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Anal Cancer Screening in High-Risk Populations: A Review of the Clinical Utility, Diagnostic Accuracy, Cost-Effectiveness, and Guidelines

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Abbreviations

AMSTAR II	A MeaSurement Tool to Assess systematic Reviews II
CI	confidence interval
CRD	Centre for Reviews and Dissemination
HPV	human papillomavirus
MeSH	Medical Subject Headings
OR	odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	quality-adjusted life year
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies 2
RNA	ribonucleic acid

Context and Policy Issues

Anal cancer is a disease in which malignant cells develop in the tissue of the anal canal. Symptoms of anal cancer include rectal bleeding (occurs in about 45% of cases), pain, or sensation of a rectal mass.[1,2] Approximately 20% of cases may be asymptomatic.[3] Once a diagnosis has been made using biopsy-proven histology,[4] treatment for anal cancer typically involves multimodal therapy consisting of chemotherapy, radiation, and local resection.[5]

Anal cancers are relatively uncommon, accounting for an estimated 4% of all anorectal malignancies and 1.5% of gastrointestinal malignancies.[3,6,7] In Canada, this translates into approximately 1.7 cases of anal cancer per 100,000 person-years.[8] However, the incidence of anal cancer has been rapidly increasing over the last few decades.[9] One study[10] estimated that the incidence of anal squamous cell carcinoma in Canada has increased by 4.5% in males and 4.9% in females per year between 1983 and 2007.

There are several recognized risk factors that are associated with significantly higher rates of anal cancer.[3] These risk factors include human papillomavirus (HPV) infection, a history of receptive anal intercourse or sexually transmitted disease, immunosuppression after solid organ transplantation or HIV infection, hematologic malignancies, certain autoimmune disorders, a history of cigarette smoking, and a history of cervical, vulvar, or vaginal cancer.[1,11,12] The most important risk factor for anal cancer is HPV infection, which is estimated to be associated with up to 90% of all anal cancers.[8]

Screening techniques such as digital rectal examination, HPV testing, cytology-based methods (e.g., anal Papanicolaou smears), and anoscopy are available; however, the utility of anal cancer screening for the prevention and early identification of anal cancer is unclear.[13]

The objective of the current report is to evaluate the evidence regarding the clinical utility, diagnostic accuracy, and cost-effectiveness of cytology-based anal cancer screening techniques in high-risk populations. Additionally, evidence-based guidelines regarding the use of anal cancer screening in-high risk populations will be reviewed. This report expands upon a previously completed CADTH report (summary of abstracts).[14]

Research Questions

1. What is the clinical utility of cytology-based anal cancer screening techniques in high-risk populations?
2. What is the comparative diagnostic accuracy of cytology-based anal cancer screening techniques versus digital rectal exam or standard anal scope in high-risk populations?
3. What is the cost-effectiveness of cytology-based anal cancer screening techniques in high-risk populations?
4. What are the evidence-based guidelines for anal cancer screening in high-risk populations?

Key Findings

This review was comprised of one systematic review of evidence-based guidelines, one non-randomized study, one diagnostic test accuracy study, and two economic evaluations regarding cytology-based anal cancer screening techniques in high-risk populations.

Evidence of limited quality from one non-randomized study indicated that a population of adults with a confirmed diagnosis of HIV who underwent a structured anal cancer screening program (which consisted of digital rectal examination and annual cytological testing) had decreased incidence of invasive anal squamous cell carcinoma compared to those who were not screened. One diagnostic test accuracy study suggested that screening with standard anoscopy was significantly less likely to detect high-grade intraepithelial neoplasia than screening with anal cytology.

The two economic evaluations concluded that the use of cytology-based screening techniques may be cost-effective in high-risk populations. The findings of one economic evaluation suggested that screening women with a new diagnosis of cervical cancer using a combination of human papillomavirus testing and anal cytology may be cost-effective for the prevention of deaths due to anal cancer, depending on willingness-to-pay and time horizons. The second economic evaluation demonstrated screening women with a previously detected cervical intraepithelial neoplasia using anal cytology was 95% likely to be cost-effective at a willingness-to-pay threshold of C$45,500 per life-year gained.

As for evidence-based guidelines, the systematic review identified two guidelines that made specific recommendations regarding the provision of anal cancer screening in-high risk populations. One guideline recommends the use of digital rectal examination with or without a Papanicolaou test every one to three years in HIV-positive men who have sex with men (the strength of the recommendation was not reported). The second guideline recommends that an annual digital anal examination may be useful to detect masses on palpation that could be anal cancer (moderate strength recommendation; the target population was not specified). Both of these recommendations were based on expert opinion.

The limitations of the available literature, such as the current lack of randomized controlled trials, and of this report should be considered when interpreting the results.

Methods

Literature Search Methods

This report made use of a literature search developed for a previous CADTH report.[14] A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were anal cancer screening and high-risk populations. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, randomized controlled trials or controlled clinical trials, economic studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between Jan 1, 2014 and Sept 11, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Individuals at high risk of developing anal cancer (e.g., immunocompromised, HIV-positive, men who have sex with men, post-transplant, women with a history abnormal gynecological histology, individuals with a history of ano-genital condyloma, patients with anal intraepithelial neoplasia)
Intervention	Cytology-based anal cancer screening techniques (e.g., anal Papanicolaou test or other anal cytology methods)
Comparator	Q1,3: Digital rectal exam; standard anal scope; no screening Q2: Digital rectal exam or standard anal scope (using high resolution anoscopy, biopsy, and/or histopathology as reference standards) Q4: Not applicable
Outcomes	Q1: Clinical utility (e.g., prevention of cancer, mortality) Q2: Diagnostic accuracy (e.g., sensitivity, specificity, cancer detection, true positive rate, false positive rate) Q3: Cost-effectiveness Q4: Evidence-based guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, and evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014. Diagnostic test accuracy studies that compared cytology-based anal cancer screening techniques to a reference standard alone (i.e., high resolution anoscopy, biopsy, and/or histopathology) without a comparison to other screening techniques (i.e., digital rectal exam or standard anal scope) were excluded. Additionally, guidelines with unclear methodology were excluded.

Critical Appraisal of Individual Studies

The included systematic review was critically appraised by one reviewer using A MeaSurement Tool to Assess systematic Reviews II (AMSTAR II),[2] the non-randomized study was critically appraised using the Downs and Black checklist,[15] the diagnostic test accuracy study was critically appraised using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) checklist,[16] and economic studies were assessed using the Drummond checklist.[17] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of the study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 850 citations were identified in the literature search. Following screening of titles and abstracts, 821 citations were excluded and 29 potentially relevant reports from the electronic search were retrieved for full-text review. In addition, five potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 34 potentially relevant articles, 29 publications were excluded for various reasons, while five publications met the inclusion criteria and was included in this report. These comprised one systematic review,[18] one non-randomized study,[19] one diagnostic test accuracy study,[20] and two economic evaluations.[21,22] Appendix 1 presents the PRISMA[23] flowchart of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

One systematic review,[18] one non-randomized study,[19] one diagnostic test accuracy study,[20] and two economic evaluations[21,22] were identified for inclusion in this review. No relevant health technology assessments, randomized controlled trials, or evidence-based guidelines were identified. Detailed characteristics are available in Appendix 2, Table 2, Table 3, and Table 4.

