National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Cervical Cancer Screening

V.1.2009

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NCCN Guidelines Panel Disclosures

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

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

SUMMARY OF GUIDELINES UPDATES

Summary of changes in the 1.2009 version of the Cervical Cancer Screening Guidelines from the 1.2008 version include:

CERVS-4

- **Cervical cytology/Pap test unsatisfactory was clarified by adding "Repeat cervical cytology/Pap test should be done within 6-12 weeks."**

CERVS-5

- **ASC-H or HSIL, unsatisfactory colposcopy, "Negative or CIN I" replaced "CIN II or less" for clarification.**
- **Unsatisfactory colposcopy, CIN II-III, NOS and CIN III, "cold-knife conization" was added as a treatment option.**

CERVS-7

- **CIN I, repeat cervical cytology/Pap test at 6 mo, ≥ ASC-US, "See Screening Follow-up (CERVS-6)" replaced "colposcopy." Also for CERVS-8.**

CERVS-9

- **Satisfactory colposcopy, lesion seen, biopsy, CIN II, footnote g, "CIN II may be followed without treatment in certain clinical circumstances at the discretion of the physician" was added.**
- **Satisfactory colposcopy, lesion seen, LEEP, "consider fertility issues" replaced "if fertility not an issue" for clarification.**

CERVS-10

- **CIN II, III with positive margins, reexcision, "not recommended unless both endocervical and ectocervical margins are positive" was added for clarification.**
- **CIN II, III with negative margins or CIN I with positive or negative margin, repeat cervical cytology/Pap test at 6 mo, ≥ ASC-US, "See Screening Follow-up (CERVS-6)" replaced "colposcopy."**

CERVS-B

- **Colposcopy during pregnancy, bullet "Colposcopically directed cervical biopsy during pregnancy should be limited to patients where high-grade neoplasia or invasive cancer is suspected" is new to the page.**

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SCREENING GUIDELINES FOR EARLY DETECTION OF CERVICAL CANCER

When to start screening

- **Cervical cancer screening should begin approximately 3 years after the onset of vaginal intercourse.**
- **Screening should begin no later than 21 years of age.**
- **It is critical that adolescents who may not need a cervical cytology test obtain appropriate preventive health care, including assessment of health risks, contraception and prevention counseling, screening and treatment of sexually transmitted diseases.**
- **The need for cervical cancer screening should not be the basis for the onset of gynecologic care.**

When to discontinue screening

- **Women at age 70 and older with an intact cervix who have had three or more documented, consecutive, technically satisfactory negative cervical cytology tests, and no abnormal/positive cytology test, within the 10 year period prior to age 70 may elect to cease cervical cancer screening.**
- **Screening is recommended for women who have not been previously screened, women for whom information about previous screening is unavailable, and when past screening is unlikely.**
- **Women who have a history of cervical cancer, in utero exposure to diethylstilbestrol (DES), and/or who are immunocompromised (including HIV+) should continue cervical cancer screening for as long as they are in reasonably good health and do not have a life-limiting chronic condition.**
- **Women over the age of 70 should discuss their need for cervical cancer screening with their health care provider based on their individual circumstances, including the potential benefits, harms, and limitations of screening, and make informed decisions about whether to continue screening.**
- **Women with comorbid or life-threatening illnesses may forego cervical cancer screening.**

Screening Guidelines continued (See CERVS-2)

From Saslow D, Runowicz C, Solomon D, et al., American cancer society guideline for the early detection of cervical neoplasia and cancer. CA: A Cancer Journal for Clinicians 52(6): 342-376, 2002. Reproduced with permission from Lippincott, Williams & Wilkins.

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SCREENING GUIDELINES FOR EARLY DETECTION OF CERVICAL CANCER

Hysterectomy

- Screening with vaginal cytology tests after total hysterectomy (with removal of the cervix) for benign gynecologic disease is not indicated.
- Efforts should be made to confirm and/or document via physical exam and review of the pathology report (when available) that the cervix was completely removed.
- Women who have had a subtotal hysterectomy should continue cervical cancer screening as per current guidelines.
- Patients with a history of cervical intraepithelial neoplasia (CIN) II-III, or for whom it is not possible to document the absence of CIN II-III prior to or as the indication for the hysterectomy, should be screened until three documented, consecutive, technically satisfactory negative vaginal cytology tests, and no abnormal/positive cytology tests, within a 10 year period are achieved.
- Women with a history of in utero diethylstilbestrol (DES) exposure and/or with a history of cervical carcinoma should continue screening after hysterectomy for as long as they are in reasonably good health and do not have a life-limiting chronic condition.

Screening interval

- After initiation of screening, cervical screening should be performed annually with conventional cervical cytology smears OR every 2 years using liquid-based cytology; at or after age 30, women who have had 3 consecutive, technically satisfactory negative cytology results may be screened every 2-3 years (unless they have a history of in utero DES exposure, are HIV+, or are immunocompromised).
- Human papillomavirus (HPV) DNA testing for primary cervical cancer screening has recently been approved by the FDA for women $\geq$ 30 y of age. It is reasonable to consider that for women age 30 and over, as an alternative to cervical cytology testing alone, cervical screening may be performed every 3 years using conventional or liquid-based cytology combined with a test for DNA for high-risk HPV types.
- Until more data are available, women who test positive for HPV DNA should continue screening at the discretion of their health care provider.[a]
- Frequency of combined cytology and HPV DNA testing should NOT be more often than every 3 years, if both tests are negative.
- Counseling and education related to HPV infection is a critical need.
- Women who received HPV vaccination should continue cervical cancer screening according to the guidelines.

See Initial Findings on Screening Exam (CERVS-3)

[a]FDA approved HPV testing for high-risk virus types. It is not useful to test for low-risk virus types.

From Saslow D, Runowicz C, Solomon D, et al., American cancer society guideline for the early detection of cervical neoplasia and cancer. CA: A Cancer Journal for Clinicians 52(6): 342-376, 2002. Reproduced with permission from Lippincott, Williams & Wilkins.

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Cervical Cancer Screening

INITIAL FINDINGS OF SCREENING EXAM[b]

- Visible/suspicious lesion on cervix → See Screening Findings (CERVS-4)
- Cervical cytology/Pap test[c,d] negative for intraepithelial lesion or malignancy → See Screening Findings (CERVS-4)
- Cervical cytology/Pap test[c,d] unsatisfactory → See Screening Findings (CERVS-4)
- Cervical cytology/Pap test[c,d] positive for invasive cancer → See Screening Findings (CERVS-4)
- Atypical squamous cells (ASC)
  - Undetermined significance (ASC-US) → See Screening Findings Adolescents or Young Women ≤ 21 y (CERVS-5)
  - Suspicion of high-grade dysplasia (ASC-H) → See Screening Findings Adolescents or Young Women ≤ 21 y (CERVS-5)
- Low-grade squamous intraepithelial lesions (LSIL) → See Screening Findings Adult > 21 y (CERVS-6)
- High-grade squamous intraepithelial lesions (HSIL) → See Screening Findings Adult > 21 y (CERVS-6)
- Atypical glandular cells (AGC) → See Follow-Up of Cervical Biopsy Findings (CERVS-11)

[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
- 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 (CERVS-A).

[d]Conventional Pap test or thin-layer technology is an acceptable method for primary screening.

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Cervical Cancer Screening

SCREENING FINDINGS	FOLLOW-UP OF SCREENING EXAM
Visible lesion on cervix	Biopsy
Cervical cytology/Pap test negative for intraepithelial lesion or malignancy	Screening frequency based on screening guidelines See Screening for Early Detection of Cervical Cancer (CERVS-1)
Cervical cytology/Pap test unsatisfactory	Repeat cervical cytology/Pap test should be done within 6-12 weeks. Treat infection if present and indicated
Cervical cytology/Pap test positive for invasive cancer	Biopsy visible lesion; diagnostic excision if no visible lesion

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Cervical Cancer Screening

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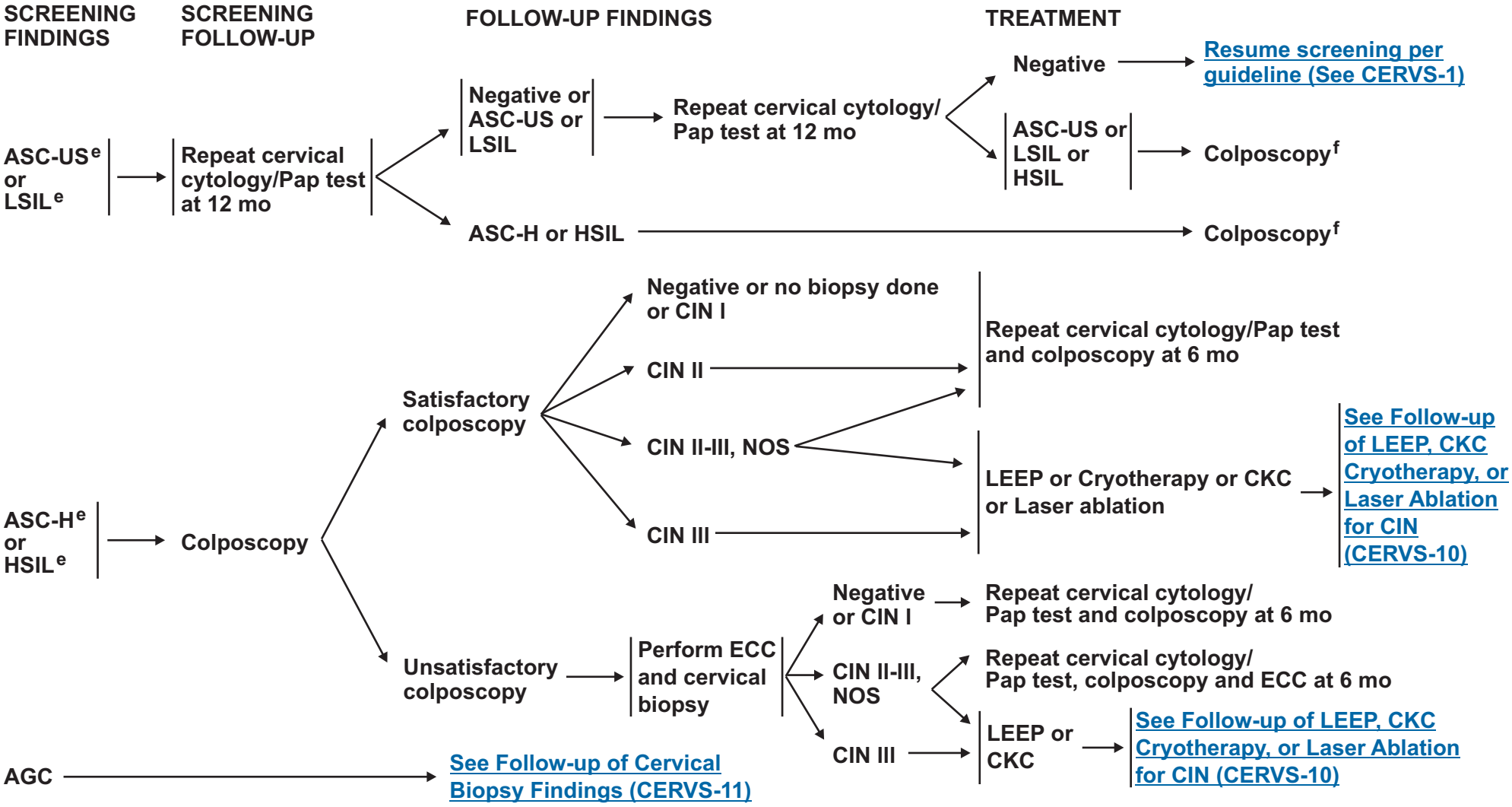
ADOLESCENTS OR YOUNG WOMEN ≤ 21 Y



[e]HPV testing is not recommended in adolescent or young women ≤ 21 y.
[f]Follow appropriate colposcopy findings pathway (i.e. satisfactory or unsatisfactory). If appropriate, see Colposcopy During Pregnancy (CERVS-B).

CIN= Cervical intraepithelial neoplasia
ECC= Endocervical curettage
LEEP= Loop electrosurgical excision procedure
CKC= Cold-knife conization

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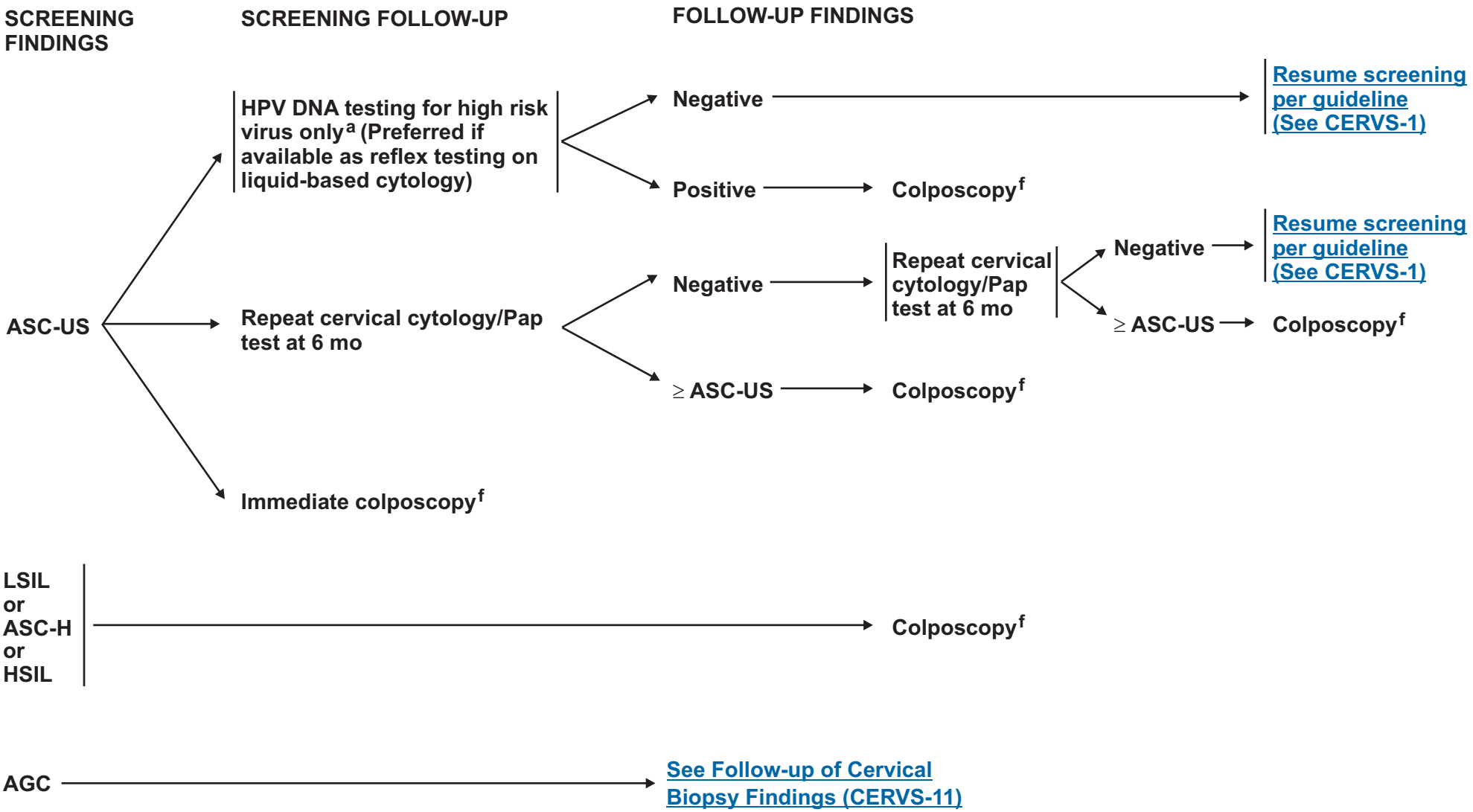
Cervical Cancer Screening

ADULT > 21Y



[a]FDA approved HPV testing for high-risk virus types. It is not useful to test for low-risk virus types.
[f]Follow appropriate colposcopy findings pathway (i.e. satisfactory or unsatisfactory). If appropriate, see Colposcopy During Pregnancy (CERVS-B).

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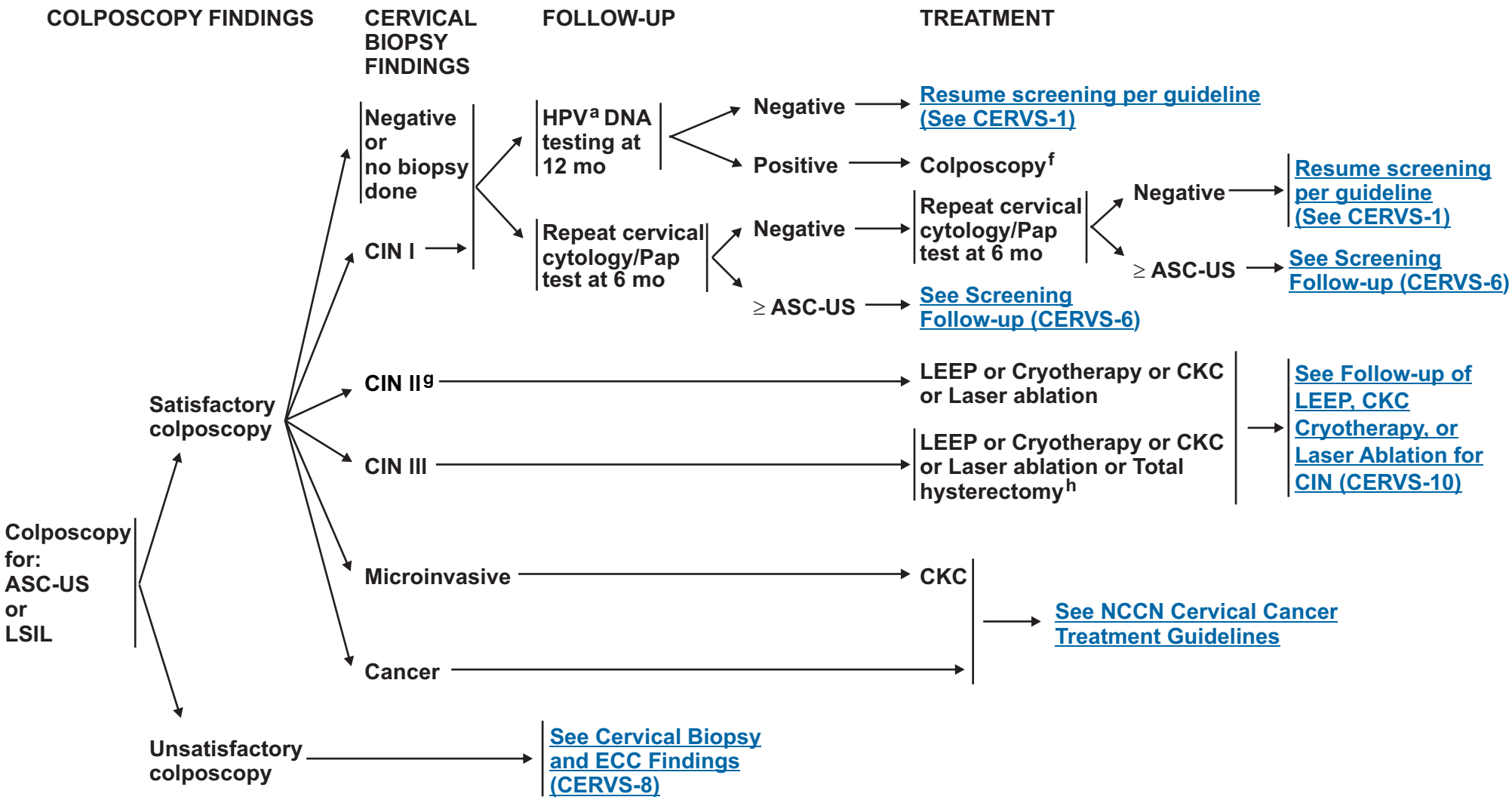
Cervical Cancer Screening

ADULT > 21Y



[a] FDA approved HPV testing for high-risk virus types. It is not useful to test for low-risk virus types.
[f] Follow appropriate colposcopy findings pathway (i.e. satisfactory or unsatisfactory). If appropriate, see Colposcopy During Pregnancy (CERVS-B).
[g] CIN II may be followed without treatment in certain clinical circumstances at the discretion of the physician.
[h] If appropriate for pre-existing pathologic condition or quality of life.

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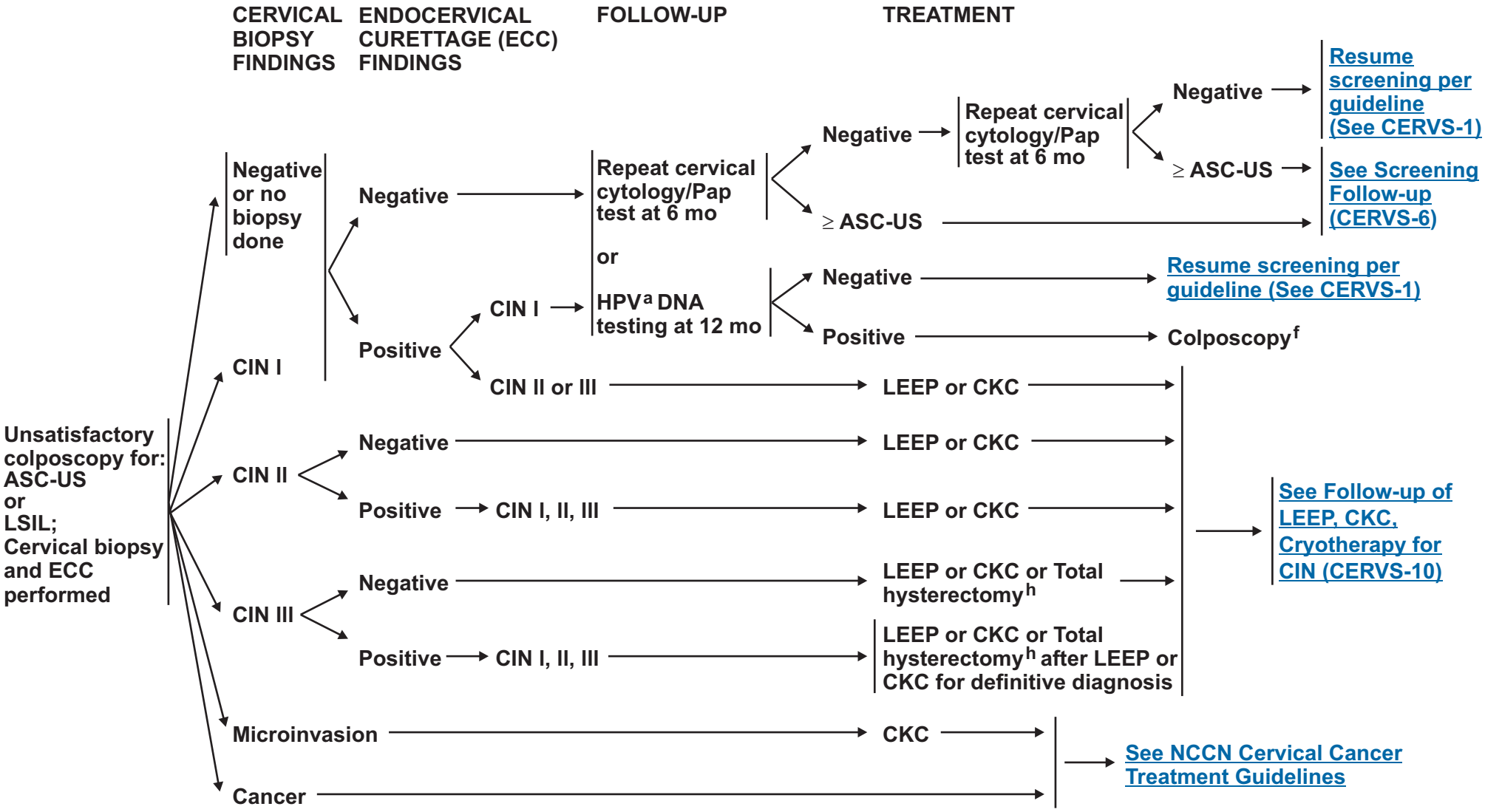
ADULT > 21Y



[a] FDA approved HPV testing for high-risk virus types. It is not useful to test for low-risk virus types.

[f] Follow appropriate colposcopy findings pathway (i.e. satisfactory or unsatisfactory). If appropriate, see Colposcopy During Pregnancy (CERVS-B).

[h] If appropriate for pre-existing pathologic condition or quality of life.

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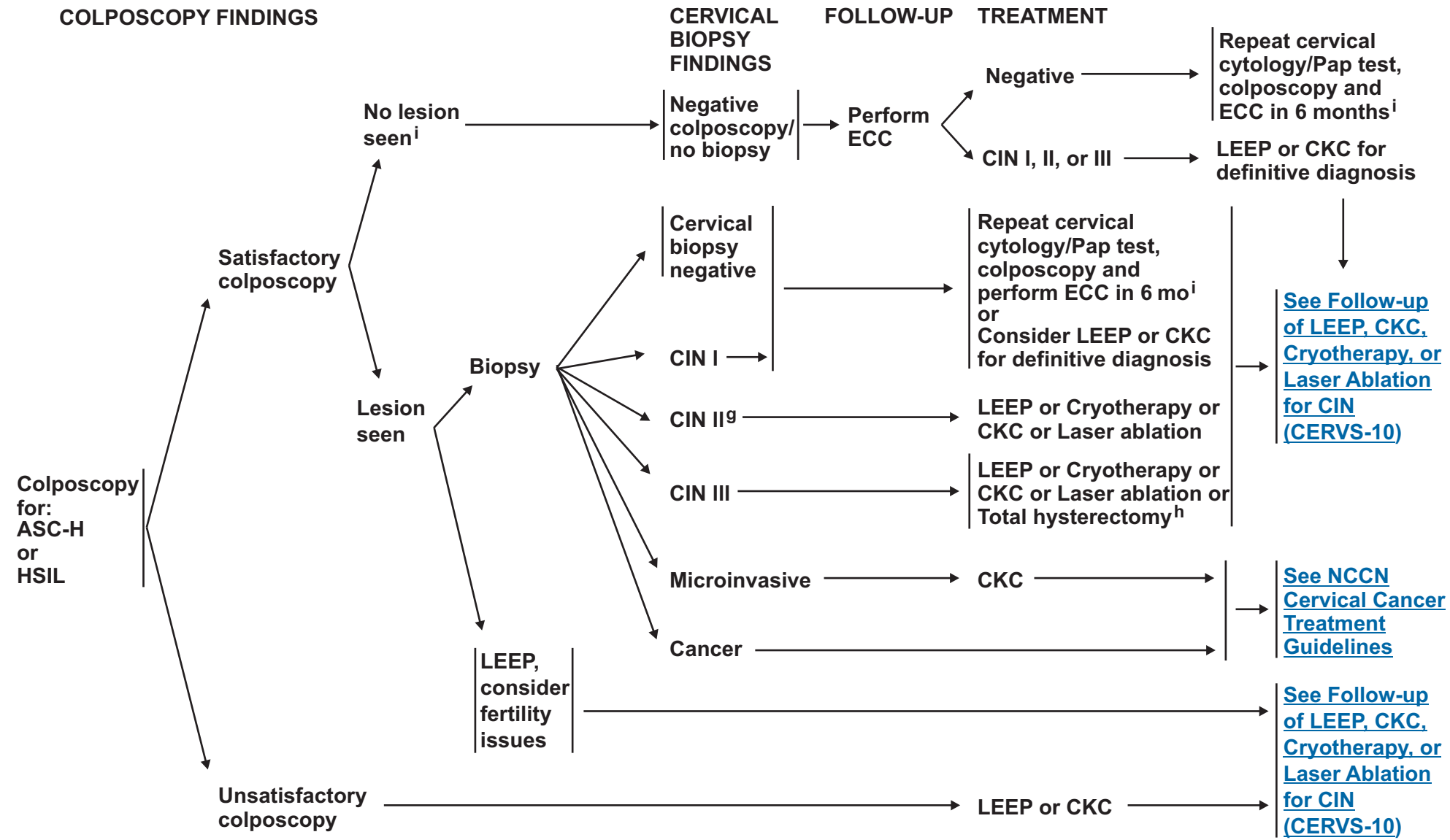
Cervical Cancer Screening



[g] CIN II may be followed without treatment in certain clinical circumstances at the discretion of the physician.
[h] If appropriate for pre-existing pathologic condition or quality of life.
[i] Perform vaginal and vulvar colposcopy.

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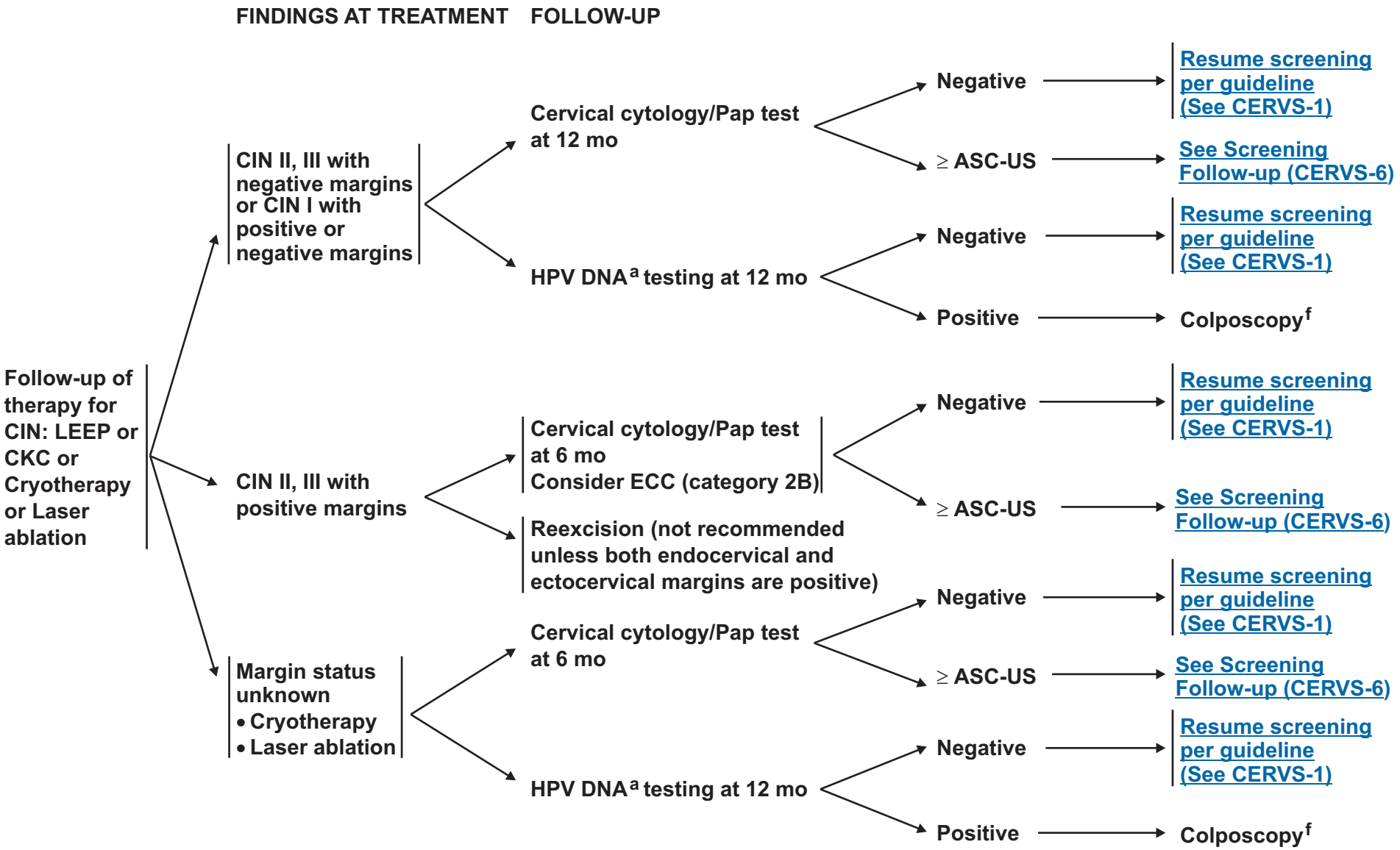
Cervical Cancer Screening



[a]FDA approved HPV testing for high-risk virus types. It is not useful to test for low-risk virus types.
[f]Follow appropriate colposcopy findings pathway (i.e. satisfactory or unsatisfactory). If appropriate, see Colposcopy During Pregnancy (CERVS-B).

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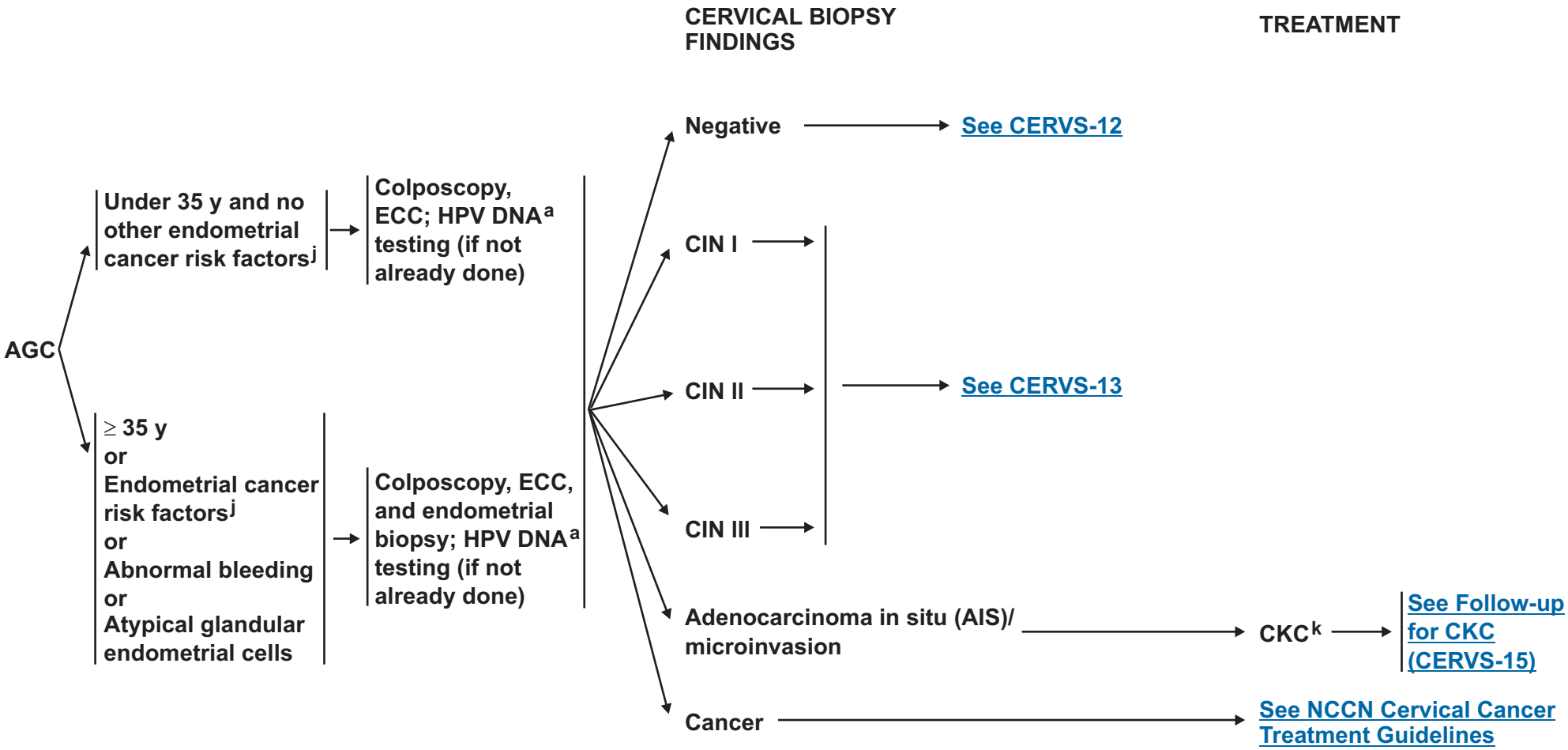
Cervical Cancer Screening

FOLLOW-UP OF CERVICAL BIOPSY FINDINGS



[a] FDA approved HPV testing for high-risk virus types. It is not useful to test for low-risk virus types.
[j] Endometrial cancer risk factors: obesity, unopposed estrogen replacement therapy, polycystic ovarian disease, tamoxifen therapy, anovulation, Hereditary Non-Polyposis Colorectal Cancer syndrome (HNPCC).
[k] If atypical glandular cells favor neoplasia or adenocarcinoma in situ, follow CKC with endometrial sampling if not yet done.

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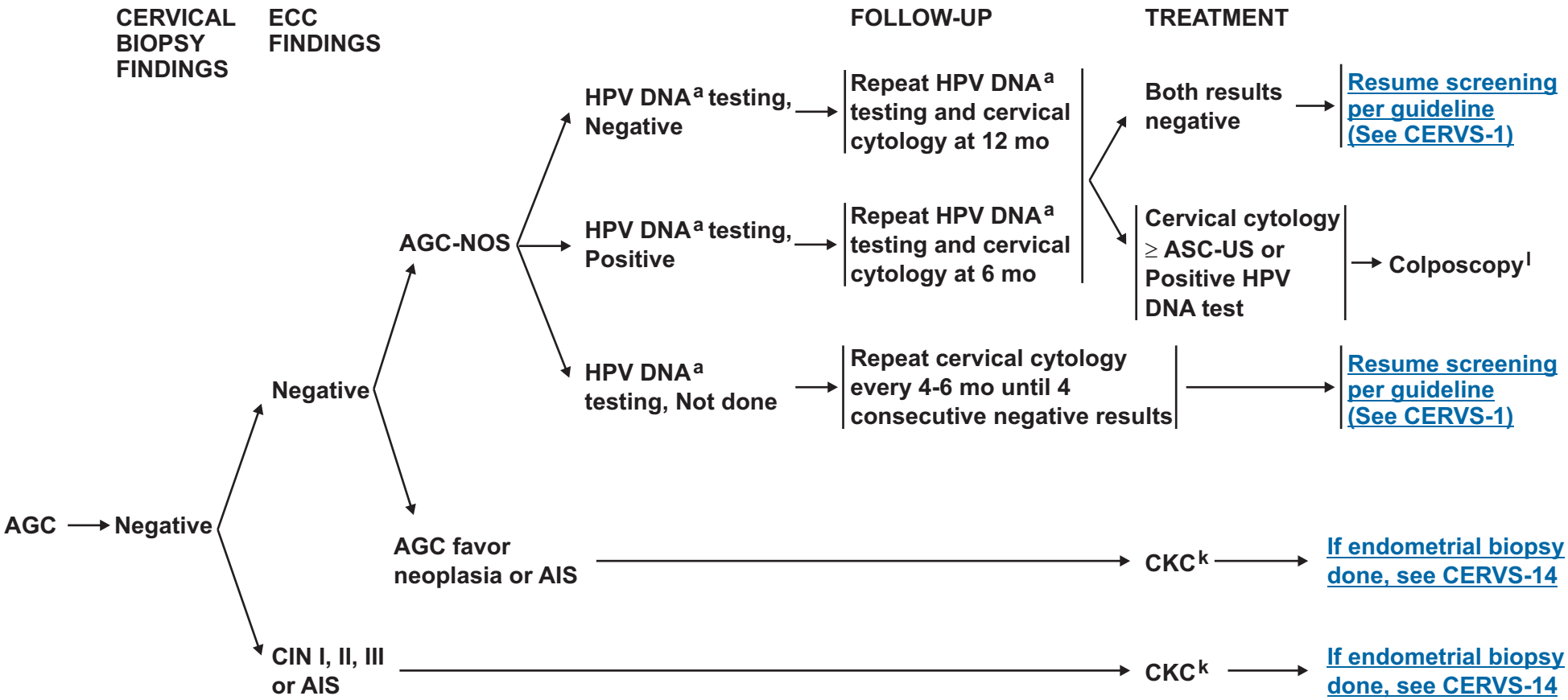
Cervical Cancer Screening

FOLLOW-UP OF CERVICAL BIOPSY FINDINGS



[a]FDA approved HPV testing for high-risk virus types. It is not useful to test for low-risk virus types.
[k]If atypical glandular cells favor neoplasia or adenocarcinoma in situ, follow CKC with endometrial sampling if not yet done.
[l]Follow appropriate colposcopy findings pathway (See CERVS-11). If appropriate, see Colposcopy During Pregnancy (CERVS-B).

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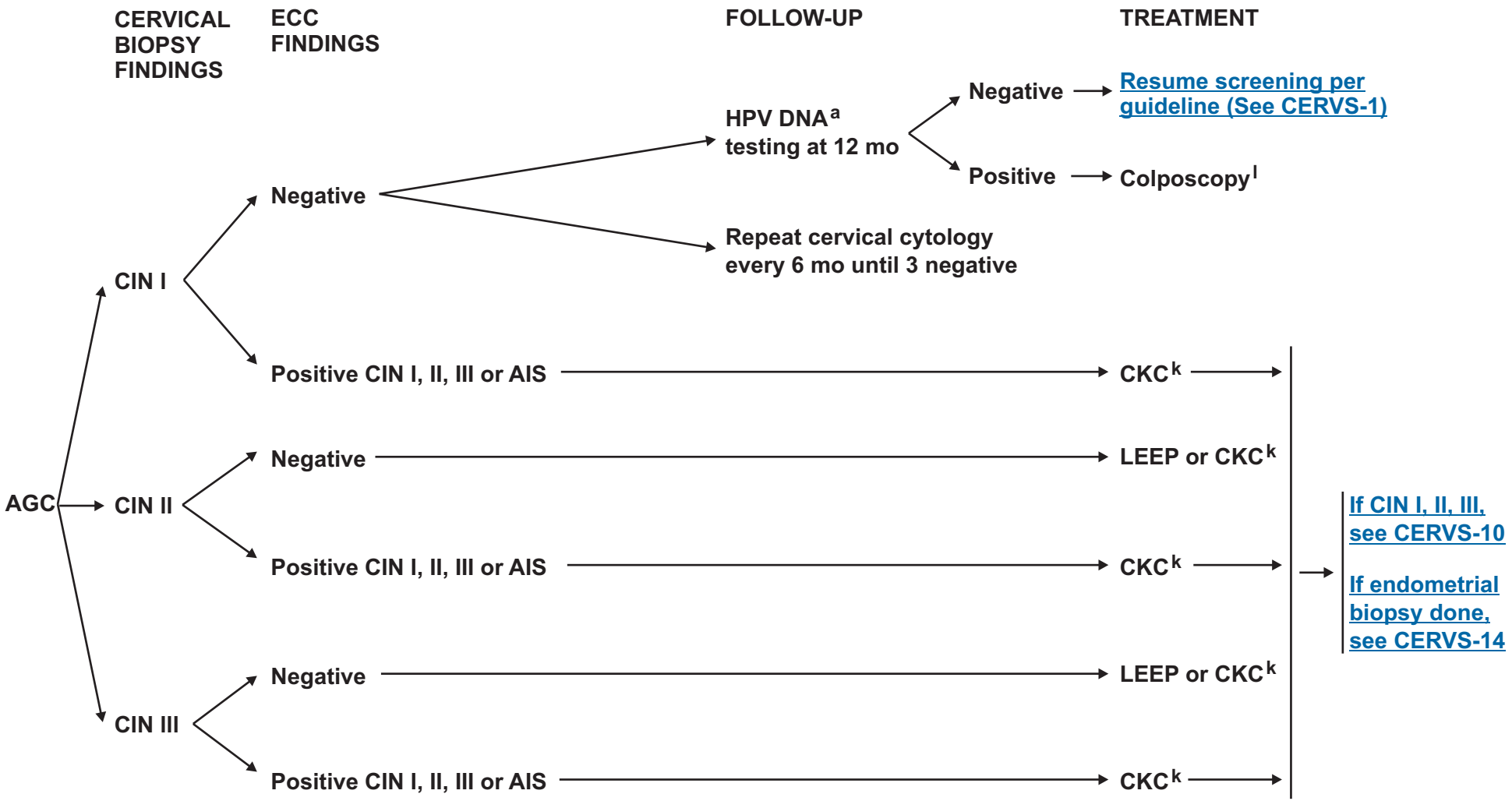
Cervical Cancer Screening

FOLLOW-UP OF CERVICAL BIOPSY FINDINGS



[a]FDA approved HPV testing for high-risk virus types. It is not useful to test for low-risk virus types.
[k]If atypical glandular cells favor neoplasia or adenocarcinoma in situ, follow CKC with endometrial sampling if not yet done.
[l]Follow appropriate colposcopy findings pathway (See CERVS-11). If appropriate, see Colposcopy During Pregnancy (CERVS-B).

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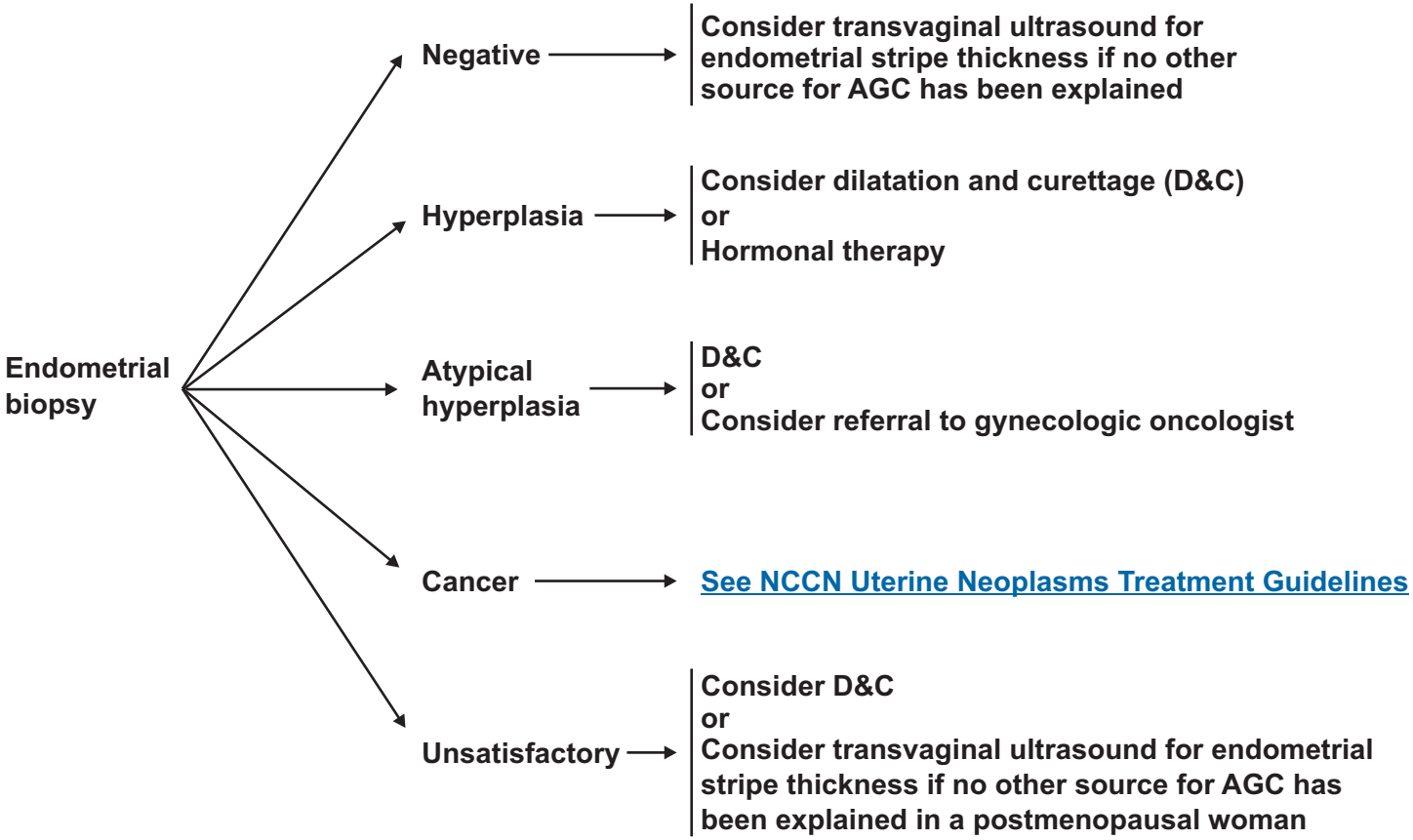
Cervical Cancer Screening

FOLLOW-UP OF ENDOMETRIAL BIOPSY FINDINGS



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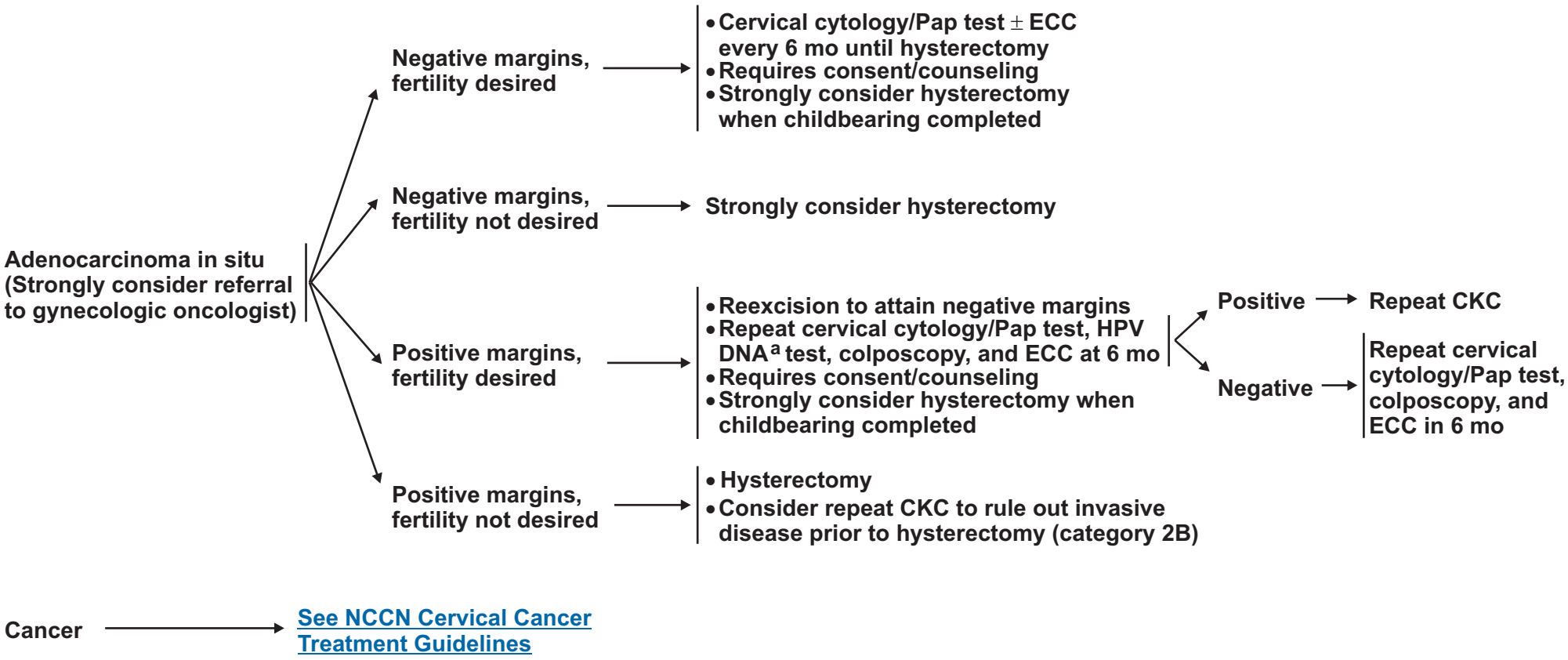
Cervical Cancer Screening

FOLLOW-UP FOR CKC



[a] FDA approved HPV testing for high-risk virus types. It is not useful to test for low-risk virus types.

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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, eg, partially obscuring blood, inflammation, etc.)
- 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)

GENERAL CATEGORIZATION (optional)
- Negative for Intraepithelial Lesion or Malignancy
- Epithelial Cell Abnormality: See Interpretation/Result (specify "squamous" or "glandular" as appropriate)
- Other: See Interpretation/Result (eg, endometrial cells in a woman ≥ 40 y of age)

AUTOMATED REVIEW
- If case examine by automated device, specify device and result

ANCILLARY TESTING
- Provide a brief description of the test methods and report the result so that it is easily understood by the clinician.

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 spp
  - Shift for 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 cells status post hysterectomy
  - Atrophy

Return to Initial Findings of Screening Exam (CERVS-3)

Bethesda System 2001 continued on next page.

NCI Bethesda System 2001. Available at: http://bethesda2001.cancer.gov/terminology.html. Accessed October 15, 2008.

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BETHESDA SYSTEM 2001

OTHER
- Endometrial cells (in a woman ≥ 40 y of age) (Specify if "negative" for squamous intraepithelial lesion)

EPITHELIAL CELL ABNORMALITIES
- **SQUAMOUS CELL**
  - Atypical squamous cells
    - of undetermined significance (ASC-US)
    - cannot exclude HSIL (ASC-H)
  - Low grade squamous intraepithelial lesion (LSIL)
    - encompassing: HPV/mild dysplasia/CIN 1
  - High grade squamous intraepithelial lesion (HSIL)
    - encompassing: moderate and severe dysplasia, CIS/CIN 2 and CIN 3
    - 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)

EDUCATIONAL NOTES AND SUGGESTIONS (optional)
- Suggestions should be concise and consistent with clinical follow-up guidelines published by professional organizations (references to relevant publications may be included).

Return to Initial Findings of Screening Exam (CERVS-3)

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NCI Bethesda System 2001. Available at: http://bethesda2001.cancer.gov/terminology.html. Accessed October 15, 2008.

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COLPOSCOPY DURING PREGNANCY

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

- **No ECC**
- **Treatment for CIN (any grade) delayed until after pregnancy**
- **Colposcopically directed cervical biopsy during pregnancy should be limited to patients where high-grade neoplasia or invasive cancer is suspected.**
- **Brush cytology is safe during pregnancy.**
- **Consultation or referral to colposcopist with experience in colposcopy during pregnancy is recommended.**
- **Diagnostic limited excisional procedure is recommended only if invasion is suspected.**

Return to Follow-up of Screening Exam (CERVS-5)

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Discussion

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.

Overview

Despite a significant decrease in the incidence and mortality of cervical carcinoma in the United States, it is estimated that 11,070 women will be diagnosed in 2008, with 3,870 expected deaths.[1] Because cervical cytology screening is the current method for early detection of this neoplasm, the purpose of the NCCN Cervical Cancer Screening Guidelines is to provide direction for the evaluation and management of cervical cytology.

The NCCN guidelines include recommendations regarding screening techniques, screening intervals, and follow-up of abnormal screening results including colposcopy. Cervical cytology screening techniques include conventional Papanicolaou (Pap) smears or liquid-based cytology. Unless specifically noted, these techniques are collectively referred to as “cervical cytology” in this manuscript. Human papillomavirus (HPV) DNA testing for primary cervical cancer has been approved by the FDA. However, HPV DNA testing is not recommended in women younger than 21 years.[2] HPV DNA testing for high-risk virus types can also be used as a component of both primary screening and work-up of abnormal cytology results; it is not useful to test for low-risk virus types.[2]

Colposcopy, along with colposcopically directed biopsies, has become 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, 10-16 times). 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 to determine the extent of preinvasive disease. If the entire squamocolumnar junction of the cervix is visualized (that is, the entire transformation zone is seen), the examination is considered satisfactory and endocervical curettage (ECC) is unnecessary.[3] Special considerations for colposcopy performed during pregnancy are also discussed (see CERVS-B).

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 (CERVS-1, and CERVS-2)

The NCCN panel adopted the recommendations of the American Cancer Society on the initiation and frequency of cervical cancer screening,[4] namely, that women should begin screening approximately 3 years after the onset of vaginal intercourse or no later than 21 years of age. After initiation, cervical screening should be performed annually

with conventional cervical cytology smears (that is, Pap smears) or every 2 years if liquid-based cytology is used (http://www.cdc.gov/std/hpv/ScreeningTables.pdf).

HPV DNA testing is not recommended in adolescent or younger women (that is, younger than 21 years) (see CERVS-5).[2] In women 30 years or older, cervical cytology combined with DNA testing for high-risk HPV types every 3 years may be considered an alternative to cervical cytology alone at 1 to 2 year intervals.[5] Combined cytology and HPV DNA testing should not be done more often than every 3 years if both tests are negative. The appropriate screening interval for women who test positive for HPV DNA is unknown. Until more data are available, these women should continue screening at the discretion of their physician. The Hybrid Capture 2 HPV DNA test (HC2) assesses whether women are positive for any of 13 high-risk types of HPV, although there are false-positive results due to slight cross reactivity with noncarcinogenic HPV subtypes.[6,7] Note that the HC2 has no internal standard to determine sample adequacy.[8] Data about the sensitivity of HC2 for disease detection are derived from studies where it was used in the setting of co-collection with cytology. The performance characteristics of HC2 as a stand-alone test are unknown. The American Society for Colposcopy and Cervical Pathology (ASCCP) has published information about the HPV DNA test ("Clinical Uses of Human Papillomavirus (HPV) DNA Self-Assessment Booklet)" (http://www.asccp.org/bookstore/hpv_booklet.html).

After a 30-year old woman at low risk for cervical cancer has had 3 or more consecutive satisfactory annual examinations with normal findings, cervical screening may be performed less frequently (that is, every 2 to 3 years, at the discretion of her physician). These recommendations are similar for women who have undergone a subtotal hysterectomy. Screening for cervical cancer is not necessary after total hysterectomy for benign disease, although efforts should be made to document via physical examination or pathology report that the cervix was completely removed. Women with a history of hysterectomy and with CIN II-III lesions should continue screening with vaginal cytology unless there is a 10-year span with no abnormal cytology results.

Ongoing screening is also recommended for women who have not been previously screened, or when prior screening was unlikely or the results are unknown. In addition, women with high-risk factors (such as a history of cervical cancer, in utero DES exposure, or immunocompromise [that is, HIV infection]), should also continue screening.

Screening for cervical cancer may be discontinued for women who are age 70 years and older with no history of abnormal cervical cytology tests in the previous 10 years. Women with comorbid or life-threatening illness can also consider stopping screening. Other situations where screening can be discontinued are given on CERVS-1. However, decisions to stop screening should be made in consultation with woman's health care provider, considering such issues as potential benefits, harms, and limitations of screening.

Vaccination with the quadrivalent HPV vaccine provides protection against infection by HPV-16 and HPV-18. After 3 years, the efficacy of the quadrivalent HPV vaccine was 99% for preventing cervical intraepithelial neoplasia grades 2 and 3 (CIN2/3, which are precursors of cervical cancer) caused by HPV 16 or 18 in females who were not previously infected with either HPV 16 or 18 before vaccination; however, efficacy was only 44% in those who had been infected prior to vaccination.[9] Although it is not clear how long immunity will last after vaccination, data suggest the quadrivalent HPV vaccine is effective for at least 5 years.[10] Another prophylactic HPV vaccine is the bivalent vaccine; however, it is not currently approved in the United States.[11,12]

The US Food and Drug Administration (FDA) has approved the HPV quadrivalent vaccine for use in girls and women ages 9 to 26 years (http://www.fda.gov/cber/label/gardasilLB.pdf). However, the vaccine is most effective if given to girls and young women before sexual intercourse is initiated. Guidelines from the American College of Obstetricians and Gynecologists (ACOG), Advisory Committee on Immunization Practices (ACIP) , and American Cancer Society (ACS) all agree that 11 to 12 year old girls should receive routine vaccination with the HPV vaccine, but they differ regarding recommendations for other age groups.[13-15]

Although HPV-16 and HPV-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 carcinogenic HPV.[16] Therefore, it is important to note that HPV vaccination does not alter screening recommendations. Vaccinated women should continue cervical cancer screening according to the guidelines.

Initial Findings (CERVS-3, CERVS-4)

The NCCN panel recommends that cervical cytology tests should be reported using the Bethesda System 2001 (see CERVS-A).[17] The 8 different possible results of an initial screening examination are summarized on CERVS-3.

It should be noted that for findings of atypical squamous cells (ASC), low-grade squamous intraepithelial lesions (LSIL), and high-grade squamous intraepithelial lesions (HSIL), the guidelines differ according to whether the patient is younger or older than 21 years.[2,18] These guidelines are discussed in the next section (see CERVS-5) and later in the manuscript (see CERVS-6). Atypical glandular cells (AGC) are also addressed later in the manuscript (see CERVS-11).

All women with cervical cytology tests reported as normal (that is, negative for intraepithelial lesion or malignancy), unsatisfactory, or positive for invasive cancer are managed as shown on CERVS-4. 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 of a visible lesion is recommended or a diagnostic excision is recommended if there is no visible lesion. 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. 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.

Squamous Epithelial Cell Abnormalities in Adolescents or Young Women Age 21 Years or Younger (CERVS-5)

The management of squamous cell abnormalities requires special consideration in adolescents or young women (21 years or younger) due both to the high prevalence of HPV positivity in this age group and to the frequent regression of LSIL lesions.[2,19] For example, various studies have reported that a high percentage of young women will be HPV positive within several years of initial sexual activity.[20-22] These statistics indicate that HPV testing cannot be used to further triage management of squamous epithelial abnormalities in this population. Therefore, the NCCN algorithms specifically note that HPV testing is not recommended in adolescent or young women younger than 21 years. Other studies have shown LSIL lesions typically regress in the younger population. 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 women with CIN III are picked up on subsequent screening.[2,23-25] Therefore, although colposcopy is routinely recommended for LSIL in women older than 21 years, younger patients may be initially followed with repeat cytology.

Atypical Squamous Cells of Undetermined Significance or Low-Grade Squamous Intraepithelial Lesion

Young women with 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 another 12 months. If the cytology results are negative after this 2-year period, then the patient can resume routine screening. If the cytology indicates ASC-US, ASC-H LSIL, or HSIL, then colposcopy is recommended. Patients then follow the "satisfactory" or "unsatisfactory" colposcopy pathway for adolescents or young women (see CERVS-5). Colposcopy is also recommended if the first rescreen at 12 months reveals atypical squamous cells – suspicion of high-grade dysplasia (ASC-H) or HSIL.

