

# **Anal Dysplasia Screening**

**Evidence-Based Analysis**

**Completed June 2007**

## Anal Dysplasia Screening

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# **Abbreviations**

<b>AIDS</b>	Acquired immune deficiency syndrome
<b>AIN</b>	Anal intraepithelial neoplasia
<b>ASCUS</b>	Atypical squamous cells of uncertain significance
<b>ASIL</b>	Atypical squamous intraepithelial lesion
<b>CE</b>	Cost-effectiveness
<b>CIN</b>	Cervical intraepithelial neoplasia
<b>CONV</b>	Conventional Papanicolaou's test
<b>GRADE</b>	Grading Recommendation Assessment Development and Evaluation
<b>HAART</b>	Highly active antiretroviral therapy
<b>HC11</b>	Hybrid capture 11
<b>HIV</b>	Human immunodeficiency virus
<b>HPV</b>	Human papillomavirus
<b>HSIL</b>	High-grade squamous intraepithelial lesion
<b>ICER</b>	Incremental cost-effectiveness ratio
<b>LBC</b>	Liquid-based cytology
<b>LSIL</b>	Low-grade squamous intraepithelial lesion
<b>MSM</b>	Men who have sex with men
<b>PAP</b>	Papanicolaou's (test or smear)
<b>PCR</b>	Polymerase chain reaction
<b>QALY</b>	Quality adjusted life years
<b>RR</b>	Relative risk
<b>SIR</b>	Standardized incidence ratio
<b>SN</b>	Sensitivity
<b>SP</b>	Specificity

# **Executive Summary**

## **Background**

In October 2003, the Medical Advisory Secretariat completed a health technology and policy assessment on anal Papanicolaou's (Pap) cytology as a screening tool for anal squamous cell carcinoma (SCC) in response to an enquiry from the Laboratory Services Branch at the Ministry of Health and Long-Term Care. Two original studies were identified evaluating the screening test performance of the anal Pap smear for anal dysplasia in different prospective cohorts: human immunodeficiency virus (HIV)-positive men in one study, and HIV-positive and HIV-negative men in the other.

In the 2003 review, the sensitivity and specificity of the Pap smears in both populations were found to have had insufficient power to discriminate between benign and squamous intraepithelial lesions presumed to be the precursor lesions to anal SCC. Nor was the utility of Pap smears over clinical examination. Furthermore, the natural history and disease progression of the premalignant lesions was not well understood, and treatment of these early disease stages had not been shown to reduce malignant disease burden. At that time, therefore, the Ministry decided that reimbursement by Laboratory Services for anal Pap smears should not be offered.

## **Purpose**

The 2007 anal dysplasia screening evidence review considered the role of the anal Pap test as a screening test for anal dysplasia in patients at high risk of anal SCC. The screening process is now thought to be improved with the addition of testing for the human papillomavirus (HPV) in high-risk populations. High-resolution anoscopy (a method to view the rectal area, using an anoscope, a lighted instrument inserted into the rectum) rather than routine anoscopy-guided biopsy, is also now considered to be the diagnostic standard. The request for the review was submitted by the Acquired Immunodeficiency Syndrome (AIDS) Bureau in the Ontario Ministry of Health and Long-Term Care, and by the director of the immunodeficiency clinic at the Toronto General Hospital.

## **Clinical Need: Target Population and Condition**

Anal cancer, like cervical cancer, is a member of a broader group of anogenital cancers known to be associated with sexually transmitted viral HPV infection. Human papillomavirus is extremely prevalent, particularly in young, sexually active populations. Sexual practices involving receptive anal intercourse lead to significantly elevated risk for anal dysplasia and cancer, particularly in those with immune dysfunctions.

Anal cancer is rare. It occurs at a rate of about 1 to 2 per 100,000 in the general population. It is the least common of the lower gastrointestinal cancers, representing about 4% of them, in contrast to colorectal cancers, which remain the third most commonly diagnosed malignancy. Certain segments of the population, however, such as HIV-positive men and women, other chronic immune-suppressed patients (e.g., after a transplant), injection drug users, and women with genital dysplasia /cancer, have a high susceptibility to anal cancer.

Those with the highest identified risk for anal cancer are HIV-positive homosexual and bisexual men, at a

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rate of 70 per 100,000 men. The risk for anal cancer is reported to be increasing dramatically in HIV-positive males and females, particularly since the introduction of highly active antiretroviral therapy in the mid-1990s. The introduction of effective viral therapy has been said to have transformed the AIDS epidemic in developed countries into a chronic disease state of long-term immunosuppression. In Ontario, there are about 25,000 people living with HIV infection; more than 6,000 of these are women. About 28% of the newly diagnosed HIV infections are in women, a doubling since 1999. It has also been estimated that 1 of 3 people living with HIV do not know it.

## **Health Technology Description**

Anal Pap test screening involves the blind insertion of a swab into the anal canal and fixing cells either on a slide or in fluid for cytological examination. Anal cytology classified by the standardized Bethesda System is the same classification used for cervical cytology. It has 4 categories: normal, atypical squamous cells of uncertain significance, or squamous intraepithelial lesions which are further classified into low- or high-grade lesions. Abnormal cytological findings are subjected to further evaluations by high-resolution anoscopy, a technique similar to cervical colposcopy, and biopsy. Several HPV deoxyribonucleic acid detection technologies such as the Hybrid 11 Capture and the polymerase chain reaction are available to detect and differentiate HPV viral strains.

Unlike cervical cancer, there are no universally accepted guidelines or standards of care for anal dysplasia. Moreover, there are no formal screening programs provincially, nationally, or internationally. The New York State Department of Health AIDS Institute has recently recommended (March 2007) annual anal pap testing in high-risk groups. In Ontario, reimbursement exists only for Pap tests for cervical cancer screening. That is, there is no reimbursement for anal Pap testing in men or women, and HPV screening tests for cervical or anal cancer are also not reimbursed.

## **Methods**

The scientific evidence base was evaluated through a systematic literature review. Assessments of current practices were obtained through consultations with various agencies and individuals including the Ministry of Health and Long-Term Care AIDS Bureau; Public Health Infectious Diseases Branch, Ministry of Health and Long-Term Care; Cancer Care Ontario; HIV/AIDS researchers; pathology experts; and HIV/AIDS clinical program directors. An Ontario-based budget impact was also done.

## **Findings**

No direct evidence was found for the existence of controlled studies evaluating the effectiveness of anal Pap test screening programs for impact on anal cancer morbidity or mortality. In addition, no studies were found on the use of HPV DNA testing in the screening or diagnostic setting for anal dysplasia. The reported prevalence of HPV infection in high-risk groups, particularly HIV-positive males, however, was sufficiently high to preclude any utility of HPV testing as an adjunct to anal Pap testing.

Nine reports involving studies in the United States, United Kingdom, and Canada were identified that evaluated the performance characteristics of anal Pap test screening for anal dysplasia. All involved hospital-based specialty HIV/AIDS care clinics with mainly HIV-positive males. All studies involved experienced pathologists, so the results generally represent best-case scenarios. Estimates of anal Pap test sensitivity and specificity were highly variable, and depended on the varying prevalence of cytology abnormality and differential thresholds for abnormality for both cytology and histopathology.

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In the largest study of HIV-positive males, sensitivity varied from 46% (95% confidence interval [CI], 36%–56%) to 69% (95% CI, 60%–78%). Specificity ranged from 59% (95% CI, 53%–65%) to 81% (95% CI, 76%–85%). In the only study of HIV-negative males, sensitivity ranged from 26% (95% CI, 5%–47%) to 47% (95% CI, 26%–68%). Specificity ranged from 81% (95% CI, 76%–85%) to 92% (95% CI, 89%–95%).

In comparison, cervical Pap testing has also been evaluated mainly in settings where there is a high prevalence of the disease, and estimates of sensitivity and specificity were also low and highly variable. In a systematic review involving cervical Pap testing, sensitivity ranged from 30% to 87% (mean, 47%) and specificity from 86% to 100% (mean, 95%).

## **Conclusions**

No direct evidence exists to support the effectiveness of an anal Pap test screening program to reduce anal cancer mortality or morbidity. There are, however, strong parallels with cervical pap testing for cervical cancer. Sexually transmitted HPV viral infection is currently the acknowledged common causative agent for both anal and cervical cancer. Anal cancer rates in high-risk populations are approaching those of cervical cancer before the implementation of Pap testing.

The anal Pap test, although it has been mainly evaluated only in HIV-positive males, has similar operating characteristics of sensitivity and specificity as the cervical Pap test. In general, the treatment options for precancer dysplasia in the cervix and the anus are similar, but treatment involving a definitive surgical resection in the anus is more limited because of the higher risk of complications. A range of ablative therapies has been applied for anal dysplasia, but evidence on treatment effectiveness, tolerability and durability, particularly in the HIV-positive patient, is limited.

# **1. Background**

## **Epidemiology of Anal Cancer**

Anal carcinoma, with about 350 incident cases in Ontario in 2001, is a rare disease in the general population. (Cancer Care Ontario) In Ontario, the age-adjusted incidence rate of anal cancer in 2001 was 1.2 per 100,000. The rates for males and females were 1.2 (152 cases) per 100,000 and 1.3 (201 cases) per 100,000, respectively.

