SCREENING FOR CERVICAL CANCER: REVISED

Toward Optimized Practice

Alberta Clinical Practice Guidelines

Administered by the Alberta Medical Association

2006 Update

This guideline is a revised version of the guideline developed in February 2000, by the Cervical Cancer Screening Working Group .

This guideline currently recommends that routine screening be performed annually for eligible women 18-69. Many expert groups recommend less frequent screening, especially if an organized screening program is in place. With the implementation of the Alberta Cervical Screening Program, which is being phased in across Alberta between 2003 and 2006, the recommendation for routine screening in Alberta will be regularly reviewed.

ISSUE

Failure to be screened or being underscreened is a significant risk factor for developing cervical cancer.

GUIDELINE GOALS

- To assist health care providers and women in the implementation of cervical screening to ultimately decrease morbidity and mortality from cervical cancer.
- To list uniform and consistent recommendations for cervical cancer screening, for cervical cancer screening tools, and the management of test results.

SUMMARY RECOMMENDATIONS

Although most invasive cervical cancers are squamous cell carcinomas that arise from premalignant lesions (squamous intra-epithelial lesion, SIL) and evolve slowly over many years, occasionally the cancer appears to have progressed more rapidly. The goal of cervical cancer screening is to detect the disease in its premalignant phase when it is completely curable.

Recruitment

- Episodic contacts should be used to develop a good physician/patient relationship and promote the value of routine screening.
- Mechanisms to recruit eligible women will be developed as a component of the ACCSP.

Eligibility (see Algorithm Chart)

- All women aged 18 and over who have had sexual intercourse should be actively encouraged to participate in cervical cancer screening unless they are:
  - Women who have had a total hysterectomy for **BENIGN DISEASE** if there is:
    - adequate pathological documentation that the cervix has been completely removed

    and
    - no history of cervical malignancy or premalignancy.
  - Women older than 69 with a cervix and who have had at least two satisfactory and negative smears (taken at least 3 months apart) in the past 3 years, provided there is no history of cervical malignancy or premalignancy.

PRACTICE POINT

Regardless of the Pap smear findings, a visibly abnormal cervix should be investigated by colposcopy and abnormal bleeding should be investigated by appropriate referral.

Frequency of Screening

a) Routine Screening

PRACTICE POINT

Eligible women aged 18 to 69 should have annual Pap smears.

- There is no evidence to support the benefit of routine Pap screening in eligible women who are under the age of 18.
- Women older than 69 and who have never been screened:
  - Should have two consecutive Pap smears six months or more apart.
    - if results are negative and satisfactory, screening may be discontinued.

b) Increased Surveillance

Some women, because of increased risk or current or past cervical disease, require more vigilant surveillance. These include:

- Women who have had a recent abnormal Pap smear result.
- Women with treated cervical malignancy or premalignancy.
- Women at increased risk because of immunosuppression.

Optimal Specimen Collection (see Appendix)

- A dual collection technique (spatula and brush) should be used to sample the transformation zone.
- Mid-cycle is the optimal time in menstruating women.
- Smears should not be repeated within a 3 month period.

Follow-up and Management of Abnormal Pap Smears

Follow-up and management of the abnormal Pap smear should be based on clinical signs, symptoms, prior history, and the Pap smear report (See Table 1).

PRACTICE POINT

Colposcopy is not a screening tool and is not appropriate for use in asymptomatic women with negative cervical cytology

ADVICE TO PATIENTS

The Alberta Clinical Practice Guidelines Program supports the right of the patient to make informed decisions about her health care options. Patient decisions will vary as a result of individual fear of cancer and the individual interpretation of the evidence relative to health benefits. It is important for women to be aware of the consequences of their decisions to be screened or not screened. The ACCSP has developed patient information pamphlets to assist women in decisions related to cervical cancer screening. These pamphlets have been endorsed by the CPG program and replace the previous CPG patient brochure.

