

LABletter

PATHOLOGY & LABORATORY MEDICINE NEWSLETTER

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Update on Consensus Management Guidelines for Abnormal Pap Tests

Christina S. Kong, M.D.
Director, Cytopathology

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Raffick A.R. Bowen, MLT (CSMLS), Ph.D., DCIChem, FCACB, DABCC, Associate Director of Clinical Chemistry and Immunology; Assistant Professor Stanford University, Department of Pathology.

Christina S. Kong, M.D.

Director of
Cytopathology at
Stanford University
Hospital and Clinics
and Assistant
Professor, Stanford



University, Department of Pathology. Dr. Kong is fellowship-trained and board-certified in Cytopathology and Anatomic and Clinical Pathology with over ten years experience as a diagnostic pathologist.

Update on Consensus Management Guidelines for Abnormal Pap Tests

The American Society for Colposcopy and Cervical Pathology (ASCCP) first published consensus guidelines for the management of women with abnormal cervical cancer screening tests in 2001. Recently, these guidelines were revised, reflecting changes that were recommended as a result of the ASCCP-sponsored consensus conference held at the NIH in September 2006. The full 2006 consensus guidelines and management algorithms can be accessed at www.asccp.org/consensus.shtml. A Management Algorithms Wall Chart is enclosed for your reference.

Atypical Squamous Cells of Undetermined Significance (ASC-US)

General population: Based on data from the ASCUS-LSIL Triage Study (ALTS), there are three acceptable methods for managing ASC-US in the general population:

- 1) Reflex testing for high-risk HPV, or
- 2) Immediate colposcopy, or

3) Repeat Pap test at 6 and 12 months (colposcopy recommended if ASC-US or greater is identified on repeat Pap test) (see Fig. 1 for details).

It should be noted that doing *both* HPV testing and repeat Pap testing is not recommended for follow-up of ASC-US as sensitivity remains the same while specificity drops when the two tests are combined. In addition, HPV testing should not be performed more frequently than once every 12 months.

Adolescent women: The 2006 Consensus Guidelines defines adolescents as women who are 20 years and younger. HPV infection and minor cytologic abnormalities are common in this population but the risk of invasive cervical cancer is very low. In addition, most HPV infections clear within 2 years without treatment. Subsequently, it is recommended that adolescent women with ASC-US be managed less aggressively with repeat Pap test at 12 and 24 months. Immediate colposcopy and reflex HPV testing are considered unacceptable. Only patients with HSIL at the 12 month Pap test or at least ASC-US at the 24 month Pap test should be referred for colposcopy.

(Fig. 1) Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US)

Figure was reprinted with the permission of the ASCCP®. Please click the link below to go to the ASCCP® Website to view the 2006 Consensus Guidelines.



<http://www.asccp.org/consensus.shtml>

To request copies of the Management Algorithms Wall Chart contact your sales/service representative, or email us at labmarketing@stanfordmed.org.

“Colposcopy with biopsy is recommended for women with a diagnosis of ASC-H”

Other Special Populations: Immunosuppressed (including HIV-positive), postmenopausal and pregnant women should be managed the same as patients in the general population, except with pregnant patients endocervical curettage is contraindicated and colposcopy can be deferred until at least 6 weeks postpartum.

Atypical Squamous Cells, Cannot Exclude HSIL (ASC-H)

Colposcopy with biopsy is recommended for women with a diagnosis of ASC-H. If high-grade SIL is not identified on biopsy, there are two options for follow-up:

- 1) HPV testing at 12 months *or*
- 2) Repeat Pap test at 6 and 12 months

If the HPV test at 12 months is positive or if the repeat Pap test shows ASC-US or above, colposcopy is recommended. If the HPV test is negative *or* both the follow-up Pap tests are negative, the patient can resume routine yearly screening.

Atypical Glandular Cells (AGC)

AGC is often associated with benign, reactive conditions but there is also a significant risk of underlying HSIL, endocervical adenocarcinoma in situ and invasive adenocarcinomas. Subsequently, colposcopy with endocervical curettage is recommended for all categories of AGC, except for “atypical endometrial cells”. In women 35 years and older or in younger women with risk factors for endometrial pathology, endometrial sampling is also indicated. For a diagnosis of “atypical endometrial cells”, endocervical and endometrial sampling are recommended; if no endometrial pathology is identified then colposcopy is indicated. For all categories of AGC, it is preferable to obtain HPV testing at the time of colposcopy. Neither HPV testing or repeat pap tests alone are acceptable for the initial management of AGC.

