National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Cervical Cancer Screening

Version 2.2012

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Cervical Cancer Screening

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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.

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NCCN Guidelines Version 2.2012 Updates Cervical Cancer Screening

Updates to Version 2.2012 of the NCCN Cervical Cancer Screening Guidelines from Version 1.2012 include:

MS-1

- **The addition of the discussion to reflect the changes in the algorithm.**

Updates in Version 1.2012 of the NCCN Cervical Cancer Screening Guidelines from Version 1.2011 include:

Global change

- **"Cancer" was clarified as "invasive carcinoma" throughout the guidelines.**
- **The management of "Screening Findings in Adolescents or Young Women < 21 y" was removed from the Guidelines and replaced with a footnote, "Cervical cancer screening should begin at age 21 years. 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. In the event that screening is performed, consultation or referral is recommended to a colposcopist with experience in colposcopy in adolescents or young women < 21 y." This footnote was added to CERVS-3 and CERVS-5.**

CERVS-1

- **"Screening Guidelines for Early Detection of Cervical Cancer" were updated based on "Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. Am J Clin Pathol 2012;137:516-542."**

CERVS-3

- **Cervical cytology/Pap test positive for epithelial abnormalities, "adenocarcinoma in situ (AIS)" was added as an initial finding of a screening exam with management on CERVS-11.**

CERVS-4

- **Follow-up for high-risk HPV DNA testing, the first testing option was modified as: "HPV DNA specific test for *16 or* 16/18 genotype" and the category was changed from a category 2A to a category 1 recommendation with a corresponding footnote "l," "Wright TC Jr, Stoler MH, Sharma A, et al. Evaluation of HPV-16 and HPV-18 genotyping for the triage of women with high-risk HPV+ cytology-negative results. Am J Clin Pathol. 2011;136:578-586."**
- **For "repeat both tests at 12 mo", the possible result outcomes were modified as:**
  - **"Both tests negative *or High-risk HPV DNA test negative and Cytology/ Pap test positive for ASC-US*"**
  - **"High-risk HPV DNA test negative and Cytology/Pap test positive *for* > *ASC-US*"**
  - **"High-risk HPV DNA test positive and Cytology/Pap test *positive or* negative"**
- **The follow-up for "both tests negative or High-risk HPV DNA test negative and Cytology/ Pap test positive for ASC-US" was modified as: "Resume routine screening per guidelines ~~in 3 y~~."**
- **Footnotes**
  - **Footnote "i" was modified as: "...High-risk HPV DNA tests detect whether any of the 12-14 high-risk types of HPV are present, although the tests do not ~~indicate~~ *specify* which types are present."**
  - **Footnote "j" was added: "Use of high-risk HPV DNA testing alone is not recommended for screening in any age group. Cotesting (ie, HPV DNA and cytology testing) is not recommended for screening in women age 21-29 years."**
  - **Footnote "k" was modified as: "The HPV ~~16/18~~ DNA ~~diagnostic~~ *specific* test ~~is a separate test that only~~ detects whether HPV 16 *and* HPV 18 are present."**
  - **Footnote "m" was modified as: "Follow appropriate colposcopy findings pathway *(See CERVS-6 or CERVS-8)*...". (Also for CERVS-6, CERVS-7, and CERVS-10.)"**

CERVS-5

- **The screening finding of "AIS" was added to the page with a link to the management.**

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NCCN Guidelines Version 2.2012 Updates Cervical Cancer Screening

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Updates in Version 1.2012 of the NCCN Cervical Cancer Screening Guidelines from Version 1.2011 include:

CERVS-6

- "Coloposcopy for" was modified by adding: "or Positive for HPV 16 or 16/18 (see CERVS-4)." (Also for CERVS-8.)
- Cervical biopsy finding: "AIS" was added to "Microinvasion" and the management was changed from "CKC" to "Diagnostic excision procedure" with two footnotes:
  (Also for CERVS-7 through CERVS-9.)
  - Footnote "r" was added: "CKC is preferred. However, LEEP is acceptable provided attention is given to adequate margins." (Also for CERVS-14)
  - Footnote "s" was added: "If results favor neoplasia, microinvasion, or adenocarcinoma in situ, follow CKC or LEEP with endometrial sampling if not yet done."

CERVS-8

- The management option was clarified as: "Repeat cervical cytology/Pap test ~~colposcopy, and ECC~~ every 6 mo until 2 consecutive negative results." (Also for CERVS-9.)
- Footnote "u" was modified as:"If preceding cervical cytology/Pap test was ASC-H, may consider follow-up *with cervical cytology/Pap test*."

CERVS-10

- CIN2, 3 with positive margins, after re-excision or consider hysterectomy, the possible result, "If AIS or microinvasion, see CERVS-15" was added.

CERVS-11

- "Adenocarcinoma in situ: Follow-up and management" is a new algorithm.
- Footnote "e" was added: "Referral to a 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." (Also for CERVS-12)

CERVS-12

- "Microinvasion" was added to "AIS." (Also for CERVS-13 and CERVS-14.)
- Adenocarcinoma in situ (AIS) or Microinvasion, after "CKC," the possible result, "If CIN1, 2, 3, see CERVS-10" was added.
- Footnote "w" was added: "CKC should be performed, because it is difficult to obtain adequate margins with glandular lesions where extent cannot be determined." (Also for CERVS-13 and CERVS-14.)

CERVS-15

- Title of page was changed from "Atypical glandular cells: Adenocarcinoma in situ" to "Adenocarcinoma in situ or microinvasion: Management of CKC or LEEP findings."

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SCREENING GUIDELINES FOR EARLY DETECTION OF CERVICAL CANCER[a]

POPULATION	RECOMMENDED SCREENING METHOD[b]	MANAGEMENT OF SCREEN RESULTS	COMMENTS
Age <21 y	No screening		HPV testing should not be used for screening or management of ASC-US in this age group
Age 21-29 y	Cytology alone every 3 y	HPV-positive ASC-US[d] or cytology of LSIL or more severe: Refer to NCCN and ASCCP guidelines[c]	HPV testing should not be used for screening in this age group
		Cytology negative or HPV-negative ASC-US:[d] Rescreen with cytology in 3 y	
Age 30-65 y	HPV and cytology "cotesting" every 5 y (preferred)	HPV-positive ASC-US or cytology of LSIL or more severe: Refer to NCCN and ASCCP guidelines[c]	Screening by HPV testing alone is not recommended for most clinical settings
		HPV positive, cytology negative: Option 1: 12-mo follow-up with cotesting Option 2: Test for HPV16 or HPV16/18 genotypes • If HPV16 or HPV16/18 positive: refer to colposcopy • If HPV16 or HPV16/18 negative: 12-mo follow-up with cotesting	
		Cotest negative or HPV-negative ASC-US: Rescreen with cotesting in 5 y	
	Cytology alone every 3 y (acceptable)	HPV-positive ASC-US[d] or cytology of LSIL or more severe: Refer to NCCN and ASCCP guidelines[c]	
		Cytology negative or HPV-negative ASC-US:[d] Rescreen with cytology in 3 y	

[a] Adapted from Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. Am J Clin Pathol 2012;137:516-542.

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[b] Women should not be screened annually at any age by any method.

[c] ASCCP= American Society for Colposcopy and Cervical Pathology. Wright TC, et al. J Low Genit Tract Dis 2007;11:201-222.

[d] ASC-US cytology with secondary HPV testing for management decisions.

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SCREENING GUIDELINES FOR EARLY DETECTION OF CERVICAL CANCER[a]

POPULATION	RECOMMENDED SCREENING METHOD[b]	MANAGEMENT OF SCREEN RESULTS	COMMENTS
Age >65 y	No screening following adequate negative prior screening		Women with a history of CIN2 or a more severe diagnosis should continue routine screening for at least 20 y
After hysterectomy	No screening		Applies to women without a cervix and without a history of CIN2 or a more severe diagnosis in the past 20 y or cervical cancer ever
HPV vaccinated	Follow age-specific recommendations (same as unvaccinated women)		

See Initial Findings of Screening Exam (CERVS-3)

[a] Adapted from Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. Am J Clin Pathol 2012;137:516-542.
[b] Women should not be screened annually at any age by any method.

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INITIAL FINDINGS OF SCREENING EXAM[e,f] → **FOLLOW-UP**

- **Visible/suspicious lesion on cervix** → **Biopsy** →
  - **If invasive carcinoma, see NCCN Cervical Cancer Guidelines**
  - **If no invasive carcinoma, consider CKC and/or referral to gynecologic oncologist/specialist**
- **Cervical cytology/Pap test[g,h] unsatisfactory** →
  - **Repeat cervical cytology/Pap test[g,h] should be done within 6-12 weeks.**
  - **Treat infection if present and indicated**
- **Cervical cytology/Pap test[g,h] 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 negative[g,h] and High-Risk HPV DNA positive ≥ 30 y** → **See Follow-up for High-Risk HPV DNA Testing in Adults ≥ 30 y (CERVS-4)**
- **Cervical cytology/Pap test[g,h] positive for epithelial abnormalities:**
  - **Atypical squamous cells (ASC)**
    - **Undetermined significance (ASC-US)** →
    - **Suspicion of high-grade dysplasia (ASC-H)** →
  - **Low-grade squamous intraepithelial lesions (LSIL)** →
  - **High-grade squamous intraepithelial lesions (HSIL)** →

  → **See Screening Findings Adult ≥ 21 y (CERVS-5)**
  - **Adenocarcinoma in situ (AIS)[e]** → **See AIS Follow-Up and Management (CERVS-11)**
  - **Atypical glandular cells (AGC)[e]** → **See AGC Follow-Up and Management (CERVS-12)**
- **Cervical cytology/Pap test[g,h] positive for invasive carcinoma[e]** → **Biopsy visible lesion; diagnostic excision if no visible lesion** →
  - **If invasive carcinoma, see NCCN Cervical Cancer Guidelines**
  - **If CIN1-3, see CERVS-10**

[e] 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.

[f] Cervical cancer screening should begin at age 21 years. 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. In the event that screening is performed, consultation or referral is recommended to a colposcopist with experience in colposcopy in adolescents or young women < 21 y.

