or non-neoplastic findings that may be included here.)

**Other**—Endometrial cells are noted if the woman is 40 years of age or older, regardless of the date of the last menstrual period, because menstrual/menopausal status, use of hormone therapy and other clinical risk factors are often unknown. Findings of endometrial cells are usually benign, but if the finding is not associated with menses or occurs after menopause, it may indicate a risk for an endometrial abnormality. In menstruating women, endometrial cells generally are no longer present seven days after the first day of the last menstrual period. In postmenopausal women who are not on hormone replacement therapy, the presence of endometrial cells in a pap smear may signify underlying endometrial cancer. Remember cervical cytology is primarily a screening test of squamous epithelial lesions and cancer. It is not reliable as a test of the detection of endometrial lesions and should not be used as such.

**Atypical Squamous Cells (ASC)**

The 2001 Bethesda System divided ASC into two reporting categories: ASC-US (Atypical Squamous Cells of Undetermined Significance) and ASC-H (Atypical Squamous Cells cannot exclude HSIL). All ASC are considered suggestive of squamous intraepithelial lesions (SIL). More than 2 million women receive an equivocal cervical cytologic diagnosis each year. Approximately 5 percent to 10 percent of these equivocal diagnoses are ASC-H. A woman with a result of ASC-US has a 5-17 percent chance of having biopsied confirmed CIN 2 or CIN 3 while a woman with ASC-H has a 23-94 percent chance of having CIN 2 or CIN 3 confirmed on biopsy. Postmenopausal women appear to have a lower risk for CIN 2 or 3 than premenopausal women.
ASC-US—indicates a result of undetermined significance and can be managed one of three ways:

1. **Repeat Pap testing** - (either conventional or liquid-based) at 4-6 month intervals until 2 consecutive results of “negative for intraepithelial lesion or malignancy” are obtained. After two normal findings, the Pap smear may be repeated in one year. If any of the Pap smears are abnormal, a colposcopy needs to be done.

2. **High-risk HPV DNA (HR HPV) testing** - if the woman tests positive, she is referred for colposcopy. If the woman tests negative, no colposcopy is needed and she can return for a Pap smear in 12 months.

3. **Colposcopy** - if no CIN (Cervical Intraepithelial Neoplasia) is found, the woman can return for a Pap smear in 12 months if HR HPV is negative or unknown. If the woman is HR HPV positive, she should return for repeat Pap smears at 6 and 12 months or HR HPV testing in 12 months.

4. If the woman is postmenopausal, has clinical or cytological evidence of atrophy, and no contraindications to using estrogen, a course of intravaginal estrogen can be tried followed by a repeat Pap test one week after completing the estrogen therapy.

ASC-H—indicates a result, which cannot exclude HSIL. These findings denote a result of atypical cells at higher-risk for association with a precancerous lesion.

1. Refer immediately for colposcopy—if no lesion is identified, the cytology, colposcopy, and histology results should be reviewed. If the interpretation of ASC-H is upheld, the woman should be followed at 6 and 12 months with a Pap test or have HR HPV testing at 12 months.

**Low-Grade Squamous Intraepithelial Lesion (LSIL)**

LSIL refers to a cervical cancer precursor. It is a Pap smear result with cellular changes of HPV (transient infection) or mild dysplasia (CIN 1). **Women with an LSIL finding need to be sent to immediate colposcopy with biopsy and possibly endocervical sampling to rule out any moderate or severe dysplasia.** While over 60 percent of LSIL Pap smears may revert to normal without treatment, some women with an LSIL Pap smear finding will harbor a significant precancerous lesion. The ALTS study showed that approximately 85 percent to 87 percent of patients with LSIL tested positive for HPV, which renders the HPV test an ineffective triage screening method. When a colposcopy was done, 25 percent of LSIL patients were found to have CIN 2 or CIN 3. The remaining 75 percent do not exhibit dysplasia. However
the ALTS study also showed the previous strategy of two follow-up Pap tests still leads to colposcopy in 85 percent of cases.

1. If the colposcopy is satisfactory and the biopsy with or without endocervical sampling fails to confirm CIN, Pap smears should be repeated at 6 and 12 months with referral back to colposcopy if cytology results show ASC-US or greater or HR HPV testing can be done at 12 months with referral for colposcopy if the HPV test is positive.

2. If the colposcopy is unsatisfactory and no CIN is identified even with the use of endocervical sampling, repeat Pap smears should be done at 6 and 12 months with referral back to colposcopy if cytology results show ASC-US or greater or HR HPV testing can be done at 12 months with referral for colposcopy if the HPV test is positive.