Low-grade Squamous Intraepithelial Lesion (LSIL)

General population: According to data from the ASC-US/LSIL Triage Study, women with a Pap test diagnosis of LSIL or high-risk HPV positive ASC-US have the same risk of harboring HSIL. Subsequently, the same management guidelines apply to both groups of women (see Fig. 1 or wall chart for ASC-US HPV positive algorithm), excluding adolescents, postmenopausal women and pregnant women.

Adolescent women: The recommended management for adolescents with LSIL is follow-up with annual Pap testing.

Referral to colposcopy is recommended only if at least HSIL is found at the 12-month Pap test or at least ASC-US at the 24-month Pap test.

The use of HPV testing in the management of adolescents with LSIL is considered unacceptable and if HPV testing is performed the results should not be allowed to influence management.

Postmenopausal women: In contrast to adolescents, reflex HPV testing is acceptable for evaluating postmenopausal women with a cytologic diagnosis of LSIL.

If the HPV test is negative or no lesions are identified at colposcopy, the patient can be followed with a Pap test in 12 months.

If the HPV test is positive or the repeat Pap test shows at least ASC-US, referral to colposcopy is recommended.

Other acceptable options include repeat Pap testing at 6 and 12 months *or* immediate colposcopy.

Pregnant women: Preferred management for pregnant women with LSIL is immediate colposcopy but it is also acceptable to defer colposcopy until at least 6 weeks postpartum. If the initial colposcopy does not show any colposcopic, histologic or cytologic features to suggest HSIL or cancer, the patient can be further evaluated postpartum; additional exams are considered unacceptable during pregnancy. Endocervical curettage is also contraindicated in pregnant women.

High-grade Squamous Intraepithelial Lesion (HSIL)

General population: HSIL can be managed by colposcopy with endocervical sampling *or* immediate LEEP of visible lesions (see Management Algorithm Wall Chart), except in special populations.

Adolescent women: HSIL in women 20 years and younger should be evaluated with colposcopy and endocervical sampling. Immediate LEEP is not acceptable. If colposcopy is satisfactory and HSIL is not identified histologically, preferred management is to follow the patient with colposcopy and Pap tests at 6 month intervals for up to 24 months. Biopsy is recommended if a high-grade lesion is identified on colposcopy *or* if there is persistent HSIL by cytology for a year. Diagnostic excision is recommended if HSIL persists by cytology for 24 months without identification of HSIL on biopsy. Patients can return to routine screening after two consecutive negative Pap tests, if no high-grade lesions are identified by colposcopy.

Pregnant women: HSIL in pregnant women should be evaluated by colposcopy with biopsy of lesions suspicious for HSIL or cancer. Endocervical curettage is unacceptable, as are excisional procedures unless invasive cancer is suspected. If HSIL is not identified, repeat colposcopy and Pap test is deferred until at least 6 weeks postpartum.

Endometrial Cells in a Woman Over 40

Endometrial biopsy is recommended when benign-appearing endometrial cells are identified in a Pap test from a post-menopausal woman. However, no further evaluation is indicated in asymptomatic pre-menopausal women since benign-appearing endometrial cells are rarely associated with significant endometrial abnormalities in this patient population.

Reference:

Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D; 2006 American Society for Colposcopy and Cervical Pathology-sponsored Consensus Conference. 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. *Am J Obstet Gynecol.* 2007 Oct;197(4):346-55.



Laboratory Update:

Special Coagulation

Expanded coagulation testing with Protein C and Protein S Antigen testing.

Test Description and Clinical Indications:

Protein C is a natural anticoagulant produced in the liver. It is vitamin K dependent and requires thrombin and thrombomodulin for activation. Activated protein C in the presence of cofactor protein S inactivates factors Va and VIIIa, thereby limiting coagulation. Patients heterozygous for deficiency of protein C or S may exhibit recurrent venous thrombosis at a young age (peak incidence between ages 15 and 40). Heterozygotes also appear to have an increased risk of coumadin-induced skin necrosis. Patients homozygous for protein C deficiency present with generalized microvascular thrombosis in the neonatal period (purpura fulminans). Normal neonates have lower levels of protein C than adults. Warfarin therapy will result in low protein C levels. See also Thrombosis screen and Activated Protein C Resistance in the Test Directory at www.stanfordlab.com.