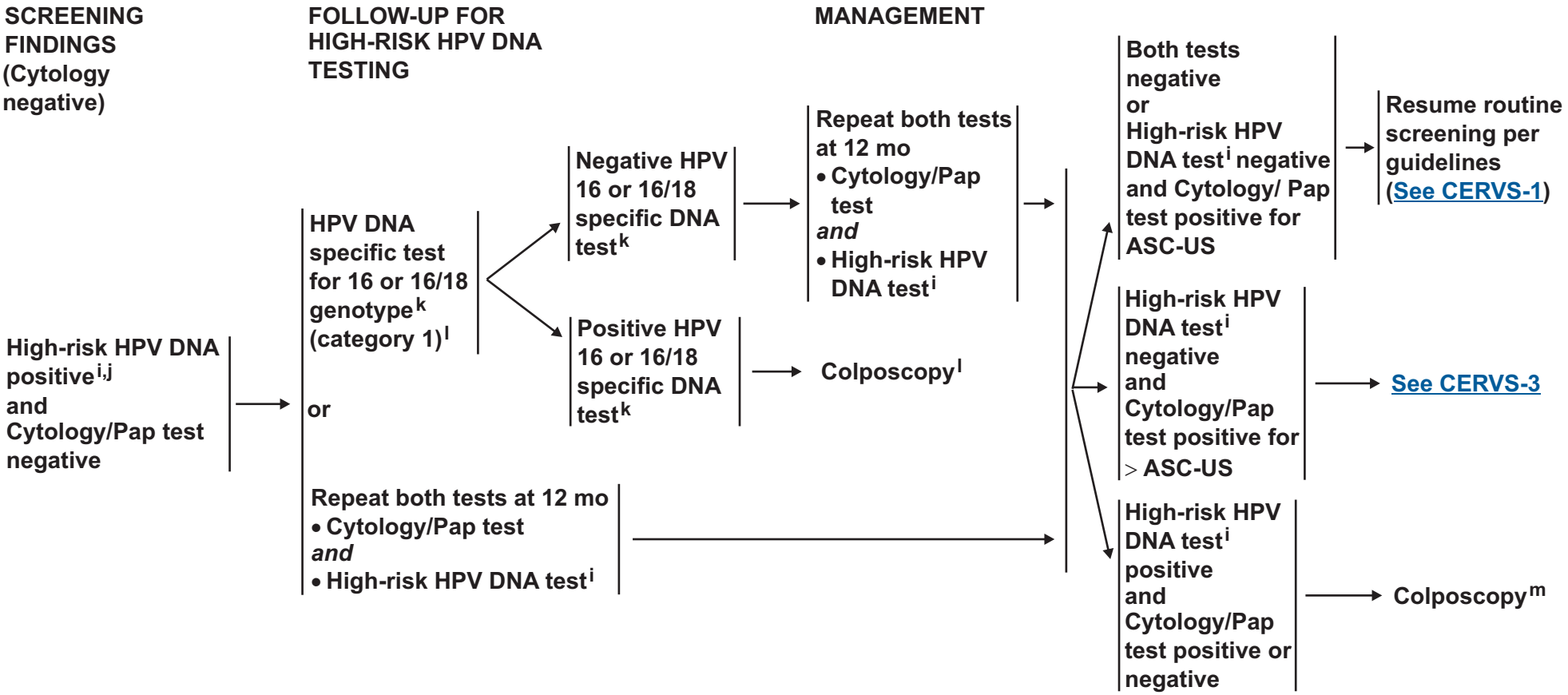
[g] Cervical cytology/Pap test results should be reported using the Bethesda System. See The Bethesda System 2001 (CERVS-A).

[h] Conventional Pap test or liquid-based technology is an acceptable method for primary screening.

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



[i] 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 12-14 high-risk types of HPV are present, although the tests do not specify which types are present.

[j] Use of high-risk HPV DNA testing alone is not recommended for screening in any age group. Cotesting (ie, HPV DNA and cytology testing) is not recommended for screening in women age 21-29 years.

[k] The HPV DNA specific test detects whether HPV 16 and HPV 18 are present.

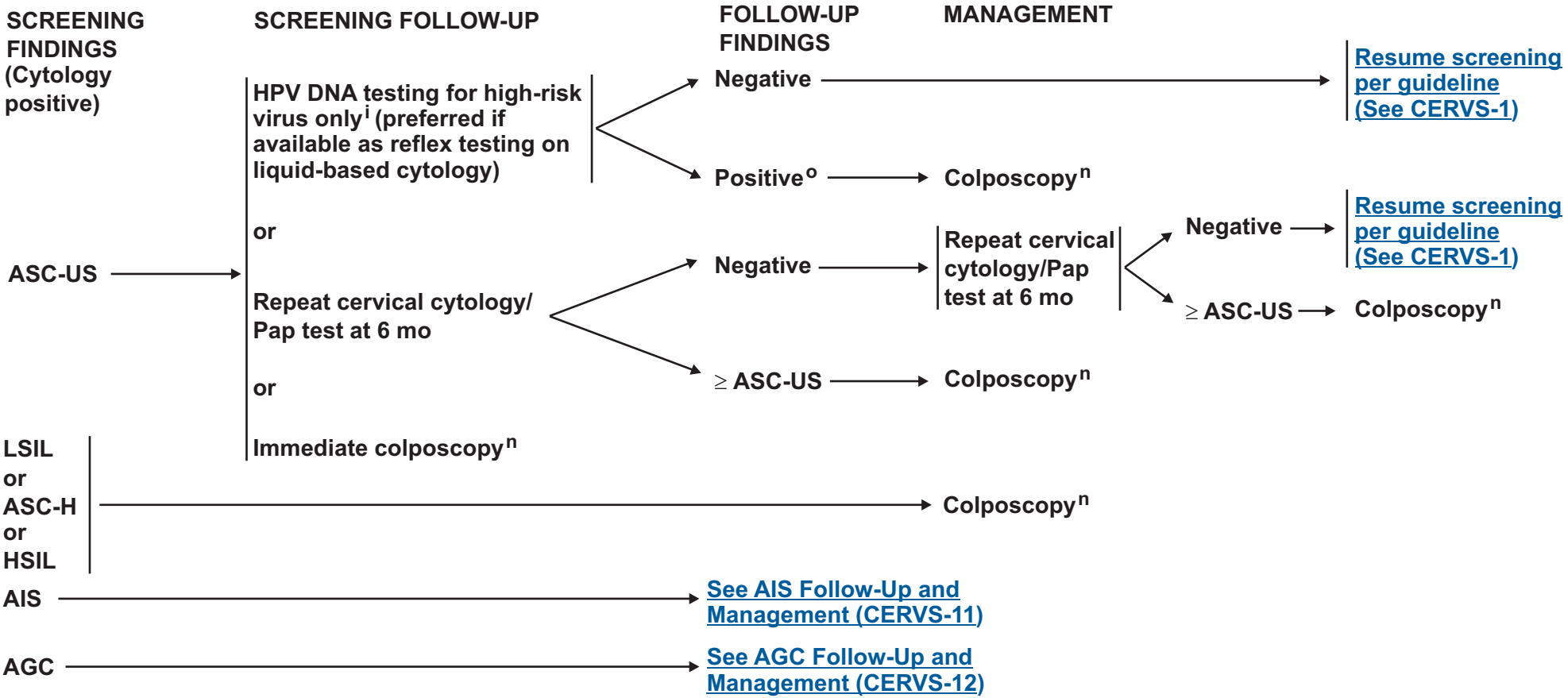
[l] Wright TC Jr, Stoler MH, Sharma A, et al. Evaluation of HPV-16 and HPV-18 genotyping for the triage of women with high-risk HPV+ cytology-negative results. Am J Clin Pathol 2011;136:578-586.

[m] Follow appropriate colposcopy findings pathway (See CERVS-6 or CERVS-8). If appropriate, see Colposcopy During Pregnancy (CERVS-B).

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ADULTS ≥ 21 Y[f]



[f]Cervical cancer screening should begin at age 21 years. 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. In the event that screening is performed, consultation or referral is recommended to a colposcopist with experience in colposcopy in adolescents or young women < 21 y.

[i]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 12-14 high-risk types of HPV are present, although the tests do not specify which types are present.

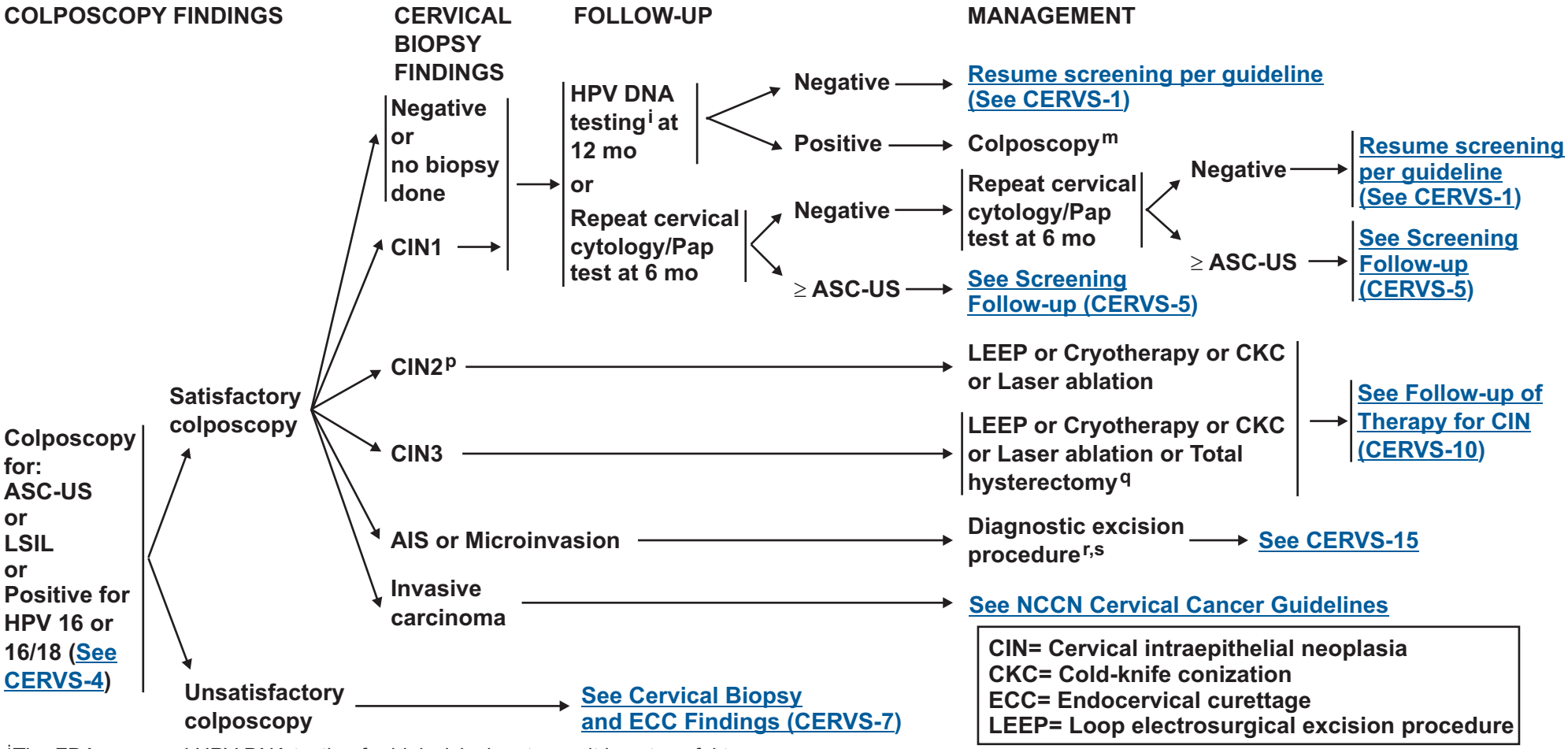
[n]For colposcopy for ASC-US or LSIL, see CERVS-6 and for ASC-H or HSIL, see CERVS-8. If appropriate, see Colposcopy During Pregnancy (CERVS-B).

[o]In women with ASC-US who are high-risk HPV positive, the NCCN and American Society for Colposcopy and Cervical Pathology (ASCCP) do not recommend using the HPV 16/18 specific DNA test (ie, HPV genotyping) to screen for who should proceed to colposcopy.