3. In postmenopausal women, follow-up without an initial colposcopy is acceptable if one of these protocols is followed:
   a. Repeat cytology at 6 and 12 months with referral for colposcopy if a result is ASC-US or greater.
   b. HR HPV testing – if result is negative, repeat Pap at 12 months. If result is positive, do a colposcopy.
   c. If clinical or cytological evidence of atrophy, and no contraindications for intravaginal estrogen therapy, a course of intravaginal estrogen therapy can be tried and a repeat Pap smear one week after completion of therapy.

4. In adolescent women, either repeat cytology at 6 and 12 months or HR HPV testing at 12 months is an acceptable alternative to immediate colposcopy for ASC-US, ASC-H, or LSIL pap smears.

**High-Grade Squamous Intraepithelial Lesion (HSIL)**

HSIL refers to cervical cancer precursors as well. These Pap smear results show cellular changes of moderate (CIN 2) to severe dysplasia (CIN 3) or carcinoma-in-situ (CIS). Up to 95 percent of HSIL Pap smears have high-grade lesions on biopsy requiring treatment. **These women need to be referred for colposcopy with biopsy and endocervical sampling.** The greater the extent of HSIL, the greater the likelihood of micro-invasive malignancy. Pregnant women with HSIL require evaluation by an obstetrician-gynecologist or a gynecological oncologist. If in the opinion of the colposcopist, HSIL is the most severe disease present, treatment may be deferred until after delivery.
1. If the colposcopy is satisfactory, but no lesion is identified or only biopsy-confirmed CIN 1 is identified, the cytology, colposcopy, and histology results should be reviewed. If the cytology result is upheld or review is not possible, the preferred follow-up is a diagnostic excisional procedure.

2. If the colposcopy is unsatisfactory and no lesion is identified, the cytology, colposcopy, and histology results should be reviewed. If the interpretation of HSIL is upheld, review is not possible, or biopsy-confirmed CIN 1 is identified, a diagnostic excisional procedure (LEEP) is recommended in non-pregnant women.

3. “See and Treat” is also acceptable. When colposcopy suggests a high-grade lesion, initial evaluation using a diagnostic excisional procedure is also an acceptable option.

Atypical Glandular Cells (AGC)

AGC refers to Pap smear results showing cellular changes in the glandular cells. AGC is subdivided into three categories.

Atypical
- Endocervical cells NOS
- Endometrial cells NOS
- Glandular cells NOS

Endocervical adenocarcinoma in situ (AIS)

Adenocarcinoma

Most women with this result do not have cancer. Studies have shown much higher rates of severe underlying pathologic conditions such as high-risk CIN, AIS, endocervical and endometrial cancer in women with AGC results than in those with either ASC or LSIL. Studies have shown 9 to 54 percent of women with AGC have biopsy confirmed CIN, up to 8 percent have AIS, and < 1 to 9 percent have invasive cervical cancer. The increased risk for cervical neoplasia varies with the AGC sub-classifications. Biopsy confirmed CIN 2 or 3, AIS, or invasive cancer has been found in 9 to 41 percent of women with AGC NOS compared to 27 to 96 percent or women with AGC “favor neoplasia.” Women with a cytologic report of AIS have a high risk of having AIS (48 to 69 percent) or invasive cervical cancer (38 percent).

Colposcopy with endocervical sampling is recommended for all categories of AGC with the exception of women with atypical endometrial cells who should initially be evaluated with endometrial sampling.

Endometrial sampling is also recommended for any women older than 35 years who had an AGC Pap or younger women who have
unexplained vaginal bleeding. **Colposcopy with endocervical sampling is also recommended for all AIS results.**

Colposcopy, cytology, and endocervical sampling have a poor sensitivity for detecting glandular abnormalities. Women with AGC who do not have a cervical lesion detected at the initial workup continue to be at increased risk. Because the risk varies with the subclassification of AGC, the recommended follow-up varies.

If the invasive disease is not identified during the initial workup:

1. Women with AGC “favor neoplasia” or AIS should have an excisional diagnostic procedure done. The preferred procedure is cold-knife conization.

2. Women with AGC NOS should be followed by having repeat Pap smears done at 4-6 months intervals until 4 consecutive “negative for intraepithelial lesions or malignancy” results are obtained. If a result of ASC or LSIL is obtained on any of the follow-up Paps, a repeat colposcopy or referral to an “expert” is recommended. If HSIL or AGC is found on any of the follow-up Paps, a diagnostic excisional procedure may be performed or the woman can be referred to an expert.