BACKGROUND

Introduction

Cancer of the cervix is the 11th most frequently diagnosed cancer amongst Canadian women. In 2002, it was estimated that 1,400 Canadian women would develop cervical cancer and 410 would die from it. There has been an overall reduction in age-standardized mortality rates from invasive cervical cancer from 7.4 per 100,000 women in 1969 to 2.2 per 100,000 women in 1996 and a reduction in incidence rates from 21.6 per 100,000 in 1969 to 9.3 per 100,000 women in 1999. This decline is mostly attributable to screening.[1]

The delivery of cervical cancer screening may be opportunistic or organized. Opportunistic screening depends entirely on the individual woman's and/or her physician's initiative and does not achieve optimal screening coverage of the eligible population. An organized screening program allows a standardized approach to screening, follow-up, and treatment and requires a registration database of eligible women.

The database of an organized screening program will enhance recruitment by identifying those women who have never been screened and facilitate the recall of women overdue for routine screening and those who have not had appropriate follow-up of an abnormal smear. Currently, the practice in Alberta is opportunisitc screening, however a population-based, organized screening program is being developed and will be implemented in Alberta over the next several years.

The Alberta Cancer Board registers 120 to 150 newly diagnosed cases of invasive cervical cancer annually and there are 30 to 50 deaths from this disease each year. In a study of the screening histories of Alberta women with invasive cervical cancer, 85% had stage 1B tumors or higher and the most significant risk factor for cancer development was infrequent or no participation in Pap smear screening.[2]

Natural History

Approximately 70% of cervical malignancies are squamous cell carcinomas and the remainder are mainly adenocarcinomas. Both types of carcinoma arise from premalignant lesions. Human Papillomavirus (HPV) has long been suspected and evidence to date indicates that it is a causative agent of both squamous and glandular premalignancy and malignancy. Transit times between low grade squamous intraepithelial lesion and invasive squamous cell carcinoma average 20 years, although the range may be quite variable.[3,4]

Occasionally the disease appears to have progressed more rapidly. This may be due to a more aggressive cancer or to specimen collection, preparation and/or interpretation issues. Premalignant squamous lesions are classified as either low grade squamous intraepithelial lesion (LSIL) or high grade SIL (HSIL). The majority of LSIL appears to clear spontaneously and infrequently progresses to invasive carcinoma. In contrast, approximately 13% of untreated HSIL will progress over time to invasive carcinoma[4]. Therefore, by detecting SIL, treatment can be implemented and invasive carcinoma obviated.

Risk Factors

The association between HPV and cervical squamous premalignancy and malignancy is virtually beyond question. The number of sexual partners, age at first sexual intercourse, age at first pregnancy, race and socioeconomic status are surrogate markers for infection with HPV [5].

In an immunocompetent host, HPV infection alone does not appear to be sufficient to induce the step from SIL to invasive carcinoma and other co-factors/exposures may be necessary.[6]

The only other independent factor that is currently accepted to be an important contributor to risk is cigarette smoking. There is increasing evidence that long term oral contraceptive use may also be a risk factor.[7]

Frequency and Eligibility for Screening

The optimal age at which to initiate and discontinue screening and the optimal screening frequency is controversial.[8-10] The Programmatic Guidelines for Screening for Cancer of the Cervix in Canada[8], a consensus document endorsed by major Canadian medical associations, recommended that all women aged 18 and over be screened, initially with two smears one year apart. If these smears are satisfactory then rescreening every three years is advised until the age of 69. The recommendation for a three-yearly interval is predicated on the presence of a system for recall and quality assurance within an organized screening program. Currently some provinces/territories recommend biennial screening, while others recommend annual screening.

The Alberta Cervical Cancer Screening Program (ACCSP) was established in 2000, but has not been fully implemented throughout Alberta. Although annual screening is currently recommended, this interval is under review and will likely change within the next few years when the ACCSP has been implemented province-wide.

Screening in pregnancy: The first prenatal visit and the '6 week postpartum' check-up are often used by physicians as opportunities to perform cervical screening. However, this may result in overscreening. In addition, cervical changes associated with pregnancy and delivery may make Pap smears more difficult to interpret. Before performing Pap smears routinely at these visits, the physician should consider if a woman has had a recent pre-pregnant Pap smear and whether she has been a regular screener, as well as the likelihood that she will return for screening at an appropriate time.

Screening in women who have had hysterectomies:

Since the yield of Pap smear screening is low in women who have had hysterectomies[10], routine screening is not recommended. A woman who has had a hysterectomy for benign disease with complete removal of the cervix and who has no history of biopsy-confirmed cervical premalignancy or malignancy, does not need to be screened. If the cervix remains, or the women has had biopsy-confirmed cervical premalignancy or cervical cancer, continued screening is recommended. Women who have hysterectomies for endometrial carcinoma should not be screened if their cervix was completely removed.