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ADULTS ≥ 21 Y



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

[i] 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 12-14 high-risk types of HPV are present, although the tests do not specify which types are present.

[m] Follow appropriate colposcopy findings pathway (See CERVS-6 or CERVS-8). If appropriate, see Colposcopy During Pregnancy (CERVS-B).

[p] CIN2 may be followed without treatment in certain clinical circumstances at the discretion of the physician.

[q] If appropriate for preexisting pathologic condition or quality of life.

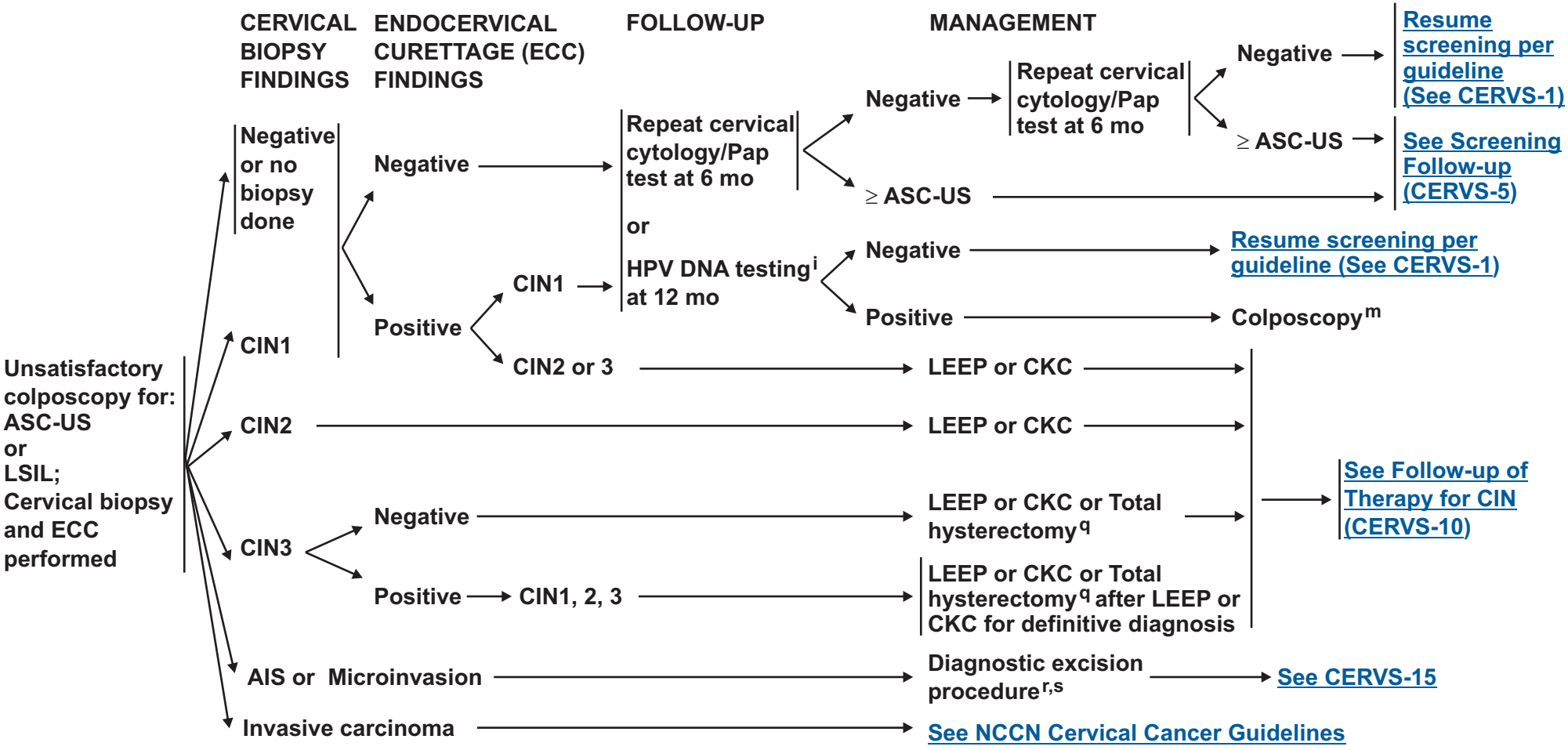
[r] CKC is preferred. However, LEEP is acceptable provided attention is given to adequate margins.

[s] If results favor neoplasia, microinvasion, or adenocarcinoma in situ, follow CKC or LEEP with endometrial sampling if not yet done.

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ADULTS ≥ 21 Y



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[m] Follow appropriate colposcopy findings pathway (See CERVS-6 or CERVS-8). If appropriate, see Colposcopy During Pregnancy (CERVS-B).

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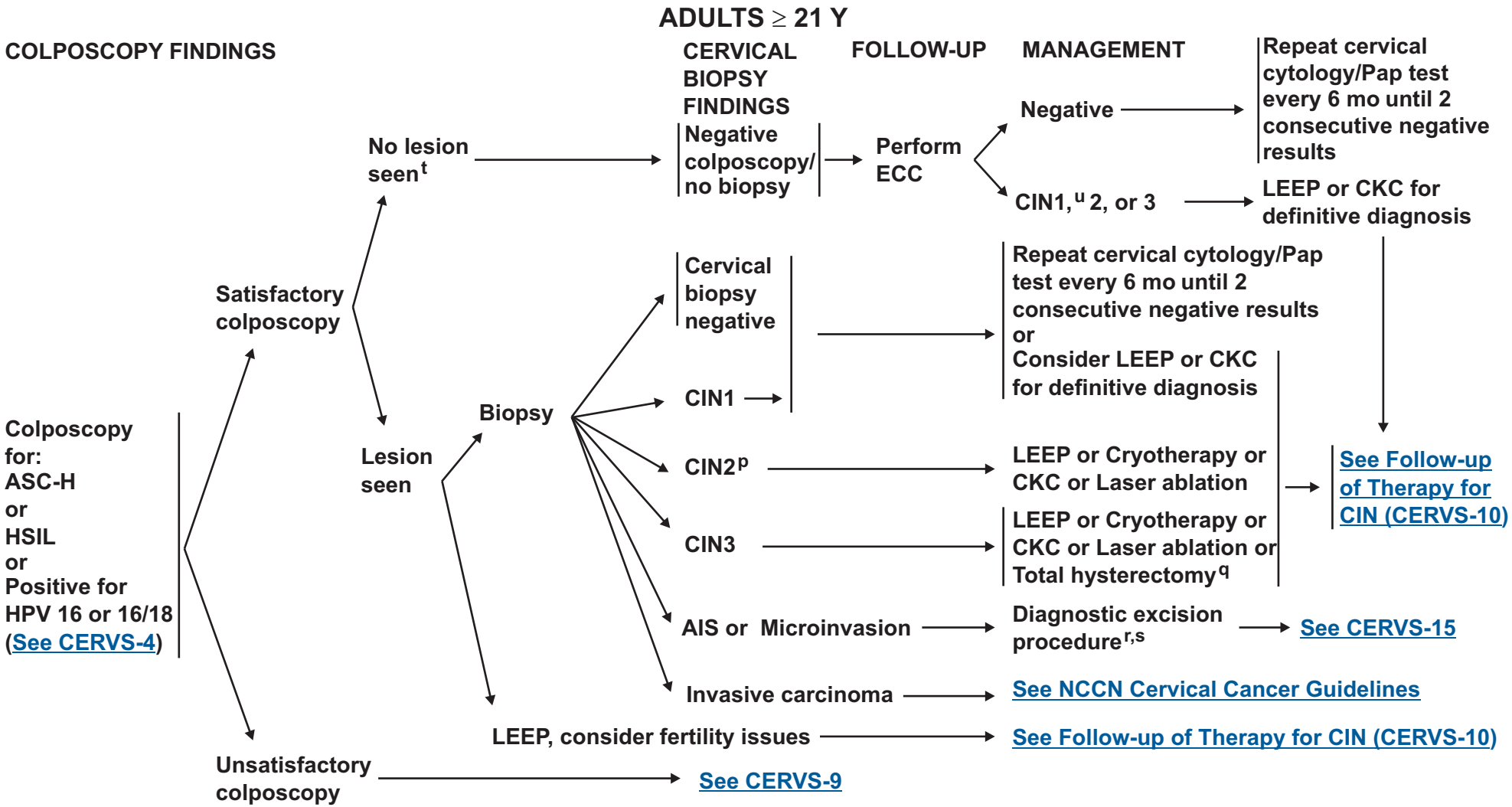
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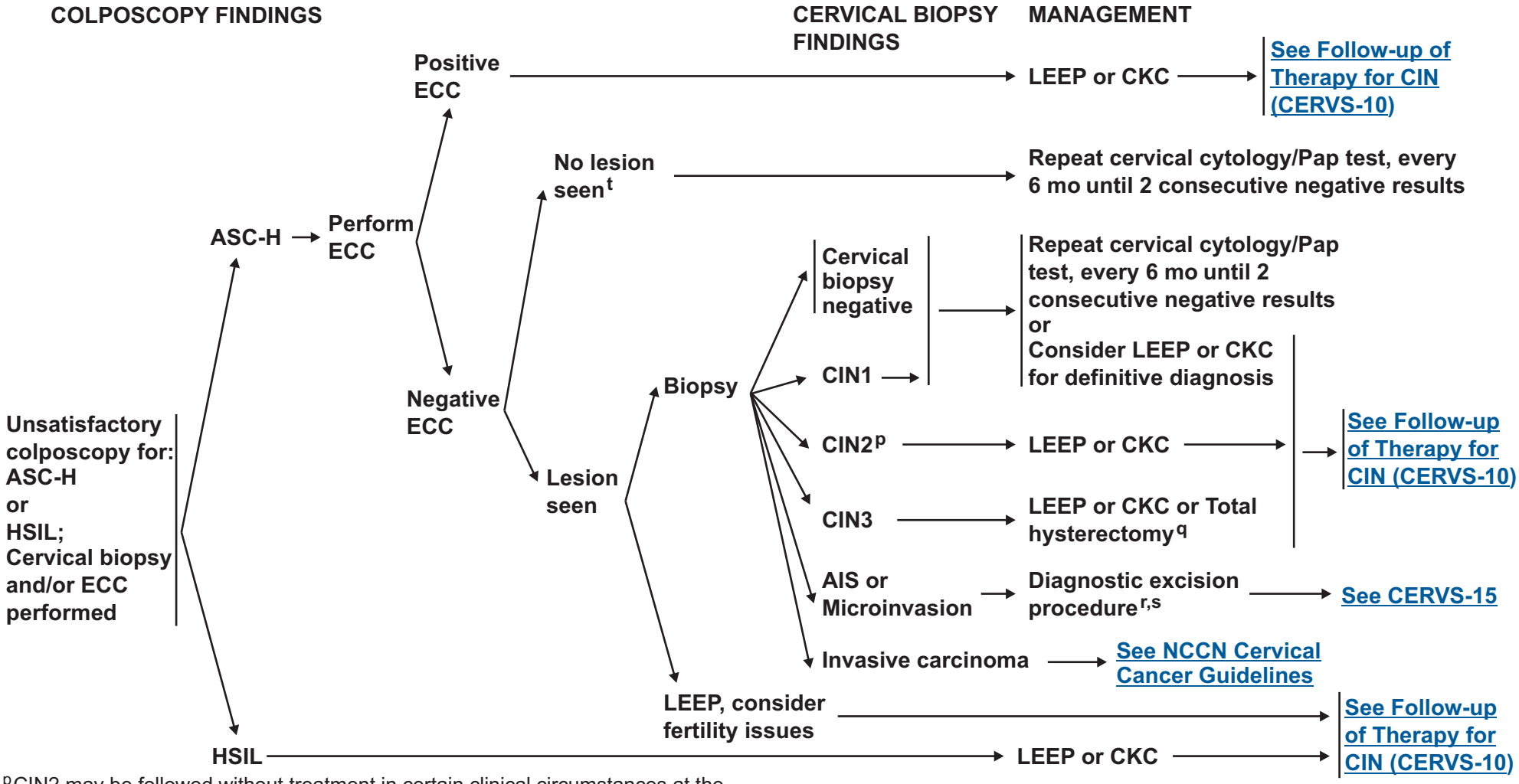
[t] Perform vaginal and vulvar colposcopy.

