

# The Pap Test and Bethesda 2014

*“The reports of my demise have been greatly exaggerated.”  
(after a quotation from Mark Twain)*

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## Key Words

The Bethesda System · Bethesda atlas · Pap test ·  
Cervical cytology · Reporting

## Abstract

The history of ‘The Bethesda System’ for reporting cervical cytology goes back almost 3 decades. This terminology and the process that created it have had a profound impact on the practice of cervical cytology for laboratorians and clinicians alike. The Bethesda conferences and their ensuing output have also set the stage for standardization of terminology across multiple organ systems, including both cytology and histology, have initiated significant research in the biology and cost-effective management for human papillomavirus-associated anogenital lesions, and, finally, have fostered worldwide unification of clinical management for these lesions. Herein, we summarize the process and rationale by which updates were made to the terminology in 2014 and outline the contents of the new, third edition of the Bethesda atlas and corresponding website. © 2015 S. Karger AG, Basel

This article is jointly published in *Journal of the American Society of Cytopathology*, *Cancer Cytopathology*, *Journal of Lower Genital Tract Disease* and *Acta Cytologica* by the American Society of Cytopathology, the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the International Academy of Cytology. © 2015 American Cancer Society Inc., American Society of Cytopathology, American Society for Colposcopy and Cervical Pathology, and International Academy of Cytology.

## Introduction

One snowy weekend in December 1988, a small group of individuals with expertise in cytopathology, histopathology, and patient management met at the National Institutes of Health in Bethesda, Maryland [1]. This meeting, which became the first Bethesda workshop, was chaired by Robert Kurman and focused on addressing the issues related to the wide variability in reporting results of cervical cytology when cytologists used either the numeric ‘Pap Class’ system or the ‘dysplasia’ terminology. The objective was to establish terminology that would provide clear-cut thresholds for management and decrease interobserver variability. During the 2 days of that historic workshop, 3 fundamental principles emerged that have guided The Bethesda System (TBS) to this day:

1. Terminology must communicate clinically relevant information from the laboratory to the patient’s health care provider.
2. Terminology should be uniform and reasonably reproducible across different pathologists and laboratories and also flexible enough to be adapted in a wide variety of laboratory settings and geographic locations.
3. Terminology must reflect the most current understanding of cervical neoplasia.

On the basis of these principles, in 1988, the first iteration of TBS recommended a 2-tiered reporting system for squamous intraepithelial lesions (SILs): low-grade SIL (LSIL) and high-grade SIL (HSIL). This terminology reflected the up-to-date understanding of human papillo-

mavirus (HPV) biology – squamous epithelium is affected by the virus in essentially 2 ways: either as viral infection or as viral-associated precancer. In addition to the SIL terminology, TBS-1988 also incorporated a ‘statement of adequacy’ as an integral component of the report and, by extension, an important quality-assurance element [2].

After experience using TBS in clinical practice and further advances in scientific knowledge, subsequent Bethesda workshops were convened in 1991 and 2001. A major recommendation from the 1991 workshop was to develop criteria for TBS interpretive categories and diagnostic terms and for the determination of specimen adequacy. These deliberations and the codification of criteria led to the production of the first Bethesda atlas in 1994 [3]. After its publication, this monograph quickly became a worldwide reference for the practice of cervical cytology.

The next Bethesda workshop, held in 2001, was the first to use the Internet to provide the international cytopathology community an opportunity to offer input to the refinements proposed by the forum work groups. Over 2,000 Internet comments were considered before the meeting, which then brought together over 400 participants, including representatives from more than 2 dozen countries, to finalize the 2001 Bethesda System Terminology [4].

#### **Noteworthy Points from the 2001 Bethesda Update Included the Following**

1. The terms ‘interpretation’ or ‘result’ were recommended instead of ‘diagnosis’ in the heading of the cervical cytology report, because it was believed that cervical cytology should be viewed primarily as a ‘screening test, which in some instances may serve as a medical consultation by providing an interpretation that contributes to a diagnosis. The final diagnosis and management plan should integrate the cervical cytology with patient history, clinical findings, and results of other laboratory tests such as cervical biopsy’ [2, 4].

2. Although TBS was developed primarily for cervical cytology, specimens from other sites in the lower anogenital tract, such as the vagina and anus, could also be reported using this terminology.

3. Between 1991 and 2001, liquid-based cytology, automation, computer-assisted imaging, and HPV testing were introduced and increasingly utilized in laboratories that offered cervical cytology testing. The 2004 Bethesda atlas addressed all of these considerations. In

addition, to facilitate widespread implementation of TBS-2001 and to improve reproducibility, more detailed interpretive criteria, ample illustrations depicting mimics and pitfalls, histologic correlation, and sample reports were added [5].

4. After TBS-2001, but before publication of the corresponding atlas, a subset of atlas images were used to develop the web-based Bethesda Interobserver Reproducibility Study (BIRST), the objectives of which were: (i) to evaluate concordance among participants with varied training and experience, and (ii) to identify specific cytomorphologic features and cytologic categories that represent sources of poor interobserver agreement [6]. The results of that study highlighted important issues about the reproducibility of the various Bethesda categories, which has led to further progress in education and to the introduction of ancillary studies to improve the predictive value of the screening process.