Protein S is a vitamin K-dependent cofactor for activated protein C, which serves to inactivate factors Va and VIIIa. Protein S deficiency is clinically indistinguishable from protein C deficiency, with heterozygous individuals at an increased risk of recurrent venous thrombosis. The assay is useful for evaluation of thrombophilic patients, in particular those who have a family history of thrombosis, thrombosis at a young age (<40 years), recurrent thrombosis or thrombosis at unusual sites (inferior vena cava, mesenteric veins). Normal neonates have lower protein S levels than adults do. Pregnancy normally results in decreased protein S levels. Patients with the factor V Leiden mutation may have artifactually low functional Protein S levels. Protein S is a vitamin K-dependent protein, so warfarin use will result in low levels.

Protein S Antigen, Total

Order Code: TOTALS

Methodology: Automated Latex Immunoassay
CPT Codes: 85305

Protein C Antigen, Total

Order Code: TOTALC

Methodology: Manual method by ELISA
CPT Codes: 85302

Protein C and S, Total Combined

Order Code: CSTOTAL

Specimen Collection & Processing (for all 3 tests):

Specimen Type: Platelet poor plasma. Full light blue-top tube (Sodium citrate 4.5ml); Minimum Volume (Pediatric): Full tube (2.7 mL blood or 1.8 mL blood depending on size of tube used). For Protein C and S, Total Combined, collect 2 full light blue-top tubes (Sodium citrate 4.5ml each).

Special Handling: Within 1 hour of collection, centrifuge tube (s) as required to obtain platelet-poor plasma. Aliquot platelet-poor plasma into screw-top plastic transport tubes (2 aliquots for single test and 4 aliquots for combined tests). Freeze immediately and transport specimens frozen. Note: If Hct >55% specimen must be drawn in special tube obtained from Coagulation Laboratory.

Heparin Therapy Monitoring Update

The clinical laboratory has changed the way heparin therapy is monitored from the Activated Partial Thromboplastin Time (aPTT) to a Heparin Activity Level assay based on anti-factor Xa activity.

Test Name Summary

- **Heparin Activity Level** assay is intended for monitoring of patients on unfractionated heparin.
- **AntiXa/LMWH** is intended for monitoring patients on low molecular weight heparin. Low intensity heparin therapy is for those patients considered to be at high bleeding risk or on concomitant thrombolytic or intravenous anti-platelet therapies.
- **Arixtra** is intended for monitoring patients on fondaparinux (Arixtra). Full intensity heparin therapy is for patients with the usual indications for heparin therapy (e.g., DVT/PE).
- **aPTT** is intended for evaluation of bleeding disorders, coagulation disorders, and monitoring direct thrombin inhibitors; argatroban and lepirudin therapy.

Changes:

All existing heparin nomograms have been changed to reflect heparin activity level in units/mL. **This change does not affect high dose unfractionated heparin therapy monitoring in the OR, Cath lab or certain ICU wards where point of care ACT is used to monitor heparin.**

Advantages to using heparin activity level to monitor therapy:

Unlike aPTT, the heparin activity level is not affected by a prolonged baseline aPTT (e.g., lupus anticoagulant), thrombolytics or direct thrombin inhibitors. Therapeutic ranges for the heparin level do not change over time, whereas therapeutic ranges for the aPTT change with new reagent lots.

There is no change in the type of sample tube (blue) used or timing of blood draws. The current heparin dosing nomograms use heparin activity levels in place of aPTT to guide treatment.

As always, when drawing blood samples from a patient on a heparin drip, it is best to draw from a peripheral site or a non-heparinized line. If drawing from a heparinized line, draw 12 mL blood and discard before drawing the test sample. For pediatric and neonatal patients, draw per protocol.

Important Notes:

- The assays for unfractionated heparin, low molecular weight heparin (LMWH) and fondaparinux are calibrated differently. Therefore, medication the patient is on must be specified.
- The default calibration for LMWH is for enoxaparin (Lovenox). To measure the concentration of a different LMWH, the lab must be informed so that a calibration for that LMWH is created.

