

The 2001 Bethesda System Terminology for Reporting Results of Cervical Cytology

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BACKGROUND

The Bethesda System for reporting the results of cervical cytology was developed as a uniform system of terminology that would provide clear guidance for clinical management.¹ The first workshop was held in 1988, to reduce widespread confusion among laboratories and clinicians created by the use of multiple classification systems and inconsistently defined numerical grading conventions.

The most important contribution of the Bethesda System was the creation of a standardized framework for laboratory reports that included a descriptive diagnosis and an evaluation of specimen adequacy. While not everyone agreed with every detail of that initial effort, the recommendations of the 1988 workshop received widespread acceptance in practice.² A second workshop was held in 1991 to modify the Bethesda System based on actual laboratory and clinical experience after its implemen-

See also pp 2120 and 2140.

Objectives The Bethesda 2001 Workshop was convened to evaluate and update the 1991 Bethesda System terminology for reporting the results of cervical cytology. A primary objective was to develop a new approach to broaden participation in the consensus process.

Participants Forum groups composed of 6 to 10 individuals were responsible for developing recommendations for discussion at the workshop. Each forum group included at least 1 cytopathologist, cytotechnologist, clinician, and international representative to ensure a broad range of views and interests. More than 400 cytopathologists, cytotechnologists, histopathologists, family practitioners, gynecologists, public health physicians, epidemiologists, patient advocates, and attorneys participated in the workshop, which was convened by the National Cancer Institute and cosponsored by 44 professional societies. More than 20 countries were represented.

Evidence Literature review, expert opinion, and input from an Internet bulletin board were all considered in developing recommendations. The strength of evidence of the scientific data was considered of paramount importance.

Consensus Process Bethesda 2001 was a year-long iterative review process. An Internet bulletin board was used for discussion of issues and drafts of recommendations. More than 1000 comments were posted to the bulletin board over the course of 6 months. The Bethesda Workshop, held April 30-May 2, 2001, was open to the public. Postworkshop recommendations were posted on the bulletin board for a last round of critical review prior to finalizing the terminology.

Conclusions Bethesda 2001 was developed with broad participation in the consensus process. The 2001 Bethesda System terminology reflects important advances in biological understanding of cervical neoplasia and cervical screening technology.

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tation.³ Currently, more than 90% of US laboratories use some form of the 1991 Bethesda System in reporting cervical cytology.⁴ With the increased utilization of new technologies and recent findings from research studies, 2001 was

considered an opportune time to re-evaluate the Bethesda System.

Bethesda 2001 Process

Eight months prior to the Bethesda 2001 Workshop, 9 forum groups (listed

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Forum Group Members are listed at the end of this article.

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at the end of the article) were established to draft recommendations for modifying the Bethesda System. A primary objective was to broaden participation by using the Internet in the premeeting development process. A dedicated Web site (<http://bethesda2001.cancer.gov>) with an electronic bulletin board was established to seek input and critiques of draft recommendations. In total, more than 1000 individual comments were posted to the bulletin board.

The workshop was held April 30–May 2, 2001, with more than 400 participants, including pathologists, cytotechnologists, clinicians, and patient advocates. Forty-four professional societies, representing more than 20 countries, were cosponsors (BOX 1). More than 20 national and international societies have endorsed the 2001 Bethesda System at this writing. The following summary highlights the most clinically relevant changes to the Bethesda System (BOX 2); a more detailed text will be published in specialty journals.

THE 2001 BETHESDA SYSTEM

Specimen Adequacy

Evaluation of specimen adequacy is considered by many to be the single most important quality assurance component of the Bethesda System. Originally, in 1988, specimen adequacy was categorized as “satisfactory,” “less than optimal” (renamed “satisfactory but limited by . . .” in 1991), or “unsatisfactory.” The middle category was used most often for cases lacking endocervical or squamous metaplastic cells as evidence of transformation zone sampling, but which were otherwise “satisfactory.” The 2001 Bethesda System maintains the “satisfactory for evaluation” and “unsatisfactory for evaluation” categories, but eliminates “satisfactory but limited by . . .” because the term was considered confusing to many clinicians and prompted unnecessary repeat testing. Nevertheless, providing information on transformation zone sampling has value in improving overall specimen quality and encourages efforts to optimize sample collection.

