NCCN® Practice Guidelines in Oncology – v.1.2001

National Comprehensive Cancer Network®

Cervical Screening

Version 1.2001

Continue

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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.

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

See NCCN Categories of Consensus

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Cervical Screening

INITIAL FINDINGS OF SCREENING EXAM

Cervical screening[a]:
- **Age 18 yr or sexually active**
- **Annual screen until 3 consecutive negative screens. Interval may be lengthened at discretion of physician after assessment of risk factors**
- **Pap test[b,c] and pelvic exam**
- **Education of patient regarding importance of compliance and follow-up**

Visible lesion on cervix →
Pap test normal →
Pap test unsatisfactory →
Satisfactory but limited by...(SBLB) →
Benign cellular changes (BCC) →

→ **See Screening Findings (CERVS-2)**

Atypical squamous cells of undetermined significance (ASCUS) →
Low-grade squamous intraepithelial lesions (LSIL) →
High-grade squamous intraepithelial lesions (HSIL) →

→ **See Screening Findings (CERVS-3)**

Atypical glandular cells of undetermined significance (AGCUS) →

→ **See Follow-Up of Cervical Biopsy/ Endometrial Biopsy Findings AGCUS (CERVS-10)**

[a] See High-Risk Factors for Cervical Cancer (CERV-A).

[b] Pap test results should be reported using the Bethesda System.

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

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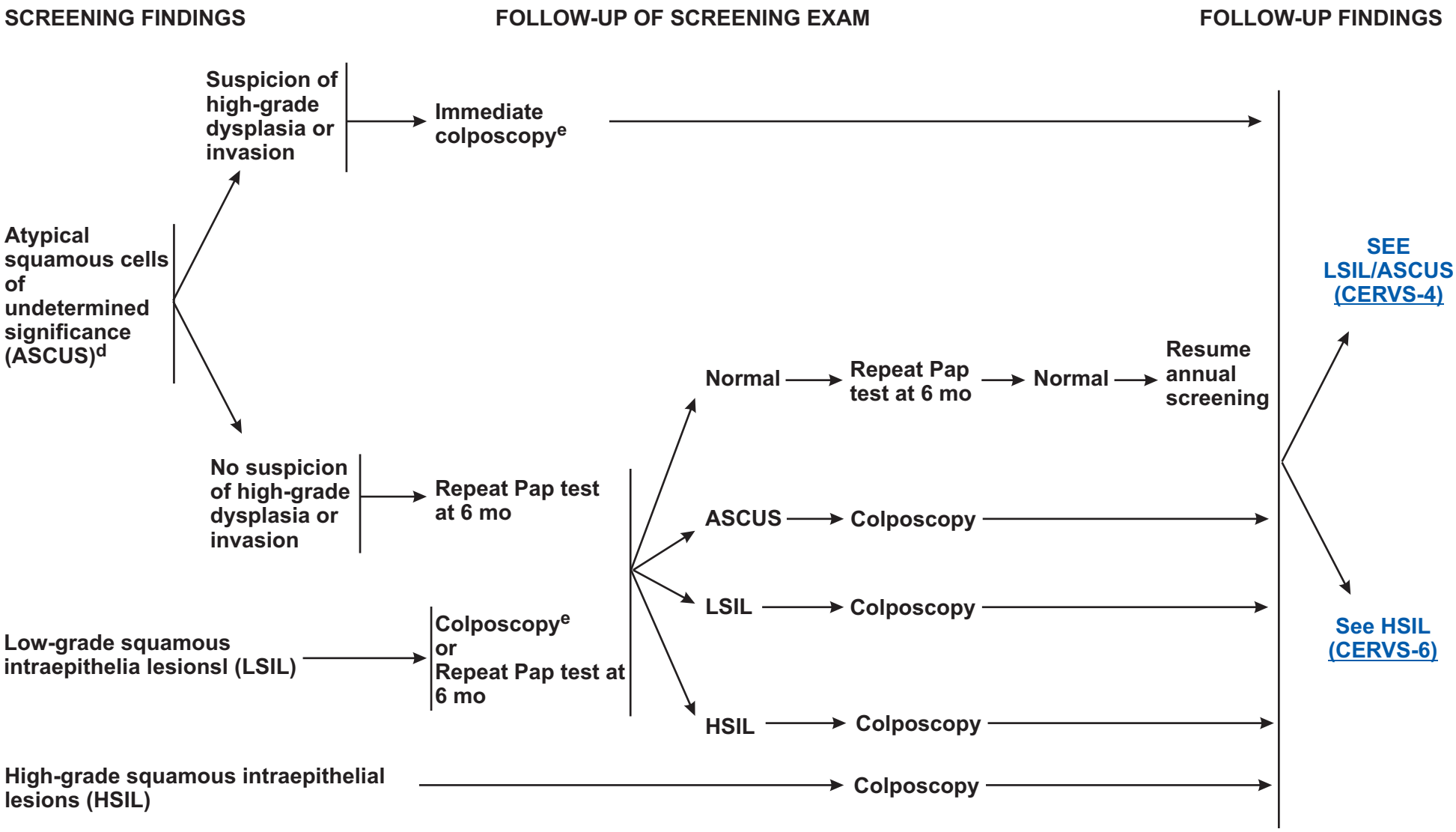
SCREENING FINDINGS	FOLLOW-UP OF SCREENING EXAM	
Visible lesion on cervix	Biopsy	
Pap test normal	Screening frequency based on risk factors	
Pap test unsatisfactory	Repeat as soon as practical (3 mo), treat infection if present and indicated	
Satisfactory but limited by...(SBLB)	Treat underlying condition, if indicated	Repeat screen in 1 yr, or closer interval if high risk
Benign cellular changes (BCC)	Treat specific underlying conditions, if indicated	Repeat screening 1 yr

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[d]Consider HPV testing for colposcopy triage. if high-risk HPV identified, proceed with colposcopy. If negative or low-risk, repeat Pap test in 6 mo (category 2B).