Test Name	Therapeutic range
Heparin Activity Level	0.3 - 0.7 units/mL
Anti-Xa/LMWH (enoxaparin, Lovenox®)	0.5 - 1.2 anti-Xa units/mL (peak)*
Fondaparinux (Arixtra®)	1.20 - 1.26 mcg/mL (peak)*

For questions please call Customer Services 1-877-717-3733 and request the Special Coagulation Laboratory.

*3-4 hours after injection. Due to the predictable pharmacokinetics of LMWH and fondaparinux, most patients treated with these drugs do not require monitoring. Select patients (e.g., renal failure with concern about drug accumulation, obesity, pregnancy) may benefit from monitoring.

Q&A: Submit Q&A topics of interest to: labmarketing@stanfordmed.org

An opportunity for the Bay Area Medical Community to request specific Q&A topics to our medical directors that are relevant to patients' clinical needs.



Raffick Bowen, Ph.D.

Autoverification

Q&A with Raffick Bowen, Ph.D., Associate Director of Chemistry & Immunology and Assistant Professor of Pathology.

Q1: What is autoverification?

A1: "Autoverification" means the use of a computer algorithm in conjunction with automated clinical laboratory instrumentation to review and verify the results of a clinical laboratory test or examination for accuracy and reliability. Currently, all test results are manually reviewed by a clinical laboratory scientist (CLS). Autoverification is the automatic release of results without this review. Each result received from the instrument by the laboratory information system (LIS) is evaluated based on parameters defined by the laboratory. If it passes, the result is released to be viewed by the ordering physician or nurse. Only results that fall outside defined parameters require manual review by the CLS.

Q2: Why is autoverification new to California?

A2: Previously, California's Department of Health Services mandated that all clinical laboratory results be reviewed by a licensed person before release to the patient's record. However, a new law* authorizing the use of autoverification was implemented this year. Many other states have already taken advantage of autoverification and now laboratories in California are able to do so as well.

Q3: What are the benefits of autoverification?

A3: There are three major benefits:

- Autoverification ensures that every result consistently receives the same review process. Interruptions, fatigue, and stress alter the technologist's ability to review results with the same consistency across all shifts at all times for all specimens. Autoverification reduces the risk of error by standardizing the review process.
- Turn-around times will be markedly improved because the LIS can validate and report results much faster than a human. This is especially important for tests ordered by intensive care units, emergency departments, and operating rooms.
- The CLS can focus his or her specialized knowledge on the more complex results (that fail review by the LIS). Also, workflow efficiency will be improved since the lab personnel are available for other duties in the lab.

Q4: What is an example of how autoverification works?

A4: One patient's test results for a comprehensive metabolic panel (CMP) might be autoverified and released without review because:

- results of all of the tests are within their reference ranges
- there are no "flags" from the instrument indicating that the patient's specimen was unusual in any way

- the latest quality control results for all of the tests are within their target ranges
- current results are similar to the previous results when the patient was tested last week

However, the next patient's CMP might fail autoverification because there is an instrument "flag" or a result discrepant with the previous one. In such a case, the CLS would need to review the results; verify that there was no labeling error; investigate whether the discrepant result represents a real change; and/or confer with the supervisor or medical director.

Q5: When is Stanford Clinical Lab implementing autoverification?

A5: Training and education of the laboratory personnel is currently underway and we will "Go Live" with autoverification sometime in January 2008 for Chemistry testing at the Medical Center. Later in 2008, other areas (including the automated laboratory at Hillview) will join the process. We will be following the requirements of the new California law, as well as the recommendations for autoverification developed by the Clinical Laboratory Standards Institute. Criteria approved by the medical directors has been extensively validated in our LIS both individually as well as in combination with other criteria, using simulated data and clinical specimens. Once implemented, we will periodically monitor the autoverification process in the same way. In addition, serum indices (i.e. hemolysis, icterus, and lipemia) with values above the level that can cause assay interference will be automatically flagged.

* Assembly Bill 2156 was signed into law on September 18, 2006 and implemented on January 1, 2007. This new law is codified under Business and Professions Code (BPC) 1209.5 and it authorizes laboratories to use autoverification to report test results. For further information go to www.dhs.ca.gov/ps/lis/lfsb



Stanford University Medical Center

SUMCCL at Hillview
3375 Hillview Ave.
Palo Alto, CA 94304
1-877-717-3733
www.stanfordlab.com

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