Box 1. Bethesda 2001 Workshop Cosponsors

American Cancer Society*
 American College Health Association*
 American College of Obstetricians and Gynecologists*
 American Social Health Association*
 American Society of Cytopathology*
 American Society for Colposcopy and Cervical Pathology*
 American Society of Clinical Pathologists*
 American Society for Cytotechnology*
 Asociación Mexicana de Patólogos
 Association of Reproductive Health Professionals
 Association of Women’s Health, Obstetric and Neonatal Nurses
 Australian Society of Cytology
 British Society for Clinical Cytology
 Canadian Society of Cytology – Société Canadienne de Cytologie*
 Centers for Disease Control and Prevention
 Chinese Society of Cytopathology
 College of American Pathologists*
 Deutsche Gesellschaft für Zytologie
 Food and Drug Administration
 Gynecologic Oncology Group, ACOG*
 Health Care Financing Administration
 International Academy of Cytology
 International Society of Gynecological Pathologists
 Irish Association for Clinical Cytology*
 Japanese Society of Clinical Cytology
 Korean Society for Cytopathology
 Magyar Onkológusok Társasága-Cytodiagnosztikai Sectio
 National Committee for Clinical Laboratory Standards
 Nurse Practitioners in Women’s Health
 Österreichische Gesellschaft fuer Zytologie*
 Papanicolaou Society of Cytopathology*
 Planned Parenthood Federation
 Romanian Society of Cytology
 Sociedad Argentina de Citología
 Sociedad Chilena de Citología
 Sociedad Española de Citología*
 Sociedad Peruana de Citología
 Sociedade Boliviana de Citologia
 Sociedade Brasileira de Citopatologia
 Società Italiana di Anatomia Patologica e Citopatologia Diagnostica
 Société Belge de Cytologie Clinique—Belgische Vereniging voor Klinische Cytologie*
 Société Française de Cytologie Clinique*
 Society of Gynecologic Oncologists*
 Suid Afrikaanse Vereniging vir Kliniese Sitologie—South African Society of Clinical Cytology*

*Indicates that the society has endorsed the 2001 Bethesda System.

Minimal squamous cellularity requirements for a specimen to qualify as “satisfactory” differ depending on specimen type: an estimated 8000 to 12000 well-visualized squamous cells for conventional smears and 5000 squamous cells for liquid-based preparations. Tech-

niques for evaluating cellularity will be presented in future publications.

A notation is made regarding the presence or absence of an endocervical/transformation zone component for specimens with adequate squamous cellularity. The numeric criterion for a

Box 2. The 2001 Bethesda System (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 posthysterectomy
 - Atrophy

Epithelial Cell Abnormalities

- Squamous cell
 - Atypical squamous cells (ASC)
 - of undetermined significance (ASC-US)
 - 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

AUTOMATED REVIEW AND ANCILLARY TESTING (Include as appropriate)**EDUCATIONAL NOTES AND SUGGESTIONS (Optional)**

transformation zone component is unchanged from the 1991 Bethesda System—there should be at least 10 well-

preserved endocervical or squamous metaplastic cells; however, clusters are no longer required.

Comments on quality indicators such as partially obscuring inflammation or blood may also be added to the “satisfactory” designation. A specimen is considered “partially obscured” when 50% to 75% of the epithelial cells cannot be visualized. Specimens with more than 75% of epithelial cells obscured are “unsatisfactory.”

Specimens that cannot be accessioned by the laboratory, if unlabelled for example, are also designated as “unsatisfactory”; these are distinguished from specimens that have been processed by the laboratory and determined to be unsatisfactory following microscopic evaluation.