Several recent population-based studies note that anal cancer rates have been increasing, and that the trend has been particularly dominant in urban populations, particularly those centres with high concentrations of homosexual males or men who have sex with men (MSM). Increasing rates have been reported in Copenhagen, (1) London, (2) and San Francisco. (3;4) The highest increases in anal cancer were reported in San Francisco, with rates in men aged 40 to 64 years increasing from 3.7 to 20.6 per 100,000 from 1996 to 1999. (3)

A broad-based cancer and acquired immune deficiency syndrome (AIDS) registry linkage study (5) examining the relationship of all human papillomavirus (HPV)-related cancers in patients with AIDS reported significantly increased risks of HPV-related cancers in men and women. The relative risk (RR) for anal cancer was significantly higher for men than for women for invasive lesions (37.9; 95% confidence interval (CI), 33.0–43.4, vs. 6.8; 95% CI, 2.7–14.0) and in situ precursor lesions (60.1; 95% CI, 49.2–72.7, vs. 7.8; 95% CI, 0.2–43.6) anal cancers. Although homosexuals with HIV exposure had the highest RR (59.5; 95% CI, 51.5–68.4) for anal cancer, both male (RR, 5.9; 95% CI, 2.7–11.2) and female (RR, 7.3; 95% CI, 1.5–21.4) intravenous drug users also had an increased RR for anal cancer.

Several studies (2;6;7) examined the changes in the incidence of anal cancer in relation to the AIDS epidemic (between 1980 and late 1990) and the introduction of highly active antiretroviral therapy (HAART) around 1996. The trends reported in the studies were consistent in that HAART therapy did not appear to have reduced the occurrence of anal cancer, as it did for other AIDS-related malignancies such as Kaposi's sarcoma and non-Hodgkin lymphoma. In the largest study (6) involving population-based cancer registries, anal cancer incidence increased from 0.6 to 0.8 per 100,000 between 1973 and 2001. There was a significant increase in incidence rates in both men and women, although more so for men, in the HAART era.

Two studies, one in the United Kingdom (2) and one in the United States (7) reported dramatically increased anal cancer rates in HIV populations before and after the introduction of HAART. In the United Kingdom study, the incidence increased from 35 to 92 per 100,000 people with HIV. The overall incidence in the HIV cohort compared to the general population was 60 versus 0.52 per 100,000. In the United States study, rates in the general population among men aged 25 to 64 years increased from 0 to 224 per 100, from 1991 to 2000. The rate of anal cancer in the HIV cohort of men compared to men without HIV/AIDS increased from 98 to 352 per 100,000.

Increased anal cancer rates have also been reported in other immunosuppressed patients, particularly in those who have had organ allograft transplantation.(8;9) Overall, 3- to 4-fold increased cancer risks have been reported for cancers in general for patients who have received a transplant. Risks for certain cancers, particularly rare cancers, increased several hundredfold compared with age-matched population controls. Most involved the lymphoid system, skin, and urogenital and anogenital tracts. These rare cancers were etiologically associated with various oncogenic viruses: Epstein-Barr virus (non-Hodgkin's lymphoma),

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HPV (squamous tumors of the skin and anogenital region), and hepatitis B virus (primary liver cancer).

Anogenital cancers differ from other post-transplant malignancies in that they occur more commonly in females (2.6 to 1); in other post-transplant malignancies, males outnumber females 2 to 1. Several studies (10;11) have reported increased anal cancer rates in renal transplant patients. In a Swedish population-based cancer registry study (10) of 5,931 transplant patients between 1970 and 1997, the standardized incidence ratio (SIR) for anal cancer was 10 (95% CI, 3–26).

Prevalence of anal dysplasia and HPV infection was examined in patients who had had a renal allograft (n = 23) in a case-control study. (11) In the control group involving patients without allografts, 12.4% were positive for HPV, and 0.7% had anal intraepithelial dysplasia (AIN 11). In the cases, patients having allografts, anal HPV infection or anal dysplasia was present in 24.1%. All of those with high-grade anal dysplasia or anal cancer were women (n = 5); in addition, all had previous or concurrent dysplasia in other genital regions including the cervix, vagina, or vulva.

For women, the occurrence of anal cancer is linked to their risk for other cancers in the anogenital region. Cancer occurring anywhere in the anogenital region puts women at increased risk for other primary or secondary cancers in the region, a phenomenon referred to as a field cancerization. (12) Several population-based cancer registry studies (13-15) have examined the risk of subsequent cancers (second primary cancer) in women initially registered with cervical cancer as the index case. In the Michigan tumor registry study (13) with 7,317 person-years of follow-up between 1985 and 1992, 6.5% of women with index cases of cervical cancer developed other cancers in the anogenital region during the 5- to 8-year follow-up period. The SIR for vaginal cancer was significantly increased (44.4; 95% CI, 16.2–96.5). (13)

Two larger cancer registry-based studies, one in the United Kingdom (14) involving 145,621 person-years of follow-up from 1960 to 1999, and one in Sweden (15) that followed-up 135,386 women from 1958 to 1996, found significantly increased risks for other genital cancers after an initial diagnosis of cervical cancer. In the United Kingdom study, rates for second primary cancers were increased for the vagina (SIR, 8.0; 95% CI, 4.4–13.5), anus (SIR, 6.3; 95% CI, 3.7–10.0), and vulva (SIR, 1.9; 95% CI, 1.0–3.3). Index cases registered with in situ cervical cancer had a higher risk for cancers occurring in other genital regions: vagina (SIR, 18.5; 95% CI, 13.0–25.5), anus (SIR, 5.9; 95% CI, 3.7–8.8), vulva (SIR, 4.4; 95% CI, 2.8–6.6), and cervix (SIR, 2.8; 95% CI, 2.4–3.2). In the Swedish study, increased rates for second cancers in the anogenital region after a primary cervical cancer were also reported with the highest being for anal cancer (SIR, 4.8; 95% CI, 3.7–6.0).

## **Etiology**

A sexually transmitted viral etiology has been largely accepted for cervical cancer, (16;17) and almost 100% of squamous cervical cancers are attributable to infection with HPV. There are also many lines of evidence (18) that suggest squamous tumors in the anal canal have similar histological, epidemiological, and pathogenetic properties to other squamous tumors in the anogenital region, notably cervical, vaginal, vulvar, and penile cancer.

High-risk oncogenic HPV viral deoxyribonucleic acid (DNA) has also been found to be associated with other anogenital cancers, including anal squamous carcinoma. (18) Multiple serotypes of HPV DNA 16, 18, 31, 33, and 35 have been reported to be associated with oncogenic potential in the anal region and, similar to the cervical region, HPV 16 occurs most commonly. (19-21)

Clinical pathological studies (22;23) also provide strong causal evidence for high-risk HPV DNA in high-

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grade anal dysplasia and cancer. In case-control studies using polymerase chain reaction (PCR), a highly sensitive assay for HPV DNA, between 80% and 100% of anal biopsy specimens contain high-risk HPV DNA, primarily HPV 16. Human papillomaviral DNA was never found in control biopsies of normal anal mucosa, hemorrhoidal tissue, or rectal adenocarcinoma.

There is also molecular evidence that high-risk viruses integrate into anal cells. (22-25) High-risk viruses encode for at least 3 oncoproteins with growth stimulating and transforming properties: E5, E6, and E7. Integration of the HPV DNA results in a break in the E1 and E2 regions of the viral genome, resulting in a loss of the E2 protein function and a subsequent increased gene expression of E6 and E7, whose cooperation is needed to maintain the malignant cell expression in vitro. Both of these proteins are expressed in anal neoplasia. (26) The premalignant changes seen in cervical high-grade dysplasia and the greater degree of angiogenesis and apoptosis than there is in the normal tissue are also seen in high-grade anal dysplasia. (27;28) The major steps in the carcinogenesis pathway have been summarized as: infection with one or more high-risk HPV; viral persistence rather than clearance; clonal progression of persistently infected epithelium to precancer; and invasion. (29)

## **Natural History**

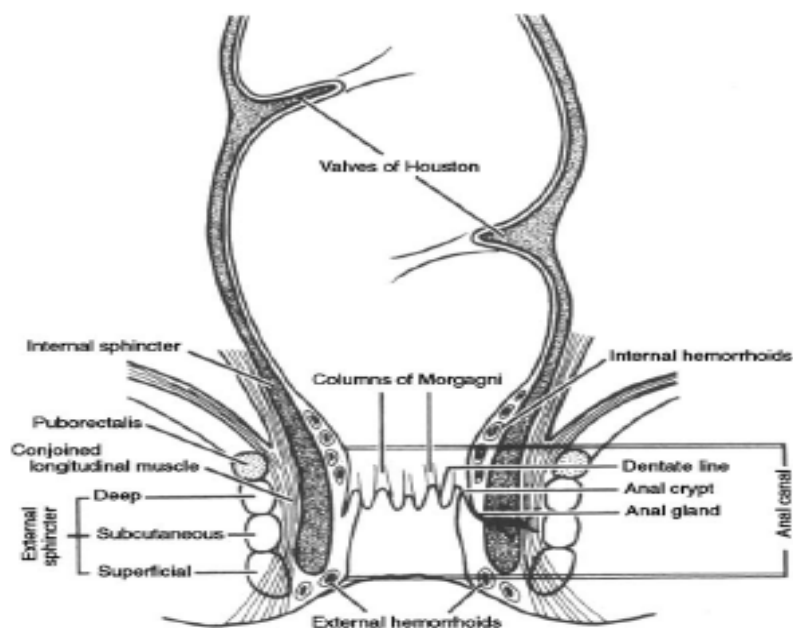
In females, the lower genital tract includes the uterine cervix, vagina, vulva, and anus, and consists of a contiguous surface of epithelium that is derived embryologically from the urogenital sinus and cloacal endoderm. (13) Cancers occurring in this region have been referred to as field cancers because of the close proximity of the regions and similar areas of exposure and risk. The cervix, like the anus, has a transitional or transformational zone with an increased risk of dysplasia. The cervical transformation zone at birth is covered with columnar epithelium. At puberty, ovarian estrogen-induced local environmental changes in the Ph from neutral to acidic stimulate reserve cells along the basement membrane to become squamous, thereby replacing the columnar cells. The transformation (squamo-columnar junction) continues most actively in the reproductive years and then slowly in menopause. Because the transforming squamous cells are metabolically more active than are the nontransforming squamous cells that cover the peripheral exocervix, vagina, vulva, perineum, and anus, they are more susceptible to viral infection and integration.