[u] If preceding cervical cytology/Pap test was ASC-H, may consider follow-up with cervical cytology/Pap test.

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ADULTS ≥ 21 Y



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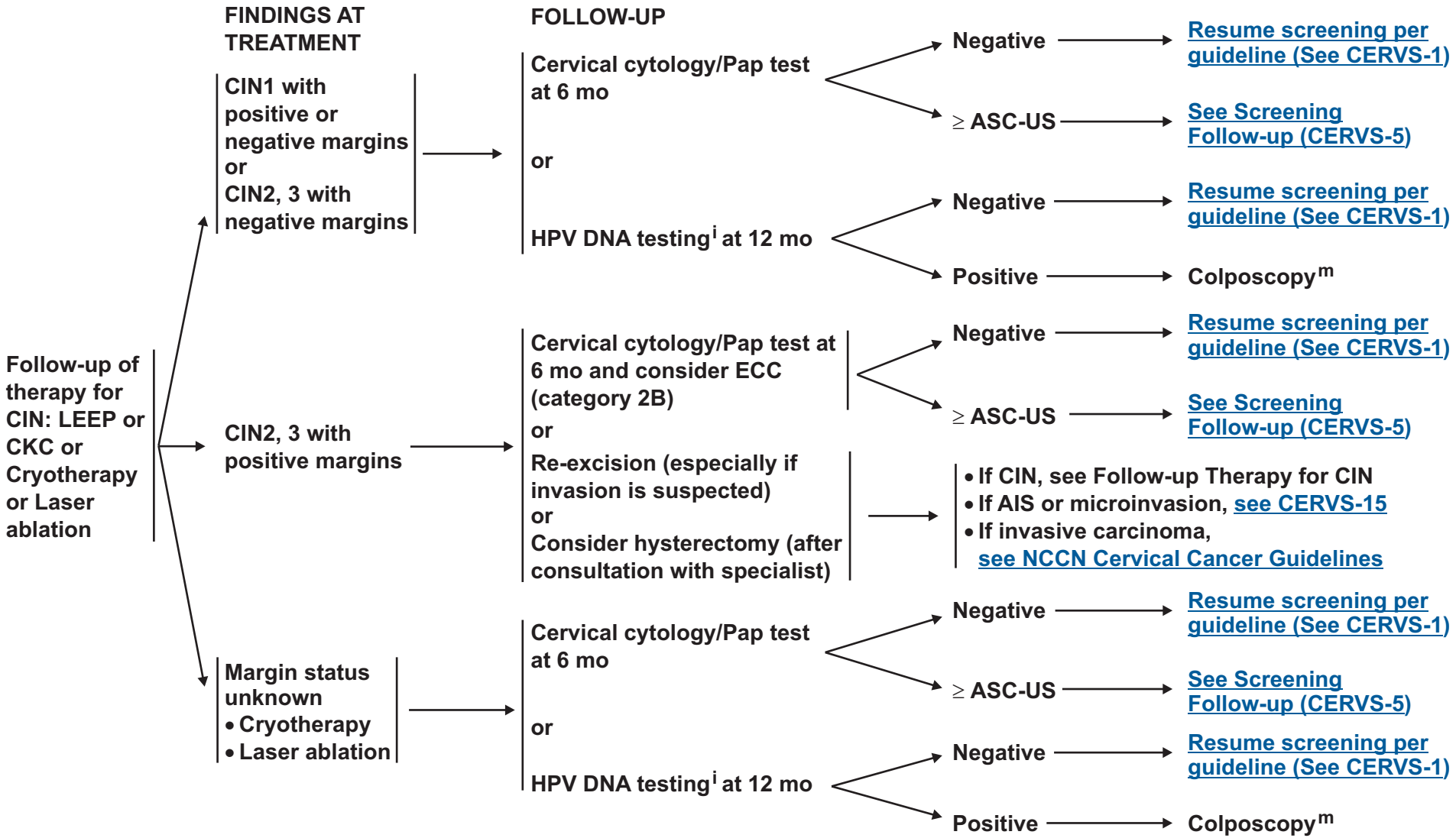
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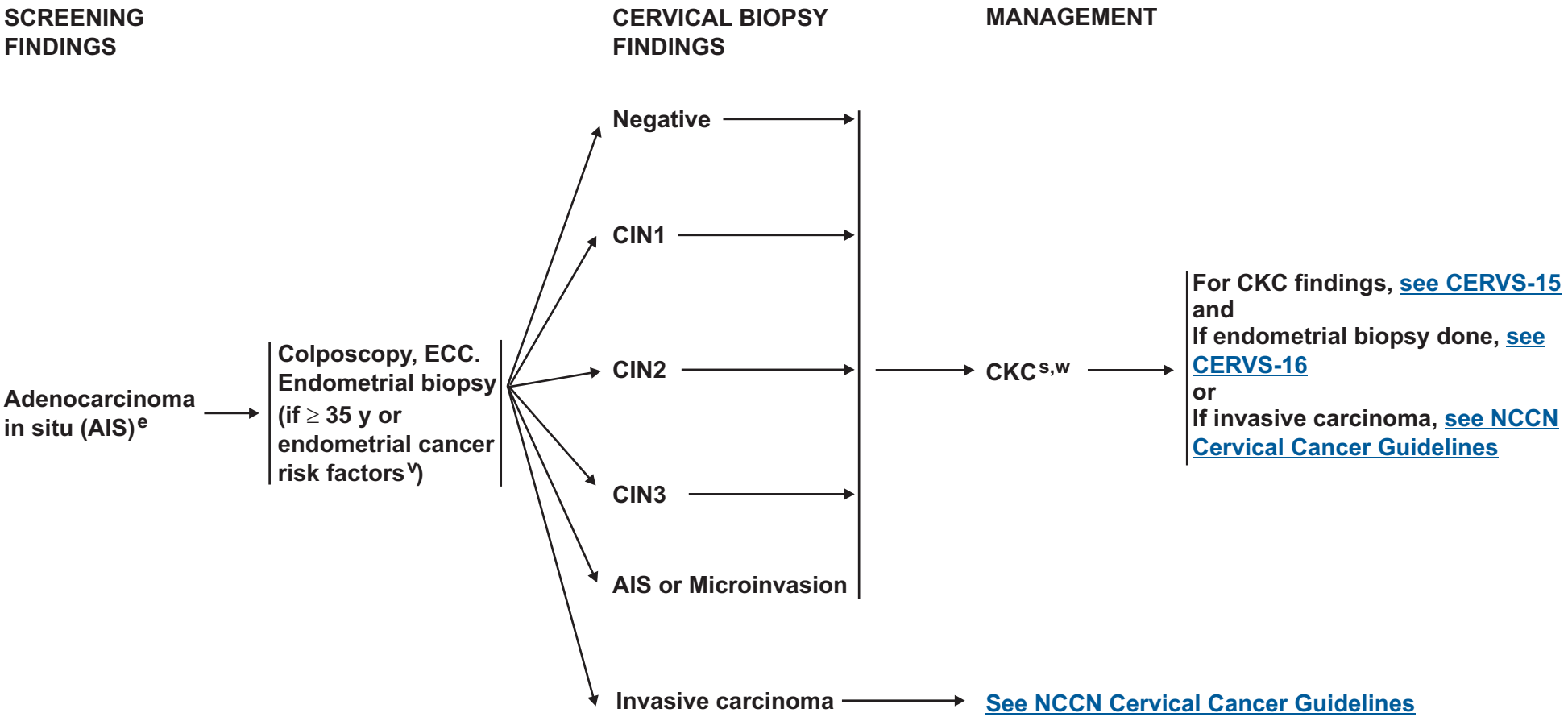
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ADENOCARCINOMA IN SITU: FOLLOW-UP AND MANAGEMENT



[e]Referral to a 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.

[s]If results favor neoplasia, microinvasion, or adenocarcinoma in situ, follow CKC or LEEP with endometrial sampling if not yet done.

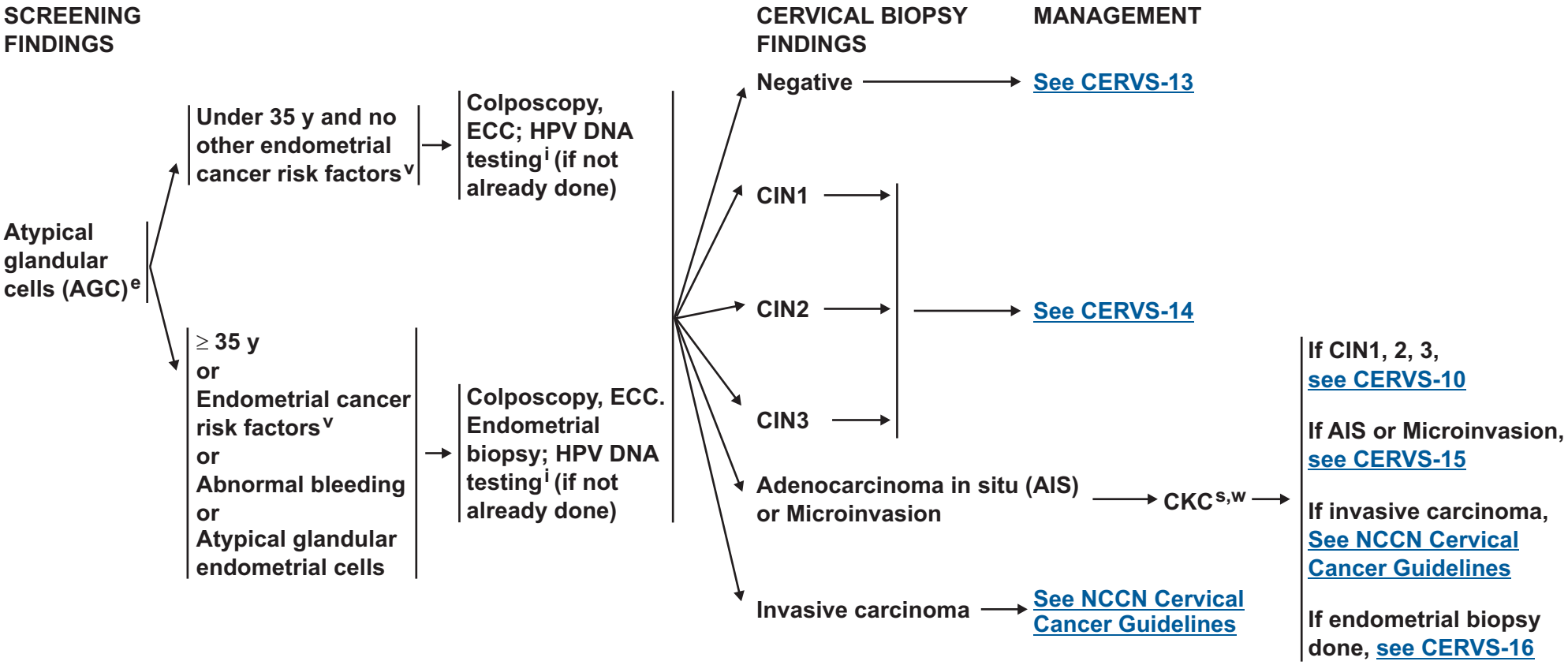
[v]Endometrial cancer risk factors: obesity, unopposed estrogen replacement therapy, polycystic ovarian disease, tamoxifen therapy, anovulation, Lynch syndrome/Hereditary Non-Polyposis Colorectal Cancer syndrome (HNPCC).