General Categorization

The “general categorization” is an optional component of the Bethesda System, designed to allow clinicians and/or their staff to triage reports readily. The previous category headings of “within normal limits” and “benign cellular changes” have been combined into a single category “negative for intraepithelial lesion or malignancy.” In this way, reactive changes are more clearly designated as “negative.” “Other” has been added as a category for cases in which there are no morphological abnormalities in the cells per se; however, the findings may indicate some increased risk: for example, benign-appearing “endometrial cells in a woman ≥ 40 years of age” (see below).

These categories are mutually exclusive; therefore, if several findings are present, the general categorization is based on the most clinically significant result (eg, epithelial cell abnormality).

Interpretation/Result

The workshop participants unanimously supported the view that cervical cytology is primarily a screening test, which in some instances may serve as a medical consultation by providing an interpretation that contributes to a diagnosis. However, a patient’s final diagnosis, and therefore management, must integrate clinical and laboratory results. Therefore, in the 2001 Bethesda

System the term “diagnosis” has been replaced by “interpretation” or “result” to convey that cervical cytology provides an interpretation of morphological findings that must be integrated into a clinical context.

Negative for Intraepithelial Lesion or Malignancy. Specimens for which no epithelial abnormality is identified are reported as “negative for intraepithelial lesion or malignancy.” Reporting non-neoplastic findings, other than the listed organisms, is optional; Box 2 includes a partial list of findings.

Epithelial Cell Abnormalities. Atypical Squamous Cells. The 1988 Bethesda System included the term “atypical squamous cells of undetermined significance” (ASCUS) to designate “cellular abnormalities that were more marked than those attributable to reactive changes but that quantitatively or qualitatively fell short of a definitive diagnosis of ‘squamous intraepithelial lesion’ (SIL).” Pathologists were encouraged to qualify ASCUS with respect to whether a reactive process or SIL was favored. In practice, pathologists reported a significant proportion of smears as “ASCUS, not otherwise specified.”

When the 1988 Bethesda System was drafted, clinical management in the United States focused on identifying all SIL, including low-grade SIL (LSIL), based on the view that all grades of SIL represented closely linked precursors that required colposcopy and treatment. However, there has been a shift in the United States with regard to management based on the recognition that most LSIL, especially in young women, represents a self-limited human papillomavirus (HPV) infection.⁵ Accordingly, the current emphasis is on detection and treatment of histologically confirmed high-grade disease (particularly cervical intraepithelial neoplasia [CIN] 3). Therefore, it is logical for the ASC category qualifiers to emphasize the importance of detecting high-grade SIL (HSIL), which has emerged as the central purpose of screening.

At the 2001 workshop, a small minority of workshop participants ar-

gued for elimination of the ASCUS category. However, the participants decided that it was essential to maintain an equivocal category because of the large number of women with underlying CIN 2 and 3 who are discovered through a workup for an equivocal cytological reading. Estimates suggest that 10% to 20% of women with ASC have underlying CIN 2 or 3 and that 1 in 1000 may have invasive cancer.⁶ The elimination of an equivocal cytology category seemed imprudent given the high expectations for very sensitive cervical cytological screening in the United States.

The 2001 Bethesda System differs in several fundamental ways with regard to reporting equivocal results. First, “atypical squamous cells” are now qualified as “of undetermined significance (ASC-US)” or “cannot exclude HSIL” (ASC-H). The qualifier “undetermined significance” was retained to emphasize that some cases of ASC-US are associated with underlying CIN 2 or 3. Second, ASC is not a diagnosis of exclusion; all ASC is considered to be suggestive of SIL. Accordingly, the category of “ASCUS, favor reactive” was eliminated. Pathologists are encouraged to judiciously downgrade to “negative for intraepithelial lesion or malignancy” a portion of the cases previously termed “ASCUS favor reactive.”

