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Cervical Cancer Screening

Clinical Practice Guidelines in Oncology

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Overview

Despite a significant decrease in the incidence and mortality of cervical carcinoma in the United States, an estimated 12,200 women will be diagnosed with the disease in 2010, with 4210 expected deaths.[1] High-risk groups include women without access to health care and those who have immigrated to the United States from countries where cervical cancer screening is not routinely performed.[2] Because cervical cytology screening is the current method for early detection of this neoplasm, the purpose of these guidelines is to provide direction for the evaluation and management of cervical cytology.

These guidelines include recommendations on screening techniques, initiation, and frequency of screening, and management of abnormal screen-

NCCN Clinical Practice Guidelines in Oncology for Cervical Cancer Screening

Key Words

NCCN Clinical Practice Guidelines, NCCN Guidelines, cervical cancer, cancer screening, Papanicolaou test, Pap test, intraepithelial neoplasia, colposcopy, cold-knife conization, biopsy, liquid-based cytology, human papillomavirus testing, loop electrosurgical excision procedure (*JNCCN* 2010;8:1358–1386)

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Please Note

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Disclosures for the NCCN Guidelines Panel for Cervical Cancer Screening

At the beginning of each NCCN Guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Guidelines for Cervical Cancer Screening panel members can be found on page 1386. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

These guidelines are also available on the Internet. For the latest update, please visit www.NCCN.org.

ing results including colposcopy. Cervical cytology screening techniques include liquid-based cytology or conventional Papanicolaou (Pap) smears. Unless specifically noted, these techniques are collectively referred to as *cervical cytology* in this discussion.

Human papillomavirus (HPV) DNA testing for primary cervical cancer has been approved by the FDA; several diagnostic tests are available (e.g., HPV high-risk and HPV 16/18 DNA tests, Hybrid Capture 2 HPV DNA test). However, HPV DNA testing is not recommended in women younger than 21 years.[3] HPV DNA testing for high-risk virus types can also be used as a component of both primary screening and workup of abnormal cytology results; it is not useful to test for low-risk virus types.[3] (See HPV DNA Testing on page 1378 for more detail about these tests.)

Colposcopy, along with colposcopically directed biopsies, is the primary method for evaluating women with abnormal cervical cytologies. During a colposcopic examination, the cervix is viewed through a long focal-length dissecting-type microscope (magnification, 10–16x). A 4% solution of acetic acid is applied to the cervix before viewing. The coloration induced by the acid and the observance of blood-vessel patterns allow a directed biopsy to rule out invasive disease and determine the extent of preinvasive disease. If the entire squamocolumnar junction of the cervix is visualized (i.e., the entire transformation zone is seen), the examination is considered satisfactory and endocervical curettage (ECC) is unnecessary.[3–5] Special considerations for colposcopy performed during pregnancy are also discussed (see page 1376).

Text continues on p. 1377

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SCREENING GUIDELINES FOR EARLY DETECTION OF CERVICAL CANCER[a]

When to Start Screening

- Cervical cancer screening should begin at 21 years of age. Screening before age 21 should be avoided, because it may lead to unnecessary and harmful evaluation and treatment in women at very low risk of cancer.
- Sexually active adolescents (i.e., women aged < 21 y) should be counseled and tested for sexually transmitted infections, and should be counseled regarding safe sex and contraception. These measures may be performed without cervical cytology and, in the asymptomatic patient, without the introduction of a speculum.
- Both liquid-based and conventional methods of cervical cytology are acceptable for screening.

Frequency of Screening

- Cervical cytology screening is recommended every 2 y for women between ages 21 and 29 y.
- Co-testing using the combination of cytology plus HPV DNA testing is an appropriate screening test for women aged > 30 y. Any low-risk woman aged ≥ 30 y who receives negative test results on both cervical cytology screening and HPV DNA testing should be rescreened no sooner than 3 y subsequently.
- Women aged ≥ 30 y who have had 3 consecutive negative cervical cytology screening test results, have no history of CIN II or III, are not HIV infected, are not immunocompromised, and were not exposed to diethylstilbestrol in utero may extend the interval between cervical cytology examinations to every 3 y.
- Women who have been immunized against HPV 16 and 18 should be screened by the same regimen as nonimmunized women.
- Regardless of the frequency of cervical cytology screening, physicians also should inform their patients that annual gynecologic examinations may still be appropriate even if cervical cytology is not tested at each visit.

When to Discontinue Screening

- Women treated in the past for CIN II, CIN III, or cancer remain at risk for persistent or recurrent disease for at least 20 y after treatment and after initial posttreatment surveillance, and should continue to have annual screening for at least 20 y.
- Women who have had a hysterectomy with removal of the cervix and have a history of CIN II or III, or in whom a negative history cannot be documented, should continue to be screened even after their period of posttreatment surveillance. Although the screening interval may then be extended, no good data support or refute discontinuing screening in this population.
- In women who have had a total hysterectomy for benign indications and have no prior history of high-grade CIN, routine cytology testing should be discontinued.
- Because cervical cancer develops slowly and risk factors decrease with age, it is reasonable to discontinue cervical cancer screening between 65 and 70 y of age in women who have 3 or more negative cytology test results in a row and no abnormal test results in the past 10 y.

[a] Cervical cytology screening. ACOG Committee Opinion No. 109. American College of Obstetricians and Gynecologists. Obstet Gynecol 2009;114:1409-1420.

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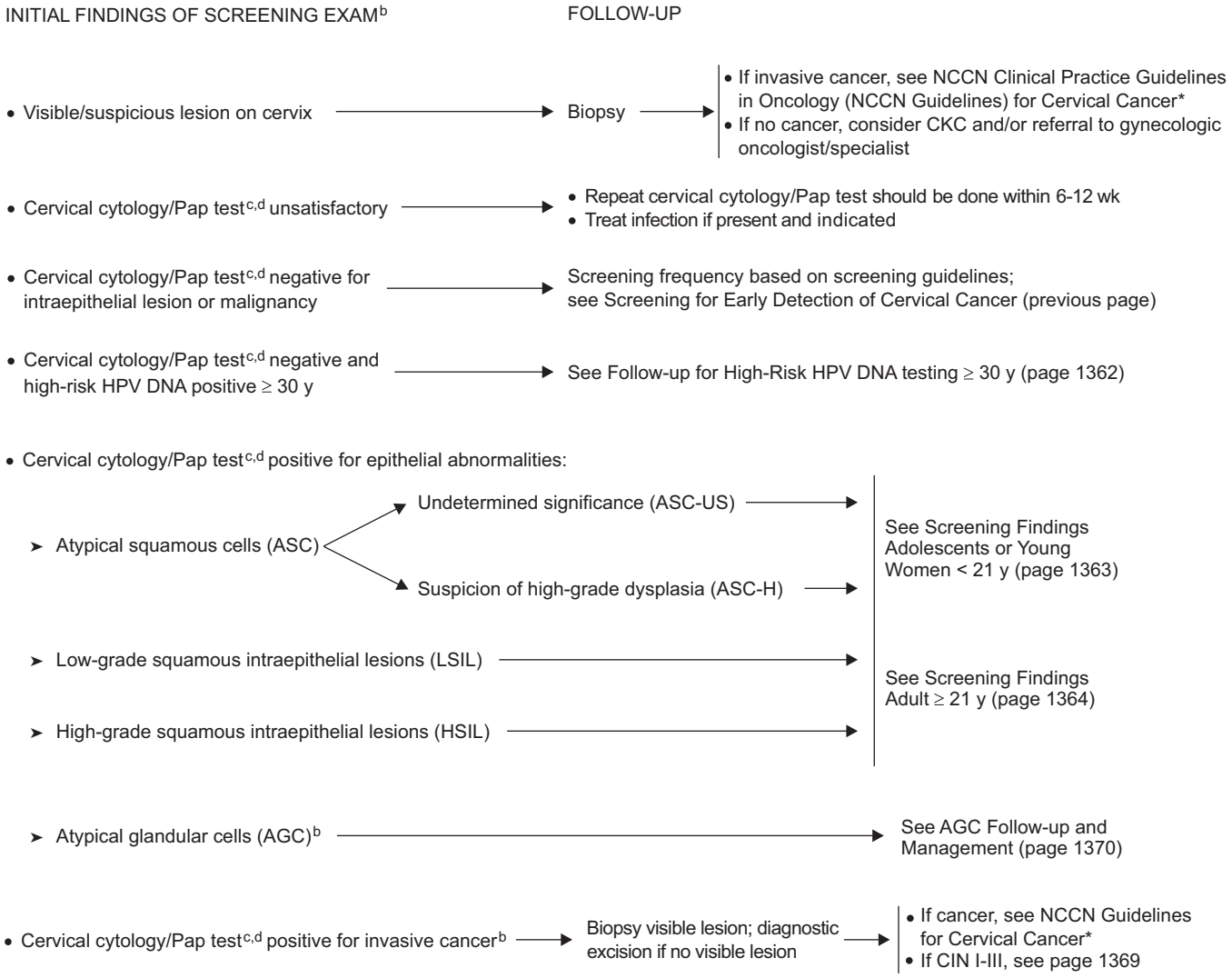

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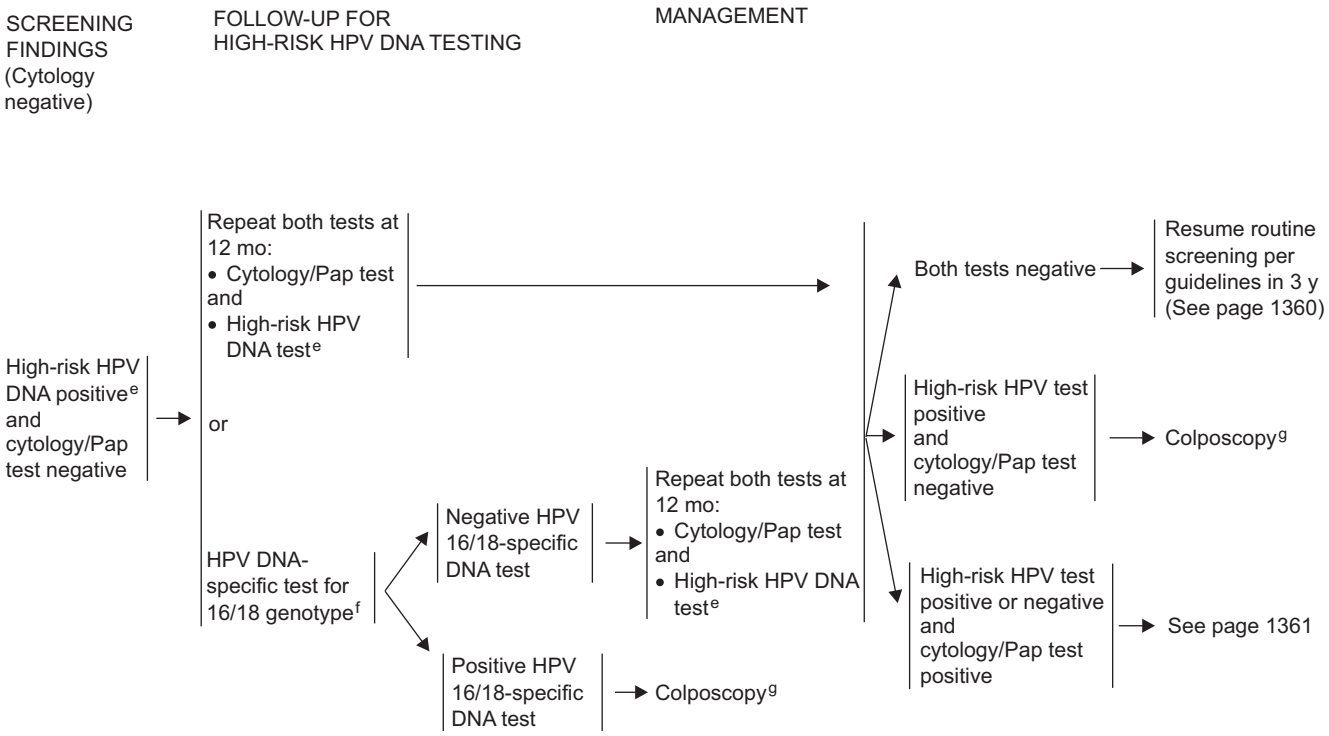
[b] Referral to specialist with oncological expertise for complex clinical situations should be strongly considered. Examples of complex clinical situations include atypical glandular cells, adenocarcinoma in-situ, pregnancy, and persistent/recurrent dysplasia with desire for fertility preservation.
[c] Cervical cytology/Pap test results should be reported using the Bethesda System. See The Bethesda System 2001 (page 1375).
[d] Conventional Pap test or liquid-based technology is an acceptable method for primary screening.