Study Design

The systematic review,[18] published in 2014, searched for national HIV guidelines with recommendations regarding the implementation of regular digital ano-rectal examination as a method of screening for anal cancer. The searches (which were conducted up to August 5, 2013) identified 30 regional and national guidelines for inclusion, of which two made specific recommendations on digital ano-rectal examination. The quality of the evidence used to inform these guidelines was not reported in the systematic review. One relevant recommendation was described as being of moderate strength, although a description of what moderate refers to was not reported. The strength of the second relevant recommendation was not reported.

One non-randomized study[19] was identified regarding the clinical utility of cytology-based anal cancer screening techniques in high-risk populations. The study was a prospective cohort study that was conducted at a single-centre. Data were collected from January 1, 2005 to December 31, 2016.

The diagnostic test accuracy study[20] was prospectively conducted at a single centre. Consecutive participants were recruited between January 2012 and August 2016.

Two economic evaluations were identified regarding the cost-effectiveness of cytology-based anal cancer screening techniques in high-risk populations. Both studies were model-based analyses (using Markov models). The clinical inputs used in these models came from various reviews, individual clinical studies, or health ministry data, as selected by the authors. Cost inputs were informed by clinical studies or directly from industry. The Ehrenpreis and Smith[21] study was conducted from the perspective of a funder responsible for the costs of cancer care in the United States using a 20-year time horizon. The second economic evaluation by Cromwell et al.[22] took the perspective of a public funder in British Columbia using a 50 year time horizon (it also included scenario analysis that took 25- and 75-year horizons).

Country of Origin

The included systematic review was by authors in Australia.[18] Relevant guidelines included in the systematic review were intended for use in Europe and the United States.

The non-randomized study and diagnostic test accuracy study were conducted in Spain[19] and France,[20] respectively.

The economic evaluations were conducted in the United States[21] and Canada.[22]

Patient Population

The systematic review[18] included guidelines regarding anal cancer screening in HIV-positive men who have sex with men. There were no restrictions placed on age. The target population of the included guidelines was HIV-positive men who have sex with men or was not specified. The intended users of the guidelines were not specified.[18]

The non-randomized study[19] recruited adults (≥ 18 years of age) with a confirmed diagnosis of HIV attending an HIV unit for routine care. Participants who did not provide at least one year of follow-up data were excluded. A total of 3,111 individuals were included in the analysis. The mean age of participants was 41 and the median follow-up duration was 4.7 years. The proportion of female participants was 20.2%.

The diagnostic test accuracy study[20] included data from consecutive HIV-positive men who have sex with men attending an anal cancer screening consultation. Individuals who underwent any previous anal screening test, were referred with acute anal symptoms, or those who did not follow the complete screening strategy were excluded. The analysis included data from 212 male patients. The median age of participants was 51 years.

One economic evaluation[21] modelled a hypothetical population of female patients with newly diagnosed cervical cancer from the Untied States. The model assumed a mean age of 49 years at the time of diagnosis of cervical cancer. The economic evaluation by Cromwell et al.[22] simulated a population of 20,000 female patients with a previous diagnosis of cervical intraepithelial neoplasia.

Interventions and Comparators

The included systematic review[18] sought guidelines that included recommendations regarding anal examination and digital ano-rectal examination as a method of screening for anal cancer.

The intervention in the non-randomized study[19] consisted of a structured anal cancer screening program that included a baseline assessment with digital rectal examination and

cytological testing. Participants with normal results were re-screened on a yearly basis. In cases of abnormal cytology results, individuals were examined using high resolution anoscopy. Biopsies were taken where lesions were visualized. Cytological examinations were performed using a ThinPrep Pap test solution. The control cohort did not receive any anal cancer screening as part of their routine care for HIV.

Participants in the diagnostic test accuracy study[20] received anal cancer screening using three screening methods: 1) digital anorectal examination and standard anoscopy, 2) anal Pap cytology, and 3) HPV-16 genotyping. If any of these screening tests raised suspicion of dysplasia a targeted biopsy was performed to determine histology.

The economic evaluations evaluated the cost-effectiveness of anal cancer screening programs versus no screening. Specifically, the Ehrenpreis and Smith[21] study evaluated a screening algorithm that first tested women with HPV testing. Individuals with high-risk anal HPV subtypes would then undergo annual anal cytological analysis. The Cromwell et al.[22] study modelled the effectiveness of screening for low-grade and high-grade anal intraepithelial neoplasia using anal cytology. Screen-positive women were further evaluated with high-resolution anoscopy and resection when warranted. Screening occurred in year one and year two, followed by every three years until year 20.

Outcomes

The systematic review[18] searched for guidelines that provided recommendations regarding digital ano-rectal examination as a method of screening for anal cancer (e.g., recommended methods for screening, frequency of screening, subpopulations who should be screened).

The outcomes in the non-randomized study[19] were the incidence of invasive anal squamous cell carcinoma and time to anal cancer diagnosis.

In the diagnostic test accuracy study,[20] the outcome of interest was high-grade intraepithelial neoplasia detection yield. This was defined as the number of cases identified as being positive for high-grade intraepithelial neoplasia as a proportion of the total population.

The economic evaluation by Ehrenpreis and Smith[21] estimated cumulative anal cancer cases, cumulative anal cancer deaths, costs associated with medical care, cost per anal cancer prevented, cost per anal cancer death prevented, and cost per quality-adjusted life year (QALY) for both the screened and unscreened cohorts. Outcomes of interest in the Cromwell et al.[22] economic evaluation were incremental cost, life years gained, quality-adjusted life years, mean incremental cost-effectiveness ratio, and cost per cancer avoided.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of the included publications are provided in Appendix 3, Table 5, Table 6, Table 7, and Table 8.

Systematic Review

The included systematic review[18] had clearly defined research questions, objectives, and eligibility criteria. The review methods were prospectively registered in a published protocol, decreasing the risk for selective reporting. Key search terms and the dates of the searches were provided, increasing the reproducibility of the literature search, and literature searches were performed in multiple databases (PubMed and Web of Science). The review[18]

included a flow chart illustrating guideline selection and provided reasons for article exclusion. Finally, the review authors disclosed their sources of funding (which were considered unlikely to have influenced the findings of the review) and stated they had no related conflicts of interest.

As for the limitations of the review,[18] it was unclear if guideline selection, data extraction, and quality assessment were conducted in duplicate, increasing the risk for inconsistencies in these processes. In addition, the literature searching did not include a grey literature search, increasing the risk for missing relevant, non-indexed guidelines, and although reasons for exclusion were provided, the review did not include a list of the excluded guidelines. Lastly, the included guidelines were published in Europe and the United States and their relevance to the Canadian setting was unclear.