The new term “ASC-H” is thought to include approximately 5% to 10% of ASC cases overall.⁷⁻⁹ This category reflects a mixture of true HSIL and its mimics. Although the interpretation is not highly reproducible among pathologists, studies suggest that ASC-H has a positive predictive value for histological CIN 2 or 3 that is intermediate between ASC-US and HSIL. It is hoped that by highlighting such cases, ASC-H will aid in more rapid detection and treatment of some cases of CIN 2 and 3. However, the equivocal nature of the ASC-H designation should encourage comprehensive review of all pathology and colposcopic findings prior to performing a diagnostic loop electrosurgical excision procedure in women with negative histology results.

Squamous Intraepithelial Lesions. The 1988 Bethesda System introduced a 2-tiered terminology, LSIL and HSIL, for reporting the spectrum of noninvasive squamous cervical abnormalities.

After thorough consideration by the Bethesda 2001 Workshop, the 2-tiered LSIL/HSIL terminology remains unchanged.

The dichotomous division of SIL reflects the substantial virological, molecular, and clinical evidence that LSIL is generally a transient infection with HPV, while HSIL is more often associated with viral persistence and higher risk for progression.¹⁰⁻¹³ In addition, data from the ASCUS LSIL Triage Study demonstrate the following: (1) LSIL vs HSIL is a fairly reproducible diagnostic breakpoint, (2) subdividing cytological HSIL into moderate and severe dysplasia or CIN 2 and 3 is not very reproducible, and (3) HPV cytopathic effect cannot be reliably separated from mild dysplasia or CIN 1 (M. Schiffman, written communication, 2001).

However, the 3-tiered CIN 1-2-3 designations may be helpful in managing some individual patients, in correlating cytopathologic and histopathologic findings, or in reporting cytology results outside the United States. Some members of the European cytopathology community in particular favor use of CIN terminology. As in previous versions of the Bethesda System, CIN or dysplasia terminology can be used, either as a substitute for SIL or as an additional descriptor.

Atypical Glandular Cells. The classification of glandular abnormalities has been significantly revised in the 2001 Bethesda System, reflecting a reappraisal of the strengths and weaknesses of cytology in assessing these findings.

The term “atypical glandular cells of undetermined significance” (AGUS) has been eliminated to avoid confusion with ASC-US. Glandular cell abnormalities are classified as “atypical endocervical, endometrial, or glandular cells.”

In the majority of cases, morphological features permit differentiation between atypical endometrial and en-

docervical cells.¹⁴ The management of patients with glandular abnormalities may vary significantly depending on cell type and justifies making this distinction when possible. The term “atypical epithelial cells” may be used for cases where a squamous vs glandular origin cannot be determined.

The finding of atypical glandular cells (AGC) is important clinically because the percentage of cases associated with underlying high-grade disease is higher than for ASC-US. On follow-up, high-grade lesions (either squamous or glandular) may be seen in 10% to 39% of such cases.¹⁵⁻¹⁷ Based on such data, the qualifier “favor reactive” was considered misleading and it has been eliminated: such cases are now included in the AGC category.

In the 1991 terminology, adenocarcinoma in situ (AIS) was included in “AGUS, probably neoplastic.” Since that time, studies have clearly documented predictive value and reproducibility of properly applied cytological criteria for this interpretation.¹⁸⁻²⁰ “Endocervical adenocarcinoma in situ” is therefore now a separate category. However, there is considerable morphological overlap between AIS and well-differentiated invasive endocervical adenocarcinoma; a percentage of cases interpreted as AIS will demonstrate invasion on histological evaluation.

For cases showing some features suggestive of, but not sufficient to reach an interpretation of AIS, an intermediate category of “atypical endocervical cells, favor neoplastic” conveys a significant level of concern. There is no basis for establishing a category of “endocervical glandular dysplasia” or “low grade glandular intraepithelial lesion.”²¹ A morphological spectrum of bona fide precursors of AIS has not been identified for endocervical glandular lesions.