FOLLOW-UP FOR HIGH-RISK HPV DNA TESTING ≥ 30 y



[e] The FDA approved HPV DNA testing for high-risk virus types; it is not useful to test for low-risk virus types. High-risk HPV DNA tests detect whether any of the 13 to 14 high-risk types of HPV are present, although the tests do not indicate which types are present.
[f] The HPV 16/18 DNA diagnostic test is a separate test that only detects whether HPV 16 or 18 is present.
[g] Follow appropriate colposcopy findings pathway (i.e., satisfactory or unsatisfactory). If appropriate, see Colposcopy During Pregnancy (page 1376).

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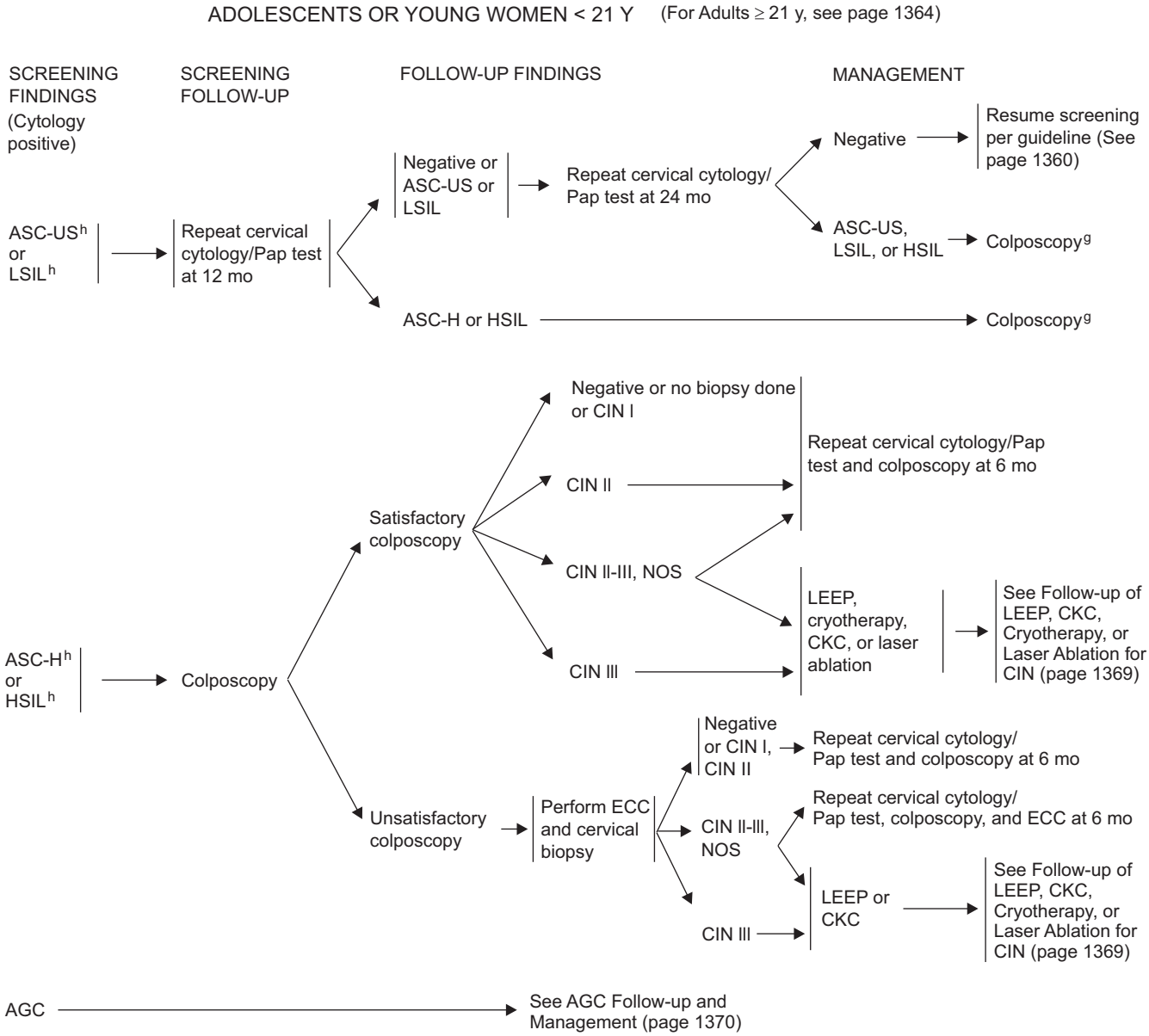
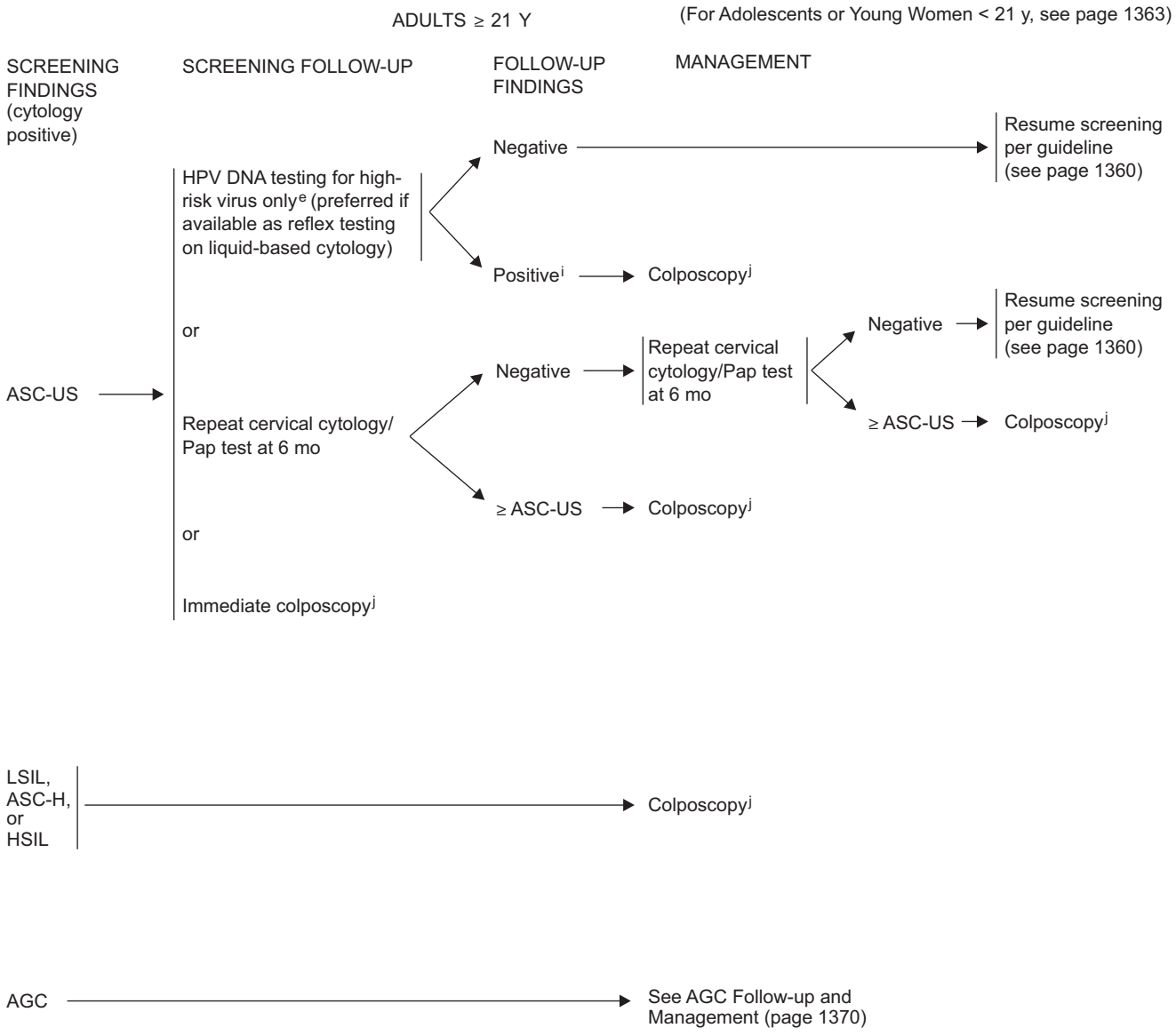


[g]Follow appropriate colposcopy findings pathway (i.e., satisfactory or unsatisfactory). If appropriate, see Colposcopy During Pregnancy (page 1376).
[h]HPV DNA testing is not recommended in adolescents or young women < 21 y.



[e] The FDA approved HPV DNA testing for high-risk virus types; it is not useful to test for low-risk virus types. High-risk HPV DNA tests detect whether any of the 13 to 14 high-risk types of HPV are present, although the tests do not indicate which types are present.

[i] In women with ASC-US who are HPV high-risk-positive, NCCN and the American Society for Colposcopy and Cervical Pathology (ASCCP) do not recommend using the HPV 16/18-specific DNA test (i.e., HPV genotyping) to screen for who should proceed to colposcopy (http://www.asccp.org/pdfs/consensus/clinical_update_20090408.pdf).

[j] For colposcopy for ASC-US or LSIL, see page 1365, and for ASC-H or HSIL, see page 1367. If appropriate, see Colposcopy During Pregnancy (page 1376).

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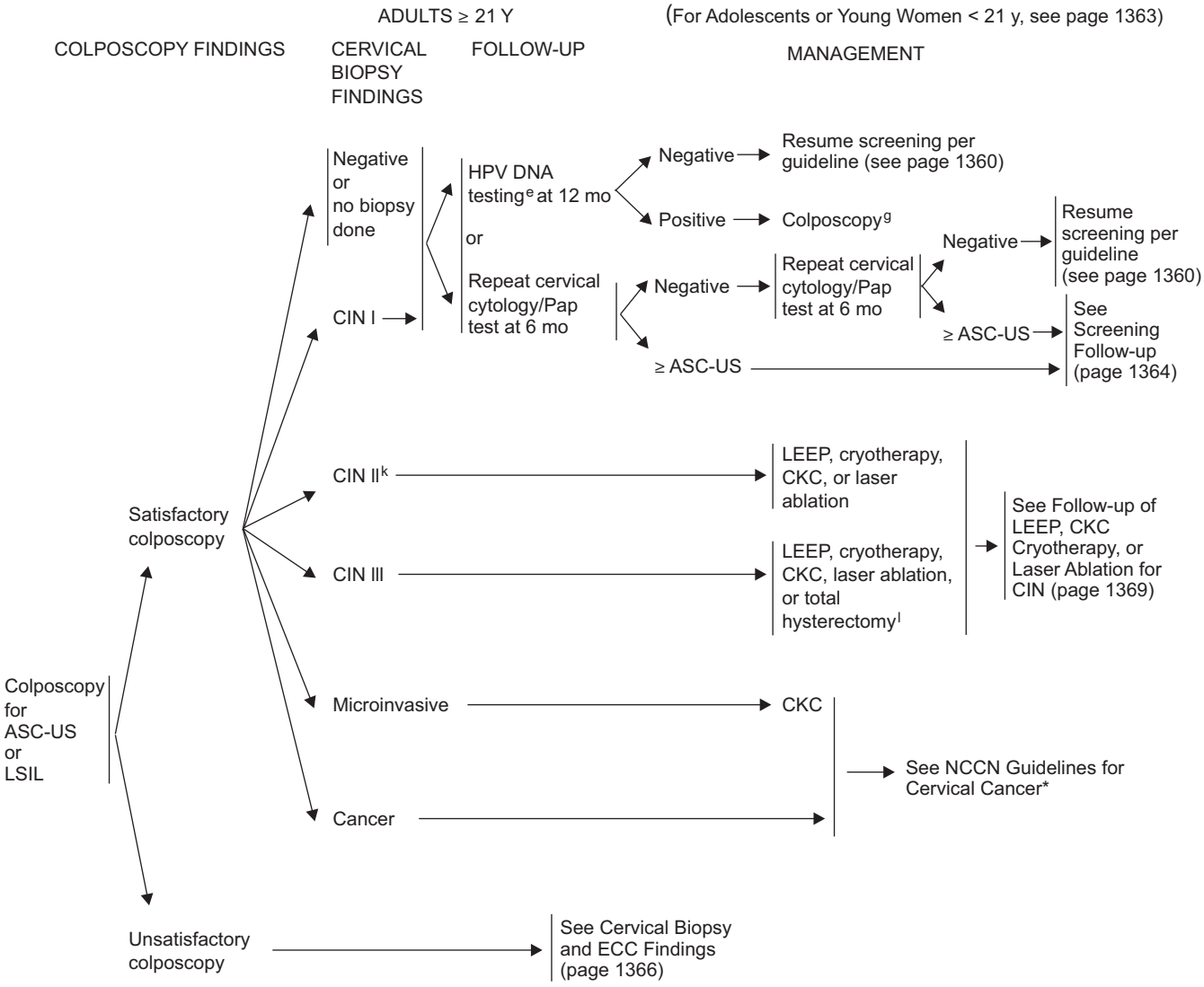

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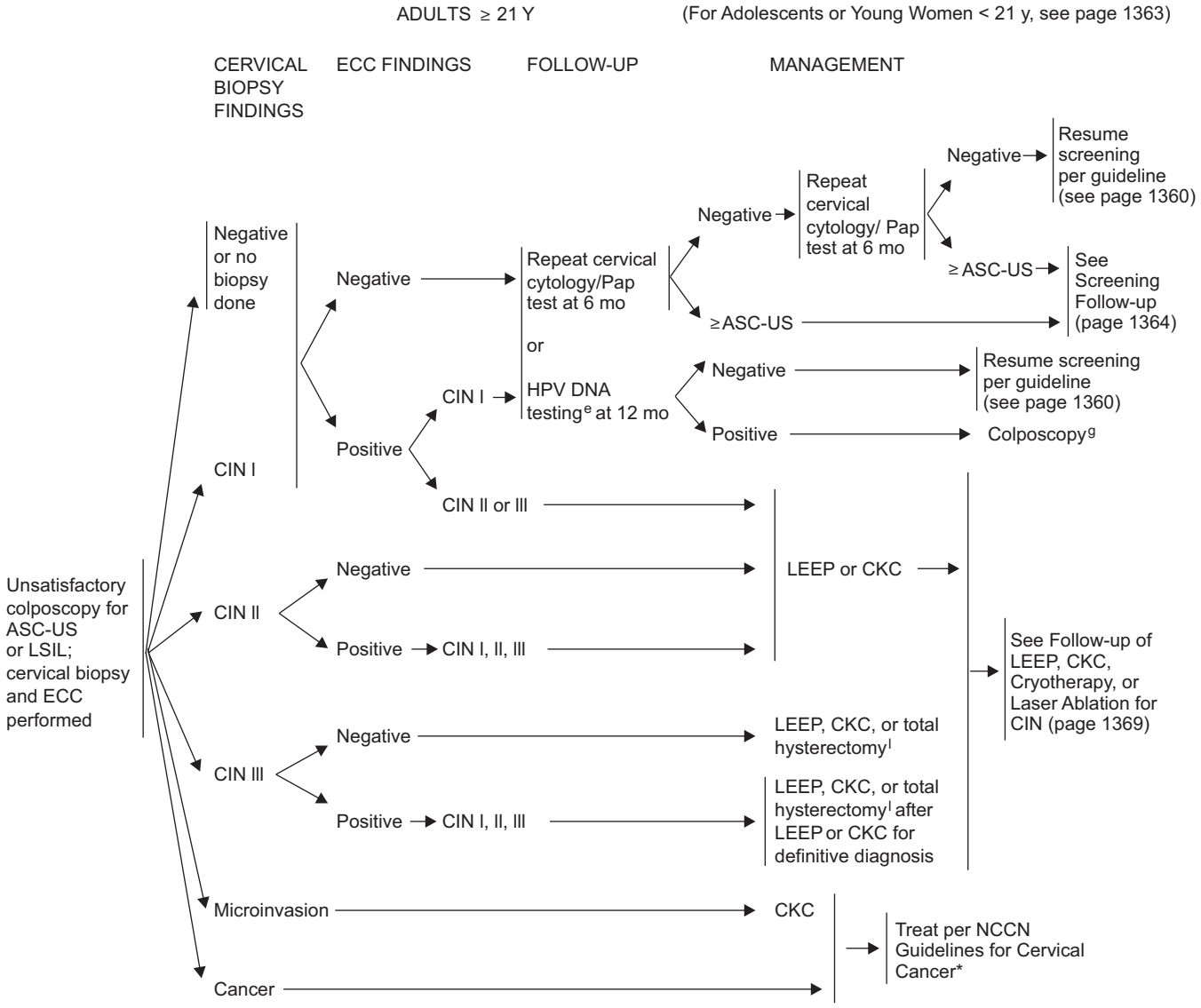
[g]Follow appropriate colposcopy findings pathway (i.e., satisfactory or unsatisfactory). If appropriate, see Colposcopy During Pregnancy (page 1376).
[k]CIN II may be followed without treatment in certain clinical circumstances at the discretion of the physician.
[l]If appropriate for preexisting pathologic condition or quality of life.



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[g] Follow appropriate colposcopy findings pathway (i.e., satisfactory or unsatisfactory). If appropriate, see Colposcopy During Pregnancy (page 1376).
[l] If appropriate for preexisting pathologic condition or quality of life.

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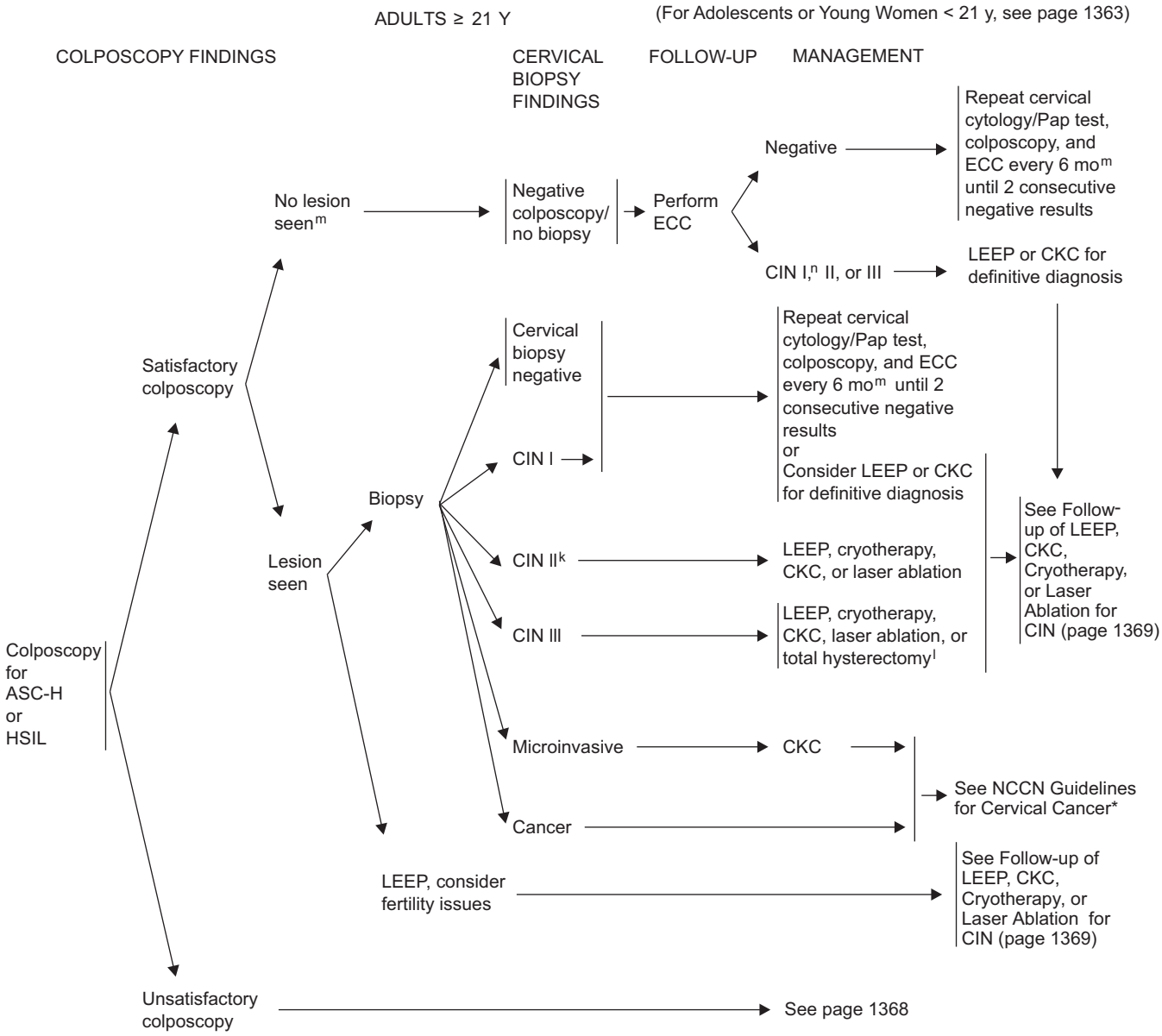

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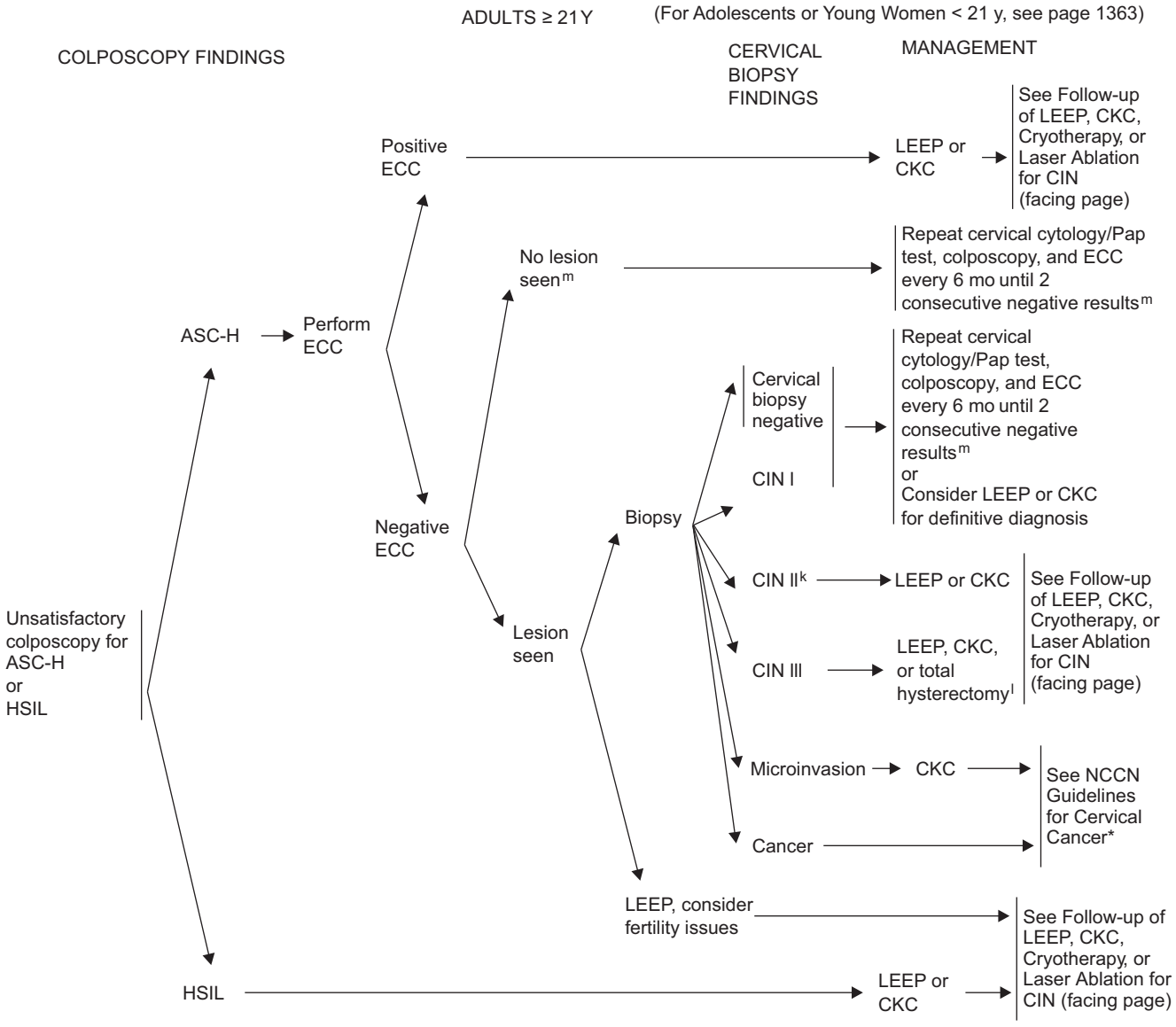
[k]CIN II may be followed without treatment in certain clinical circumstances at the discretion of the physician.
[l]If appropriate for preexisting pathologic condition or quality of life.
[m]Perform vaginal and vulvar colposcopy.
[n]If preceeding cervical cytology/Pap test was ASC-H, may consider follow-up.



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[k]CIN II may be followed without treatment in certain clinical circumstances at the discretion of the physician.
[l]If appropriate for preexisting pathologic condition or quality of life.
[m]Perform vaginal and vulvar colposcopy.

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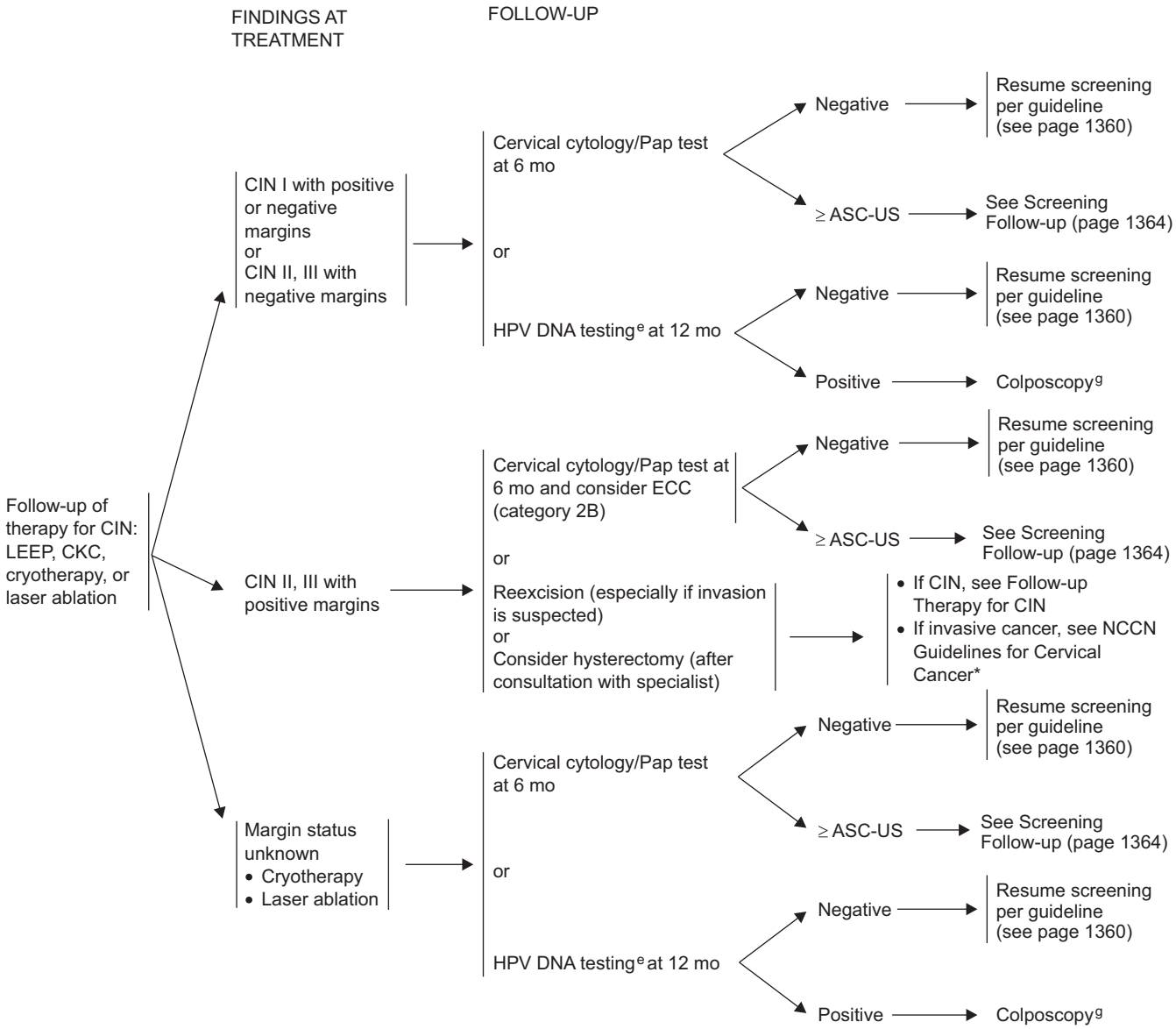

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[e] The FDA approved HPV DNA testing for high-risk virus types; it is not useful to test for low-risk virus types. High-risk HPV DNA tests detect whether any of the 13 to 14 high-risk types of HPV are present, although the tests do not indicate which types are present.
[g] Follow appropriate colposcopy findings pathway (i.e., satisfactory or unsatisfactory). If appropriate, see Colposcopy During Pregnancy (page 1376).

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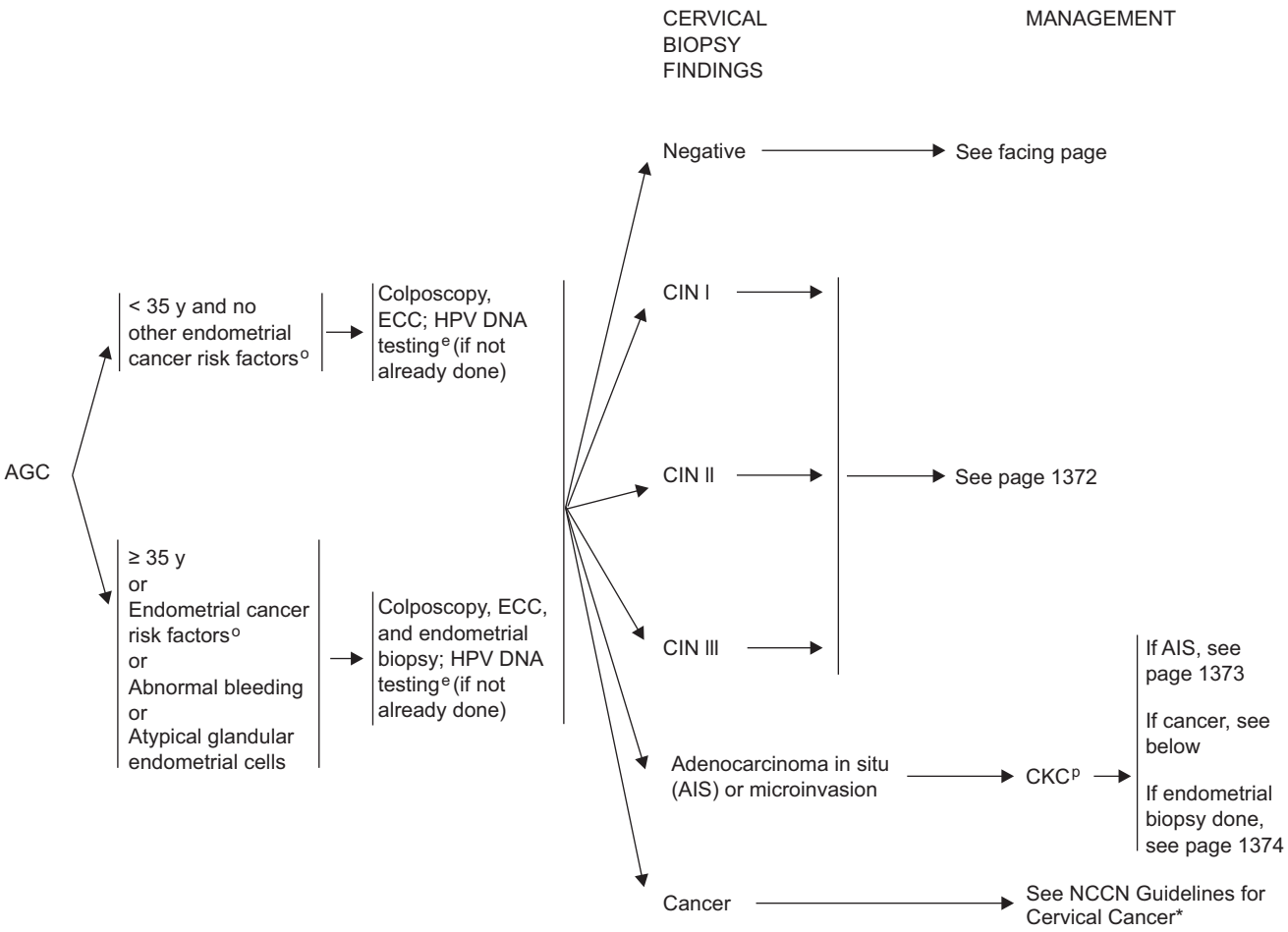
ATYPICAL GLANDULAR CELLS: FOLLOW-UP AND MANAGEMENT



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[e] The FDA approved HPV DNA testing for high-risk virus types; it is not useful to test for low-risk virus types. High-risk HPV DNA tests detect whether any of the 13 to 14 high-risk types of HPV are present, although the tests do not indicate which types are present.
[o] Endometrial cancer risk factors: obesity, unopposed estrogen replacement therapy, polycystic ovarian disease, tamoxifen therapy, anovulation, hereditary nonpolyposis colorectal cancer syndrome (HNPCC).
[p] If atypical glandular cells favor neoplasia or adenocarcinoma in situ, follow CKC with endometrial sampling if not yet done.

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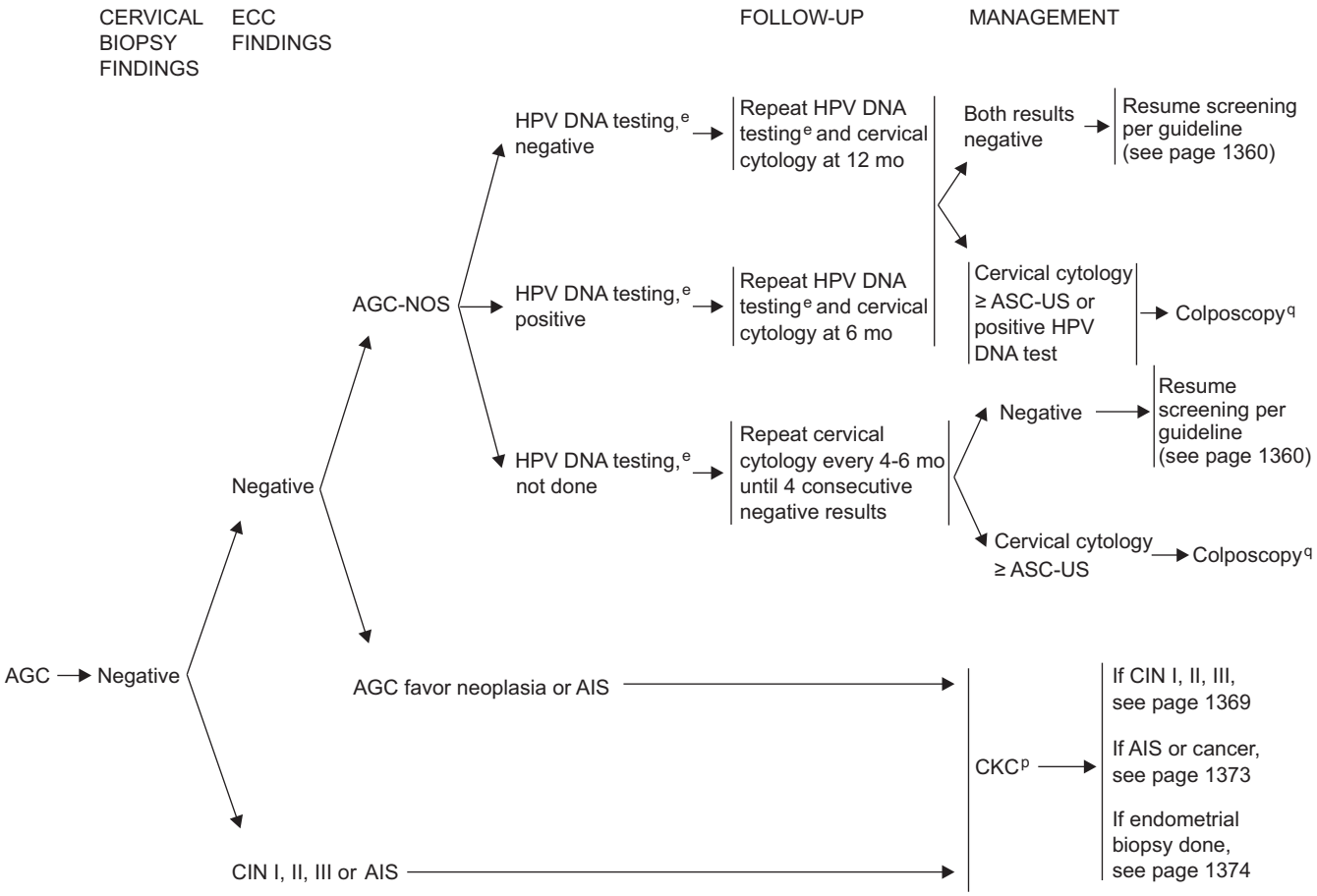
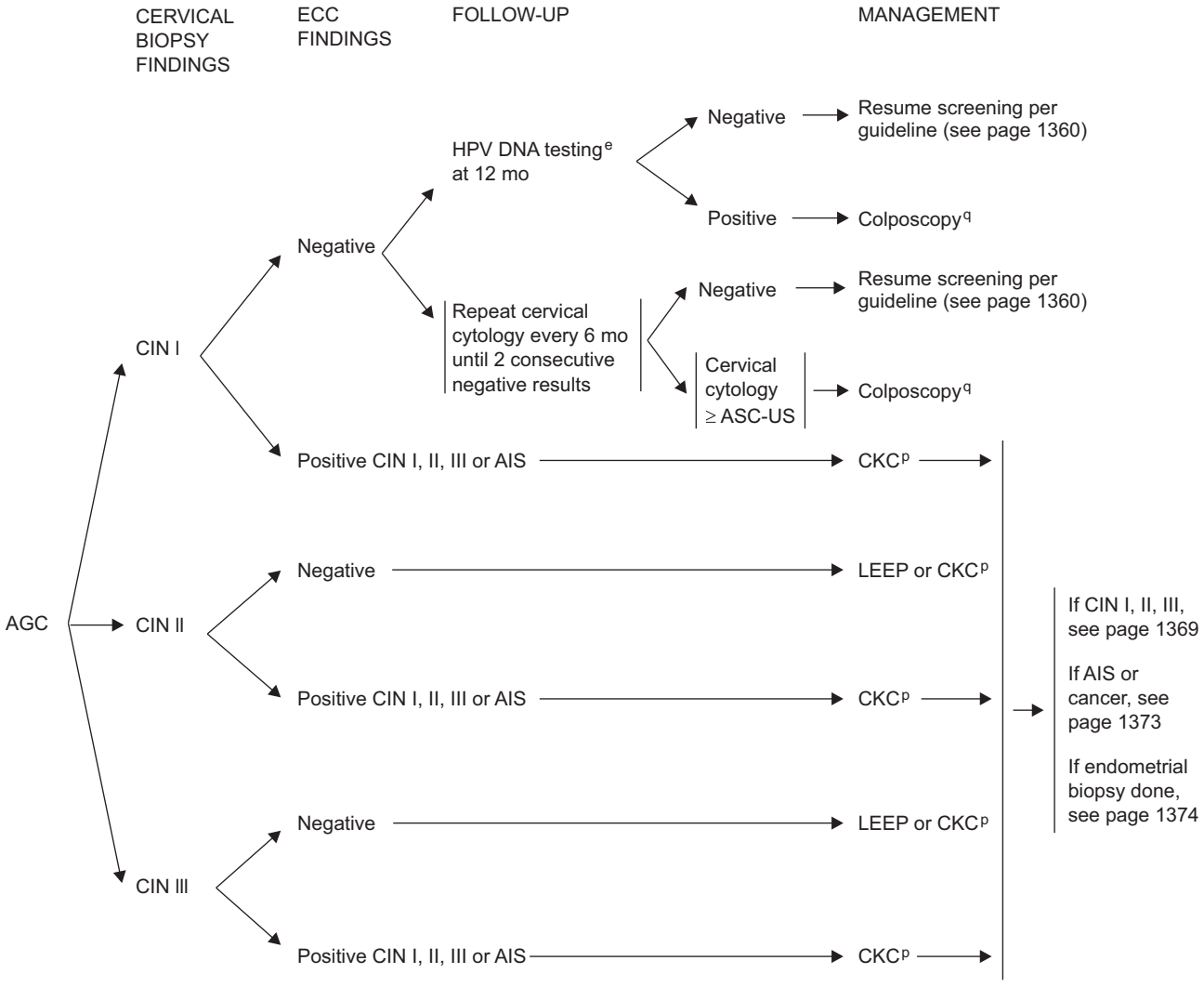
ATYPICAL GLANDULAR CELLS: FOLLOW-UP AND MANAGEMENT



[e] The FDA approved HPV DNA testing for high-risk virus types; it is not useful to test for low-risk virus types. High-risk HPV DNA tests detect whether any of the 13 to 14 high-risk types of HPV are present, although the tests do not indicate which types are present.
[p] If atypical glandular cells favor neoplasia or adenocarcinoma in situ, follow CKC with endometrial sampling if not yet done.
[q] Follow appropriate colposcopy findings pathway (see opposite page). If appropriate, see Colposcopy During Pregnancy (page 1376).

ATYPICAL GLANDULAR CELLS: FOLLOW-UP AND MANAGEMENT



[e] The FDA approved HPV DNA testing for high-risk virus types; it is not useful to test for low-risk virus types. High-risk HPV DNA tests detect whether any of the 13 to 14 high-risk types of HPV are present, although the tests do not indicate which types are present.
[p] If atypical glandular cells favor neoplasia or adenocarcinoma in situ, follow CKC with endometrial sampling if not yet done.
[q] Follow appropriate colposcopy findings pathway (see page 1370). If appropriate, see Colposcopy During Pregnancy (page 1376).

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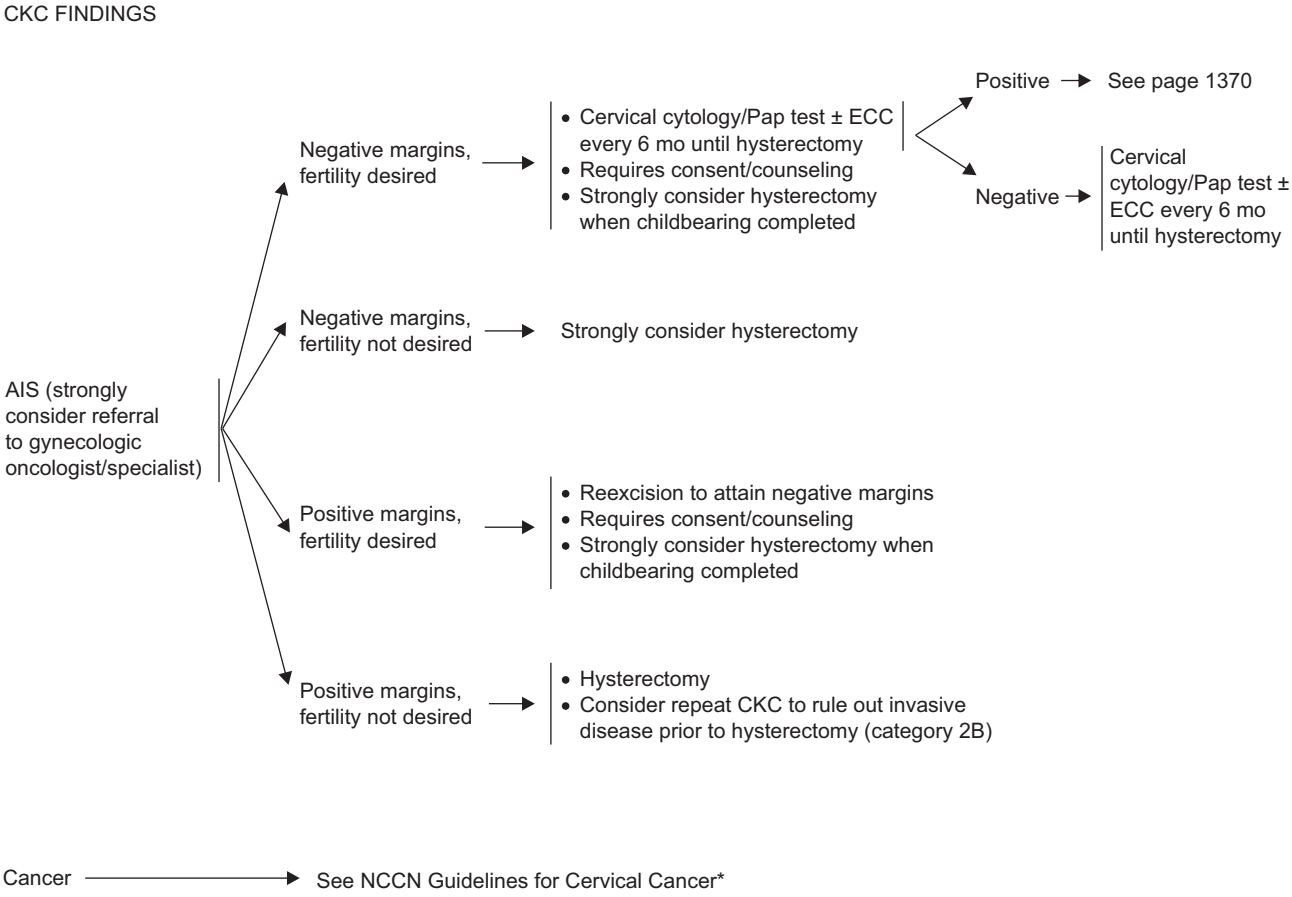
ATYPICAL GLANDULAR CELLS: ADENOCARCINOMA IN SITU MANAGEMENT



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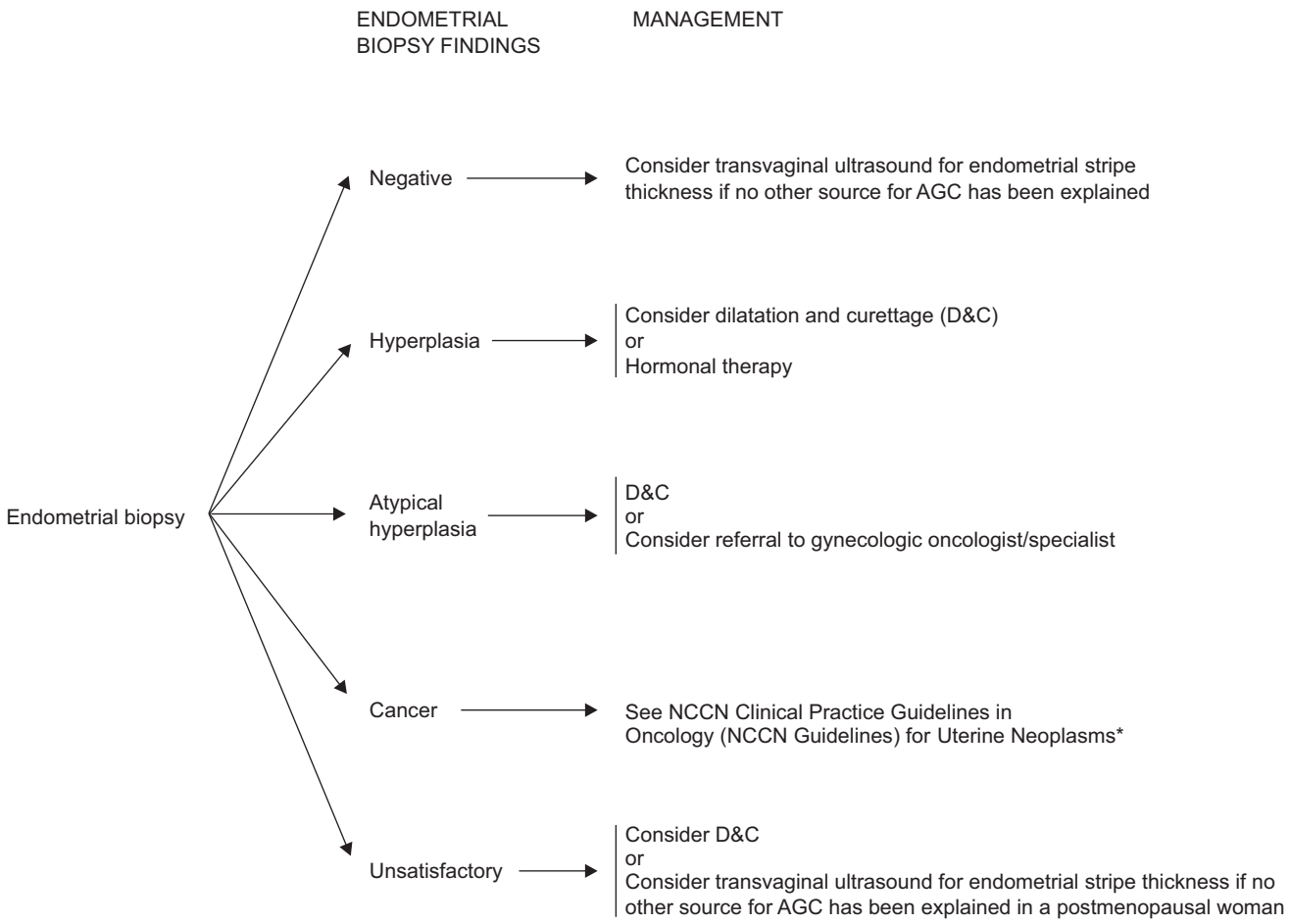
ATYPICAL GLANDULAR CELLS: ENDOMETRIAL BIOPSY FINDINGS



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BETHESDA SYSTEM 2001

SPECIMEN TYPE: Indicate conventional smear (Pap smear) vs. liquid-based vs. other

SPECIMEN ADEQUACY
- Satisfactory for evaluation (describe presence or absence of endocervical/transformation zone component and any other quality indicators, such as partially obscuring blood or inflammation)
- 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)

INTERPRETATION/RESULT
NEGATIVE FOR INTRAEPITHELIAL LESION OR MALIGNANCY
(When there is no cellular evidence of neoplasia, state this 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* spp
  - Shift in flora suggestive of bacterial vaginosis
  - Bacteria morphologically consistent with *Actinomyces* spp
  - Cellular changes consistent with Herpes simplex virus
- Other non-neoplastic findings (optional to report; list not inclusive):
  - Reactive cellular changes associated with
    - inflammation (includes typical repair)
    - radiation
    - intrauterine contraceptive device (IUD)
  - Glandular cell status post hysterectomy
  - Atrophy
- OTHER
  - Endometrial cells (in a woman aged ≥ 40 y; specify if "negative for squamous intraepithelial lesion")

EPITHELIAL CELL ABNORMALITIES
- Squamous cell
  - ASC
    - of undetermined significance (ASC-US)
    - cannot exclude HSIL (ASC-H)
  - LSIL
    - encompassing: HPV/mild dysplasia/CIN I
  - HSIL
    - encompassing: moderate and severe dysplasia, CIS, and CIN II and III
    - with features suspicious for invasion (if invasion is suspected)
  - Squamous cell carcinoma
- Glandular cell
  - Atypical
    - endocervical cells (NOS or specify in comments)
    - endometrial cells (NOS or specify in comments)
    - glandular cells (NOS or specify in comments)
  - Atypical
    - endocervical cells, favor neoplastic
    - glandular cells, favor neoplastic
  - Endocervical adenocarcinoma in situ
  - Adenocarcinoma
    - endocervical
    - endometrial
    - extrauterine
    - not otherwise specified (NOS)
- OTHER MALIGNANT NEOPLASMS (specify)

Note: The NCI Bethesda System 2001 Web site includes additional information such as the definitions of terms used for this table and information about ancillary testing and automated review.

NCI Bethesda System 2001. Available at: http://nih.techriver.net/bethesdaTable.php Accessed August 17, 2010.

COLPOSCOPY DURING PREGNANCY

Recommendations for colposcopy and follow-up are the same as delineated in these guidelines except:

- Consultation or referral to colposcopist with experience in colposcopy during pregnancy
- No ECC
- Treatment for CIN (any grade) delayed until after pregnancy
- Colposcopy and cervical biopsy for LSIL and ASC-US can be deferred until 6 weeks postpartum
- Colposcopy and cervical biopsy should be limited to patients in whom high-grade neoplasia or invasive cancer is suspected
- Diagnostic limited excisional procedure is recommended only if invasion is suspected
- Brush cytology is safe during pregnancy

Text continued from p. 1359

Techniques for definitive treatment of cervical abnormalities include excision with the loop electrosurgical excision procedure (LEEP), cold-knife conization (CKC), or total hysterectomy. Ablative procedures include laser ablation or cryotherapy.

Cervical Cancer Screening

Initiation and Frequency

The NCCN Guidelines for Cervical Cancer Screening Panel adopted the recent recommendations of the American College of Obstetricians and Gynecologists (ACOG) on the initiation and frequency of cervical cancer screening (see page 1360). Women should begin screening at 21 years of age, regardless of whether sexual intercourse has already occurred.[2] Recent data indicate that cervical screening should be avoided in women younger than 21 years, because these women are at very low risk of cancer and because treatment can lead to complications (e.g., significant increase in premature births in women previously treated for dysplasia).[6] However, adolescents who are immunocompromised (e.g., HIV infection, organ transplants, long-term steroid use) must undergo cervical screening.[2] For example, those infected with HIV should be tested every 6 months during the first year and then annually. Cervical cytology screening should still be initiated in young women (≥ 21 years) who have been vaccinated against HPV 16 and 18, because other high-risk subtypes of HPV are oncogenic (e.g., HPV 31).

The onset of gynecologic care should not be based on the need for cervical screening. Thus, sexually active adolescents should receive counseling and testing for sexually transmitted diseases and should also receive counseling about safe sex and contraception. In asymptomatic adolescents, gynecologic care can be performed without using a speculum. After initiation, cervical screening should be performed every 2 years in women 21 to 29 years of age with either liquid-based cytology or conventional cervical cytology smears (i.e., Pap smears). However, women with high-risk factors (e.g., a history of cervical cancer, diagnosis of cervical intraepithelial neoplasia [CIN] II–III, in-utero exposure to diethylstilbestrol, and/or immunocompromised [e.g., HIV infection]) should undergo more frequent screening, usually annually, as determined by their physician. HPV DNA testing is not recommended in adolescents or younger women (i.e., < 21 years; see page 1363).[3] HPV DNA testing is also not recommended as routine screening in women younger than 30 years and in women with atypical squamous cells with suspicion of high-grade dysplasia (ASC-H), low-grade squamous intraepithelial lesions (LSIL; except in postmenopausal women), or high-grade squamous intraepithelial lesions (HSIL) cytology (http://www.asccp.org/pdfs/consensus/clinical_update_20090408.pdf).[2] See HPV DNA Testing on page 1378 for more detail.

Screening options for women 30 years and older include cervical cytology alone or cervical cytology combined with DNA testing for high-risk HPV types (i.e., combined testing).[2] After a 30-year-old woman at low risk for cervical cancer has 3 or more consecutive (and technically satisfactory) cytologic examinations with normal (i.e., negative) findings, cervical screening may be performed less frequently (i.e., every 3 years, at the discretion of the physician).[2] Combined cytology and HPV DNA testing should not be performed more often than every 3 years if both tests were negative. However, physicians should also inform their patients that annual gynecologic examinations may still be appropriate even if cervical cytology is not tested at each visit.

Women with high-risk factors (e.g., a history of cervical cancer, diagnosis of CIN II or III, in-utero exposure to diethylstilbestrol, and/or immunocompromised [e.g., HIV infection]) who are 30 years and older should receive more frequent screening, usually annually, as determined by their physician. Women who have had a hysterectomy with removal of the cervix should have annual screening with vaginal cytology if they have history of CIN II or III lesions or cancer, or if a negative history cannot be documented (see page 1360).

Combined cytology and HPV DNA testing seems to increase the detection rate of CIN III, which is a precursor of cervical cancer.[7–9] Although some studies have used HPV DNA testing alone without cervical cytology for screening women aged 30 years and older, currently this strategy is not used in the United States.[7,10] The appropriate screening interval for women with negative cytology who test positive for HPV DNA is shown on page 1362 and is described later (see Squamous Epithelial Cell Abnormalities in Adult Women Aged 21 Years or Older, page 1380).

Continue or Discontinue Screening

Cervical cytology screening should continue in women who have been vaccinated against HPV 16 and 18 (see page 1360). Women previously treated for CIN II, CIN III, or cancer should continue to undergo annual screening for at least 20 years after treatment and after initial postoperative surveillance, because they remain at risk for persistent or recurrent disease.[2] Women who have had a hysterectomy with removal of the cervix should have screening for vaginal cancer if they have history of CIN II or III lesions or cancer, or if a negative history cannot be documented. Cervical cytology screening should continue for women with other high-risk factors (e.g., in-utero diethylstilbestrol exposure, immunocompromised [e.g., HIV infection]).

Screening for cervical cancer can be discontinued after total hysterectomy for benign disease, although efforts should be made to confirm through physical examination or pathology report that the cervix was completely removed. Screening for cervical cancer may be discontinued for women with an intact cervix who are aged 65 to 70 years and older with 3 or more negative cytology test results in a row and with no history of abnormal cervical cytology tests in the previous 10 years, because cervical cancer develops slowly, and risk factors decrease with age.[2] Women with comorbid or life-threatening illness may discontinue screening.