Non-Randomized Study

The objectives, interventions, controls, methods for patient recruitment, outcomes, and main findings were clearly described within the included non-randomized study.[19] Details on baseline participant characteristics (e.g., age, sex, time of known HIV infection, CD4 cell counts, HIV-1 plasma ribonucleic acid [RNA]) were included and were tested for statistically significant differences between cohorts at baseline. Confidence intervals and actual probability values (*P*-values) were reported, increasing the strength of reporting. Participants in the intervention and control groups were recruited over the same period of time and compliance with the assigned intervention was reliable. Although the average length of follow-up was not equal between groups (median length of follow-up was 4.6 years in the screened group versus 4.8 years in the unscreened group; the between-group difference was not statistically tested), the results were adjusted to reflect the incidence rates of invasive anal squamous cell carcinoma per 100,000 patient-years, which should partially compensate for this difference. Study participants, care providers, and health care settings appeared to be representative of the population and care setting of interest, increasing the external validity of the study. Both the sources of funding and potential conflicts of interest were disclosed (three authors disclosed honoraria received for speaking and participating in advisory board for various companies) and were unlikely to have influenced the findings of the study.

As for methodological limitations, the study[19] was at risk of confounding from unmeasured variables due to the lack of randomization (intervention assignment was done based on participant preference); however, the risk for selection bias was reduced by the use of a propensity score analysis. Additionally, because this was an open-label study there was a risk for bias in either direction depending on the perceptions and expectations of participants and outcome assessors; although this risk was mitigated using an objective primary outcome (i.e., incidence of invasive anal squamous cell carcinoma). The authors of the study did not report on any adverse events resulting from the intervention and did not describe the characteristics of patients lost to follow-up. Finally, the study was conducted at a single centre in Spain; therefore, the generalizability of the findings to the Canadian setting was unclear.

Diagnostic Test Accuracy Study

The included diagnostic test accuracy study[23] had clearly described objectives, interventions, controls, patient inclusion and exclusion criteria, clinical outcomes, and main findings. Details on baseline participant characteristics (e.g., age, time since HIV diagnosis, CD4 cell counts, smoking history) and actual probability values (*P*-values) were reported,

increasing the strength of reporting. Consecutive patients were enrolled prospectively to the study;[19] a case-control study design was not used. The reference standard, which was scope-guided biopsy, was likely to classify the target condition (i.e., high-grade intraepithelial neoplasia) and was conducted after the index test following an appropriate time interval. Study participants, care providers, and health care settings appeared to be representative of the "real-world" and inappropriate exclusion criteria were avoided, increasing the external validity of the study.

As for the limitations of the study, it was unclear if index test results and reference standards were conducted independently from each other and if assessors were blinded to the results of the screening tests. As a result, there was a risk for bias in either direction depending on the perceptions and expectations of clinicians and outcome assessors. Additionally, the reference standard was only conducted in patients who were screened positive by other methods; therefore, this study was not designed to assess sensitivity and specificity and false negatives would have gone undetected. Although the study authors declared they had no potential conflicts of interest, the source of funding for the study was not disclosed. Finally, the study[23] was conducted at a single centre in France; the generalizability to the Canadian setting was unclear.

Economic Evaluations

In both included economic evaluations,[21,22] the research questions, objectives, economic importance of the research questions, time horizons, and rationale for choosing alternative interventions compared were clearly stated. However, neither study clearly described or justified the viewpoint of the analysis. The 20-year[21] and 50-year time[22] horizons used in these model-based analyses was appropriate for examining the cost-effectiveness of anal cancer screening interventions. Additionally, the choice of form of economic evaluations (Markov health state transition models) were justified and the model structures were illustrated with figures. These methodological strengths increase confidence in the findings of the studies.

The sources of effectiveness estimates and costs associated with cancer screening and treatment were provided in both studies[21,22] (i.e., various literature or health system databases); however, there was limited information included on the design and results of effectiveness studies from which assumptions were drawn. The approach to sensitivity analyses and the choice of variables for sensitivity analysis were justified in both studies.[21,22] While the Cromwell et al.[22] study clearly stated all costs were expressed in 2014 Canadian dollars, the Ehrenpreis and Smith[21] study did not mention details of currency adjustments or conversions. Similarly, the Cromwell et al.[22] study applied a 5% discount rate for the costs and outcomes; however, the Ehrenpreis and Smith[21] study did not apply a discount rate. Neither of the included studies[21,22] considered changes in productivity as a model parameter.

The Cromwell et al. study was conducted using data from British Columbia and should therefore have good generalizability to the Canadian setting. The Ehrenpreis and Smith[21] study used estimates based on American populations, therefore it is less clear how the findings apply to the Canadian setting. The authors of both included economic evaluations[21,22] disclosed their sources of funding and potential conflicts of interest, none of which were considered likely to have had an effect on the findings of the study.

Summary of Findings

The overall findings of the included studies are highlighted below. Detailed summaries of the main findings are available in Appendix 4, Table 9, Table 10, and Table 11.

Clinical Utility of Cytology-Based Anal Cancer Screening Techniques

Prevention of cancer

Evidence regarding the clinical utility of cytology-based anal cancer clinical screening techniques for the prevention of cancer was available from one non-randomized study.[19]

The authors of the study[19] reported a decreased incidence of invasive anal squamous cell carcinoma per 100,000 person-years in a cohort of participants who received a structured anal cancer screening program that consisted of digital rectal examination and cytological testing on a yearly basis versus those who were not screened (21.9 [95% CI: 2.7 to 70.3] cases per 100,000 person years vs. 107.0 [95%CI: 46.2 to 202.0] cases per 100,000 person-years; *P* = 0.027).

Comparative Diagnostic Accuracy of Cytology-Based Anal Cancer Screening Techniques

Detection yield

Information regarding the comparative diagnostic accuracy of cytology-based anal cancer screening techniques versus standard anoscopy and HPV genotyping was available from one study.[20]

The findings of this study[20] suggested that screening with standard anoscopy was significantly less likely to detect high-grade intraepithelial neoplasia than testing with anal cytology (OR = 0.35 [95% CI: 0.12 to 0.89]; *P* = 0.02). The screening strategy with the highest detection yield was the combined strategy, which included standard anoscopy, HPV-16 testing, and anal cytology; however, it was not statistically more likely to detect high-grade intraepithelial neoplasia than testing with anal cytology alone (OR = 1.48 [95% CI: 0.76 to 2.92]; *P* = 0.27).

Cost-Effectiveness of Cytology-Based Anal Cancer Screening Techniques

Cost per anal cancer prevented

Evidence on the cost-effectiveness of cytology-based anal cancer screening techniques for the prevention of anal cancer was available from two economic evaluations.[21,22]

One study[21] estimated incremental costs per anal cancer prevented of $291,409 after five years, $168,796 after 10 years, and $98,631 after 20 years for their modelled screening intervention compared to a no screening alternative. Furthermore, their model estimated the incremental costs per anal cancer death prevented, which were $3,205,127 by year five, $210,057 after 10 years, and $26,133 after 20 years. These findings are assumed to be expressed in US dollars based on the location of the study (although it was not explicitly stated in the publication).