OPTIMAL SPECIMEN COLLECTION

Most cervical squamous premalignancy and malignancy develop in the transformation zone and extend to the ectocervix. The purpose of specimen collection is to obtain a specimen of cells from both areas. The transformation zone is an area of cells characterized by columnar cells proximally, squamous metaplastic cells centrally, and mature squamous cells distally. This zone is located 8 to 13mm proximal to the ectocervix, but may extend as far as 20 to 30 mm into the cervical canal. The area of transformation is higher within the cervix in older women and those who are pregnant.

The ideal sample has both ectocervical and transformation zone cells in adequate numbers to detect abnormalities. Factors resulting in variability in this ideal sample are the sample taker's skill, individual variations in the transformation zone, and hormonal influences.

The technique with the least variability between sample takers and the highest consistency in providing an adequate sample involves the use of both a cervical spatula and an endocervical brush. This technique improves the adequate smear rate to 94-98%[11]. Use of the double collection technique also corrects for individual hormonal variability in the transformation zone.

In general, during the reproductive years, the mid-cycle is the best time for taking a smear. This produces the most easily interpreted specimen and avoids the menstrual and premenstrual leucocytic component in the mucous. Excess mucous on the cervix may be removed with a cotton swab prior to sampling if this is a problem.

PRACTICE POINT

Smears should not be repeated within 3 months. This time is required for the surface layer of epithelial cells to regenerate and be available for sampling.

The use of the endocervical brush in pregnant women was contraindicated in the past because of the increased incidence of bleeding and concern regarding the possibility of spontaneous abortion. A literature review[12] indicates that this concern is unfounded and endocervical sampling with the brush is an option.

Collection of smears in women without a cervix, but with a previous history of SIL requires scraping of the vaginal vault. The apex of the vault should be swiped with the blunt end of a spatula.

PRACTICE POINT

In some instances, a smear may not provide representative material and additional investigations for diagnosis are more appropriate.

This is true in circumstances where the physician observes an obvious lesion of the cervix and is suspicious of cancer. They include lesions that are:

- **i) elevated;**
- **ii) keratotic;**
- **iii) ulcerated or covered with bloody necrotic exudate.**

LIMITATIONS

False Negative Results

A false negative result occurs when the Pap smear fails to detect an abnormality that is present on the cervix. False negatives occur because either the abnormal cells are not present on the smears due to limitations of cervical sampling and smear preparation or because abnormal cells in the smears were not identified by the laboratory. Cervical cancer screening is not completely sensitive; the Pap test has a a false negative rate that varies widely (13-70%) in published studies and may be higher for a single patient visit.[13,14] Repeat screening at regular intervals is necessary to provide adequate lifetime protection from cervical cancer.

NOTES ON REPORTING TERMINOLOGY: THE BETHESDA SYSTEM

The Bethesda System (TBS) for reporting Pap smears is the recommended standard for use in Canada and by the Alberta Cervical Cancer Screening Program. The Bethesda 2001 Workshop reviewed issues regarding terminology and reporting of cervical cytology and made changes to the system.[15]

The report includes a statement of adequacy and the diagnosis. There are two categories of specimen adequacy. "**Satisfactory For Evaluation**" and "**Unsatisfactory For Evaluation**." The "**Unsatisfactory For Evaluation**" category indicates the smear was rejected/not processed or that the specimen was processed and examined but was unsatisfactory for evaluation of epithelial abnormality. The reasons the smear was considered "**Unsatisfactory For Evaluation**"will be given in the report (e.g. too few cells were collected or the cells on the smear were spread too thickly).

PRACTICE POINT

Unsatisfactory smears are mostly due to cervical sampling and specimen collection issues.

The diagnostic categories are "**Negative for Intraepithelial Lesion or Malignancy**", "**Epithelial Cell Abnormality**"and "**Other**". Smears interpreted as "**Negative for Intraepithelial Lesion or Malignancy**" indicates that the smear was satisfactory and that the woman should continue with routine screening, or that the smear was satisfactory with qualifiers and that it should be repeated in 12 months. The latter is the

category formerly called “Satisfactory but limited for evaluation”. The type of qualifier will be given in the report. Smears interpreted as “**Epithelial Cell Abnormality**” include both those that represent cervical carcinoma and those that have changes considered to indicate increased risk of cervical carcinoma.