**TREATMENT MODALITIES**

Once a histologic diagnosis warranting treatment is established, the goal is to eradicate the source(s) of premalignancy completely. This usually involves ablation or excision of the transformation zone and other identified abnormalities.

**Ablative Techniques:**

**Cryotherapy**

Cryotherapy involves freezing the transformation zone by applying a metal probe cooled by a refrigerant such as nitrous oxide. While being done less often, this procedure is relatively inexpensive and uses simple, portable equipment. It generally causes mild discomfort with watery vaginal discharge occurring for 4 to 6 weeks. Complications may include cervical stenosis and recurrence of the neoplasia. Cure rates are on the order of 90 percent for small and low-grade lesions. Because adequate freezing is limited to a few millimeters of depth (the cellular “lethal zone”), cryotherapy is not appropriate for lesions that extend into the endocervical canal, for severe dysplasia/CIN 3, or for lesions in which abnormalities extend into the stroma and might escape the effects of freezing. It is critical that HSIL or early malignancy not be treated with cryotherapy since more significant disease can continue to grow beneath the mucosa and can be undetected by subsequent Pap smears or colposcopies.
Laser

Laser ablation involves the use of a carbon dioxide laser with the colposcope for improved visualization of the cervix. Compared with cryotherapy, an advantage of laser ablation is the depth and width of destruction can be controlled by direct visualization through the colposcope. During laser ablation, the cervical transformation zone is vaporized. Laser ablation is indicated for large lesions not covered by the cryoprobe, for an irregular cervix with scars and deep clefts, for instances where the disease has extended to the vagina, and for CIN lesions with extensive glandular involvement. Advantages of laser ablation include less post-treatment vaginal discharge and a shorter healing phase. However, laser ablation is more expensive and is performed in the operating room. Laser ablation is contraindicated for cervical lesions obviously suspicious for invasive carcinoma.

Excisional Techniques:

Loop Electrocautery Excision Procedure (LEEP)

Loop Electrocautery Excision Procedure (LEEP) is used as a therapeutic procedure for the treatment of all grades of CIN as well as a diagnostic procedure when the colposcopic exam has been unsatisfactory or when there is uncertainty regarding the presence of invasive cancer. This procedure is also referred to as LLETZ (Large Loop Excision of the Transformation Zone). LEEP uses a wire loop and electrical current to excise the transformation zone. It is an outpatient procedure performed under local anesthesia. It is an appropriate procedure for all grades of dysplasia/CIN. LEEP is not appropriate if invasive cancer is suspected. Varying sizes of loops allow for both small and large excisional biopsies. Larger biopsies or two-step “top hat” procedures are considered by many to be equivalent to a “LEEP conization” procedure. The pathologic specimen is sent for histologic diagnosis. Although LEEP provides both histologic diagnosis and treatment, the practice of performing the initial colposcopy and a LEEP during one visit is discouraged. This so called “see and treat” LEEP bypasses the step of colposcopic biopsy and may lead to overly aggressive treatment based on colposcopic appearance alone.

Complications of LEEP may include infection, hemorrhage, and accidental electrical damage to other tissues. However, most women have no complications and experience only a light, bloody discharge for 5 to 10 days post-therapy followed by a watery discharge for up to two months.

Conization (Laser; Cold Knife)

Conization can be used for both diagnosis and treatment. It involves the removal of a cone of tissue from the cervix and/or endocervical canal. The size of the cone is based on the level of suspicion for significant underlying disease. This is the procedure of choice when
colposcopy has been unsatisfactory or when less aggressive techniques have failed to diagnose the source of an abnormal Pap smear. As a treatment modality, conization may be used when other methods have failed to fully eradicate a significant abnormality. Conization is also an alternative to hysterectomy for women with micro-invasive cancer who wish to maintain childbearing ability. Conization can be performed by laser or by cold knife. Cold knife conization is preferred in treating glandular lesions. Complications in the cold knife conization may involve bleeding up to 2 weeks post-procedure, possible “silent” hematoma formation, pelvic cellulitis, or cervical incompetence.