Squamous tumors of the anogenital region have similar histological, epidemiological, and pathogenetic properties. (30;31) The anus is an organ that lies at the end of the digestive tract below the rectum and consists of 2 sections: the anal canal and the anus or anal verge (Figure 1). (32) The anal canal is a 3 to 4 cm long structure that lies between the anal sphincter, one of the muscles controlling bowel movements, to just below the rectum and the anal verge, which represents the transition point between the digestive system and the skin on the outside of the anus. The upper part of the anal canal, where it meets the rectum, is called a transitional zone. The lower end, called the anal margin, contains the sphincter, which is a circular muscle responsible for bowel control. The canal is lined with squamous cells which are similar to those lining the bladder, vagina, urethra, and mouth and throat. The skin on the outside of the anus is called perianal skin, and lesions in this area have been named Bowen's disease. (33)

The anal canal epithelium differs according to its localization. (33) There is a difference between the skin-like anal margin and mucosal, lined anal canal. The distal end of the anal canal is lined with squamous epithelium, which changes to transitional epithelium near the dentate line and, ultimately, to nonsquamous rectal mucosa. Distal anal tumors tend to have a keratinizing morphology, whereas proximal tumors are less likely to be keratinized. Tumors originating above the dentate line drain to the inguinal and femoral nodes, areas rarely involved with rectal cancer.

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**Figure 1: Anatomy of the Anal Region**



*Reprinted from Surgical Oncology, Vol. 14, Rousseau DL, Thomas CR, Petrelli NJ, Kahlenberg MS. Squamous cell carcinoma of the anal canal, pp. 121-132, Copyright (2005), with permission from Elsevier.*

Potentially precancerous precursors of the epithelium referred to as dysplasia when developing in the anus are referred to as intraepithelial neoplasia or AIN. Dysplastic cells have abnormal changes, but they do not show evidence of invasion into surrounding tissue. The most severe form is called carcinoma in situ, where the cells appear like cancer cells, but have not invaded beyond the basement membrane (membrane separating epithelium from tissue below). Intraepithelial neoplasia has been characterized into various grades, low and high, based on their potential to progress toward invasive cancer.

Intraepithelial lesions generally arise in the transitional zone of the anus, a region that extends from the squamous mucosa of the anus through the dentate line to the squamo-columnar junction with the rectal columnar mucosa. In this area of transition there is active changeover of columnar epithelium to squamous epithelium through the process of squamous metaplasia. This process can be accelerated by trauma, healing, and repair, such as might be expected to occur in receptive anal intercourse. Although several malignant forms can occur—squamous, cloacogenic, adenocarcinoma, basal carcinoma (type of skin cancer in the perianal skin) malignant melanoma (developing from melanin skin producing cells)—squamous occurs most commonly.

### **Prevalence of Human Papillomavirus Infection and Disease Progression**

The prevalence of HPV infection and anal cancer precursors were estimated in a large multicentre clinical trial known as the EXPLORE study, (34) which involved 1,409 HIV-negative MSM, aged 18 to 89 years, recruited from 4 cities: Boston, Denver, New York, and San Francisco. The median age in the study was 37 years, 49% were current or former smokers, and 8% were injection drug users. The median age of first

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anal receptive intercourse was 20 years, and a median number of 8 sex partners were reported in the previous 6 months.

The study produced two reports. In the first report, (34) the study examined the age-related prevalence of anal HPV. The overall prevalence of HPV infection was 57% and was similar across all age groups. Prevalence for both low- and high-risk HPV DNA strains were also similar across age groups. The most common type of HPV (12%) was HPV 16. Of those infected, 45% were infected with more than one type of HPV.

The second report (35) examined the age-related prevalence of and risk factors for anal cancer precursors. Overall, the prevalence of any cytological abnormality was 32%, which was similar across age groups. The prevalence of low-grade and high-grade anal lesions was 15% and 5%, respectively, and was also similar across age groups. Factors significantly associated with risk of high-grade anal lesions were increasing number of male sex partners ( $P = .047$  trend), and anal infection with increasing HPV types ( $P < .001$  for linear trend).

Several prospective cohort studies have evaluated the rate of developing anal cancer or anal cancer precursor lesions in both HIV-positive and HIV-negative MSM (36;37) and in HIV-positive women. (20;38) In the San Francisco study, (36) 2-year incidence and progression rates were reported in 346 HIV-positive and 262 HIV-negative MSM men. The incidence of high-grade anal lesions within 2 years was 20% in HIV-positive men and 8% in HIV-negative men who were normal at baseline. Low-grade anal lesions at baseline progressed to become high grade lesions in 62% of HIV-positive and 36% of HIV-negative men. Disease progression to high-grade from atypical squamous cells of uncertain significance (ASCUS) at baseline was even higher in both groups. Of the 27 HIV-positive men with ASCUS at baseline, only 8 (30%) were normal at the 2-year visit, compared with 8 (62%) of the 13 HIV-negative men.

In the Seattle-based study, (37) a smaller prospective cohort of 158 HIV-positive and 147 HIV-negative MSM presenting to a community-based clinic with initially negative cytology and colposcopic findings were followed-up for a mean of 21 months. High-grade lesions developed in 15.2% (24/158) of the HIV-positive and 5.4% (8/147) of the HIV-negative men. The presence of HPV 16,18 had a central role in the development of high-grade lesions in both HIV-positive and -negative men. High-grade lesions did not develop in any of the 44 HIV-negative or 12 HIV-positive men without HPV 16,18 infection. The 31% rate of high-grade lesion development in HIV-negative men with HPV 16,18 was also similar to the 39% rate of cervical high-grade lesion development reported in women within 2 years of HPV 16,18 infection. (39)

In women, the prevalence of anal HPV 16,18 infection in a cohort study of 251 HIV-positive and 68 HIV-negative women in the San Francisco Bay area was reported to be 76% and 42%. (20) Among the 200 women for whom there were concurrent anal and cervical data, anal HPV was more common than cervical HPV in both HIV-positive (79% vs. 53%) and HIV-negative (43% vs. 24%) women.

A second study (38) examined the natural history of anogenital infection in women recruited from an outreach community areas in Massachusetts. The 86 HIV-infected women with normal cytology at baseline and on HAART therapy at some point (25.7 person-years of follow-up), were followed-up for 113.5 person-years. At baseline, high-risk HPV DNA was detected in both the anus and the cervix: anus only, 14%; cervix only, 1%; anus and cervix, 30%; anus and cervix, same HPV type, 13%; and neither region, 55%. In this cohort, the incidence of newly detected cytological abnormalities was 22 per 100 person-years. The 25 incident anal cytological abnormalities included 17 ASCUS, 7 low-grade squamous intraepithelial lesions (LSILs) and 1 high-grade squamous intraepithelial lesion (HSIL). Independent risk

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factors for cytological abnormalities were depressed immune function defined as CD4+ T-cell count less than 500 cell/mm<sup>3</sup> (RR, 4.11), current smoker (RR, 3.88) and HPV infection (RR, 2.54).

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### **Screening of Intraepithelial Lesions in the Anogenital Region**

Screening for cervical or anal intraepithelial lesions involves the same 2-stage procedure: a Pap test and, for abnormal cytological findings, a referral for an anoscopic examination, similar to a cervical colposcopic examination, and biopsy if necessary. Conventional cervical Pap testing involves sampling the cervical canal using a collection device such as a swab or cytobrush to smear the sample on a slide, followed by spraying or placing the sample in a fixative prior to it being sent to the laboratory.

Anal Pap smear screening involves the same technique of blind insertion of a swab into the anal canal. The swab is inserted into the anus and vigorously rotated to scrape cells from the anal lining. Disadvantages with the conventional method include inadequate sample being spread, drying artefacts, obscured cells due to multiple layers of cell material or obscuring factors such as blood or inflammatory cells. Samples taken from the anal canal have the additional disadvantage of potential fecal contamination.

Liquid-based cytology (LBC) is a variation on the conventional technique in that collected cells are stirred or placed in a methanol-based fixative to suspend the sample. A technician at the lab uses filtering techniques to collect the cells and transfer them to a small area of a microscope in a monolayer. The advantages of this technique include better preservation of cytologic features of the cells, improved specimen sampling, and less clumping and obscuring of cells. An additional advantage is the use of residual material for the testing of HPV and other molecular biological tests, particularly if the initial test indicates atypical cells.

The second stage involves referral for an anoscopic examination and possible biopsy, when cytological findings are abnormal. (40) After an initial application of acetic acid, Lugol's iodine solution is applied. Then, an anoscope, a high-resolution microscope, is used to inspect visually the entire anal canal, particularly the transformation zone, an area of increased risk for dysplastic changes. In the cervix, high-grade lesions do not take up the iodine solution because of the lack of glycogen in the dysplastic cells; they appear yellow to tan, whereas normal or low-grade lesions appear dark brown or black. (41) Any abnormalities such as acetowhitening (a temporary change to a white color when acetic acid is applied topically), papillation (raised bumps) and ulceration or irregular surface changes noted in the inspection are biopsied.

Additional training to that acquired for colposcopy is needed for anoscopic examination, because the anatomy in the anal region, although similar to the cervix, is not identical. An appreciation for differential diagnoses in this area is essential because of the various types of benign, premalignant, and malignant growths that can occur in the anogenital region, creating potential for diagnostic confusion. Included among the diverse benign growths in the area are polyps (inflammatory or lymphoid), condylomas (or warts), folliculitis (inflammation of a follicle), hemorrhoids, hypertrophied papillae and/or fistulae and fissures. Other less common conditions can also occur. These include adnexal tumors beginning in the hair follicles or sweat glands, leiomyomas developing from smooth muscle tissue, hemangiomas developing from blood vessel lining, lipomas from fat cells and schwannomas developing from the covering of nerve cells.