The Cromwell et al.[22] study estimated that the incremental cost per cancer avoided in their base case model was C$67,933 (versus no screening). Alternative scenarios considered in

the study had incremental costs per cancer avoided of C$148,532 (Scenario A; five years of screening) and C$102,806 (Scenario B; “one-off” screening).

Incremental cost-effectiveness ratios

Two economic evaluations[21,22] estimated the incremental cost-effectiveness of anal cancer screening programs versus no screening.

One study[21] reported costs per QALY of $71,229 after five years, $9,785 after 10 years, and $1,687 after 20 years (assumed to be expressed in US dollars).

Cromwell et al.[22] estimated a mean incremental cost-effectiveness ratio of C$20,561 per life year gained in their baseline model (screening in year one and year two, followed by every three years until year 20). Alternative screening scenarios had mean incremental cost-effectiveness ratio of C$29,673 per life year gained in Scenario A (five years of screening) and C$52,602 per life year gained in Scenario B (“one-off” screening). Both alternative screening strategies were dominated by the baseline model. According to the cost-effectiveness acceptability curves, the baseline screening intervention became cost-effective at a willingness-to-pay threshold of C$45,500 per life-year gained.

Guidelines

The systematic review of guidelines included two guidelines that made specific recommendations regarding the provision of anal cancer screening in-high risk populations.[18] The European AIDS Clinical Society Guidelines recommend the use of digital rectal examination with or without a Papanicolaou test every one to three years in HIV-positive men who have sex with men. The process used to derive this recommendation was unclear, although it seemed to be based on expert opinion. The strength of the recommendation was not reported in the systematic review.[18] The US Guideline for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents includes the following moderate recommendation: “An annual digital anal examination may be useful to detect masses on palpation that could be anal cancer”[18] (p. 4). This recommendation was based on expert opinion and did not identify a specified population that should be screened.

Limitations

A number of limitations were identified in the critical appraisal (Appendix 3, Table 5, Table 6, Table 7, and Table 8), however, additional limitations exist.

Although one study[20] was identified regarding the comparative diagnostic accuracy of cytology-based anal cancer screening techniques versus digital rectal exam or standard anal scope in high-risk populations, several diagnostic test parameters (e.g., sensitivity, specificity, negative predictive value, positive predictive value) were unavailable due to the design of the study.

With regards to the diagnostic test accuracy findings, only studies that directly compared cytology-based techniques versus digital rectal exam or standard anal scope (using high resolution anoscopy, biopsy, and/or histopathology as reference standards) for the identification of anal cancer in high-risk populations were included in this report. Although the diagnostic accuracy of cytology-based techniques versus the reference standard alone was outside of the scope of this report, there are several recently published systematic reviews[24-27] that reviewed this evidence.

The literature reviewed in this report was limited to populations of HIV-positive men who have sex with men,[18,20] adults with a confirmed diagnosis of HIV,[19] female patients with newly diagnosed cervical cancer,[21] and female patients with a previous diagnosis of cervical intraepithelial neoplasia.[22]

None of the included studies[18-22] contained information specific to high-risk pediatric populations, non-HIV immunocompromised populations (e.g., post-transplant individuals taking immunosuppressant medication), and those with a history of ano-genital condyloma; thus, the clinical utility, cost-effectiveness, and evidence based-guidelines regarding the use of anal cancer screening in these populations is unknown. Additionally, the diagnostic test accuracy study[20] only included males; therefore, the comparative diagnostic accuracy of cytology-based anal cancer screening techniques versus digital rectal exam or standard anal scope in high-risk female populations is unclear. Conversely, both included economic evaluations[21,22] were specific to female populations; therefore, the cost-effectiveness of cytology-based anal cancer screening techniques in males is unknown.

Conclusions and Implications for Decision or Policy Making

This review was comprised of one systematic review (of national HIV guidelines),[18] one non-randomized study,[19] one diagnostic test accuracy study,[20] and two economic evaluations[21,22] regarding cytology-based anal cancer screening techniques in high-risk populations.

Evidence of limited quality (from one non-randomized study)[19] demonstrated that a cohort of people living with HIV who were enrolled in an anal cancer screening program that used cytology-based techniques had a significantly decreased incidence rate of invasive anal squamous cell carcinoma compared to a similar group of patients who were not screened. Evidence from the diagnostic test accuracy study[20] indicated the detection yield for high-grade intraepithelial neoplasia was significantly higher using cytology-based screening techniques than standard anoscopy in a population of HIV-positive men who have sex with men.

The cost-effectiveness of cytology-based anal cancer screening techniques was reported as favourable versus no screening comparators by the authors of both economic evaluations.[21,22] These cost-effectiveness analyses were modelled using hypothetical populations of females with newly diagnosed cervical cancer[21] and females with a previous diagnosis of cervical intraepithelial neoplasia.[22]

The systematic review[18] identified two guidelines that made specific recommendations regarding the provision of anal cancer screening in-high risk populations. One guideline recommends the use of digital rectal examination with or without a Papanicolaou test every one to three years in HIV-positive men who have sex with men (the strength of the recommendation was not reported in the systematic review). The second guideline recommends an annual digital anal examination to detect masses on palpation that could be anal cancer (moderate recommendation). Both recommendations were based on expert opinion.

Although this review was intended to provide further analysis of the literature identified within a previously published CADTH report,[14] four systematic reviews[24-27] and three evidence-based guidelines[1,28,29] included in the previous report were excluded in this review following full-text assessment. The systematic reviews[24-27] were excluded due to ineligible comparators, as the included primary studies estimated the diagnostic accuracy of

cytology-based screening methods against a reference standard alone, and not against digital rectal exam or standard anal scope. As for the three evidence-based guidelines,[1,28,29] although these publications included some commentary on the availability of literature on anal cancer screening in high-risk populations, none made explicit recommendations as per the inclusion criteria of the current report and were therefore excluded.

The limitations of the included studies[18-22] and of this report should be considered when interpreting the results. The findings highlighted in this review come with a high degree of uncertainty. Further research investigating the clinical utility, comparative diagnostic accuracy, and cost-effectiveness of cytology-based anal cancer screening techniques in high-risk populations would help reduce this uncertainty.

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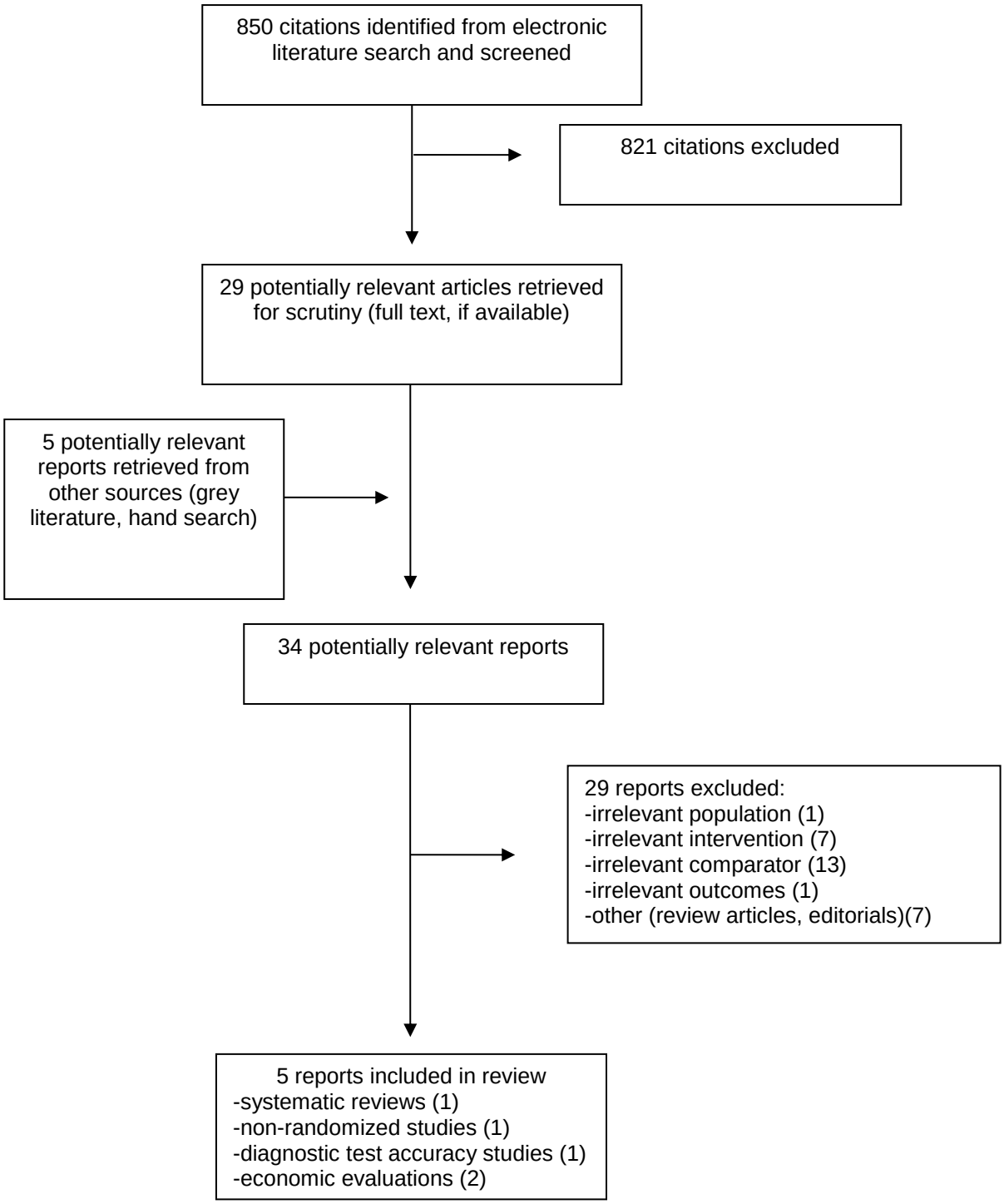
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of the Included Systematic Review

Study Citation, Country, Funding Source	Objective, Study Designs, Search Strategy, Number of Primary Studies Included, Quality Assessment Tool	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes
Ong et al., 2014[18] Australia **Funding source**: A National Health and Medical Research Council Postgraduate Scholarship.	**Objective**: To systematically identify and review national HIV guidelines and the current recommendations regarding the implementation of regular digital ano-rectal examination as a part of routine HIV care. **Study design**: Systematic review of national HIV guidelines. **Literature search strategy**: Authors searched for guidelines in UCSF's HIV InSite, PubMed, and Web of Science up to August 5, 2013. **Number of studies included**: 30 guidelines were included in the qualitative synthesis (two of which were relevant to the current report). **Quality assessment tool**: The level of evidence used to support each recommendation was assessed using the US preventive Services Task Force for ranking evidence for the effectiveness of screening.	HIV-positive men who have sex with men.	Guidelines that included statements regarding anal examination and digital ano-rectal examination as a method of screening for anal cancer were included.	The review sought guidance regarding: - Methods for screening - Frequency of screening - Populations who should be screened

HIV = human immunodeficiency virus; UCSF = University of California, San Francisco.

Table 3: Characteristics of Included Primary Clinical Studies

Study Citation, Country, Funding Source	Objective, Study Design, Setting	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Non-Randomized Study				
Revollo et al., 2019[19] Spain **Funding source**: Grants from the Lluita Contra La SIDA Foundation, Spain.	**Objective**: To examine the incidence of invasive anal squamous cell carcinoma among individuals who had participated in a structured standard anal cancer screening program compared to those who did not. **Study design**: Single-centre, retrospective analysis of a prospective cohort. **Setting**: Data from adults attending the HIV Unit of the Hospital Germans Trias i Pujol in Spain between January 1, 2005 and December 31, 2016 was analyzed.	**Inclusion criteria**: Adults (≥ 18 years of age) with a confirmed diagnosis of HIV. **Excluded**: Individuals who did not provide at least one year of follow-up data. **Number of participants**: 3,111 (1,691 in the screened cohort; 1,420 in the unscreened cohort). **Mean age, years (SD)**: 41.5 (9.7) in the screened cohort; 41.6 (8.9) in the unscreened cohort. **Sex**: 20.1% female in the screened group (15.2% MSW, 64.8% MSM); 20.3% female in the unscreened cohort (44.4% MSW, 35.3% MSM). **Median time since HIV diagnosis, years (IQR)**: 7.9 (0.9 to 16.1) in the screened cohort; 10.1 (3.4 to 15.2) in the unscreened cohort.	**Intervention**: A structured anal cancer screening program that consisted of digital rectal examination and cytological testing on a yearly basis. Individuals with abnormal cytology results were examined using high resolution anoscopy and biopsy in cases where lesions were visualized. Cytological examinations were performed using a ThinPrep Pap test solution. **Comparator**: The control cohort did not receive any anal cancer screening. Follow-up data was collected as part of their routine care for HIV.	**Clinical outcomes**: - Incidence of invasive anal squamous cell carcinoma - Time to anal cancer diagnosis **Follow-up**: Median length of follow-up was 4.6 years in the screened cohort and 4.8 years in the unscreened cohort.
Diagnostic Test Accuracy Study				
Pernot et al., 2018[20] France **Funding source**: NR.	**Objective**: To determine the diagnostic yield of various screening techniques for detecting high-grade intraepithelial neoplasia. **Study design**: Single-centre, prospective diagnostic test accuracy study.	**Inclusion criteria**: All consecutive HIV-positive MSM attending an anal cancer screening program. **Excluded**: Individuals who underwent any previous anal screening test, were referred with acute anal symptoms, or those who did not follow the complete screening strategy were excluded. **Number of participants**: 212.	Study participants received assessment with an anal cancer screening algorithm. The included screening methods included digital anorectal examination, standard anoscopy, anal Pap cytology, and HPV genotyping. When initial tests raised suspicion of dysplasia a targeted	**Clinical outcomes**: - High-grade intraepithelial neoplasia detection yield **Follow-up**: NR.

Table 3: Characteristics of Included Primary Clinical Studies

Study Citation, Country, Funding Source	Objective, Study Design, Setting	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Setting: Data from consecutive patients attending an anal cancer screening consultation between January 2012 and August 2016 were included in the study.	**Median age, years (IQR)**: 51 (45 to 57). **Sex**: 100% male. **Median time since HIV diagnosis, years (IQR)**: 15.2 (5.5 to 22.6).	biopsy was performed. The detection yields were compared across various screening interventions.	

HIV = human immunodeficiency virus; HPV = human papillomavirus; IQR = interquartile range; MSM = men who have sex with men; MSW = men who have sex with women; NR = not reported; SD = standard deviation.

Table 4: Characteristics of Included Economic Evaluations

Study Citation, Country, Funding Source	Type of Analysis, Approach, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator(s)	Clinical and Cost Data Used in Analysis	Main Assumptions
Ehrenpreis and Smith, 2018[21] United States **Funding source**: An unrestricted grant from the Keyser Family Fund.	**Analysis**: Cost-effectiveness analysis using dynamic computer simulation and modeling with STELLA software (Markov model). **Approach**: Model-based analysis. **Time horizon**: 20 years **Perspective**: A funder responsible for the costs of cancer care in the United States.	To estimate the cost-effectiveness of screening for anal HPV and anal cancer in women with histories of cervical cancer.	Female patients with newly diagnosed cervical cancer. **Number of participants**: The model assumed 11,500 women were affected by cervical cancer each year in the United States (thus entering the model). **Mean age**: The model assumed a mean age of 49 years at time of diagnosis of cervical cancer. **Sex**: 100% female.	**Intervention**: Anal cancer screening using a combination of HPV testing and anal cytology. **Comparator**: No screening for anal cancer.	- Rates of progression from anal HPV to low-grade dysplasia, high-grade squamous intraepithelial lesion, and anal cancer - Anal cancer prevention rates with high resolution anoscopy and electrocautery techniques - Costs of cancer treatment - Costs of screening techniques (e.g., HPV screen, anal cytology, high resolution anoscopy and biopsy) - Annual and five-year anal cancer death rates - Quality of life weight adjustments for women at various stages of the model	- A series of assumptions around the proportion of women with various anal pathologies at the time of cervical cancer diagnosis (which came from a single study) - Evolution of anal cytologic changes were based on data from MSM due to the lack of data in women with anal HPV infection - Quality of life weight adjustments for women at various stages of the model - Costs of screening techniques and cancer treatments
Cromwell et al., 2016[22] Canada **Funding source**: The	**Analysis**: Cost-effectiveness analysis using a Markov health state transition model. The model	To estimate the cost-effectiveness of adding anal cancer screening to routine follow-	Female patients with a previous diagnosis of cervical intraepithelial neoplasia.	**Intervention**: Women with a previously detected cervical intraepithelial neoplasia were screened for AIN1	- Costs were based on estimates published in British Columbian provincial source, with literature sources used when	- ASCC cases were managed according to British Columbia Cancer Agency guidelines - Anal screening utility weights were

Table 4: Characteristics of Included Economic Evaluations

Study Citation, Country, Funding Source	Type of Analysis, Approach, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator(s)	Clinical and Cost Data Used in Analysis	Main Assumptions
authors had no funding to disclose but noted the Canadian Centre for Applied Research in Cancer Control is funded by a grant from the Canadian Cancer Society (#2015-703549).	ran in 1-year cycles. **Approach**: Model-based analysis. **Time horizon**: 50 years. **Perspective**: A public funder in British Columbia.	up for women with a history of cervical intraepithelial neoplasia.	**Number of participants**: The model simulated 10,000 women in each cohort (screened and unscreened; 20,000 total). **Mean age**: NR. **Sex**: 100% female.	or AIN2+ using anal cytology. Screen-positive women were further evaluated with high-resolution anoscopy and resection when warranted. Screening occurred in year 1 and year 2, followed by every 3 years until year 20. **Comparator**: No screening for anal cancer.	BC-specific estimates were unavailable. - Estimates for transition probabilities were derived from health economic and clinical literature with the selection process taking into consideration several factors (e.g., sample sizes, recency of the publication, other appropriateness factors) - Diagnostic accuracy of Pap testing came from a single study - Health utilities were derived from various clinical source; utilities for cervical cancer were substituted when anal cancer-specific values were unavailable	unavailable, therefore utilities from women screened and treated for cervical lesions or cancer were used - Women who undergo a resection for an anal lesion have a loss of health utility throughout the entire year (which may be an overestimation) - The model does not consider recurrence of cervical intraepithelial neoplasia - Women with cervical cancer were not included as treatment of comorbid cancers (i.e., cervical and anal) would greatly increase the complexity of the model.

AIN1 = low-grade squamous anal intraepithelial neoplasia; AIN2+ = high-grade squamous anal intraepithelial neoplasia; ASCC = anal squamous cell carcinoma; HPV = human papillomavirus; MSM = men who have sex with men; NR = not reported; STELLA = Systems Thinking, Experimental Learning Laboratory with Animation.

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of the Systematic Review using AMSTAR II[2]

Strengths	Limitations
Ong et al., 2014[18]	
• The objectives and inclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes • Review methods were established prior to conducting the review (a protocol was prospectively registered) • The choice of included study designs (i.e., guidelines) was explained • Multiple databases were searched (PubMed and Web of Science). Additionally, UCSF's HIV InSite was screened • Key search terms (anal, anus, ano, cancer, carcinoma, neoplasm, malignancy, squamous cell carcinoma, squamous cell cancer, and screen) and the date of search (August 5, 2013) were provided • A flow chart of study selection was provided • The level of evidence used to support recommendations was provided when available • Source of funding was disclosed and was unlikely to have had an effect on the findings of the review (the study was funded by a National Health and Medical Research Council Postgraduate Scholarship) • The authors stated that they had no conflicts of interest related to this review	• It was unclear if study selection, data extraction, or quality assessment were done in duplicate • A grey literature search was not completed • A list of excluded studies was not provided (although the reasons for exclusion were) • Review authors did not report on source of funding for the included guidelines • The two relevant guidelines studies were published by groups in Europe and the United States; recommendations may not be generalizable to the Canadian setting

HIV = human immunodeficiency virus; UCSF = University of California, San Francisco.