**Hysterectomy**

With the widespread use of colposcopy and the development of new and improved excisional therapies, hysterectomy is seldom necessary to manage premalignant cervical disease. However, hysterectomy remains an acceptable management choice for women who have completed childbearing and who have recurrent high-grade squamous intraepithelial lesion (HSIL) smears. A hysterectomy is also indicated for AIS in most cases due to the difficulties in treating lesions in the endocervix and the multifocal nature of AIS. In addition, hysterectomy and cancer staging are the appropriate steps following a biopsy or conization procedure that confirms the presence of invasive cervical cancer. If a hysterectomy has been performed for cancer, postoperatively the woman should have a vaginal smear of the upper one-third of the vagina every 6 months for 2 years and then annually.

**MANAGEMENT OF BIOPSY-CONFIRMED CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)**

The recommended management described in this section follows the 2001 Consensus Guidelines for the management of women with cervical intraepithelial neoplasia. These guidelines are available on the ASCCP website, www.asccp.org or were published in the American Journal of Obstetrics and Gynecology, Vol. 189, Issue 1, Pg. 295-304 (July, 2003).

**Low-Grade Lesions**

**CIN 1 (mild dysplasia, HPV)**

Women with a histologic diagnosis of CIN 1 (mild dysplasia) do not necessarily need treatment. Most studies suggest at least 57 percent of these smears regress to normal, approximately 32 percent will persist, and 11 percent will progress to CIN 2 or CIN 3. The overall progression to invasive cervical cancer
The preferred follow-up for women with CIN 1 who had a satisfactory colposcopy is to follow them without treatment. Recommended follow-up is either repeat Pap tests at 6 and 12 months or HR HPV testing at 12 months. If any of the repeat Pap results are ASC or greater or the woman is HR HPV positive, a repeat colposcopy is recommended.

If the follow-up Pap tests are negative or the woman is HR HPV negative at 12 months, she can return to annual screening. A combination of repeat Pap and colposcopic exam at 12 months is also acceptable. If the Pap and colposcopy show regression, the woman can return to annual Pap tests. Treatment with use of ablative or excisional methods is also acceptable. Cryotherapy, laser ablation, and LEEP are all acceptable methods and the decision of which method to use rests with the clinician. Endocervical sampling is recommended before ablation of CIN 1 since studies have shown pretreatment endocervical sampling can help identify women with invasive cervical cancer.

If the colposcopy is unsatisfactory, a diagnostic excisional procedure (LEEP, laser conization, or cold-knife conization) should be done. An exception is made for adolescents, pregnant, and immunosuppressed women. These women can be followed without treatment. Adolescents should be followed expectantly since the regression rate for LSIL/CIN 1 can be up to 95 percent. If a woman has persistent CIN 1, whether or not she seeks treatment should be based on discussion with her provider. If treatment is desired, excisional methods (LEEP, laser conization, or cold-knife conization) are the preferred. Hysterectomy is not acceptable as the primary treatment for CIN 1.

**High-Grade Lesions**

**CIN 2 (moderate dysplasia), CIN 3/CIS (severe dysplasia/carcinoma-in-situ)**

The 2001 Consensus Guidelines combines the management of these forms of dysplasia since all of these lesions are likely to persist or progress. Studies show 43 percent of CIN 2 will regress, 35 percent will persist, and 22 percent will progress to CIN 3, and 5 percent will progress to invasive cervical cancer. In CIN 3, 32 percent will regress, 56 percent will persist, and 14 percent will progress to invasive cancer. The recommended management for women with a satisfactory colposcopy is either excision or ablation of the transformation zone. If a woman has a reoccurrence of CIN 2/3, then an excisional procedure is preferred. If the woman has an unsatisfactory colposcopy, a diagnostic excisional procedure is recommended. Hysterectomy is not accepted as a primary treatment method.
Post-treatment follow-up is essential since risk of reoccurrence, while low, is still significantly higher than the background population. Post-treatment follow-up can be done either with pap smears and/or colposcopy or HR HPV testing. If follow-up is done using Pap smears, the woman must return for a Pap smear or for a Pap smear and a colposcopy every 4-6 months until at least 3 negative results are obtained. Once she has three negative results, she can return to annual screening. If a result of ASC or greater is obtained, she must have another colposcopy. If follow-up is done using HR HPV testing, the HPV test is performed at least 6 months after treatment. If the result is negative, the woman returns to annual screening. If the result is positive, she is referred for colposcopy.

If CIN is found on the margins of a diagnostic excisional procedure or on any follow-up endocervical sampling, a 4-6 month follow-up colposcopy and endocervical sampling should be done. If CIN 2/3 is again identified in either the endocervical margins or in the endocervical sampling, a repeat diagnostic excisional procedure is warranted. If the excisional procedure cannot be done, a hysterectomy can be considered. A hysterectomy is also acceptable treatment of recurrent/persistent biopsy-confirmed CIN 2/3.