Atypical Squamous Cells – Suspicion of High Dysplasia

Colposcopy is recommended if initial screening reveals ASC-H or HSIL, due to the increased risk of 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 less, or if no biopsy was done. Additionally, patients with CIN II-III "not otherwise specified" (NOS) findings may elect to have an ablative or excision procedure (such as, laser ablation, cryotherapy, LEEP, or CKC). Patients with an unsatisfactory colposcopy should undergo ECC and cervical biopsy. These patients are then managed similarly to those with a satisfactory colposcopy with exception that LEEP or CKC is recommended for CIN III.

Squamous Epithelial Cell Abnormalities in Adults (CERVS-6)

Atypical Squamous Cells of Undetermined Significance or Low-Grade Squamous Intraepithelial Lesion

The guideline offers 3 options for the management of ASC-US. Unlike adolescents, HPV DNA testing for high-risk virus is informative in adult women due to 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 demonstrated 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.[26] A second option is immediate colposcopy.[2] A third option is to repeat the cervical cytology. If 2 consecutive cytology tests 6 months apart are negative, annual screening may be resumed. However, if the repeat cytology test reveals persistent ASC-US or greater, a colposcopic evaluation of the cervix is appropriate.

Low-Grade Squamous Intraepithelial Lesion, Atypical Squamous Cells-Suspicion of High Dysplasia, or High-Grade Intraepithelial Lesion

In adolescent patients, LSIL often regresses spontaneously; therefore, repeat cervical cytology is an effective triage strategy. In contrast, in adults, the ALTS trial demonstrated that LSIL cytology is best managed by colposcopy initially, because no useful triage strategy was identified.[26] Therefore, colposcopy is recommended for all squamous lesions other than ASC-US (that is, LSIL, ASC-H, HSIL).

Colposcopy for LSIL or ASC-US in Adult Women

Satisfactory Colposcopy (CERVS-7)

The first consideration in evaluating the colposcopy result is a determination of whether the colposcopy visualized the entire transition zone of the cervix and was considered satisfactory.[2] Unsatisfactory colposcopies are addressed in the next section. Note that the ASCCP recently revised their 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).[2,18]

Women found to have negative findings or CIN I on cervical biopsy after satisfactory colposcopic examination may be followed 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 over-treatment. If negative cervical cytology is found at 6 and at 12 months, a normal screening schedule can be reinstated, reflecting the finding that most of these lesions will regress to normal.[19] If ASC-US or greater is found on one of these examinations, the screening follow-up recommendations should be followed (see CERV-6). 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 the most efficient test for identifying women with CIN grade II or III after an initial diagnosis of CIN I or less by colposcopy might be an HPV test alone at 12 months.[27]

If the cervical biopsy reveals CIN II or III, further therapy is indicated consisting of LEEP, cryotherapy, CKC, or laser ablation. However, CIN II may be followed without treatment in certain clinical circumstances at the discretion of the physician. Total hysterectomy may also be considered an option for CIN III, if indicated for other reasons or for enhancement of quality of life. The panel favored the use of CKC in patients in whom microinvasive cervical cancer was suspected. 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 Cervical Cancer Guidelines.

Unsatisfactory Colposcopy (CERVS-8)

If the colposcopic examination is unsatisfactory, ECC should be performed in addition to the directed cervical biopsy. If the cervical biopsy is negative and the ECC findings are negative or CIN I, repeat cytologic examinations at 6 and 12 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.[28]

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. Cold-knife conization is performed for microinvasive biopsy findings; CKC or LEEP can serve as definitive treatment if the lesion is confirmed to be intraepithelial. A diagnosis of microinvasive or invasive cancer on cervical biopsy, LEEP, or CKC requires treatment according to the NCCN Cervical Cancer Guidelines.

Colposcopy for ASC-H or HSIL in Adult Women (CERVS-9)

All women with a diagnosis of ASC-H or HSIL on cytology require colposcopic evaluation. Again, management depends on whether the colposcopy is considered satisfactory. A LEEP or CKC is recommended for those with unsatisfactory colposcopies, with follow-up as outlined in the next section (see CERVS-10). 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. If the ECC is negative, then the cytology, colposcopy (including vaginal or vulvar colposcopy), and ECC should be repeated in 6 months.

Two options are available if a lesion is identified. A patient may opt for a LEEP procedure, particularly if maintaining fertility is not an issue; this patient should then have follow-up as described in the following section (see CERVS-10). 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 in 6 months; or 2) a LEEP or CKC can be considered for definitive diagnosis. 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 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. Again, CKC should be performed for microinvasive biopsy findings, and any confirmed invasive cancers need treatment according to the NCCN Cervical Cancer Guidelines.

Follow-up After Treatment of Cervical Intraepithelial Neoplasia (CERVS-10)

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.[29] Treatment of those initially managed with excision (that is, LEEP or CKC) depends on the status of the margins. Cervical cytology at 12 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. Cervical cytology at the shorter interval of 6 months is recommended for CIN II and CIN III lesions with positive margins; re-excision is another option but only if both the endocervical and ectocervical margins are positive. An ECC can be considered (category 2B). If repeat cervical cytology or HPV DNA testing is negative, screening as per the guidelines may be resumed (see CERVS-1). If HPV DNA testing is positive, then colposcopy is recommended. If the repeat cervical cytology identifies ASC-US or greater, then the screening follow-up recommendations should be followed as previously mentioned (see CERVS-6).

Atypical Glandular Cells (CERVS-11)

The finding of AGC on cervical cytology is associated with a clinically significant lesion in 45% of patients,[30] including CIN, cervical adenocarcinoma in situ (AIS), cervical cancer, and endometrial cancer. For this reason, all patients with a finding of AGC on cervical cytology and who are younger than 35 years of age with no risk factors for endometrial cancer should undergo colposcopy, ECC, and HPV DNA testing (if not already done). Risk factors include obesity, unopposed estrogen replacement therapy, polycystic ovarian syndrome, tamoxifen therapy, anovulation, or hereditary non-polyposis cancer syndrome (HNPCC). Patients who are 35 years of age 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 done) as part of their initial evaluation. Management is then directed by the combination of results of the cervical biopsy, ECC, and HPV testing. Additional management may be dictated by the results of the endometrial biopsy (see CERVS-14). 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.[31]

If cervical biopsy and ECC identify CIN (I, II, or III) or AIS, further evaluation by CKC is indicated. 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 3 negative tests are obtained or with HPV DNA testing at 12 months. For patients with cervical biopsy findings of CIN II or III but with a negative ECC result, LEEP or CKC is recommended (see CERVS-13).

The panel felt that most patients with a cervical cytology revealing AGC and an abnormal cervical biopsy result or ECC should undergo CKC to both confirm the diagnosis and to serve as potential treatment. The use of LEEP in patients with AIS has been associated with an increased incidence of positive margins of excision in the tissue specimen.[32] For this reason, CKC is the preferred diagnostic procedure in patients at risk for AIS or microinvasion. CKC should be followed by endometrial sampling, if “atypical glandular cells favor neoplasia” or ”AIS” is reported.

Follow-up of Endometrial Biopsy (CERVS-14)

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. 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 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 Uterine Cancer Guidelines.

Follow-Up of Cold-Knife Conization for Adenocarcinoma In Situ (CERVS-15)

The NCCN panel recommends that all patients with AIS should be strongly considered for referral to a gynecologic oncologist. The choice of treatment depends on the patient's desire for fertility. The definitive treatment for AIS is hysterectomy. Patients desiring to preserve fertility and who have a CKC specimen with negative margins of excision, may be followed conservatively by repeat cervical cytology with (or without) ECC every 6 months until hysterectomy; these patients should also receive counseling regarding the risks of this strategy. Hysterectomy should be strongly considered when childbearing is completed.

However, clear margins of excision do not rule out persistent AIS, because approximately 30% of patients have residual disease on subsequent hysterectomy.[33] If CKC margins are positive for abnormal glandular cells, a hysterectomy is recommended if the patient does not desire to remain fertile. Consider repeating CKC to rule out invasive disease before the hysterectomy (category 2B).

Patients with positive margins who wish to remain fertile should receive repeat cervical cytology, HPV DNA testing, colposcopy, and ECC at 6 months. If any of these tests are again positive, they should have a repeat CKC. Re-excision to attain positive margins is also recommended. These patients should also receive counseling regarding the risks of this strategy. Hysterectomy should be strongly considered when childbearing is completed.

Finally, patients with invasive adenocarcinoma on cervical biopsy, ECC, CKC, or endometrial biopsy should undergo treatment according to the NCCN Cervical Cancer Guidelines or NCCN Uterine Cancer Guidelines.

Colposcopy During Pregnancy (CERVS-B)

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. Colposcopically directed cervical biopsy during pregnancy should be limited to women in whom high-grade neoplasia or invasive cancer is suspected. Treatment for CIN (any grade) should be delayed until after the pregnancy.[34-37] Because colposcopic evaluation in pregnant women can be problematic, consultation with or referral to an experienced colposcopist should be considered. Diagnostic limited excisional procedure is recommended only if invasive cancer is suspected.

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