5. In conjunction with the print atlas, an educational Bethesda website [7] was established that provides additional images beyond those available in the print atlas, images, histograms from the BIRST [6], and a self-evaluation test. This site has been extensively used – over 60,000 unique individuals from all over the world have taken the self-test alone.

By early 2003, 85.5% of laboratories in the United States had implemented Bethesda 2001 terminology, and the adoption of TBS in the international cytopathology community had produced a significant impact [8].

#### **Implementation of TBS Initiated Several Downstream Events That Significantly Influenced Cervical Cancer Screening and Management and Also Impacted Terminology Development for Other Areas in Cytopathology and Histopathology**

##### *Initiation of Research and Clinical Trials*

TBS played a vital role in facilitating research related to the biology of cervical cancer and exploring new approaches and strategies for patient management. The introduction of TBS terminology of ‘atypical squamous cells of undetermined significance’ (ASCUS) highlighted the inherent limitations of morphologic interpretation. Because ASCUS is the most common cytologic abnormality reported on Papanicolaou (Pap) tests, it accounts for over a million results annually in the United States and previously posed a significant clinical management problem, leading to billions of dollars in colposcopic follow-up and/or treatment of these women [1]. To deter-

mine the best course of management (immediate colposcopy, HPV triage, or conservative management) for equivocal and low-grade abnormalities, the US National Cancer Institute sponsored the ASCUS/LSIL Triage Study (ALTS), which began in 1997 [9]. The results from ALTS established high-risk HPV (hrHPV) testing as the most cost-effective triage test for ASCUS. This was endorsed as the preferred management option for the Bethesda category re-named as ASC-US, under the category of atypical squamous cells (ASC) in 2001 [10]. Additional assessment of the ALTS database resulted in numerous publications, which have provided a great deal of information related to cervical cancer, including the characteristics of cytology, colposcopy, the role of HPV testing, and the biology/management of HPV-related cervical lesions.

#### *Alignment of Management with Terminology*

TBS provided the framework necessary for the development of systematic, evidence-based cervical cancer screening and management guidelines. After the 2001 Bethesda conference, the American Society for Colposcopy and Cervical Pathology (ASCCP) held a consensus conference to tailor management strategies that conformed to the Bethesda reporting categories. This meeting was also a significant historic event because it was the first time that there was coordination of reporting terminology that correlated with both HPV biology and clinical management. The results of ALTS and other clinical research formed the basis for development of the 2001 clinical management algorithms – a process that involved dozens of organizations and professional societies, spearheaded by the ASCCP. With continued development of additional insight into HPV biology, results from subsequent clinical trials, and experience in the United States, these management guidelines were subsequently updated in 2006 and 2012 [11, 12].

#### *TBS as a Prototype for Standardized Reporting Terminology in Pathology*

On the basis of the key principles of TBS, standardized terminology systems have been developed for cytology of other body sites, including thyroid [13], pancreas [14], and, most recently, urine [15]. The 2-tiered terminology of LSIL and HSIL used in TBS is now also recommended by the World Health Organization, the ASCCP, and the College of American Pathologists for reporting histopathology of HPV-associated squamous lesions of the lower anogenital tract [16–19].

### **Bethesda 2014: Why?**

The past decade has witnessed several changes in the realm of cervical cancer screening, prevention, and management. These include the increased use of liquid-based preparations; the addition of co-testing (Pap and hrHPV testing) and, more recently, primary hrHPV testing as additional screening options; further insights into HPV biology; changes in histopathology terminology; approval and implementation of prophylactic HPV vaccines, and updated guidelines for cervical cancer screening and clinical management.

Over the past few years, evidence-based consensus guideline processes have incorporated the fundamental principles of balancing harms and benefits and providing equal management for equal risk [20]. Management guidelines for abnormal cervical cytology results were updated in 2006 and 2012, with increased incorporation of hrHPV and genotyping for triage and follow-up. When HPV testing is used alone for primary screening, cervical cytology has been proposed as a ‘reflex’ test or triage for non-16/18 HPV-positive screens. With increased uptake of HPV vaccination and its downstream effects of decreased prevalence of HPV16/18-associated lesions, cervical cytology will become even more challenging with respect to locator and interpretation skills because of the inherent loss of sensitivity when prevalence of the disease is low. On the basis of all of these changes, 2014 was an appropriate time for a review and update of the 2001 Bethesda System terminology, refinements of morphologic criteria, and incorporation of revisions and additional new information into a third edition of the Bethesda atlas for cervical cytology [21].