[w]CKC should be performed because it is difficult to obtain adequate margins with glandular lesions where extent cannot be determined.

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ATYPICAL GLANDULAR CELLS: FOLLOW-UP AND MANAGEMENT



[e] Referral to a 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.

[i] 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 12-14 high-risk types of HPV are present, although the tests do not specify which types are present.

[s] If results favor neoplasia, microinvasion, or adenocarcinoma in situ, follow CKC with endometrial sampling if not yet done.

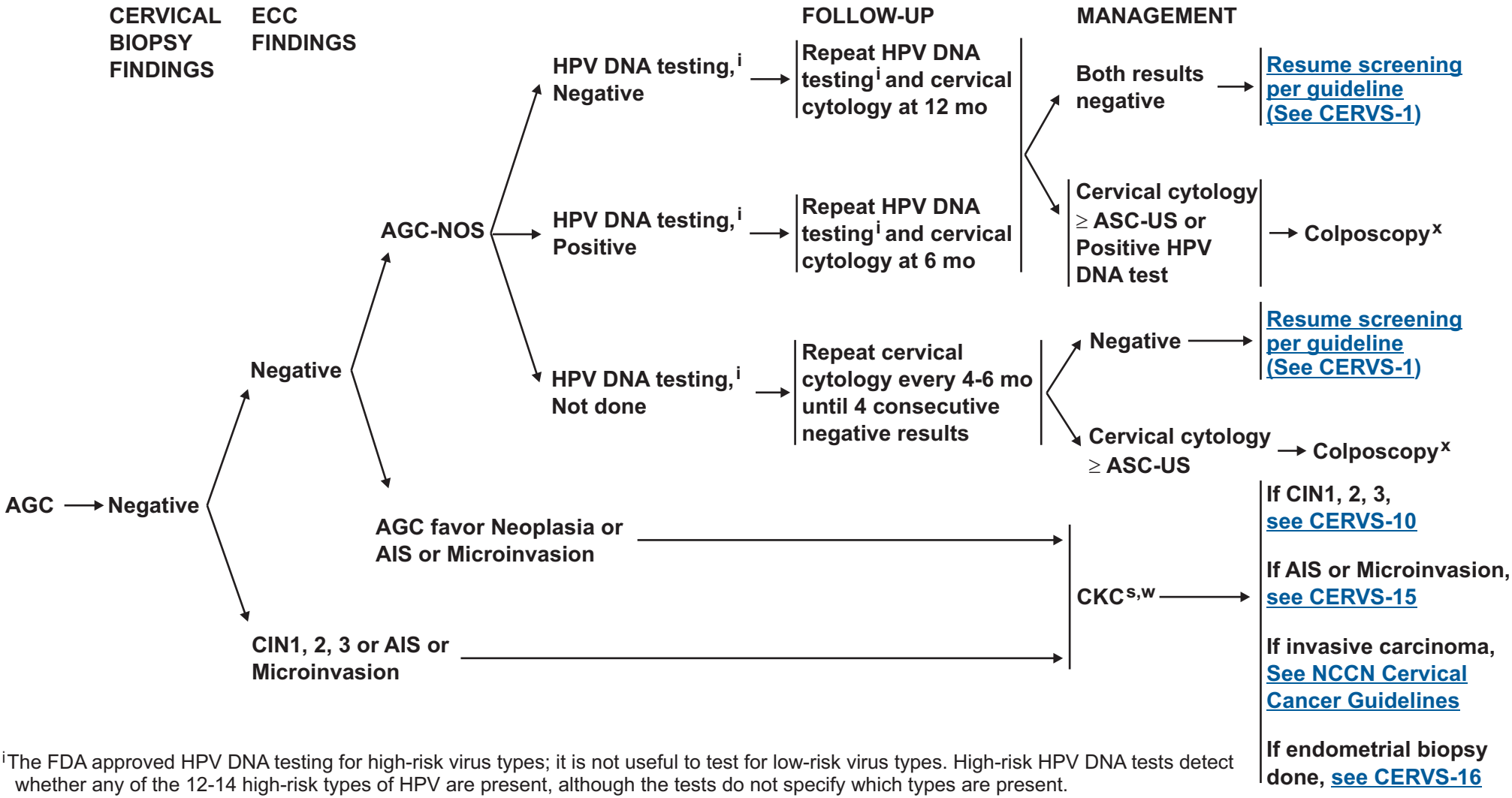
[v] Endometrial cancer risk factors: obesity, unopposed estrogen replacement therapy, polycystic ovarian disease, tamoxifen therapy, anovulation, Lynch syndrome/Hereditary Non-Polyposis Colorectal Cancer syndrome (HNPCC).

[w] CKC should be performed, because it is difficult to obtain adequate margins with glandular lesions where extent cannot be determined.

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ATYPICAL GLANDULAR CELLS: FOLLOW-UP AND MANAGEMENT



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[s]If results favor neoplasia, microinvasion, or adenocarcinoma in situ, follow CKC or LEEP with endometrial sampling if not yet done.

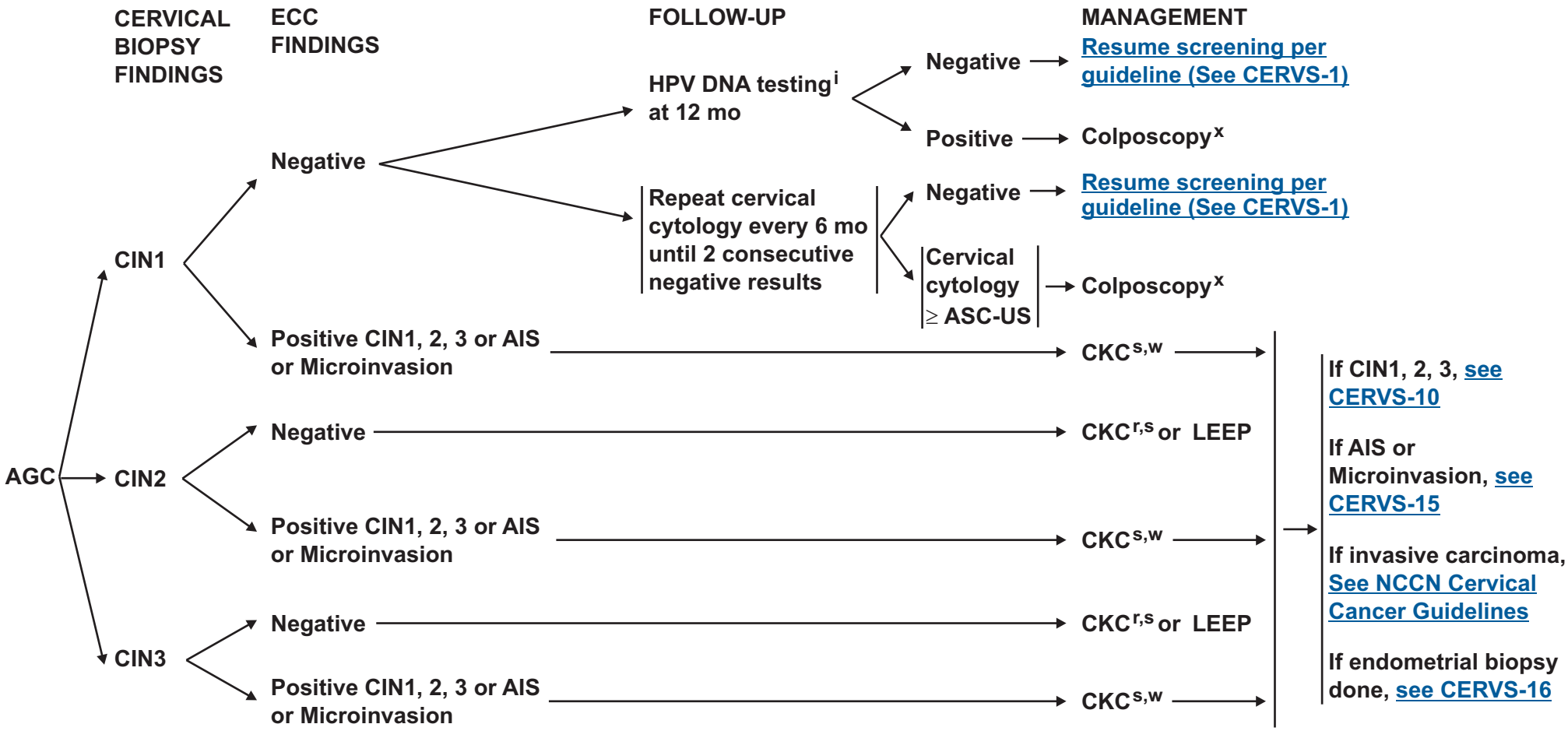
[w]CKC should be performed, because it is difficult to obtain adequate margins with glandular lesions where extent cannot be determined.

[x]Follow appropriate colposcopy findings pathway (See CERVS-12). If appropriate, see Colposcopy During Pregnancy (CERVS-B).

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ATYPICAL GLANDULAR CELLS: FOLLOW-UP AND MANAGEMENT



[i]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 12-14 high-risk types of HPV are present, although the tests do not specify which types are present.

[r]CKC is preferred. However, LEEP is acceptable if margins are adequate.

[s]If results favor neoplasia, microinvasion, or adenocarcinoma in situ, follow CKC or LEEP with endometrial sampling if not yet done.

[w]CKC should be performed, because it is difficult to obtain adequate margins with glandular lesions where extent cannot be determined.