HPV DNA Testing

Note that the recently approved HPV 16/18 and the HPV high-risk DNA tests are 2 different diagnostic tests (http://www.asccp.org/pdfs/consensus/clinical_update_20090408.pdf). The HPV high-risk DNA test detects whether any of the 14 high-risk (oncogenic) types of HPV are present, although it does not indicate which types are present. The HPV 16/18 DNA test detects whether HPV 16 or 18 is present, termed *HPV genotyping*. The American Society for Colposcopy and Cervical Pathology (ASCCP) provides information about HPV DNA testing (http://www.asccp.org/hpv.shtml#provider). The HPV 16/18 DNA test is not used alone; it is used together with the HPV high-risk DNA test. Currently, these tests should not replace other cervical cancer screening methods (i.e., regular Pap tests and gynecologic examinations; http://www.sgo.org/WorkArea/showcontent.aspx?id=2474).

The other high-risk HPV DNA test, Hybrid Capture 2 HPV DNA test (Digene HPV HC2 DNA Test), assesses whether women are positive for any of 13 high-risk types of HPV, although false-positive results can occur because of slight cross-reactivity with nononcogenic HPV subtypes.[11,12] Note that the HC2 has no internal standard to determine sample adequacy.[13] Data on the sensitivity of HC2 for disease detection are derived from studies that used it in the setting of co-collection with cytology. The performance characteristics of HC2 as a stand-alone test are unknown.

HPV Vaccines

Vaccination with the quadrivalent HPV vaccine provides protection against infection by certain types of HPV that cause cervical, vulvar, and vaginal cancer (types 16, 18) and genital warts (types 6, 11).[14–18] After 3 years, the efficacy of the quadrivalent HPV vaccine was 99% for preventing CIN grades II and III caused by HPV 16 or 18 in women who were not previously infected with either HPV 16 or 18 before vaccination; however, efficacy was only 44% in those who had been infected before vaccination.[15] Many agree that CIN III (which is essentially squamous cell carcinoma in situ [i.e., stage 0]) is the best marker for risk of progression to invasive cancer.[19] Recent data suggest that 40% of CIN II lesions will regress after 2 years; however, CIN II lesions from HPV 16 seem less likely to regress.[20] In addition, a meta-analysis reported that 22% of CIN II lesions progress to carcinoma in situ.[21]

Although how long immunity lasts after vaccination is unclear, data suggest the quadrivalent HPV vaccine is effective for at least 5 years and up to 9.5 years.[22–24] Recent data suggest that the quadrivalent HPV vaccine decreases abnormal Pap results, colposcopies, and cervical biopsies.[25]

Another prophylactic HPV vaccine is the bivalent vaccine, which was recently approved in the United States for preventing cervical cancer and precancerous lesions from HPV 16 and 18 in girls and women aged 10 to 25 years (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm187048.htm). The bivalent vaccine is also approved in more than 90 other countries.[17,26–28]

The FDA also approved the HPV quadrivalent vaccine for use in girls and women aged 9 to 26 years (http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM111263.pdf). However, the vaccine is most

effective if given to girls and young women before sexual intercourse is initiated. Guidelines from the Advisory Committee on Immunization Practices (ACIP), ACOG, American Cancer Society, and Society of Gynecologic Oncologists all agree that girls aged 11 to 12 years should receive routine vaccination with the HPV vaccine, but they differ regarding recommendations for other age groups (http://www.sgo.org/WorkArea/showcontent.aspx?id=950).[29–31] The quadrivalent HPV vaccine was recently approved to prevent genital warts in boys and men aged 9 to 26 years. Data from the Vaccine Adverse Event Reporting System indicate that the quadrivalent HPV vaccine is safe, although syncope and venous thrombotic events have been reported.[32] Both the bivalent and the quadrivalent vaccines are preventive not therapeutic.

Although HPV 16 and 18 are responsible for an estimated 70% of cervical cancer, vaccinated women are still at risk for cervical cancer related to other less-common types of oncogenic HPV (http://www.asccp.org/hpv_history.shtml).[16] Both HPV vaccines also offer some cross-protection against non-HPV vaccine types that also cause cervical cancer (e.g., HPV-31).[33,34]

However, HPV vaccination does not alter screening recommendations. Vaccinated women should continue cervical cancer screening according to the guidelines. In addition, HPV testing and typing should not be used to determine whether patients are eligible for HPV vaccination (http://www.sgo.org/WorkArea/showcontent.aspx?id=2474).

Initial Findings

The panel recommends that cervical cytology tests should be reported using the Bethesda System 2001 (http://nih.techriver.net/bethesdaTable.php; see page 1375).[35] Note that this table represents a summary, and the Web site has numerous links for definitions of terms used within (e.g., images for the specific cell abnormalities, additional information about specimen adequacy). The different possible results of an initial screening examination are summarized on page 1361.

Notably, for findings of ASC, LSIL, and HSIL, the guidelines differ according to whether the patient is younger or older than 21 years.[3,36] These guidelines are discussed in the next section for younger women (see page 1363) and later for older women (see page 1364). Atypical glandular cells (AGCs) are also addressed later (see page 1370).

All women with cervical cytology tests reported as normal (i.e., negative for intraepithelial lesion or malignancy), unsatisfactory, or positive for invasive cancer are managed as shown on page 1361. A biopsy should be performed on any grossly visible or suspicious lesion on the cervix, because cervical cytology can be reported as negative when invasive cancer is grossly present. If the cervical cytology is positive for invasive cancer, a biopsy is recommend if a lesion is visible, or a diagnostic excision is recommended if no lesion is visible (see page 1369 or the NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Cervical Cancer in this issue; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). If the initial cervical cytology is negative and the cervix is grossly normal, then subsequent screening should be based on the recommendation for frequency discussed earlier (see page 1360). Cervical cytology tests reported as unsatisfactory should be repeated within 6 to 12 weeks. Underlying infection should be treated, if indicated, before obtaining the subsequent cytology. Combined testing using cervical cytology and HPV high-risk DNA testing is discussed in the following sections.

Squamous Epithelial Cell Abnormalities in Adolescents or Young Women (Age < 21 Years)

The management of squamous cell abnormalities requires special consideration in adolescents or young women (age < 21 years) because of both the high prevalence of HPV positivity in this age group and the frequent regression of LSIL lesions (see page 1363).[3,37,38] For example, various studies have reported that a high percentage of young women will be HPV-positive within several years of initial sexual activity.[39–41] These statistics indicate that HPV testing cannot be used to further triage management of squamous epithelial abnormalities in this population. Therefore, the algorithm specifically notes that HPV testing is not recommended in adolescents or women younger than 21 years.[42] Although a small number of adolescents or young adults may have CIN III, progression to cancer is extremely rare in women younger than 21 years, and most instances of CIN III are detected on subsequent screening.[3,37,43,44] Therefore, although colposcopy is routinely recommended for LSIL in women 21 years or older, younger patients may be initially followed up with repeat cytology.

ASC of Undetermined Significance or LSIL: Young

women (aged < 21 years) with ASC of undetermined significance (ASC-US) or LSIL should undergo repeat screening at 12 months. Those with negative cervical cytology results or with persistent ASC-US or LSIL should undergo repeat screening after 24 months. If the cytology results are negative after this 3-year period, then the patient can resume routine screening. If the cytology indicates ASC-US, LSIL, or HSIL, then colposcopy is recommended. Patients then follow the "satisfactory" or "unsatisfactory" colposcopy pathway for adolescents or young women (see page 1363). Colposcopy is also recommended if the first rescreen at 12 months shows ASC-H or HSIL.

ASC-H: Colposcopy is recommended if initial screening reveals ASC-H or HSIL, because of the increased risk for CIN II or higher. Further management depends on colposcopy findings. For a satisfactory colposcopy, repeat cervical cytology and colposcopy at 6 months are recommended if the findings are reported as CIN II or I-negative, or if no biopsy was performed. Options for patients with CIN II or III not otherwise specified (NOS) findings include 1) an ablative or excision procedure (i.e., laser ablation, cryotherapy, LEEP, or CKC); or 2) repeat cervical cytology and colposcopy at 6 months. Patients with unsatisfactory colposcopy results should undergo ECC and cervical biopsy, and should then be managed as shown on page 1363.

Squamous Epithelial Cell Abnormalities in Adult Women Aged 21 Years or Older

ASC-US or LSIL: The guideline offers 3 options for the management of ASC-US in adults (see page 1364). Unlike adolescents, HPV DNA testing for high-risk virus is informative in adult women because of the lower underlying prevalence. The inclusion of HPV testing as an option is based on the results of the ASCUS-LSIL Triage Study (ALTS) trial, which showed that HPV triage ("reflex" HPV testing for atypical Pap smears from liquid-based cytology) is at least as sensitive as immediate colposcopy for detecting CIN grade III and refers about half as many women to colposcopy.[45] However, in women with ASC-US who are positive for oncogenic HPV high-risk DNA, the NCCN and ASCCP do not recommend the use of HPV 16/18–specific DNA testing (i.e., HPV genotyping) as a screen to determine who should proceed to colposcopy (http://www.asccp.org/pdfs/consensus/clinical_update_20090408.pdf). Only approximately 50% of CIN II-positive infections are associated with HPV 16 or 18.[46] Thus, the risk of CIN II-positive disease is approximately 20% in women with ASC-US who are positive for other oncogenic HPV types (e.g., HPV 31, 45). Therefore, the NCCN and ASCCP recommend referring women with ASC-US who are positive for HPV high-risk DNA for colposcopy.

A second option is immediate colposcopy.[3] A third option is to repeat the cervical cytology. If 2 consecutive cytology tests performed 6 months apart are negative, screening every 2 years may be resumed. However, if the repeat cytology test shows persistent ASC-US or greater, a colposcopic evaluation of the cervix is appropriate.

Women aged 30 years and older who are high-risk HPV DNA–positive but cytology negative have several options: 1) repeating both tests (i.e., cytology and high-risk HPV DNA) at 12 months; or 2) HPV genotyping (i.e., specific HPV 16/18 DNA test; see page 1362). Several studies suggest that it is appropriate and safe to wait 1 year before rescreening.[7,47] Approximately 60% of women who are high-risk HPV–positive will become HPV-negative during follow-up.[48] Data suggest that the incidence of CIN III-positive is 17% in women who are HPV 16-positive, 14% in those who are HPV 18-positive, and only 3% with other high-risk HPV types.[49] Thus, it is also appropriate to use HPV genotyping because HPV 16 and 18 are more oncogenic than the other high-risk types of HPV, and patients with persistent HPV 16/18 infection are at greater risk.

