ICSI
Institute for Clinical Systems Improvement

Health Care Guideline:

Initial Management of Abnormal Cervical Cytology (Pap Test) and HPV Test in Adult and Adolescent Females

Ninth Edition
September 2010

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- physicians, nurses, and other health care professional and provider organizations;
- health plans, health systems, health care organizations, hospitals and integrated health care delivery systems;
- health care teaching institutions;
- health care information technology departments;
- medical specialty and professional societies;
- researchers;
- federal, state and local government health care policy makers and specialists; and
- employee benefit managers.

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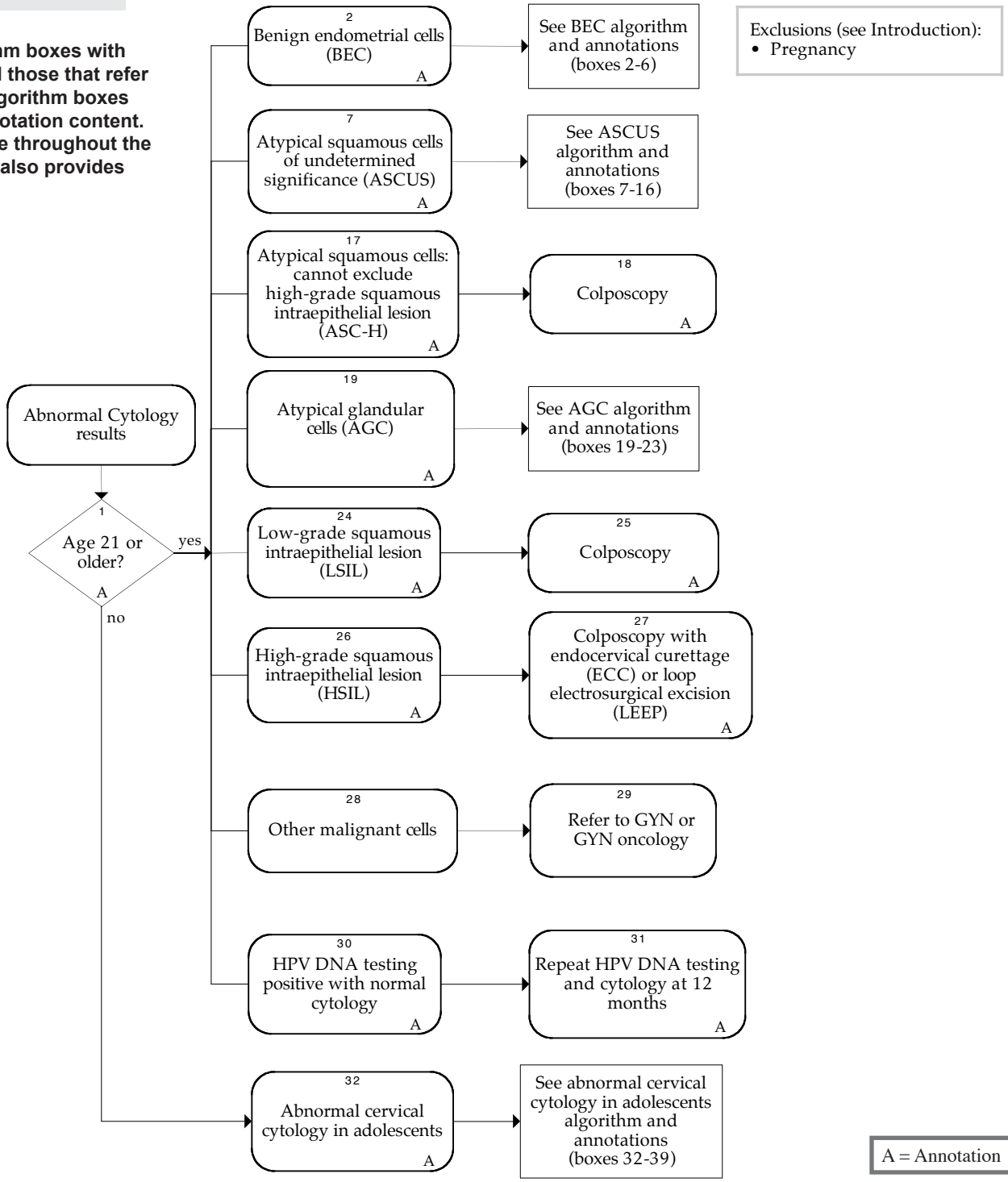
All algorithm boxes with an "A" and those that refer to other algorithm boxes link to annotation content. Text in blue throughout the document also provides links.

Initial Abnormal Cytology Result Algorithm



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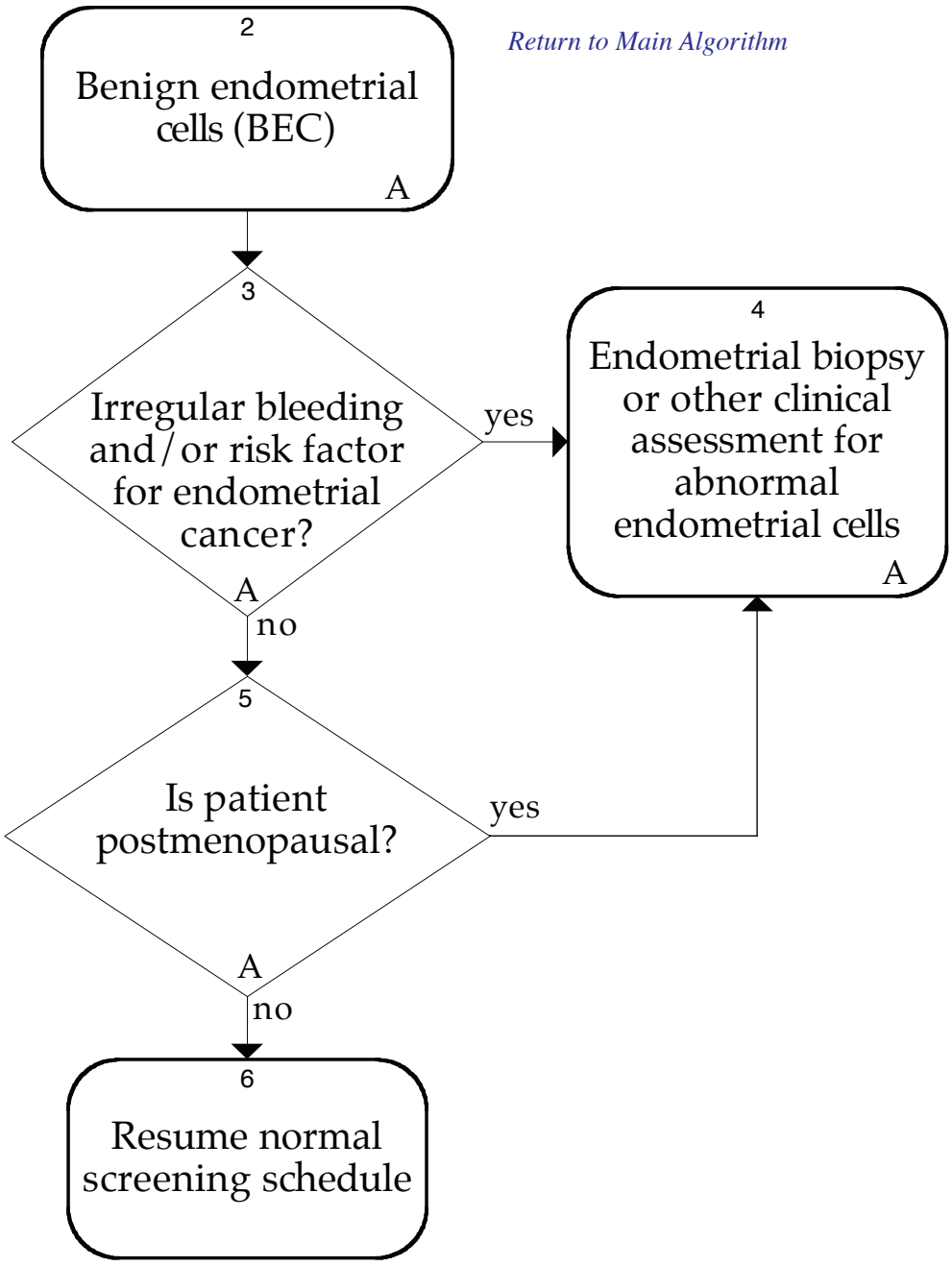
Benign Endometrial Cells (BEC) Algorithm

All algorithm boxes with an "A" and those that refer to other algorithm boxes link to annotation content. Text in blue throughout the document also provides links.