Table 6: Strengths and Limitations of the Non-Randomized Study using the Downs and Black Checklist[15]

Strengths	Limitations
Revollo et al., 2019[19]	
• The objectives, interventions, controls, and main outcomes were clearly described • Detailed methodology on patient recruitment and assessment of inclusion/exclusion criteria was included • Population characteristics (e.g., age, sex, time of known HIV infection, CD4 cell counts, HIV-1 plasma RNA) were clearly described and were tested for statistically significant differences between cohorts • Study subjects in the intervention and control groups were recruited over the same period of time • Compliance with the assigned treatment was reliable • Outcome measures were valid and reliable • The major findings of the study were presented in graphic form and clearly described • Length of follow-up was not equal between groups; however, results were adjusted to reflect the incidence rates per 100,000 patients-years • Confidence intervals and actual probability values (*P*-values) were reported • Study participants, care providers, and setting appeared to be representative of the population and care setting of interest • Sources of funding and conflicts of interest were disclosed (three authors disclosed honoraria received for speaking and participating in advisory board for various companies) and were unlikely to have had an effect on the findings of the study	• Intervention assignment was not done at random (assignment was done based on participant preference to be screened or not). • There were significantly more MSM and less MSW in the screened cohort. Additionally, participants in the screened cohort had high CD4 counts at baseline and higher HIV-1 plasma RNA (potential confounders; although these were considered in the propensity score adjustment) • This was an open-label study with no blinding of study participants or outcome assessors • There was no mention of adverse events that may have been a consequence of the screening intervention • Characteristics of patients lost to follow-up were not described (i.e., participants who did not provide at least one year of follow-up data) • Single-centre study (conducted in the Spain); the generalizability to the Canadian setting was unclear

HIV = human immunodeficiency virus; MSM = men who have sex with me; MSW = men who have sex with women; RNA = ribonucleic acid.

Table 7: Strengths and Limitations of the Diagnostic Test Accuracy Study using the QUADAS-2 Checklist[16]

Strengths	Limitations
Pernot et al., 2018[20]	
• The objectives, interventions, controls, and main outcomes were clearly described • Consecutive patients were enrolled prospectively to the study • A case-control study design was avoided • Patient inclusion and exclusion criteria were included • Inappropriate exclusion criteria were avoided • Population characteristics (e.g., age, time since HIV diagnosis, CD4 cell counts, smoking history) were clearly described • The reference standard (scope-guided biopsy) was likely to correctly classify the target condition (i.e., high-grade intraepithelial neoplasia) • There was an appropriate time interval between index tests and reference standard • Confidence intervals and actual probability values (*P*-values) were reported • The reference standard was conducted by the same • Study participants, care providers, and setting appear to be representative of the population and care setting of interest • The authors declared that they had no potential conflicts of interest	• It was unclear if index test results and reference standards were conducted independently and if the gastrointestinal pathologist was blinded to the results of the screening tests • The reference standard was only conducted in patients who were screened positive by other methods; there was a risk for false negatives (this study was not designed to assess sensitivity and specificity) • The source of funding for the study was not disclosed • Single-centre study conducted as part of an annual anal cancer screening program for HIV-positive MSM in France; the generalizability to the Canadian setting was unclear

HIV = human immunodeficiency virus; MSM = men who have sex with men.

Table 8: Strengths and Limitations of Economic Studies using the Drummond Checklist[17]

Strengths	Limitations
Ehrenpreis and Smith, 2018[21]	
Study design • The research question, economic importance of the research question, and rationale for choosing alternative interventions compared were clearly stated • The treatment strategies being compared were clearly described • The form of economic evaluation used was stated • The choice of form of economic evaluation was justified in relation to the questions addressed **Data collection** • The sources of effectiveness estimates and screening/treatment costs were provided • The primary outcome measures for the economic evaluation were clearly stated • Methods to value benefits were stated • Details of the subjects from whom valuations were obtained were given • Methods for the estimation of unit costs were described • The structure of the model was clearly described using figures **Analysis and interpretation of results** • Time horizon of costs and benefits was stated (20 years) • The approach to sensitivity analysis was given • The choice of variables for the sensitivity analysis were justified • Major outcomes were presented in a disaggregated form • The answer to the study question was given • Incremental analysis was reported • Conclusions follow from the data reported • Conclusions were accompanied by appropriate caveats **Miscellaneous** • The authors declared that they had no potential conflicts of interest • Sources of funding were disclosed and were unlikely to have had an effect on the findings of the study	• The viewpoint/perspective of the analysis was not clearly stated or justified • The design and results of effectiveness studies from which assumptions were drawn were not provided • Data input were taken from single references, rather than a synthesis or meta-analysis of estimates from multiple sources • The relevance of productivity changes was not discussed • Details of currency adjustments or conversions were not provided (assumed to be US dollars) • Discount rates, choices of discount rates, and explanation of costs/benefits not being discounted were not provided • The findings of this United States-based study may not be generalizable to other health systems
Cromwell et al., 2016[22]	

Table 8: Strengths and Limitations of Economic Studies using the Drummond Checklist[17]

Strengths	Limitations
Study design • The research question, economic importance of the research question, and rationale for choosing alternative interventions compared were clearly stated • The treatment strategies being compared were clearly described • The form of economic evaluation used was stated (a Markov health state transition model) • The choice of form of economic evaluation was justified in relation to the questions addressed **Data collection** • The sources of effectiveness estimates and screening/treatment costs were provided • The primary outcome measures for the economic evaluation were clearly stated • Methods to value benefits were stated • Details of the subjects from whom valuations were obtained were given • Methods for the estimation of unit costs were described • Details of currency were given (all costs were expressed in 2014 Canadian dollars, adjusted for inflation using the Consumer Price Index for health care) • The structure of the model was clearly described using figures **Analysis and interpretation of results** • Time horizon of costs and benefits was stated (50 years) • The discount rate for costs and outcomes was stated and justified (5% per year, as recommended by CADTH) • The approach to sensitivity analysis was given • The choice of variables for the sensitivity analysis were justified • Major outcomes were presented in a disaggregated form • The answer to the study question was given • Incremental analysis was reported • Conclusions follow from the data reported • Conclusions were accompanied by appropriate caveats **Miscellaneous** • The authors declared that they had no potential conflicts of interest • Sources of funding were disclosed and were unlikely to have had an effect on the findings of the study • The study was conducted from the perspective of a public funder in British Columbia; there should be relatively high generalizability to Canadian settings	• The viewpoint/perspective of the analysis was not clearly stated or justified • The design and results of effectiveness studies from which assumptions were drawn were not provided • Data input were taken from single references, rather than a synthesis or meta-analysis of estimates from multiple sources • The relevance of productivity changes was not discussed

Appendix 4: Main Study Findings and Authors' Conclusions

Table 9: Summary of Findings the Included Systematic Review

Main Study Findings	Authors' Conclusion
Ong et al., 2014[18]	

Systematic review that identified and reviewed national HIV guidelines and the current recommendations regarding the implementation of regular digital ano-rectal examination as a part of routine HIV care.
 	