### **Human Papillomavirus Testing**

There are 2 tests available to detect the presence of HPV viral DNA: the Hybrid Capture11 test and the DNA PCR test. (42) The Hybrid Capture11 test is a more general test that can detect the presence or

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absence of the high-risk form of the virus but cannot specify the subtypes of the high-risk virus. Its advantages are that it is quick and less expensive compared to PCR tests. The PCR test can detect the type of HPV present, but sensitivity varies by the type of PCR system used. It is also generally more expensive and requires the presence of a greater viral load. More detailed comparisons of these techniques have been reported elsewhere. (43-45)

## **Reporting System for Cytology and Histopathology**

The Bethesda System for reporting cervical/vaginal cytology was first developed in 1988 to reduce confusion associated with multiple classification systems in use. (46) The Bethesda System introduced a standardized framework for laboratory reports that included descriptive diagnosis and evaluation of specimen adequacy. The Bethesda consensus terminology has generally been adopted everywhere, although in Europe some still use the former classification with 3 categories (cervical intraepithelial neoplasia [CIN] 1,2,3 or AIN 1,2,3) known as Richart Reagan, or the World Health Organization system, which uses 4 categories (mild atypia, moderate atypia, severe dysplasia or in situ ca).

The system was modified in a second workshop conducted in 1991 convened by the National Cancer Institute and cosponsored by more than 20 national and international associations. (47) The initial classification system included 4 levels for epithelial abnormalities based on cytology: normal, ASCUS, LSIL, and HSIL. The high-grade lesion is the presumed precursor to invasive cancer.

Cytological diagnosis of HSIL occurs infrequently: 0.45% of cytology specimens in the United States in 1996. (48) Those with a diagnosis of HSIL have a 70% to 75% change of biopsy confirmed CIN 2, 3; and a 1% to 2% chance of invasive cervical cancer. (48-50)

The major change for the 2001 consensus resulted in a subdivision of the atypical squamous cells (ASC) into 2 categories: atypical squamous cells of undetermined significance (ASCUS) and atypical squamous cells that cannot exclude HSIL (ASC-H). The change was made for 2 reasons: the unreliability of histological diagnoses even when made by expert pathologists and the observation that the categories were clinically different with different risks of high-grade lesions. (51) Those with cervical cytology rated as ASC had a 5% to 17% risk of having CIN 2,3 confirmed at biopsy, whereas ASC-H had a 24% to 94% risk of having CIN2,3 confirmed at biopsy. It was noted in the report that immunosuppressed women with ASC constitute a special circumstance because of their higher risk for CIN 2,3.

Because of the unreliability of the 3-category grading system for histopathology dysplasia, a 2-tiered classification system was also adapted: CIN1 for low-grade precursors and CIN 2,3 for high-grade precursors.

Although no formal recommendations have been made for the application of the Bethesda terminology to anal cytological findings, the terms are routinely used in laboratories to describe anal cytology. The classification system for anal cytology similarly includes normal, ASCUS, or atypical squamous intraepithelial lesions (ASIL) which are further classified as low (LSIL) or high (HLSL) grade.

## **Treatment of Anal Intraepithelial Lesions**

In general, the risk of complications in the anal region with treatment of intraepithelial neoplasia is higher than in the cervix, and the treatment threshold is much higher in the anal region. Treatment approaches for AIN vary depending on the lesion stage, location, depth, whether it is localized or regional, and whether or not the patient is symptomatic. Choices between these therapies also depend on patient preference, local expertise, and availability. The procedures are associated with variable recurrence rates,

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levels of convenience (single or repeat sessions), complications, postprocedural pain, and costs.

For small, localized lesions, there are a range of treatment options including trichloroacetic acid and various ablative therapies with lasers, infrared coagulation, or cryosurgery. Surgical excision is generally reserved for deeper or more diffusely spread lesions. In some cases the lesions may be too widespread to allow for resection and the only choice is to “watch and wait,” only initiating chemoradiation if the lesion becomes invasive.

There is limited evidence on the treatment effectiveness of any of these approaches. Two reports (52;53) examined treatment of high-grade lesions in women. In one report (52) involving a 20-month mean follow-up of 325 women from 3 groups at increased risk of anal cancer (high-grade CIN, vulvar cancer, renal allograft), 70 were diagnosed with anal lesions. Twenty-seven of the anal lesions were high-grade and 8 were associated with invasive squamous cell carcinoma. The high-grade lesions were treated with surgical excision, and 6 patients with circumferential disease required resurfacing of the anal canal and perineum with skin grafting. Of the 27 treated, 8 (30%) developed further foci within 6 months and underwent further excision.

The second report (53) involved the 63-month median follow-up of 35 patients (26 women) who were diagnosed with high-grade anal lesions. The study group included a diverse group with 10 having prior genital lesions and 6 taking long-term systemic immunosuppressant medication. Of the 28 with well-localized perianal/anal lesions amenable to complete resection, 4 (14%) underwent a second procedure for recurrent/residual disease. All 6 immunosuppressed patients had multifocal anal lesions untreated by protocol, and 3 developed invasive cancers less than 2 cm within 5 years of initial lesion diagnosis.

Two other reports evaluated treatment effectiveness for anal lesions in HIV-positive MSM. One (41) involved surgical resection and the other (54) infrared coagulation. Chang et al. followed-up 37 males (29 HIV-positive) for a mean of 32 months after surgical resection for high-grade high volume anal lesions. Recurrence was estimated by Kaplan Meier survival analysis. None occurred in the HIV-negative patients, but 23 (79%) of the 29 HIV-positive patients had persistent/recurrent lesions with mean time to recurrence of 12 months. Recurrence was 100% in all HIV-positive patients within 5 years.

Similar results were reported in the study involving infrared coagulation therapy for high-grade anal lesions in 68 HIV-positive males. In that retrospective series, 65% (44/68) developed recurrence within a year (median, 217 days). (54)

Management strategies for anal dysplasia also include expectant management or close follow-up without treatment of high-grade lesions. This practice was reported on for a consecutive group of HIV-positive males referred to a colorectal surgical practice and followed-up every 6 months for a mean of 32 months. (55) Of the 98 eligible consecutive patients, however, follow-up longer than 1 year was only available for 40. In this group, 3 developed invasive squamous carcinoma, 2 treated by excision, and 1 requiring chemoradiation. All continue to be followed-up in the program.

A variety of new treatment approaches for anal dysplasia are being investigated, particularly for the immunocompromised patient. The addition of locally acting surface immune modulating agents such as 5-fluorouracil or imiquimod (56;57) or generalized antiviral (cidofovir) agents (58) indicated for external surface applications, are being investigated for use on internal mucosal surfaces in clinical trials. Strategies involving application of multiple agents such as imiquimod and 5-fluorouracil have also been used (59) Clinical trials are also in progress examining the effectiveness of therapeutic vaccines directed to anal precancer lesions. (60-62)

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Survival with anal cancer, as with most cancers, is greatly improved if detected at the early stages. The 5-year survival rate for anal cancer when diagnosed at the local, regional, or distant disease state is 78%, 56%, and 18%, respectively. (63) About 10% of patients with anal squamous carcinoma will have distant disease at diagnosis. (32) The overall 5-year survival is similar for men and women for squamous (62% vs. 67%) and adenocarcinoma (51% vs. 48%).

# **2. Evidence-Based Analysis of Effectiveness**

## **Objectives**

The objectives were to evaluate the role of screening for anal dysplasia and to determine if screening is justified according to World Health Organization screening criteria. (64) There are several established criteria that determine whether a screening program should be implemented. (65) The key criteria are that the natural history and disease progression is known, there are diagnostic methods capable of detecting these early precursor lesions, and there are treatments or interventions with minimal morbidity that would prevent the progression of these earlier stage precursor lesions to invasive cancer.

The analyses focused on several questions. Among them:

- What is the effectiveness of the components of an anal cancer screening program?
- What are the test performance characteristics of the anal Pap screening test for anal dysplasia?
- Who were the targets for the anal Pap screening studies?
- What is the role of oncogenic HPV testing in screening programs for anal dysplasia in patients at high risk for anal cancer?

## **Methods**

### **Search Strategy**

The literature search was conducted in several stages. The first stage involved a search for systematic reviews or health technology assessments on anal dysplasia screening and treatment using the Cochrane Library, ECRI, and The International Agency for Health Technology Assessment HTA database. The Web sites of other health technology agencies were reviewed, including the Canadian Agency for Drugs and Technologies in Health, the National Institute for Clinical Excellence in the United Kingdom, and the Australian Efficacy Register of New Interventional Procedures-Surgical. The International Agency for Research on Cancer was also searched for reports on anal dysplasia screening. In addition, a general Internet search using the Goggle search engine was also conducted.

Searches were also conducted of the Web sites of various professional organizations and guideline databases to determine existing professional practices, recommendations, consensus statements, and policies or guidelines regarding anal dysplasia screening. Included in the search were the following:

- Society of Obstetricians and Gynecologists Canada
- American College of Obstetricians and Gynecologists
- American College of Pathologists
- American Society for Colposcopy and Cervical Pathology
- American Cancer Society

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- Canadian Cancer Society
- Centers for Disease Control and Prevention
- Canadian Task Force on Preventive Health Care
- United States Preventive Services Task Force
- Ontario Guidelines Advisory Committee
- National Institutes Consensus Panel
- Australian National Health and Medical Research Council Guidelines
- National Guideline Clearinghouse.

The second stage of the review was conducting several literature searches to address the question of whether or not a screening program for anal dysplasia should be implemented. The first involved a search to review the evidence for screening and diagnosis of anal dysplasia. The second focused on treatment options and outcomes for anal dysplasia, the presumed precursor lesions to invasive anal cancer.

Finally, a search was done for reports on costs and cost-effectiveness using a parallel search strategy.