Special Circumstances

Pregnancy – It is rare for CIN 2/3 to progress to invasive cervical cancer during pregnancy. Pregnant woman also have a high rate of spontaneous regression postpartum if no invasive cervical cancer is present. Therefore, the use of diagnostic excisional procedures during pregnancy should only occur when invasive cervical cancer cannot be ruled out.

Adolescents – While HPV lesions are common in younger woman, invasive cervical cancer is not. For adolescents with CIN 2, observation with colposcopy at 4-6 month intervals for one year is acceptable management as long as the colposcopies and endocervical sampling remain negative. An adolescent with CIN 3 needs excisional or ablative treatment just like any other woman.

Invasive Cervical Cancer

The mode of treatment for invasive cervical cancer depends on the stage of the disease at diagnosis. Determining appropriate treatment recommendations requires the special expertise of a board-certified gynecological oncologist. Treatment options include simple hysterectomy, radical hysterectomy with or without pelvic and peri-aortic lymph adnexectomy, and/or irradiation therapy.
PAP SMEAR TERMINOLOGY

Specimen Type
Indicate conventional smear (Pap smear), liquid based, or other

Specimen Adequacy
- Satisfactory for evaluation (note presence/absence of endocervical/transformation zone component)
- Unsatisfactory for evaluation... (specify reason)
- Specimen rejected/not processed... (specify reason)
- Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of... (specify reason)

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<tr>
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THE BETHESDA SYSTEM 2001

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<tr>
<th>General</th>
<th>Epithelial Cell Abnormalities</th>
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<tbody>
<tr>
<td>Negative for Intraepithelial Lesions or Malignancy</td>
<td>Other</td>
</tr>
<tr>
<td>Endometrial cells in a woman ≥40 (Specify if negative for SIL)</td>
<td>ASC-US</td>
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General Categorization (optional)
- Negative for intraepithelial lesion or malignancy
- Epithelial cell abnormality
- Other

Interpretation/Result:
Negative for Intraepithelial Lesion or Malignancy
(when there is no cellular evidence of neoplasia, state this in the General Categorization above and/or in the interpretation/result section of the report, whether or not there are organisms or other non-neoplastic findings)

Organisms:
- Trichomonas vaginalis
- Fungal organisms morphologically consistent with Candida species
- Shift in flora suggestive of bacterial vaginosis
- Bacteria morphologically consistent with Actinomyces species
- Cellular changes consistent with herpes simplex virus

Epithelial Cell Abnormalities

Squamous Cell
- Atypical squamous cells (ASC) (ASC-US) - of undetermined significance (ASC-H) - cannot exclude HSIL
- Low-grade squamous intraepithelial lesion (LSIL) encompassing: HPV/mild dysplasia/cervical intraepithelial neoplasia (CIN 1)
- High-grade squamous intraepithelial lesion (HSIL) encompassing: moderate and severe dysplasia, carcinoma in situ (CIS); CIN 2 and CIN 3
- Squamous cell carcinoma

Glandular Cell
- Atypical glandular cells (AGC) (specify endocervical, endometrial, or not otherwise specified (NOS))
- Atypical glandular cells, favor neoplasia (specify endocervical, or not otherwise specified)
- Endocervical adenocarcinoma in situ (AIS)
- Adenocarcinoma

Other Non-Neoplastic Findings (Optional to report; list not comprehensive)
- Reactive cellular changes associated with:
  - inflammation (includes typical repair)
  - radiation
  - intrauterine contraceptive device (IUD)
- Glandular cells status posthysterectomy
- Atrophy

Other (List not comprehensive)
- Endometrial cells in a woman ≥ 40 years of age

Sources: JAMA, 2002, 287:2114-2119
Note:
The Sage program recognizes care must be tailored to the specific needs of each patient. These recommendations will serve as a program standard for screening and follow-up.

ASC-US
Atypical Squamous Cells of Undetermined Significance
Repeat cytology at 4–6 month intervals x 2. If a result is ASC or worse, go to colposcopy with biopsy and endocervical sampling. If both results are negative, repeat Pap smear in 12 months; or Test for HPV-DNA. If HPV is negative for high-risk types, repeat Pap smear in 12 months. If HPV is positive for high-risk types, do colposcopy with biopsy and endocervical sampling; or If not testing for HPV DNA and concerned about patient compliance, do colposcopy with biopsy and endocervical sampling.