Changes indicative of increased risk for cervical carcinoma are reported as “**Atypical Squamous Cells of Undetermined Significance (ASC-US)**”, “**Low Grade Squamous Intraepithelial Lesion (LSIL)**”, “**Atypical Squamous Cells – cannot exclude HSIL (ASC-H)**”, **“High Grade Squamous Intraepithelial Lesion (HSIL)”,** “**Atypical Glandular Cells” and “Adenocarcinoma in Situ**.”

MANAGEMENT OF WOMEN BASED ON PAP SMEAR RESULTS

Table 1 on the following page provides guidelines on the management of women based on Pap smear results. The management of abnormal Pap smears in pregnant women is the same as for non-pregnant women with the following exception: if a woman has an ASC-US or LSIL result in a Pap smear taken at the first prenatal visit and has not had any other recent abnormal Pap smear, the usual recommendation would be to repeat the Pap smear in 6 months. However, rather than doing this repeat Pap smear in the third trimester, it is recommended to wait until at least 6 weeks postpartum.

Endometrial cells after age 40 may be associated with benign endometrium, hormonal alterations and less commonly endometrial or uterine abnormalities. The management recommendation is: clinical correlation is recommended and endometrial biopsy and or endocervical curretage may be appropriate.

Women who are estrogen depleted may have atrophic cells on the Pap smear. These may falsely mimic intraepithelial abnormalities and may be reported as ASC-US. In this circumstance, repeating the Pap smear after a course of intravaginal estrogen is recommended (see Appendix 2 for recommended protocol). If the repeat Pap smear is normal (NIL), the woman can return to routine screening.

Women with atypical glandular cells on the Pap smear should be referred for colposcopy; repeat cytology is not sufficient.

Women who have undergone colposcopic assessment and treatment and have been discharged from colposcopy should be managed according to the guidelines in Table 1, and should not be referred back to colpsocopy after a single ASC-US or LSIL result.

Colposcopy

Colposcopy is a technology that has been used for several decades to identify sub-clinical abnormalities of the uterine cervix. The cervix is magnified through a binocular scope with a high intensity light. This allows for the identification of abnormalities based upon epithelial density (white epithelium) and vascular patterns (punctation, etc.). Using these parameters, an area of abnormality can be identified in order to direct a tissue biopsy by one of several available methods (punch biopsy, loop electrosurgical excision, etc.).

HPV Testing

The prevalence of cervical HPV DNA in women with **NORMAL** Pap smears and no history of premalignancy is approximately 10% whereas the rate amongst those with a history of cervical premalignancy is approximately 30%. The HPV can be detected by a number of methods. The most sensitive are those that detect viral deoxyribinucleic acid (DNA). There are more than 85 types of the virus and approximately 30 are associated with cervical carcinoma. Viral DNA detection rates correlate directly with the grade of cervical premalignancy and upwards of 99% of cervical carcinomas are HPV DNA positive.[16]

Amongst those with a smear result of ASC-US, HPV testing is sensitive in detecting HSIL.[17] Future use of routine HPV testing in this group will be decided by the Alberta Cervical Cancer Screening Program following appropriate consultation. Routine HPV testing is currently not available in Alberta.

Future Directions

At this time, a population-based, organized screening program is being developed in Alberta. The ACCSP will implement an information system that will invite women who haven’t been screened, recall women when their next screening is due and ensure that women with abnormal screening results are being followed up. The ACCSP will also develop strategies and resources to increase recruitment of unscreened women and implement quality improvement initiatives at all stages of the screening process. When all the components of an organized screening program are in place, the recommended routine screening interval will be reviewed, and may be extended. However, until that time, the recommended routine screening interval is annual.