### **Databases Searched**

The search strategies with keywords and subject headings for anal dysplasia screening and treatment are outlined in Appendices 1 and 2. Databases searched were MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, The Cochrane Library and the International Agency for Health Technology Assessment/Center for Reviews and Dissemination for literature published between January 2003 and January 5, 2007. An updated search was conducted on May 11, 2007 to capture the literature published since January 5, 2007. Select conference proceedings indexes were also searched: Conference Papers Index, Proceedings First, and Institute for Scientific Information Proceedings.

In addition to the above databases, the Health Economic Evaluation Database was searched for additional economic information.

### **Inclusion and Exclusion Criteria**

Nonsystematic reviews, letters, comments, and editorials were excluded. Case reports or case series involving fewer than 20 subjects were excluded. The search was also restricted to English-language reports and human studies.

The citations from different databases were merged into one database using Reference Manager 10 software, and duplicates were subsequently removed. In total, 401 citations involving screening and diagnosis, and 172 citations involving AIN treatment were identified. The updated search identified an additional 43 citations in screening and 20 citations on intraepithelial treatment. The citation lists were reviewed, and articles were excluded based on title and abstract. Excluded articles included those discovered to be nonsystematic review articles, those describing invasive cancer treatment, and articles describing diagnosis of known malignancies (e.g., at follow-up). The full text of eligible articles was obtained, and reference lists were hand-searched.

Journal articles eligible for inclusion in the review included those reporting primary data on the operating characteristics of test performance (Pap and/or HPV DNA testing) to detect anal cancer and its precursor lesions. The review also included studies that determined the reliability of the detection methods for anal cancer and precursor lesions. Adequate study methods of the reports were based on several criteria, including simultaneous cytology and histological or pathological studies, independent readings of test and standard assessments, and reasonable confirmation by biopsy (at least one-half of cytology confirmed by

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biopsy). Outcome measures of test performance, sensitivity, and specificity, were based on a reasonable study size.

### **Additional Information Sources**

Additional information on costing and estimates of disease prevalence were obtained from several local sources and informants. Cost data were obtained from Ministry of Health and Long Term Care sources such as the physician services schedule of benefits. Cancer statistics were obtained from Cancer Care Ontario. Incidence rates of anal carcinoma were identified through the cancer registry using ICD-9 codes (154.2, 154.3, 154.8) for anatomic sites and ICD-0 codes (8070-8075, 8120, 8123, 8124) for histology. Human immunodeficiency virus prevalence estimates in the province were obtained from reports by the HIV Social, Behavioral and Epidemiological Studies Unit in the Faculty of Medicine at University of Toronto.

### **Quality of Evidence**

An overall assessment of the quality of evidence was based on the grading of recommendations assessment, development and evaluation (GRADE) system. (66) The recommendations of the GRADE working group can also be viewed at the Grade Working Group Web site. (67)

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Accordingly, the quality of the evidence was assessed as high, moderate, low, or very low. The potential level of impact of further evidence on decision-making was also rated according to GRADE definitions:

- High: Further research is very unlikely to change our confidence in the estimate of effect
- Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
- Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- Very low: Any estimate of effect is very uncertain

## Results of Evidence-Based Analysis

One structured health technology review (68) of an anal dysplasia screening program was identified. The review, performed for the United Kingdom National Screening Committee in 2003, assessed the viability, effectiveness, and appropriateness of an anal cancer screening program in the United Kingdom. Although the evidence on test performance characteristics of anal dysplasia were not presented, the reviewers concluded that there was reasonable evidence of possible benefit from LBC as an anal screening test in certain high-risk populations. They also stated that focused studies were needed in several areas involving substantial uncertainty: natural history, patient acceptability, and cost-effectiveness of a program in a United Kingdom setting.

Since then, another health technology assessment project involving anal dysplasia screening in the United Kingdom was established with a completion and publication date projected for the end of 2007.

### Medical Advisory Secretariat Literature Findings

No direct evidence involving controlled randomized studies were found evaluating the impact of anal Pap test screening programs for anal dysplasia on morbidity or mortality from anal cancer.

No studies were found on the use of HPV DNA testing in the screening or diagnostic setting for anal dysplasia.

### Studies Evaluating Anal Pap Test Performance

Nine reports (69-77) were identified that evaluated test performance characteristics of anal Pap test screening for anal dysplasia (Table 1).

**Table 1: Studies Evaluating Pap Testing For Anal Dysplasia**

Author	Publication Year	Country, City	Setting
Cranston et al. (69)	2004	United States, San Francisco	University Health Clinic
De Ruiter et al. (74)	1994	United Kingdom, London	Hospital Genitourinary Dpt-STD Clinic
Fox et al. (75)	2006	United Kingdom, London	Hospital Based Anoscopy Clinic
Friedlander et al. (70)	2004	United States, New York	Cytology Service
Lampinen et al. (76)	2006	Canada, Vancouver	University Clinic

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Mathews et al. (71)	2004	United States, San Diego	University HIV Clinic
Palefsky et al. (72)	1997	United States, San Francisco	University HIV Clinic
Panther et al. (73)	2004	United States, Boston	Hospital ID Dysplasia Clinic
Salit, et a l. (77)	2006	Canada, Toronto	University Hospital Based HIV Clinic

## Generalizability of Studies

The reports involved studies in the United States, (69-73) United Kingdom, (74;75) and Canada. (76;77) All involved hospital-based specialty HIV/AIDS care clinics. All involved either male HIV patient populations or a general population of MSM. Only one study (69;72) included a subgroup of HIV-negative MSM (Table 2). Patients were generally symptomatic or being followed-up or in surveillance for various conditions. (72)

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**Table 2: Pap Testing for Anal Dysplasia: Study Evaluation Details\***

Study Author	Subjects	Prevalence Normal (Cytology) %	Pathology Guidance	Tests Performed PAP Test/HPV Test	Cytology Pathology Pairs
Cranston et al. (69)	102 MSM (82 HIV +) Avg age 45 (29-72 yrs)	32	HRA	LBC*/ NO	102
De Ruiter et al. (74)	215 MSM (169 HIV+) Age NS**	20	Colposcope	CONV**/Morphology	154
Fox et al. (75)	99 MSM (89 HIV+) Age NS	21	Colposcope	CON / PCR	141
Friedlander et al. (70)	51 (33 HIV+, 27M + 6F) Avg age = 43 yrs (26-74yrs)	13	HRA	LBC / NO	39
Lampinen et al. (76)	222 MSM (28 HIV-) Age range 18-30 yrs	30	NS	LBC / NO	64
Matthews et al. (71)	1864 HIV+ (1707 M) Median age = 39 yrs	20	HRA	CONV / NO	154
Palefsky et al. (72)	658 MSM (407 HIV+) HIV+ Avg age 41 (26-66 yrs)	51	Colposcope	CON / YES	406
	HIV- Avg age 44 (2-73 yrs)	90	HRA		251
Panther et al. (73)	153 MSM (100 HIV+) Age NS	12	HRA	CONV / NO	153
Salit et al. (77)	357 HIV + MSM Median age = 45 yrs	39	HRA	LBC / HC11	357

\*CONV refers to conventional Papanicolaou's test; HC11, hybrid capture 11; HIV, human immunodeficiency virus; HRA, high-resolution anoscopy; LBC, liquid-based cytology; MSM, men who have sex with men; NS, not stated.

The screening reports involved the use of both monolayer LBC and conventional smear-based cytology. Abnormal findings were followed-up with visual inspection by high-resolution anoscopic or colposcopic examinations in about one-half of the studies. All studies involved experienced pathologists so the results generally represent best-case scenarios. Although only 2 studies (72;77) simultaneously performed Pap and HPV DNA testing, the information was not presented in combination with cytology findings. The majority (7/9) of the studies involved less than 200 cytology pathology pairs for evaluation of Pap test performance.

The prevalence of normal cytology findings varied greatly ranging from 12% to 90%, depending on the proportion of HIV-positive patients in the study groups. In the only study (72) to include large groups of HIV-positive (n = 407) and HIV-negative (n = 251) patients, the prevalence of normal cytology was 90% in the HIV-negative group and 51% in the HIV-positive group. The high prevalence of abnormal cytology in these studies is representative of high-risk populations in a diagnostic rather than a screening setting.

Estimates of test performance, sensitivity, and specificity were evaluated in the studies using different degrees for cytological abnormalities, either at least ASCUS or at least ASIL, and were also compared to different thresholds for histopathologically defined diagnosis, either any grade (AIN 1, 2,3) or only high-grade abnormality (AIN 2,3) (Table 3). Likelihood ratios were not calculated in any of the studies.

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**Table 3: Anal Pap Test Validation Over Varying Degrees of Cytological Abnormality and Histopathology Test Thresholds\***

	Study Author	Histopathology Any Grade (AIN 1,2 or 3)	Histopathology High Grade only (AIN 2,3)
<b>Degree Cytology Abnormality</b>			
<b>≥ ASCUS</b>			
	Cranston et al. (69)	SN = 70% (95% CI, 60-79) SP = 36% (95% CI, 28-99)	SN = 73% (95% CI, 62-84) SP = 47% (95% CI, 29-65)
	Friedlander et al. (70)	SN = 91% (95% CI, 77-98) SP = 50% (95% CI, 7-93)	- -
	Lampinen et al. (76)	SN = 63% (95% CI, 44-80) SP = 41% (95% CI, 25-59)	SN = 75% (95% CI, 43-95) SP = 42% (95% CI, 29-57)
	Palefsky et al. (72)	SN = 69% (95% CI, 60-78) SP = 59% (95% CI, 53-65)	- -
	Palefsky et al. (72) HIV-	SN = 47% (95% CI, 26-68) SP = 92% (95% CI, 89-95)	- -
	Panther et al. (73)	SN = 93% (95% CI, 87-97) SP = 33% (95% CI, 18-52)	SN = 98% (95% CI, 91-99) SP = 20% (95% CI, 12-30)
	Salit et al. (77)	-	SN = 72% (95% CI, 60-81) SP = 44% (95% CI, 38-50)
<b>≥ ASIL</b>			
	Matthews et al. (71)	SN = 84% (95% CI, 77-90) SP = 53% (95% CI, 29-76)	SN = 92% (95% CI, 84-97) SP = 36% (95% CI, 24-48)
	Palefsky et al. (72)	SN = 46% (95% CI, 3-56) SP = 81% (95% CI, 76-85)	-
	Palefsky et al. (72)	SN = 26% (95% CI, 5-47) SP = 98% (95% CI, 96-100)	- -
<b>&gt; AIN</b>			
	Fox et al. (75)	SN = 82% (95% CI, 74-89) SP = 38% (95% CI, 20-59)	- -
<b>≥ AIN or HPV morphology</b>			
	De Ruiter et al. (74)	SN = 88% (95% CI, 76-95) SP = 16% (95% CI, 9-25)	- -
<b>≥ AIN</b>			
	De Ruiter et al. (74)	SN = 34% (95% CI, 22-48) SP = 72% (95% CI, 63-81)	- -

\*AIN refers to anal intraepithelial neoplasia; ASCUS, atypical squamous cells of undetermined significance; ASIL, atypical squamous intraepithelial lesion; SN, sensitivity; SP, specificity.

The effects of prevalence of cytological abnormalities on estimates of test performance are detailed in Table 4. Sensitivity estimates based on any cytological abnormality (≥ ASCUS) ranged from 69% (cytologically normal prevalence of 51%) to 93% (cytologically normal prevalence of 12%). Sensitivity estimates based on low- or high-grade lesions (≥ ASIL) ranged from 46% (cytologically normal prevalence of 51%) to 84% (cytologically normal prevalence of 20%).

Overall, in the studies involving HIV-positive MSM, specificity ranged from 33% to 50% and was always lower than sensitivity. In the one study group involving HIV-negative MSM, specificity was 92% (95% CI, 53%–65%), and was higher than the reported sensitivity (47%; 95% CI, 26%–68%).

**Table 4: Effect of Prevalence on Estimates of Pap Test Diagnostic Performance for Anal Dysplasia**

	Study Author	Prevalence Normal (Cytology)	Histopathology (AIN 1,2 or 3)	
			Sensitivity (95% CI)	Specificity (95% CI)
<b>Degree Cytology Abnormality</b>				
<b>&gt; ASCUS</b>				
	Panther et al. (73)	12%	93% (87%-97%)	33% (18%-52%)
	Friedlander et al. (70)	13%	91% (77%-98%)	50% ( 7%-93%)
	(Cranston et al. (69)	32%	70% (60%-79%)	36% (28%-99%)
	Salit et al. (77)	39%	-	-
	Palefsky et al. (72)	51%	69% (60%-78%)	59% (53%-65%)
	Palefsky et al. (72)	90%	47% (26%-68%)	92% (89%-95%)
<b>≥ ASIL</b>				
	Matthews et al. (71)	20%	84% (77%-90%)	53%(63%-81%)
	Fox et al. (75)	21%	82% (74%-97%)	38% (20%-59%)
	(Palefsky et al. (72)	51%	46% (36%-56%)	81% (76%-85%)
	Palefsky et al. (72)	90%	26% ( 5%-47%)	98% (96%-99%)

\* AIN refers to anal intraepithelial neoplasia; ASCUS, atypical squamous cells of uncertain significance; ASIL, atypical squamous intraepithelial lesion; CI, confidence interval.

## Comparison of Anal Pap Testing to Cervical Pap Testing

Several systematic reviews (78-80) have been performed between 1966 and 2000 for cervical Pap tests. In the review by Fahey et al. (78) 59 studies were reported with a Pap test mean sensitivity of 58% and a mean specificity of 69%. These reviews also generally reported that few studies evaluated Pap testing in the low disease prevalence setting. In the Nanda et al. (80) review, the prevalence of disease ranged from 0.02 to 0.94%. Many of the studies were conducted in high-risk samples, such as those with prior cervical Pap test abnormalities, visible cervical lesions, or immunocompromised systems.

Nanda et al. reported that most studies were biased in the estimation of test performance. In the 12 studies with the least bias, sensitivity ranged from 30% to 87%; specificity ranged from 86% to 100%. For the 9 studies that provided data at the LSIL/CIN1 threshold, sensitivity ranged from 30% to 87% (mean, 47%); specificity ranged from 86% to 100% (mean, 95%).

In general, the best estimates suggest only modest levels of sensitivity for the Pap test to detect cervical cancer, and concurrent high sensitivity and specificity were not achieved. Despite this low performance, the Pap test is the only test to reduce cervical cancer incidence and mortality. These reductions are mainly based on the serial testing approach of the Pap smear, which is possible because of the slow progression of the disease.

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### Test Reliability

Three studies (81-83) evaluated the reliability of anal cytology and pathology. Of these, one (81) evaluated the reliability of both anal cytology and biopsy pathology, and 2 (82;83) evaluated only the reliability of biopsy pathology.

Lytwyn et al. (81) evaluated inter-rater reliability of 4 raters using 3 different binary disease cut-points for 100 samples of liquid-based anal cytology. The median kappa values for the 3 disease cut-points were 0.90 (normal vs.  $\geq$  ASCUS), 0.79 (<ASCUS vs.  $\geq$  LSIL) and 0.62 ( $\leq$  LSIL vs.  $\geq$  HSIL).

Estimates of reproducibility of cervical cytology and pathology were conducted in a study alongside a major multicentre clinical trial. (84) The study used 4,948 liquid-based cervical cytology samples comparing decisions by 7 pathologists to a quality control reference panel of pathologists. The kappa for 3 disease cut-points were 0.56 (normal vs.  $\geq$  ASCUS), 0.64 (<ASCUS vs.  $\geq$  LSIL) and 0.51 ( $\leq$  LSIL vs.  $\geq$  HSIL).

## 3. Economic Analysis

### Disclaimer

The Medical Advisory Secretariat uses a standardized costing methodology for all of its economic analyses of technologies. The main cost categories and the associated methods from the province's perspective are as follows:

**Hospital:** Ontario Case Costing Initiative (OCCI) cost data is used for all program costs when there are 10 or more hospital separations, or one-third or more of hospital separations in the ministry's data warehouse are for the designated International Classification of Diseases-10 diagnosis codes and Canadian Classification of Health Interventions procedure codes. Where appropriate, costs are adjusted for hospital-specific or peer-specific effects. In cases where the technology under review falls outside the hospitals that report to the OCCI, PAC-10 weights converted into monetary units are used. Adjustments may need to be made to ensure the relevant case mix group is reflective of the diagnosis and procedures under consideration. Due to the difficulties of estimating indirect costs in hospitals associated with a particular diagnosis or procedure, the Medical Advisory Secretariat normally defaults to considering direct treatment costs only. Historical costs have been adjusted upward by 3% per annum, representing a 5% inflation rate assumption less a 2% implicit expectation of efficiency gains by hospitals.

**Non-Hospital:** These include physician services costs obtained from the Provider Services Branch of the Ontario Ministry of Health and Long-Term Care, device costs from the perspective of local health care institutions, and drug costs from the Ontario Drug Benefit formulary list price.

**Discounting:** For all cost-effective analyses, discount rates of 5% and 3% are used as per the Canadian Coordinating Office for Health Technology Assessment and the Washington Panel of Cost-Effectiveness, respectively.

**Downstream cost savings:** All cost avoidance and cost savings are based on assumptions of utilization, care patterns, funding, and other factors. These may or may not be realized by the system or individual institutions.

In cases where a deviation from this standard is used, an explanation has been given as to the reasons, the

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assumptions and the revised approach.

The economic analysis represents an estimate only, based on assumptions and costing methods that have been explicitly stated above. These estimates will change if different assumptions and costing methods are applied for the purpose of developing implementation plans for the technology.

## **Economic Literature Review: Summary**

Two reports were identified evaluating the cost-effectiveness of Pap test screening for anal cancer. One (85) involved HIV-positive males; the other, (86) HIV-negative males.

Both analyses involved state transition Markov modeling approaches to hypothetical cohorts. The HIV-positive cohort involved those at different stages of HIV disease based on CD4 T lymphocyte levels. The other report involved a hypothetical cohort of 30-year-old homosexual HIV-negative men. A societal perspective was adopted in each study and all costs were reported in American dollars. Outcomes included estimated lifetime costs, life expectancies, quality-adjusted life years (QALY), cost-effectiveness (CE) ratios and incremental cost-effectiveness ratios (ICERs) for various anal Pap test screening strategies ranging from none to 6-month intervals and 1-, 2- and 3-year intervals for the HIV-positive cohort, and up to 6-year intervals for the HIV-negative cohort.

In the HIV-positive cohort study, the CE ratios were most sensitive to rates of disease progression from high-grade lesion to invasive cancer and lesion treatment. As the actual disease progression is not known and ethically cannot be followed to evaluate, estimates were made by fitting prevalence estimates of high-grade lesions to epidemiological estimates of anal cancer rates. However, even with extremely low progression rates, CE ratios as low as 1/1000 were still acceptable (screening every 3 years, the CE ratio was less than \$30,000 QALY). Treatment effectiveness of anal lesions was assumed to be 75% in the base case, but even if effectiveness was only 25%, CE ratios for screening every 2 or 3 years remained acceptable (less than \$40,000 per QALY).

In the HIV-negative cohort of men, the CE ratios were similarly influenced by the progression and treatment of anal high-grade intraepithelial lesions. However, CE ratios remained below \$50,000 for a range of screening intervals: every 1-year (\$34,800), every 2 years (\$15,100), and every 3 years (\$7,000). In general, the CE ratios in the HIV-negative cohort favored less frequent screening intervals than those in the HIV-positive cohort.

