Frequently Asked Questions on Cervical Dysplasia and Human Papillomavirus

A Reference Guide for Clinicians

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Acknowledgements
The authors acknowledge the staff of the Ontario Cervical Screening Program who assisted in preparing this book for publication.

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ISBN: 0-9782128-0-0
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Introduction

The Gynecologic Oncology Program (Department of Obstetrics and Gynecology, University of Ottawa) and the Ontario Cervical Screening Program (OCSP) receive numerous inquiries about cervical cancer screening, screening practice guidelines, and the diagnosis and management of patients with abnormal Papanicolaou tests. *Top 100 Most Frequently Asked Questions on Cervical Dysplasia: A Reference Guide for Family Physicians*, was originally published in 1999. Subsequent widespread distribution across the province was sponsored by the OCSP to provide health care providers and consumers with concise and thoroughly referenced information regarding dysplasia. For quick reference, the topics have been grouped by subject and question number in the index.

This reference guide is an update to the original research and efforts of Drs. Fung-Kee-Fung and Amimi. Extensive literature reviews were performed to ensure the accuracy of responses and to provide readers with a comprehensive list of references from which to acquire additional information. Appendices include the Ontario Modified Bethesda System 2001 (Revised Terminology), revised (2005) Ontario Cervical Screening Practice Guidelines, and the Ontario Cervical Screening Reference Card, developed by the OCSP, which is a program of Cancer Care Ontario. Further to numerous advances in technology, new scientific discoveries, and a wealth of published literature, the OCSP agreed to support and participate in the revision of this resource, consistent with evidence-based and clinical information. The Program partnered with Drs. Fung-Kee-Fung and Amimi to achieve this revision.

We believe this document will be a valuable resource for family practitioners by providing answers to the most commonly asked questions. In addition, this publication will help bridge the gap between superficial and thorough knowledge of dysplasia.

Your comments and suggestions are greatly appreciated and can be forwarded to Dr. Michael Fung-Kee-Fung at The Ottawa Hospital (General Campus), 501 Smyth Road, Ottawa, CANADA, K1H 8L6.

Answers to Your Frequently Asked Questions

1. What is the status of cancer of the cervix in Canada?

In Canada, most cervical cytology tests are conducted by physicians at either a primary care or consultative level. Unfortunately, new cases of invasive cervical cancer continue to occur. In 2006, there will be an estimated 1,350 new cases of cervical cancer and 390 deaths (Canadian Cancer Society/National Cancer Institute of Canada, [CCS/NCIC], 2006). Cervical cancer ranks twelfth among all cancers in women, but is the third most common cancer among women aged 20–49. Over the past three decades, the age-standardized mortality rate for invasive cervical cancer dropped from 7.4 per 100,000 women in 1969 to an estimated 1.9 per 100,000 women in 2006 (CCS/NCIC, 2006; Stuart & Parboosingh, 1996). The incidence rate also fell from 21.6 per 100,000 women in 1969 to an estimated 7.5 per 100,000 women in 2006 (CCS/NCIC, 2006; Stuart & Parboosingh, 1996). Since the mid-1970s, however, the decline in the incidence rate slowed, particularly among women younger than 50 years. Nevertheless, it must be acknowledged that Canada currently has one of the lowest rates of cervical cancer in the world (Parkin, Whelan, Ferlay, Teppo, & Thomas, 2002). Overall, Canadian women have a 1 in 138 chance of developing cervical cancer and a 1 in 385 chance of dying from the malignancy (CCS/NCIC, 2006). Cervical cancer ranked eleventh for potential years of life lost (PYLL) to cancer in 2002 (9,300 years or 1.8% of all female cancers) (CCS/NCIC, 2006). The five-year relative survival rate is approximately 72%.

2. Is it true that adenocarcinomas represent a growing proportion of new cervical cancers? Which groups of women are at greatest risk?

Unlike the steady decline that has been observed for the incidence of squamous cell carcinoma, adenocarcinoma of the cervix accounts for a growing proportion of new cervical cancer cases in many jurisdictions, particularly among younger women (20–49 years) (Vizcaino et al., 1998). In Canada, the age-adjusted incidence rates of cervical adenocarcinoma increased significantly over the last 20 years, from 1.30 per 100,000 women between 1970 and 1972, to 1.83 per 100,000 women in 1994–1996 (Liu, Semenciw, & Mao, 2001). Conversely, age-adjusted cervical squamous cell carcinoma incidence rates dropped from 13.39 per 100,000 in 1970–1972, to 6.56 per 100,000 in 1994–1996. The reasons for the observed increase in incidence of adenocarci-

noma are likely multifactorial and may be related to improved awareness among clinicians of glandular lesions in cytology, improved specimen collection (dual collection techniques — see Questions 58 and 59), or improved quality assurance initiatives. It may also reflect a true increase in the rates of disease in the absence of significant changes to screening.

In Ontario, a recent trend analysis revealed a significant decrease — by 4.0% per year — in adenocarcinoma of the cervix since 1995 (Howlett, Marrett, Innes, Rosen, & McLachlin, 2006). The decrease is thought to be a function of quality assurance efforts that were implemented throughout the 1990s, including dual specimen collection.

Based on an analysis of 8 pooled case-control studies, cervical adenocarcinoma was strongly associated with human papillomavirus (HPV) types 16 and 18, but other types were also detected. Women with adenocarcinomas were more likely HPV-positive (OR = 81.3; CI: 42.0–157.1) compared to those who were negative for HPV (Castellsague et al., 2006). The following co-factors were associated with adenocarcinoma and among those who were positive for HPV: never attending school, poor hygiene, sexual behaviour variables, long-term use of oral contraceptives, high parity and co-infection with Herpes Simplex Virus 2. Interestingly, those who had ever used an intrauterine device were less likely (OR = 0.41; CI: 0.18–0.93) to have adenocarcinoma. There was no association between adenocarcinoma and smoking and Chlamydia (Castellsague et al., 2006).

3. What are the risk factors for cervical cancer?

More recent studies have identified the following as the main risk factors irrespective of marital status:

1. High number of intimate (sexual) partners
2. Early age at onset of sexual intercourse
3. Number of partners of male sexual partner
4. Sexual partners who are HPV carriers
   (Franco, Schlecht, & Saslow, 2003)

Evidence supports a sexual mode of transmission of a carcinogen, and HPV is strongly implicated from laboratory and epidemiological studies as the main infectious etiologic agent (Franco, Schlecht, et al., 2003; Walboomers et al.,

1999). Although it is now accepted that HPV infection is necessary for progression to cervical cancer, it is not a sufficient (i.e., sole) cause of disease. Several risk modifiers or cofactors appear to play an important role in the acquisition of HPV and/or in influencing the natural history of HPV infection and cervical dysplasia. These cofactors include:

1. **Oral contraceptive** use for 5 years or longer (see Question 24) (Smith, Green, et al., 2003).
2. **Cigarette smoking** (see Question 26) (Kjellberg et al., 2000).
3. **High parity** (see Question 30) (Muñoz et al., 2002).
4. **Other sexually transmitted agents** (human immunodeficiency virus [HIV], Chlamydia trachomatis, and herpes simplex virus [HSV] 2 — see Question 31) (Ahdieh et al., 2001; Ellerbrock et al., 2000; Smith, J. S., Herrero, et al., 2002; Smith, J. S., Muñoz, et al., 2002).
5. Having **compromised immunity** (e.g., infection with HIV, transplant patients, or those taking immunosuppressive medications — see Question 36) (Palefsky & Holly, 2003).
6. Certain **host-specific factors** (i.e., p53 gene polymorphisms and women expressing certain human leukocyte antigen [HLA] haplotypes) (Franco, Schlecht, et al., 2003; Koushik, A., Platt, R. W., & Franco, E. L., 2004).

The exact impact and the mechanism(s) of action of these factors have not been completely elucidated. Also, the risk association between these factors and cancer varies depending on the morphology studied. For example, oral contraceptive use may be more important for cervical adenocarcinomas, whereas a stronger association has been reported between high parity and squamous cell carcinoma versus adenocarcinomas. Ongoing research will hopefully provide more information on the role of cofactors in cervical cancer development.

4. What is the Cervical Cancer Prevention and Control Network?

The Cervical Cancer Prevention and Control Network consists of representatives from Canadian provincial and federal health departments, provincial screening programs, other key stakeholders, and members of clinical professional bodies, including the College of Family Physicians of Canada, the Canadian Society of Cytology, the Society of Obstetricians and Gynaecologists of Canada, the Society of Gynecologic Oncologists of Canada, and the Society of Canadian Colposcopists.

5. What is the goal of the Ontario Cervical Screening Collaborative Group (OCSCG)?

The OCSCG is an advisory committee supported by Cancer Care Ontario (CCO) and comprised of public and professional representatives across the province; physician, nursing, and laboratory bodies; and consumers dedicated to improving cervical cancer screening in Ontario. The primary goals set by the OCSCG are:

- to promote the importance of regular screening among Ontario women
- to raise public and health care provider awareness of the OCSP
- to raise awareness among health care providers of the Ontario Cervical Screening Practice Guidelines (Appendix B), and
- to address health professionals' continuing education needs related to cervical screening.

Further goals of the OCSP are to reach unscreened and underscreened women and encourage them to seek regular Pap testing, and to increase the rate of regular screening among underscreened women (Cancer Care Ontario [CCO], 2002a).

To obtain copies of the *1997–2000 Ontario Cervical Screening Program Report*, contact the Canadian Cancer Society, Ontario Division, at 1-888-939-3333. To see the *2001– 2005 Ontario Cervical Screening Program Report*, please see www.cancercare.on.ca/index_cervicalscreening.htm

6. When did cervical cancer screening begin in Canada?

Cervical Cancer screening in Canada began in British Columbia in 1949 and gradually spread across the country. A full historical perspective is available in Stuart and Parboosingh's 1996 article, "Implementation of comprehensive screening for cervical cancer in Canada: Impediments and facilitators."

7. Which provinces have screening programs?

Seven provinces — British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Nova Scotia, and Newfoundland — and one territory (Nunavut) have cervical cancer screening programs. These programs target all women within

their province between the ages of 18 and 69 (20 and 69 in Ontario); however, none of the programs have implemented population-based recruitment.

8. How many Papanicolaou (Pap) tests are taken annually? How many are abnormal?

National estimates regarding the frequency of Pap tests and the proportion that are abnormal are largely unavailable and unreliable. No national registry exists in Canada to collect data on Pap test participation rates and results, and self-reported cervical screening participation is almost 20% higher than the actual rates (Fehringer et al., 2005). Data from the handful of provinces that have comprehensive screening programs are the most reliable source of such information. For example, in Ontario, the hysterectomy-corrected proportion of women aged 20–69 who received a Pap test in 2000 was 47%. Just over 4% of Pap tests in women of the same age were categorized as abnormal (CCO, 2002a).

9. What is the screening history of women with abnormal Pap tests?

Women who have never been screened (with a Pap test) or who are screened irregularly are most likely to have abnormal Pap tests (National Cancer Institute, 2006). Many women over age 60, for example, are particularly at increased risk. Because it can take 10 years or longer for cervical dysplasia to develop into cancer, in most cases a Pap test is the most important step that a woman can take to prevent cervical cancer.

10. Is there evidence that the Pap test has prevented the occurrence of cancer of the cervix?

There is ample evidence that the Pap test has contributed substantially to the prevention of invasive carcinoma of the cervix. Numerous studies clearly document a statistically significant decrease in the incidence and mortality rates of this disease. Quinn, Babb, Jones, and Allen (1999) reported that mortality was reduced by almost half following the implementation of a cervical screening program in the United Kingdom. In 1987, one year prior to program implementation, the mortality rate due to cervical cancer was 6.1 per 100,000. It dropped to 3.7 per 100,000 by 1997. Similar results from the UK were more recently reported by Peto, Gilham, Fletcher, and Matthews (2004): Among women aged

20–34 (a population for which cervical cancer mortality increased three-fold between 1967 and 1988), the death rate declined from 2.2 per 100,000 in 1983–1987, to 1.03 per 100,000 in 1998–2002. Similar reductions have been observed in Canada and the United States. Declines in cervical cancer incidence and mortality were proportional to the intensity of screening (Laara, Day, & Hakama, 1987; Sigurdsson, 1993). Mortality was reduced most remarkably in British Columbia (the province with the first cervical screening program), which had screening rates 2 to 5 times those of the other provinces (Benedet, Anderson, & Matisic, 1992).

11. Why does cervical cancer screening sometimes fail?

The complex multifactorial nature of the cervical cancer detection system means that failures are possible at many levels. An effective screening program includes recruitment, screening quality assurance, recall for abnormal results, and referral for treatment where appropriate. The failures may occur at several points:

a) failure to recruit women not being screened or who are not screened as frequently as recommended
b) initial clinical examination and test
c) subsequent collection of Pap test samples (failure to do regular Pap tests or improper collection)
d) laboratory errors in screening and interpretation
e) clinician's failure to understand the report
f) clinician's failure to take appropriate action
g) patient's failure to follow the recommendations of the physician, or
h) ineffective or absent recall measures (Gage et al., 2003).

Screening programs that fail to fully recruit women at risk for cervical cancer will be unsuccessful in preventing the disease. Less than optimal declines in incidence and mortality will also be realized if quality measures are suboptimal. Reliability of the screening tool (i.e., conventional Pap test or liquid-based cytology) depends on the technique employed to obtain the cytologic specimen and the adequacy of its review by the cytopathologist. The Pap test failure rate in the presence of invasive cancer can be as high as 50% (Nanda et al., 2000) emphasizing the need to biopsy any visible lesions of the cervix, even if associated with a normal Pap test. However, improved sensitivity and specificity are possible with liquid-based cytology (LBC) in place of the conventional Pap test

(McNeeley, 2003; Monsonego et al., 2001). Loss to follow-up of patients with abnormal Pap test results is another important area of potential failure. Depending upon the jurisdiction of the screening program, loss to follow-up often ranges between 20% and 40% (Gage et al., 2003; Peterson, Han, & Freund, 2003; Sarfati et al., 2003).

12. How has Ontario developed and implemented a quality assurance program?

At present, a centralized cytology database has been established that covers more than 80% of all Pap tests taken annually. The OCSP, along with the Quality Management Program and Laboratory Services (QMP-LS, 2006), have developed the components of a cytology quality assurance program based on Ontario-specific standards, key indicators, and benchmarks for laboratory performance (CCO, 2002a). The mission statement of QMP-LS is to promote quality improvement of laboratories and related services for the public good and the benefit of health professionals.

13. How can we improve the effectiveness of cervical cancer screening?

The effectiveness of cervical cancer screening is most likely to be improved by extending testing to women who are not currently being screened or who are screened irregularly. (See Ontario Cervical Screening Practice Guidelines, Appendix B.) Studies suggest that those women at greatest risk for cervical cancer are those least likely to have access to testing (Calle, Flanders, Thun, & Martin, 1993; Maxwell, Bancej, Snider, & Vik, 2001). Infrequent Pap testing is most common among women with a low level of education, who live in poverty, who are new to Canada, who are over age 60, and/or who are Aboriginal (CCO, 2002a). A provincial recall system would allow for recall at appropriate intervals, leading to a decrease in annual screening. Although it is important to increase screening among those not being screened, overscreening is also detrimental and needs to be reduced (Health Canada, 2002). Furthermore, remote, rural, and under-serviced areas face several challenges to the delivery of cervical screening services. Improved access to health services and health providers and the use of effective health promotion educational materials designed for the population (especially for Aboriginal populations) are necessary in order to improve screening rates and reduce incidence and mortality

from cervical cancer. The OCSP has a broad range of patient education materials available, including website and order information.

14. What patient education materials about dysplasia are effective?

Education regarding risk factors for cervical cancer may lead to behaviour modifications resulting in diminished exposure (Shepherd, Peersman, Weston, & Napuli, 2000). Recent studies showed that a lack of information leads to increased anxiety, stress, and embarrassment among women diagnosed with HPV (Anhang, Wright, Smock, & Goldie, 2004; Mast, 2004; McCaffery et al., 2003; McCaffery et al., 2004; McCaffery & Irwig, 2005; Waller, McCaffery, Nazroo, & Wardle, 2005). Studies have shown that the distribution of patient education materials that explain the meaning of abnormal results is associated with a reduction in patient anxiety and stress and a better patient understanding of test results (Bekkers, van der Donck, Klaver, van Minnen, & Massuger, 2002; Greimel, Gappmayer-Locker, Girardi, & Huber, 1997; Stewart, Lickrish, Sierra, & Parkin, 1993).

The most effective interventions to decrease high-risk behaviours (i.e., promoting delaying onset of sexual activity, emphasizing monogamous relationships, use of condoms) have been gender and culturally sensitive community-based educational programs (DiClemente & Wingood, 1995; Oakley et al., 1995). Active participation of the health care provider has significantly improved patient compliance, particularly for improved screening participation. In several studies, women were more likely to be screened if their health care provider recommended it (Anhang et al., 2004; Lantz et al., 1995; Mandelblatt et al., 1993).

15. How can patient compliance and follow-up be improved?

A motivational brochure (along with a tracking system) can enhance adherence to treatment recommendations among women with abnormal Pap tests. Caucasian women, nonsmokers, and nulliparas were most likely to adhere to treatment recommendations. A recent review suggested that there can be different levels of response to educational efforts. In particular, the never-screened may not respond to news clips. The need for multiple strategies through different vehicles that are multiculturally sensitive is evident (Dignan et al., 1996; Maxwell et al., 2001). Future studies should focus on techniques for enhancing adherence among more resistant participants. Furthermore,

effective patient education and a provincial system for recall and follow-up would ensure women are screened at appropriate intervals. Loss to follow-up after abnormal cytology is a significant problem, particularly among younger women (Gage et al., 2003; Peterson et al., 2003; Sarfati et al., 2003). A physician-based system for recall may be best. A 1997 Dutch study (Palm et al.) compared a family doctor system to the already established national recall system. The study showed a strong association between involvement of the family physician and compliance with follow-up. Additional compliance with follow-up was gained in those practices in which the physicians had introduced a system for monitoring and surveillance of follow-up of women with cytological abnormalities.