### **Bethesda 2014: Process**

Dr. Ritu Nayar, President of the American Society of Cytopathology in 2014, appointed a task force (see Appendix), chaired by Dr. David Wilbur (American Society of Cytopathology President in 2002), comprised of a relatively small group of cytopathologists, clinicians, and epidemiologists, to accomplish the 2014 update. Because minimal changes were anticipated to the terminology recommended by TBS-2001, no formal consensus meeting was held in association with this update. The task force was divided into 12 groups, each of which was responsible for 1 of 12 atlas chapters. The groups performed a literature review and proposed new and expanded content. The draft recommendations were shared with the

international cytopathology community during an open comment period from March to June of 2014 through a widely advertised, Internet-based bulletin board. In total, 2,454 responses were received from individuals in 59 countries and were compiled and reviewed by the chapter-based task force working groups. This process culminated in the refinement of positions and content, which were then incorporated into TBS-2014 (table 1) and into the third edition of the Bethesda atlas [21].

## Bethesda 2014: What Has Changed?

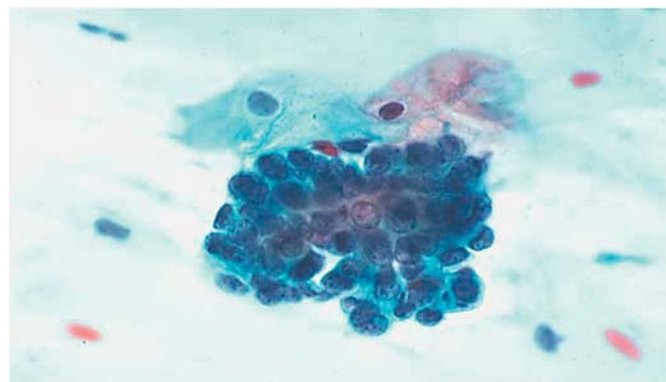
### *Bethesda Terminology Changes*

There were minimal changes relating to the terminology itself. The 2014 Bethesda terminology is summarized in table 1. Of note:

#### *Reporting of Benign-Appearing Endometrial Cells Is Now Recommended for Women Aged $\geq 45$ Years*

**Rationale:** Although exfoliated endometrial cells are a normal finding during menses and the proliferative phase of the menstrual cycle, in postmenopausal women, their presence is considered abnormal and raises the possibility of endometrial neoplasia (fig. 1). Thus, TBS-1988 recommended reporting 'cytologically benign-appearing' endometrial cells in postmenopausal women to alert clinicians to the possibility of an endometrial abnormality [2]. In 2001, because menopausal status is often unclear, inaccurate, or unknown to the laboratory, it was suggested that this reporting should be done in women aged  $\geq 40$  years to maximize the likelihood of including all postmenopausal women and that clinical correlation should be left to the ordering physician's discretion [4]. Evaluation of this TBS-2001 recommendation in clinical practice indicated that, although endometrial investigation increased, the predictive value for endometrial hyperplasia/carcinoma decreased significantly compared with the pre-TBS-2001 experience [21]. In the 2012 management guidelines, the ASCCP advised using histologic endometrial assessment only in postmenopausal women [12].

During the TBS-2014 update, after literature review and public comment consensus, it was decided that, to increase the predictive value of this category, cytologically 'benign-appearing' endometrial cells should be reported in women aged  $\geq 45$  years, and the suggested educational note should specify that endometrial evaluation be done only in postmenopausal women (table 1) [21].



**Fig. 1.** Exfoliated endometrial cells (conventional preparation) are shown. Cells are arranged in 3-dimensional clusters. Nuclei are small and are similar in size to an intermediate squamous cell nucleus. Nucleoli are inconspicuous. Cytoplasm is scant, and cell borders are indistinct (From: *The Bethesda System for Reporting Cervical Cytology*. Nayar R, Wilbur DC, (Eds), 3rd Edition, Springer, 2015.).

#### *No New Category Was Created for Squamous Lesions with LSIL and Few Cells Suggestive of Concurrent HSIL*

**Rationale:** Occasionally, a specimen is encountered with cytologic features that lie between LSIL and HSIL; however, attention to morphologic features usually supports classification as either LSIL or HSIL. In cases with unequivocal HSIL, the presence of concurrent LSIL is not necessary to make an interpretation of HSIL.

Since the publication of TBS-2001, it has been suggested that these intermediate morphologic patterns might be better designated with a diagnostic term other than LSIL or HSIL. Terms such as 'LSIL, cannot exclude HSIL' or 'LSIL-H' have been proposed. In preparation for the 2014 TBS update, opinions regarding this topic were openly solicited, and consensus was achieved that formal TBS nomenclature should be limited to the original LSIL and HSIL categories, maintaining the 2-tiered classification scheme. Adding terminology such as 'LSIL-H' would lead to a de facto 3-tiered system, essentially negating the beneficial aspects of the 2-tiered TBS nomenclature. Furthermore, current management guidelines all use LSIL and HSIL nomenclature without an intermediate category, and recent histopathology reporting recommendations also encourage reporting as LSIL or HSIL. Poor reproducibility and overuse of any new indeterminate cytology terminology would likely lead to confusion among clinicians and, possibly, inappropriate management.



**Table 1.** The 2014 Bethesda System

**SPECIMEN TYPE:**

*Indicate conventional smear (Pap smear) vs. liquid-based preparation vs. other*

**SPECIMEN ADEQUACY**

- ☐ Satisfactory for evaluation (*describe presence or absence of endocervical/transformation zone component and any other quality indicators, e.g., partially obscuring blood, inflammation, etc.*)
- ☐ Unsatisfactory for evaluation . . . (*specify reason*)
  - ☐ Specimen rejected/not processed (*specify reason*)
  - ☐ Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of (*specify reason*)

**GENERAL CATEGORIZATION (optional)**

- ☐ Negative for Intraepithelial Lesion or Malignancy
- ☐ Other: See Interpretation/Result (*e.g., endometrial cells in a woman  $\geq 45$  years of age*)
- ☐ Epithelial Cell Abnormality: See Interpretation/Result (*specify 'squamous' or 'glandular' as appropriate*)

**INTERPRETATION/RESULT**

**NEGATIVE FOR INTRAEPITHELIAL LESION OR MALIGNANCY**

*(When there is no cellular evidence of neoplasia, state this in the General Categorization above and/or in the Interpretation/Result section of the report--whether or not there are organisms or other non-neoplastic findings)*

**Non-Neoplastic Findings (optional to report)**

- ☐ Non-neoplastic cellular variations
  - ☐ Squamous metaplasia
  - ☐ Keratotic changes
  - ☐ Tubal metaplasia
  - ☐ Atrophy
  - ☐ Pregnancy-associated changes
- ☐ Reactive cellular changes associated with:
  - Inflammation (includes typical repair)
    - ☐ Lymphocytic (follicular) cervicitis
  - Radiation
  - Intrauterine contraceptive device (IUD)
- ☐ Glandular cells status post hysterectomy

**Organisms**

- ☐ *Trichomonas vaginalis*
- ☐ Fungal organisms morphologically consistent with *Candida* spp.
- ☐ Shift in flora suggestive of bacterial vaginosis
- ☐ Bacteria morphologically consistent with *Actinomyces* spp.
- ☐ Cellular changes consistent with herpes simplex virus
- ☐ Cellular changes consistent with cytomegalovirus

**OTHER**

- Endometrial cells (*in a woman  $\geq 45$  years of age*)  
(*Specify if "negative for squamous intraepithelial lesion"*)

**Table 1** (continued)

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**EPITHELIAL CELL ABNORMALITIES**

**SQUAMOUS CELL**

- Atypical squamous cells
  - of undetermined significance (ASC-US)
  - cannot exclude HSIL (ASC-H)
- Low-grade squamous intraepithelial lesion (LSIL)  
(*encompassing: HPV/mild dysplasia/CIN 1*)
- High-grade squamous intraepithelial lesion (HSIL)  
(*encompassing: moderate and severe dysplasia, CIS; CIN 2 and CIN 3*)
  - with features suspicious for invasion (*if invasion is suspected*)
- Squamous cell carcinoma

**GLANDULAR CELL**

- Atypical
  - endocervical cells (NOS *or specify in comments*)
  - endometrial cells (NOS *or specify in comments*)
  - glandular cells (NOS *or specify in comments*)
- Atypical
  - endocervical cells, favor neoplastic
  - glandular cells, favor neoplastic
- Endocervical adenocarcinoma in situ
- Adenocarcinoma
  - endocervical
  - endometrial
  - extrauterine
  - not otherwise specified (NOS)

**OTHER MALIGNANT NEOPLASMS: (*specify*)**

**ADJUNCTIVE TESTING**

*Provide a brief description of the test method(s) and report the result so that it is easily understood by the clinician.*

**COMPUTER-ASSISTED INTERPRETATION OF CERVICAL CYTOLOGY**

*If case examined by an automated device, specify device and result.*

**EDUCATIONAL NOTES AND COMMENTS APPENDED TO CYTOLOGY REPORTS (*optional*)**

*Suggestions should be concise and consistent with clinical follow-up guidelines published by professional organizations (references to relevant publications may be included).*

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For occasional cases in which it is not possible to categorize an SIL as either low-grade or high-grade, a comment explaining the nature of the uncertainty may be appropriate. Alternatively, an interpretation of ASC cannot rule out HSIL (ASC-H) may be made in addition to an LSIL interpretation. This would indicate that definite

LSIL is present as well as some cells that suggest the possibility of HSIL. In general, follow-up guidelines for these interpretations are for colposcopy and biopsy; however, in patients (such as young women) who have samples for which the guidelines differ between LSIL and ASC-H, the addition of the ASC-H interpretation should lead to col-

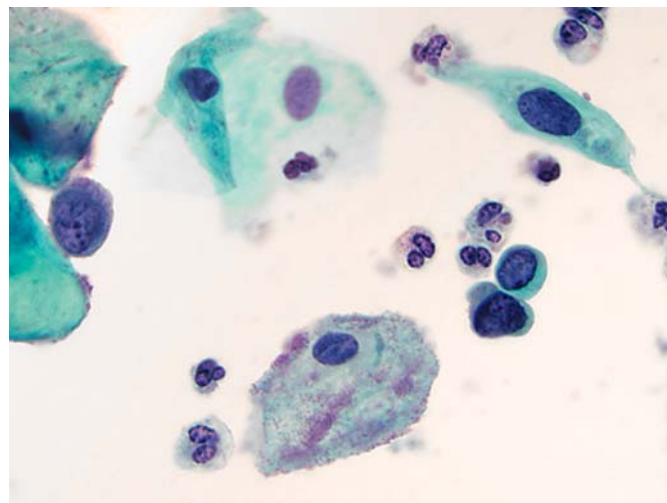
poscopic evaluation. Intermediate interpretations should comprise only a small minority of cases in any laboratory, because classification into either LSIL or HSIL is possible in most instances after a careful overall evaluation of the cellular morphology (fig. 2).

### Third Edition of the Bethesda Atlas

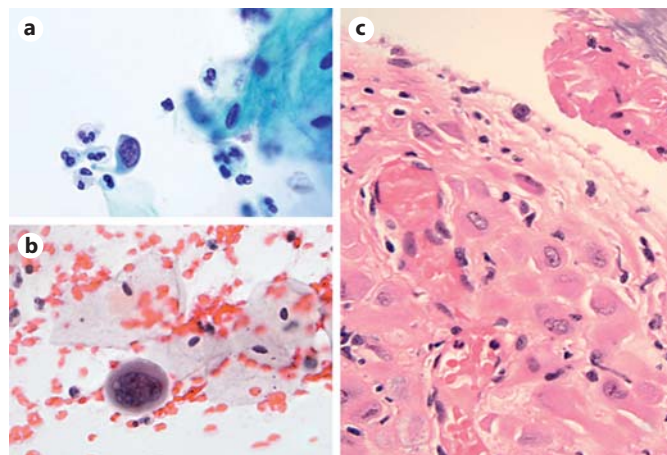
Providing an updated atlas with retention of the popular features of the 2004 edition and additional images and content, reflecting continued experience and changes in practice, was the main motivation for the 2014 update [21]. The content, both text and illustrations, have been increased by approximately 66% compared with the second edition [5]. Among the 12 chapters, 6 correspond to the major Bethesda interpretive categories, and the remaining chapters are dedicated to other malignant neoplasms, anal cytology, reporting of adjunctive testing, computer-assisted screening, educational notes, and a new chapter on cervical cancer risk assessment [21].

Each chapter has been extensively updated, and the format includes: (1) background and introduction, including basic cell biology; (2) description of definitions, cytologic criteria, explanatory notes covering difficult morphologic patterns, mimics of epithelial lesions, and current clinical management guidelines for reporting in the 6 interpretation category-based chapters; (3) sample reports, and (4) selected key references. The cytomorphologic criteria are described in general terms, followed by any significant differences related to specific preparation types where relevant, and tables have been added to compare and contrast criteria. *Note that TBS does not endorse any particular methodology or manufacturer(s) for specimen collection, computer-assisted screening, adjunctive HPV or other testing.*

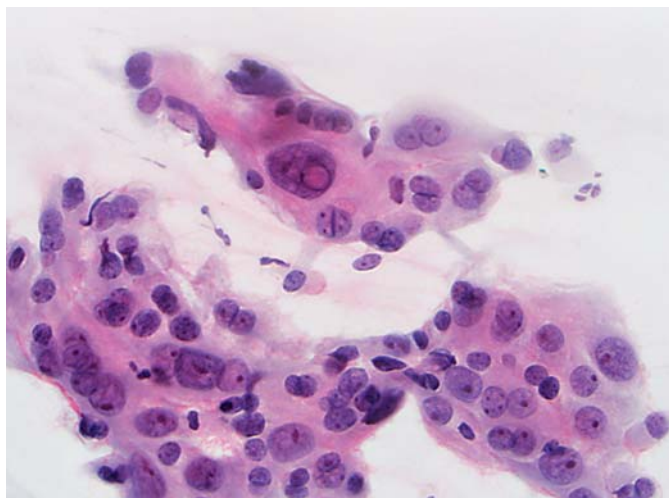
More than 1,000 images were evaluated for the third edition of the Bethesda atlas, including all 186 images from the second edition. Final selections were made after a multistage review process: first by the dedicated chapter group and, second, by a subgroup of the Bethesda 2014 Task Force. The 370 atlas illustrations, complemented by robust legends, illustrate a spectrum of morphologic variations observed on both conventional smears and liquid-based cytologic preparations; 58% of the images are new, and 42% are from the second edition; 40% are from conventional preparations, and 60% are from liquid-based preparations. Some images represent classic examples of an entity, whereas others were selected to illustrate interpretive dilemmas or 'borderline' morphologic features



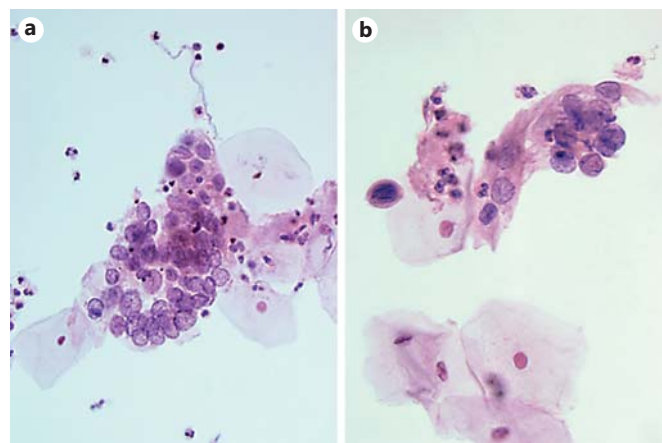
**Fig. 2.** HSIL is shown (liquid-based preparation, ThinPrep). In this specimen, diagnostic HSIL cells are present. Even if these cells are observed in the background of a majority of low-grade squamous intraepithelial lesion cells elsewhere on the slide, the final interpretation should be HSIL (From: *The Bethesda System for Reporting Cervical Cytology*. Nayar R, Wilbur DC, (Eds), 3rd Edition, Springer, 2015.).



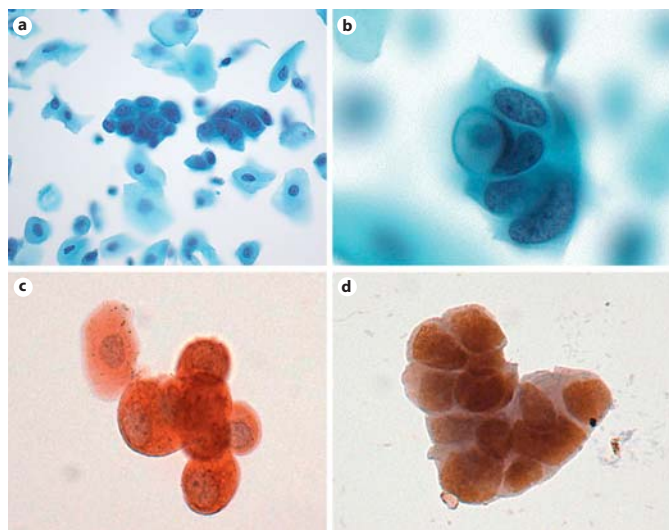
**Fig. 3.** This sample from a young woman in the late second trimester of pregnancy was interpreted as negative for intraepithelial lesion or malignancy (NILM). **a, b** These single cells (liquid-based preparation, ThinPrep) with an increased nuclear to cytoplasmic ratio and nuclear hyperchromasia are worrisome for high-grade squamous intraepithelial lesion. Features suggesting the true stromal decidual nature of the cells include the smudgy chromatin and the presence of a nucleolus. **c** Similar cells are observed in a follow-up cervical biopsy (HE stain) (From: *The Bethesda System for Reporting Cervical Cytology*. Nayar R, Wilbur DC, (Eds), 3rd Edition, Springer, 2015.).



**Fig. 4.** ASC-US atypical repair (conventional preparation). In this image, cells are arranged in a 2-dimensional sheet with abundant cytoplasm showing a 'pulled-out' or streaming effect. Nuclei exhibit pleomorphism of size and shape, and some cells have multiple nuclei. Most nuclei have prominent nucleoli. These changes, although indicative of a reparative reaction, may be classified as ASC-US because of the nuclear pleomorphism noted. In favor of a reactive process is the generally fine granularity of the chromatin pattern (From: *The Bethesda System for Reporting Cervical Cytology*. Nayar R, Wilbur DC, (Eds), 3rd Edition, Springer, 2015.).



**Fig. 5.** This HSIL (liquid-based preparation, ThinPrep) is markedly hypochromatic, but a diligent search may reveal more classic cells elsewhere on the same slide. **a** Note the syncytial arrangement and nuclear grooves. **b** Abnormal, naked nuclei and a single, hyperchromatic HSIL cell with a high nuclear to cytoplasmic ratio are shown (From: *The Bethesda System for Reporting Cervical Cytology*. Nayar R, Wilbur DC, (Eds), 3rd Edition, Springer, 2015.).



**Fig. 6.** These are images of lobular breast carcinoma (liquid-based preparation, SurePath). Lobular breast cancer presenting in an atrophic background pattern can be challenging. Small clusters of cells (**a**) and individual cells (**b**) with mucin vacuoles contrast with a background of parabasal cells. Confirmation with immunostains can be helpful, including gross cystic disease fluid protein 15 (**c**) and estrogen receptor immunocytochemistry (**d**) (From: *The Bethesda System for Reporting Cervical Cytology*. Nayar R, Wilbur DC, (Eds), 3rd Edition, Springer, 2015.).

that may not be interpreted in the same way by all cytologists. Unique to this edition is the substantially larger number of composite images for a side-by-side illustration of mimics and cytologic-histologic correlations (fig. 3–6). A brief summary of the atlas chapter updates and their rationale is provided below.

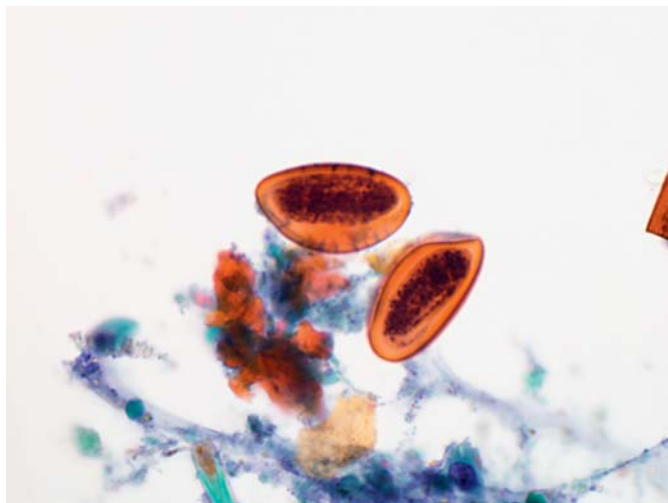
#### Chapter 1: Adequacy

Evaluation of specimen adequacy is considered by many to be the single most important quality assurance component of the Bethesda system. Data and clinical experience regarding specimen adequacy since 2001 were reviewed, leading to the inclusion of additional guidance for special situations, such as assessing cellularity in specimens obtained from postradiation patients, interfering substances (e.g. lubricant, blood), and the effects of adequacy on HPV testing.

#### Chapter 2: Non-Neoplastic Changes

An expanded variety of 'normal' findings as well as non-neoplastic mimics of classic epithelial abnormalities are included, providing a more complete representation of the morphologic variations that can be encountered in cervical cytology preparations (fig. 3).





**Fig. 7.** Pinworm eggs are shown (anal cytology; liquid-based preparation, ThinPrep) (From: *The Bethesda System for Reporting Cervical Cytology*. Nayar R, Wilbur DC, (Eds), 3rd Edition, Springer, 2015.).

### Chapter 3: Endometrial Cells

The age for reporting of ‘cytologically benign appearing’ endometrial cells has been increased to women aged ≥45 years (the rationale for this is presented above).

### Chapter 4: Atypical Squamous Cells

The category of ASC is by far the most commonly reported abnormal cervical cytology interpretation. ASC continues to be defined as the general category with sub-categorization as ASC-US and ASC-H. The dichotomous reporting for ASC mirrors that observed for LSIL and HSIL. *It must be emphasized that the ASC category was developed to designate the interpretation of an entire specimen, not individual cells, because atypia in individual cells remains a highly subjective and, hence, variable interpretation.* Common patterns interpreted as ASC-US and ASC-H are reviewed and guidance provided to enable laboratories to use this reporting category along with HPV test results to monitor quality and consistency among practitioners and laboratories (fig. 4).

### Chapter 5: Squamous Epithelial Cell Abnormalities

The dichotomous reporting terminology for LSIL and HSIL is maintained and reflects our current understanding of the natural history of HPV-related infections – low-grade changes represent productive, largely transient HPV infection, and high-grade morphology represents a precancerous lesion. On the basis of our understanding

of HPV biology and the behavior of pre-invasive, HPV-associated squamous lesions, the focus of cervical cancer screening is primarily aimed at detection and treatment of HSIL. Thus, this chapter has been substantially expanded to include problematic patterns and mimics that may lead to locator and/or interpretation errors of non-neoplastic changes as HSIL/ASC-H and vice versa (fig. 3, 5). A new category was *not* created for squamous lesions with LSIL that also contain a few cells suggestive of concurrent HSIL, the rationale for which is described above.

### Chapter 6: Glandular Epithelial Cell Abnormalities

The Pap test was not designed to screen for glandular lesions of the cervix, and these abnormalities are more difficult to sample and interpret compared to their squamous counterparts. However, because of improvement in sampling devices and the increase in endocervical adenocarcinoma relative to squamous cell carcinoma over the past 2 decades, cytologists currently encounter more challenging presentations of glandular lesions and their mimics in cervical cytology specimens. This update includes many more images of glandular lesions and differential diagnostic considerations. Tables illustrating differences in criteria are included for quick reference.

### Chapter 7: Other Malignant Neoplasms

New published literature since TBS-2001 has described malignant neoplasms, other than the usual variants of primary squamous carcinomas and endocervical adenocarcinomas, that infrequently involve the uterine cervix but that nevertheless may be observed in cervical cytologic preparations (fig. 6). These may create interpretation challenges and result in diagnostic pitfalls. Most often, these tumors are special variants of cervical carcinoma or uncommon primaries arising in the uterine corpus or adnexa that appear in the cervical cytology specimens either as exfoliated cells or through direct sampling of tumors. Increased numbers of such cases are now illustrated.

### Chapter 8: Anal Cytology

Although anal cancer is relatively uncommon in the general population, rates have been increasing over the last several decades, especially in high-risk groups. Anal cytology was first included in the 2001 Bethesda atlas and has gained acceptance as a tool for anal cancer screening in conjunction with high-resolution anoscopy and biopsy – in a role similar to that of the Pap test. This edition further elaborates on new epidemiologic literature and defines high-risk populations. Sampling devices used to collect anal cytology specimens, criteria for adequacy,

and the role of cytohistologic/high-resolution anoscopy correlation data are reviewed. Additional images of carcinoma, organisms, and mimickers of squamous lesions are included (fig. 7).

#### Chapter 9: Adjunctive Testing

Reporting of the results from ancillary studies has evolved since the second edition, and this chapter updates reporting schemes. Data concerning use and reporting for the current HPV testing schemes and adjunctive immunocytochemistry procedures (e.g. p16) are included.