LSIL, ASC-H, or HSIL: In adolescent patients, LSIL often regresses spontaneously; therefore, repeat cervical cytology is an effective triage strategy. In contrast, in adults, the ALTS trial showed that LSIL cytology is best managed with colposcopy initially, because no useful triage strategy was identified.[45] Therefore, colposcopy is recommended in adults older than 30 years for all squamous lesions other than ASC-US (i.e., LSIL, ASC-H, HSIL). HPV DNA testing is not recommended in women with ASC-H, LSIL, or HSIL cytology. Note that cytologic LSIL is not the same as histologic CIN I; cytologic HSIL is not the same as histologic CIN II, III.[3]

Colposcopy for LSIL or ASC-US in Adult Women

Satisfactory Colposcopy for LSIL or ASC-US: The first consideration in evaluating the colposcopy result is determining whether the colposcopy visual-

ized the entire transition zone of the cervix and was considered satisfactory (see page 1365).[3] Unsatisfactory colposcopies are addressed in the next section. The ASCCP published 2 consensus guidelines: "2006 Consensus Guidelines for the Management of Women With Abnormal Cervical Cancer Screening Tests" and "2006 Consensus Guidelines for the Management of Women With Cervical Intraepithelial Neoplasia or Adenocarcinoma in Situ" (http://www.asccp.org/consensus.shtml).[3,36]

Women found to have negative findings or CIN I on cervical biopsy, or those who did not have a biopsy, after satisfactory colposcopic examination for ASC-US or LSIL may be followed up with a repeat cytology at 6 months or with HPV DNA testing for high-risk viruses at 12 months. Excision or ablation procedures are not recommended for these patients to avoid potential overtreatment. If negative cervical cytology is found at 6 and 12 months, a normal screening schedule can be reinstated, because most of these lesions will regress to normal.[38] If ASC-US or greater is found on one of these examinations, the screening management recommendations should be followed (see page 1364). For patients followed by HPV DNA at 12 months, a positive result requires a colposcopy, whereas negative findings permit returning to a normal screening schedule. The ALTS trial suggested that after an initial diagnosis of CIN I or less with colposcopy, the most efficient test for identifying women with CIN grade II or III might be an HPV test alone at 12 months.[50]

If the cervical biopsy shows CIN II or III, further therapy is indicated, consisting of LEEP, cryotherapy, CKC, or laser ablation. However, CIN II may be followed up without treatment in certain clinical circumstances (e.g., young woman who desires fertility, is reliable about office visits, and prefers no treatment) at the discretion of the physician. Total hysterectomy may also be considered an option for CIN III, if indicated for preexisting pathologic conditions or enhancement of quality of life. The panel favored the use of CKC for patients in whom microinvasive cervical cancer was suspected.[51] The LEEP has been associated with a cautery artifact that may compromise the pathologic evaluation of the tissue specimen. Diagnosis of microinvasive or invasive cancer at cervical biopsy requires treatment according to the NCCN Guidelines for Cervical Cancer (in this issue and at www.NCCN.org).

Unsatisfactory Colposcopy for LSIL or ASC-US: If the colposcopic examination is unsatisfactory for ASC-US or LSIL, ECC should be performed in addition to the directed cervical biopsy (see page 1366). If the cervical biopsy is negative (or no biopsy is performed) and the ECC findings are negative or CIN I, repeat cytologic examinations at 6 months or HPV DNA testing at 12 months can be performed. The same strategy as previously outlined for a satisfactory colposcopy should be followed. ECC with a diagnosis of CIN II or III requires LEEP or CKC for definitive diagnosis.[52]

A cervical biopsy result of CIN II requires a LEEP or CKC to establish a definitive diagnosis. If CIN III is identified, options include LEEP, CKC, or a total hysterectomy. However, in patients with CIN III, an initial LEEP or CKC is recommended before the total hysterectomy to confirm the diagnosis. CKC is performed for microinvasive biopsy findings; CKC or LEEP can serve as definitive treatment if the lesion is confirmed to be intraepithelial.[51] A diagnosis of microinvasive or invasive cancer on cervical biopsy, LEEP, or CKC requires treatment according to the NCCN Guidelines for Cervical Cancer (in this issue and at www.NCCN.org).

Colposcopy for ASC-H or HSIL in Adult Women

All women diagnosed with ASC-H or HSIL on cytology require colposcopic evaluation. Again, management depends on whether the colposcopy is considered satisfactory or unsatisfactory (see either page 1367 or 1368). A LEEP or CKC is recommended for those with HSIL or with ASC-H and positive ECC who have unsatisfactory colposcopy results, with management as outlined (see page 1368). Patients with ASC-H who have a negative ECC with no lesion seen, however, can have cytology, colposcopy (including vaginal or vulvar colposcopy), and ECC repeated every 6 months until 2 results in a row are negative. Patients can resume regular screening after 2 consecutive negative results (see page 1360).

Management of those with a satisfactory colposcopy depends on whether a lesion is seen. ECC should be performed in those without a lesion or biopsy or with a negative colposcopy. If the ECC is negative, then the cytology, colposcopy (including vaginal or vulvar colposcopy), and ECC should be repeated in every 6 months until 2 results in a row are negative. If CIN I is identified on ECC, follow-up may be considered in women with a preceding ASC-H.

If a lesion is identified, 2 options are available.

A patient may choose a LEEP procedure as the first option, particularly if maintaining fertility is not an issue; this patient should then undergo follow-up as described in the next section (see page 1369). Biopsy is the second option. A negative cervical biopsy or CIN I lesion can be managed with either 1) a repeat cervical cytology, colposcopy (including vaginal and vulvar colposcopy), and ECC every 6 months (until 2 consecutive results are negative and then regular screening can resume); or 2) a LEEP or CKC can be considered for definitive diagnosis or for positive findings. A diagnosis of CIN II or III requires treatment with LEEP, cryotherapy, CKC, or laser ablation. However, CIN II may be followed without treatment in certain clinical circumstances (e.g., young woman who desires fertility, is reliable about office visits, and prefers no treatment) at the discretion of the physician. Total hysterectomy is another recommended option if the lesion is CIN III and if other indications for hysterectomy are present (e.g., symptomatic fibroids, persistent abnormal bleeding). Again, CKC should be performed for microinvasive biopsy findings, and any confirmed invasive cancers need treatment according to the NCCN Guidelines for Cervical Cancer (in this issue and at www.NCCN.org).

Follow-Up After Treatment of CIN

Surgical margins cannot be assessed after ablative procedures with cryotherapy or laser ablation; recommended follow-up for these patients consists of cervical cytology at 6 months or HPV DNA testing at 12 months (see page 1369).[53] Treatment of those initially managed with excision (i.e., LEEP or CKC) depends on the status of the margins. Cervical cytology at 6 months or HPV DNA testing at 12 months is recommended for those with CIN II or III lesions with negative margins and for all CIN I lesions. For CIN II and III lesions with positive margins, options include 1) cervical cytology at 6 months; an ECC can be considered (category 2B); 2) reexcision, especially if invasion is suspected; or 3) consider hysterectomy. If repeat cervical cytology or HPV DNA testing is negative, screening as per the guidelines may be resumed (see page 1360). If HPV DNA testing is positive, then colposcopy is recommended. If the repeat cervical cytology identifies ASC-US or greater, then the screening recommendations should be followed as previously mentioned (see page 1364).

Atypical Glandular Cells

The finding of AGC on cervical cytology is associated with a clinically significant lesion in 45% of patients,[54] including CIN, cervical adenocarcinoma in situ (AIS), cervical cancer, and endometrial, ovarian, and fallopian tube cancers (see page 1370).[3] CIN is the most common finding; 3% to 17% of women have invasive cancer.[3] Cervical cytologic screening methods are less useful for diagnosing AIS, because AIS affects areas of the cervix that are harder to sample (i.e., endocervical canal).[55,56] However, liquid-based cytology seems to improve detection of abnormal glandular lesions (http://www.sgo.org/WorkArea/showcontent.aspx?id=952). Thus, all patients with a finding of AGC on cervical cytology and who are younger than 35 years with no risk factors for endometrial cancer should undergo colposcopy, ECC, and HPV DNA testing (if not already done). Risk factors for endometrial cancer include obesity, unopposed estrogen replacement therapy, polycystic ovarian syndrome, tamoxifen therapy, anovulation, or hereditary nonpolyposis cancer syndrome (HNPCC).

Patients aged 35 years or older and all those with atypical glandular endometrial cells, abnormal bleeding, or endometrial cancer risk factors should also undergo endometrial biopsy, along with colposcopy, ECC, and HPV DNA testing (if not already performed), as part of their initial evaluation. Management is then directed by the results of the cervical biopsy, ECC, and HPV testing. Additional management may be dictated by the results of the endometrial biopsy (see page 1374). Note that it is not appropriate to repeat cervical cytology in the initial triage of AGC. HPV DNA testing alone is also not appropriate in the initial triage of all subcategories of AGC.[57]

If cervical biopsy and ECC identify CIN (I, II, or III) or AIS, further evaluation using CKC is indicated (see page 1372). However, a patient with an adequate colposcopic examination, a cervical biopsy revealing CIN I, and a negative ECC may be managed conservatively either with a repeat cervical cytology every 6 months until 2 consecutive negative results are obtained, or with HPV DNA testing at 12 months. Colposcopy is recommended for those with cervical cytology greater than ASC-US. For patients with cervical biopsy findings of CIN II or III but with a negative ECC result, LEEP or CKC is recommended (see page 1372).

The panel felt that most patients with a cervical cytology showing AGC and an abnormal cervical biopsy result or ECC should undergo CKC to both confirm the diagnosis and serve as potential treatment. The use of LEEP in patients with AIS has been associated with an increased incidence of positive excision margins in the tissue specimen.[58] Therefore, CKC is the preferred diagnostic procedure in patients at risk for AIS or microinvasion. CKC should be followed by endometrial sampling if "AGCs favor neoplasia" or "AIS" is reported.

Management of AIS

The panel recommends that all patients with AIS should be strongly considered for referral to a gynecologic oncologist or similar specialist (see page 1373). Treatment choice depends on the patient's desire for fertility. The definitive treatment for AIS is hysterectomy.[36] Patients desiring to preserve fertility and who have a CKC specimen with negative margins of excision may be followed up conservatively with repeat cervical cytology with (or without) ECC every 6 months until hysterectomy, and should also receive counseling on the risks of this strategy. Hysterectomy should be strongly considered in these patients when childbearing is completed. Women with positive findings on cervical cytology/ECC should then be managed according to the options on page 1370. Those with negative findings can continue screening every 6 months.

However, clear margins of excision do not rule out persistent AIS, because approximately 30% of patients have residual disease on subsequent hysterectomy.[36,59] If CKC margins are positive for abnormal glandular cells, a hysterectomy is recommended if the patient does not desire to remain fertile. Repeat CKC should be considered before hysterectomy to rule out invasive disease (category 2B).

Reexcision to attain negative margins is recommended for patients with positive margins who wish to remain fertile. These patients should also receive counseling regarding the risks of this strategy. Hysterectomy should be strongly considered in these patients when childbearing is completed.

Finally, patients with invasive adenocarcinoma on cervical biopsy, ECC, CKC, or endometrial biopsy should undergo treatment according to the NCCN Guidelines for Cervical Cancer (in this issue and at www.NCCN.org) and for Uterine Neoplasms (available at www.NCCN.org).

Management of Endometrial Biopsy

If the result of the endometrial biopsy is negative, transvaginal ultrasound to determine the endometrial stripe thickness may be considered if no other source for the AGC has been identified (see page 1374). If the endometrial biopsy result is hyperplasia, recommended options are either hormone therapy or consideration of a uterine dilatation and curettage (D&C). Patients with atypical hyperplasia on biopsy should undergo a D&C; additionally, referral to a gynecologic oncologist or similar specialist should be considered. For patients with unsatisfactory endometrial biopsy results, consider D&C or transvaginal ultrasound for endometrial stripe thickening if no other source of AGC has been identified in a postmenopausal woman. A diagnosis of endometrial cancer requires treatment according to the NCCN Guidelines for Uterine Neoplasms (available at www.NCCN.org).

Colposcopy During Pregnancy

During pregnancy, the recommendations for colposcopy and follow-up are the same as outlined previously, with the following exceptions:

- Brush cytology is safe during pregnancy; however, to avoid possible disruption of the pregnancy, ECC should not be performed.[3]
- Colposcopy and cervical biopsy during pregnancy should be limited to women in whom high-grade neoplasia or invasive cancer is suspected; LSIL and ASC-US can be deferred until 6 weeks postpartum.
- Treatment for CIN (any grade) should be delayed until after pregnancy.[60–63]

Because colposcopic evaluation in pregnant women can be problematic, consultation with or referral to an experienced colposcopist should be considered. A diagnostic limited excisional procedure is recommended only if invasive cancer is suspected (see page 1376).

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Individual Disclosures for the NCCN Cervical Cancer Screening Panel					
Panel Member	**Clinical Research Support**	**Advisory Boards, Speakers Bureau, Expert Witness, or Consultant**	**Patent, Equity, or Royalty**	**Other**	**Date Completed**
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