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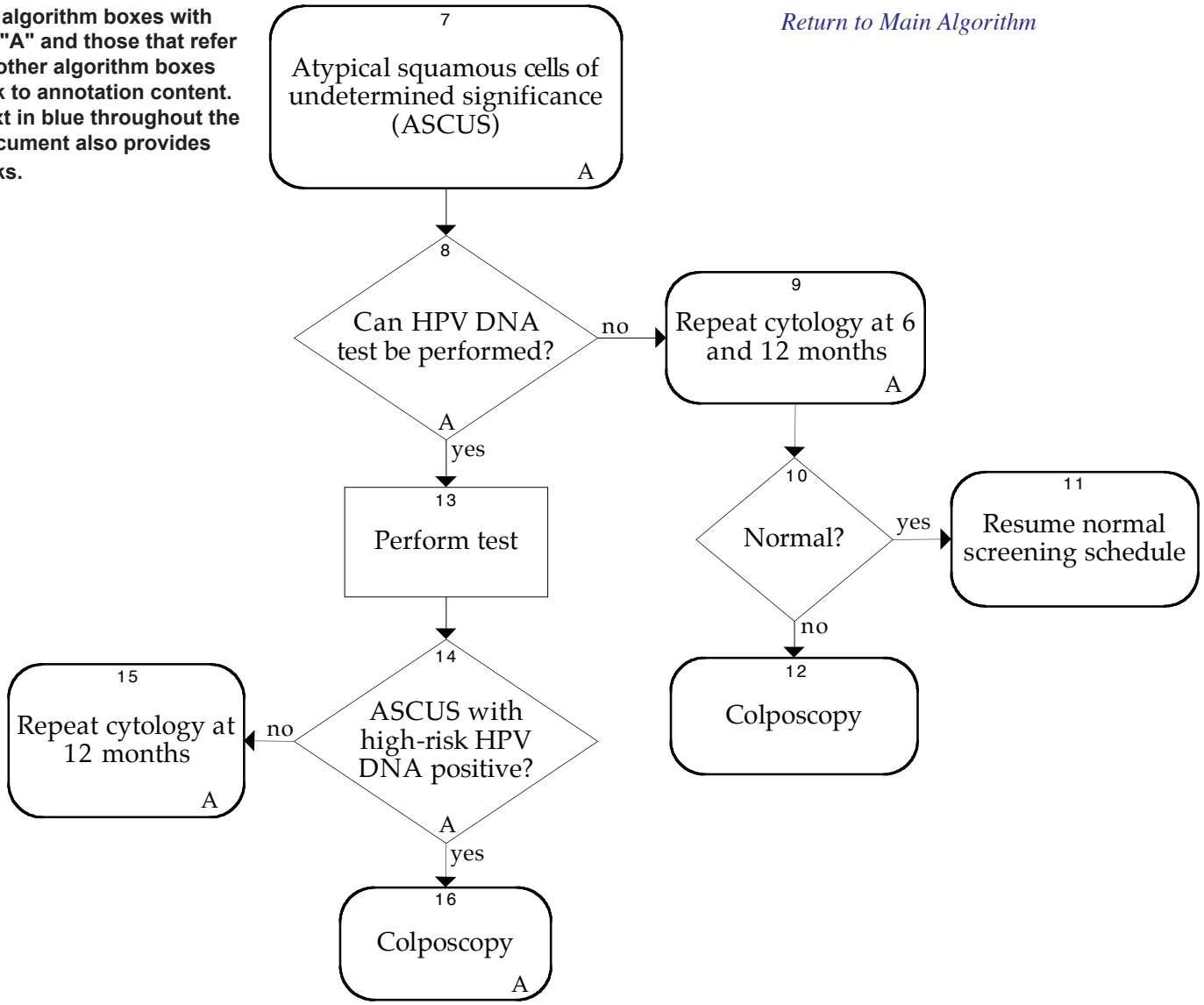
Atypical Squamous Cells of Undetermined Significance (ASCUS) Algorithm

All algorithm boxes with an "A" and those that refer to other algorithm boxes link to annotation content. Text in blue throughout the document also provides links.

Return to Main Algorithm



A = Annotation

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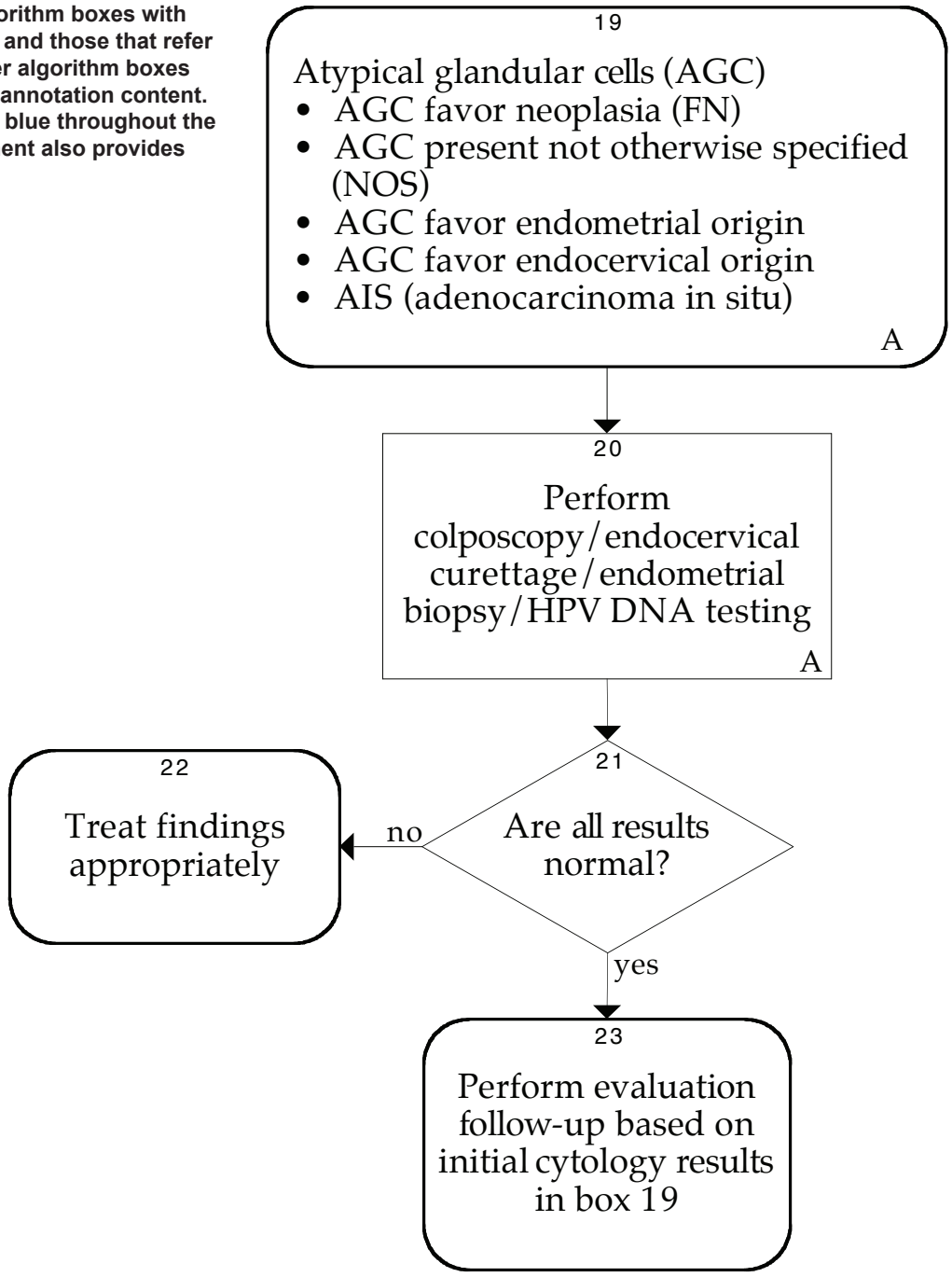
Atypical Glandular Cells (AGC) Algorithm

Return to Main Algorithm

All algorithm boxes with an "A" and those that refer to other algorithm boxes link to annotation content. Text in blue throughout the document also provides links.