Table 1 (See text for additional information)

Guidelines for the Management of Women Based on Pap Smear Results

Result	Recommended Management
Unsatisfactory	Repeat smear in 3 months.
Negative for Intraepithelial Lesion or Malignancy (NILM)	a) Satisfactory smear - routine screening b) Satisfactory with qualifiers - repeat smear in 12 months. Benign endometrial cells in women >40: Endometrial biopsy and/or cervical curettage for confirmaiton
ASC-US (Atypical Squamous Cells of Undetermined Significance)	If specific pathogen identified, treat if clinically appropriate. • Repeat smears every 6 months for 2 years (4 smears); if any of these smears is ASC-US or worse, refer for colposcopy. If smears in follow-up period are all NILM, return to routine screening. • If smear is atrophic, repeat smear 1 week after completion of a course of intravaginal estrogen therapy. The Pap smear should not be repeated before 3 months. • If smear was at first prenatal visit and there are no other recent abnormal Pap smears, recommend waiting for repeat smear until at least 6 weeks post partum.
LSIL (Low Grade Squamous Intraepithelial Lesion)	• Repeat smears every 6 months for 2 years (4 smears); if any of these smears is ASC-US or worse, refer for colposcopy. If smears in follow-up period are all NILM, return to routine annual screening. -- • If smear was at first prenatal visit and there are no other recent abnormal Pap smears, recommend waiting for repeat smear until at least 6 weeks post partum.
ASC-H (Atypical Squamous Cells-cannot exclude HSIL)	Refer for colposcopy.
HSIL (High Grade Squamous Intraepithelial Lesion)	Refer for colposcopy.
Atypical Glandular Cells Adenocarcinoma in Situ (AIS)	Refer for colposcopy and endocervical curettage. Endometrial biopsy may be appropriate. Repeat PAP smears are insufficient
Squamous Cell Carcinoma Adenocarcinoma Other Malignant Types	Refer to specialist care.

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Toward Optimized Practice (TOP) Program

Arising out of the 2003 Master Agreement, TOP succeeds the former Alberta Clinical Practice Guidelines program, and maintains and distributes Alberta CPGs. TOP is a health quality improvement initiative that fits within the broader health system focus on quality and complements other strategies such as Primary Care Initiative and the Physician Office System Program.

The TOP program supports physician practices, and the teams they work with, by fostering the use of evidence-based best practices and quality initiatives in medical care in Alberta. The program offers a variety of tools and out-reach services to help physicians and their colleagues meet the challenge of keeping practices current in an environment of continually emerging evidence.

TO PROVIDE FEEDBACK

The Working Group encourages your feedback. If you need further information or if you have difficulty applying this guideline, please contact:

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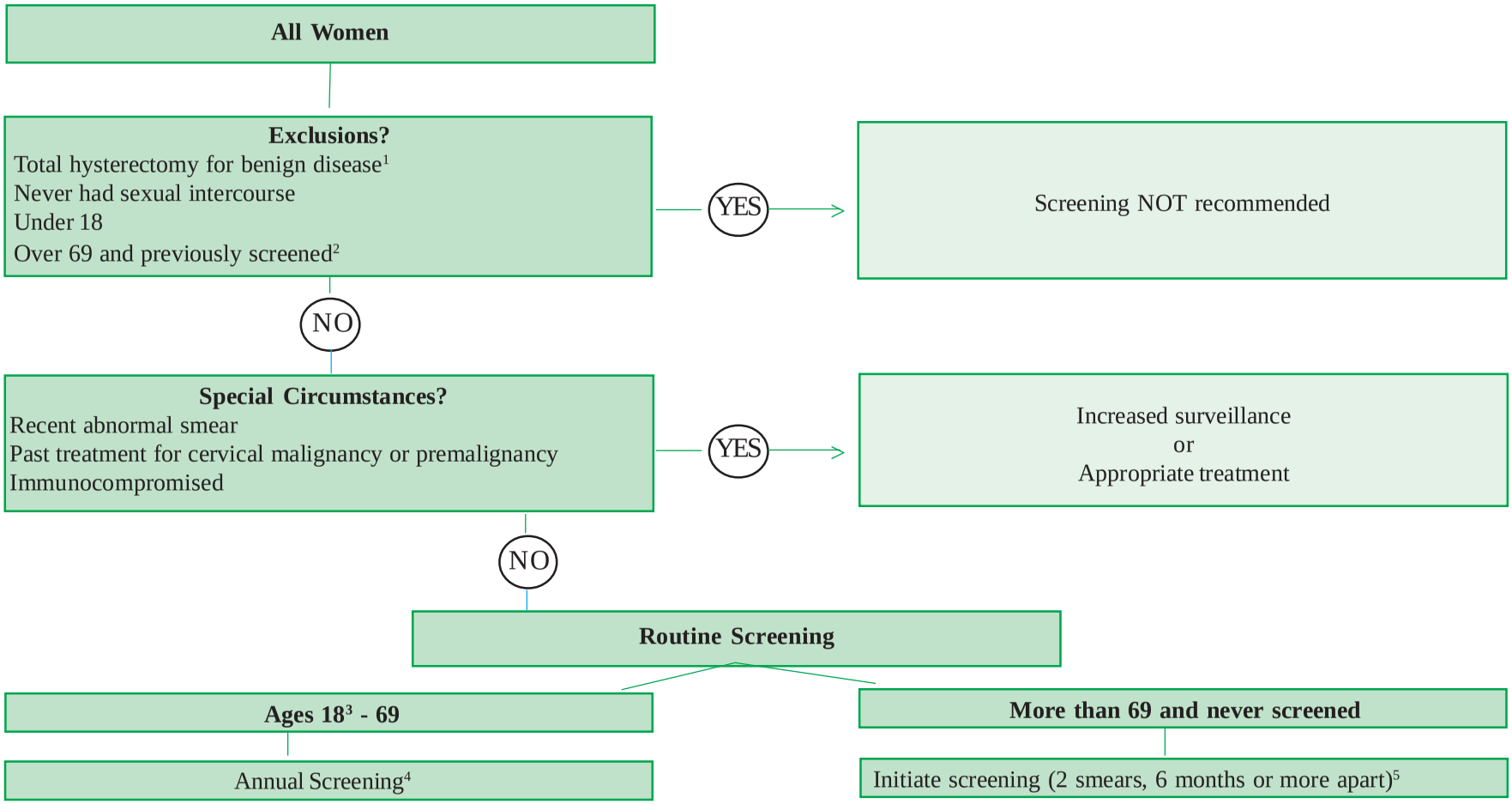
ALGORITHM: CERVICAL CANCER SCREENING