Other. In the previous version of the Bethesda System, the finding of endometrial cells was reported only for postmenopausal women. However, in the 2001 Bethesda System, endometrial cells are noted if the woman is 40 years of age or older, regardless of the date of the last menstrual period, because

menstrual/menopausal status, exogenous hormone therapy, and other clinical risk factors are often unknown or unclear. Although usually benign in nature, identification of endometrial cells, particularly if not associated with menses or after menopause, may indicate risk for an endometrial abnormality.²²⁻²⁵ As noted above, this finding is categorized as “other.”

It is important to emphasize that cervical cytology is primarily a screening test for squamous epithelial lesions and squamous cancer. It is unreliable for the detection of endometrial lesions and should not be used to evaluate suspected endometrial abnormalities.

Automated Review and Ancillary Testing

“Automated review and ancillary testing” are elements of the report that are included as appropriate. For slides scanned by automated computer systems, the instrumentation used and the automated review result should be included in the cervical cytology report. If an ancillary molecular test has been performed, the type of assay should be specified in addition to the results. Ideally, cytology and ancillary testing results should be reported concurrently; however, this may not always be possible.

Educational Notes and Suggestions

Written comments regarding the validity and significance of a cytology result are the responsibility of the pathologist and are directed to the clinician who requested the test. The laboratory should avoid communicating results directly to the patient, as this may interfere with the patient-clinician relationship. Direct contact between the patient and the laboratory may be acceptable, however, if specifically requested by the clinician.

The use of educational notes or suggestions is optional. If used, the format and style may vary depending on the preferences of the laboratory and its clinicians. Nevertheless, any comments should be carefully and thoughtfully crafted, concise but not direc-

tive, consistent with clinical follow-up guidelines published by professional organizations, and phrased in the form of a suggestion. A qualifying phrase (eg, “as clinically indicated”) should generally be added since the pathologist may be unaware of other pertinent clinical information. One study has shown that including suggestions for further evaluation improves the likelihood that appropriate follow-up occurs.²⁶ Providing references for consensus clinical follow-up guidelines for abnormal cervical cytology results published by medical organizations (eg, American College of Obstetricians and Gynecologists, American Society for Colposcopy and Cervical Pathology) may also be helpful.²⁷

SUMMARY

The goal of the Bethesda System is to promote more effective communication of cervical cytology results from the laboratory to clinicians. The 2001 revision of the terminology was developed through a process designed to incorporate new scientific data and encourage input from a broad range of individuals involved in cervical cancer screening. Management guidelines for women with abnormal cytology results, based on the 2001 Bethesda System, have been developed at a consensus conference sponsored by the American Society for Colposcopy and Cervical Pathology.²⁸ Such collaborative and integrated development of reporting terminology and management guidelines should provide more uniform, evidence-based care of women with cervical abnormalities.

The Forum Group Members include the following: *Specimen Adequacy:* Diane D. Davey, MD, George Birdsong, MD, Henry W. Buck, MD, Teresa Darragh, MD, Paul Elgert, CT(ASCP), Michael Henry, MD, Heather Mitchell, MD, Suzanne Selvaggi, MD; *Benign Cellular Changes and Infections:* Nancy Young, MD, Marluce Bibbo, MD, Sally-Beth Buckner, CT(ASCP), Terence Colgan, MD, Dorothy Rosenthal, MD, Edward Wilkinson, MD; *ASCUS:* Mark Sherman, MD, Fadi Abdul-Karim, MD, Jonathan Berek, MD, Patricia Braly, MD, Robert Gay, CT(ASCP), Celeste Powers, MD, Mary Sidawy, MD, Sana Tabbara, MD; *AGUS:* David Wilbur, MD, David Chhieng, MD, J. Thomas Cox, MD, Jamie Covell, BS, CT(ASCP), Barbara Guidos, SCT(ASCP), Kenneth Lee, MD, Dina Mody, MD; *HPV Triage:* Stephen Raab, MD, Karen Allen, CT(ASCP), Christine Bergeron, MD, PhD, Diane Harper,

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