A = Annotation

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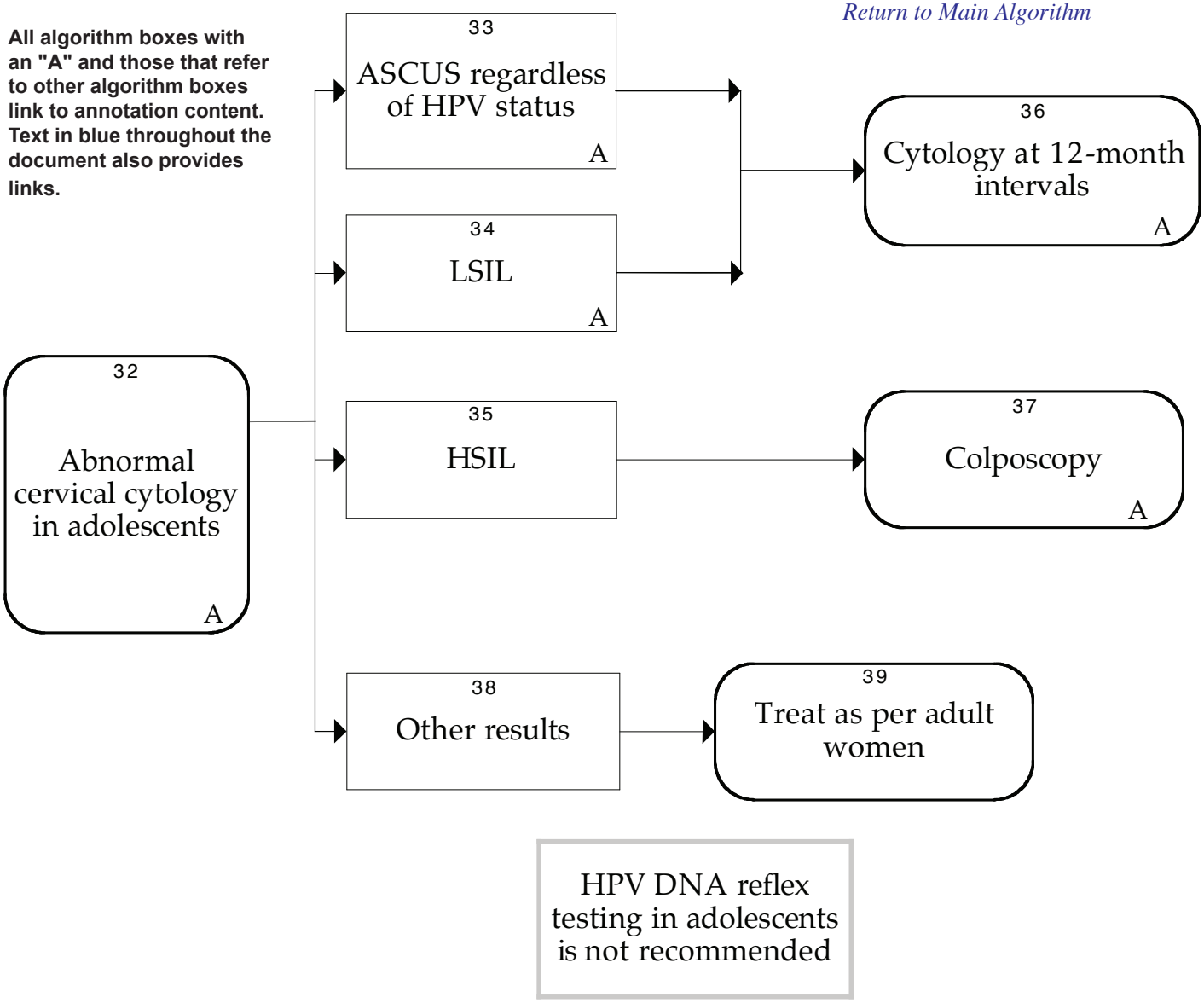
Abnormal Cervical Cytology in Adolescents (Less than 21 Years) Algorithm

Return to Main Algorithm

All algorithm boxes with an "A" and those that refer to other algorithm boxes link to annotation content. Text in blue throughout the document also provides links.



A = Annotation

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Disclosure of Potential Conflict of Interest

In the interest of full disclosure, ICSI has adopted a policy of revealing relationships work group members have with companies that sell products or services that are relevant to this guideline topic. It is not assumed that these financial interests will have an adverse impact on content. They are simply noted here to fully inform users of the guideline.

Brendon Cullinan is a consultant for the Minnesota Department of Human Services.

Melissa Geller received grant support from Aventis.

No other work group members have potential conflicts of interest to disclose.

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Evidence Grading

A consistent and defined process is used for literature search and review for the development and revision of ICSI guidelines. Literature search terms for the current revision of this document include: management of atypical glandular cells, HPV testing used as the only screening method, cervicography and age to start screening for cervical cancer from October 2009 through March 2010.

Individual research reports are assigned a letter indicating the class of report based on design type: A, B, C, D, M, R, X.

Evidence citations are listed in the document utilizing this format: *(Author, YYYY [report class]; Author, YYYY [report class] – in chronological order, most recent date first)*. A full explanation of ICSI's Evidence Grading System can be found on the ICSI Web site at http://www.icsi.org.

Class	Description
Primary Reports of New Data Collections	
A	Randomized, controlled trial
B	Cohort-study
C	Non-randomized trial with concurrent or historical controls Case-control study Study of sensitivity and specificity of a diagnostic test Population-based descriptive study
D	Cross-sectional study Case series Case report
Reports that Synthesize or Reflect upon Collections of Primary Reports	
M	Meta-analysis Sytematic review Decision analysis Cost-effectiveness analysis
R	Consensus statement Consensus report Narrative review
X	Medical opinion

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Foreword

Introduction

The guideline work group recognizes the difficulties faced by clinicians who must respond to abnormal cervical cancer screening test results. The group also recognizes this is an area of changing technology. Mindful of these concerns, the work group strives to present a framework based on objective evidence that will provide guidance to the clinician and patient in the management of abnormal cervical cancer screening test results. We will discuss three concepts that we hope will be helpful to clinicians in managing results.

Natural History of Cervical Intraepithelial Neoplasia (CIN)

The natural history of CIN is linked to the presence of high-risk human papillomavirus (HPV) types. Carriage of high-risk HPV DNA is extremely common; the lifetime cumulative risk is at least 80%. The vast majority of women clear the virus or suppress it to levels not associated with significant cervical dysplasia, and for most women this occurs promptly *(Ho, 1998 [B]; Hildesheim, 1994 [B])*.

Persistent high-risk HPV is a necessary but not sufficient condition for the development of almost all invasive cervical cancers *(Nobbenhuis, 1999 [B])*. The longer HPV is present in the adult patient, the greater the risk of CIN *(Castle, 2002 [C])*. Conversely, the risk of cervical cancer in women who do not harbor high-risk HPV is extremely low *(Wright, 2003 [R])*. The likelihood of progression to cancer is higher and the time to progression shorter as the grade of dysplasia increases *(Barron, 1968 [B])*. Yet the average time course from CIN-3 to invasive cancer averages between 8.1 and 12.6 years *(American College of Obstetricians and Gynecologists, 2005a [R])*. This means the detection of CIN-2 or CIN-3 is not a failure of the cervical cancer screening program, but rather a success. The detection of such neoplasia allows intervention to prevent early invasive cervical cancer and to reduce mortality.

The work group has found no evidence to support the use of HPV testing alone as a primary cervical cancer screening tool. HPV testing is a useful adjunct to cytological screening in cases of lower-level cytologic abnormalities; however, it is not useful in higher-grade cytological abnormalities.

A. The concept of CIN-2/3+

As noted, the goal of cervical cancer screening tests is to distinguish which intraepithelial neoplasia will progress to invasive cancer if left untreated. Cancer precursors include CIN-3, adenocarcinoma in situ (AIS), and to a lesser extent, CIN-2. Along with screening test results suggestive of frank malignancy, these diagnostic categories are known collectively as CIN-2/3+.

As stated in the practice bulletin from the American College of Obstetrics and Gynecology, "Effective cervical cancer prevention requires recognition and treatment of the precursors of invasive cancer…" *(American College of Obstetricians and Gynecologists, 2005a [R])*. The current system of nomenclature is the Bethesda System 2001. The authors of this Bethesda System devised various classifications for cervical cytological reports to more accurately convey the risk of CIN-2, CIN-3, AIS or cancer. It is important to remember that CIN is a histological, not cytological, diagnosis. Cytological results are meant to convey to the clinician the cytopathologist's concern that the patient in question may have a significant cervical lesion, placing her at significant risk for cervical malignancy. This significant risk is collectively referred to as CIN-2/3+. Cervical cancer screening results that suggest a high probability for CIN-2/3+ should alert the clinician that the patient in question needs immediate and thorough evaluation to rule out gynecologic malignancy.

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B. The concept of equivalent risk

The presence of high-risk HPV DNA in an atypical squamous cells (ASC) cytology result carries an equivalent risk of CIN2/3+ as an LSIL cytology result. Therefore, adult women with either low-grade squamous intraepithelial lesion (LSIL) or ASC/HPV+ should be evaluated with colposcopy and close monitoring.

C. Pregnancy

In pregnancy, the only diagnosis that may alter clinical management is invasive cancer. The presence of cancer may change treatment goals for the route and timing of delivery. Cervical cancer screening test results that are not likely to be associated with cancer may undergo colposcopic evaluation either during pregnancy or postpartum. The colposcopic examination during pregnancy should have as its primary goal the exclusion of invasive cancer. If colposcopy is performed for low-grade squamous intraepithelial lesion (LSIL) during pregnancy, additional colposcopy examinations are not indicated. The practice of repeating the colposcopy once per trimester in pregnant women with LSIL is unnecessary unless CIN 2/3+ is diagnosed *(American College of Obstetricians and Gynecologists, 2008 [R]); Boardman, 2005 [B]; Cristoforoni, 1999 [C])*. Pregnant women whose cervical cancer screening test results indicate a high risk for CIN 2/3+ should undergo colposcopy without endocervical sampling, reserving biopsy for visible cervical lesions consistent with CIN-3, AIS or cancer *(Wright, 2007 [R]; American College of Obstetricians and Gynecologists, 2005a [R]; Massad, 2005 [R])*.

Health Education

Receiving the diagnosis of abnormal cervical cytology is a traumatic occurrence for many women. The work group was made aware of this fact repeatedly and felt that education attempts need to be improved if patient anxiety is to be successfully reduced. It was felt that written general information provided at the time of the initial cervical cancer screening test could serve to educate patients about the role of cervical cytology, as well as to provide basic information about some of the potential results, and to emphasize the fact that most such findings may require nothing further than repeating the cytology or undergoing relatively simple evaluations such as colposcopy. It was felt to be imperative that physicians or health care personnel who provide the initial diagnosis of an abnormal result to a patient have sufficient training to allay most fears and answer basic questions. Finally, it was felt that mailing written material specific to the diagnosis and recommended procedures and follow-up would help prepare the patient for the next phase of evaluation. With a commitment to such education and continued sensitivity to the anxiety produced by the finding of abnormal cervical cytology result, physicians and other health care workers can provide effective and compassionate evaluation and treatment as needed *(Paskett, 1995 [A]; Stewart, 1993 [C]; Paskett, 1990 [A])*. See the Resources Table for further information.

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The Bethesda System 2001 (Abridged)

SPECIMEN ADEQUACY

Satisfactory for evaluation *(Note presence/absence of endocervical/transformation zone component)*
Unsatisfactory for evaluation *(Specify reason)*
Specimen rejected/not processed *(Specify reason)*
Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of *(Specify reason)*

GENERAL CATEGORIZATION *(Optional)*

Negative for intraepithelial lesion or malignancy
Epithelial cell abnormality
Other

INTERPRETATION/RESULT

Negative for intraepithelial lesion or malignancy
Organisms
Trichomonas vaginalis
Fungal organisms morphologically consistent with Candida species
Shift in flora suggestive of bacterial vaginosis
Bacteria morphologically consistent with Actinomyces species
Cellular changes consistent with herpes simplex virus
Other non-neoplastic findings (optional to report: list not comprehensive)
Reactive cellular changes associated with inflammation (includes typical repair)
Radiation
Intrauterine contraceptive device
Glandular cells status post hysterectomy
Atrophy

Epithelial Cell Abnormalities
Squamous cell
Atypical squamous cells (ASC)
- Of undetermined significance (ASCUS)
- Cannot exclude HSIL (ASC-H)

Low-grade squamous intraepithelial lesion (LSIL)
- Encompassing: human papillomavirus/mild dysplasia/cervical
- Intraepithelial neoplasia (CIN-1)

High-grade squamous intraepithelial lesion (HSIL)
- Encompassing: moderate and severe dysplasia, carcinoma in situ; CIN-2 and CIN-3
- Squamous cell carcinoma

Glandular cell
- Atypical glandular cells (AGC) *(Specify endocervical, endometrial or not otherwise specified)*

Atypical glandular cells, favor neoplastic *(Specify endocervical or not otherwise specified)*
Endocervical adenocarcinoma in situ (AIS)
Adenocarcinoma

Other *(List not comprehensive)*
Endometrial cells in a woman 40 years of age or older

AUTOMATED REVIEW AND ANCILLARY TESTING *(Include as appropriate)*

EDUCATIONAL NOTES AND SUGGESTIONS *(Optional)*

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Scope and Target Population

Any woman who has undergone cervical cytological analysis (Pap test) and has received an abnormal result.

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Aims

1. All women age 21 years and older with an ASCUS cervical cytological result will receive appropriate clinical follow-up. *(Annotations #7, 9, 14)*
2. All adult women age 21 years and older with a high-grade squamous intraepithelial lesion (HSIL) cervical cytological result will have a colposcopy with endocervical curettage (ECC) or LEEP. *(Annotations #26, 27)*
3. All women age 21 years or older with a low-grade squamous intraepithelial lesion (LSIL) cervical cytological result will have a colposcopy. *(Annotation #24, 25)*

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Clinical Highlights

- ASCUS as an initial cytology result in women age 21 and older necessitates HPV testing. If HPV testing is unavailable, a repeat Pap test in six months or immediate colposcopy is recommended. *(ASCUS Algorithm; Annotations #7, 9; Aim #1)*
- AGC as an initial cytology result requires a colposcopy and endocervical curettage (ECC) and possible endometrial biopsy. AGC cytology results can, in some cases, be indicative of extracervical malignancy. Follow-up is mandatory. *(AGC Algorithm Annotations #19, 20; Aim #1)*
- LSIL as an initial cytology result in an adult generally warrants a colposcopy. Special considerations may be made for adolescents who have had a Pap test performed. *(LSIL Annotations #24, 25 and Abnormal Cervical Cytology in Adolescents Annotations; Aim #3)*
- HSIL as an initial cytology result requires colposcopy in adolescents, or colposcopy with endocervical curettage (ECC) or loop electrosurgical excision (LEEP) in adults. *(Annotations #26, 27; Aim #2)*
- Although cervical cancer screening in adolescents is not recommended, if a test is performed and shows ASCUS or LSIL cytological screening results, the HPV regression rate is so high that conservative management without colposcopy is recommended. *(Abnormal Cervical Cytology in Adolescent Algorithm, Annotations #30-34)*

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Implementation Recommendation Highlights

The following system changes were identified by the guideline work group as key strategies for health care systems to incorporate in support of the implementation of this guideline.

1. Disseminate recommendations for appropriate follow-up for each of the Bethesda classifications for abnormal cervical cytology results.
2. Implement a program or process to ensure complete follow-up of all abnormal results obtained by cervical cytology.

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Related ICSI Scientific Documents

Guidelines

- Immunizations
- Preventive Services for Adults

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Algorithm Annotations

Initial Abnormal Cytology Result Algorithm Annotation

1. Age 21 or Older?

Abnormal cervical cytology results for patient's less than 21 years of age constitute a special circumstance as in the Introduction. A separate algorithm is provided.

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Benign Endometrial Cells Algorithm Annotations

2-5. Benign Endometrial Cells (BEC)

Key Points:

- The Bethesda System 2001 reports the presence of normal, cytological benign-appearing exfoliated endometrial glandular cells only in women ages 40 or greater.
- Benign-appearing endometrial cells are noted in up to 12% of cervical cancer screenings, and are more common in premenopausal than in postmenopausal women.

The presence of benign endometrial glandular cells on cervical screening tests may reflect physiologic shedding or shedding in response to a pathological process. In women over age 40, the presence of benign-appearing endometrial cells on cervical cytology has been found to be less than 2% *(Beal, 2007 [B]; Bean, 2006 [B])*. Benign-appearing endometrial cells are more likely to be identified on cervical cytology in the first 10-12 days of the menstrual cycle (prevalence 21%-24%) than in the remainder of the cycle (prevalence 2%) *(Vooijs, 1987 [C]; Liu, 1963 [B])*. The presence of benign endometrial cells on cervical cytology is reported so that a clinician can determine the significance of the finding in an individual woman.

If a woman has symptoms of endometrial cancer (abnormal uterine bleeding/spotting) or she is at increased risk of endometrial cancer (i.e., postmenopausal; family or personal history of ovarian, breast, colon or endometrial cancer; tamoxifen use; chronic anovulation; obesity *(Pellerin, 2005 [D])*; or prior endometrial hyperplasia), a sampling of the endometrium with endometrial biopsy or D & C is suggested to rule out endometrial cancer. If the above symptoms or risk factors are not present, routine gynecological care should be continued, as women have not been proven to be at increased risk of endometrial cancer based on the presence of benign endometrial cells on cytology alone *(Simsir, 2005 [B]; Thrall, 2005 [C]; Ashfaq, 2001 [D]; Chang, 2001 [B])*.

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Atypical Squamous Cells of Undetermined Significance (ASCUS) Algorithm Annotations

7. Atypical Squamous Cells of Undetermined Significance (ASCUS)

Key Points:

- Atypical squamous cells of undetermined significance (ASCUS) is used by pathologists to denote cellular changes that are more marked than those attributable to reactive changes, but that are quantitatively or qualitatively short of a definitive diagnosis of squamous intraepithelial lesion (SIL).
- A conservative approach can be taken; however, the presence of high-risk factors may influence the decision for a more aggressive approach.

The Bethesda System 2001 has identified criteria for ASCUS on cervical cytology screening. Atypical squamous cells of undetermined significance (ASCUS) is used by pathologists to denote cellular changes that are more marked than those attributable to reactive changes, but that are quantitatively or qualitatively short of a definitive diagnosis of squamous intraepithelial lesion (SIL) *(Solomon, 2002 [R]; Davey, 1994 [D]; Pearlstone, 1992 [C])*.

A conservative approach can be taken with ASCUS on Pap tests because:

- The diagnosis is poorly reproducible between observers *(American College of Obstetricians and Gynecologists, 2005a [R]);*
- Spontaneous regression is common *(Jones, 1992 [C]; Kirby, 1992 [C]);*
- The likelihood of a non-diagnostic or normal colposcopy is high *(Nuovo, 1993 [D])*;
- Even in patients who progress to higher-grade lesions, the rate of progression is relatively slow *(Holowaty, 1999 [B]; Montz, 1992 [D]);*
- Other research demonstrates that while the majority of ASCUS cytology test results reflect a benign reactive process, 5% to 10% of the women with ASCUS results harbor underlying high-grade squamous intraepithelial lesions (HSILs) *(Manos, 1999 [C]; Melnikow, 1998 [M])*; and
- A patient with three consecutive normal tests (after ASCUS initially) has a low likelihood of having a persistent abnormality or a false-negative test *(Miller, 1991 [R])*.

Despite the evidence that supports a conservative approach, some clinicians favor immediate colposcopy for all ASCUS tests. In counseling the patients with high-risk results, the presence of these high-risk factors may influence the decision toward a more aggressive approach: teenage sexual activity, multiple sexual partners, intercourse with a male who has HPV, history of sexually transmitted disease or genital warts, tobacco use or history of tobacco use, intrauterine exposure to DES, poor compliance for follow-up, lack of normal immune response, no history of regular Pap tests.

Advantages of immediate colposcopy for all ASCUS Pap test results include:

- Reduced risk of missing a significant lesion;
- Reduced risk of being lost to follow-up;
- Faster reassurance to patient of normalcy or avoidance of multiple follow-up Pap smears, resulting poor compliance, and potentially overburdened clinics; and
- Avoidance of delay in diagnosis of cancer or high-grade CIN.

Options for evaluation include triage to colposcopy by HPV DNA testing, immediate colposcopy, or repeat cytology tests at 6 and 12 months *(Wright, 2007 [R])*.

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8. Can HPV DNA Test Be Performed?

In 2003, the Food and Drug Administration approved HPV DNA testing in conjunction with cervical cytology screening for women aged 30 years and older *(Wright, 2007 [R])*. Due to the high prevalence and spontaneous clearance of HPV DNA in adolescents and women in their 20s, HPV DNA should not be used for routine screening before age 30 *(Saslow, 2002 [R])*.

The work group is advocating the use of HPV testing to help triage patients with ASCUS. It can be cost effective when done in a setting that includes liquid-based cytology collection methods, since the residual fluid can be saved for HPV analysis rather than calling the patient back for sampling. Since HPV testing is another viable option for evaluation of the ASCUS cytology result, colposcopy could be deferred and performed only for those women who have tested positive for high-risk HPV types *(Atypical Squamous Cells of Undertermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study [ALTS] Group, The, 2000 [D])*.

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9. Repeat Cytology at 6 and 12 Months

Key Points:

- Two consecutive negative cytology results at 6 and 12 months approach the sensitivity of a single HPV test for the detection of CIN-2/3 or greater.
- Immediate colposcopy may be an option for some women who have an initial cytology result of ASCUS.

One option for the low-risk reliable patient with an ASCUS result would be to have a follow-up cytology test at 6 and 12 months. Two consecutive negative follow-up tests will approach the sensitivity of a single HPV test for the detection of CIN-2/3+. Routine testing intervals can be resumed after normal results at 12 months. If either the 6- or 12-month test is ASCUS or higher, colposcopy is recommended *(Wright, 2007 [R]; American College of Obstetricians and Gynecologists, 2005a [R]; Solomon, 2002 [R])*.

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14. ASCUS with High-Risk HPV DNA Positive?

Key Points:

- Human papillomavirus (and more specifically, certain DNA subtypes like #16 and #18) causes cervical dysplasia and development of squamous cervical cancer in almost all cases.
- Reflex HPV DNA testing for ASCUS Pap results is recommended.

Clinicians ordering HPV tests should be aware of the strengths and limitations of the assay. The report that clinicians will receive from the high-risk assay will often state that the patient tested positive or negative for "one or more of the following high-risk types," followed by a list of the HPV types. The careful wording is intended to convey to clinicians that the assay does not test for all HPV types known to associate

with cervical cancer. A positive test for high-risk HPV types should indicate a need to educate the patient about HPV infection. A colposcopic examination should be scheduled. A negative HPV test result tells the clinician that the patient does not have a detectable burden of the high-risk virus types included in the test.

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15. Repeat Cytology at 12 Months

Women who test negative for high-risk HPV can be reassured that their risk of having CIN-2/3+ is less than 2%. They can be scheduled for repeat cytology in 12 months.

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16. Colposcopy

Women who test positive for high-risk HPV have a 15%-27% chance of having CIN 2/3 or worse. They should be scheduled for colposcopy. The exception to this recommendation is the adolescent, for whom the risk of invasive cancer approaches zero and the likelihood of HPV clearance is very high *(Sherman, 2002 [C])*.

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17. Atypical Squamous Cells: Cannot Exclude High-Grade Squamous Intraepithelial Lesion (ASC-H)

The Bethesda System 2001 recognizes a category of atypical squamous cells – high-grade dysplasia (ASC-H) cannot be ruled out. In the 1988 system, emphasis was placed on identifying all SIL results, including LSIL and high-grade squamous intraepithelial lesion (HSIL). Currently, the emphasis of the Bethesda System 2001 is to identify HSIL and cytology associated with histologically proven high-grade disease.

ASC-H is thought to include 5%-10% of all ASC cases and includes mixtures of true HSIL and mimics. The positive predictive value of ASC-H in detecting CIN-2 and CIN-3 lies somewhere between 48% and 56% *(Solomon, 2002 [R]; Schoolland, 1998 [D])*.

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18. Colposcopy

Colposcopic examination is the established appropriate evaluation of women with ASC-H Pap test reports, regardless of the patient's HPV status. ECC should be performed if no lesion can be visualized. Initial evaluation of the ASC-H Pap test should not routinely include the use of LEEP.

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Atypical Glandular Cells (AGC) Algorithm Annotations

19. Atypical Glandular Cells (AGC)

AGC is a rare finding; it is present in less than 0.5% of cervical-cancer screening specimens. The causes of AGC include cervical and uterine adenocarcinoma, inflammation, hyperplasia, dysplasia, and (rarely) metastatic cancer. Therefore aggressive further evaluation is important *(Sharpless, 2005a [C])*.

Atypical glandular cells (which can be either uterine or cervical in origin) have enlarged nuclei, decreased cytoplasmic volume and a variety of other unusual characteristics. Cells are classified as AGC (atypical

glandular cells) with one of the following subheadings: NOS (not otherwise specified), FN (favor neoplasia) and favor either endocervical or endometrial origin *(Lia, 2007 [C])*.

Some studies reported that 9% to 38% of women with AGC have significant neoplasia (CIN-2, -3, AIS or cancer) and 3% to 17% have invasive cancer *(DeSimone, 2006 [D]; Sharpless, 2005a [C]; Derchain, 2004 [D]; Tam, 2003 [D])*.

Those patients having a previous diagnosis of CIN had an almost threefold increase in findings of significant lesions *(Cheng, 1999 [D]; Raab, 1999 [D])*.

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20. Perform Colposcopy/Endocervical Curettage/Endometrial Biopsy/ HPV DNA Testing

Atypical glandular cells may indicate precancerous change or frank malignancy. Colposcopic evaluation including endocervical curettage should be used to evaluate for CIN and adenocarcinoma of the cervix. HPV DNA testing should be done to stratify the risk of cervical dysplasia and neoplasia. Endometrial tissue sampling should be used to assess for endometrial cancer and hyperplasia. A pathologist should correlate the histology of the endometrial tissue with the cells on the original cytology screening specimen so as to explain the original abnormality. If the sampling does not explain the original abnormality, the provider should refer the patient to a gynecologist or a gynecologic oncologist. Findings from these initial steps will dictate further evaluation and treatment.

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Low-Grade Squamous Intraepithelial Lesion (LSIL) Annotations

24. Low-Grade Squamous Intraepithelial Lesion (LSIL)

The LSIL category includes changes consistent with human papillomavirus (HPV), mild dysplasia or CIN-1 (grade 1 cervical intraepithelial neoplasia). Eighty percent (80%) will be high-risk HPV-positive, and 15%-30% have moderate or severe dysplasia at initial colposcopy. The ALTS group could not identify a useful triage strategy for this category that could spare colposcopic evaluation. Therefore, colposcopy is recommended for initial evaluation of LSIL *(Castle, 2008 [B]; American College of Obstetricians and Gynecologists, 2005a [R]; ASCUS-LSIL Triage Study (ALTS) Group, 2003 [R])*.

Postmenopausal patients

There is consensus and expert opinion that follow-up without immediate colposcopy may be appropriate in the postmenopausal patient. HPV testing is recommended prior to considering colposcopy. If negative, patients can return to routine surveillance *(Wright, 2007 [R])*.

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25. Colposcopy

The most common management option is to perform a colposcopy. One must be cautious about overaggressive biopsy and treatment. Specifically, routine LEEP of the transformation zone as a method for evaluating a LSIL Pap test is not recommended.

Rates of regression have been quoted as high as 62%-80% on follow-up. (Some investigators believe this reported regression rate is falsely high because prior biopsy, in effect, "treated" the original lesion; under

this assumption, regression rates of unbiopsied low-grade lesions may be as low as 25%) *(American College of Obstetricians and Gynecologists Practice Bulletin, 2005a [R]; Ferris, 1998 [C])*.

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High-Grade Squamous Intraepithelial Lesion (HSIL) Annotations

26. High-Grade Squamous Intraepithelial Lesion (HSIL)

The Bethesda System 2001 combines moderate dysplasia with severe dysplasia and carcinoma in situ (CIS) into a single category of high-grade intraepithelial lesion (HSIL). Up to 95% of patients with high-grade cervical cytology results have been found to have high-grade lesions *(Melnikow, 1997 [C])*.

Of all the categories in current nomenclature for cervical cytology results, perhaps the least ambiguity and the least controversy in management is with HSIL. Histological evaluation of directed cervical biopsies from women with HSIL will commonly show moderate or severe dysplasia or even carcinoma in situ. Thus the standard of practice for management is clearly to perform colposcopy and directed biopsy *(Posalaky, 1998 [C])*.

Further management of the patient will then be guided by the biopsy results *(American College of Obstetricians & Gynecologists, 2005 [R])*.

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27. Colposcopy with Endocervical Curettage (ECC) or Loop Electrosurgical Excision (LEEP)

Colposcopic examination with endocervical curettage (ECC)-directed biopsies or LEEP is the appropriate management for women with HSIL cytology results. If follow-up for the patient is unreliable, LEEP may be performed immediately. When a LEEP is performed immediately, it is not necessary to automatically do an ECC. But if endocervical disease is suspected as a result of the colposcopy and LEEP is not done, an ECC should still be performed *(Wright, 2007 [R]; Holschneider, 1999 [M])*.

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HPV DNA Positive Test Result Annotations

30. HPV DNA Testing Positive with Normal Cytology

In 2003, the Food and Drug Administration approved HPV DNA testing in conjunction with cervical cytology screening for women aged 30 years and older *(Wright, 2007 [R])*. Due to the high prevalence and spontaneous clearance of HPV DNA in adolescents and women in their 20s, HPV DNA should not be used for routine screening before age 30 *(Saslow, 2002 [R])*.

The use of HPV DNA testing as an adjunct to cervical cytology for women aged 30 years and older increases the sensitivity of cervical cancer screening. Review of recent screening studies reported pooled sensitivity and specificity of HPV DNA testing for CIN-2/3+ for women 35 years and older was 95% and 93%, respectively *(Cuzick, 2006 [C])*. Sensitivity using a combination of HPV DNA testing and cervical cytology was higher than either test alone; negative predictive values were 99%-100% *(American College of Obstetricians & Gynecologists, 2005b [R])*.

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Based on this kind of evidence, the American Cancer Society and subsequently the American College of Obstetricians and Gynecologists both concluded this combination of HPV DNA testing and cervical cytology was a reasonable screening strategy for women aged 30 years and older *(American College of Obstetricians & Gynecologists, 2005 [B]; Saslow, 2002 [R])*. Furthermore, testing should not be done more often than every three years if both results are negative, based on a study showing less than 2% of patients with negative HPV DNA and cervical cytology screening developed CIN-3+ in 10 years of follow-up *(Khan, 2005 [B])*. As there is no evidence of improved outcomes with this combination of screening tests, screening with cervical cytology alone remains an acceptable screening option.

Many women screened with a combination of HPV DNA and cervical cytology will test positive for HPV DNA and simultaneously have a negative cervical cytology. The risk for undetected CIN-2/3+ for patients with such a combination of screening results is quite low, with published study results varying from 2.4% to 5.1% *(Ronco, 2006 [A]; Cuzick, 2003 [A])*. Based on this low risk for CIN-2/3+, repeat HPV DNA testing combined with cervical cytology in 12 months appears to be reasonable for patients in this group. If the HPV DNA test remains positive on the repeat screening, the patient should undergo colposcopic evaluation despite a second negative cervical cytological result *(Wright, 2007 [R])*.