16. Are women of low socioeconomic status (SES) at increased risk?

Increased prevalence and risk of cervical cancer in women of lower SES has been documented in several studies in Canada (Goel, 1994; Gupta, Roos, Walld, Traverse, & Dahl, 2003; Katz & Hofer, 1994; Maxwell et al., 2001). Prior research indicated that socioeconomic disparities are attributed to associated risk factors (e.g., sexual behaviour of the patient and her partner, more frequent cigarette smoking) (Bornstein, Rahat, & Abramovici, 1995). More recent research shows women of higher SES have more knowledge and resources as well as more optimal attitudes towards cancer and screening, and are therefore more likely to use preventive care measures such as regular Pap tests (Gupta et al., 2003; Katz & Hofer, 1994; Link, Northridge, Phelan, & Ganz, 1998). Furthermore, the SES-related disparity in cervical cancer mortality has declined considerably in urban Canada from 1971 to 1996 (Ng, Wilkins, Fung-Kee-Fung, & Berthelot, 2004). One of the important factors that may have contributed to the decrease was the implementation of screening programs in several provinces.

17. What is HPV? How many types are there?

Papillomaviruses are double-stranded DNA viruses from the *Papovaviridae* family. Papillomaviruses, in general, are highly species specific (i.e., human papillomaviruses [HPV], bovine papillomaviruses, canine papillomaviruses, etc.), demonstrate considerable tropism for particular anatomic sites, and primarily induce epithelial cell proliferation, or papillomas (Galloway, 1999). Each papillomavirus has its own degree of oncogenicity and can induce both benign and malignant disease.

Although the typical reservoir of HPV is the moist mucosa and adjacent cutaneous epithelia of male and female genitalia, HPV may infect any part of the body, including the upper aero-digestive tract and conjunctiva. HPV infections are very common and are likely the most prevalent sexually transmitted infectious agent (Cox, 1995; Franco, Schlecht, et al., 2003).

Over 100 types of HPV have been identified, of which about 40 infect the epithelium of the anogenital region (Muñoz et al., 2003). Currently, 13 HPV types have been sub-classified as high-risk — that is, they have relatively higher oncogenic potential than other HPV types (Cogliano et al., 2005). The so-called low-risk types are rarely, if ever, found in cervical cancer, and are more associated with sub-clinical and clinically visible benign lesions (condylomata) (Brown, Schroeder, Bryan, Stoler, & Fife, 1999).

18. Which HPV types are "high-risk"?

HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66 are considered high-risk types because they have been found in cervical and other lower genital tract cancers (Cogliano et al., 2005). However, they are also associated with "flat" warts and with pre-cancerous cervical lesions. Approximately 80% of cervical cancers are associated with only four types of the virus (16, 18, 31 and 45) (Muñoz et al., 2003). Type 16 predominates in women with squamous cell carcinoma, while type 18 is more common among women with adenocarcinoma of the cervix (Muñoz et al., 2003).

19. What is the role of HPV in cervical dysplasia and cervical cancer?

The prevailing theory for cervical carcinogenesis is a sexually transmitted disease model, with HPV as the putative infectious agent (Bosch, Lorincz, Muñoz, Meijer, & Shah, 2002; Walboomers et al., 1999). Relative risks for the association between oncogenic HPV types and cervical cancer are among the strongest in cancer epidemiology, with values ranging from 20–70 (Franco, Duarte-Franco, & Ferenczy, 2001). Moreover, laboratory results from cervical tumor specimens have shown that HPV DNA is present in 99.7% of cervical cancer cases (Walboomers et al., 1999). However, the mechanism of carcinogenesis of HPV infection is complex and, thus far, poorly understood.

20. How is HPV transmitted?

HPV is easily transmitted by intimate sexual activity, yet not restricted to penetrative vaginal intercourse (Kjaer et al., 2001; Marrazzo, Koutsky, Kiviat, Kuypers, & Stine, 2001; Winer et al., 2003). However, it is clear that although the vast majority of genital HPV infection is sexually transmitted, sexual transmission is not absolute. Fomite (from sex toys, underwear, exam tables, and other inanimate objects) and vertical modes of transmission have also been suggested, but these have been difficult to document and little research has been done to date (Bergeron, Ferenczy, & Richart, 1990; Watts et al., 1998). Transmission of more than one HPV type is common.

21. How common is HPV infection?

HPV is probably the most common sexually transmitted agent with conservative prevalence estimates between 5% and 40%, depending on the woman's age, country of residence, and the sampling technique (Franco, Villa, Richardson, Rohan, & Ferenczy, 1997; Winer & Koutsky, 2004b). In general, sexually active younger women are more likely than older women to have HPV DNA detected in genital tract specimens. Ho, Bierman, Beardsley, Chang, & Burk (1998) studied 608 female university students and found that genital HPV prevalence increased from 26% at baseline to approximately 60% at some point during the 3-year study period. Nevertheless, the majority of these infections are subclinical, unrecognized, and benign. In certain populations, however, an increase in prevalence at ages older than 45 has been observed (Herrero et al., 2000; Sellors et al., 2000). Further research is necessary to explain this bimodal distribution. The estimated prevalence of genital warts is only about 1%, and fewer than 10% develop detectable cervical subclinical HPV-induced lesions (Winer & Koutsky, 2004b).

22. What is the natural history of HPV infection?

Exposure to HPV is very common in the teens and twenties, soon after onset of sexual activity. Yet, the majority of HPV infections go unnoticed and do not exhibit any clinically visible signs or symptoms (Mao et al., 2003). Pre-cancerous and cancerous lesions, as well as condylomata, are therefore rare outcomes of HPV infection. For example, in a study of 608 university women, 60% were infected with HPV at some time during the three-year follow-up period, yet only 5% at this age range developed squamous intraepithelial lesions (SIL) (Ho,

Bierman, et al., 1998). The reason for this is the transient nature of HPV infection; in the same study, 70% of women were no longer infected at 12 months after incident infection, and only 9% were still HPV DNA positive at 24 months (Ho, Bierman, et al., 1998). The median duration of oncogenic HPV infection is 8 months (for HPV 16 the median is 10 months and for HPV 18 the median is 7 months) (Franco et al., 1999; Woodman et al., 2001). The biological reasons for HPV transience or why some individuals develop persistent infection are poorly understood. Presumably, infections are resolved by the immune system, are self-limited, or are suppressed into long-term latency. Little is known in particular about the possible latent state of the viral cycle; it is not known how frequently latency occurs, how long it can last, what causes re-emergence into a detectable state, and what fraction of cancers arises after a period of latency (Schiffman & Kjaer, 2003; Stubenrauch & Laimins, 1999). The best determinants of clearance of HPV infection are younger age, infection with low-risk types of HPV, and infection with one type of HPV (Franco et al., 1999). Clearance of infection is considerably slower (if at all) in HIV-infected women (Delmas et al., 2000). Moreover, a concrete definition of persistent infection has not been established, but several months to a year are currently considered the appropriate time frame.

23. Does barrier protection decrease the risk of HPV?

Condom use has not been consistently shown to reduce the risk of becoming HPV-positive, although this may be in part due to study methodological issues (Franceschi et al., 2002; Gerberding, 2004; Manhart & Koutsky, 2002). Although a properly applied condom would cover the parts of the penis where HPV infection has been demonstrated to occur, HPV infections have also been detected in sites not covered by a condom, such as the base of the penis, scrotum, groin, and anus (Weaver et al., 2004). Contamination of the external side of the condom may occur from contact with the vulva, an area where HPV infection may also be detected. Moreover, penile-vaginal intercourse is not necessary for HPV transmission; HPV can be transmitted via skin-to-skin as well as oral-genital contact (Genuis & Genuis, 2004; Marrazzo et al., 2001). However, some studies have shown a beneficial effect of condom use, both in preventing transmission and regression of cervical and penile lesions (Bleeker et al., 2003; Bleeker et al., 2005; Hogewoning et al., 2003). In one clinical trial, Bleeker et al. (2003) reported condom use was associated with accelerated regression of HPV-associated penile lesions; regression occurred significantly quicker among men who used condoms (7.4 months) versus men not using condoms (13.9

months). However, a recent study which followed young women for an average of 34 months, reported that women whose partners used condoms 100% of the time (during observed period) had a 70% reduced risk of acquiring HPV infection compared to women whose partners used condoms less than 5% of the time. (Winer et al,. 2006). Other studies have shown that male condom use reduces the risk of infection with genital herpes and Chlamydia, both of which may be cofactors in the etiology of cervical neoplasia (Castle & Giuliano, 2003; Smith, J. S., Herrero, et al. 2002; Smith, J. S., et al., 2004; Wald et al., 2001; Williams et al., 2002).

24. Are oral contraceptive users at increased risk for cervical cancer?

Use of oral contraceptives is suspected to be associated with cervical cancer, particularly among long-term users (Smith, J. S., et al., 2003). Recent epidemiologic research has shown a dose-response relationship exists, where around 5 years or more the risk is about three-fold compared to non-users (Smith, J. S., et al., 2003). The limited available data suggest that the risk of cervical cancer may decrease after use of oral contraceptives ceases. The association seems somewhat stronger for adenocarcinomas than for squamous cell carcinoma. Scant data are available concerning the mechanisms by which hormonal influences may modify the risk of progression to higher-grade lesions among HPV-infected women. Hormone-related mechanisms may influence HPV DNA integration into the host genome (International Agency for Research on Cancer [IARC], 1995). Studies using animal models indicate a synergistic mechanism between long-term estrogen exposure and HPV 16 oncogenes (Elson et al., 2000). However, study designs varied and there was a degree of heterogeneity between study results.

25. What about douching?

A handful of epidemiologic studies have reported marginally significant associations between douching and cervical cancer (Peters, Thomas, Hagan, Mack, & Henderson, 1986; Zhang, Thomas, & Leybovich, 1997). Peters et al. (1986) found a link between increased risk of cancer and both frequency of douching and number of years douched, and that women who regularly douched with commercial products were 2.4 times more likely to develop invasive cervical cancer than women who never douched, yet women who usually douched with water and vinegar showed no increased risk.

One plausible mechanism for elevated risk of cervical cancer with douching is that douching causes irritation of the vagina and cervix, and may destroy natural antiviral agents, thereby facilitating transmission of infectious agents like HPV. Douching after sex may push disease-causing agents, such as HPV, further into the body and make infection more likely. Furthermore, the constituents of the commercial douches, including tars and other chemicals, may have direct carcinogenic actions (Peters et al., 1986; Zhang et al., 1997).

26. Are smokers at increased risk for cervical cancer? By how much? Why are smokers at increased risk for cervical cancer?

A role for smoking has been observed for cervical cancer and its precursor lesions. However, the exact role of smoking has yet to be elucidated. Tobacco smoking may increase susceptibility to infection by HPV (Poppe, Ide, Drijkoningen, Lauweryns, & Van Assche, 1995), or have a direct carcinogenic effect on cervical tissue (Prokopczyk, Cox, Hoffmann, & Waggoner, 1997), or both. Some studies have demonstrated an elevated risk with number of cigarettes smoked and duration of smoking, with lower risks for former smokers (de Vet, Sturmans, & Knipschild, 1994; Kjellberg et al., 2000). Smoking seems to be a more important risk factor for higher-grade lesions and invasive cancer, suggesting a late-stage effect on carcinogenesis (Ho, Kadish, et al., 1998). In two recent IARC pooled analyses restricted to HPV-positive women, smokers had an approximately two-fold increased risk for invasive disease or CIN compared to those who had never smoked (Castellsague, Bosch, & Muñoz, 2002; Plummer et al., 2003).

Direct carcinogenic action of cigarette smoking on the cervix is conceivable since nicotine and tobacco-specific carcinogens have been detected in the cervical mucus of smokers. In one study, the tobacco metabolite 4-(methylnitrosamino)-L-(3-pyridl)-1-butannone was detectable in 15 out of 15 smokers and in only 1 out of 10 non-smokers (Prokopczyk et al., 1997). The traces of the substance found in the non-smoker were suspected to be from environmental exposure. Another plausible mechanism is via suppression of the local immune response to HPV infection (Poppe et al., 1995). The depletion of Langerhans cells has been correlated with the presence of HPV infection and reduced expression in cutaneous warts and in the squamous epithelium of smokers (Feldman, Chirgwin, DeHovitz, & Minkoff, 1997). Lastly, a prospective study (Giuliano et al.) conducted in 2002 presented convincing evidence that smokers maintain cervical HPV infections significantly longer than women who have never smoked.

27. How about passive smoke exposure?

Environmental tobacco smoke significantly increases the likelihood of pre-cancerous cervical lesions. A recent study reported the odds of detecting HSIL among women whose spouse was a cigarette smoker were increased 4.6% after adjusting for age, age at first sexual intercourse, oral contraceptive use, and the women's own cigarette smoking status (Tay & Tay, 2004). Furthermore, a dose-response effect has been observed; among nonsmoking women in Taiwan who were exposed to passive cigarette smoke, those exposed to the equivalent of 1–20 pack-years or more than 20 pack-years had an almost 2-fold (95% confidence interval 0.72–5.03) and 3-fold (95% CI 1.10–8.09) increased rate of cervical intraepithelial neoplasia, respectively (Wu et al., 2003).

28. What is the role of the male partner in dysplasia and cancer of the cervix?

Much consideration has been given to the role of men in the transmission and acquisition of HPV in women. Men likely act as carriers and vectors of HPV; surveys of sexual behaviour of the husbands or sexual partners of patients with cervical cancer and control respondents, as well as exfoliated cells from the penile shaft and the distal urethra, offer evidence of this fact (Bosch et al., 1996; Lazcano-Ponce et al., 2001; Adami & Trichopoulos, 2002; Svare et al., 2002). Pooled data from multicentre case-control studies coordinated by the IARC reported that the prevalence of penile HPV infection ranged between 3% and 39%, depending upon country and sampling technique (Franceschi et al., 2002). HPV-positive penile specimens were found in 21% of husbands of those women with *in situ* carcinoma, 18% of husbands of women with invasive cervical cancer, and 13% of husbands of control women. HPV types 16 and 18 were rare, but of these, HPV 16 was the most common. Moreover, the overall penile HPV prevalence appears to increase with increasing lifetime number of sexual partners of the men and with an early age at initiation of sexual intercourse.

29. Does the partner's occupation affect the patient's risk of developing cervical cancer?

Several investigators (Green 1979; Wakefield, Yule, Smith, & Adelstein, 1973) suggested that the partner's occupation may be significant if it involves exposure to carcinogens such as metals, chemicals, tar, and oils, which may be of etiological importance in the development of cervical cancer. More likely, the

partner's occupation may be important if it involved prolonged absence from home and extramarital activity, leading to a higher incidence of sexually transmitted infections (Bornstein et al., 1995).

30. What is the role of parity in cervical dysplasia?

Multiparous women are at increased risk of cervical dysplasia and invasive cancer independent of sexual behaviour. In general, a linear trend in the parity-risk relationship has been observed in large studies in North America and in Latin America (Brinton et al., 1989; Hildesheim et al., 2001). A pooled analysis of HPV-positive women in the IARC multicentre case-control studies confirmed this relationship for both squamous cell carcinoma and adenocarcinomas (Muñoz et al., 2002), although the trend of increasing risk with increasing parity was specific to squamous cell carcinoma. The odds ratio (OR) for cervical cancer in women with seven or more full-term pregnancies was four-fold higher than that in nulliparous women. More recently, a study from Finland reported significantly elevated standardized incidence ratios for parity (5 and 6 births) and CIN 3 as well as decreasing intervals between births (< 3.0 years) and CIN 3, yet these associations disappeared in the multivariate modeling (Hinkula, Pukkala, Kyyronen, Laukkanen, Koskela, Paavonen, et al., 2004). Nutritional, traumatic, immunologic, and hormonal mechanisms have been hypothesized as biologically plausible explanations for the association between high parity and cervical cancer (Castellsague & Muñoz, 2003; Hinkula et al., 2004).

31. What about sexually transmitted agents other than HPV?

Other sexually transmitted infections (STIs), particularly HIV, *Chlamydia trachomatis*, and herpes simplex virus type 2 (HSV-2), act as cofactors for HPV carcinogenesis of the cervix.

HPV-associated diseases, including genital warts and malignancies of the lower anogenital tract, are particularly common among HIV-infected women (Ahdieh et al., 2001; Conley et al., 2002; Jay & Moscicki, 2000). HIV infection impairs cell-mediated immunity, thus increasing the risk of infections by other agents, such as HPV. Both HPV prevalence and squamous intraepithelial lesion (SIL) prevalence estimates are at least 2- to 3-fold higher among HIV-positive women compared with their HIV-negative counterparts (see Table 1 below) (Ellerbrock et al., 2000). A meta-analysis of studies published between 1986 and 1998 indicated that HPV and HIV infection seem to interact synergistically to increase

risk of SIL, with some further mediation by the degree of immunosuppression (Mandelblatt, Kanetsky, Eggert, & Gold, 1999). The pooled odds ratio for HPV infection and neoplasia was almost 2 times higher among HIV-positive women compared with HIV-negative women.

Table 1: *The prevalence of HPV and SIL among HIV-positive and HIV-negative women according to Ellerbrock et al. (2000)*

	HPV Prevalence (%)	SIL Prevalence (%)
HIV-positive	40–95	10–36
HIV-negative	23–55	1–12

Co-infection of either *C. trachomatis* or HSV-2 with HPV might induce a local inflammatory response that could facilitate the establishment of an HPV infection. Epidemiologic studies have been generally consistent in detecting an association between *C. trachomatis* and invasive cervical cancer and its precursors (Anttila et al., 2001; Koskela et al., 2000; Smith, J. S. et al., 2004), although residual confounding by sexual activity cannot be ruled out. A study involving countries from the IARC multicentre study reported an odds ratio of 1.8 (95% CI, 1.2–2.7) for *C. trachomatis* seropositivity among HPV-positive women (Smith, J. S. et al., 2004). Furthermore, the effect appeared to be more relevant for squamous cell carcinoma than for adenocarcinoma.

An increased risk for cervical cancer for HSV-2 seropositivity has also been shown (Smith, J. S., Herrero, et al., 2002), although this has not been consistently verified (Lehtinen et al., 2002; Tran-Thanh et al., 2003). In the IARC case-control studies of HPV-positive women, an increased risk of 2-fold (OR = 2.0; 95% CI, 1.3–3.0) and 3-fold (OR = 2.6; 95% CI, 1.3–5.3) was observed with HSV-2 seropositivity for squamous cell carcinoma and adenocarcinoma, respectively (Smith, J. S., Herrero, et al., 2002). In contrast, Tran-Thanh et al. (2003) reported that HSV-2 (using PCR) was not detected in any of 439 cervical samples and 150 cervical cancer biopsy specimens.

32. Are any nutrients protective against cervical dysplasia or carcinoma?

Some attention has been given to the role of dietary factors and serum micronutrients in the etiology of cervical cancer. Epidemiologic studies have been relatively consistent indicating protective effects for consumption of vegetables

and fruit, beta-carotene, and vitamins A, C, and E (Giuliano et al., 2003; Kwasniewska, Charzewska, Tukendorf, & Semczuk, 1998; VanEenwyk, Davis, & Bowen, 1991). Other nutrients such as lycopene, tocopherols, and folates have also been shown to be inversely associated with risk (Cuzick, De Stavola, Russell, & Thomas, 1990; Kwasniewska, Tukendorf, & Semczuk, 1997; Palan et al., 1996). There is sufficient biological plausibility for a protective effect of a healthy diet for cervical neoplasia, particularly the potent antioxidants gained from diets high in vegetables and fruit. In addition to their anti-cancer benefits, dietary factors may also play a role in cervical immunity (Potischman & Brinton, 1996). However, assessing the effect of nutritional predictors is complicated by inadequate measures of factors like circulating micronutrients, in obtaining reasonably accurate diet intake information from interviews, and because of the multifactorial etiology of cervical cancer (Giuliano, 2000).

33. Can women who have sex with women (WSW) develop cervical dysplasia?

Data from studies on lesbians indicates that HPV infections are easily transmitted and that intercourse in which an infected penis enters the vagina is not strictly necessary for transmission (Marrazzo et al., 2001). Sexual contact is all that is necessary for transmission; in fact, self-inoculation from one site to another site is possible. Furthermore, most WSW (53%–99%) have a history of sexual intercourse with men and many continue to have sex with men (21%–30%) (Diamant, Schuster, McGuigan, & Lever, 1999; O'Hanlan & Crum, 1996). In one study, HPV DNA was detected in 13% of WSW and SIL occurred in women who reported never having sex with men (Marrazzo et al., 2001). According to Marrazzo et al. (2001), many WSW do not perceive themselves at risk for cervical cancer and a substantial proportion fail to ever have a Pap test or are screened irregularly, putting them at risk for cervical cancer. These two factors put WSW at risk for developing cervical neoplasia and invasive cancer.

34. What is the natural history of cervical dysplasia (i.e., regression, persistence, progression)?

Following infection with high-risk oncogenic HPV types, progression to detectable, pre-cancerous lesions can take 10 years or longer to manifest (Schiffman & Kjaer, 2003). Most invasive cervical cancers are diagnosed after age 45 (Parkin et al., 2002). Yet, there is a small subset of patients (approximately 9%) that appear to progress rapidly to invasive cancer, sometimes within a few months (Hildesheim et al., 1999).

The majority of low-grade SIL (LSIL) regress spontaneously, especially in women under age 35. A meta-analysis of data collected on SIL between 1966 and 1996 demonstrated that the likelihood of regression of LSIL was about 50% (Melnikow, Nuovo, Willan, Chan, & Howell, 1998). The likelihood of developing high-grade SIL (HSIL) or invasive cancer from LSIL at 24 months was about 21% and 0.15%, respectively. The likelihood of HSIL regressing was 35%, and the likelihood of progression to invasive cancer was less than 2%. Thus, the probability of SIL becoming invasive carcinoma increases with the severity of the dysplasia but does not occur in every case. The interpretation of studies that follow the natural history of dysplasia with biopsy diagnoses is difficult since the biopsies themselves may amount to treatment of these lesions.

35. What is the ratio of pre-cancerous to invasive cervical lesions?

A 2003 review of the literature indicated that for every incident case of invasive cancer found by Pap test, about 50 other cases of abnormal Pap tests are labeled as LSIL or HSIL (Franco, Schlecht, et al., 2003). A more conservative estimate of "true" pre-cancerous lesions of the cervix compared to invasive cancer is in the order of 10 to 1 (Koss, 1989). Based on Pap test results in Ontario women aged 20–69 in 2003, the ratio of LSIL/HSIL and HSIL to invasive cancer was about 150 to 1 and 26 to 1, respectively (CCO, 2006).

The challenge is to define which lesions are truly pre-cancerous and to appropriately triage and aggressively treat these lesions. Strategies to address this challenge, including HPV subtype genetic markers, warrant further study.

36. What is the role of illness associated with immunosuppression (e.g., organ transplantation), immunosuppressive drugs, and connective tissue diseases (e.g., systemic lupus erythematosus [SLE]) relative to dysplasia/neoplasia?

The following groups of women may be prone to immunosuppression and an increased risk of cervical dysplasia:

1. Renal transplant and other patients receiving immunosuppressive drugs (e.g., patients on steroid medications)
2. Cancer patients after treatment, particularly if drugs are used that induce immunosuppression

3. HIV-positive women (see Question 31 for more detail)
4. Women with SLE are at increased risk of atypia, regardless of previous cytotoxic therapy (Dhar et al., 2001; Cibere, Sibley, & Haga, 2001). Dhar et al. (2001) found that women with SLE were three times as likely to develop HSIL and 2.5 times as likely to develop LSIL compared to the general population.

The mechanism by which immunosuppression and immunosuppressive drugs increases the incidence of neoplasia is still uncertain. Immunosuppression most likely conveys a high risk for viral infection, including HPV and cofactors like *C. trachomatis* and HSV-2 (Palefsky & Holly, 2003). Hence, progression to invasive cancer among immunosuppressed individuals is likely not linked with immunosuppression per se, but to the inability to clear a persistent HPV infection.

The lack of precise biomarkers of cell-mediated immunity to HPV restricts many studies on the relationship between immunosuppression and incidence of neoplasia. Nevertheless, evidence of decreased number of Langerhans cells and levels of interferon-alpha in persistent dysplasia compared to those of regressed dysplasia strongly support a decreased local immune response (Connor, Ferrer, Kane, & Goldberg, 1999; Li, S., et al., 1999)

37. Are genital warts more prevalent among immunocompromised patients?

In general, HPV infections, including low-risk types most often associated with genital warts, are more common among individuals with immunologic deficiencies (Brown et al., 1999). Immunosuppression due to organ transplantation (Alloub et al., 1989), HIV infection (Ferenczy, Coutlee, Franco, & Hankins, 2003), pregnancy (Koutsky, Galloway & Holmes, 1988) and lupus (Yell & Burge, 1993) can cause recrudescence of an existing subclinical HPV infection.

For example, one group described a high prevalence of cutaneous warts in lupus erythematosus, regardless of whether the patients were taking immunosuppressive drugs. This observation suggests that there is a primary immunological defect among patients with lupus erythematosus. They also found this high prevalence among patients with discoid lupus (Yell & Burge, 1993).

38. What is the transformation zone?

The transformation zone is the area of the cervix where columnar cells of the endocervix meet squamous cells of the ectocervix – the area between the original squamous columnar junction (SCJ) (at birth) and the new SCJ (at present.) The location of the transformation zone varies among women. In teenage girls the transformation zone is on the outer surface of the cervix, where it is more susceptible to infection (particularly by oncogenic HPV) than in adult women. Because the transformation zone is an area of changing cells, it is the most common place for abnormal or pre-cancerous lesions to develop. However, abnormal lesions may arise in areas of the cervix outside the transformation zone, and research indicates inclusion of a transformation zone component in a screening liquid-based Pap test may not be necessary to detect high-grade lesions (Baer et al., 2002).

39. What is the Bethesda System? What are its strengths and weaknesses?

The Bethesda System for classifying the results of cervical cytology (Pap tests) was developed in 1988, and revised in 1991 and 2001, to provide a uniform system of terminology and standardized cytological interpretations (National Cancer Institute Workshop, 1989). The Bethesda System is now widely used across North America: in 2003, the OCSP introduced revised terminology consistent with the 2001 Bethesda System. The 2001 revised system reflects the most up-to-date knowledge about the biology of Pap test abnormalities and emerging technologies (Solomon et al., 2002). The Bethesda System itself does not include guidelines on how to manage abnormalities. Rather, it facilitates communication of test results between laboratories and physicians. The categories of abnormal cells are reviewed in questions 40–49. (See Appendix A for further details regarding the Bethesda System.)

As mentioned, one of the strengths of the Bethesda System is that it provides uniform diagnostic terminology to facilitate unambiguous communication between the laboratory and the clinician (Henry, 2003). It also requires an evaluation of specimen adequacy, and encourages a descriptive diagnosis of abnormalities. Furthermore, Henry (2003) stated that the Bethesda System eliminates Pap class numbers.

40. What does it mean when a Pap test is reported as "satisfactory for evaluation"?

The 2001 Bethesda System has two specimen adequacy categories: "satisfactory for evaluation" and "unsatisfactory for evaluation" (see Appendix A). The category "satisfactory for evaluation but limited by…" was eliminated. The presence or absence of a transformation zone (see Question 39) component or any other quality indicators may be provided after "satisfactory for evaluation."

A Pap test reported as "satisfactory for evaluation" implies that the test contains either normal squamous metaplastic and endocervical cells or abnormal cells (Canadian Society of Cytology, 1994). Minimum requirements for specimen adequacy of "satisfactory for evaluation" differ depending on the specimen sampling method: about 8,000–12,000 well-visualized squamous cells for conventional Pap tests and 5,000 for liquid-based samples (Solomon et al., 2002). The number of cells with a transformation zone component is the same as the 1991 Bethesda System; there should be at least 10 well-preserved endocervical or squamous metaplastic cells (clusters are no longer required) (Solomon et al., 2002).

Table 2: *Factors influencing the proportion of adequate* tests (Davey et al., 2002; Selvaggi & Guidos, 2000).*

Factor	Effect on proportion of adequate tests
Shape of spatula	Higher with narrow top
Oral contraceptive use	Lower
Pregnancy	Lower
Person who takes sample	Low for inexperienced practitioners
Postmenopausal	Lower
Use of cervical brush	Higher
Use of cervical broom	Higher

* Samples containing cells from the transformation zone (see Question 38)

41. Should a patient come back for a repeat Pap test if the endocervical component is absent?

Mitchell (2001) reported no significant differences in outcomes for women with the endocervical component detected on both initial and repeat Pap tests, compared with women who had the endocervical component missing

on the first Pap test and present on the second. The American Society for Colposcopy and Cervical Pathology recommends a repeat Pap test in 12 months (Davey et al., 2002). Earlier repeat testing (i.e., within 6 months) may be necessary if the patient has not had regular Pap tests, has a history of previous abnormal Pap tests, or has additional risk factors for cervical intraepithelial lesions and cancer.

42. What is LSIL?

In the Bethesda System, the confusing terms "mild dysplasia," "koilocytotic effect," "CIN 1," and "condyloma" are combined into one category: low-grade squamous intraepithelial lesions, or LSIL. This single label implies that all the aforementioned situations represent an epithelial abnormality with little or no oncogenic risk. In LSIL, early changes in the shape, size, and number of abnormal cells is evident (Meyers & Cox, 2005). Eliminating "HPV effect" and "koilocytosis" reduces the temptation to over-interpret perinuclear haloing as koilocytes and reflects more closely the natural history of these changes over time (i.e., about 50% will regress without treatment) (Melnikow et al., 1998).

43. What is the recommended follow-up for women with LSIL?

The Ontario Guidelines recommend that patients with an LSIL Pap test should have either repeat cytology in 6 months or be referred for colposcopy (see Appendix B) (McLachlin, Mai, Murphy, Fung-Kee-Fung, & Chambers, 2005). The following is the rationale for this treatment recommendation:

a) About 10% of women with LSIL Pap tests have HSIL on colposcopic biopsy (Duggan, M. A., & Brasher, 1999).
b) Likelihood of progression from LSIL to HSIL or invasive cancer is about 10%–20% (Melnikow et al., 1998) and progression typically takes years (6–7 years on average) (Schlecht, Platt, Duarte-Franco, Costa, Sobrinho, Prado et al., 2003).
c) The prevalence of HPV infection among women diagnosed with LSIL is 83%, making HPV DNA testing of low clinical utility as a triage test (ASCUS-LSIL Triage Study [ALTS] Group, 2003).
d) Although younger patients (especially <25 years) have a high incidence of LSIL, the rate of regression is considerable (61% regress by 12 months and 91% regress by 36 months) (Moscicki et al., 2001) and they have a very low incidence of cervical cancer. Therefore,

repeat cytology is preferred over colposcopy in younger women and in settings where follow-up can be tracked (McLachlin et al., 2005).

There is little data on referral patterns for LSIL Pap test results. However, there are concerns that referring all women with LSIL for colposcopy will potentially over-treat certain populations (especially younger women) among whom LSIL is likely to regress. In addition, the psychological stress of unnecessary colposcopy cannot be underestimated. Furthermore, unnecessary colposcopy will potentially also block access to other patients needing evaluation.

44. What is HSIL?

Moderate to severe dysplasia, CIN 2, CIN 3, and carcinoma in situ have been gathered into one category: high-grade squamous intraepithelial lesions, or HSIL. It has been established that these lesions all have a significant risk of progressing to cancer if untreated (i.e., pre-cancerous cells) (Holowaty, Miller, Rohan, & To, 1999; Melnikow et al., 1998). The older terms were combined based on the assertion that they are indistinguishable morphologically in any reproducible fashion, even with expert slide analysis (Sherman, Schiffman, Erozan, Wacholder, & Kurman, 1992; Solomon et al., 2002).

45. Why should HSIL be referred for colposcopy?

HSIL require colposcopy and histologic diagnosis with no exceptions since these are the lesions that may progress to invasive carcinoma of the cervix (Meyers & Cox, 2005). Refer to Question 34.

46. How do LSIL and HSIL correlate with CIN 1, 2, and 3?

Critics of the Bethesda System note that the two-tiered terminology of LSIL and HSIL provides less information to clinicians than the three-tiered CIN or dysplasia terminology (Henry, 2003). Some clinicians contend that patients who have a cytologic interpretation of CIN 2 (moderate dysplasia) should be managed differently than patients who have CIN 3 (severe dysplasia/carcinoma in situ). Similarly, some assert that the dividing line between LSIL and HSIL was set incorrectly (Henry, 2003). LSIL consists of CIN 1, while HSIL includes CIN 2 and CIN 3. Some investigators believe that the natural history of CIN 2 is closer to that of CIN 1 than it is to that of CIN 3. Another criticism, according to Henry (2003), is that a given cytologic diagnosis should not be considered

absolute, but rather should indicate that there is a certain probability that a specific grade of histologic lesion is present on the cervix. This criticism takes into account the inherent error rate associated with cervical cytology. One study found that approximately 15%–18% of women who have LSIL on cervical cytology have CIN 2 or CIN 3 when biopsy is performed (Jones & Novis, 2000).

Despite these criticisms, there is convincing virologic, molecular, and clinical evidence that the dichotomous categories used in the Bethesda System are fairly specific. For example, HPV infections associated with LSIL results are generally transient, whereas those found in HSIL results are often associated with viral persistence and increased risk of cancer (Einstein & Burk, 2001; Park, Richart, Sun, & Wright, 1996; Wright & Kurman, 1994; zur Hausen, 2000). Additionally, findings from the ALTS Study showed the diagnostic cut-point between LSIL and HSIL is reproducible and that subdividing HSIL results into moderate or severe dysplasia or CIN 2 or 3 is not reproducible (Schiffman & Solomon, 2003; Solomon et al., 2002).

47. What is the significance of "ASCUS" and "ASC-H" on a Pap test report?

The 1988 Bethesda System included a category termed "atypical squamous cells of undetermined significance (ASCUS)," implying that the cytopathologist observed squamous atypia of uncertain significance. The updated 2001 Bethesda System has revised this category to "atypical squamous cells," subdivided into two categories: those of unknown significance (ASCUS) and those in which high-grade lesions cannot be excluded (ASC-H) (CCO, 2002b; Solomon et al., 2002). (See Appendix A, Conversion Table.) The ALTS Study Group (2003) reported that approximately 5% of all Pap tests in the USA have an ASCUS interpretation. In Ontario, the proportion of Pap tests labeled as ASC ranges between 2% and 3% (CCO, 2006).

If the result is ASCUS and the patient is younger than age 30 years, the patient should have a repeat Pap test in 6 months. If the repeat test is abnormal (i.e., ASCUS or higher), the woman should be referred for colposcopy. If negative, the test should be repeated in another 6 months. Once a woman has had two negative Pap tests, she can return to routine screening (McLachlin et al., 2005). If an ASCUS result occurs and the woman is age 30 or older, she should be sent for HPV DNA testing, where available (if HPV DNA testing is not available, follow guidelines for women under age 30). If the patient is positive for HPV DNA

she should be referred for colposcopy; if it is negative, Pap testing should be repeated in 12 months (McLachlin et al., 2005).

If an interpretation of ASC-H is reported, then the woman should be referred for colposcopy (see Question 48).

48. How do you manage an ASC-H Pap test result?

Pap test results of atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H) are recommended for referral to colposcopy (McLachlin et al. 2005). Results from two trials showed a high number of ASC-H cases have underlying LSIL or HSIL pathology (Selvaggi, 2003; Louro, Roberson, Eltoum, & Chhieng, 2003). In one of the trials, from 22 cases of ASC-H out of 9, 214 Pap tests sampled, 2 cases were colposcopically identified as LSIL and 15 cases as HSIL (Selvaggi, 2003). The authors concluded that given the high proportion of cases confirmed as LSIL or HSIL, women with ASC-H Pap results should be referred for colposcopy.

49. What are "atypical endocervical cells," "atypical endometrial cells," and "atypical glandular cells" on a Pap test?

Changes to the Bethesda System in 2001 now classify glandular cell abnormalities of undetermined significance into three categories: atypical endocervical cells, atypical endometrial cells, or atypical glandular cells, all of which are subclassified as "not otherwise specified" or "favour neoplasia" (Solomon et al., 2002). The former term, "atypical glandular cells of undetermined significance (AGUS)," was eliminated to prevent confusion with ASCUS.

These categories (collectively known as "atypical glandular cells," or AGC) are associated with a greater increased risk for cervical neoplasia than ASC or LSIL categories (Ronnett et al., 1999). Different studies have reported the underlying prevalence of high-grade lesions (either squamous or glandular) or invasive carcinoma to range from 10%–39% and 1%–9%, respectively (Chan & Cheung, 2003; Eddy, Strumpf, Wojtowycz, Piraino, & Mazur, 1997; Hammoud, Haefner, Michael, & Ansbacher, 2002; Jones & Novis, 1996, 2000; Ronnett et al., 1999; Soofer & Sidawy, 2000; Valdini, Vaccaro, Pechinsky, & Abernathy, 2001; Zweizig, Noller, Reale, Collis, & Resseguie, 1997). Certain studies have also noted a difference between "not otherwise specified" and "favour neoplasia" specifications in terms of their relative risk for significant disease, either squamous or glandu-

lar. A somewhat higher risk of high-grade lesions has been reported for "favour neoplasia" (Jones & Novis, 2000; Ronnett et al., 1999; Valdini et al., 2001; Zweizig et al., 1997).

Women with an AGC interpretation should be referred for colposcopy and receive endocervical and endometrial sampling (McLachlin et al., 2005).

50. What about endocervical adenocarcinoma in situ?

Adenocarcinoma in situ (AIS) is a premalignant lesion of glandular origin. Infection with HPV type 18 and use of oral contraceptives for six years or more have been cited as significant risk factors for AIS (Madeleine et al., 2001). Several studies indicate AIS incidence has been increasing over the past decade (Alfsen, Thoresen, Kristensen, Skovlund, & Abeler, 2000; Kennedy & Biscotti, 2002), possibly, in part, due to better endocervical sampling devices, better morphologic definitions, and awareness by pathologists (Lee et al., 2002; Mody, 1999; Roberts, Thurloe, Bowditch, Humcevic, & Laverty, 1999). However, compared with squamous cell lesions, AIS is rare and its management remains controversial.

In general, AIS is not as easily recognized or categorized as other cervical lesions. Sensitivity of cytology for detecting AIS is not optimal. Pap tests have been estimated to detect between 38% and 70% of AIS cases (Lee, Minter, & Granter, 1997; Levine, Lucci, & Dinh, 2003; Mitchell, Medley, Gordon, & Giles, 1995; Muntz et al., 1992; Nieminen, Kallio, & Hakama, 1995; Wright, Cox, Massad, Twiggs, & Wilkinson, 2002). Additionally, there is significant variability in interpretation of glandular lesions (Lee et al., 2002; Raab, Geisinger, Silverman, Thomas, & Stanley, 1998) and the false negative rates tend to be higher than for other lesions. Renshaw et al. (2004), using pathologists' reviews in the 2001 and 2002 College of American Pathologists Interlaboratory Comparison Program in Cervicovaginal Cytology Program, calculated the false negative rate for AIS to be 11.7% compared with 4.6% for HSIL, 3.3% for squamous cell carcinoma, and 8.9% for adenocarcinoma. The existence of morphologic features that increase the likelihood of false negative interpretations is not currently known.

If AIS is suspected, the patient should be referred for colposcopy. An excisional cone biopsy extending deep into the endocervical canal is necessary to confirm the diagnosis and to exclude the presence of invasive adenocarcinoma (Krivak

et al., 2001). Excisional biopsy techniques include cold knife cone, laser excisional cone, and loop excision, of which cold knife conization has been reported as the most reliable (Krivak et al., 2001; Ostor, Duncan, Quinn, & Rome, 2000; Shin, Schorge, Lee, & Sheets, 2000; Shipman & Bristow, 2001). However, complete removal of the lesion is often not achieved with conization and the risk of persistent disease is related to the margin status and is low if the margin is negative (Azodi et al., 1999; Krivak et al., 2001; Ostor et al., 2000; Shin et al., 2000). In addition, AIS can be multi-focal, accounting for persistence even among patients with negative margins (Hopkins, 2000; Shipman & Bristow, 2001). Residual AIS may exist in approximately 80% of cases with positive conization margins and 0%–44% of cases with negative margins (Azodi et al., 1999; Hopkins, 2000; Shipman & Bristow, 2001; Widrich, Kennedy, Myers, Hart, & Wirth, 1996).

Because of the high likelihood of residual AIS with conservative treatment (i.e., conization alone), the traditional treatment for AIS is hysterectomy, or at a minimum repeat conization if the margins are not clear. However, AIS is often discovered in younger women and treatment may be influenced by whether the patient desires fertility preservation. Whether a patient should have a hysterectomy after childbearing is complete and after negative follow-up remains controversial.

51. What is the significance of "invasive adenocarcinoma" on a Pap test report?

In Ontario, about 26% of cervical cancers start in glandular tissue (i.e., adenocarcinoma and adenosquamous carcinoma) (Marrett, Innes, Howlett, & Cotterchio, 2005). The precise anatomic origin of malignant cells consistent with invasive adenocarcinoma may be difficult to specify since endocervical adenocarcinomas have histologic appearances similar to endometrial adenocarcinomas (Ansari-Lari, Staebler, Zaino, Shah, & Ronnett, 2004). An endocervical origin is more likely in premenopausal women while an endometrial, fallopian tube, or ovarian origin is more likely in postmenopausal women. However, age is not an absolute discriminator. The incidence of endocervical adenocarcinoma has increased recently in women aged 35 and under, doubling in most technologically advanced countries in the last two decades (Liu et al., 2001; Vizcaino et al., 1998; Wang, Sherman, Hildesheim, Lacey, & Devesa, 2004). In Ontario, a recent trend analysis revealed a significant decrease by 4.0% per year (95% CI: -7.4%, -0.5%) in adenocarcinoma of the cervix since 1995 (Howlett et al., 2006). See also Question 2.

Moreover, distinguishing between endocervical versus endometrial origins using fractional curettage is not definitive since these can be present in either or both fractions (Ansari-Lari et al., 2004). Recent research is attempting to identify cell markers (e.g., immunohistochemical markers) to identify the origin of the adenocarcinoma. Further diagnostic imaging of the genital tract, cone biopsy, and endometrial biopsy can be completed by a gynecologist or referral made to a gynecological oncologist for further assessment and treatment.

52. How has the Bethesda System affected colposcopy referrals?

In the United States, data indicate colposcopy referrals have increased, especially secondary to the ASCUS and AGC categories. Since the introduction of the Bethesda System, the prevalence of abnormal Pap tests has doubled from 5%–10% in the United States, particularly because of atypical squamous (or glandular) cells of undetermined significance (Guidozzi, 1996; Melnikow, Sierk, Flocke, & Peters, 1993). Similarly, one study observed patients received follow-up testing for ASCUS and AGC at shorter intervals than those suggested by the practice guidelines despite a low likelihood of finding high-grade lesions (Suh-Burgmann, Darragh, & Smith-McCune, 1998).

Colposcopy data is not yet collected at a provincial level in Ontario. Further information on how practice could be better informed is necessary; the final report of the Ontario HPV Pilot will be published in 2007, and will address the impact of reflex HPV-DNA testing on colposcopy, after implementation of the 2001 Bethesda System.

53. Why is the Pap test a good screening test?

The Pap test for cervical cancer fulfills all the criteria for a good screening test. It is cost-effective, acceptable to most patients, adaptable to widespread screening, and is sensitive enough to detect preinvasive disease, resulting in decreased morbidity and mortality.

There is convincing evidence that the Pap test for cervical cytology reduces morbidity and mortality from cervical cancer (see Question 10) (Peto et al., 2004; Quinn et al., 1999; Sawaya, Brown, Washington, & Garber, 2001). Furthermore, more than half the new cases of cervical cancer will be diagnosed in women who have not received proper screening (Colgan, Clarke, Hakh, & Seidenfeld, 2002; National Institutes of Health, 1996).

54. How did the Pap test come to be? What about the Ayre spatula?

In or about the year 1924, George N. Papanicolaou, MD, PhD, an investigator interested in endocrinology of the menstrual cycle, made an incidental observation that cancer cells from the uterine cervix could be observed in human vaginal cytology (Koss, 1989; Papanicolaou, 1928) In 1947, a Canadian gynecologist, J. Ernest Ayre, MD, found that using a wooden spatula was more efficient and produced a sample from the uterine cervix that was easier to examine than vaginal pooled cytology (Ayre, 1947; Koss, 1989). Shortly after the introduction of the test, it was noted that cancerous changes still confined to the epithelium of the uterine cervix (carcinoma in situ) could be identified in the cytologic samples (Ayre, 1948; Foote & Li, 1948; Koss, 1989; Pund, Nieburgs, Nettles, & Caldwell, 1947). Since the name Papanicolaou is long, the term Pap test was coined and applied to the screening procedure that entered slowly into the mainstream of laboratory testing (Koss, 1989).

55. What is the sensitivity and specificity of the Pap test?

A meta-analysis of 62 studies on cytology conducted between 1984 and 1992 reported a mean sensitivity of 58% (range: 11%–99%) and a mean specificity of 68% (range: 14%–97%) (Fahey, Irwig, & Macaskill, 1995). A more recent review reported sensitivity and specificity ranges of 30%–87% and 86%–100%, respectively (Nanda et al., 2000).

56. What are the false-positive and false-negative rates associated with the Pap test?

The Pap test has an estimated false-positive rate of less than 1%, but a false-negative rate ranging from 15%–40%. A truly negative cytology is a satisfactory test with no malignant cells and no evidence of dysplasia. False-negative tests that do not reflect underlying pathology arise because of inadequate cell sampling or because abnormal cells are missed or misinterpreted (Association of Reproductive Health Professionals, 2005). However, repetition of the Pap test usually compensates for this (by improved specificity) (Mayeaux, Harper, Abreo, Pope, & Phillips, 1995), and if an abnormality is missed on one test it is usually detected with the next.

57. How often should Pap tests be done?

Numerous recommendations have been made on screening intervals (ACOG Practice Bulletins, 2003; IARC Press Release No. 151, 2004; Saslow et al., 2002; Wright et al., 2002). Despite a large body of scientific literature, considerable uncertainty regarding the optimal screening interval remains.

A prospective cohort analysis of a randomized controlled trial found that among 2,561 women (mean age 67 years) with normal Pap tests at baseline, only 4% had an abnormal Pap test within 2 years of follow-up (Sawaya, Grady, et al., 2000). None of the women developed HSIL, while one woman was diagnosed with LSIL. The positive-predictive value of screening 1 year after a negative test was 0%, compared with 0.9% after 2 years. The authors concluded there is no significant benefit for repeat Pap tests within 2 years of a prior negative test.

Other reports have recommended that women aged 25–49 years should be screened every 3 years, while women aged 50 years or older should undergo screening every 5 years (IARC Press Release No. 151, 2004).

The Ontario Guidelines recommend that any woman who is sexually active and who has had three consecutive negative tests at one-year intervals can be screened every two to three years thereafter (Appendix B). Annual Pap tests are still advocated in high-risk groups (i.e., patients who have multiple sexual partners and a history of sexually transmitted disease), particularly immunosuppressed and immunodeficient patients (i.e., HIV positive, transplant recipients, recently undergone chemotherapy) (McLachlin et al., 2005). Those previously treated for dysplasia also warrant yearly screening (McLachlin et al., 2005).

58. How do you take a Pap test?

Pap tests can be done by conventional methods or liquid-based cytology (LBC) (see Question 74). To obtain a cell sample from the uterine cervix, the cervix must be visualized with a vaginal speculum. Lubricant should not be used to avoid contamination of the cell sample with foreign material (Koss, 1989).

Complete instructions for conventional cytology are detailed on the Ontario Cervical Screening Reference Card (Appendix C). Instructions for liquid-based cytology are provided by the manufacturer and included in the test kit.

59. Does the method of sampling or choice of sampling instrument matter?

Correct methods of sampling are essential for obtaining adequate cervical samples for cytological diagnosis of cervical abnormalities. In particular, an adequate sample will include cells from both the endocervix and ectocervix.

With the introduction of the combined spatula and endocervical brush/broom method, the number of tests containing cells from the transformation zone (adequate tests) has increased significantly. Several studies have demonstrated improved sampling using the combined method compared to the spatula or brush/broom alone (Chalvardjian, De Marchi, Bell, & Nishikawa, 1991; Davey-Sullivan, Gearhart, Evers, Cason, & Replogle, 1991; Rammou-Kinia, Anagnostopoulou, & Gomousa, 1991). For instance, one study found that the combined method produced at least a 3% increase in correct diagnoses compared with the brush alone (Buntinx, Boon, Beck, Knottnerus, & Essed, 1991).

It is anticipated that the combined spatula and brush/broom sampling method (as well as the introduction of LBC) will result in fewer repeat and false-negative tests, and the observed relative increase of endocervical adenocarcinoma may be halted (Kristensen, Holund, & Grinsted, 1989) (see Questions 2 and 11). A recent study in Ontario suggests that this dual sampling method is associated with effective detection and reduced incidence of adenocarcinoma (Howlett et al., 2006).

60. For a conventional Pap test, should the cotton-tipped applicator still be used to sample the endocervical canal? What is the advantage of using the endocervical brush or broom?

The use of a cotton-tipped swab (moistened or not) is not recommended. Boon, de Graaff Guilloud, and Rietveld (1989) showed that a significant amount of cellular material becomes trapped in the network of cotton fibres and thus lost to diagnostic evaluation. Since the introduction of the endocervical brush and broom, research has shown that the cotton swab is relatively inferior for collecting an adequate endocervical sample (Chalvardjian et al., 1991; Davey-Sullivan et al., 1991; Schettino et al., 1993). The combined spatula and brush/broom method is also superior to the combined spatula-cotton swab method in obtaining endocervical cells (Koonings, Dickinson, d'Ablaing, & Schlaerth, 1992;

Kristensen et al., 1989). This is a logical effect of sampling in a higher part of the endocervical canal.

The cells in endocervical brush samples are not deformed but are spread smoothly with the mucus onto the slide (Chalvardjian et al., 1991).

It is unclear as to whether the endocervical brush/broom increases the detection of cervical abnormalities or affects clinical outcome; however, it is clear that the detection of pre-cancerous lesions is related to an adequate cervical sample containing endocervical cells (Luzzatto & Boon, 1996). Use of the brush/broom appears to improve the contribution of the endocervical sample relative to the cotton swab. The brush/broom is more expensive than the cotton swab, but studies suggest that this cost is easily recovered by the reduced need for repeat testing (Harrison, Hernandez, & Dunton, 1993).

61. Should one or two slides be used when taking a conventional Pap test?

A single slide with endocervical and ectocervical samples is more economical than two slides and is sufficient for diagnosis (Quackenbush, 1999).

62. How do you prevent "drying artifact" in a conventional Pap test?

To prevent air-drying artifacts, the cytology must be fixed rapidly. This is done either by immersing it in a fixative, such as 70% alcohol, for 20 minutes or by spraying the surface with one of the commonly available fixatives (American Society of Cytopathology [ASC], 2005). The fixative should be held at an optimal distance of 25 cm between the spray bottle nozzle and the slide (ASC, 2005). This prevents drying artifact, particularly with postmenopausal women who are not taking hormone replacement and who may have only scanty mucus surrounding the harvested cells.

63. At what age should Pap test screening start? Why are low-risk patients screened every 2–3 years?

The Ontario Guidelines for cervical screening recommend annual screening for all women who are sexually active. After 3 consecutive negative Pap tests, screening should be repeated every 2 to 3 years to age 69 if there is an ade-

quate negative screening history in the previous 10 years (i.e., 3–4 negative tests). If a recall mechanism is in place, screening at a 3-year interval is sufficient. However, more frequent screening for women at increased risk is recommended (McLachlin et al., 2005). (Refer to Question 57.)

There is little evidence that women who receive annual screening are at significantly lower risk for invasive cervical cancer than are women who are tested every 3 years. These findings were confirmed in a retrospective study of 938,576 women younger than 65 years who participated in the Centre for Disease Control's (CDC) cervical screening program (Sawaya et al., 2003).

Table 3: *The estimated risk of invasive cervical cancer among women screened annually for 3 years compared with those screened once every 3 years after the last negative Pap test*[a]

Age group	Interval between screening[b]	
	1 year	3 years
30–44	2	5
45–59	1	2
60–64	1	1

[a] Projected outcome based on Markov modeling in hypothetical cohorts of 100,000 women

[b] If ≥ 3 previous negative Pap tests

According to Sawaya et al. (2003), preventing one additional case by screening 100,000 women annually for 3 years, compared with once every 3 years after the last negative test, requires (on average) 69,665 additional Pap tests and 3,861 colposcopic examinations among women aged 30–44 and (on average) 209,324 Pap tests and 11,502 colposcopic exams among women 45–59.

64. What is the yield of abnormal Pap tests in teens with recent sexual activity?

Screening of women who have only recently become sexually active (e.g., adolescents) is likely to have low yield. The incidence of invasive cancer in women under age 25 is only about 1–2 per 100,000 (it is estimated at 0 per 100,000 among those younger than 20 years), a rate that is much lower than that of older age groups (Marrett et al., 2005; Saslow et al., 2002). Moreover, it takes several years (about 10) before invasive cancer manifests following initial HPV infection. In general, regression of HPV infection is high; approximately 70% of

high-risk types and 90% of low-risk types regress in adolescent women (Ho, Bierman, at al., 1998; Moscicki et al., 1998; Saslow et al., 2002). Regression of LSIL is also more likely among this age group, with 61% at 12 months and 91% at 36 months (Moscicki et al., 2004).

65. Should a virgin be screened with Pap tests?

Women who have never been sexually active, especially women under age 25, are at low risk for cervical cancer and therefore do not require screening (McLachlin et al., 2005). This is because women who have not had vaginal sexual intercourse are highly unlikely to become infected with HPV. However, their risk of developing cervical cancer is not zero and clinicians should proceed with caution because patients do not always report their sexual experiences. One study (of 132 women aged 18–42 years) reported detecting genital HPV lesions among 88 women who had never had intercourse (Frega et al., 2003). The authors suggested that other modes of transmission, such as vertical transmission, fomites (objects, such as clothing, towels, and utensils that may harbour infectious agents), and skin-to-skin contact (including non-penetrative vaginal sexual activity) were likely. Thus, although women who have not had sexual intercourse do not need Pap tests, screening may be justified if the credibility of the sexual history is in question.

66. What is the appropriate Pap test screening regimen for the elderly female patient?

Ontario Guidelines indicate screening may be discontinued at age 70, provided the woman has had three consecutive negative tests over the past 10 years (McLachlin et al., 2005). In general, the incidence of cervical cancer in older women is related to those who are never or seldom screened (Sawaya, Kerlikowske, Lee, Gildengorin, & Washington, 2000; Sigurdsson, 1999).

67. Should Pap tests be done in women after hysterectomy?

Women who have undergone a hysterectomy in which the cervix was removed (for benign reasons) and who have no history of cervical dysplasia or HPV infection may discontinue cervical screening (McLachlin et al., 2005). Pap tests following hysterectomy for benign diseases are not cost-effective.

Post-hysterectomy screening has the potential to detect vaginal cancer, but the yield and predictive value are very low (Pearce, Haefner, Sarwar, & Nolan,

1996). The incidence of vaginal cancer is also very low. Women who have had sub-total hysterectomies, where the cervix was left behind, still require screening (McLachlin et al., 2005).

68. Can a Pap test be done if a patient is menstruating?

Pap tests should be scheduled for a week or more after menses because blood washes off exfoliated cells resulting in hypocellular cytology (ASC, 2005). Abundant blood may obscure the epithelial cells on the slide and the quality of the cells is less optimal (degenerative changes).

To further optimize collection conditions, women should not douche, use tampons, birth control foams, jellies, or other vaginal creams or vaginal medications, and they should refrain from sexual intercourse for 48 hours prior to the test (ASC, 2005). However, a Pap test should not be delayed if the patient is menstruating and recall is difficult.

69. Can a Pap test be done during an active genital tract infection?

If inflammation or cervical infection is present, a culture should be taken and the patient treated according to its results. Her Pap test should be deferred until after treatment is successful (McLachlin et al., 2005).

70. What is the significance of endometrial cells in a Pap test?

The detection of endometrial cells in a Pap test was only reported for post-menopausal women in the previous version of the Bethesda System. In the updated 2001 Bethesda System, endometrial cells are noted if the woman is age 40 or older, regardless of the date of the last menstrual period (Solomon et al., 2002). Identification of endometrial gland cells not associated with menses or after menopause may indicate risk for an endometrial abnormality (Montz, 2001). Between 0% and 26% of women over age 40 with endometrial cells detected on cytology have endometrial carcinoma; 2.9% to 43% have endometrial hyperplasia (Browne, Genest, & Cibas, 2005). Women with evidence of AGC on cytology are also at risk for endometrial cancer; in one study, 11 out of 114 women with AGC had endometrial cancer detected (Hammoud et al., 2002). In another study, 5 out of 43 women had AGC (Chan & Cheung, 2003). The endometrium should, therefore, be assessed. Endometrial sampling and/or

vaginal ultrasound is appropriate for all postmenopausal women with endometrial cells on the Pap test.

71. What is the role of vaginal estrogen cream in the management of an abnormal Pap test?

In postmenopausal women, epithelial atrophy may be confused with LSIL. However, there is little evidence of efficacy of intravaginal estrogen cream to reverse cytologic changes in postmenopausal women with LSIL (Abati, Jaffurs, & Wilder, 1998; McLachlin et al., 2005).

72. Should an abnormal Pap test be repeated within a day or weeks of the first one?

It is misleading to obtain a second cytology within a few days or weeks after the first one, either to confirm the previous results or to clarify the diagnosis in "atypical" cases. The sensitivity of a single repeat test for detecting SIL is relatively low (Wright et al., 2002). For unknown reasons, the second sample may be completely negative in patients with significant neoplastic lesions. Thus, in many cases, the first abnormal test is considered a "laboratory error" and instead of being referred for further care, the patient is reassured. This setting is an invitation for greater problems because some women in these situations may develop cancer of the cervix. Ideally, tests (including possible colposcopy) should be repeated 6 months later (McLachlin et al., 2005).

73. Is there any sense in doing a Pap test of a lesion that is clinically suspicious for cancer?

With invasive cancer, the surface of the lesion is often necrotic and covered by debris, and the test can fail to reveal obvious cancer cells. The Pap test does not replace a careful clinical examination. A biopsy must be done of any visible, suspicious cervical lesions (McLachlin et al., 2005).

The Pap test failure rate in diagnosing invasive cancer can be as high as 50% (Fahey et al., 1995). Careful inspection of the cervix and lower genital tract for areas of nodularity and friability should be part of each examination (Wright et al., 2002).

74. What is liquid-based cytology (LBC)? How is LBC different from a conventional Pap test?

LBC is a variation of conventional cytology (i.e., Pap test). Two liquid-based techniques are available: ThinPrep (Cytyc Corporation; Boxborough, MA) and SurePath (formerly AutoCyte; TriPath Imaging; Burlington, NC). The sample is collected in a similar way to the conventional Pap test, using a spatula and endocervical brush/broom combination. Rather than smearing the sample onto a microscope slide as with the conventional method, the sample is placed into a vial containing cell-preserving fluid, which is transported to the laboratory where the slide is prepared. For ThinPrep, the sample is rinsed into the vial; with Autocyte, the collection device along with the sample is retained in the vial. In this way, virtually all cellular material is available to the laboratory for analysis (Franco, Duarte-Franco, & Ferenczy, 2003). Before the slide is prepared, the sample is treated to remove cellular debris, for example blood or mucus. A thin layer of the cells is deposited onto a slide. For both liquid-based techniques, slide preparation is automated, but ThinPrep slides are stained and examined in the usual way under a microscope by a cytologist, whereas Autocyte slides can be examined by automated primary screening.

75. What are the advantages and disadvantages of LBC?

Potential advantages of the LBC method include an improved means of slide preparation, producing more homogeneous samples than the Pap test (which may make slides easier to read), increased sensitivity and specificity, and improved efficiency of handling laboratory samples (including shorter interpretation times), resulting in increased laboratory productivity.

A meta-analysis showed that unsatisfactory specimens were significantly less likely for LBC than the Pap test; unsatisfactory specimens ranged from 0.1%–1% for LBC and 0.1%–12% for the Pap test (Noorani, Brown, Skidmore, & Stuart, 2003). In an Ontario study, unsatisfactory specimens detected by LBC were half that detected with conventional cytology (Colgan et al., 2004).

The previously mentioned meta-analysis also reported only slight improvements in sensitivity and specificity in favour of LBC over the Pap test (Noorani et al., 2003). It should be noted that the relative utility of LBC compared with the Pap test will vary from one setting to another and with the study design (i.e., split-sample studies versus historical control studies) (IARC, 2005; Noorani et al., 2003).

One important advantage of LBC is the ability to save the cell suspension in preservative for later testing for HPV DNA and other microbial agents, such as *Chlamydia trachomatis*.

Disadvantages of liquid-based techniques include the need for additional training of cytotechnologists and cytopathologists and significant conversion costs. Also, the laboratory cost of LBC is considerably more than that of the conventional Pap test (McNeeley, 2003).

76. Is there a role for naked-eye inspection of the cervix after acetic acid application as an adjunct to Pap testing in the family doctor's office?

Visual inspection with acetic acid application (VIA) has emerged as a low-technology alternative to cytology screening. The method involves naked eye examination of the cervix after swabbing it with 3%–5% acetic acid and using artificial bright illumination. Findings of acetowhite lesions (noticeable opacity and a decrease in the typical reddish hue of the subepithelial vasculature) are considered positive. Of all the visual methods — (1) VIA, "downstaging" (i.e., unaided, non-magnified visual inspection), (2) VIA with low level magnification, (3) visual inspection with Lugol's iodine, and (4) cervicography — VIA has received the most attention. VIA has been found at least as sensitive as conventional cytology for detecting CIN 2 or worse, but it has lower specificity (Basu et al., 2003; Sankaranarayanan et al., 2004).

A disadvantage to visual tests such as VIA is their inherent subjectivity. Also, the marker of a positive test, acetowhitening, is not specific to cervical neoplasia and is often observed in immature squamous metaplasia and in inflamed, regenerating cervical epithelium (IARC, 2005).

The IARC (2005) recently concluded that there is not yet sufficient evidence to recommend VIA as a primary screening test.

77. Is there a role for automated (computer-assisted) systems in cervical screening?

Attention has been given to automated or semi-automated systems in an effort to minimize the false-positive and false-negative results inherent in the interpretation of Pap tests. Several automated systems for detection of cervical neo-

plasia have been developed. These include PAPNET (Neuromedical Systems Inc.; Suffern, NY [no longer in production]), FocalPoint (formerly AutoPap, TriPath Imaging; Burlington, NC), and ThinPrep Imaging System (Cytyc Corp.; Boxborough, MA). FocalPoint was originally designed to scan and categorize specimens collected conventionally, but was later approved for LBC specimens in the United States. ThinPrep has also received approval from the U.S. Food and Drug Administration (FDA) for use in primary screening of LBC specimens.

Numerous studies have examined the accuracy of automated systems (Bergeron et al., 2000; Duggan, M. A., 2000; Kok, Boon, Schreiner-Kok, & Koss, 2000; PRISMATIC Project Management Team, 1999; Wilbur et al., 1999) reporting generally better test sensitivity with at least the same specificity as the Pap test. Automated systems may be most useful in jurisdictions with suboptimal screening organization, but less advantageous when used in well-organized, high-quality screening programs, except for handling more samples with the same quality (Nieminen, Hakama, Viikki, Tarkkanen, & Anttila, 2003). Studies have shown that the screening time for Pap tests can be halved by using automated systems (Chang, Lin, Chan, & Chong, 2002).

Concerns about automated cytology include too much dependence on technology and, because the technology is expensive, it is suitable only for high- and middle-income countries (Franco, Duarte-Franco, & Ferenczy, 2003). In a recent evaluation of cervical cancer screening, the IARC (2005) concluded there is sufficient evidence to recommend automated cytology and that this method of screening can reduce both incidence and mortality due to cervical cancer.

78. Is there a role for HPV DNA testing in cervical screening?

With the acknowledgement of HPV as a necessary cause of cervical cancer and its precursors, much attention has turned to HPV DNA testing of cervical specimens as a screening modality. The distinction between the role of high-risk HPV types in the etiology of cervical cancer versus low-risk HPV types, which primarily cause benign lesions (warts), offers a unique potential for improved sensitivity and specificity for detecting patients at risk for cervical cancer.

Since the initial studies in the late 1980s, techniques for detecting the presence of HPV have evolved. In particular, the development of new DNA sequencing methods, such as polymerase chain reaction (PCR) and Hybrid Capture assay, have greatly improved the accuracy of HPV DNA testing and have made it an

efficacious screening option in certain situations. Ontario Cervical Screening Practice Guidelines recommend HPV testing, as a triage mechanism, for women over age 30 with ASCUS Pap test results (McLachlin et al., 2005).

Recently, numerous observational studies and clinical trials have examined the utility of HPV DNA testing for cervical screening (ALTS Group, 2003; Arbyn et al., 2004; Cuzick, Sasieni et al., 1999; Noorani et al., 2003). Two modalities have received the most attention: triage by HPV DNA testing and HPV DNA testing as a primary screening tool (see Questions 81 and 82). Currently, only triage HPV testing has received approval in any jurisdiction (USA), yet it is being recommended in Canada and the UK and will likely receive acceptance in other countries. Many questions, however, still remain to be answered about the use of HPV testing as a primary screening tool despite evidence that it may be at least as effective as conventional cytology (Cuzick et al., 2006; IARC, 2005).

CCO is conducting an HPV Pilot in Ontario (funded by the Ontario Women's Health Council) to evaluate the use of reflex HPV-DNA testing as a triage mechanism for ASCUS Pap test results, and to assess the impact on colposcopy usage. The final report of the Pilot is expected in early 2007.

79. What test can we use for HPV testing?

Numerous techniques, ranging in complexity and accuracy, can detect the presence of HPV in the cervix:

1. Scoring of koilocytes
2. Immunocytochemical staining in cervical samples
3. Non-amplified nucleic acid hybridization techniques (dot blot, Southern blot, and filter in-situ)
4. Amplified acid hybridization techniques (the Hybrid Capture [HC] assay and polymerase chain reaction [PCR])
5. Serological assays to detect antibodies to HPV

Serological assays have not been considered for cervical screening since a positive test might reflect lifetime exposure to HPV infection and from sites other than the cervix.

The majority of studies over the past decade have used the first- and second-generation HC systems (Digene, Inc.; Gaithersburg, MD) and a few PCR proto-

cols because of their higher sensitivity and specificity relative to non-amplified DNA hybridization methods (Franco, 1992). The HC systems are the only HPV tests currently approved by the US FDA. The HC system uses DNA-RNA signal amplification for the qualitative detection of DNA of high-risk HPV types. The assay uses a combined probe mix and therefore cannot identify specific types of HPV. HC-I detects 9 high-risk types: 16, 18, 31, 33, 35, 45, 51, 52, and 56; the improved HC-II targets 13 types: the 9 from HC-I plus 39, 58, 59, and 68. A probe for certain low-risk types of HPV (6, 11, 42, 43, and 44) is available for both systems, but the utility of this supplement has not been sufficiently studied yet (IARC, 2005). In Ontario, HC-II is available on a patient-pay basis at two community laboratories.

PCR is based on the self-replicating nature of DNA, to amplify (replicate) certain, known DNA sequences in vitro. The amount of DNA product increases exponentially, and thus PCR has a very high level of molecular sensitivity permitting detection of a very small amount of viral DNA (<10 copies). Thus, PCR has a lower threshold of detectability than the HC assay. High molecular sensitivity combined with direct DNA sequencing allows one to distinguish the HPV types present in a specimen. No PCR technique is available commercially.

The very high sensitivity of PCR is also its limiting factor clinically. Because PCR produces millions of copies of the DNA target there is a high probability of cross-specimen contamination through airborne droplets and aerosolized reaction mixtures, requiring extreme care in PCR testing laboratories (IARC, 2005). HC systems are signal- rather than target-amplified and are therefore less prone to contamination from other specimens (Coutlee, Mayrand, Provencher, & Franco, 1997).

Self-collected specimens for HPV DNA testing are not yet approved for use, but have been tested in several studies. Please refer to "CCO guidelines for self-collected specimens for HPV DNA testing" for more information (Stewart, Mai, Howlett, Barata, Gagliardi, & Lewis, 2006).

80. How is the HPV test done?

Cervical samples intended for HPV testing may be taken separately from (if conventional cytology), or at the same time (if LBC) as a Pap test. The preferred method is to use a sample drawn from the residual medium during LBC. In fact, sampling protocols for the HC2 system (the most commonly used HPV

DNA test) match those for LBC: the cervical sample is collected using a spatula/brush/broom inserted into the cervical canal and fully rotated 3 times. The brush (or broom) is carefully removed (without touching the vaginal wall) and inserted into a collection tube containing specimen transport medium. This is then analyzed at a laboratory.

HPV testing also lends itself to self-sampling. One study among South African women found the detection rate of pre-cancerous lesions was similar for self-sampling methods (66%) and conventional cytology performed by healthcare providers (68%) (Wright, Denny, Kuhn, Pollack, & Lorincz, 2000). A potential advantage of self-sampling is improved compliance (Stewart et al., 2006).

81. What is the sensitivity and specificity of HPV testing?

Numerous studies have been conducted using either HC or PCR protocols to detect HSIL (CIN 2 or 3) among Asian (Belinson et al., 2001; Sankaranarayanan et al., 2004), African (Blumenthal et al., 2001; Kuhn et al., 2000; Wright et al., 2000), Latin American (Schiffman et al., 2000), European (Clavel, Masure, Bory, Putaud, Mangeonjean, Lorenzato, et al., 2001; Cuzick et al., 1995; Cuzick et al., 1999; Schneider, Hoyer, Lotz, Leistritza, Kuhne-Heid, Nindl, et al., 2000) and North American (Kulasingam et al., 2002; Ratnam, Franco, & Ferenczy, 2000) populations. HPV testing is, on average, approximately 30% more sensitive than conventional cytology, but about 9% less specific for detecting high-grade lesions. The performance of HPV testing improved when tests were restricted to women aged 30 or older. Women in these age groups are less likely to have a transient HPV infection than younger women (Franco, Schlecht, et al., 2003).

Some studies have found that the combination of HPV testing and cytology performed very well, with sensitivity and negative predictive values approaching 100% (Belinson et al., 2001; Ratnam et al., 2000; Schiffman et al., 2000).

82. What is primary HPV screening?

The IARC (2005) defines primary screening as "detection of cases of cervical cancer or of its precursor lesions among asymptomatic women without a referral diagnosis, i.e., as true population screening, either opportunistic or systematic." HPV testing has been proposed to fulfill the role of primary screening given the overwhelming epidemiologic evidence that HPV is the causative agent

of cervical neoplasia. Those who test positive for HPV will be recalled or referred for further assessment or diagnostic confirmation as would be the case if conventional cytology were used as the screening tool. HPV testing has been proposed as a screening modality alone and as an adjunct (i.e., in combination with) cytology (Pap test or LBC). Despite evidence of the efficacy of HPV DNA testing as a primary screening tool, further research is needed to determine the optimal mode of delivery (alone or as an adjunct to cytology), age of initiation, the screening interval, and the molecular test to be used (IARC, 2005).

83. What is triage HPV testing?

Triage is a second screening test that is performed when the first test is neither normal nor definitively indicative of need for treatment.

Several studies have shown triage by HPV DNA testing to be efficacious, and the approach is now common in the United States (ALTS Group, 2003; Arbyn et al., 2004; Wright et al., 2002). Triage HPV DNA testing allows clinicians to further stratify individuals with selected Pap test results (i.e., ASCUS) for which management is not definitively indicated. This modality may save women from having to endure a repeat Pap test or possibly unnecessary colposcopy. Triage by HPV DNA testing is particularly useful if the initial cytology was liquid-based ("reflex" HPV testing); the sample is drawn from the residual LBC medium. Reflex testing is a recommended triage option in the revised OCSP Guidelines for women over age 30 with an ASCUS Pap test result (McLachlin et al., 2005).

CCO is conducting an HPV Pilot in Ontario (funded by the Ontario Women's Health Council) to evaluate the use of reflex HPV DNA testing as a triage mechanism for ASCUS Pap test results, and to assess the impact on colposcopy usage. The final report of the Pilot is expected in early 2007.

84. Who should get HPV screening?

This is still a much debated question. The answer largely depends on the HPV testing modality (i.e., triage for equivocal Pap tests such as ASCUS or primary screening).

Women with an initial diagnosis of ASCUS with conventional cytology are candidates for HPV testing. The ALTS Study, a large, multi-centre randomized

trial designed to find the optimal way to manage equivocal Pap test results, has shown that for women with an ASCUS interpretation, triage HPV DNA testing identified almost all women with underlying abnormalities (Solomon, Schiffman, & Tarone, 2001). Of the women who had pre-cancer or cancer on colposcopy, more than 96% also had a positive HPV test. The overall conclusion from this trial is that triage by high-risk HPV DNA testing is effective at detecting the underlying abnormalities. Triage HPV testing is approved by the U.S. FDA and is recommended for women over age 30 in the revised Ontario Cervical Screening Guidelines (McLachlin et al., 2005).

The ALTS group reported that, unlike a Pap test result of ASCUS, HPV testing for an LSIL Pap test is not useful because LSIL is so highly associated with HPV that an HPV triage test would have too low specificity (ALTS Study Group, 2003; Arbyn et al., 2004).

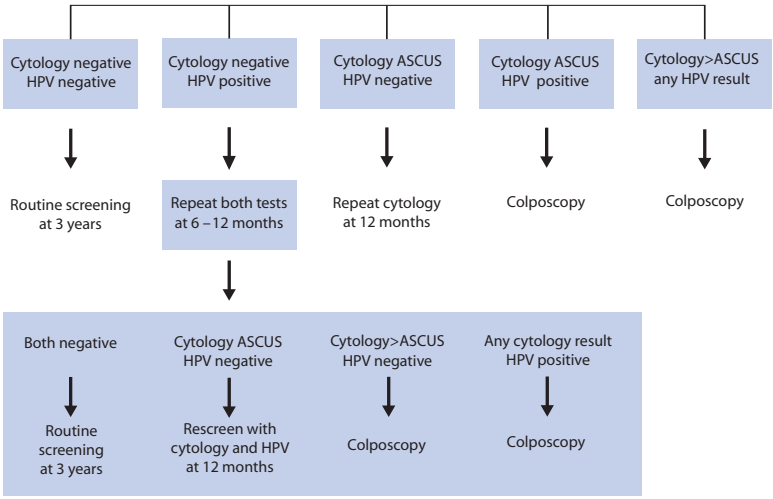
Currently, there are insufficient data to recommend HPV testing as a replacement for, or in combination with, conventional cytology (IARC, 2005; Wright et al., 2004). As a result, there are conflicting recommendations as to the utility of HPV testing as a primary screening modality. Ontario guidelines state that HPV DNA testing may be added to conventional cytology for screening in women age 30 or older and discontinued at the same age, and under the same circumstances, as conventional screening.

Women who are immunocompromised or who have had a total hysterectomy (including removal of the cervix) should not be screened for HPV. A proposed advantage to screening with both cytology and HPV testing is that it may extend the time between screenings; if an individual is both cytology and HPV negative they are at very low risk for developing cervical neoplasia (Wright et al., 2004). Immunocompromised women are at increased risk for both high-risk HPV infection and high-grade lesions or cancer (Palefsky & Holly, 2003). Consequently, the screening interval should not be extended in this population, and there would be little benefit from the use of HPV DNA testing. Women who have had a total hysterectomy are no longer at risk for developing cervical cancer, thus HPV testing would not benefit them (Wright et al., 2004).

85. What do you do with a patient who is positive for high-risk HPV?

Management of HPV-positive patients depends on the nature of the HPV test. If performed as triage for an ASCUS Pap test, HPV positive women should be referred for colposcopy. If the test is performed primarily in combination with conventional cytology, then a number of options may be taken. Figure 1 shows the interim recommended management of women using combined cytology/HPV testing (Wright et al., 2004).

Figure 1. *Algorithm for the management of women using a combination of cervical cytology and HPV testing for primary cervical cancer screening*



HPV = human papillomavirus; ASCUS = atypical squamous cells of undetermined significance. (Figure reproduced with permission from *Obstetrics & Gynecology* [Wright et al., 2004]).

It should be stressed that these interim recommendations were made for HPV as an adjunct to cervical cytology, and that no single screening test or combination of tests is perfect. Furthermore, the lifetime risk of infection with high-risk types of HPV is considerable. Thus, a positive test does not necessarily indicate persistent infection or that cervical cancer is inevitable (Wright et al., 2004).

86. What is colposcopy?

Colposcopy is a diagnostic procedure to determine the cause of abnormalities found in Pap tests. Colposcopy is the magnified visual examination of the cervix using an instrument called a colposcope (a low-power stereoscopic binocular field microscope with a powerful light source) that magnifies the cervical tissue. The woman is placed in the lithotomy position with a bivalve speculum in place. The cervix is visualized, by a trained colposcopist, with the colposcope and various solutions (normal saline, 3%–5% dilute acetic acid, and Lugol's iodine) applied to the cervical epithelium. The aim is to examine the transformation zone. The area suspicious for pre-cancer or cancer is biopsied (see Question 107 for surgical treatment modalities) to arrive at a diagnosis to decide on a management plan.

CCO is working in partnership with the Program in Evidence-Based Care and the Gynecologic Disease Site Group to develop Colposcopy Standards and Guidelines, which will likely be available in mid-2007.

87. What is the sensitivity and specificity of colposcopy?

Two recent meta-analyses have examined the accuracy of colposcopy as a diagnostic tool for cervical abnormalities. Mitchell, Schottenfeld, Tortolero-Luna, Cantor, and Richards-Kortum (1998) found that at a cut-off level of normal versus abnormal on colposcopy, the average weighted sensitivity and specificity were 96% and 48%, respectively. At a cut-off of normal and LSIL versus HSIL and cancer on colposcopy, the corresponding results were 85% and 69%. Thus, high-grade lesions are diagnosed with higher sensitivity than low-grade lesions. Similar findings were reported by Olaniyan (2002).

88. Why is colposcopy important?

Colposcopy is important because it provides an additional layer of evaluation to identify causes for an abnormal Pap test.

Before making a management decision on any patient with SIL, it is mandatory to perform a colposcopic evaluation to exclude the presence of an HSIL or cancer. In patients with an LSIL Pap test finding, between 15% and 30% will have underlying HSIL, while 0.3% to 0.5% will have invasive cancer (Jones & Novis, 2000; Lonky, Sadeghi, Tsadik, & Petitti, 1999).

89. Why is colposcopy not used as a screening tool along with the Pap test?

Colposcopy is generally regarded as a diagnostic tool to assess women with cervical abnormalities identified on various screening tests. Although colposcopy is used extensively as such, understanding of its use as a screening test is incomplete. There is reluctance to use it as a primary screening modality along with conventional cytology because there is no evidence that the quality of Pap tests is improved (Hilgarth & Menton, 1996; IARC, 2005). Earlier studies found that colposcopy as a screening tool has poor sensitivity (34%–43%), specificity (68%), and positive predictive value (4%–13%) (Hockstad, 1992; Nathan & Moss, 1991; Olatunbosun, Okonofua, & Ayangade, 1991). More recent research reports sensitivity and specificity ranging from 13% to 81% and 77% to 99%, respectively (Belinson et al., 2001; Schneider et al., 2000). One of the reasons why colposcopy fails to identify invasive carcinoma is that carcinoma of the endocervical canal is not visualized at the time of colposcopic examination (National Health Service Cervical Screening Programme, 2004). Additional constraints, such as its high cost relative to cytology, the availability and accessibility of adequately trained colposcopists, and the lower ability of colposcopy to detect endocervical lesions, make colposcopy less desirable than cytology as a screening tool (Belinson et al., 2001; IARC, 2005).

90. What is the level of accuracy of cervical biopsy and colposcopy?

A study of the accuracy of colposcopy and colposcopy-directed biopsy undertaken in China found that among women with satisfactory colposcopy, directed biopsy detected (sensitivity) 57% of high-grade lesions and cancers, compared with 37% for four-quadrant biopsy and 6% for endocervical curettage (ECC) (Pretorius et al., 2004). Moreover, directed biopsies were almost 5 times more likely to show a high-grade lesion or cancer than four-quadrant biopsies (27% versus 6%).

91. When should a patient be referred for colposcopy?

Current indications for colposcopy include (IARC, 2005):

- Positive screening test (e.g., cytology,* visual inspection with acetic acid [VIA]) result suggesting an increased risk of cervical neoplasia
- Suspicious-looking cervix, regardless of the screening test used

- Presence of visible leukoplakia (a hyperkeratotic area may obscure a lesion, thereby preventing adequate cytological sampling)
- Presence of external genital warts (only in some systems) (Howard, Sellors, & Lytwyn, 2002; Li, J., Rousseau, Franco, & Ferenczy, 2003)
- Women at increased risk of cervical neoplasia (i.e., HIV-positive, those with external genital warts)

*Abnormal cytology including ASCUS (i.e., 2 or more ASCUS Pap test results, OR ASCUS plus positive high-risk HPV test where available), LSIL, HSIL, or suspicion of cancer.

92. Should a family doctor still do Pap tests if the patient is being followed by a colposcopist? When do patients referred for colposcopy return to their family doctor for future annual Pap tests?

Family physicians need not duplicate Pap tests while the patient is followed by a colposcopist. Once the patient is officially discharged from the colposcopist's care, then the family doctor is usually asked to resume screening.

Patients are returned to their family doctor's care for follow-up after two completely normal colposcopic examinations are accompanied by normal Pap tests. This may follow spontaneous resolution of the cervical lesion or its persistence or progression that required treatment.

93. What is endocervical curettage (ECC)?

ECC is a diagnostic procedure in which the mucous membrane of the cervical canal is scraped using a narrow, spoon-shaped instrument called a curette. This type of biopsy is usually performed during colposcopy and usually does not require anesthetic.

94. What is the utility of ECC?

Although the use of ECC has become a routine part of detection, controversy exists as to its clinical utility. Proponents argue ECC should be performed to avoid more invasive procedures (e.g., conization) and that it can exclude the possibility of glandular abnormalities. Opponents of ECC argue that cost, patient discomfort, relatively high false-positive and false-negative rates, as well as the fact that most cases of cervical intraepithelial neoplasia are cur-

rently treated by excision rather than ablation, are reasons to discontinue the use of the technique (Abu & Davies, 2005; Bidus, Elkas, Rodriguez, Maxwell, & Rose, 2005).

A lack of properly conducted randomized trials on the efficacy of ECC contributes to the uncertainty surrounding the utility of the procedure. One review reported that the evidence is inconclusive and that no clear consensus on the role of ECC exists (Abu & Davies, 2005). In their review, Abu et al. (2005) outlined indications for ECC at the time of colposcopy to assess an abnormal Pap test: unsatisfactory colposcopy (especially in postmenopausal women when the transformation zone may not be as visible), atypical glandular cells on cytology (when a deep cone biopsy should also be performed), and when a second excision is contemplated, especially for an incompletely treated high-grade disease. However, they stressed caution to prevent over-reliance on the result of ECC to plan the management of HSIL, adenocarcinoma in situ, or invasive disease. Surgical excision is advisable regardless of the ECC results.

95. Should an ECC be performed by curette or endocervical brush or broom?

Several studies have compared the performance of ECC to the endocervical brush during colposcopy, but the literature is unclear with respect to which tool is more effective (Boardman, Meinz, Steinhoff, Heber, & Blume, 2003; Klam, Arseneau, Mansour, Franco, & Ferenczy, 2000; Mogensen et al., 1997). Klam et al., for instance, reported that the two procedures were not statistically different in terms of diagnostic yield and patient discomfort, as well as false-positive rates (ECC 31%, brush 29%), false-negative rates (ECC 3.6%, brush 2.1%), sensitivity (ECC 64.3%, brush 76.9%), and specificity (ECC 97.1%, brush 97.2%). Contamination of the sample was an issue in both instances and was considered the reason for the high false-positives. Thus, brushing may be an acceptable alternative to ECC, but further comparative research is necessary.

96. Is ECC necessary at the time of cervical cone biopsy?

A negative conization endocervical margin virtually assures no disease in the upper endocervical canal for squamous cell lesions. The negative predictive value in one study population was 97% (Spann, Brown, Kennedy, & Wheeless, 1993); these findings were echoed by others (Dinh, Schnadig, Logrono, Hannigan, & Santoso, 2002; Vierhout & de Planque, 1991). They concluded that

routine ECC is unnecessary for most patients and should be considered primarily for patients who are postmenopausal or for those receiving suboptimal conizations. However, in any case where the adequacy of the cone is suspect an ECC should be done.

97. What happens to warts (condyloma) in pregnancy?

Despite the fact that genital warts are the most common vulvar viral condition, remarkably little has been written about HPV infection in pregnancy. There are conflicting reports as to whether there is an increased prevalence of genital HPV infection in pregnancy (Fife, Katz, Brizendine, & Brown, 1999; Hagensee et al., 1999; Kemp, Hakenewerth, Laurent, Gravitt, & Stoerker, 1992; Morrison, Gammon, Goldberg, Vermund, & Burk, 1996; Peng, Searle, Shah, Repke, & Johnson, 1990; Rando et al., 1989; Schneider, Hotz, & Gissmann, 1987; Taylor, 1995). Anecdotally, genital warts are said to grow more rapidly in pregnancy and can become florid or bleed profusely (Roberts, 1990; Taylor, 1995). This increase in the number of warts could be related to a change in cellular immunity during pregnancy (Peng et al., 1990; Purtilo, Hallgren, & Yunis, 1972; Taylor, 1995). The hyperestrogenic milieu may play a role, along with the slight immunosuppressive effect of pregnancy (Bornstein et al., 1995; Schneider et al., 1987). See also Questions 36 and 37.

One study concluded that a significant relationship has yet to be established between pregnancy and HPV prevalence (Kemp et al., 1992). Their multivariate analysis in 115 pregnant women indicated no statistically significant association between the prevalence (at any level of infection) and pregnancy status. This is also supported by other studies (Nobbenhuis et al., 2002; Smith, E. M. et al., 1991). See also questions 36 and 37.

98. What is considered safe local therapy for genital warts in pregnancy?

Visible warts can be treated during pregnancy and typically regress following delivery (Lacey, 2005). Podophyllin and podophylotoxin are contraindicated in pregnancy. Administration during the first trimester has been associated with possible teratogenicity, and fetal death has been reported following its use in late pregnancy (Beutner, Reitano, Richwald, & Wiley, 1998; Taylor, 1995). Imiquimod (5%) cream is a relatively new and effective topical therapy that directly enhances the local immune response to HPV; its safety during pregnan-

cy, however, has not been established (Beutner et al., 1998). Trichloroacetic acid therapy (85%) is an alternative topical method that can be used safely in pregnancy (Beutner et al., 1998). The acid must be applied carefully because of the risk of ulceration and scarring. Pain on application is common (Taylor, 1995).

Cryotherapy in pregnancy can be effective, does not require any anesthetic, and causes little or no scarring. It has been suggested as the first choice of therapy, as it has a higher cure rate than topical chemotherapy and significantly fewer applications are required (Beutner et al., 1998; French & Nashelsky, 2002; Taylor, 1995). Other acceptable treatments include surgical removal and laser ablation.

99. Is cervical screening different in pregnant women?

Relatively little research has examined the optimal protocol for cervical screening among pregnant women. There is no evidence to indicate pregnant women should be screened any more or less frequently than non-pregnant women. Most recently, the New Zealand Guidelines Group (NZGG) published recommendations on the cervical screening of pregnant women (Members of the Working Party on Cervical Screening, 1998). The NZGG recommended that pregnant and postnatal women follow the same screening regimen as non-pregnant women (every 3 years for women with normal screens). Pap tests should be done more frequently only if there are indications, such as follow-up of abnormal cytology.

Revised Ontario Cervical Screening Guidelines recommend that pregnant women should follow the same screening regimen as women who are not pregnant (McLachlin et al., 2005).

100. Can an endocervical brush or broom be used when doing a Pap test during pregnancy?

Manufacturers of the endocervical brush list pregnancy as a contraindication for its use (after 10 weeks of gestation). However, studies have failed to show an increase in adverse maternal or fetal outcomes when the brush is used for cervical cytologic screening during pregnancy. Cervical specimens collected using an endocervical brush were examined in 222 pregnant women (Stillson, Knight, & Elswick, 1997). There were no complications attributable to the brush. The endocervical brush-spatula technique yielded 96% specimens with

adequate endocervical cells compared with 70% with a cotton swab and spatula. There was no difference between the use of the swab and brush in the prevalence of cellular abnormalities. These findings are supported by other studies (Paraiso, Brady, Helmchen, & Roat, 1994). Some clinicians may prefer to use the broom in pregnancy because these bristles are softer and may cause less spotting (Huff, 2000).

101. How is dysplasia followed and treated during pregnancy?

Colposcopy and directed biopsies are safe to perform during pregnancy. Colposcopy does not increase the risk of adverse pregnancy outcomes (Wright et al., 2002). However, dramatic alterations in the appearance and physiology of the cervix (e.g., increased mucus congestion, microvascularization, and collapsing vaginal walls) make colposcopy more technically challenging than in nonpregnant patients. Therefore, colposcopic management of a pregnant patient with an abnormal Pap test requires specific experience and expertise.