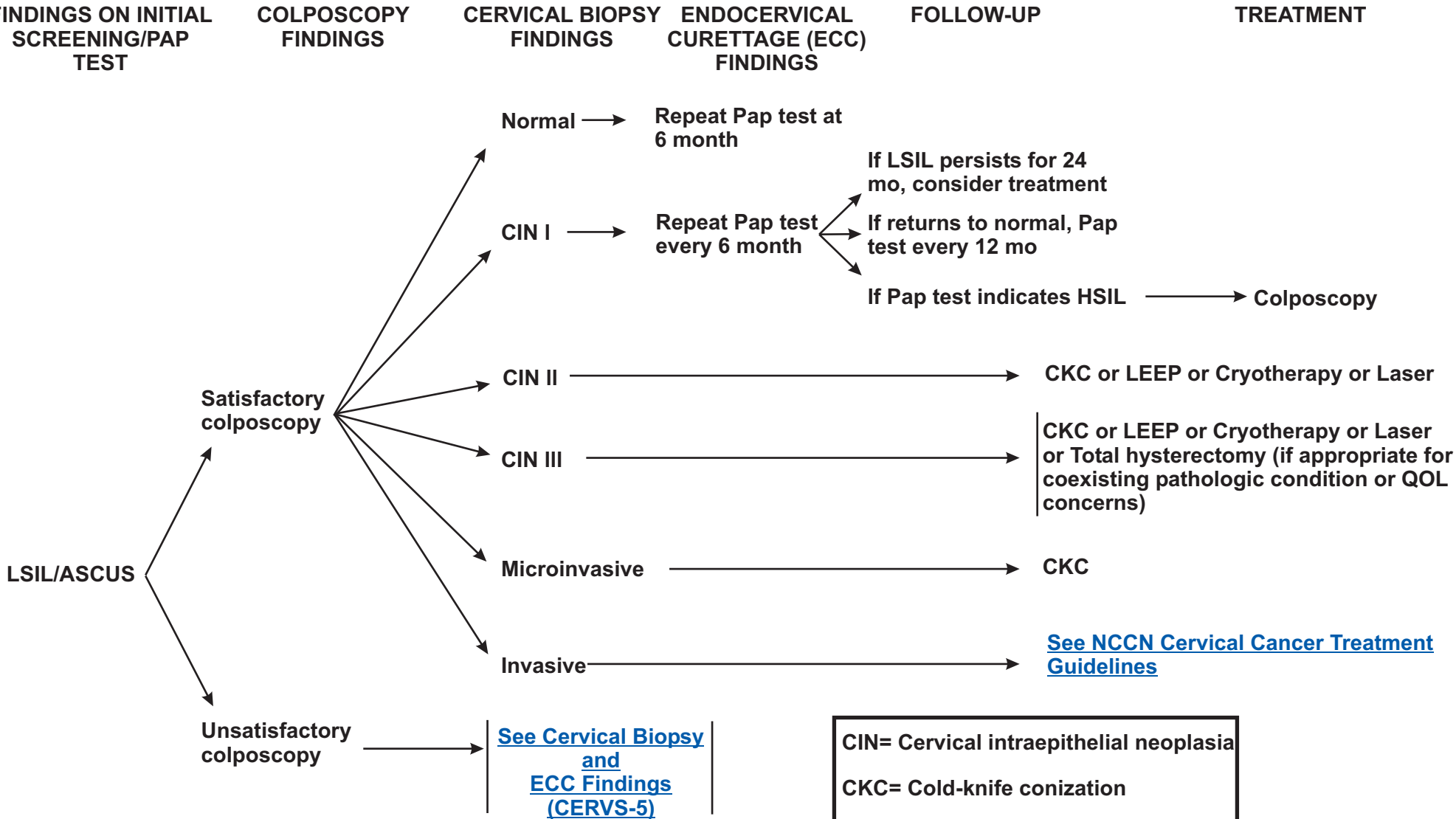
[e]See Colposcopy During Pregnancy (CERVS-B).

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CIN= Cervical intraepithelial neoplasia

CKC= Cold-knife conization

LEEP= Loop electrosurgical excision procedure

QOL= Quality of life

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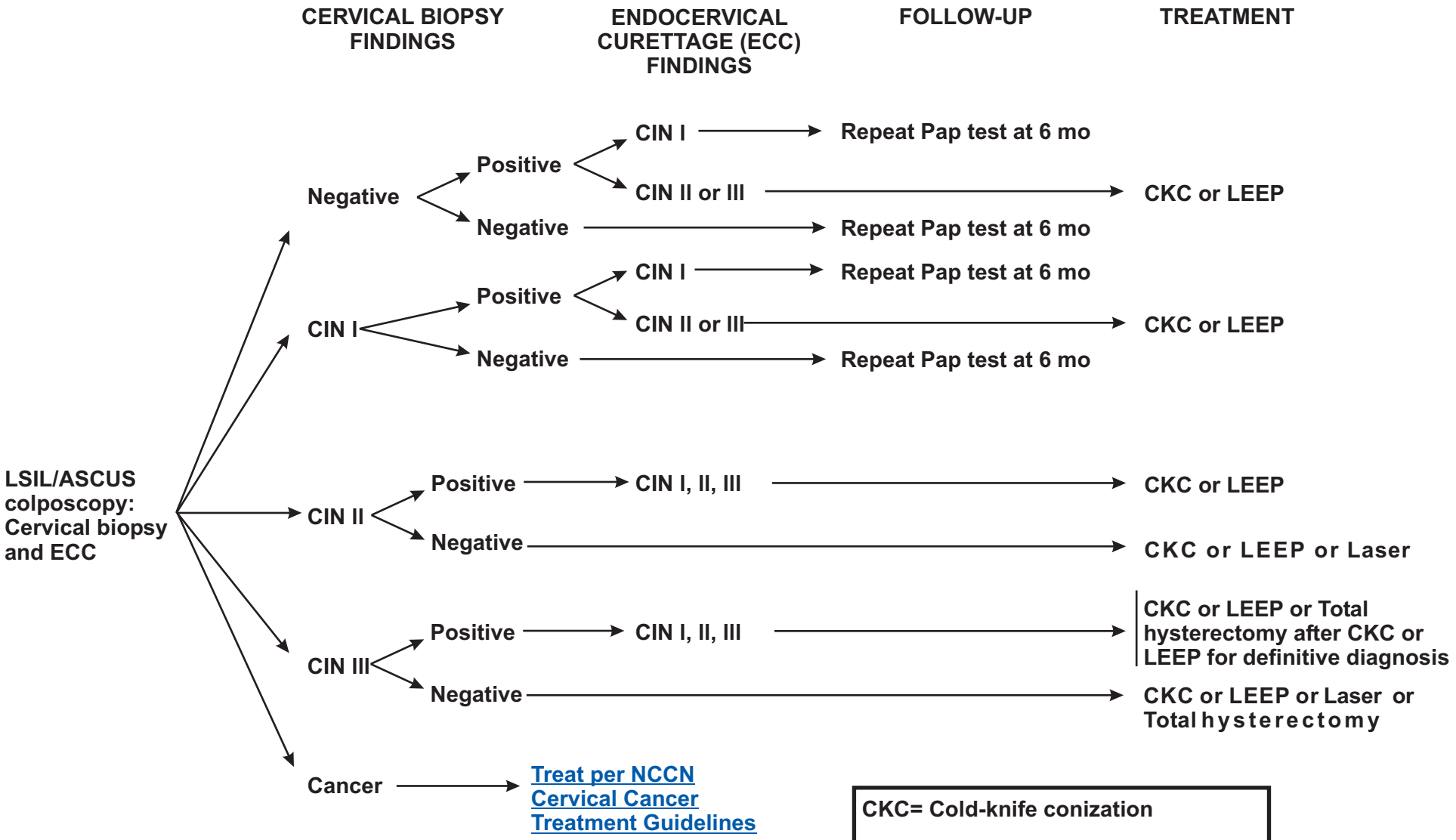
CERVS-4

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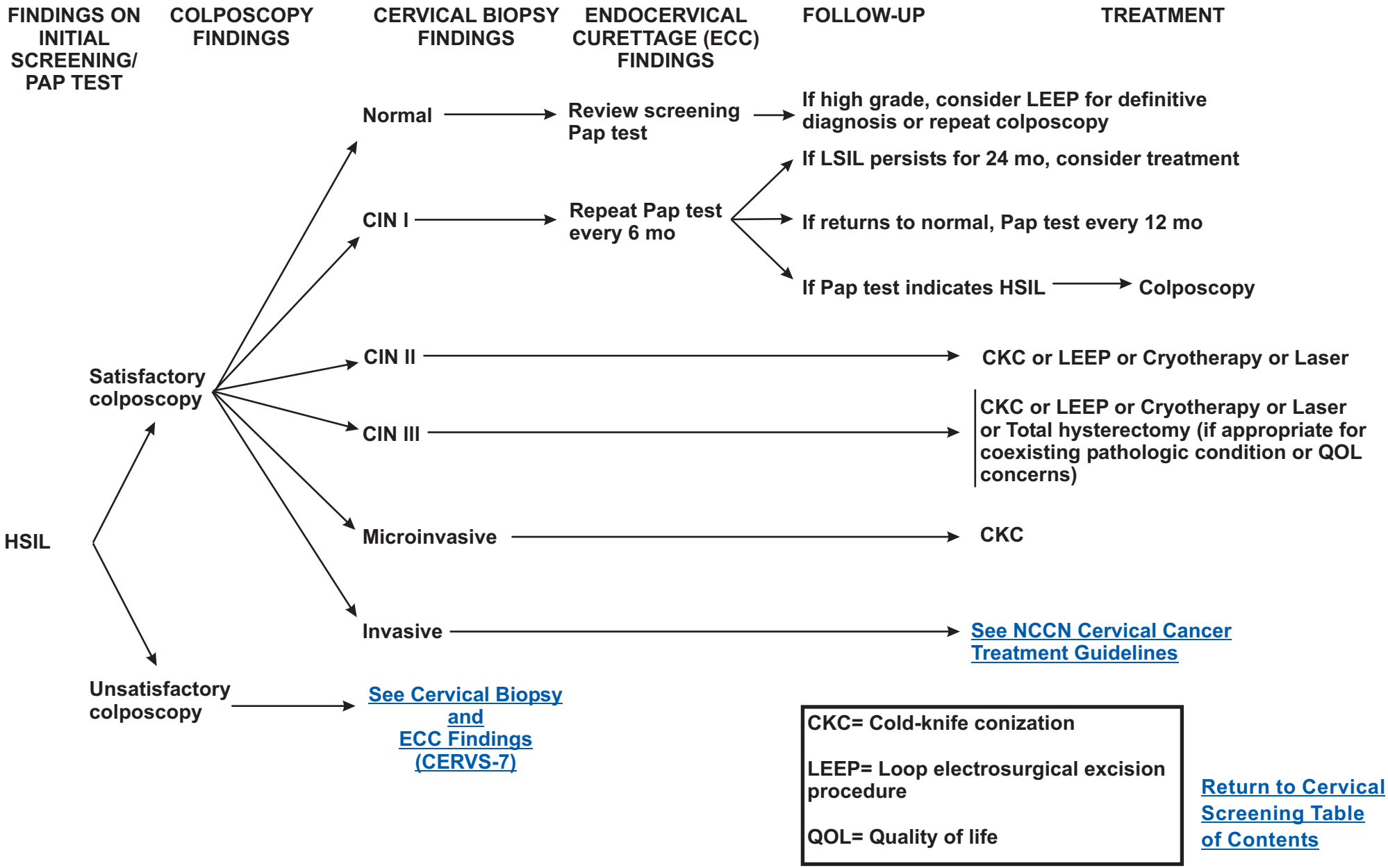
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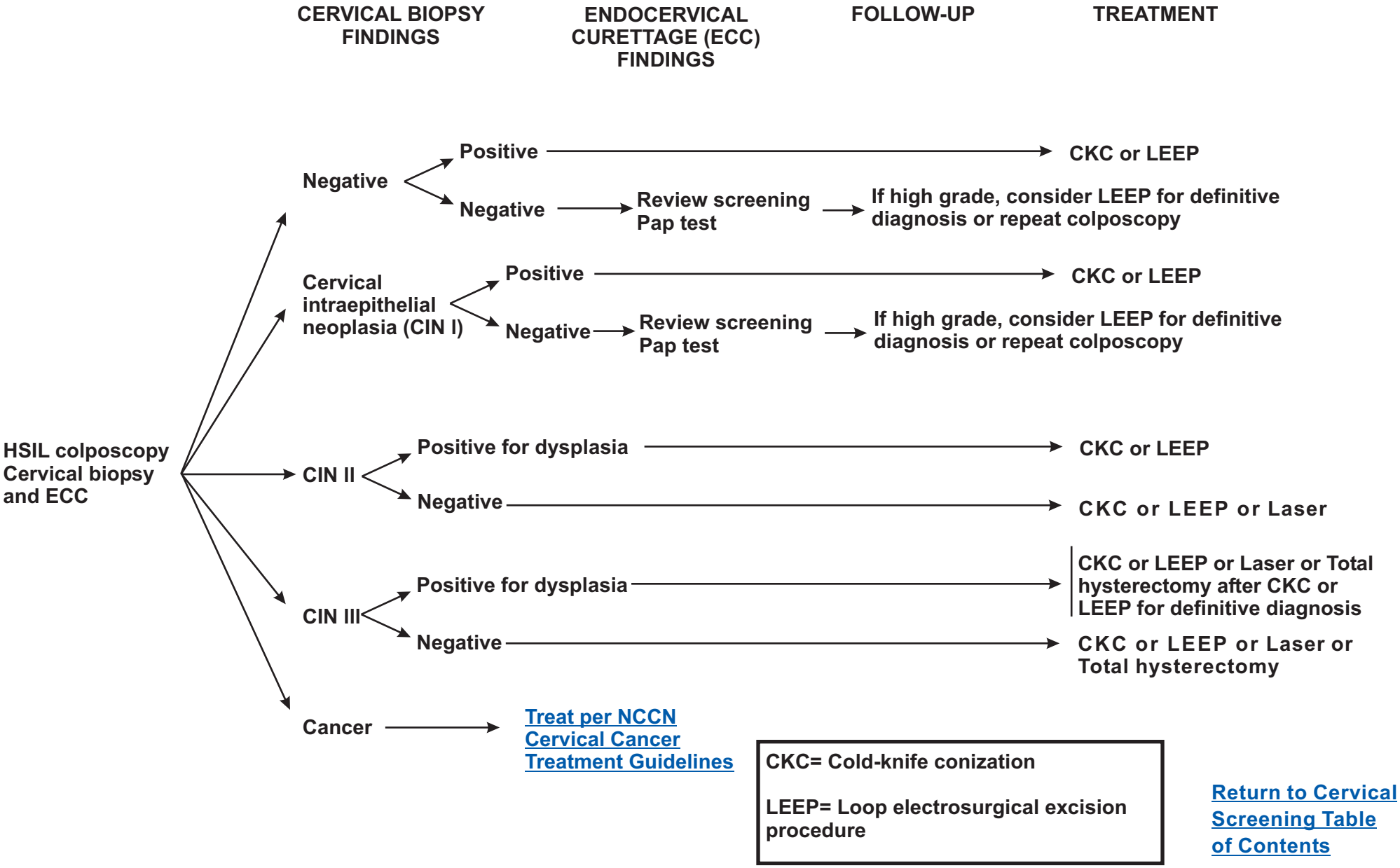
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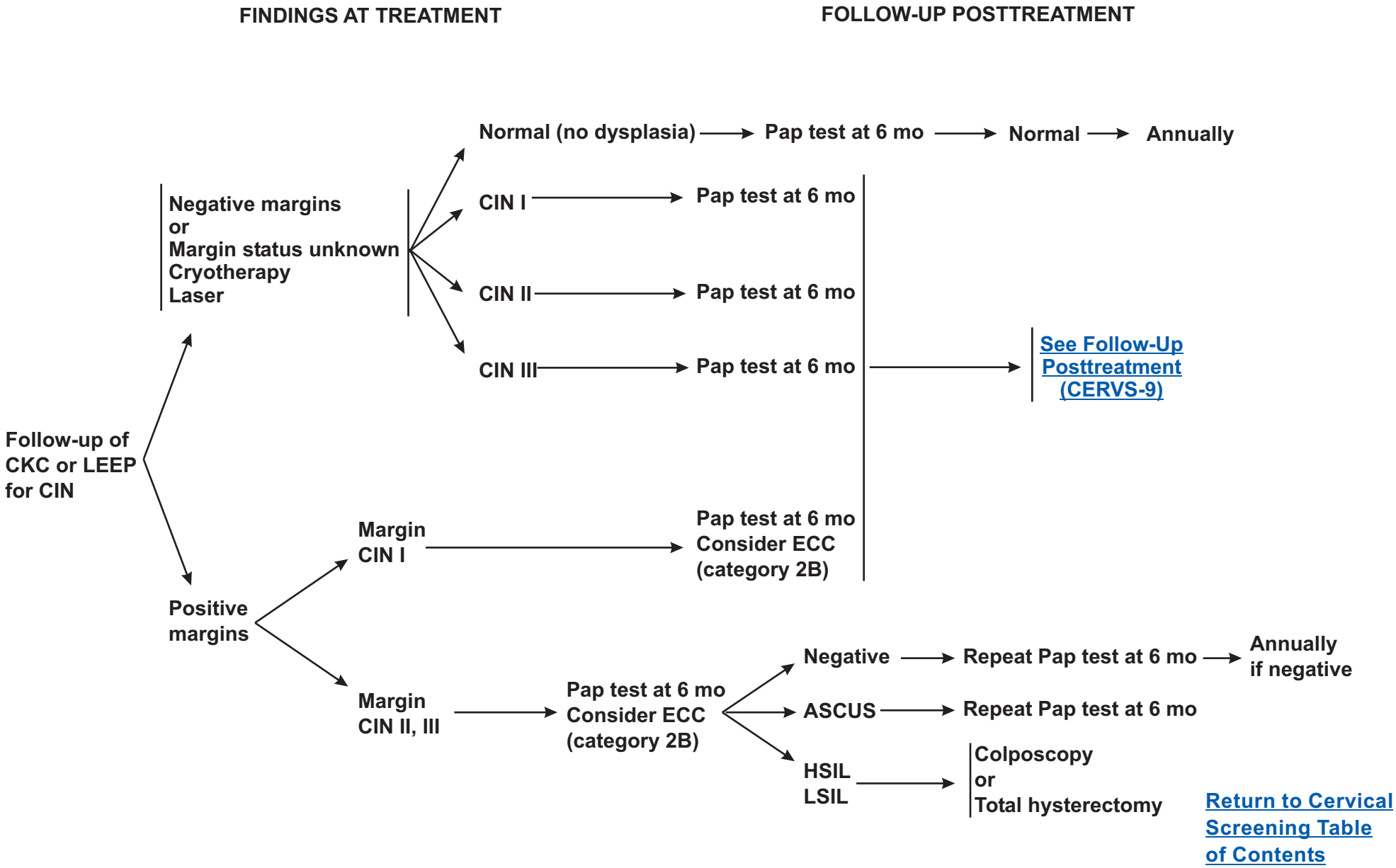
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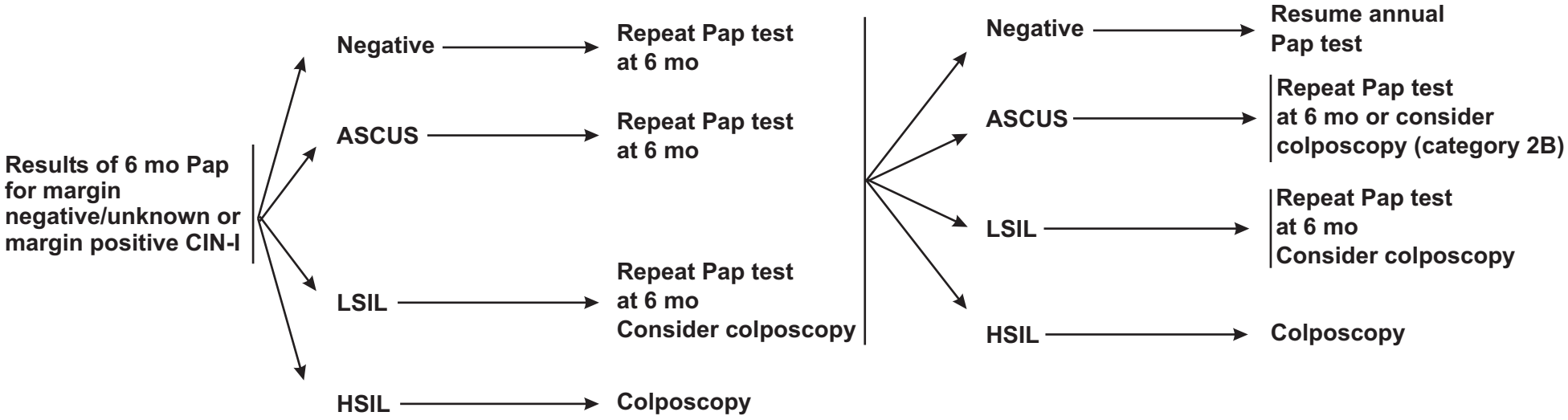
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FOLLOW-UP POST-TREATMENT



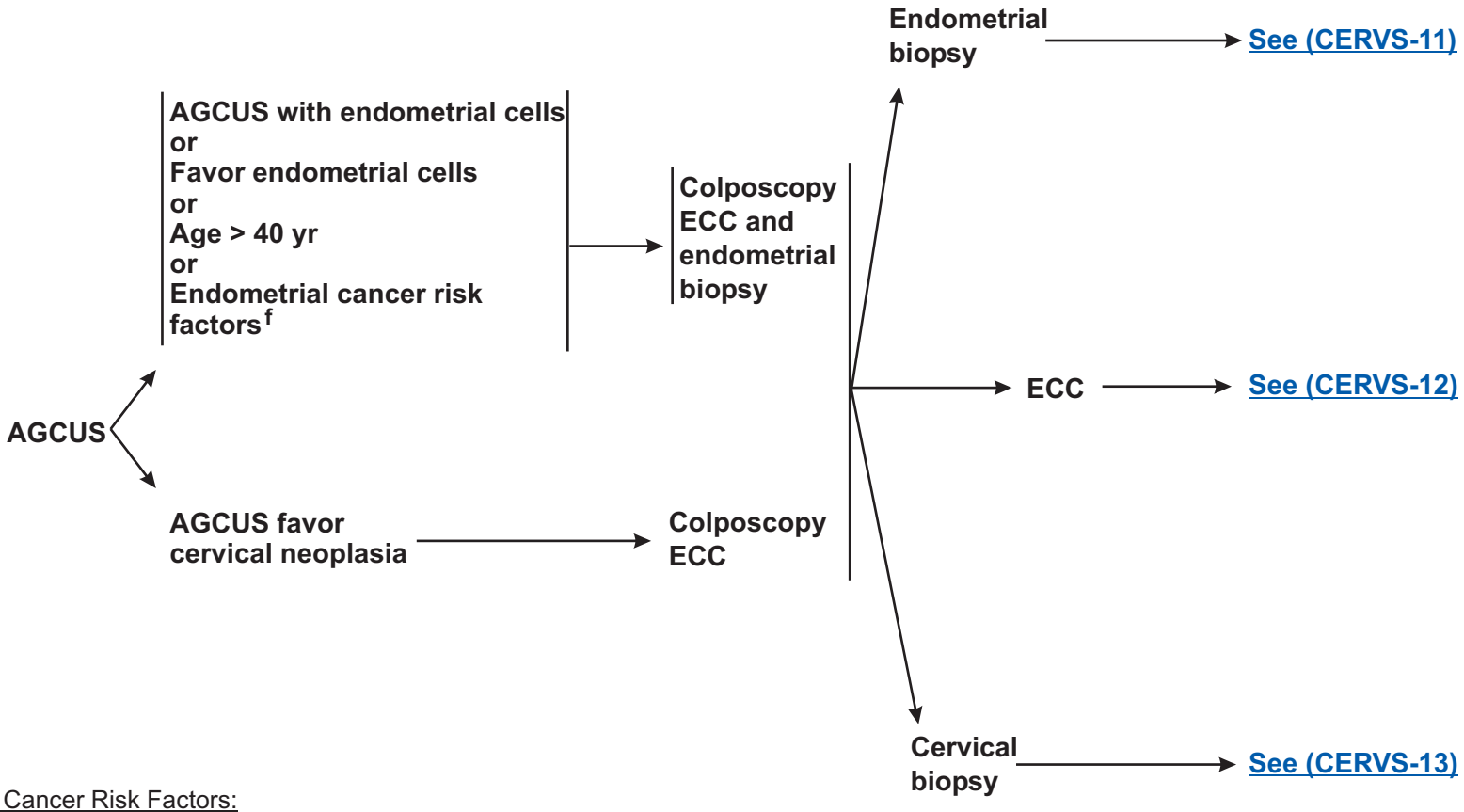
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Cervical Screening

FOLLOW-UP OF CERVICAL BIOPSY/ENDOMETRIAL BIOPSY FINDINGS



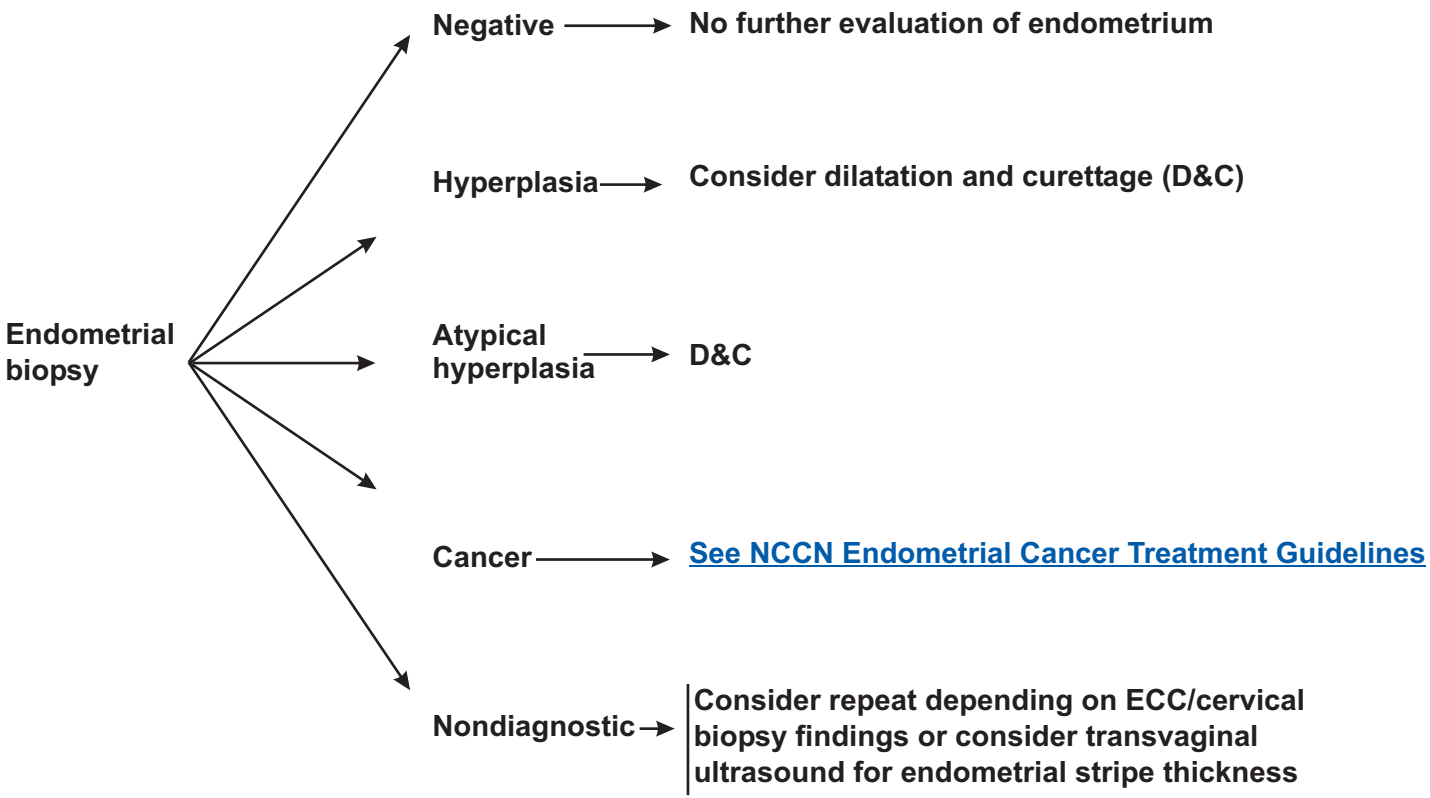
[f]Endometrial Cancer Risk Factors:
- Obesity
- Estrogen replacement therapy
- Polycystic ovarian disease
- Tamoxifen therapy
- Anovulation

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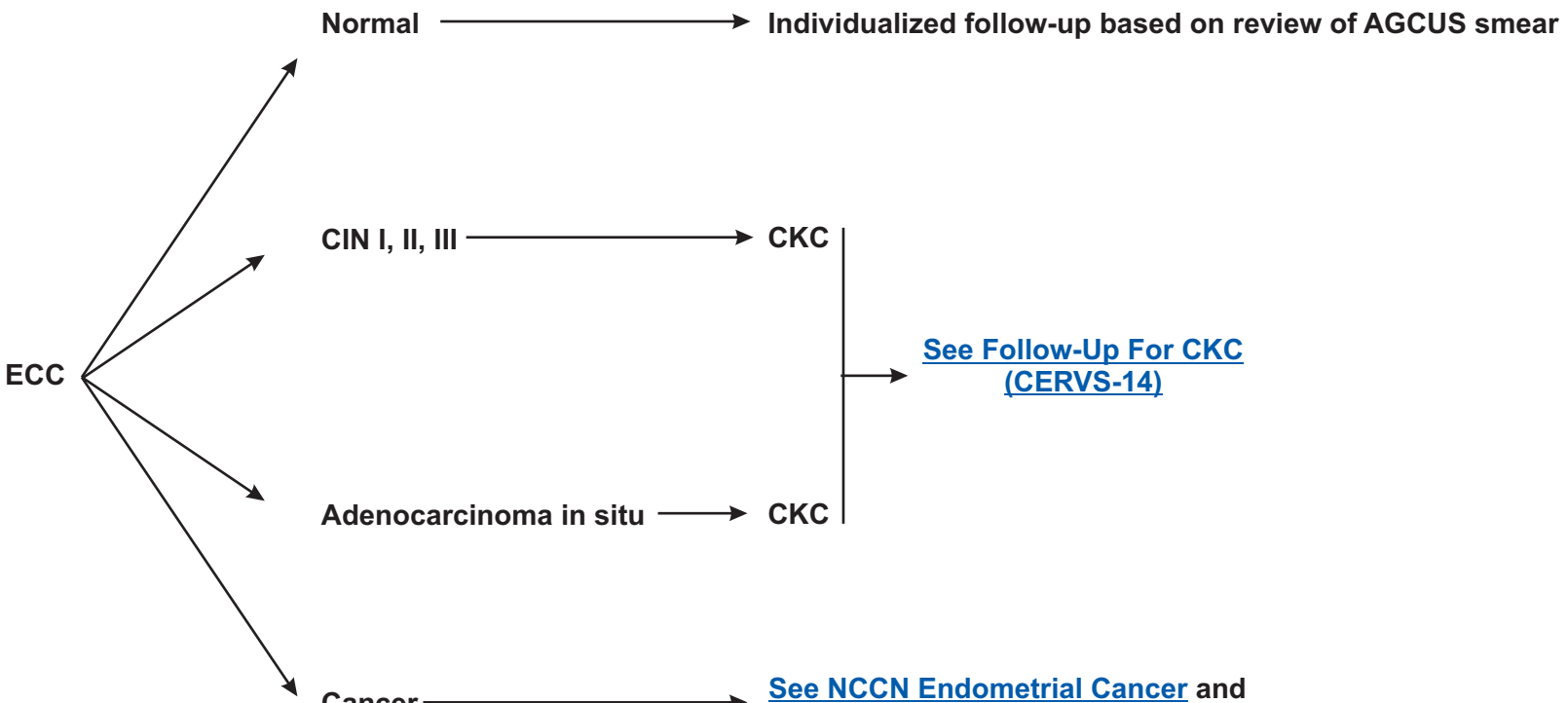
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FOLLOW-UP OF CERVICAL BIOPSY/ENDOMETRIAL BIOPSY FINDINGS



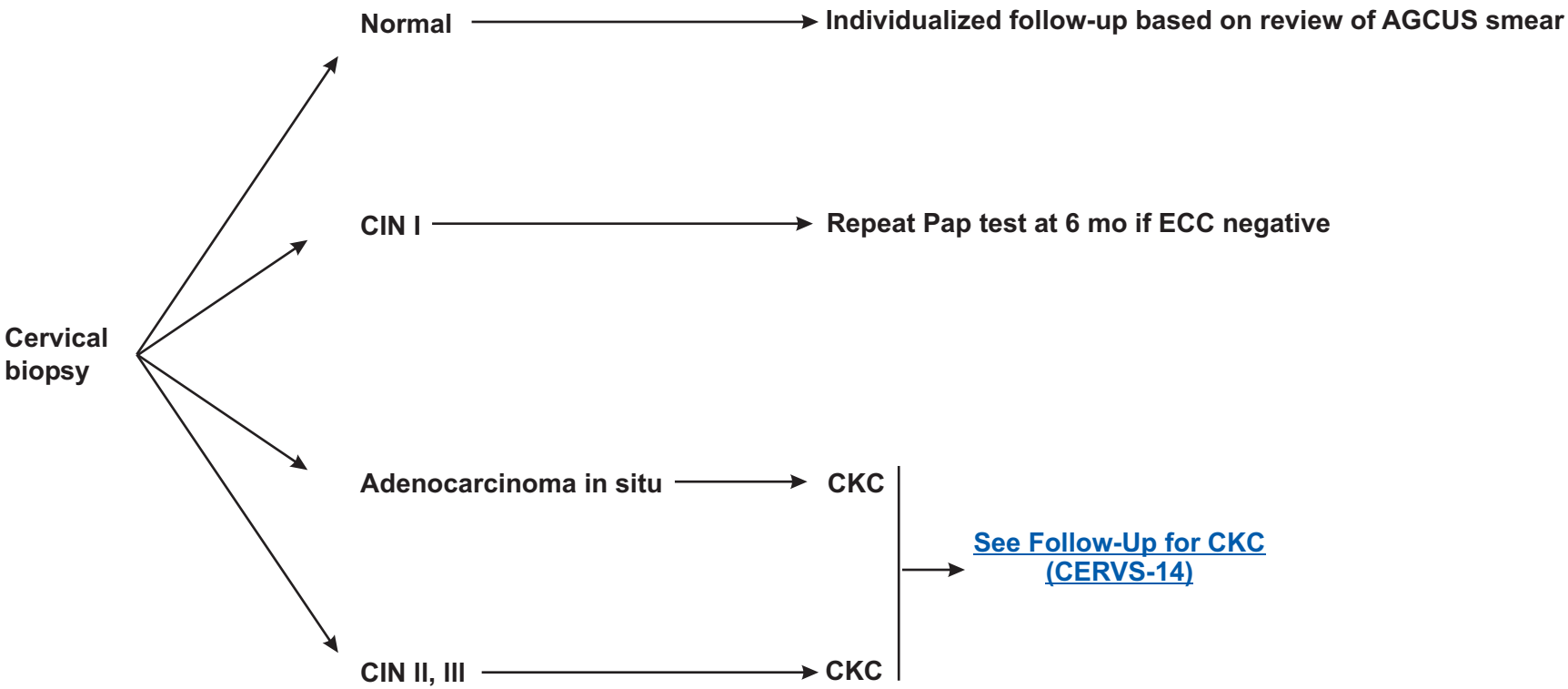
CKC= Cold-knife conization

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FOLLOW-UP FOR CKC

CIN I, II, III → See Follow up Posttreatment (CERV-8)

Adenocarcinoma in situ/glandular intraepithelial neoplasia (Consider referral to gynecologic oncologist)

- Negative margins → Hysterectomy (standard preferred)
- Negative margins, fertility desired → Pap test with ECC at 6 mo
  Requires consent/counseling
  Recommend hysterectomy when childbearing completed
- Positive margins → Total hysterectomy
  or
  Repeat CKC at 3 mo
  If fertility desired, consent/counseling required
  Recommend hysterectomy when childbearing completed

Cancer → See NCCN Cervical Cancer Treatment Guidelines

CKC= Cold-knife conization

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HIGH-RISK FACTORS FOR CERVICAL CANCER

Women with a social or sexual history that includes:
- **Lower socioeconomic status**
- **Multiple sexual partners**
- **Began having intercourse at a young age**

Woman with current or former history of the following infections:
- **Human papillomavirus**
- **Condylomata**
- **Herpes simplex virus**
- **Human immunodeficiency virus**
- **Other sexually transmitted disease**

Women with medical histories which include:
- **Immunosupression**
- **Smoking**
- **Substance abuse, including alcohol**
- **Cervical dysplasia**
- **Cervical cancer**
- **Endometrial cancer**
- **Vaginal cancer**
- **Vulvar cancer**

Patient's male sexual partner sexual history:
- **Multiple partners**
- **Other partners who have had cervical cancer**

[g]Low socioeconomic status appears to be a surrogate for a number of closely related risk factors that place these women at greater risk for cervical cancer.

Return to Initial Findings of Screening Exam

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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**
- **Cervical biopsy or colposcopically directed brush cytology is safe during pregnancy**
- **For biopsy-proven CIN II or III early in pregnancy, consider repeat colposcopy later in pregnancy to rule out advancement in lesion**
- **Consultation or referral to colposcopist with experience in colposcopy during pregnancy is recommended**

Return to Follow-up of Screening Exam (CERVS-3)

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NCCN Categories of Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

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, 12,900 women are expected to develop the disease in 2001, with 4,400 expected deaths (Greenlee et al, 2001). Since 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.

Pap Test Screening

Frequency

The panel adopted the current recommendations of the American College of Obstetricians and Gynecologists (ACOG) on the frequency of Pap test screening (American College of Obstetricians and Gynecologists, 1995), namely, that all women who are or who have been sexually active or who have reached age 18 years should undergo an annual Papanicolaou (Pap) test and pelvic examination. After a woman at low risk for cervical cancer has had three or more consecutive satisfactory annual examinations with normal findings, the Pap test may be performed less frequently, at the discretion of her physician.

The panel also adopted the ACOG recommendation that women with one or more high-risk factors (See CERVS-A) associated with the development of cervical intraepithelial neoplasia (CIN) or carcinoma may require more frequent Pap tests (American College of Obstetricians and Gynecologists, 1995). The panel further recommends that Pap tests should be reported using the Bethesda System (National Cancer Institute, 1989; Sherman et al, 1992), as shown in Table 1.

Initial Findings

A biopsy should be performed on any grossly visible lesion on the cervix, because a Pap test can be reported as negative when invasive cancer is grossly present. If the initial Pap test is negative and the cervix is grossly normal, then subsequent screening should be based on the recommendation for frequency of Pap test screening discussed earlier. Pap tests reported as unsatisfactory should be repeated as soon as practical. Underlying infection, if indicated, should be treated prior to obtaining the subsequent Pap test. Pap tests reported as “satisfactory, but limited by” or with “benign cellular changes,” but otherwise negative for epithelial abnormalities, should be repeated at 1 year, or sooner if high-risk factors are present.

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Squamous Epithelial Cell Abnormalities

Atypical Squamous Cells of Undetermined Significance: Pap tests revealing atypical squamous cells of undetermined significance (ASCUS) should be repeated at 6 months. If the ASCUS diagnosis is further qualified by the pathologist as suspicious for high-grade dysplasia, an immediate colposcopy should be performed to rule out or confirm high-grade dysplasia or an invasive process. If two consecutive Pap tests, 6 months apart, are normal, annual screening may be resumed. However, if the repeat Pap test reveals persistent ASCUS, a low-grade squamous intraepithelial lesion (LSIL), or a high-grade squamous intraepithelial lesion (HSIL), a colposcopic evaluation of the cervix is appropriate.

Low-Grade Squamous Intraepithelial Lesion: Although some members of the panel felt that colposcopy is the appropriate evaluation after an initial Pap test reveals LSIL, the majority recommended a repeat Pap test at 6 months. Excellent data demonstrate the regression of low-grade intraepithelial lesions to normal in the majority of cases (Holowaty et al, 1999). If the repeat Pap test at 6 months confirms ASCUS, persistent LSIL, or HSIL, the patient should then undergo colposcopy.

High-Grade Squamous Intraepithelial Lesions: The panel recommends that all patients with HSIL undergo a colposcopic examination.

Human Papillomavirus Testing: There was agreement among the panel members that, in the absence of published data from large, prospective clinical trials, human papillomavirus (HPV) testing for triage to colposcopy in a woman whose Pap test reveals ASCUS is not appropriate for routine care. The panel did acknowledge, however, that new information may be forthcoming from the National Cancer Institute-sponsored ASCUS Low-Grade Triage Study (ALTS trial) and other studies that may alter this recommendation.

The ALTS trial has completed enrollment and is in the follow-up phase. This study is evaluating the clinical management of women diagnosed with ASCUS and LSIL by randomizing them into one of three arms: immediate colposcopy, HPV triage, or conservative management.

Colposcopy

Colposcopy, along with colposcopically directed biopsies, has become the primary method for evaluating women with abnormal Pap tests. During a colposcopic examination, the cervix is viewed through a long focal-length dissecting-type microscope at a magnification of 10 to 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 determine the extent of preinvasive disease. If the entire squamocolumnar junction of the cervix is visualized (ie, the transformation zone is seen in its entirely), the examination is considered satisfactory and endocervical curettage is unnecessary (Crispens et al, 1996).

Low-grade Squamous Intraepithelial Lesions or ASCUS

Women with CIN I confirmed on cervical biopsy and a satisfactory colposcopic examination may be followed with a repeat Pap test at 6 months and no definitive treatment, because the majority of these lesions will regress to normal (Holowaty et al, 1999). However, if persists for 24 months, initiating treatment after colposcopic reevaluation may be a consideration. A normal repeat Pap test following evaluation indicating CIN I should lead to a resumption of

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annual Pap testing. A repeat Pap test revealing HSIL requires colposcopic evaluation. If the cervical biopsy reveals CIN II or III, further therapy, consisting of cold-knife conization, LEEP, cryotherpay, or laser, is indicated. Total hysterectomy may also be considered an option, if indicated for other reasons or for enhancement of quality of life.

A cervical biopsy result that confirms invasive cancer, but no grossly visible lesion, requires a cone biopsy to excise the cervical transformation zone. This allows for a definitive diagnosis of invasive cancer and for measurement of the lesion dimensions. These findings are critical in determining the clinical stage of the cancer, and for making further treatment recommendations. The panel favored the use of cold-knife conization in patients in whom invasive cervical cancer was suspected. The loop electrosurgical excision procedure (LEEP) has been associated with a cautery artifact that may compromise the pathologic evaluation of the tissue specimen.

If the colposcopic examination is unsatisfactory, endocervical curettage should be performed in addition to the directed cervical biopsy. If the cervical biopsy and endocervical curettage findings are negative, the Pap test should be repeated at 6 months. An endocervical curettage with a diagnosis of CIN II or III requires cold-knife conization or LEEP for definitive diagnosis (Naumann et al, 1995). However, if endocervical curettage indicates CIN I only, the cervical biopsy is negative, and the initial Pap test reveals ASCUS/LSIL, then the Pap test may be repeated in 6 months.

A cervical biopsy finding of CIN II or III lesions with a positive endocervical curettage finding and an unsatisfactory colposcopic examination also requires a cold-knife conization or LEEP to establish a definitive diagnosis. The cold-knife conization or LEEP can serve as definitive treatment if the lesion is confirmed to be intraepithelial. Ablative therapy with either cryotherapy or laser is inappropriate with a positive endocervical curettage finding and unsatisfactory colposcopy. If the endocervical curettage findings are negative, however, treatment can be accomplished with cold-knife conization, LEEP, cryotherapy, or laser ablation. A diagnosis of cancer on cervical biopsy, cold-knife conization, or LEEP requires treatment according to the NCCN Cervical Cancer Guidelines. A total hysterectomy may also be a therapeutic option for women with CIN II or III whose diagnosis has been confirmed by cold-knife conization or LEEP.

High-Grade Squamous Intraepithelial Lesions

All women with a diagnosis of HSIL on a Pap test require colposcopic evaluation, followed up by a directed biopsy if a lesion is seen. Again, a diagnosis of CIN II or III requires treatment with cold-knife conization, LEEP, cryotherapy, or laser ablation, with total hysterectomy being a consideration if the lesion is CIN III. All women with a diagnosis of HSIL on a Pap test and an unsatisfactory colposcopic examination require cold-knife conization or LEEP to establish a definitive diagnosis if the result of endocervical curettage is positive (CIN I, II, or III). If the endocervical curettage finding is negative and the cervical biopsy is negative or indicates CIN I, the patient may be followed with a repeat Pap test at 6 months. The screening Pap test should be reviewed, and if confirmed to be HSIL, LEEP should be considered for definitive diagnosis.

Follow-up After Treatment of CIN

After definitive treatment of CIN with either cold-knife conization or LEEP (leaving clear margins), or ablative therapy with cryotherapy

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or laser (with the margins status unknown), the patient should have an initial follow-up Pap test at 6 months. If the previous final diagnosis on cold-knife conization or LEEP was normal (ie, no CIN) and the repeat Pap test at 6 months is normal, the patient may resume annual Pap test screening. An ASCUS or LSIL revealed on a Pap test at 6 months posttreatment requires a follow-up test 6 months later. If the follow-up Pap test at 6 months is negative, the patient may resume annual Pap testing.

Women with persistent ASCUS or LSIL may be followed with Pap tests at 6-month intervals. Colposcopy should be considered if the ASCUS or LSIL persists for 24 months or if LSIL is revealed at the initial follow-up Pap test. A diagnosis of HSIL on a follow-up Pap test always requires colposcopy.

Patients undergoing LEEP or cold-knife conization and found to have CIN extending to the margin of excision should undergo a repeat Pap test in 6 months, with consideration of endocervical curettage (category 2B). If the repeat test is negative and the original LEEP or cold-knife conization diagnosis indicated CIN I, annual Pap testing may be resumed. However, if the original LEEP or cold-knife conization diagnosis revealed CIN II or III, the patient should undergo Pap tests every 6 months until two consecutive negative tests have been reported.

Patients with LSIL or HSIL on a follow-up Pap test after cold-knife conization or LEEP should undergo colposcopy. A total hysterectomy could be considered as definitive treatment for persistent intraepithelial lesions after LEEP or cold-knife conization.

Atypical Glandular Cells of Undetermined Significance (AGCUS)

The finding of AGCUS on a Pap test is associated with a clinically significant lesion in 45% of patients (Veljovich et al, 1998). Potential associated pathology includes CIN, cervical adenocarcinoma in situ, and endometrial cancer. For this reason, all patients whose Pap tests reveal AGCUS should undergo colposcopy and endocervical curettage. If the endocervical curettage and the cervical biopsy results are negative, the Pap test should be repeated in 6 months or individualized, based on a review of the AGCUS Pap test.

Patients with a Pap test result revealing AGCUS and suggesting endometrial cells, who are greater than 40 years of age, or who have endometrial cancer risk factors (eg, obesity, estrogen replacement therapy, polycystic ovarian syndrome, tamoxifen therapy, or anovulation) should also undergo an endometrial biopsy as part of their initial evaluation. If the result of the endometrial biopsy is negative, no further evaluation of the endometrium is necessary. If the endometrial biopsy result is hyperplastic or nondiagnostic, a uterine dilatation and curettage or transvaginal ultrasound for endometrial stripe thickening should be considered. A diagnosis of endometrial cancer requires treatment according to the NCCN Endometrial Cancer Guidelines.

If cervical biopsy or endocervical curettage is remarkable for CIN (I, II, or III) or for adenocarcinoma in situ, further evaluation by cervical conization is indicated. However, a patient with an adequate colposcopic examination, a cervical biopsy revealing CIN I, and a normal endocervical curettage may be managed conservatively with a repeat Pap test in 6 months.

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The panel felt that most patients with a Pap test revealing AGCUS and an abnormal cervical biopsy result or endocervical curettage should undergo cold-knife conization to both confirm the diagnosis and serve as potential treatment. The use of LEEP in patients with adenocarcinoma in situ has been associated with an increased incidence of positive margins of excision in the tissue specimen (Adozi et al, 1999). For this reason, cold-knife conization is the preferred diagnostic procedure in patients at risk for adenocarcinoma in situ.

Cold-knife conization leading to a diagnosis of CIN I, II, or III following a Pap test that indicates AGCUS may serve as definitive treatment. A follow-up Pap test should be performed in 6 months. The choice of treatment of adenocarcinoma in situ diagnosed by cold-knife conization depends on the patient's desire for fertility. The definitive treatment for adenocarcinoma in situ is hysterectomy. Patients desiring to preserve fertility, and who have a cold-knife conization specimen with normal margins of excision, may be followed conservatively by repeat Pap test and endocervical curettage at 6-month intervals.

However, clear margins of excision do not rule out persistent adenocarcinoma in situ, as approximately 30% of patients have been found to have residual disease on subsequent hysterectomy (Wolf et al, 1996). If cold-knife conization margins are positive for abnormal glandular cells, strong consideration should be given to performing a hysterectomy. An alternative treatment would be a repeat cold-knife conization at 3 months. Finally, patients with invasive adenocarcinoma on cervical biopsy, endocervical curettage, cold-knife conization, or endometrial biopsy should undergo treatment according to the NCCN Cervical or Endometrial Cancer Guidelines.

Colposcopy During Pregnancy

During pregnancy, the recommendations for colposcopy and follow-up are the same as outlined previously, with the following exceptions. Cervical biopsy is safe during pregnancy. However, to avoid possible disruption of the pregnancy, endocervical curettage should not be performed. Treatment for CIN (any grade) should be delayed until after the pregnancy. In the case of biopsy-proven CIN II or III in early pregnancy, consideration should be given to performing a repeat colposcopy later in the pregnancy to rule out progression of the lesion. Since colposcopic evaluation in pregnant women can be problematic, consultation with or referral to an experienced colposcopist should be considered.

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Table 1

The 1991 Bethesda System[a]

Adequacy of the specimen

- Satisfactory for evaluation
- Satisfactory for evaluation but limited by: Specify reason
- Unsatisfactory for evaluation: Specify reason

General categorization (optional)

- Within normal limits
- Benign cellular changes: See descriptive diagnoses
- Epithelial cell abnormalities: See descriptive diagnoses

Descriptive diagnoses

- Benign cellular changes
- Infection (Trichomonas vaginalis)
  - Fungal organisms morphologically consistent with Candida species
  - Predominance of coccobacilli consistent with shift in vaginal flora
  - Bacteria morphologically consistent with Actinomyces species
  - Cellular changes associated with herpes simplex virus
  - Other[b]

Reactive changes

- Reactive cellular changes associated with inflammation (includes typical repair)
- Atrophy with inflammation ("atrophic vaginitis")
- Radiation I
- Intrauterine contraceptive device
- Other

Epithelial cell abnormalities

- Squamous cell
- Atypical squamous cells of undetermined significance: Qualify[c]
- Low-grade squamous intraepithelial lesion encompassing HPV[d], mild dysplasia/CIN I
- High-grade squamous intraepithelial lesion encompassing moderate and severe dysplasia, CIS/CIN II, and CIN III
- Squamous cell carcinoma

Glandular cell

- Endometrial cells, cytologically benign, in a postmenopausal woman
- Atypical glandular cells of undetermined significance: Qualify[c]
- Endocervical adenocarcinoma
- Endometrial adenocarcinoma
- Extrauterine adenocarcinoma
- Adenocarcinoma, nonorgan-specific

Other malignant neoplasms: Specify

Hormonal evaluation (applies to vaginal smears only)

- Hormonal pattern compatible with age and history
- Hormonal pattern incompatible with age and history: Specify reason
- Hormonal evaluation not possible due to: Specify reason

[a]CIN = cervical intraepithelial neoplasia; CIS = carcinoma in situ; HPV = human papillomavirus.
[b]Cellular changes of HPV previously termed koilocytosis, koilocytic atypia, or condylomatous atypia are included in the category of low-grade squamous intraepithelial lesion.
[c]Atypical squamous or glandular cells of undetermined significance should be further qualified, if possible, as to whether a reactive or a premalignant/malignant process is favored.
[d]Cellular changes of HPV previously termed koilocytosis, koilocytic atypia, or condylomatous atypia are included in the category of low-grade squamous intraepithelial lesion.

Modified From: National Cancer Institute Workshop. The revised Bethesda system for reporting cervical and/or vaginal diagnoses; report of the 1991 Bethesda workshop. Acta Cytol. 36:273-275, 1992.

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