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31. Repeat HPV DNA Testing and Cytology at 12 Months

The work group recommends that cytology and HPV DNA testing are repeated in 12 months *(Wright, 2007 [R])*.

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Abnormal Cervical Cytology in Adolescents (Less than 21 Years) Algorithm Annotations

Based on the natural history of cervical neoplasia and the rarity of cervical cancer in women younger than 21 years, the American Cancer Society and the American College of Obstetricians and Gynecologists have recommended initial cervical cytology screening at age 21 *(American College of Obstetricians and Gynecologists, 2009 [R]; American College of Obstetricians and Gynecologists, 2008 [R]; Saslow, 2002 [R])*. Mindful that any cutoff is somewhat arbitrary, but in keeping with the available science, the work group has chosen to define adolescents for this guideline as those women younger than 21 years of age.

See ICSI Preventive Services for Children and Adolescents guideline.

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32. Abnormal Cervical Cytology in Adolescents

Key Point:

- In adolescents, HPV testing should not be used. If the test is inadvertently performed, a positive test should not be used to guide management.
- In adolescents, the HPV regression rate is so high that conservative management without colposcopy is recommended.

Natural History of HPV Infections in Adolescents

In studies of adolescents with newly acquired HPV infection, the average length of detectable HPV is 13 months *(American College of Obstetricians and Gynecologists, 2006 [R])*. In most adolescent patients with

an intact immune system, the HPV infection will resolve within 24 months *(Woodman, 2001 [B])*. HPV infections in this age group resolve without treatment in 71% of the cases of CIN-1 and in 50% of the cases of CIN-2 *(Wright, 2007 [R]; Cox, 2003 [D]; Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study [ALTS] Group, The, 2000 [R])*.

This high regression rate makes it important to avoid aggressive management of low-grade cervical abnormalities in adolescents, because most such lesions undergo spontaneous regression. Surgical excision or destruction of cervical tissue in the nulliparous adolescent may be detrimental to future fertility and cervical competency. The work group recognizes that such conservative management is predicated upon a compliant, health-conscious adolescent who will be available for long-term monitoring of her cervical cancer screening status.

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33. ASCUS Regardless of HPV Status

Management of ASCUS Cervical Cancer Screening Test Results in Adolescents

A report of ASCUS on a cervical cytological screening test often indicates a woman is harboring an HPV infection. In the adolescent population, the prevalence of HPV in that subset with an ASCUS report will be much higher than in an older population. As noted, the risk of invasive cancer in adolescents approaches zero, and the likelihood of HPV clearance is very high; therefore, the work group does not recommend HPV testing.

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34. LSIL

Management of LSIL Cervical Cancer Screening Test Results in Adolescents

The ALTS trial showed that patients with cytological report of LSIL and ASCUS behave in a similar manner regarding clearance of HPV and the risk of developing CIN-2/3+. Due to the similarities in the natural history of these cervical cancer screening findings, management for adolescents is the same as for ASCUS *(American College of Obstetricians and Gynecologists, 2006 [R])*.

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36. Cytology at 12-Month Intervals

The preferred method of triage for adolescent patients with ASCUS is monitoring with cytology at 12-month intervals. If the repeat cytology test results are abnormal for 24 months, colposcopy should be performed. These alternatives avoid the expense of colposcopy and biopsy, and they allow for the high likelihood of clearance of CIN-1 and HPV in this population *(American College of Obstetricians and Gynecologists, 2006 [R]; Wright, 2006 [B]; Guido, 2003 [B])*.

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37. Colposcopy

Management of All Cervical Cancer Screening Test Results with High Probability of CIN-2/3+ in Adolescents

Screening test results of ASC-H, HSIL and AGC all indicate a higher probability for a CIN-2/3+ lesion and should be managed by immediate colposcopy and endocervical assessment as for older women. The management algorithm is identical to the main algorithm for these cervical cancer screening test results *(Wright, 2007 [R])*. However, immediate loop electrosurgical excision (LEEP) is not recommended in adolescents since surgical excision may be detrimental to future fertility and cervical competency.

Surgical treatment should be delayed until persistent disease is proven.

In pregnancy, the only diagnosis that may alter clinical management is invasive cancer. The presence of cancer may change treatment goals for the route and timing of delivery. Cervical cancer screening test results that are not likely to be associated with cancer may undergo colposcopic evaluation either during pregnancy or at least six weeks postpartum. Pregnant women whose screening test results indicate a high risk for CIN-2/3+ should undergo colposcopy without endocervical sampling, reserving biopsy for visible cervical lesions consistent with CIN-3, AIS or cancer *(American College of Obstetricians and Gynecologists, 2005a [R])*.

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This section provides resources, strategies and measurement for use in closing the gap between current clinical practice and the recommendations set forth in the guideline.

The subdivisions of this section are:

- Aims and Measures
  - Measurement Specifications
- Implementation Recommendations
- Resources
- Resources Table

Aims and Measures

1. All women age 21 years and older with an ASCUS cervical cytological result will receive appropriate clinical follow-up. *(ASCUS Algorithm Annotations #7, 9, 14)*

   Measure for accomplishing this aim:

   a. Percentage of women aged 21 years and older with an ASCUS cervical cytological result with high-risk HPV type who have a follow-up colposcopy within six months.

2. All women age 21 years or older with a high-grade squamous intraepithelial lesion (HSIL) cervical cytological result will have a colposcopy with endocervical curettage (ECC) or LEEP. *(Annotations #26, 27)*

   Measure of accomplishing this aim:

   a. Percentage of women aged 21 years and older with a high-grade squamous intraepithelial lesion (HSIL) cervical cytological result who have a colposcopy with endocervical curettage (ECC) or LEEP within six months.

3. All women age 21 or older with a low-grade squamous intraepithelial lesion (LSIL) cervical cytological result will have a colposcopy. *(Annotations #24, 25)*

   Measure for accomplishing this aim:

   a. Percentage of women age 21 years and older with a low-grade squamous intraepithelial (LSIL) cervical cytological result who have a colposcopy within six months.

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Measurement Specifications

Measurement #1a

Percentage of women aged 21 years and older with an ASCUS cervical cytological result with high-risk HPV type who have a follow-up colposcopy within six months.

Population Definition

Women aged 21 years and older with an ASCUS cervical cytological result with high-risk HPV type.

Data of Interest

$$\frac{\text{\# of women with follow-up colposcopy within six months}}{\text{\# of women with an ASCUS cervical cytological result with high-risk HPV type}}$$

Numerator/Denominator Definitions

Numerator: Number of women aged 21 years and older who have a follow-up colposcopy.

Denominator: Number of women aged 21 years and older with an ASCUS cervical cytological result with high-risk HPV type identified by ICD-9 code 795.05.

Method/Source of Data Collection

Identify women with an abnormal cervical cytological result of ASCUS with high-risk HPV type by ICD-9 code: 795.05. Identify the number of women who had a follow-up within six months of diagnosis.

This is a cohort analysis, so you will need to identify a set of women with ASCUS result and whether they had a follow-up within six months.

Time Frame Pertaining to Data Collection

The suggested time period is quarterly.

Notes

This is a process measure. Improvement is associated with a higher score.

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Measurement #2a

Percentage of women aged 21 years and older with a high-grade squamous intraepithelial lesion (HSIL) cervical cytological result who have a colposcopy with endocervical curettage (ECC) or LEEP within six months.

Population Definition

Women aged 21 years and older with a high-grade squamous intraepithelial lesion (HSIL) cervical cytological result.

Data of Interest

$$\frac{\text{\# of women who have a colposcopy with endocervical curettage (ECC) or LEEP within six months}}{\text{\# of women aged 21 years and older with a high-grade squamous intraepithelial lesion (HSIL) cervical cytological result}}$$

Numerator/Denominator Definitions

Numerator: Number of women age 21 years and older who have a colposcopy with endocervical curettage (ECC) or LEEP within six months.

Denominator: Number of women aged 21 years and older with a high-grade squamous intraepithelial lesion (HSIL) cervical cytological result.