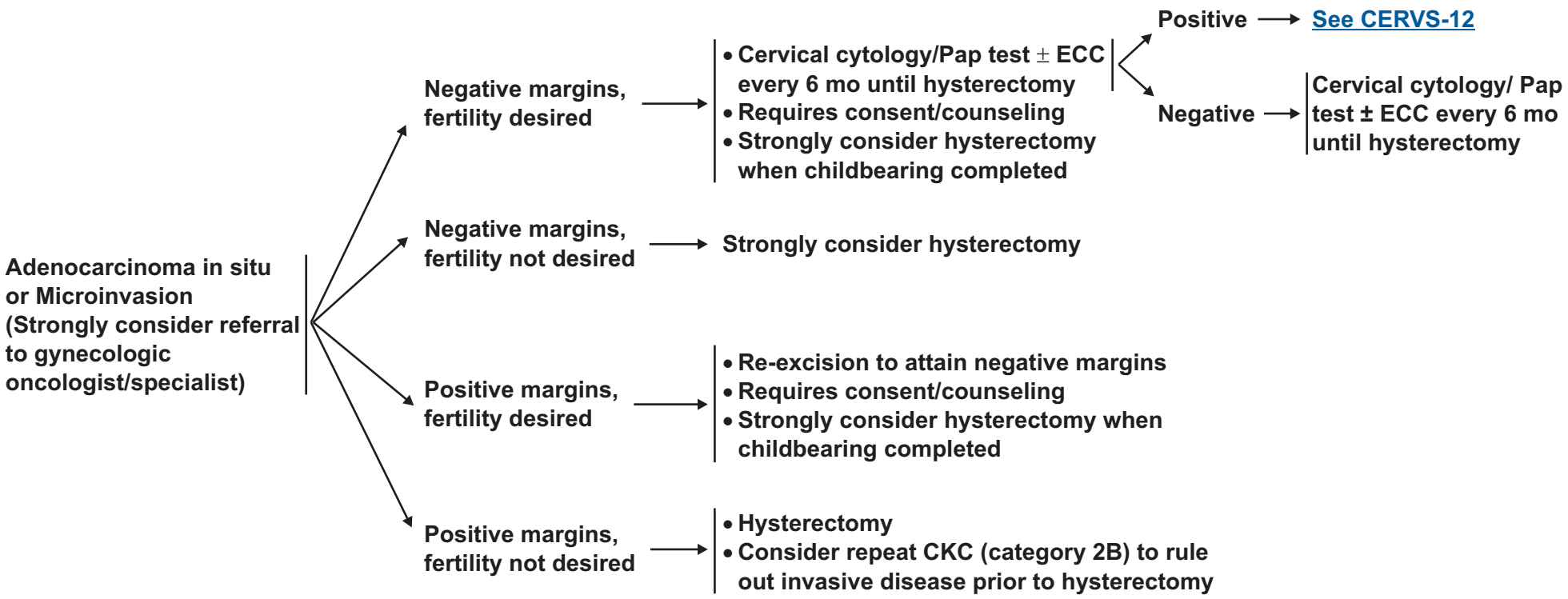
[x]Follow appropriate colposcopy findings pathway (See CERVS-12). If appropriate, see Colposcopy During Pregnancy (CERVS-B).

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ADENOCARCINOMA IN SITU OR MICROINVASION: MANAGEMENT OF CKC OR LEEP FINDINGS

CKC OR LEEP FINDINGS

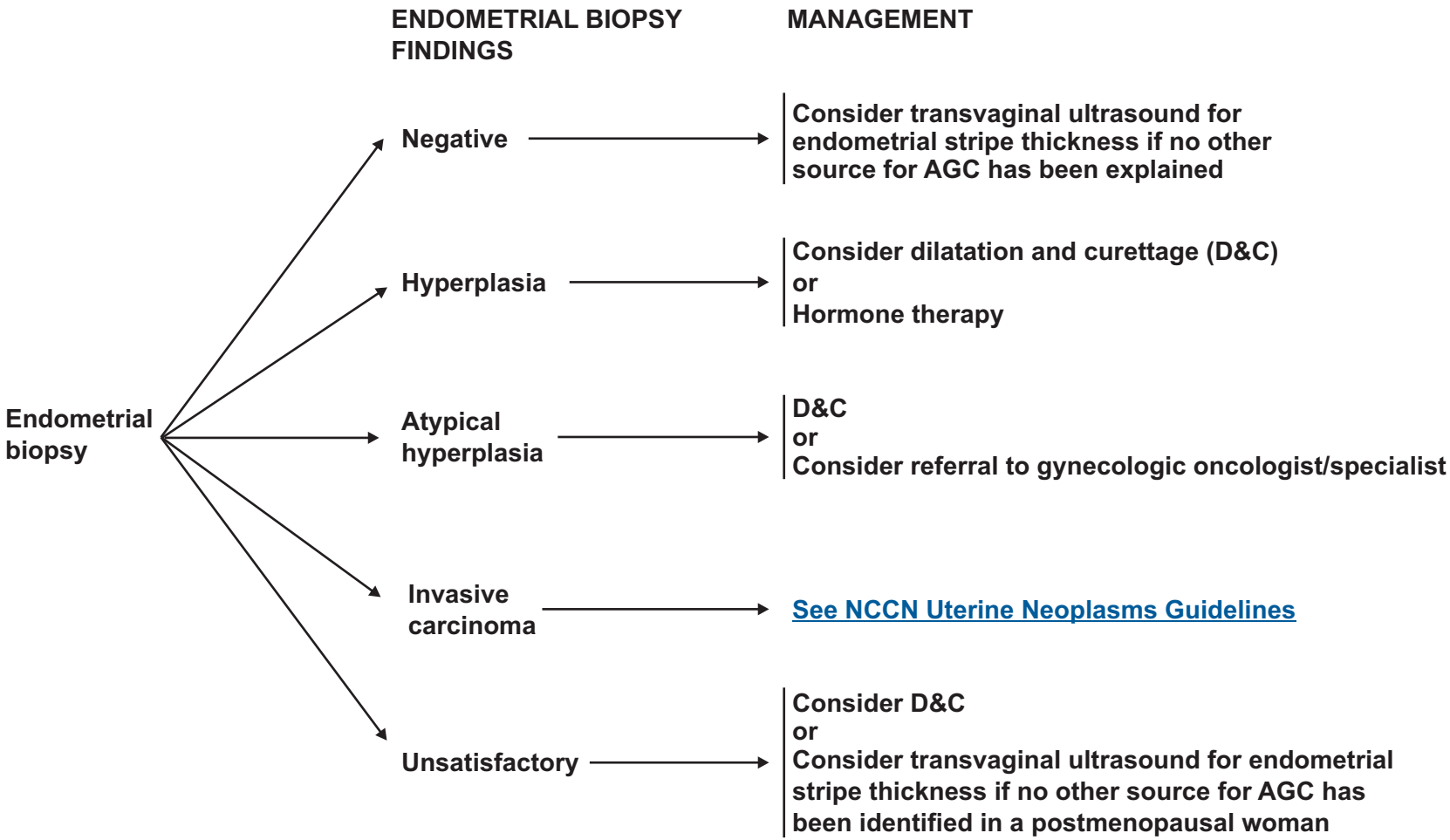


Invasive carcinoma → **See NCCN Cervical Cancer Guidelines**

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ENDOMETRIAL BIOPSY: FINDINGS AND MANAGEMENT



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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)

INTERPRETATION/RESULT

NEGATIVE FOR INTRAEPITHELIAL LESION OR MALIGNANCY (when there is no cellular evidence of neoplasia, state this in the General Categorization and/or 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 ≥ 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)

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 February 1, 2012.

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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 where high-grade neoplasia or invasive carcinoma is suspected.**
- **Diagnostic limited excisional procedure is recommended only if invasion is suspected.**
- **Brush cytology is safe during pregnancy.**

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Cervical cytology screening has been proven to decrease the incidence and mortality of squamous cell cervical cancer and to increase the cure rate of cervical cancer.[1-4] Despite a significant decrease in the incidence and mortality of cervical carcinoma in the United States because of screening, it is estimated that 12,170 women will be diagnosed in 2012, with 4,220 expected deaths.[5, 6] 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 done. Because cervical cytology screening is the predominant 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. Use of DNA testing for high-risk subtypes of human papillomavirus (HPV) is also a useful adjunct to cervical cytology screening in select patients and is described in these NCCN guidelines.

The NCCN guidelines include recommendations regarding screening techniques, initiation and frequency of screening, and management of abnormal screening results including colposcopy. Cervical cytology screening techniques include liquid-based cytology or conventional Papanicolaou (Pap) smears; data suggest that the 2 techniques are similar.[1, 2] Unless specifically noted, these techniques are collectively referred to as “cervical cytology” in this manuscript (i.e., Discussion). Most cervical cytology testing in the United States is now done with liquid-based cytology.[7] When compared with conventional Pap testing, advantages of liquid-based cytology include: 1) combined testing for HPV can be done using the same sample; and 2) it is easier to read.[7]

Risk factors for cervical cancer include persistent infection with high-risk subtypes of HPV; HPV 16 and HPV 18 account for about 70% of cervical cancer.[8-11] However, most HPV 16/18 infections in women are not persistent, especially those in young women (< age 30 years).[12-14] Other epidemiologic risk factors associated with cervical cancer are a history of smoking, parity, contraceptive use, early age of onset of coitus, larger number of sexual partners, history of sexually transmitted disease, and chronic immunosuppression. Squamous cell carcinomas account for about 80% of all cervical cancers and adenocarcinoma for about 20% (see the NCCN Cervical Cancer Guidelines).[11]

HPV DNA testing for high-risk virus types is used as a component of both primary screening (e.g., combined testing also known as co-testing) and workup of abnormal cytology results; it is not useful to test for low-risk virus types (see “HPV DNA Testing” in this Discussion).[15] HPV DNA testing for primary cervical cancer screening

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has been approved by the FDA; several diagnostic tests are available (i.e., cobas 4800 HPV test, the 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 30 years (see next section in this Discussion).[1, 15]

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, 10-16 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 (i.e., the entire transformation zone is seen), the examination is considered satisfactory and endocervical curettage (ECC) is unnecessary.[15-17] 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. Clinicians should inform patients that treatment may be associated with adverse pregnancy outcomes.[18]

Cervical Cancer Screening

Initiation and Frequency (see CERVS-1 and CERVS-2)

The NCCN panel adopted the recommendations of the American Cancer Society (ACS), the American Society for Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology (ASCP) on the initiation and frequency of cervical cancer screening (see CERVS-1).[1] Women should begin screening at 21 years of age, regardless of whether sexual intercourse has already occurred.[1] However, annual cervical cancer screening, regardless of the method (e.g., cervical cytology) is no longer recommended in any age group.