PRACTICE POINT

Regardless of the Pap smear findings, a visibly abnormal cervix should be investigated by colposcopy, and abnormal bleeding should be investigated by appropriate referral.



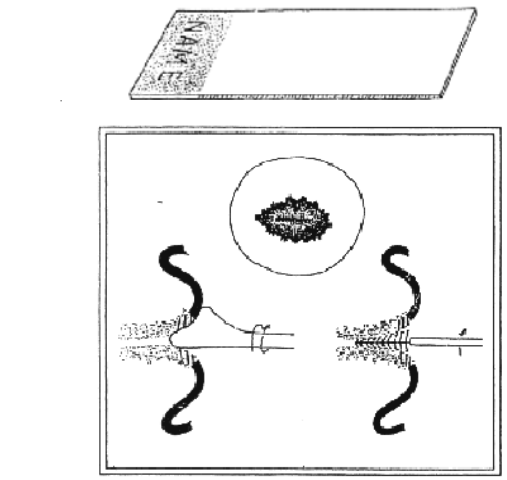
Notes:

1. ***If there is adequate evidence that the cervix has been completely removed and there is no history of cervical pre-malignancy or malignancy***
2. ***Screening may be discontinued in women over 69, provided there have been at least two satisfactory and negative Pap smears, taken at least 3 months apart, in the past three years and there is no history of cervical malignancy or premalignancy.***
3. ***The Alberta Cervical Cancer Screening Program does not recommend routine screening in women <18 or >69. Screening in these age groups may be needed in some individual cases.***
4. ***At present the Alberta Cervical Cancer Screening Program recommends annual screening. When the Program is fully implemented, recommended frequencies will be reviewed.***
5. ***If these smears are NIL and satisfactory, no further screening is necessary.***

Appendix 1:

Pap Smear Preparation

This appendix is adapted from the Ontario Cervical Screening Reference Card. It compliments the CPG: Screening for Cervical Cancer prepared by the Alberta Clinical Practice Guidelines Program.