#### Chapter 10: Computer-Assisted Interpretation

Several new US Food and Drug Administration approvals in the field of automated cervical cytology screening have occurred in the past decade. These have included the so-called 'location-guided screening' devices that identify areas at highest risk for containing potential abnormalities – essentially providing a prescreened slide. The third edition provides an overview of the currently used systems and updates recommendations, which now include the reporting items for 'location-guided screening' devices in addition to those covered previously.

#### Chapter 11: Educational Notes and Comments

One of the guiding principles of TBS has always been to improve communication from the laboratory provider to the physician caring for the patient. It is the responsibility of both laboratorians and clinicians to stay current with recent developments and communicate these to each other. The use of written recommendations and/or comments in cervical cytology reports is optional; and, when included in the cytology report, they must be worded carefully and relay clear, concise, current, evidence-based information. In the second edition of the Bethesda atlas, it was recommended that such comments be directed to the clinician and that the laboratorian/laboratory not communicate directly with the patient unless specifically instructed to do so. In the United States, as of 2014, there are changes to the rules regarding patient access to test reports. In addition, standardization of reports to facilitate widespread electronic health record implementation has been encouraged. These changes may have further implications for the use of recommendations in pathology reports, and a relevant discussion is now included.

#### Chapter 12: Risk Assessment in Cervical Cancer

This new chapter is an important addition to the third atlas, because it is key to understanding how the results of various screening and triage test combinations relate to

the patient's risk for cervical cancer [20]. The concept of 'equal management for equal risk', along with balancing benefits and harms of screening, formed the basis of the 2012 management guidelines for abnormal cervical cancer screening tests and cancer precursors [12].

#### *Bethesda Interobserver Reproducibility Study (BIRST-II)*

Although knowledge of normal morphology, its variations, and epithelial abnormalities is essential, some degree of interobserver and interlaboratory variability in cervical cytology and histology interpretation will always remain a reality [6, 22]. In an effort to build on the information gathered from our experience with the BIRST project in 2003 [6], 85 images from the third atlas were posted as 'unknowns' on a website that was open to the international cytopathology community. Data from this effort, which is currently ongoing, will provide a realistic gauge of interpretive reproducibility across a wide (and defined) demographic. The results of this exercise will be posted during spring of 2015 on the American Society of Cytopathology website [23] and will be discussed in a subsequent publication.

#### *Bethesda 2014 Web Atlas*

An accompanying Bethesda website resource is being developed under the direction of Dr. Daniel Kurtycz and Dr. Paul Staats and with the help of a Bethesda Website Task Force (see Appendix). In addition to all of the images from the third edition of the atlas, this website will contain many other examples of presentations and entities that could not be provided in the print atlas. A variety of search options will be provided, and the results of the reproducibility study (BIRST-II) and accompanying histograms will be posted on this site. The group will also explore new avenues for delivery of the content that has been assembled during this update process. For further information on the Bethesda web atlas, please visit the educational resources page on the American Society of Cytopathology website.

## Conclusions

Given all the recent press about new methods of cervical cancer screening and the lack of sensitivity of the Pap test, some may question the significance of a new edition of the Bethesda atlas. Before exaggerating the demise of the Pap test, it must be remembered that it still has significant utility worldwide. Because of its greater specificity compared with HPV testing, the Pap test will have importance

as a diagnostic triage tool after a positive HPV screening test. In locales where HPV testing is not available or reimbursed, regular Pap testing will remain the screening method of choice. An updated and enhanced Bethesda atlas will continue to serve its current purpose – that of being an inexpensive, portable, single-volume resource that will be widely available internationally. Compared with the second edition, the new atlas contains a greater discussion of HPV biology and pathogenesis, includes all current recommendations for management, and has a more comprehensive group of illustrations that contains, in addition to the prior version's classic examples, a robust content of look-alikes and equivocal presentations. An increased number of recommended report formats and a comprehensive reference list have also been included. Overall, this makes the third edition a greatly enhanced resource.

As in previous editions, the current editors and authors have committed to making the third edition affordable and, hence, widely accessible to all, including practitioners in low-resource environments. No honoraria or royalties will be accepted by the editors/authors, and the edition will remain a graphically high-quality, paperbound monograph. The publisher, Springer, will also make the corresponding electronic version (ebook) available online.

## Appendix

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## Acknowledgments

On behalf of the American Society of Cytopathology, we thank Dr. Diane Solomon and Dr. Robert Kurman for their pioneering vision in initiating and organizing the implementation of The Bethesda System, the 2014 Bethesda Task Force members, the contributors of the first and second editions of the Bethesda atlas, and all of the other dedicated cytopathologists, cytotechnologists, and clinical colleagues who have volunteered to contribute to this effort over the past quarter of a century [3–5, 21].

## Disclosure Statement

Dr. Nayar (Immediate Past President, American Society of Cytopathology in 2013–14). Dr. Wilbur (Past President, American Society of Cytopathology, 2002–2003).

There was no funding support for The Bethesda 2014 Atlas Update Project.

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