Although invasive cervical cancer is rare (with an incidence of approximately 1–15 cases per 10,000 pregnancies), cervical cancer is the most commonly diagnosed cancer in pregnancy (Wright et al. 2002). However, management of cervical neoplasia in pregnancy is conservative, especially since the majority of low-grade lesions will regress. Women with low-grade lesions on a Pap test during pregnancy may be followed up with colposcopy 6 months postpartum (especially if the patient/history is known). The purpose of colposcopy during pregnancy should be reserved for suspected high-grade lesions or cancer. Treatment is unacceptable unless invasive cancer is identified (Wright et al., 2002). Serial cytology and colposcopy could be performed during pregnancy to monitor less severe lesions as appropriate. Such assessments must consider that the natural history of pregnancy is 40 weeks and the natural history of dysplasia is years, often decades.

102. Is a postpartum Pap test important? Is it necessary to do one even if the prenatal Pap was normal?

Levitt et al. (2004) conducted a systematic review of the literature on postpartum Pap testing. They reported that data are lacking on the effectiveness and optimal timing of postpartum screening. Almost 5% of subjects in studies that recommended postpartum screening (due to a significant yield of neoplasia) had abnormal Pap tests (Londo, Bjelland, Girod, & Glasser, 1994; Weiss, Senf, &

Udall, 1989). However, studies that also examined the timing of the postpartum Pap test found that the incidence of abnormal tests decreased as the postpartum interval increased (Jazayeri, Heffron, Harnetty, Jazayeri, & Gould, 1999; Rarick & Tchabo, 1994). In general, there is significant spontaneous regression of CIN 2 and 3 postpartum (Yost, Santoso, McIntire, & Iliya, 1999). These studies tended to recommend that for patients without risk factors for cervical intraepithelial neoplasia and a normal antepartum Pap test, screening should be repeated as recommended for non-pregnant women. The New Zealand Guidelines Group recommended that pregnant and postnatal women follow the same screening regimen as non-pregnant women (every 3 years for women with normal screens) (Members of the Working Party on Cervical Screening, 1998). More recently, the IARC recommendations for screening (2005) did not differentiate pregnant or postpartum women from the general population.

103. How does HPV affect the neonate?

The risk of transmission of HPVs, although present, is likely very low (<3%) (Watts et al., 1998; Winer & Koutsky, 2004a). Studies have documented varying rates of HPV infection in newborns, with estimates ranging from 4% to 72% among infants of HPV positive mothers, and 0.6% to 20% among infants born to mothers without detectable HPV infection during pregnancy (Smith, E. M., et al., 2004; Tseng, Liang, Soong, & Pao, 1998; Watts et al., 1998).

Research has demonstrated a clear association between perinatal HPV transmission and recurrent laryngeal papillomatosis (Mounts, Shah, & Kashima, 1982; Shah, Stern, Shah, Bishai, & Kashima, 1998); the association is particularly strong for HPV types 6 and 11, which are most commonly detected in genital warts. The most likely mode of transmission is exposure of the child's upper aerodigestive tract to the cervix and vagina of a mother (with an HPV infection) during delivery. Although rare, recurrent laryngeal papillomatosis causes significant morbidity and occasionally mortality in infected infants.

Some evidence of intra-uterine infection with HPV has been reported (Tseng et al., 1998).

Infection in newborns typically does not persist; most infections clear as soon as 6 weeks postpartum (Carter et al., 1995; Pakarian et al., 1994). However, more long-term studies are needed to establish the real risks of HPV infection to both pregnant women and their children.

104. Should pregnant women with HPV be delivered by caesarean section?

There is not enough evidence to justify caesarean section delivery in pregnant women with HPV infection (Derkay, 1995; Kosko & Derkay, 1996; Silverberg, Thorsen, Lindeberg, Grant, & Shah, 2003). Occasionally, warts may grow large enough to obstruct the birth canal, with the consequence that delivery has to be performed by caesarean section (Lacey, 2005). Cesarean delivery did not protect against respiratory papillomatosis (Silverberg et al., 2003). Further research is necessary.

105. Does HPV infection affect the spontaneous abortion rate or increase morbidity during pregnancy?

There is no known association between HPV infection and spontaneous abortion, intra-uterine growth retardation, preterm delivery, or perinatal death (Ooi & Dayan, 2004).

106. How is the follow-up of the HIV-positive woman different? Why?

The risk of cervical pre-cancer and cancer appears to be increased in women with HIV infection. Progression of cervical neoplasia may be more rapid and the severity of the disease increased, particularly in women with HIV-related immunocompromise (Ellerbrock et al., 2000; Palefsky et al., 1999).

Several studies from different countries have shown that HIV-infected women have a much higher prevalence of HPV infection, intraepithelial lesions, and cervical cancer. Prevalence estimates for these range from 2- to 20-fold higher among HIV-positive women compared with HIV-negative women (Ellerbrock et al., 2000; Mandelblatt et al., 1999; Mayans, Maguire, Miret, & Casabona, 1999; Thomas et al., 2001). Furthermore, the rate of recurrence following treatment for pre-cancerous lesions and cancer is significantly higher among HIV-infected women (38%–62%) relative to the general population (15%–18%) (Chirenje, Rusakaniko, Akino, Munjoma, & Mlingo, 2003; Maiman et al. 1999).

With significantly higher recurrence rates and prevalence of HPV infection, cancer, and pre-cancer, HIV-positive women may benefit from more frequent screening. In a recent evaluation of the scientific literature, the IARC (2005)

recommended that HIV-positive women should be screened more frequently than women without HIV, yet the appropriate interval was not specified.

Sensitivity of the Pap test does not appear to be diminished in HIV-positive women. Screening colposcopy may be justified in view of the high prevalence of cervical and vulvar neoplasia, as well as the high noncompliance rate observed in this patient population (IARC, 2005).

107. What surgical treatment modalities exist for the management of cervical neoplasia?

Commonly used methods of treatment for preinvasive lesions include cold-knife conization, laser vaporization or excision, cryotherapy, loop electrosurgical excision procedure (LEEP), and hysterectomy. Strategies that combine diagnosis and treatment, such as LEEP, may be of particular value, especially in women for whom follow-up is not effective (IARC, 2005; Spitzer, Chernys, & Seltzer, 1993).

Cryotherapy, LEEP, and laser procedures are minimally painful (performed under local anesthesia), quicker, and cause less intraoperative blood loss and immediate postoperative complications than cold-knife conization (Martin-Hirsch, Paraskevaidis, & Kitchener, 2000; Oyesanya, Amerasinghe, & Manning, 1993).

Electrosurgical excision of the transformation zone is now the most popular technique. Martin-Hirsch et al. (2000) conducted a meta-analysis of trials examining various treatments for CIN. Excisional techniques were not found to be significantly superior to ablative techniques.

108. What are the non-surgical options for treatment of cervical neoplasia?

Topical imiquimod cream (5%) has shown promise as a treatment for low-grade lesions, particularly genital warts (IARC, 2005). Imiquimod acts as a local immune modulator, stimulating both the innate and the cell-mediated immune response systems (Gunter, 2003). Clearance of genital warts with imiquimod treatment occurs in 72%–84% of patients with few side effects (typically mild or moderate local erythema) (Edwards, 2000; Edwards et al., 1998). HPV recurrence with imiquimod occurs in 5%–19% of cases.

5-Fluorouracil (5-FU) has been used alone or in combination in the treatment of cervical neoplasia. Topical preparations (1%–5% creams) have been studied for the treatment of vaginal warts and cervical squamous epithelial lesions with up to 50% of cases responding (Gunter, 2003; Maiman et al., 1999).

The concept of therapeutic vaccines (treatment) are being evaluated, but await data from appropriately powered studies.

109. Do LEEP treatments affect future fertility and/or pregnancy outcome?

While the safety and effectiveness of loop electrosurgical excision procedure (LEEP) have been documented, relatively little data has been collected on the long-term effect of the procedure on fertility. The published data have not confirmed an association between LEEP and impaired fertility (Montz, 2000).

A systematic review of studies on LEEP treatment for intraepithelial lesions and pregnancy outcomes revealed mixed results from reviewed studies. However, the pooled odds of preterm birth were significantly increased among women who had this mode of treatment (Crane, 2003). Many of the studies reviewed did not adjust for potential confounding variables, such as smoking status or depth of the tissue sample. More recent studies involving larger sample sizes and multivariate analyses have provided better evidence that LEEP may be associated with preterm birth (<37 weeks) and possibly lower birth weight (<2500 g) (Crane, Delaney, & Hutchens, 2006; Sadler et al., 2004; Samson, Bentley, Fahey, McKay, & Gill, 2005). Further studies of sufficient size and analysis are required to confidently answer this question.

110. How do you follow patients with cone biopsies that have margins positive for neoplasia?

Conservative management — including cytology, colposcopy, and ECC — of patients with cone biopsies that had margins positive for neoplasia is more common than hysterectomy at present (Jakus, Edmonds, Dunton, & King, 2000). In examining outcomes of 93 patients with cone biopsies that had margins positive for neoplasia, it was concluded that these patients can be followed appropriately with cytology (Lapaquette et al., 1993). For management of suspected microinvasive carcinoma, one study recommended that patients undergo repeat conization to determine the true extent of disease (Roman et al.,

1997). Cases of AIS with involved margins require additional surgical intervention (conization) (Denehy, Gregori, & Breen, 1997; Duggan, B. D., et al., 1999; Widrich et al., 1996).

111. What is the current status of HPV vaccines?

Considerable research has studied two types of HPV vaccines: 1) prophylactic vaccines to prevent HPV infection and associated disease, and 2) therapeutic vaccines to induce regression of warts, pre-cancerous lesions, or remission of advanced cervical cancer. The latter have received far less attention, have progressed slowly, and have shown less efficacy in clinical trials than prophylactic vaccines.

Prophylactic vaccines consisting of DNA-free virus-like particles (VLPs) — based on the L1 major capsid protein — have been developed against certain types of HPV. Two vaccines, Gardasil (Merck & Co., Inc.) and Cervarix (GlaxoSmithKline [GSK]), have demonstrated remarkable protection against infection from specific types of HPV and related cervical abnormalities.

Gardasil is a quadrivalent vaccine containing VLPs derived from the two most common high-risk HPV types, 16 and 18, as well as VLPs derived from the two most common genital wart types, HPV 6 and 11. During Phase II/III trials, primarily in young women in their late teens and mid-twenties, the vaccine produced a significant reduction in the incidence of HPV infections and related clinical disease (CIN 2+ and genital warts): in the range of 90%–100%, compared with placebo (Lowy & Schiller, 2006; Villa et al., 2005), providing protection against HPV infection and disease for at least five years (Villa et al., 2006). Based in large part on these results, Health Canada and the FDA provided regulatory approval for Gardasil for females between ages 9 and 26 in 2006. (See Question 113) (Lowy & Schiller, 2006; Villa et al., 2005).

Similar Phase II/III results have been observed for Cervarix, which is a bivalent vaccine containing HPV 16 and 18 VLPs (Harper et al., 2004). Phase II/III trials have demonstrated considerable efficacy in preventing 90%-100% of incident and persistent cervical infection and HPV-related disease. An extended follow-up analysis of women who received Cervarix reported it was immunogenic and safe for at least 4.5 years (Harper et al., 2006). Of interest, preliminary reports suggest that this vaccine might also induce some cross-protection against infection with HPV types 31 and 45 (Dubin, Zahaf, Quint,

Martin, & Jenkins, 2005; Harper et al., 2006). However, cross-protection against disease has not been shown to date. Merck & Co. has reported in-vitro research that serum antibodies from vaccinated women can cross-react and neutralize HPV types closely related to HPV 16 and 18 (i.e., 31 and 45). This will be an important topic for further research (see Question 113). GSK is expected to apply for regulatory approval for Cervarix by the end of 2006; their bivalent vaccine may be approved in 2007.

Both HPV VLP vaccines appear to be generally safe and well tolerated. Minor pain, swelling, and redness at the site of injection are the primary side effects.

Although both preventive and therapeutic vaccine development began around the same time, no therapeutic vaccine has made it beyond a Phase II trial. Research has primarily focused on strategies to induce a cell-mediated cytotoxic T-cell response to eliminate HPV infected cells expressing HPV oncogenes E6 and E7; other treatment strategies, however, such as fusion proteins, peptides, and genetic-based and dendritic cell-based vaccines, have been investigated (Kahn & Bernstein, 2005). Despite promising results in animal models, clinical results from Phase I/II studies have been disappointing and therapeutic vaccines have not yet been demonstrated to be efficacious in eliminating cancer, CIN, or genital warts (Kahn & Bernstein, 2005). Much more research is required. An overview of this issue is incorporated in the *Vaccine* journal monograph, Chapter 13 (Koutsky & Harper, 2006).

112. Will the advent of an HPV vaccine affect cervical screening? What about colposcopy?

Even with widespread vaccination, the introduction of a prophylactic HPV vaccine(s) to prevent infection will not eliminate the need for cervical cancer screening. Vaccines, so far, prevent infection from only two of the more than a dozen identified high-risk HPV types. HPV 16 and 18 account for 70% of cervical cancers.

Thus, screening will be essential to detect cancers and pre-cancerous changes by other high-risk HPV types. Likewise, women who are currently sexually active are still at risk and will require continued screening even if vaccinated in the near future. Screening guidelines may be revised to account for women who received the vaccine before becoming sexually active. A combined strategy of vaccination for younger women and screening for older women may well be

the future for programs for the prevention of cervical cancer (Schiffman & Castle, 2005). Additionally, if the vaccines are effective, it is expected that the need for medical care, biopsies, and invasive procedures to follow up abnormal Pap test results will be reduced (Steinbrook, 2006). As much as 60% of the colposcopy referrals and activity in most western countries may be reduced (Franco, Cuzick, Hildesheim, & de Sanjosé, 2006).

If there is a substantial increase in the proportion of those who are vaccinated (in countries with established screening programs), then this increase will have an impact on Pap test utility (sensitivity and specificity). As the prevalence of HPV-related disease decreases, one can expect the sensitivity (and the positive predictive value) of the test to drop as abnormal test results become rarer. In addition, specificity may drop as the finding of such lesions and the heightened awareness of the possibility of missing a lesion results in more tedious screening work (Franco, Cuzick, et al., 2006) In otherwise constant conditions, it is hypothesized that the positive predictive value of the abnormal Pap test could decrease from present-day standards of 50%–70% to potentially 10%–20%.

As uptake of vaccination increases, screening practice guidelines will require revision. Revised guidelines must consider the best test to use — continued use of the existing Pap test or primary screening with HPV-DNA tests that have a higher sensitivity than the Pap test (Franco, Cuzick, et al., 2006).

113. What are the key issues in understanding the prophylactic vaccine and its relationship with cervical cancer?

1) Regular Pap tests are still required to screen for cervical cancer, consistent with current screening practice guidelines.
2) HPV vaccines do not provide 100% protection against cancer of the cervix.
3) Both vaccines protect against HPV types 16 and 18, which are associated with up to 70% of cases of cervical cancer.
4) HPV vaccine is ideally recommended for use prior to exposure to HPV through sexual contact.
5) The vaccine has been approved for use in females between the ages of 9 and 26 years.
6) The vaccine is given in a three-dose schedule at a cost of $400-500 for the series.
7) Sustained immunogenicity has so far been documented up to 4.5 years for the bivalent vaccine (Harper et al., 2006) and 5 years for

the quadrivalent vaccine (Villa et al., 2006). As yet, there is no indication of erosion of immunity in the study populations.

8) Knowledge in the general public has been limited with respect to HPV and its causal connection with cancer of the cervix. Extensive education efforts are still required, for both clinicians and the general public, regarding the virus and the potential of the vaccine, to assist the public with informed decision-making (see Question 115).

114. Where is the prophylactic vaccine made and is it infectious?

The vaccine does not incorporate any live or attenuated parts of active virus and, as such, is not infective. It is made up of virus-like particles. The vaccine is made using one of the proteins (the L1 protein) that make up the outer shell of the virus. The proteins are re-assembled to look like the complete virus; hence the name virus-like particle. The immunogenicity of these particles is several times greater than that of the actual virus itself and the antibodies produced in response to these virus-like particles are protective for actual live virus infections (White et al., 1998).

115. What is the status of recommendations of the vaccine in North America?

The Centers for Disease Control (CDC) and the United States Advisory Committee on Immunization Practices have published provisional recommendations for the quadrivalent vaccine that was licensed at the time of writing (CDC, 2006).

Recommendations from the National Advisory Committee on Immunization for vaccine implementation in Canada were released in February 2007 in the Canada Communicable Disease Report (PHAC, 2007).

The quadrivalent vaccine has been licensed for use in girls and women ages 9 to 26 by Health Canada. Of note, the Canadian Communicable Disease Report, published by Health Canada, has produced a supplement on the Canadian Human Papillomavirus Vaccine Research Priorities Workshop, held in November 2005. The workshop was comprised of multi-disciplinary participants from across Canada who identified research priorities specific to HPV and HPV vaccine. (Refer to the following website: Public Health Agency of Canada. Canadian human papillomavirus vaccine research priorities workshop: Final report http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/06pdf/32s1_e.pdf.)

116. Who should get the vaccine?

Recommendations for use of the vaccine are similar in Canada (PHAC, 2007) and the United States (CDC, 2006) (see Question 113). Recommended use of the quadrivalent vaccine, the only one to be licensed (as of printing date), is as follows in Canada:

a. For females aged 9 to 13 years, but approved for use from 9 to 26 years.
b. The preventive vaccine is best administered prior to HPV exposure through sexual contact.
c. Catch-up immunization is recommended for those from 14 to 26 years who were not previously vaccinated or who did not complete the full three-shot vaccine series.
d. Immunization for boys and men is not recommended; efficacy of the quadrivalent vaccine is not yet known.
e. The vaccine may benefit females from 14 to 26 years with previous abnormal Pap tests, including cancer of the cervix, genital warts or identified HPV infection.
f. This vaccine is not recommended for pregnant women.