ASC-H
Atypical Squamous Cells: Cannot Exclude High-grade SIL
Do colposcopy with biopsy and endocervical sampling.

LSIL
Low-grade Squamous Intraepithelial Lesions
Do colposcopy with biopsy and endocervical sampling.

HSIL
High-grade Squamous Intraepithelial Lesions
Do colposcopy with biopsy and endocervical sampling.

AGC (AGUS)
Atypical Glandular Cells:
- Atypical Endometrial Cells
  Do endometrial sampling.
- (Other) All Subcategories
  Do colposcopy with biopsy and endocervical sampling.
  If older than 35, or if having abnormal bleeding, do endometrial sampling.
Sage Evaluation-Algorithm:
Program Standards for the Initial Management of an Abnormal Screening Pap Smear

*American Society for Colposcopy and Cervical Pathology (ASCCP) Consensus Guidelines can be found in JAMA, 2002, 287:2120-2129 or at [http://www.asccp.org/consensus/cytological.shtml](http://www.asccp.org/consensus/cytological.shtml) and includes more detailed management for special circumstances including adolescents, pregnant women and post-menopausal women.*
GLOSSARY

Bethesda System:
Updated in 2001. A classification system for reporting cervical and vaginal cytological diagnoses. Initiated in 1988, the system introduced standardization of laboratory reports with both a descriptive diagnosis and an evaluation of specimen adequacy.

AGC (Atypical Glandular Cells):
AGC is a Bethesda System 2001 classification. The AGC category is associated with a substantially greater risk for cervical neoplasia than the ASC or LSIL categories. The increased risk for cervical neoplasia varies with the AGC subclassifications:

- AGC – NOS (not of significance); can be endocervical cells, endometrial cells or glandular cells
- AGC – favor neoplasia. Both results require colposcopy.

ASC (Atypical Squamous Cells):
ASC is a Bethesda System 2001 classification. ASC, Atypical Squamous Cells, is subdivided into two reporting categories:

- ASC-US indicates a result of undetermined significance; and may be managed by repeat Pap smears, HPV-DNA testing or colposcopy.
- ASC-H indicates a result that cannot exclude HSIL (High-Grade Squamous Intraepithelial Lesions). Colposcopy is required.

LSIL (Low-Grade Squamous Intraepithelial Lesion):
LSIL is a Bethesda System 2001 classification and refers to a cervical cancer precursor. The Pap smear result shows cellular changes of HPV or mild dysplasia (CIN 1). Colposcopy is the next step.

HSIL (High-Grade Squamous Intraepithelial Lesion):
HSIL is a Bethesda System 2001 classification and refers to a cervical cancer precursor. The Pap smear result shows cellular changes of moderate (CIN 2) to severe dysplasia/carcinoma-in-situ (CIN 3/CIS). Colposcopy is the next step.

CIN (Cervical Intraepithelial Neoplasia):
Precancerous cellular changes in the cervix encompassing mild dysplasia (CIN 1), moderate dysplasia (CIN 2), and severe dysplasia/cancer-in-situ (CIN 3/CIS).

Endocervical Sampling:
This procedure can be done by curette (endocervical curettage or ECC) or by brush (endocervical brushing or ECB). The lining of the endocervix is scraped and sent to pathology for further study. The specimen obtained is forwarded for either histological evaluation or for cytological evaluation.

Endometrial Sampling:
A procedure to obtain an endometrial specimen for histological evaluation. An endometrial biopsy, a “dilation and curettage” or a hysteroscopy are methods to collect the specimen.

False Negative:
The screening test fails to detect disease when it is present.

HPV (Human Papillomavirus):
A sexually transmitted virus implicated in cervical cancer and its precursor lesions. Over 100 types of HPV have been identified, but only 30-40 infect the genital tract. There are high-risk or low-risk types. High-risk HPV is related to cervical and other cancers.

SCJ (Squamo-columnar Junction):
The point on the cervix where the columnar and squamous epithelium meet. It is a dynamic point that changes in response to the woman’s hormonal state during puberty, pregnancy, menopause, etc. A vast majority of cancers arise near the SCJ so it is essential to obtain cells from this area when doing a Pap smear.

Transformation Zone:
The region on the cervix between the original squamo-columnar junction (SCJ) and the anatomic squamo-columnar junction. The area where precancerous and cancerous cervical lesions are most likely to begin. It is essential to obtain a sample from the transformation zone when doing a Pap smear.
REFERENCES:


