

Pap test results

Responding to Bethesda system reports

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ABSTRACT

OBJECTIVE To review the adequacy and diagnostic categories of the Bethesda system for reporting Pap test results (cervicovaginal cytology) and summarize management options.

QUALITY OF EVIDENCE The latest research evidence and guidelines from both international and Canadian sources are reviewed. With a few exceptions, good evidence supports particular management approaches for each adequacy statement and diagnostic category.

MAIN MESSAGE Women with unsatisfactory Pap smears should be re-examined and retested. Women with satisfactory smears and a diagnosis of “within normal limits” (WNL) or “benign cellular changes” (BCC) should be retested only at recommended screening intervals. Women with “satisfactory but limited by...” results and a diagnosis of WNL or BCC should have individualized follow up. Women with diagnoses of high-grade squamous intraepithelial lesions, atypical glandular cells of uncertain significance, or malignancy should have further investigation (colposcopy). Optimal management of asymptomatic women with normal cervixes and reports of atypical squamous cells of uncertain significance or low-grade squamous intraepithelial lesions is still controversial.

CONCLUSION Management of women following Pap tests is determined by both the adequacy of the test and diagnoses based on the results.

RÉSUMÉ

OBJECTIF Passer en revue la conformité et les catégories de diagnostic du système Bethesda pour présenter les comptes-rendus de résultats de frottis vaginaux (cytologie cervicovaginale) et faire la synthèse des options de prise en charge.

QUALITÉ DES DONNÉES Les données probantes de recherche et les lignes directrices les plus récentes de sources canadiennes et internationales ont fait l'objet d'une étude. À quelques exceptions près, de solides données probantes privilégient certaines approches particulières de prise en charge pour chaque énoncé de conformité et catégorie de diagnostic.

PRINCIPAL MESSAGE Les femmes dont les résultats du test de Papanicolaou sont non conformes devraient subir à nouveau un examen et une épreuve. Celles dont les résultats sont conformes et dont le diagnostic est « dans les limites normales » ou présentant des « altérations cellulaires bénignes » ne devraient subir le test à nouveau qu'après l'intervalle recommandé pour le dépistage. Celles qui ont des résultats « conformes mais limités par... » et un diagnostic soit dans les limites normales ou avec altérations cellulaires bénignes devraient faire l'objet d'un suivi individualisé. Les femmes ayant reçu un diagnostic de lésions intra-épithéliales malpighiennes de haut grade, de cellules glandulaires atypiques à caractère significatif indéterminé ou de néoplasmes malins devraient subir une investigation plus approfondie (colposcopie). La prise en charge optimale des femmes asymptomatiques avec un col normal mais des rapports de cellules malpighiennes atypiques ou de lésions intra-épithéliales malpighiennes de bas grade reste un sujet de controverse.

CONCLUSION La prise en charge des femmes à la suite d'un test de Papanicolaou est déterminée par la conformité du test et les diagnostics fondés sur les résultats.

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Cet article a fait l'objet d'une évaluation externe.

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Few preventive maneuvers offer as much benefit to women as exfoliative cervico-vaginal cytology (Papanicolaou smear). To reap this benefit, however, the results of every Pap test should lead to an appropriate response.

For many years, most Canadian laboratories reported Pap test results using squamous dysplasia (Walton) terminology.^{1,2} Some of the important cyto-diagnostic categories of this terminology, however, could not be consistently and precisely used, and others were not consistent with current knowledge concerning the pathogenesis of cervical preneoplasia. For example, distinguishing condylomatous effects from mild squamous dysplasia is neither feasible nor scientifically sound.

The Bethesda system for reporting gynecologic cytology was developed during a workshop sponsored by the National Cancer Institute in the United States. It was developed to promote standardization of Pap test reporting and to bring terminology in line with current pathogenic concepts.³ Canadian laboratories and programs are more and more frequently using Bethesda terminology for reporting Pap test results.⁴ This article reviews the adequacy statement and diagnostic categories of the Bethesda system and presents guidelines for optimal management.

Pap test

Invasive cervical carcinoma is usually preceded by preinvasive intraepithelial abnormalities. The primary objective of Pap tests is to detect these abnormalities in the uterine cervical transformation zone. The lesions are not detectable by unaided visual examination. Treating the lesions will usually prevent progression to invasive carcinoma.

Even though suboptimal screening is commonly found in the history of women who have developed cervical cancer, inappropriate or no management of women with abnormal Pap test results remains an important cause of failure of Pap screening programs.⁵⁻⁹ Fifteen percent or more of Canadian women who have developed invasive cervical carcinoma while participating in screening programs have had abnormal test results that might have been managed outside conventional protocols.⁵⁻⁹

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The Pap test continues to be important despite advances in our understanding of the pathogenesis of cervical cancer. Infection with human *Papillomavirus* (HPV) is regarded as a necessary, but not sufficient, cause of carcinoma of the uterine cervix.^{10,11} Persistent infection with oncogenic HPV appears to be the crucial factor associated with development of cervical carcinoma.¹² Oncogenic HPV is found in virtually all high-grade squamous intraepithelial lesions (HSIL) and carcinomas. Early age of first intercourse and multiple sexual partners, the well-known predisposing risk factors for cervical carcinoma, increase the likelihood of acquiring oncogenic HPV infection.

In combination with other factors, such as smoking, persistent HPV infection leads to preinvasive epithelial abnormalities and later invasive carcinoma. Vaccines against HPV are currently under development and are as yet unproven.^{11,13} Screening asymptomatic women for HPV is not recommended as part of a periodic health examination.¹⁴

Pap tests, therefore, are likely to remain the main screening method for cervical neoplastic disease for some time. They are most often done by family physicians or other primary caregivers who are then responsible for further management. Squamous intraepithelial lesions are most commonly detected cytologically in women younger than 40.¹³ Proper management of women with abnormal or inadequate Pap test results will validate screening programs and help avoid potential physical and psychological damage.¹⁵

Clinical management requires a clear understanding of Pap test reporting terminology. If Pap test results are reported using the Bethesda system for cervicovaginal cytology (**Table 1**^{1,16}), the definition and management options for each of the adequacy statements and diagnostic categories must be understood.

Quality of evidence

Many clinical and laboratory studies focus on management of women with abnormal Pap test results, and numerous consensus and recommended practice guidelines and statements have been issued by Canadian, American, and other international organizations. Relevant Canadian sources include statements from the Task Force on the Periodic Health Examination and the Cervical Cancer Prevention Network, as well as consensus statements by medical specialty groups. This article appraises statements from these sources in light of recent Canadian studies and synthesizes their recommendations. Pertinent recent landmark clinical studies, identified through a MEDLINE search from January 1997 to March 2000, are cited.

Adequacy of smears

In contrast to some other Pap test classification systems, the Bethesda system classifies all Pap test results with respect to adequacy (Table 1^{1,16}). Smears that are markedly paucicellular, poorly preserved, or obscured by debris or inflammatory exudate are labeled unsatisfactory for evaluation. A Pap test should be repeated if a specimen is reported unsatisfactory unless a gross abnormality in the cervix indicates re-examination and biopsy.

Satisfactory Pap smears show an adequate number of squamous epithelial cells and a representation of the endocervical or transformation zone component. Follow up of women with satisfactory smears is determined solely by the cytodiagnosis.

Pap smears partially obscured by blood, inflammatory exudate, smear thickness, or other factors and lacking material from the endocervical or transformation zone are reported as "satisfactory for evaluation but limited by...." In general, management of women with these results is determined by the clinical situation and their history of Pap test results.¹⁷ If a woman's previous results have been negative, her cervix appears normal, and she has no symptoms, repeat testing should be done at recommended screening intervals.¹⁸ Otherwise, women with these results should be retested only if they have had positive Pap test results in the past. As women age or if they have had ablative or surgical treatment, the transformation zone moves upward into the endocervical canal, and Pap test results will often be reported as satisfactory for evaluation but limited by....

Diagnostic categories

Normal results. Results that show no notable epithelial abnormalities are labeled "within normal limits" (WNL) in the Bethesda system. Previously, they would have been labeled "no abnormal cells" (or class 1 in the Papanicolaou Class System).