The analyses for both of these reports were largely based on data from cohort studies in San Francisco and Seattle, and their generalizability is limited. The authors also recommended that there should be an evaluation and consideration of barriers associated with the implementation of screening programs.

## **Ontario-Based Budget Impact**

To date, no published study has reflected Ontario's population or practices. There are no physician fee codes for anal Pap tests, but the cost (all reported in Canadian dollars) of a Pap test in Ontario, including laboratory and physician fees, is \$6.75 for a conventional Pap smear and an additional \$33.15 for a visit

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fee. There are also no physician fee codes for high-resolution anoscopy. The fee for colposcopy, an analogous procedure, is \$50.90, and a colposcopic-directed biopsy is \$77.35. Work-up and treatment costs for high-grade anal dysplasia in Canadian centres have not been published. In general, fees for lesion treatments vary based on the size of the lesion, from \$82.35, to \$142.40 to \$219.00. Treatment costs for anal cancer based on Ontario Case Costing estimates is about \$6,503 per case.

If an anal Pap test screening program were applied to an approximate population of 95,000 MSM subjects in Ontario, 32% (n = 30,400) could be expected to have Pap test cytological abnormalities. (35) Of these, 15% (n = 14,250), 12% (n = 11,400), and 5% (n = 4,750) would be low-grade, atypical, or indeterminate and high-grade lesions respectively. Those with low-grade lesions would be followed-up with another anal Pap test. The 16,150 subjects with indeterminate or high-grade lesions would be referred for anoscopic examination. Of the 16,150 cases scoped, about 22% (n = 3,553) will have a biopsy-proven high-grade lesion and undergo treatment or intensive surveillance. (77)

The results of the hypothetical screening program can be considered against the background of the approximately 353 cases (152 males and 201 females) diagnosed in Ontario (2001) with cancers of the anus, anorectum, and anal canal (n = 68). (Cancer Care Ontario). It is also estimated that 84 of these people will die from the disease.

# **4. Ontario Health System Impact Analysis**

## **Current Management and Care Issues**

**Labs, Pathologist and Samplers:** Freestanding facilities can bill under the Ontario Health Insurance Plan for Pap smears, but the facility has to be able to pay for any required nursing backup. Pathologists can accept Pap tests from both inpatient and outpatient sources. For a screening Pap test, there is a weighted fee for Pap smears: a technical fee for the cytotechnologist and a professional fee for the pathologist who generally reviews only flagged cases and abnormalities. This is in comparison to screening mammographies, where radiologists read every mammogram. The majority (85%) of pathologists are on salary paid through the hospital global budget (Personal communication, February 26, 2007). Liquid-based cervical cytology has been introduced into some Ontario hospitals but it is not yet routine practice.

Cervical Pap tests are performed by various physicians, including family physicians, gynecologists, and gynecology oncologists. Gynecology oncologists, however, are not on fee-for-service for Pap testing. Anal Pap tests are currently only performed in research settings at specialized multidisciplinary HIV/AIDS clinics.

## **Technology Comments**

The high-resolution anoscope is a device similar to the colposcope. Both involve the insertion of a scope and use of a microscope to augment direct visualization. A high-resolution anoscope costs about \$25,000 (Cdn), plus \$300 (Cdn) for annual maintenance. Few supplies are involved, generally disposable tubes costing about \$1 (Cdn) each. A Pap test takes about 30 seconds to perform. An anoscopic examination is longer; it takes about 30 to 45 minutes. Purchasing a high-resolution anoscope would be a hospital decision based on the global budget, and some centres have acquired them through participation in

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research trials.

## **Screening Capacity**

At present, the physicians who are performing anosopic examinations could not keep up with the surveillance load if Pap testing and follow-up recommendations are made. Currently, only 2 physicians are routinely performing anosopic examinations (about 400–500 per year) in the Greater Toronto Area, and few, if any, are performing them in other regions of the province (Personal communication, January 23, 2007). Three settings have been considered for screening high-risk patients: multidisciplinary tertiary care hospital-based clinics, community-based HIV/AIDS centres or STD clinics, and gynecology offices. Issues were identified in all settings.

The feasibility of offering anosopic examinations and biopsy as well as Pap tests in the community setting is uncertain largely due to the limited availability of clinical experts. Using nurse practitioners to perform anal Pap testing to increase capacity is a consideration; and similar options are being investigated for colorectal screening, specifically the use of nurses to perform flexible sigmoidoscopy. Nurse practitioners in the United States perform high-resolution anoscopy and can treat anal lesions (Personal communication, May 31, 2007).

Any screening program would require efforts to increase training in Pap testing for physicians and education for members of the high-risk populations. Although gynecologists are likely the group best suited to perform screening and scoping procedures in high-risk women, an effort would be needed to orient gynecologists to the high-risk groups and the techniques for screening and surveillance in the anus. Although the procedures are similar to cervical Pap testing, it would not be a straightforward transfer of knowledge.

## **HIV/AIDS in Canada and Ontario**

In 2005, about 94,900 MSM were living in Ontario, 53,200 in the Toronto area (Personal communication, June 7, 2007). There are about 24,891 HIV-infected people living in the province, 6,223 (25%) of them female. (87) Of these, about 1,670 were newly diagnosed. An estimated 36% were living with, but unaware of, their HIV infection. (88)

## **HIV/AIDS Treatment Centres in Ontario**

The Ministry of Health and Long-Term Care AIDS Bureau supports over 20 established HIV/AIDS outpatient clinics in the province. Major clinics are located in Ottawa, Kingston, Hamilton, Windsor, Sudbury, and Toronto. Several large clinics are located in Toronto at The Toronto General Hospital, St. Michael's Hospital and Sunnybrook Health Sciences Centre. Clinics are resourced depending on their patient volumes.

The Toronto General Hospital immunodeficiency clinic is a multidisciplinary site that manages about 1,200 patients annually. Over 400 patients are in clinical trials, and the results of the Toronto trial (TRACE) have been published in abstract form. (77) The TRACE trial is unique in that patients underwent Pap testing, anoscopy, and HPV testing at every clinical encounter. Once published, the study will be one of the largest to date on Pap test screening for anal dysplasia in HIV-positive males.

Treatment options for localized high-grade lesions vary but at Toronto General options include

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trichloroacetic acid or laser coagulation. Patients are reported to prefer the laser coagulation (a one-time, albeit painful, treatment) versus trichloroacetic acid (which comprises staged treatments but is less painful). There are several reasons to treat lesions: to prevent progression, relieve symptoms, and prevent further transmission. The treatment morbidity considerations in the anus are mainly infection, bleeding, and pain. Clinical experience is that complications are infrequent, and, although patient tolerance levels are variable and unpredictable, most are reported to tolerate the procedure and require only minimal pain management (e.g., a short course of oral painkillers or anti-inflammatory medication). Biopsy and treatments are all performed in the office-based outpatient setting without general anesthesia.

The St. Michael's Hospital program consists of a hospital-based positive care clinic and a community-based family practice clinic, which together manage a high number of HIV patients. The St. Michael's hospital clinic manages over 1,000 patients annually. Although most are male patients, over time the rate of female patients has increased (from 10% to 30%). In addition, more patients who are immigrants are being seen. The hospital multidisciplinary team consists of physicians (3 specialists in infectious diseases and 1 in genitourinary medicine), social workers, occupational therapists, pharmacists, dieticians, physiotherapists, and nurses. The social workers at the clinic deal mainly with basic needs such as housing, food, and drug access. Patients are generally referred to the community for supportive needs. Patients presenting with anal warts or who are symptomatic for potential anal lesions are referred to surgeons for further investigations and treatment.

## **Primary Care Management Protocols HIV/AIDS Patients**

Primary care protocols for HIV/AIDS patients in Canada usually follow those established by the United States Centers for Disease Control, Department Health Human Services (Personal Communication, February 15, 2007). In general, patients have a baseline assessment; one month later, they return to review baseline results. After starting treatments, if things are stable, patients are followed-up every 4 months or every 3 months if changes such as CD4 lymphocyte cell counts show a trend toward falling.

Patients are followed-up to monitor for a variety of opportunistic infections and diseases. The tracked sexually transmitted diseases include gonorrhea, syphilis, chlamydia, viral Hepatitis B and C, and herpes. Syphilis infection rates at baseline can be as high as 30% to 40%. Tests are routinely performed for HIV viral loads, HIV resistance, and CD4 lymphocyte count.

Routine anal pap testing is not performed at most HIV/AIDS centres. Generally, if patients are symptomatic, for example, they have anal warts or bleeding, they are referred to a general (rectal) surgeon for investigation, biopsy, and lesion resection, followed by chemoradiation therapy if the lesions are discovered to be malignant. Female HIV patients present more complex management considerations and are often referred to gynecologists with infectious disease expertise.

## **Relevant Guidelines**

Although no formal programs for anal cancer screening have been implemented in Canada or elsewhere, guidelines on anal dysplasia screening have recently been developed by agencies in the United States, by the United States Public Health Service, Centers for Disease Control and Prevention, and the New York State Department of Health AIDS Institute.

In 2004, the United States Public Health Service mentioned anal screening in their guidelines for the prevention of HIV-associated opportunistic infections of HIV-infected MSM. (89) The guideline states

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"...anal cytological screening of HIV-infected men who have sex with men has not yet become standard of care but is now being done for high-risk persons in some health care centres and may become a useful preventive measure in the near future." They also stated that "...additional studies of screening and treatment programs for anal high-grade SILs need to be carried out."

In March 2007, the New York State Department of Health AIDS Institute (90) updated its primary care approach to the HIV-infected patient and released guidelines, which recommended routine anal Pap testing (at baseline and annually) in several high-risk groups. These were MSM, patients with a history of anogenital condylomas, and women with abnormal cervical/vulvar histology. It was further recommended that patients with abnormal anal Pap test findings be referred for high-resolution anoscopy and/or examination with biopsy.