COMPLETE REQUISITION FORM

- Ensure consistency of labelling
- Ensure relevant history is complete

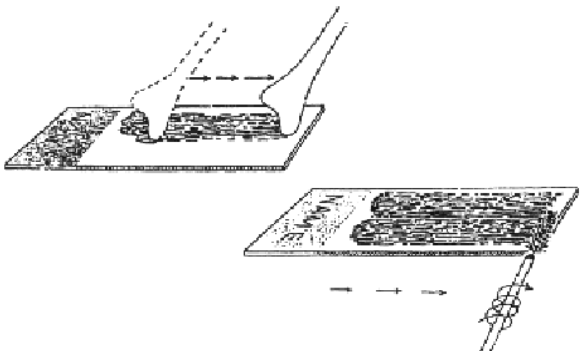
LABEL SLIDE WITH FULL NAME

- With PENCIL, on frosted side of slide

VISUALIZE CERVIX

- lubricate speculum with warm water
- use lubricant gel sparingly

Assess position of transformation zone.
Ensure zone will be sampled with appropriate device.



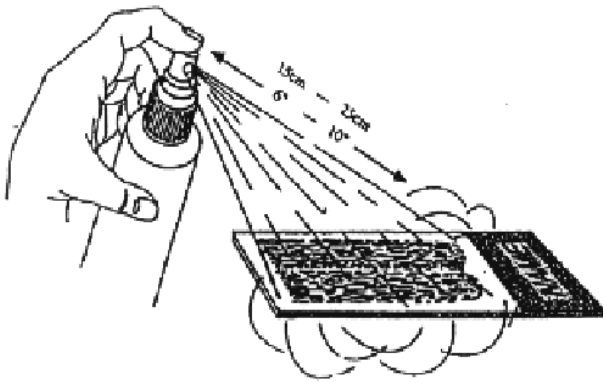
OBTAIN BOTH SAMPLES

To obtain a proper Pap smear, use a spatula and an endocervical sampling device (e.g., brush) and then apply both specimens on a single slide

(1) SPATULA - rotate once through $360^{0.}$
- keep spatula well applied
- end in the horizontal position. Retain the sample on the upper side of the spatula during transfer

(2) BRUSH - or other endocervical sampling device
- insert gently
- **TURN THROUGH 90^{0} ONLY.**

NOTE: Over inserting the brush increases trauma without improving the quality of the sample. Insert no further than the bristles.



APPLY SAMPLE

Use ONE slide. Apply each sample on one half of slide, in immediate sequence, as shown - keep separate

(1) SPATULA - spread in a single uniform motion

(2) BRUSH - sample will dry quickly
- roll on in one motion

THIS SEQUENCE SHOULD BE PRACTICED TO AVOID DELAY. APPLY BOTH SAMPLES SIMULTANEOUSLY.

FIX SAMPLE

- immediately
- allow sample to dry before closing mailer

Appendix 2:
Recommended Management of Women with Atrophic Pap Smears

Issue:

Pap smears in post menopausal women may be reported as atrophic, with either a result of NIL or ASC-US. Experts recommend the Pap smear be repeated after a course of estrogen therapy. However, clear guidelines on the duration or timing of the estrogen therapy are lacking. The ACCSP Colposcopy Working Group members were asked for recommendations on this issue.

Recommended Management:

If the laboratory recommendation is that the Pap smear be repeated after a course of estrogen therapy (this may accompany either a NIL or an ASC-US diagnosis), one of the following forms of estrogen should be prescribed:

a) **Estrogen intravaginal cream:** 1 gm 2-3 times per week (or every other day). Repeat Pap test no sooner than 3 months after the initial Pap test. Estrogen cream should be discontinued 1 week before scheduled Pap test (to allow time for it to be cleared from the cervical area).

b) **Estring –** (intravaginal estradiol ring)- insert as deeply as possible into the upper third of the vagina. The ring does not need to be removed in order to do the repeat Pap smear. Repeat Pap test no sooner than 3 months after the initial Pap test.

c) **Vagifem –** (estradiol tablets): 1 tablet (inserted in vagina using the applicator) 2-3 times per week. Repeat Pap test no sooner than 3 months after the initial Pap test. Vagifem should be discontinued 1 week before scheduled Pap test (to allow time for it to be cleared from the cervical area).

Contraindication to Intravaginal Estrogen:

Women with a prior history of hormone receptor positive breast cancer offered intravaginal estrogen for the management of atrophic Pap smears should be informed of the theoretical, but unproven, risk of augmenting breast cancer recurrence.

Other potential contraindications are described in the manufacturers' information.

Produced by ACCSP Colposcopy Quality ImprovmentI Committee 2005.04.21