Data indicate that cervical screening should be avoided in women younger than 21 years old, because these women are at very low risk of cervical cancer and because treatment can lead to complications (e.g., significant increase in premature births in women previously treated for dysplasia).[19-21] Although a few adolescents or young adults may have cervical intraepithelial neoplasia (CIN) 3, progression to cervical cancer is extremely rare in women younger than 21 years; most women with CIN 3 are picked up on subsequent screening.[15, 22-24] A high percentage of young women will be HPV positive within several years of initial sexual activity.[25-27] Thus, adolescents or young women (< 21 years) who are sexually active have a high prevalence of high-risk HPV infection; however, many infections will regress.[15, 22, 28] Therefore, HPV DNA testing is not recommended for screening in adolescents or women younger than 30 years.[1, 15,20]

However, adolescents or young adults who are immunocompromised (e.g., HIV infection, organ transplants, long-term steroid use) may need to have more frequent cervical screening. For example, those infected with HIV should be tested every 6 months the first year after their diagnosis and then annually. Cervical cytology screening should still be initiated in young women (21 years or older) who have been vaccinated against HPV 16 and HPV 18, because there are at least 12 other high-risk subtypes of HPV that are oncogenic (e.g., HPV 31, HPV 45).[1]

The onset of gynecologic care should not be based on the need for cervical screening. Thus, sexually active adolescents should receive

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counseling and testing for sexually transmitted diseases and should also receive counseling about safe sex and contraception. In asymptomatic adolescents, this can be done without using a speculum. After initiation, cervical screening should be performed every 3 years in women 21-29 years of age with cervical cytology alone.[1] However, women with high-risk factors (e.g., a history of cervical cancer, diagnosis of CIN 2-3, in utero exposure to diethylstilbestrol [DES], and/or who are immunocompromised [e.g., HIV infection]) should receive more frequent screening, usually annually, as determined by their physician.

HPV DNA testing is also not recommended 1) as routine screening in women younger than 30 years, and 2) in women with ASC-H, LSIL, or HSIL cytology.[1] In postmenopausal women with LSIL, HPV DNA testing may be used. Although women younger than age 30 years have about a 20% rate of high-risk HPV infection, most of the HPV 16/18 infections will regress. See section on "HPV DNA Testing" for more detail.

Screening options for women 30 years and older include: 1) cervical cytology combined with DNA testing for high-risk HPV types (i.e., co-testing) every 5 years, which is preferred; or 2) cervical cytology alone every 3 years (see CERVS-1).[1, 8, 12, 29, 30] Cervical cytology alone is more effective at detecting squamous cell carcinoma and less effective at detecting adenocarcinoma.[31] Therefore, co-testing is preferred because adding HPV DNA testing increases detection of adenocarcinoma and adenocarcinoma in situ.[29] However, cervical cytology testing alone every 3 years is also an option, because this method has been proven to decrease cervical cancer, most cervical cancer is squamous cell carcinoma, and clinicians feel that lack of access to HPV testing should not deter screening. The screening intervals should not be increased in women 21-65 years with negative tests. Use of HPV DNA testing alone for screening is not currently recommended (see "HPV DNA Testing" in this Discussion). 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 who have had a hysterectomy with removal of the cervix should have routine screening with vaginal cytology if they have history of CIN 2 or a more serious diagnosis (see CERVS-2). However, those who have had a hysterectomy with removal of the cervix, but do not have these risk factors, do not need cervical cancer screening.[1]

Combined cervical cytology and high-risk HPV DNA testing appear to increase the detection rate of CIN 3, which is a precursor of cervical cancer.[32-34] A positive co-test is either 1) HPV positive; or 2) HPV negative and LSIL or more severe cytology. A negative co-test is HPV negative and either ASC-US or negative cytology. Although some studies suggest that HPV DNA testing may be used alone (i.e., without cervical cytology) for screening women who are 30 years and older, currently this strategy is not recommended in the United States (see "HPV DNA Testing" in this Discussion).[1, 32, 35] The appropriate screening interval for women with negative cytology who test positive for high-risk HPV DNA is shown on CERVS-4 and is described later (see "Squamous Epithelial Cell Abnormalities in Adult Women Age 21 Years or Older").

Continue or Discontinue Screening (see CERVS-1 and CERVS-2)

Cervical cytology screening should be initiated and should continue in women who have been vaccinated against HPV 16 and HPV 18 (see CERVS-1).[1] Women previously treated for CIN 2, CIN 3, or AIS should *continue* to have routine screening for at least 20 years after treatment and after initial postoperative surveillance, because they remain at risk for persistent or recurrent disease.[7] Cervical cytology screening should

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continue for women with other high-risk factors (i.e., in utero DES 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 via 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 older than 65 years with adequate negative previous results (i.e., 3 consecutive negative cytology test results or 2 consecutive negative co-test results within the previous 10 years) and with no history of abnormal cervical cytology tests, because cervical cancer develops slowly and risk factors decrease with age.[7, 19] Women with comorbid or life-threatening illness may *discontinue* screening.

HPV DNA Testing

HPV DNA testing should not be used alone for screening (e.g., it is used with cervical cytology [co-testing]). At the current time, HPV DNA testing should not replace other cervical cancer screening methods (see end of this section).The FDA has approved several high-risk HPV DNA tests, including the newer “second-generation” test (e.g., cobas 4800 HPV test) and the older “first-generation” tests (e.g., the HPV high-risk and HPV 16/18 DNA tests, Hybrid Capture 2 HPV DNA test). The new cobas HPV DNA test yields 3 separate results (HPV 16, HPV 18, and a pooled result of 12 other high-risk HPV subtypes [31,33,35,39,45,51,52,56,58,59,66,68]).[36, 37]

The first-generation HPV 16/18 and the HPV high-risk DNA tests are 2 different diagnostic tests (see ASCCP website). The HPV high-risk DNA test detects whether any of the 14 high-risk (oncogenic) types of HPV are present, although it does not specify which types are present. The HPV 16/18 DNA test detects whether HPV 16 or HPV 18 is present, which is termed *HPV genotyping*. The ASCCP website provides information about HPV DNA testing.

Another first-generation 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 there are false-positive results due to slight cross reactivity with nononcogenic HPV subtypes.[38, 39] Note that the HC2 has no internal standard to determine sample adequacy.[40] 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.

At the current time, these high-risk HPV DNA tests should not be used as stand-alone screening tests and thus should not replace other effective cervical cancer screening methods (i.e., regular cervical cytology tests and gynecologic examinations) (www.sgo.org/News/Media_Archive/Media_Archive/).[1, 3] Long-term follow-up data are not available for these HPV DNA tests.[1] HPV is often a transient infection and typically does not cause CIN 3 or cervical cancer; persistent infection with high-risk HPV is required to cause cervical cancer.[8, 13, 14, 41] In addition, women with invasive carcinoma may have false-negative HPV test results.[42, 43] Therefore, HPV DNA testing alone is not currently recommended as a screening method (especially in women younger than 30 years).[1, 44] The FDA has only approved the high-risk HPV DNA tests as an adjunct to the cervical cytology tests not as stand-alone tests.

HPV Vaccines

Vaccination with the quadrivalent HPV vaccine provides protection against infection by certain types of high-risk HPV, which cause cervical, vulvar, and vaginal cancer (types 16, 18) and genital warts

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(types 6, 11).[45-49] After 3 years, the efficacy of the quadrivalent HPV vaccine was 99% for preventing CIN grades 2 and 3 (CIN 2/3) 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.[46] Many agree that CIN 3 (which is essentially squamous cell carcinoma in situ [i.e., stage 0]) is the best marker for risk of progression to invasive carcinoma.[50] Data suggest that 40% of CIN 2 lesions will regress after 2 years; however, CIN 2 from HPV 16 appears less likely to regress.[51] In addition, a meta-analysis reported that 22% of CIN 2 lesions progress to carcinoma in situ.[52]

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 and up to 9.5 years.[53-55] Recent data suggest that the quadrivalent HPV vaccine decreases abnormal Pap results, colposcopies, and cervical biopsies.[56] In addition, in young women treated for HPV-related disease, previous vaccination with quadrivalent HPV vaccine was associated with a decrease in the incidence of subsequent HPV-related disease.[57]

The US Food and Drug Administration (FDA) approved the HPV quadrivalent vaccine for use in girls and women ages 9 to 26 years (www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM094042). 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), American College of Obstetricians and Gynecologists (ACOG), ACS, and Society of Gynecologic Oncology (SGO) 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 (www.sgo.org/WorkArea/showcontent.aspx?id=950).[10, 58, 59] The quadrivalent HPV vaccine has also been approved for other indications (e.g., to prevent genital warts in boys and men ages 9 to 26 years) (www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM094042).

Another prophylactic HPV vaccine is the bivalent vaccine, which was approved in the United States to prevent cervical cancer and precancerous lesions due to high-risk HPV 16 and 18 in girls and women ages 10 to 25 years (www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm187048.htm). The bivalent vaccine is effective for at least 8 years and is approved in more than 90 other countries.[48, 60-64]

Data from the Vaccine Adverse Event Reporting System (VAERS) indicate that the quadrivalent HPV vaccine is safe, although syncope and venous thrombotic events have been reported.[65] Reports also indicate that the bivalent vaccine is safe.[66, 67] Both the bivalent and the quadrivalent vaccines are preventive not therapeutic. Currently, the HPV vaccination rate is about 32% in adolescents in the United States.[68]

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 oncogenic HPV (see ASCCP website).[47] Both HPV vaccines also offer some cross-protection against non-HPV vaccine types that also cause cervical cancer (e.g., HPV-31, HPV-45).[69-71] However, it is important to note that 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 (www.sgo.org/News/Media_Archive/Media_Archive/).

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Initial Findings (see CERVS-3)

The NCCN panel recommends that cervical cytology tests should be reported using the Bethesda System 2001 (see CERVS-A and the ASCCP website).[72] The different possible results of an initial screening examination are summarized on CERVS-3.

All women with cervical cytology tests reported as normal (i.e., negative for intraepithelial lesion or malignancy), unsatisfactory, or positive for abnormalities (e.g., high-grade squamous intraepithelial lesions [HSIL]) or invasive carcinoma are managed as shown on CERVS-3. 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 carcinoma is grossly present. If the cervical cytology is positive for invasive carcinoma, a biopsy of a visible lesion is recommended or a diagnostic excision is recommended if there is no visible lesion (see NCCN Cervical Cancer Guidelines or CERVS-10). 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 CERVS-1).

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 (i.e., co-testing) is discussed in the following sections. The ASCCP has published a consensus guideline: "2006 Consensus Guidelines for the Management of Women With Abnormal Cervical Cancer Screening Tests".[15, 73]

Women With Negative Cytology Results and Positive High-Risk HPV DNA Results (CERVS-4)

Women 30 years and older with positive high-risk HPV DNA results but negative cytology results have several options: 1) HPV genotyping (category 1) (i.e., specific HPV 16/18 DNA test); or 2) repeating both tests (i.e., cytology and high-risk HPV DNA) at 12 months (see CERVS-4). The category 1 recommendation for genotyping is based on data from a recent phase III randomized trial (i.e., ATHENA).[74] The ATHENA (Addressing THE Need for Advanced) HPV Diagnostics trial found that women positive for high-risk HPV 16 or 18 have a high risk for cervical cancer even if their cytology results are negative.[36, 74] Thus, immediate colposcopy is recommended for these women.[74] Women with persistent HPV 16/18 infection have a greater risk for cervical cancer than those with infection from other high-risk HPV genotypes.

Several studies suggest that it is appropriate and safe to wait 1 year before rescreening.[1, 29, 32, 74, 75] In women who are HPV positive, the 1-year risk of CIN 3+ ranges from 0.8% to 4%.[1] About 60% of women who are high-risk HPV positive will become HPV negative during follow-up.[76] Data suggest that the incidence of CIN 3+ is 17% in women who are HPV 16+, 14% in HPV 18+ women, and only 3% with other high-risk HPV types.[77] 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.