## **5. Conclusion**

No direct evidence exists to support the effectiveness of an anal Pap test screening program to reduce anal cancer mortality or morbidity. However, there are strong parallels with Pap testing for cervical cancer, where the implementation of this screening approach has led to a significant reduction in the incidence of cervical cancer. Anal cancer rates in high-risk populations are approaching those of cervical cancer before the implementation of cervical Pap testing. Diverse high-risk groups have been identified, including HIV-positive and HIV-negative MSM, HIV-positive women, women with prior anogenital disease, and patients who have received transplants and others with suppressed immune systems.

Sexually transmitted HPV viral infection is the acknowledged common causative agent for both anal and cervical cancer. The prevalence of HPV infection and intraepithelial lesions in the MSM population differs, however, from cervical rates in that rates of HPV infection and low-grade and high-grade lesions are independent of age and consistently high across a wide age range. The rates of disease progression for cervical and anal high-grade lesions are not known, because high-grade lesions are generally treated, as they are the presumed precancer state for both cancers, and studies to follow their progression would be unethical.

The anal Pap test would seem to be a suitable screening test for cervical dysplasia. It has similar operating characteristics of sensitivity and specificity as the cervical Pap test. The variability (depending on the prevalence of disease in the studied population and the set diagnostic thresholds) and low sensitivity that have been reported for the anal Pap test have similarly been reported for the cervical Pap test in several systematic reviews. The specificity of the anal Pap test is generally reported to be lower than that for the cervical Pap, particularly for the HIV patients. Low specificity would yield a higher rate of false positives, resulting in over referrals for anoscopic follow-up. Estimates of test reproducibility are moderate and similar for both cervical and anal cytology reporting. Testing in both regions is dependent on the inherent limitations of subjective assessment of morphology-based technology for both cytological and histopathological reporting. Despite identifying a diverse group of patients at risk for anal cancer, the Pap test has mainly been evaluated only in HIV-positive males.

In general, the treatment options for precancer dysplasia in the anus and the cervix are similar, but treatment options involving a definitive surgical resection in the anus are more limited because of the higher risk of complications. A range of ablative therapies has been applied in this region with variable tolerance, success, and rates of recurrence, particularly in HIV-positive patient. There are, however, limited data available on the treatment effectiveness or durability of the various therapeutic approaches.

## **Anal Dysplasia Screening**

# Appendices

## Appendix 1- Search Strategy – Anal Cancer Screening

Search date: December 15, 2006

Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, OVID Cochrane Library, INAHTA/CRD

Database: Ovid MEDLINE(R) <1996 to November Week 3 2006>

Search Strategy:

- 
- 1 exp Anus Neoplasms/ (1077)
  - 2 ((anal or anus or anorectal or perianal) adj2 (cancer\$ or precancer\$ or melanoma\$ or neoplas\$ or dysplas\$ or carcinoma\$)).mp. (1263)
  - 3 1 or 2 (1263)
  - 4 exp Anus Diseases/ or exp Anal Canal/ (5375)
  - 5 exp Papillomavirus Infections/ (8171)
  - 6 (Papilloma\$ or HPV).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (14455)
  - 7 exp Carcinoma, Squamous Cell/ or exp Carcinoma, Basal Cell/ (31065)
  - 8 exp Precancerous Conditions/ (9373)
  - 9 (low grade squamous intraepithelial lesion\$ or high grade squamous intraepithelial lesion\$ or atypical squamous cell\$ of undetermined significance or squamous dysplasia).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1174)
  - 10 or/5-9 (51130)
  - 11 4 and 10 (618)
  - 12 3 or 11 (1366)
  - 13 exp mass screening/ (44477)
  - 14 ((anal or anus or anorectal or perianal) adj1 (Papanicolaou or Pap or smear or swab or cytology)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (88)
  - 15 screen\$.mp. (163734)
  - 16 exp Diagnosis/ (1575910)
  - 17 diagnos\$.mp. (554616)
  - 18 sensitivity.mp. or exp "Sensitivity and Specificity"/ (308156)
  - 19 specificity.mp. (277550)
  - 20 (accurac\$ or false positive\$ or false negative\$ or false rate\$ or likelihood or probabilit\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (155567)
  - 21 exp "Reproducibility of Results"/ (104153)
  - 22 exp Likelihood Functions/ (7221)
  - 23 exp "Predictive Value of Tests"/ or predictive value.mp. (63277)
  - 24 exp Area Under Curve/ (11561)
  - 25 receiver operat\$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (8283)
  - 26 or/13-25 (2180900)
  - 27 12 and 26 (853)
  - 28 limit 27 to (humans and english language and yr="2003 - 2006") (302)
  - 29 ((systematic\$ adj1 review\$) or metaanalysis or meta-analysis).mp. [mp=title, original title, abstract,

## Anal Dysplasia Screening

name of substance word, subject heading word] (26421)

30 28 and 29 (3)

31 28 (302)

32 limit 31 to (case reports or comment or editorial or letter or "review") (141)

33 31 not 32 (161)

34 30 or 33 (164)

Database: EMBASE <1980 to 2007 Week 01>

Search Strategy:

- 
- 1 exp Anus Tumor/ (2059)
  - 2 ((anal or anus or anorectal or perianal) adj2 (cancer\$ or precancer\$ or melanoma\$ or neoplas\$ or dysplas\$ or carcinoma\$)).mp. (2386)
  - 3 exp Anus Disease/ or exp Anus/ (12826)
  - 4 exp Papilloma virus/ (17138)
  - 5 (Papilloma\$ or HPV).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (24650)
  - 6 exp Squamous Cell Carcinoma/ or exp Basal Cell Carcinoma/ (38392)
  - 7 exp Precancer/ (5406)
  - 8 (low grade squamous intraepithelial lesion\$ or high grade squamous intraepithelial lesion\$ or atypical squamous cell\$ of undetermined significance or squamous dysplasia).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1370)
  - 9 or/4-6 (62654)
  - 10 3 and 9 (1041)
  - 11 1 or 2 or 10 (2697)
  - 12 ((anal or anus or perianal or anorectal) adj1 (Papanicolaou or Pap or smear or swab or cytology)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (114)
  - 13 exp SCREENING/ (158152)
  - 14 screen\$.mp. (282860)
  - 15 exp diagnosis/ (1755225)
  - 16 diagnos\$.mp. (1361543)
  - 17 exp "SENSITIVITY AND SPECIFICITY"/ (31637)
  - 18 (sensitivity or specificity).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (499506)
  - 19 (accurac\$ or false positive\$ or false negative\$ or false rate\$ or likelihood or probabilit\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (314828)
  - 20 exp DIAGNOSTIC ACCURACY/ (101911)
  - 21 exp reproducibility/ (28837)
  - 22 exp Probability/ or exp Maximum Likelihood Method/ (21101)
  - 23 exp Diagnostic Value/ or exp Prediction/ or predictive value.mp. (196335)
  - 24 exp Area Under the Curve/ or exp Receiver Operating Characteristic/ or exp ROC CURVE/ (30280)
  - 25 or/12-24 (2823866)
  - 26 11 and 25 (1441)
  - 27 limit 26 to (human and english language and yr="2003 - 2006") (427)
  - 28 ((systematic\$ adj1 review\$) or metaanalysis or meta-analysis).mp. (44607)
  - 29 27 and 28 (7)
  - 30 27 (427)

## **Anal Dysplasia Screening**

- 31 limit 30 to (editorial or letter or note or "review") (159)
- 32 Case Report/ (918631)
- 33 30 not (31 or 32) (199)
- 34 29 or 33 (204)

**Appendix 2: Precancer Treatment Search Strategy**

Search date: January 15, 2007

Databases searched: OVID MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Cochrane Library, INAHTA/CRD

Database: Ovid MEDLINE(R) <1950 to January Week 1 2007>

Search Strategy:

- 
- 1 exp Anal Canal/ (9835)
  - 2 exp Anus Diseases/ (7042)
  - 3 exp Precancerous Conditions/ (28071)
  - 4 3 and (1 or 2) (131)
  - 5 low grade squamous intraepithelial lesion\$.mp. (592)
  - 6 high grade squamous intraepithelial lesion\$.mp. (711)
  - 7 atypical squamous cells of undetermined significance.mp. (482)
  - 8 ((squamous or intraepithelial) adj1 (lesion\$ or neoplasia\$ or dysplasia\$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (8976)
  - 9 (anal or anus or perianal or anorectal).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (28997)
  - 10 1 or 2 or 9 (29446)
  - 11 or/5-8 (9035)
  - 12 10 and 11 (261)
  - 13 4 or 12 (352)
  - 14 limit 13 to (humans and english language) (299)
  - 15 limit 14 to yr="1993 - 2007" (226)
  - 16 limit 15 to (case reports or comment or editorial or letter) (32)
  - 17 15 not 16 (194)

## Anal Dysplasia Screening

Database: EMBASE <1980 to 2007 Week 02>

Search Strategy:

- 
- 1 exp ANUS/ or exp ANUS DISEASE/ (12832)
  - 2 exp "Precancer and Cancer-In-Situ"/ (19513)
  - 3 1 and 2 (169)
  - 4 low grade squamous intraepithelial lesion\$.mp. (617)
  - 5 high grade squamous intraepithelial lesion\$.mp. (731)
  - 6 atypical squamous cells of undetermined significance.mp. (501)
  - 7 ((squamous or intraepithelial) adj1 (lesion\$ or neoplasia\$ or dysplasia\$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (7340)
  - 8 (anal or anus or perianal or anorectal).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (23928)
  - 9 1 or 8 (24008)
  - 10 or/4-7 (7427)
  - 11 9 and 10 (249)
  - 12 3 or 11 (342)
  - 13 limit 12 to (human and english language and yr="1993 - 2007") (253)
  - 14 limit 13 to (editorial or letter or note) (20)
  - 15 Case Report/ (918866)
  - 16 13 not (14 or 15) (210)

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