Results labeled "benign cellular changes" (BCC) indicate that cytologic changes secondary to inflammation are apparent. In some cases, a causative organism, such as *Candida*, *Trichomonas*, or herpes, is detected and reported as well. Treatment of these infections might be warranted, depending on the clinical situation.

Results reported as either WNL or BCC are considered negative, and women with such results are highly unlikely to harbour precancerous cervical lesions. False-negative Pap test results do occur but, if a woman has a history of negative results, the already low likelihood of an undetected lesion decreases even further.

Table 1. Equivalency of terminology used to report Pap test results

BETHESDA SYSTEM ¹⁶	MODIFIED WALTON SYSTEM/CIN ¹
ADEQUACY	
<ul style="list-style-type: none"> Satisfactory for evaluation Satisfactory for evaluation but limited by: state reason Unsatisfactory 	<ul style="list-style-type: none"> Unsatisfactory
DIAGNOSTIC CATEGORY	
<ul style="list-style-type: none"> Within normal limits (WNL) Benign cellular changes (BCC) Specific types: <i>Trichomonas vaginalis</i>, <i>Candida</i> species, herpes simplex, radiation Atypical squamous cells of undetermined significance (ASCUS) Atypical glandular cells of undetermined significance (AGUS) Low-grade squamous intraepithelial lesion (LSIL) High-grade squamous intraepithelial lesion (HSIL) Squamous cell carcinoma Malignant cells present consistent with adenocarcinoma Other 	<ul style="list-style-type: none"> No abnormal cells Abnormal cells consistent with benign atypia: <i>Trichomonas</i>, yeast, viral (herpes type), inflammatory, and irradiation effects Other Atypical metaplasia Atypical parakeratosis Other Atypical glandular cells Abnormal cells consistent with HPV effect Mild squamous dysplasia CIN 1 Moderate squamous dysplasia CIN 2 Severe squamous dysplasia CIN 3 Consistent with adenocarcinoma in situ Consistent with invasive squamous cell carcinoma Consistent with adenocarcinoma Abnormal cells not otherwise specified

CIN—cervical intraepithelial neoplasia,
HPV—human Papillomavirus.

There is widespread agreement that asymptomatic women with either WNL or BCC results, normal-appearing cervixes, and no history of recent abnormal Pap test results should return for further screening only at recommended intervals (Table 2).⁴ Since most screening Pap test results (90%) are negative, most women tested will follow this route. Recommendations on screening intervals vary from annual to biennial or even longer. The screening interval, however, should not be lengthened beyond 1 year unless both a Pap test registry and laboratory quality assurance programs are in place.² More frequent cervicovaginal screening with Pap tests has been suggested for women with human

Table 2. Management guidelines for Pap test results reported using the Bethesda system

CATEGORY	MANAGEMENT
ADEQUACY	
<ul style="list-style-type: none"> Satisfactory for evaluation Satisfactory for evaluation but limited by: state reason Unsatisfactory 	<ul style="list-style-type: none"> According to cytodiagnosis According to Pap test history and clinical situation Repeat test in 6-8 weeks unless cervix abnormal
DIAGNOSTIC CATEGORY	
<ul style="list-style-type: none"> Within normal limits (WNL) and benign cellular changes (BCC) Atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesion (LSIL)* High-grade squamous intraepithelial lesion (HSIL), atypical glandular cells of undetermined significance (AGUS), and malignancies 	<ul style="list-style-type: none"> For asymptomatic women with normal cervixes, repeat test as per screening recommendations (manage specific infections as required) Repeat Pap test or recommend colposcopic assessment Colposcopic assessment or biopsy of visible lesions

*See comments in text on role of human Papillomavirus testing.

immunovirus infection, but it is not clear whether such increased surveillance of HIV-infected women is effective.¹⁹

Serious abnormalities. At the opposite end of the Pap test spectrum are results reported as HSIL. This category includes conditions previously labeled moderate-to-severe squamous dysplasia and squamous carcinoma in situ and cervical intraepithelial neoplasia (CIN) 2 to 3. In screened populations, HSIL results are uncommon (<0.5% of all results). Most women who have reports of HSIL have these results confirmed by colposcopic biopsy.²⁰

The Pap test has high positive predictive value. The proportion of women with HSIL results who subsequently have these results proven by biopsy can be used as a performance standard or benchmark for laboratory practice. In Australia, for example, it is expected that no less than 65% of women with Pap test results showing HSIL will subsequently be shown to have histologically proven HSIL; the remainder will show low-grade squamous intraepithelial lesions (LSIL) or be negative.²¹

Left untreated, many HSILs progress to invasive carcinoma; some women with HSIL results, in fact,

already show invasive carcinoma on complete investigation. Good evidence and consensus opinion indicate that women with HSIL (or invasive carcinoma) must be referred for colposcopic assessment.^{1,2,10,22} Occasionally, marked atrophy of the squamous epithelial cells, cellular repair, and stromal or endometrial cells are responsible for a mistaken diagnosis of HSIL (ie, false-positive Pap test), and ensuing colposcopy results will be negative. Concluding that a Pap test result is false-positive, however, should be done only after complete and exhaustive colposcopic evaluation.

Pap test results that were previously classified as mild squamous dysplasia, condylomatous effects, or CIN 1 are labeled LSIL in the Bethesda system (Table 1). In a screened population, about 1% to 3% of all Pap test results are reported as LSIL. Colposcopic findings of women with previous LSIL results vary much more than those for women with HSIL findings. Colposcopy, and biopsy in some cases, can reveal LSIL; sometimes HSIL is identified.¹⁰ Some women appear to have no lesions despite a history of LSIL findings on Pap smear and thorough investigation, possibly because of spontaneous resolution of HPV infection.²³ Presence of invasive carcinoma following LSIL findings is extremely uncommon.

Given the variety of colposcopic outcomes, it is unsurprising to find that no uniform recommendations for management of women with LSIL findings exist. Referral for colposcopy has been advocated as the safest and most cost-effective course because it leads to definitive diagnosis and treatment, if needed. An alternative, particularly for compliant patients, is to repeat Pap tests at 6-month intervals for up to 2 years. Referral for colposcopy would be necessary only if an intervening HSIL is detected or if the LSIL persists at the end of 2 years.^{1,2,10,24} This course avoids unnecessary investigation of women whose LSILs spontaneously regress and avoids repeat visits and Pap tests for all patients.

The proportion of LSILs that spontaneously regress during cytologic surveillance is still unclear. One study reported 30%,²⁵ another 62%.²⁶ Noncompliant patients can escape proper follow up and present later with progressed, undetected HSIL or even invasive carcinoma. Initially, researchers hoped that adjunctive oncogenic HPV testing of women with LSIL findings on Pap test would identify women with true HSIL. We now know that the high prevalence of oncogenic HPV DNA in women with LSIL findings limits the usefulness of HPV testing for clinical management decisions.²⁷

Uncertain findings. Results of some Pap tests show abnormalities that cannot be definitively identified within any of the above categories because the abnormal cells

are either poorly visualized or few in number. In these cases, cells are labeled "atypical squamous cells of undetermined significance" (ASCUS), if considered squamous in type, or "atypical glandular cells of undetermined significance" (AGUS), if considered glandular in origin. Diagnoses of both ASCUS and AGUS indicate uncertainty as to whether any preinvasive or preneoplastic lesions are present. These diagnostic categories are not part of the spectrum of precancerous abnormalities. In a screened population, the proportion of ASCUS results should be no more than 5% of all tests; reports of AGUS should be even less common (< 0.5%).

Colposcopic investigation of women with ASCUS results reveals that a few harbour LSIL or HSIL confirmed by biopsy.^{28,29} Colposcopy of women with AGUS results reveals that some harbour HSIL, and some have either endocervical adenocarcinomas in situ or adenocarcinomas,³⁰ or endometrial hyperplasia or adenocarcinomas.

As for LSIL, recommendations for management of ASCUS also vary. Immediate colposcopy and investigation to detect underlying lesions is one option.²⁹ Others recommend 6-monthly Pap tests for up to 2 years to detect underlying lesions and recommend that only women who have these lesions or ASCUS on satisfactory Pap tests should be referred for colposcopic investigation.^{22,24} A course of estrogen therapy for postmenopausal women immediately before repeat tests might assist cytologic interpretation of subsequent Pap specimens. Pap tests should not be repeated at intervals of less than 6 to 8 weeks.²²

Human *Papillomavirus* DNA testing for oncogenic viral types is not widely available, but such testing could be useful in selecting women for referral for colposcopy.²² Several studies have examined the usefulness of oncogenic HPV viral testing of women with ASCUS findings on Pap test and have shown that absence of an HPV oncogenic virus identifies women who do not have either HSIL or malignancy (ie, the test has high negative predictive value).^{27,31-34} Whether HPV testing becomes the management option of choice for women with ASCUS reports remains to be seen.