For more information for clinicians, including limitations and special circumstances, please see: www.phac-aspc.gc.ca/publicat/ccdr-rmtc/07pdf/acs33-02.pdf www.cdc.gov.std/HPV/STDFact-HPV-vaccine-hcp.htm

117. What are the emergent questions regarding the implementation of an HPV vaccine?

HPV immunization appears to be an efficacious (and perhaps a cost-effective) means to reduce the burden of HPV infection and associated clinical disease. Although one commercial vaccine has been approved for use in Canada and the United States (and other developed countries), many questions must still be addressed, including the ethical and social implications of vaccination against a sexually transmitted agent. Key questions to be answered are:

1) What will be the length of duration of immunity? Will it differ between vaccines and will booster doses be necessary to maintain immunity?
2) What is the optimal number of HPV types to include in a vaccine?
3) Do the current vaccines induce any level of cross-protection against HPV types not present in the vaccine?

4) At what age should vaccination begin and to whom should the vaccine be given — young women alone or both men and women?
5) Will people be vaccinated universally or opportunistically/privately, or both?
6) How will widespread vaccination efforts affect current cervical cancer screening recommendations and programs? How will health services coordinate vaccinations with cervical cancer screening?
7) Will vaccines alter the natural history of prevalent HPV infection through decreased incidence of persistent infection or cytological abnormalities?
8) Will vaccines be accepted by doctors, parents, adolescents, and the population in general?
9) What will be the effect, if any, on sexual behaviour?
10) What will be the cost and availability of vaccines in developing countries where the need and impact are likely to be most dramatic (Frazer et al., 2006; Lowy & Schiller, 2006; Steinbrook, 2006)?
11) How will cost-effectiveness be achieved in developed countries with established screening programs?
12) What will be the role of primary HPV screening in an era of vaccination and vaccination's impact on screening interval?

The effect of vaccination on cervical cancer rates will not be measurable until at least 10 to 15 years after introduction. One can expect to see a significant reduction in the burden of abnormal tests, evaluation, and earlier treatment. Nonetheless HPV vaccination has the potential to significantly reduce the incidence of cervical cancer (Lowy & Frazer, 2003; Franco, Bosch et al., 2006).

118. Where can I get more detailed information on the prophylactic vaccine and cervical cancer screening?

The following is a short list of key websites and references and is not exhaustive.

1) The journal *Vaccine* published a monograph entitled "HPV Vaccines and Screening in the Prevention of Cervical Cancer" (edited by F. X. Bosch), which is the most current review and authoritative information source at the time of printing. It incorporates the work of more than 100 lead authors in this domain and is a must-read for those wanting an in-depth knowledge of these issues.

2) The United States Centers for Disease Control and Prevention website [http://www.cdc.gov/] provides current information about HPV and HPV vaccines and issues related to implementation in the United States.
3) Health Canada [http://www.hc-sc.gc.ca/index_e.html] and the National Advisory Committee on Immunization [http://www.phac-aspc.gc.ca/naci-ccni/] websites.
4) Camo, M. S. (Ed.). (2006). *Papillomavirus research: From natural history to vaccines and beyond*. Norfolk, UK: Caister Academic Press.
5) IARC (2005). *Cervix cancer screening*. (Volume 10). Lyon: IARC Press.
6) McLachlin, C., Mai, V., Murphy, J., Fung-Kee-Fung, M., Chambers, A. (2005) Clinical practice guidelines for cervical cancer screening in Ontario. A Quality Initiative of the Program in Evidence-based Care, Cancer Care Ontario, developed by the Cervical Screening Guidelines Development Committee of the Ontario Cervical Screening Program and the Gynecology Cancer Disease Site Group of Cancer Care Ontario. Available at: http://www.cancercare.on.ca/pdf/pebc_cervical_screen.pdf.
7) Rohan, T. E., Shah, K. V. (Eds.). (2004). *Cervical cancer: From etiology to prevention*. Dordrecht, The Netherlands: Kluwer Academic Publishers.
8) Stuart G., Taylor G., Bancej C. M., Beaulac J., Colgan T., Franco E. L et al. (2004). Report of the 2003 pan-Canadian forum on cervical cancer prevention and control. *Journal of the Society of Obstetricians and Gynecologists of Canada, 26*(11), 1004–1028.
9) Professional societies
    a. Society of Gynecologic Oncologists of Canada [http://www.g-o-c.org/]
    b. Society of Obstetricians and Gynecologists of Canada [http://www.sogc.org/]
    c. Canadian Family Practice Association [http://www.cfpc.ca/global/splash/default.asp?s=1]
    d. Canadian Paediatric Association [http://www.cps.ca/]

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Appendix A:
Ontario Modified Bethesda System, 2001

Revised Terminology: Conversion Table

Ontario Modified Bethesda System, 1997	Ontario Modified Bethesda System, 2001
Specimen Adequacy	
Satisfactory for evaluation	Satisfactory for evaluation
Satisfactory for evaluation but limited by	• presence/absence of T-zone • other quality indicators
Unsatisfactory for evaluation	Unsatisfactory for evaluation
Interpretation/result	
Within normal limits	Negative for intraepithelial lesion or malignancy
Benign cellular changes	
Endometrial cells, cytologically benign in a post-menopausal woman	Endometrial cells in a woman >40 years of age
Atypical squamous cells of undetermined significance (ASCUS) • Favour reactive • Favour SIL	Atypical squamous cells • Undetermined significance (ASCUS) • Cannot exclude HSIL (ASC-H)
Low-grade squamous intraepithelial lesion (LSIL)	Low-grade squamous intraepithelial lesion (LSIL)
High-grade squamous intraepithelial lesion (HSIL)	High-grade squamous intraepithelial lesion (HSIL)
Squamous cell carcinoma	Squamous cell carcinoma
Atypical glandular cells of undetermined significance (AGUS) • Favour reactive endocervical • Favour neoplastic endocervical • Favour endometrial • Not otherwise specified	Atypical endocervical cells • Not otherwise specified • Favour neoplastic
	Atypical endometrial cells • Not otherwise specified • Favour neoplastic
	Atypical glandular cells • Not otherwise specified • Favour neoplastic
Atypical glandular cells, consistent with adenocarcinoma in situ	Endocervical adenocarcinoma in situ
Malignant cells present consistent with adenocarcinoma	Adenocarcinoma • Endocervical • Endometrial • Extra-uterine • Not otherwise specified

Ontario Modified Bethesda System, 2001: Terminology[1]

Specimen type

- Indicate conventional smear vs. liquid based vs. other

Specimen adequacy

- Satisfactory for evaluation
  - Describe presence or absence of transformation zone component
  - If necessary describe other quality indicators
    (e.g., partially obscuring blood, inflammation, etc.)
- Unsatisfactory for evaluation
  - Specify reason

General categorization (optional)

- Negative for intraepithelial lesion or malignancy
- Epithelial cell abnormality: see interpretation/result
- Other: see interpretation/result

Interpretation / result

Negative for intraepithelial lesion or malignancy

- **Organisms**
  - Trichomonas vaginalis
  - Fungal organisms morphologically consistent with *candida* spp
  - Shift in flora consistent with bacterial vaginosis
  - Bacteria morphologically consistent with *actinomyces* spp
  - Cellular changes consistent with Herpes simplex virus

- **Other non-neoplastic findings**
  - Reactive cellular changes associated with inflammation, repair, radiation, IUD, other
  - Glandular cells status post hysterectomy
  - Atrophy

Other

- Endometrial cells in a woman >40 years of age

(1) See also: Notes for Ontario Modified Bethesda System 2001, and post-workshop recommendations at http://www.bethesda2001.cancer.gov/.

Squamous cell abnormalities

- **Atypical squamous cells**
  - Atypical squamous cells of undetermined significance (ASCUS)
  - Atypical squamous cells, cannot exclude HSIL (ASC-H)
- **Low-grade squamous intraepithelial lesion (LSIL)**
  (Encompassing HPV, mild dysplasia, CIN I)

- **High-grade squamous intraepithelial lesion (HSIL)**
  (Encompassing moderate/severe dysplasia, CIN II/III, CIS)
  - With features suspicious for invasion

- **Squamous cell carcinoma**

Glandular cell abnormalities

- **Atypical endocervical cells**
  - Atypical endocervical cells (not otherwise specified)
  - Atypical endocervical cells, favour neoplastic

- **Atypical endometrial cells**
  - Atypical endometrial cells (not otherwise specified)
  - Atypical endometrial cells, favour neoplastic

- **Atypical glandular cells**
  - Atypical glandular cells (not otherwise specified)
  - Atypical glandular cells, favour neoplastic

- **Endocervical adenocarcinoma in situ**

- **Adenocarcinoma**
  - Endocervical
  - Endometrial
  - Extra-uterine
  - Not otherwise specified

Other malignant neoplasms (specify)

Additional information

- **Automated review:** If a case was examined by an automated device the device and result should be stated.
- **Ancillary testing:** A brief description of the test method and result should be clearly reported.

Notes for Ontario Modified Bethesda System, 2001[2]

Specimen adequacy

1. The presence or absence of transformation zone component should be stated in the report. The criteria for adequate transformation component as described by TBS 2001 are supported.
2. Unsatisfactory — TBS 2001 recommends using "specimen not processed" for cases that are damaged or lost prior to receipt in the laboratory. However, it is generally the practice in Ontario not to accession or issue a report on these cases.

Laboratories should maintain a log of cases that are rejected prior to accessioning.

General categorization

1. The general categorization is optional and is not widely used in Ontario.

Interpretation/results

1. *Negative for intraepithelial lesion or malignancy*
   - The reporting of other non-neoplastic findings is optional. The list of non-neoplastic findings may be expanded to include other findings according to the laboratory's practice. The laboratory should develop a policy for the triage of negative cases requiring hierarchical/pathologist review. This should include reactive changes associated with repair but may be expanded to include other findings according to the laboratory's practice.
   - As the negative category may contain clinically significant findings, (e.g., organisms), the report should be designed to indicate these findings clearly.

2. *Endometrial cells in a woman >40 years of age*
   - This indicates exfoliated glandular cells, not endometrial cells that have been abraded by the sampling device.
   - For further explanation see TBS 2001 Notes. Laboratories may either report these under the negative diagnosis or as a separate diagnosis. An accompanying educational comment such as the one detailed in the TBS 2001 Notes is recommended.

(2) For further information and explanatory notes on the use of the Ontario Modified Bethesda System, 2001, please refer to the forum notes on each section at http://www.bethesda2001.cancer.gov/. The notes included here refer to Ontario-specific recommendations only.

3. *Atypical squamous cells (ASC)*
   - The elimination of atypical squamous cells, favour reactive is strongly supported. Whenever possible these minor changes should be reported as negative rather than ASCUS.
   - Atypical squamous cells, cannot exclude HSIL, should be limited to 5–10% of all ASC cases and the use of this diagnosis should be monitored with internal quality assurance indicators such as individual rates of use and histologic correlation. The overuse of this category for cases that could be reported as HSIL is discouraged.

4. *Squamous intraepithelial lesion (LSIL/HSIL)*
   - The inclusion of secondary terminology (dysplasia/CIN) is optional.
   - The inclusion of HSIL with features suspicious for invasion is supported.

5. *Atypical endocervical/endometrial/glandular cells*
   - As with ASC, the elimination of "atypical glandular cells, favour reactive" is supported. Whenever possible these minor changes should be reported as negative rather than atypical.

Endorsement

Revised terminology for the Ontario Modified Bethesda System 2001 has been endorsed by:

- Ontario Medical Association, General and Family Practice Section
- Ontario Medical Association, Laboratory Medicine Section
- Ontario Medical Association, Obstetrics & Gynecology Section
- Ontario Society of Medical Technologists
- Quality Management Program — Laboratory Services (QMP–LS)

Appendix B:
Revised (2005) Ontario Cervical Screening Practice Guidelines

Ontario Cervical Screening Practice Guidelines

Revised June 2005

Initiation of Screening	• **All women** who are, or have ever been, sexually active should be screened. • Cervical cytology screening should be initiated within three years of first vaginal sexual activity, i.e., vaginal intercourse, vaginal/oral and/or vaginal/digital sexual activity.
Screening Interval	• Screening should be done annually until there are three consecutive negative Pap tests. • After three annual negative Pap tests, screening should continue every two to three years. (These recommendations do not apply to women with previous abnormal Pap tests) – See over for management of abnormal cytology. – Screening at a three year interval is recommended, supported by an adequate recall mechanism. – Women who have not been screened in more than five years should be screened annually until there are three consecutive negative Pap tests.
Cessation of Screening	• Screening may be discontinued after the age of 70 if there is an adequate negative screening history in the previous 10 years (i.e., 3 or more negative tests).

Screening Women with Special Circumstances

- **Immunocompromised or HIV positive women** should receive annual screening.
  – Examples of situations where women may be immunocompromised include women who have received transplants, or women who have undergone chemotherapy.
- Screening can be discontinued in **women who have undergone total hysterectomy** for benign causes with no history of cervical dysplasia or human papillomavirus (HPV).
  – Women who have undergone **subtotal hysterectomy (with an intact cervix)** should continue screening according to the guidelines.
- Indications for screening frequency for **pregnant women** should be the same as for women who are not pregnant. Manufacturer's recommendations for the use of individual screening tools in pregnancy should be considered.
- **Women who have sex with women** should follow the same cervical screening regimen as women who have sex with men.

Optimal Cervical Screening Tool

- Liquid-based cytology (LBC) is the preferred tool for cervical cytology screening.
- Conventional smear cytology remains an acceptable alternative.

Optimal Screening Circumstances

- A province-wide cervical screening program with an adequate recall mechanism is recommended.

For more detail on the guidelines, please refer to: www.cancercare.on.ca/index_cervicalScreening.htm

08/2005 271890

See reverse

ontario cervical screening program
a cancer care ontario program
programme ontarien de dépistage du cancer du col de l'utérus
un programme de action cancer ontario

Recommendations for Follow-up of Abnormal Cytology

Revised June 2005

ONTARIO GUIDELINES

Diagnosis	Recommended Management				
Atypical Squamous Cells of Undetermined Significance (ASCUS)	**For women < 30 years of age**				
	Repeat cytology in 6 months	Result: Negative	Repeat cytology in 6 months	Result: Negative	Routine screening
				Result: >=ASCUS	Colposcopy
		Result: >=ASCUS	Colposcopy		
	For women >= 30 years of age				
	HPV-DNA testing	Result: Negative	Repeat cytology in 12 months		
		Result: Positive	Colposcopy		
	If HPV-DNA testing is not available				
	Repeat cytology in 6 months	Result: Negative	Repeat cytology in 6 months	Result: Negative	Routine screening
				Result: >=ASCUS	Colposcopy
		Result: >=ASCUS	Colposcopy		
	All women Immediate referral to colposcopy is only recommended in situations where there is a high probability of patient loss to follow-up, ***OR*** If there are other symptoms suggesting cervical abnormality (e.g., abnormal bleeding, etc.)				
Atypical Squamous Cells, Cannot exclude HSIL (ASC-H)	Colposcopy				
Atypical Glandular Cells, Atypical Endocervical Cells, Atypical Endometrial Cells	Colposcopy and/or endometrial sampling				
Low Grade Squamous Intraepithelial Lesion (LSIL)	Repeat cytology in 6 months	Result: Negative	Repeat cytology in 6 months	Result: Negative	Routine screening
		Result: >=ASCUS	Colposcopy		
	Colposcopy				
High Grade Squamous Intraepithelial Lesion (HSIL)	Colposcopy				
Squamous Carcinoma, Adenocarcinoma, Other Malignant Neoplasms	Colposcopy				
Unsatisfactory	Repeat cytology in 3 months				

Regular Pap tests can save your life

Distributed with the help of the Canadian Cancer Society / Société canadienne du cancer

Appendix C:
Ontario Cervical Screening Reference Card

Instructions for Preparing Conventional Pap Tests

How to take a Pap test Ontario Cervical Screening Reference Card
Instructions for "Pap" test preparation

Label Slide

- with PENCIL, on frosted side of slide
- unlabelled slides will not be processed
- complete requisition

Ensure ID and relevant history are complete. NOTE: Ideally, smear will be taken close to mid-cycle.

Visualize Cervix

Refer to Adequate "Pap" Smears, Figure 1 (see below)

- lubricate speculum with warm water
- rinse talcum from outer surface of gloves
- do not use lubricant gel

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

Take Sample

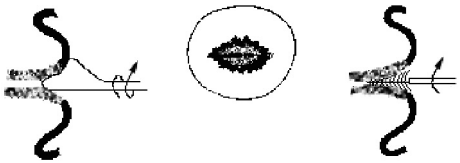
To obtain a proper "Pap" smear, use a spatula and an endocervical sampling device. (e.g., brush) and apply on a single slide.

1. SPATULA

- rotate once through 360°
- keep spatula well applied

2. BRUSH

- or other endocervical sampling device
- insert gently
- turn through 90° only



NOTE: Do NOT use brush in pregnancy

Apply Sample

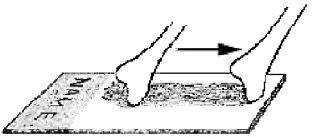
Use ONE slide. Apply each sample on one half of slide as shown — keep separate.

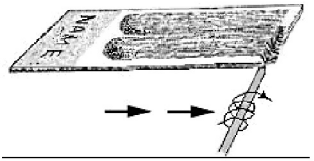
1. SPATULA

- spread in a single uniform motion

2. BRUSH

- sample will dry quickly
- roll on in one motion

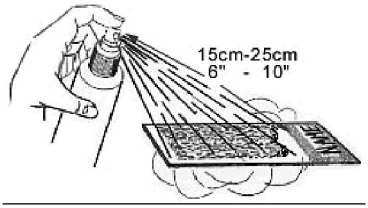




This sequence should be practiced to avoid delay.

Fix Sample

- immediately
- allow sample to dry before closing mailer



Adequate "Pap" Smears:A Guide for Sampling Techniques in Screening for Abnormalities of the Uterine Cervix,2nd ed., by Donald W. Thompson, MD

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Produced on behalf of the Ontario Cervical Screening Collaborative Group, November 1996.
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Index

Note: Topics are indexed by question number, not page number[1]

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(1)"Papanicolaou test" is abbreviated as "Pap test" throughout.

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