Method/Source of Data Collection

Identify women age 21 years and older with a high-grade squamous intraepithelial lesion (HSIL) cervical cytological result. Identify how many of these women had a colposcopy with endocervical curettage (ECC) or LEEP within six months.

Time Frame Pertaining to Data Collection

The suggested time period is quarterly.

Notes

This is a process measure. Improvement is associated with a higher score.

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Measurement #3a

Percentage of women age 21 years and older with a low-grade squamous intraepithelial (LSIL) cervical cytological result who have a colposcopy within six months.

Population Definition

Women aged 21 years and older with a low-grade abnormal cytology (LSIL) cervical cytological result

Data of Interest

$$\frac{\text{\# of women age 21 and older who have a colposcopy within six months}}{\text{\# of women aged 21 years and older with a low-grade abnormal cytology (LSIL) cervical cytological result}}$$

Numerator/Denominator Definitions

Numerator: Number of women age 21 years and older who have a colposcopy within six months.

Denominator: Number of women aged 21 years and older with a low-grade abnormal cervical cytological result.

Method/Source of Data Collection

Identify women age 21 years and older with a low-grade abnormal cytology (LSIL) cervical cytological result. Identify how many of these women had a colposcopy within six months.

Time Frame Pertaining to Data Collection

The suggested time period is quarterly.

Notes

This is a process measure. Improvement is associated with a higher score.

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Implementation Recommendations

Prior to implementation, it is important to consider current organizational infrastructure that address the following:

- System and process design
- Training and education
- Culture and the need to shift values, beliefs and behaviors of the organization

The following system changes were identified by the guideline work group as key strategies for health care systems to incorporate in support of the implementation of this guideline.

1. Disseminate recommendations for appropriate follow-up for each of the Bethesda classifications for abnormal cervical cytology results.
2. Implement a program or process to ensure complete follow-up of all abnormal results obtained by cervical cytology.

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Resources

Criteria for Selecting Resources

The following resources were selected by the guideline work group as additional resources for providers and/or patients. The following criteria were considered in selecting these resources.

- The site contains information specific to the topic of the guideline.
- The content is supported by evidence-based research.
- The content includes the source/author and contact information.
- The content clearly states revision dates or the date the information was published.
- The content is clear about potential biases, noting conflict of interest and/or disclaimers as appropriate.

Resources Available to ICSI Members Only

ICSI has knowledge resources that are ***only*** available to ICSI members (these are indicated with an asterisk in far left-hand column of the Resources Table). In addition to the resources listed in the table, ICSI members have access to a broad range of materials including tool kits on Continuous Quality Improvement processes and Rapid Cycling that can be helpful. To obtain copies of these or other Resources, go to Education and Quality Improvement on the ICSI Web site. To access these materials on the Web site, you must be logged in as an ICSI member.

The resources in the table on the next page that are not reserved for ICSI members are available to the public free-of-charge.

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Resources Table

*	Author/Organization	Title/Description	Audience	Web sites/Order Information
	American Academy of Family Physicians	Contains literature on Pap tests description and results as well as HPV testing and colposcopy.	Patients and Families	http://www.aafp.org On home page select "patients." On patient's page, select "women" and search "abnormal Pap"
	American College of Obstetricians and Gynecologists (ACOG)	Loop Electrosurgical Excision Procedure; Pamphlet AP110	Patients and Families	http://www.acog.org/publications/patient_education Search for LEEP. Order online or call 800-762-2264.
	American Society for Colposcopy and Cervical Pathology (ASCCP)	Multiple patient education pamphlets are available in English, Spanish and Vietnamese.	Patients and Families	http://www.asccp.org/ Click on Patient Education
	Association of Reproductive Health Professionals	Educational needs for providers.	Health Care Providers	http://www.arhp.org/
	Family Doctor	Provides health information from a family medicine perspective to educate users about healthful behaviors, and effective prevention and management of common diseases, and to support the relationship between patients and physicians.	Patients and Families	http://familydoctor.org/
*	Initial Management of Abnormal Cervical Cytology (Pap Smear) and HPV Testing Guideline Work Group (2008)	Follow-up Pap Smear Results Letters for Patients; examples of follow-up result letters.	Health Care Providers	http://www.icsi.org/improvement_resources/knowledge_resources/tools/
*	Initial Management of Abnormal Cervical Cytology (Pap Smear) and HPV Testing Guideline Work Group (2008)	Colposcopy; patient information sheet	Patients and Families	http://www.icsi.org/improvement_resources/knowledge_resources/tools/
*	Initial Management of Abnormal Cervical Cytology (Pap Smear) and HPV Testing Guideline Work Group (2008)	Abnormal Pap Results; patient information sheet listing common terms	Patients and Families	http://www.icsi.org/improvement_resources/knowledge_resources/tools/
	Mayo Clinic	Information on Pap tests, HPV testing, colposcopy and cervical cancer.	Patients and Families	http://www.mayoclinic.com

* Available to ICSI members only.

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*	Author/Organization	Title/Description	Audience	Web sites/Order Information
	Multilingual Health Resources Exchange	Collaboration of Minnesota-based health providers that have access to health education targeted to multilingual audiences.	Health Care Providers	http://www.health-exchange.net Contact Health Advocates (651) 489-4238 for membership information, fees, and materials index
	National Cancer Institute	Pap Test Questions & Answers fact sheet that describes the procedure, possible results and the link between HPV and cervical cancer.	Patients and Families	http://www.cancer.gov Search "Pap test"
	National Cervical Cancer Public Education Campaign	Information about cervical cancer	Patients and Families	http://www.cervicalcancercampaign.org
	Planned Parenthood	HPV and Cervical Cancer, Colposcopy and Cryotherapy and LEEP questions and answers fact sheets.	Patients and Families	http://www.plannedparenthood.org Search on health topics and link to Women's Health
	UpToDate	UpToDate is an information resource where topics are reviewed and include a synthesis of the literature, the latest evidence, and specific recommendations for patient care.	Patients and Families (cost applies) Health Care Providers	http://uptodate.com

* Available to ICSI members only.

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The subdivision of this section is:

- References

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Links are provided for those new references added to this edition (author name is highlighted in blue).

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ICSI Document Development and Revision Process

Overview

Since 1993, the Institute for Clinical Systems Improvement (ICSI) has developed more than 60 evidence-based health care documents that support best practices for the prevention, diagnosis, treatment or management of a given symptom, disease or condition for patients.

Document Development and Revision Process

The development process is based on a number of long-proven approaches. ICSI staff first conducts a literature search to identify pertinent clinical trials, meta-analysis, systematic reviews, regulatory statements and other professional guidelines. The literature is reviewed and graded based on the ICSI Evidence Grading System.

ICSI facilitators identify gaps between current and optimal practices. The work group uses this information to develop or revise the clinical flow and algorithm, drafting of annotations and identification of the literature citations. ICSI staff reviews existing regulatory and standard measures and drafts outcome and process measures for work group consideration. The work group gives consideration to the importance of changing systems and physician behavior so that outcomes such as health status, patient and provider satisfaction, and cost/utilization are maximized.

Medical groups, who are members of ICSI, review each guideline as part of the revision process. The medical groups provide feedback on new literature, identify areas needing clarification, offer recommended changes, outline successful implementation strategies and list barriers to implementation. A summary of the feedback from all medical groups is provided to the guideline work group for use in the revision of the guideline.

Implementation Recommendations and Measures

Each guideline includes implementation strategies related to key clinical recommendations. In addition, ICSI offers guideline-derived measures. Assisted by measurement consultants on the guideline development work group, ICSI's measures flow from each guideline's clinical recommendations and implementation strategies. Most regulatory and publicly reported measures are included but, more importantly, measures are recommended to assist medical groups with implementation, thus both process and outcomes measures are offered.

Document Revision Cycle

Scientific documents are revised every 12-24 months as indicated by changes in clinical practice and literature. Each ICSI staff monitors major, peer-reviewed journals every month for the guidelines for which they are responsible. Work group members are also asked to provide any pertinent literature through check-ins with the work group mid-cycle and annually to determine if there have been changes in the evidence significant enough to warrant document revision earlier than scheduled. This process complements the exhaustive literature search that is done on the subject prior to development of the first version of a guideline.

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