There is less controversy about management of women with AGUS reports if the laboratory's use of the term is limited to important glandular cell abnormalities. Because quite a few of these women harbour HSILs or glandular malignancy involving the endocervix or endometrium, colposcopic evaluation, evaluation of the endocervix, and possibly evaluation of the endometrium is warranted.^{24,30} Unnecessary colposcopic investigations are likely to occur, however, if the term AGUS is inappropriately used to designate reactive endocervical cells only.

Editor's key points

- Fifteen percent or more of Canadian women who have developed cervical carcinoma while participating in a screening program have had abnormal Pap test results that might have been managed outside conventional protocols.
- Patients should be retested if a specimen is judged unsatisfactory.
- Pap test results "satisfactory for evaluation but limited by..." should be managed based on clinical findings and previous Pap test history.
- High-grade squamous intraepithelial lesions require colposcopy; there are no uniform recommendations for managing women with low-grade squamous intraepithelial lesions.
- Human *Papillomavirus* testing is a potential management tool; its final role is not yet defined.

Points de repère du rédacteur

- Environ 15% ou plus des femmes qui ont développé un carcinome cervical alors qu'elles participaient à un programme de dépistage avaient eu des résultats de frottis vaginaux anormaux qui auraient pu être pris en charge en dehors des protocoles conventionnels.
- Les patientes devraient à nouveau subir un test si le spécimen est jugé non conforme.
- Les patientes présentant des résultats de test de Papanicolaou « conformes mais limités par... » devraient être prises en charge en fonction des conclusions cliniques et des antécédents de résultats de frottis vaginaux.
- Les lésions intra-épithéliales malpighiennes de haut grade exigent une colposcopie; les recommandations ne sont pas unanimes quant à la prise en charge de celles qui ont des lésions intra-épithéliales malpighiennes de bas grade.
- Les épreuves de dépistage du *Papillomavirus* humain sont un instrument potentiel de prise en charge; leur rôle définitif reste à confirmer.

Pathologists sometimes further qualify or subtype ASCUS and AGUS results as "favour reactive" or "favour neoplastic" based on cytologic appearance. Whether this subtyping of atypical smears is really useful is controversial; no conclusive evidence indicates that it is useful, with one exception. One particularly notable form of ASCUS is generally recognized; Pap test results labeled "ASCUS rule out HSIL" should lead to referral for further investigation.³⁵

Pap test results showing important abnormalities or uncertainties can be a great source of distress to women. Counseling and educational brochures can help to alleviate their anxiety and should be considered.^{36,37}

Screening using HPV testing

In the future, alternative methods of detecting cervical pre-invasive lesions using HPV DNA testing of vaginal samples, possibly self-collected, might be used.³⁸ Although this test compares favourably with the Pap test's sensitivity for detecting cervical lesions, it lacks specificity among populations such as young Canadian women who have a high prevalence of HPV infection.^{33-36,38} This lack of specificity is a serious impediment to using HPV DNA testing as a screening tool. In addition, selection of cutoff values (and, thus, the optimal analytic sensitivity) for the HPV DNA test is crucial.³⁹

Conclusion

Management of women with Pap test reports in the Bethesda system can be determined by the adequacy statement and the cytodiagnosis. Women with unsatisfactory smears need to be retested in 6 to 8 weeks. Management of women with satisfactory but limited by... reports needs to be individualized. Management of women with satisfactory tests is determined by the diagnosis. Management response to WNL, BCC, AGUS, HSIL, and malignant diagnoses is straightforward and without controversy (Table 2). Various approaches can be selected for managing women with LSIL and ASCUS results, depending on the clinical situation, the patient, and the availability of colposcopy and HPV testing. ♦

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