Squamous Epithelial Cell Abnormalities in Adult Women Age 21 Years or Older (CERVS-5)

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

The NCCN guideline offers 3 options for the management of ASC-US in adults. Unlike adolescents, HPV DNA testing for high-risk virus is informative in adult women due to the lower underlying prevalence.[78] Because ASC-US is an equivocal description, HPV testing is useful to determine the risk in patients with ASC-US. The inclusion of HPV testing as an option is based on the results of the ASC-US–LSIL Triage

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Study (ALTS) trial, which demonstrated that HPV triage (i.e., "reflex" HPV testing for atypical Pap smears from liquid-based cytology) is at least as sensitive as immediate colposcopy for detecting CIN 3 and refers about half as many women to colposcopy.[79]

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 (see the ASCCP website). Only about 50% of CIN 2+ infections are associated with HPV 16 or 18.[80] Thus, the risk of CIN 2+ is about 20% in women with ASC-US who are positive for other high-risk oncogenic HPV types (e.g., HPV 31, 45). Therefore, the NCCN and ASCCP recommend that women with ASC-US who are positive for HPV high-risk DNA should be referred for colposcopy.

A second option is immediate colposcopy.[15] A third option is to repeat the cervical cytology in 6 months. If 2 consecutive cytology tests 6 months apart are negative, screening may be resumed (see CERVS-1). 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

I In adults, the ALTS trial demonstrated that LSIL cytology is best managed by colposcopy initially, because no useful triage strategy was identified.[79] Therefore, colposcopy is recommended in adults older than 21 years for LSIL, ASC-H, and HSIL. As previously mentioned, high-risk HPV DNA testing is not recommended in women with ASC-H, LSIL, or HSIL cytology because the results would not change management. Note that cytologic LSIL is not the same as histologic CIN 1; cytologic HSIL is not the same as histologic CIN 2,3.[15]

Colposcopy for LSIL, ASC-US, or Positive HPV 16 or 16/18

Satisfactory Colposcopy (see CERVS-6)

When evaluating the colposcopy result, it is important to determine whether the colposcopy visualized the entire transition zone of the cervix and was considered satisfactory.[15] Unsatisfactory colposcopies are addressed in the next section. The ASCCP has published a consensus guideline: "2006 Consensus Guidelines for the Management of Women With Cervical Intraepithelial Neoplasia or Adenocarcinoma in Situ".[15, 73]

Colposcopy is recommended for women with ASC-US, LSIL, or a positive HPV16/18 test. After a satisfactory colposcopic examination, women with negative findings or CIN 1 on cervical biopsy (or those who did not have a biopsy) may be followed with repeat cytology testing at 6 months or with high-risk HPV DNA testing 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, because most of these lesions will regress to normal.[28] If ASC-US or greater is found on one of these examinations, follow-up evaluation is recommended (see CERV-5). For patients followed by high-risk HPV DNA testing at 12 months, a positive result requires a colposcopy, whereas negative findings permit returning to a normal screening schedule (see CERVS-1). The ALTS trial suggested that after an initial diagnosis of CIN 1 or less by colposcopy, the most efficient test for identifying women with CIN 2 or 3 might be a high-risk HPV DNA test alone at 12 months.[81] However, HPV genotyping is not recommended in these patients, because there are other oncogenic HPV types besides HPV 16 or 18 (e.g., HPV 31, HPV 45).

If the cervical biopsy reveals CIN 2 or 3, further therapy is indicated consisting of LEEP, cryotherapy, CKC, or laser ablation. However, CIN

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2 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 an option for CIN 3, if indicated for pre-existing pathologic conditions or for enhancement of quality of life. The panel preferred the use of CKC in patients in whom AIS or microinvasive cervical cancer was suspected.[82] LEEP has been associated with a cautery artifact that may compromise the pathologic evaluation of the tissue specimen. However, LEEP is acceptable if clinicians are aware of this risk and strive for adequate margins. The diagnosis of invasive carcinoma at cervical biopsy requires treatment according to the NCCN Cervical Cancer Guidelines. Endometrial sampling (if not previously done) is recommended in patients with glandular neoplasia, microinvasion, or AIS.

Unsatisfactory Colposcopy (see CERVS-7)

An ECC should be performed in addition to the directed cervical biopsy if the colposcopy is unsatisfactory for ASC-US, LSIL, or positive HPV 16 or 16/18. If the cervical biopsy is negative (or no biopsy is done) and the ECC findings are negative or CIN 1, repeat cytologic examinations at 6 months or high-risk HPV DNA testing at 12 months can be performed. The same strategy as previously outlined for a satisfactory colposcopy should be followed.

After performing an ECC, a diagnosis of CIN 2 or 3 requires LEEP or CKC for definitive diagnosis.[83] After cervical biopsy, a result of CIN 2 requires a LEEP or CKC to establish a definitive diagnosis in a patient with an unsatisfactory colposcopy.[83] If CIN 3 is identified, options include LEEP or CKC with (or without) a total hysterectomy. In patients with CIN 3, an initial LEEP or CKC is recommended to confirm the diagnosis before the total hysterectomy. Diagnostic excision (CKC is preferred) is recommended for AIS or microinvasive biopsy findings; CKC or LEEP can serve as definitive treatment if the lesion is confirmed to be intraepithelial.[82] A diagnosis of invasive carcinoma requires treatment according to the NCCN Cervical Cancer Guidelines.

Colposcopy for ASC-H or HSIL, or Positive HPV 16 or 16/18 (see CERVS-8)

All women with ASC-H, or HSIL, or positive HPV 16 or 16/18 require colposcopic evaluation. Again, management depends on whether the colposcopy is considered satisfactory or unsatisfactory (see either CERVS-8 or CERVS-9). 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 cervical cytology should be repeated in every 6 months until 2 consecutive results in a row are negative. Regular screening is recommended after 2 consecutive negative results (see CERVS-1). If CIN 1 is identified in ECC, follow-up with cervical cytology may be considered in women with a preceding ASC-H.

Two options are available if a lesion is identified in patients who have had a satisfactory colposcopy. A patient may opt for a LEEP procedure as the first option, particularly if maintaining fertility is not an issue; this patient should then have follow-up for CIN as described in the following section (see CERVS-10). Biopsy is the second option. A negative cervical biopsy or CIN 1 lesion can be managed with either 1) a repeat cervical cytology 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 2 or 3 requires treatment with LEEP, cryotherapy, CKC, or laser ablation. However, CIN 2 may be followed without treatment in certain clinical circumstances (e.g., young woman who

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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 3 and if other indications for hysterectomy are present (e.g., symptomatic fibroids, persistent abnormal bleeding). Again, CKC is preferred for AIS or microinvasive biopsy findings. Any confirmed invasive carcinomas need treatment according to the NCCN Cervical Cancer Guidelines.

A LEEP or CKC is recommended for those with HSIL who have unsatisfactory colposcopies, with management as outlined (see CERVS-10). For patients with ASC-H who have a negative ECC with no lesion seen, the panel recommends that cytology be repeated every 6 months until 2 consecutive results in a row are negative. Regular screening is recommended after 2 consecutive negative results (see CERVS-1). Vaginal and vulvar colposcopy may also be done to evaluate these sites for potential neoplasia which can present as abnormalities in cervical cancer screening tests.[84]

Follow-up After Treatment of Cervical Intraepithelial Neoplasia (see 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 high-risk HPV DNA testing at 12 months.[85] 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 2 or 3 lesions with negative margins and for all CIN 1 lesions.

For CIN 2 and CIN 3 lesions with positive margins, options include 1) cervical cytology at 6 months; an ECC can be considered (category 2B); 2) re-excision, 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 CERVS-1). If HPV DNA testing is positive, then colposcopy is recommended. If the repeat cervical cytology identifies ASC-US or greater, patients should be managed as previously described (see CERVS-5).

Adenocarcinoma In Situ (see CERVS-11)

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).[31, 86-88] Thus, cervical cytology testing alone has not been effective in decreasing the incidence of adenocarcinoma.[89-91] Adenocarcinomas are often diagnosed in patients with negative cytology results but positive HPV results.[29] Thus, HPV co-testing is useful in diagnosing adenocarcinoma.

Colposcopy and ECC are recommended for patients with AIS along with endometrial biopsy if indicated (i.e., for those 35 years or older or with endometrial risk factors) (see CERVS-11). CKC is recommended for almost all findings (e.g., negative, CIN 1-3, AIS, or microinvasion). Patients with invasive carcinoma should be managed using the NCCN Cervical Cancer guidelines.

Atypical Glandular Cells (see CERVS-12)

The finding of atypical glandular cells (AGC) on cervical cytology is associated with a clinically significant lesion in 45% of patients,[92] including CIN; AIS; microinvasion; invasive cervical carcinoma; or endometrial, ovarian, and fallopian tube cancer.[15, 43] However, CIN is the most common finding and 3% to 17% of women have invasive carcinoma.[15] Liquid-based cytology appears to improve detection of AGC (www.sgo.org/WorkArea/showcontent.aspx?id=952). Thus, all patients with a finding of AGC on cervical cytology and who are

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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 for endometrial cancer include obesity, unopposed estrogen replacement therapy, polycystic ovarian syndrome, tamoxifen therapy, anovulation, or Lynch syndrome/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 results of the cervical biopsy, ECC, and HPV DNA testing. Additional management may be dictated by the results of the endometrial biopsy (see CERVS-16). 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.[93]

If cervical biopsy and ECC identify CIN (1, 2, or 3), AIS, or microinvasion, further evaluation by CKC is indicated (see CERVS-14). However, a patient with an adequate colposcopic examination, a cervical biopsy revealing CIN 1, 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 2 or 3 but with a negative ECC result, LEEP or CKC is recommended (see CERVS-14).

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.[94] 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.

Management of Adenocarcinoma In Situ (see CERVS-15)

The NCCN panel recommends that all patients with AIS should be strongly considered for referral to a gynecologic oncologist or similar specialist. The choice of treatment depends on the patient’s desire for fertility. The definitive treatment for AIS is hysterectomy.[73] 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 in these patients when childbearing is completed. Women with positive findings on cervical cytology/ECC should then follow the management options on CERVS-12. Those with negative findings can continue screening every 6 months until hysterectomy is done.

However, clear margins of excision do not rule out persistent AIS, because approximately 30% of patients have residual disease on subsequent hysterectomy.[73, 95] If CKC margins are positive for AGC, a hysterectomy is recommended if the patient does not desire to remain fertile. Consider repeating CKC (category 2B) to rule out invasive disease before the hysterectomy.

Re-excision 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.

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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 Cervical Cancer Guidelines or NCCN Uterine Neoplasms Guidelines.

Management of Endometrial Biopsy (see CERVS-16)

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 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 Uterine Neoplasms Guidelines.

Colposcopy During Pregnancy (see 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.[15] Colposcopy and cervical biopsy during pregnancy should be limited to women in whom high-grade neoplasia or invasive carcinoma is suspected; follow-up for LSIL and ASC-US can be deferred until 6 weeks postpartum. However, ASC-H, HSIL, AGC, or AIS should at least be evaluated colposcopically during pregnancy. Treatment for CIN (any grade) should be delayed until after the pregnancy.[96-99] Treatment for AIS, microinvasion, or invasive carcinoma should be decided in consultation with a specialist in gynecologic cancers and should not be routinely delayed until after pregnancy. 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 carcinoma is suspected.

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