Summary of relevant findings:
- Thirty regional and national guidelines were identified and included in the systematic review. Of these 30 guidelines, two made specific recommendations on the use of digital ano-rectal examination
  ○ The European AIDS Clinical Society Guidelines recommend the use of digital rectal examination with or without a Papanicolaou test every 1 to 3 years in HIV-positive MSM (based on Level III evidence, which is evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees)
  ○ The US Guideline for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents noted "An annual digital anal examination may be useful to detect masses on palpation that could be anal cancer."[18] (p. 4) (based on Level III evidence)
	"Anal cancer is an urgent health priority for HIV-positive MSM. Although some experts have recommended regular DARE as a means of detection of anal cancer, few HIV guidelines discuss or recommend DARE as a means of anal cancer screening. There is a need for further studies of the efficacy, acceptability and cost-effectiveness of DARE before its role in anal cancer screening can be determined."[18] (p. 6)

DARE = digital ano-rectal examination; HIV = human immunodeficiency virus; MSM = me who have sex with men.

Table 10: Summary of Findings of the Included Primary Clinical Studies

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Non-Randomized Study</td></tr>
<tr><td colspan="2">Revollo et al., 2019[19]</td></tr>
<tr><td>Single-centre, retrospective analysis of a prospective cohort that examined the incidence of invasive anal squamous cell carcinoma among individuals who had participated in a structured standard anal cancer screening program (N = 1,691) compared to those who did not (N = 1,420).

Summary of findings:
- Cumulative incidence of invasive anal squamous cell carcinoma
o Screened cohort: 0.1% (95% CI: 0.03% to 0.4%)
o Unscreened cohort: 0.6% (95% CI: 0.3% to 1.1%)
o P-value = 0.051
- Incidence rate of invasive anal squamous cell carcinoma per 100,000 person-years
o Screened cohort: 21.9 (95% CI: 2.7 to 70.3)
o Unscreened cohort: 107.0 (95%CI: 46.2 to 202.0)
o P-value = 0.027
- "The cox regression model showed a statistically significant protective effect of being enrolled in the screening program (HR: 0.20; 95% CI: 0.04-0.97)."[19] (p. 12)
- "After adjusting for propensity score, Cox model yielded also a significantly protective effect in favor of being enrolled in the screening program (HR: 0.17; 95% CI: 0.03-0.86)."[19] (p. 13)</td><td>"In conclusion, in a prospective cohort analysis the number of cases of [invasive anal squamous cell carcinoma] was significantly lower in [people living with HIV/AIDS] (MSM, MSW and women) who were enrolled in a preventative screening program compared to a similar group who were not. These results support the continued implementation of such programs while results from randomized clinical trials and analyses involving larger cohorts are eagerly awaited to further clarify the efficacy of this strategy."[19] (p. 17)</td></tr>
<tr><td colspan="2">Diagnostic Test Accuracy Study</td></tr>
<tr><td colspan="2">Pernot et al., 2018[20]</td></tr>
<tr><td>A single-centre, prospective diagnostic test accuracy study that examined the diagnostic accuracy of various screening techniques for detecting high-grade intraepithelial neoplasia in HIV-positive MSM (N = 212).

High-grade intraepithelial neoplasia detection yields of various screening strategies comprised of standard anoscopy (SA), HPV-16 genotyping, and anal Pap cytology compared to the complete assessment (all three screening methods plus high-resolution anoscopy and targeted biopsy when indicated) and anal Pap cytology alone
<table>
<tr><th>Screening strategy (N = 212)</th><th># of positive screening tests</th><th># of HRAs performed</th><th># of biopsies performed</th><th>HGAIN detection rate (%)</th><th>Strategy vs. complete strategy (OR [95% CI])</th><th>Strategy vs. anal Pap alone (OR [95% CI])</th></tr>
<tr><td colspan="7">Single screening strategies</td></tr>
<tr><td>SA</td><td>19</td><td>0</td><td>19</td><td>7 (3.3%)</td><td>0.23
[0.08 to 0.57]
P < 0.001</td><td>0.35
[0.12 to 0.89]
P = 0.02</td></tr>
</table>
</td><td>"In conclusion, among the single screening strategies, anal Pap alone had a higher HGAIN detection yield than [standard anoscopy] and HPV-16 genotyping. Among the dual combination strategies, anal Pap+HPV-16 and [standard anoscopy]+anal Pap had detection yields similar to that of the complete strategy. However, even though</td></tr>
</table>

Table 10: Summary of Findings of the Included Primary Clinical Studies

Main Study Findings							Authors' Conclusion
HPV-16 genotyping	40	39	26	14 (6.6%)	0.48 [0.23 to 0.99] *P* < 0.05	0.72 [0.32 to 1.56] *P* = 0.47	[standard anoscopy] decreased the number of [high-resolution anoscopy] performed, it is likely that it might also affect participation or acceptance."[20] (p. 385)
Anal Pap	62	59	40	19 (9.0%)	0.67 [0.34 to 1.30] *P* = 0.27	Ref.	
Dual screening strategies							
SA + HPV-16 genotyping	53	33	40	19 (9.0%)	0.67 [0.34 to 1.30] *P* = 0.28	1.00 [0.48 to 2.06] *P* = 1.00	
HPV-16 genotyping + anal Pap	75	75	48	23 (10.9%)	0.83 [0.44 to 1.57] *P* = 0.65	1.24 [0.62 to 2.48] *P* = 0.63	
SA + anal Pap	70	51	52	24 (11.3%)	0.87 [0.46 to 1.64] *P* = 0.77	1.30 [0.66 to 2.59] *P* = 0.52	
The complete screening strategy							
SA + HPV-16 genotyping + anal Pal	86	67	59	27 (12.7%)	Ref.	1.48 [0.76 to 2.92] *P* = 0.27	

CI = confidence interval; HGAIN = high-grade intraepithelial neoplasia; HRA = high-resolution anoscopy; N = number of participants; OR = odds ratio; SA = standard anoscopy.

HGAIN = high-grade intraepithelial neoplasia; HIV = human immunodeficiency virus; HR = hazard ratio; MSM = men who have sex with men; MSW = men who have sex with women; N = number of participants.

Table 11: Summary of Findings of Included Economic Evaluations

Main Study Findings	Authors' Conclusion
Ehrenpreis and Smith, 2018[21]	

Economic evaluation that examined the cost-effectiveness of screening for anal HPV using a combination of HPV testing and anal cytology in women with histories of cervical cancer.

Model estimates of cumulative anal cancers and anal cancer deaths for both screened and unscreened cohorts

Year	Cumulative anal cancers		Cumulative anal cancer deaths	
	Unscreened population	Screened population	Unscreened population	Screened population
0	0	0	0	0
1	113	113	0	0
2	239	239	9	9
3	388	366	29	29
4	557	494	61	60
5	744	620	108	101
6	945	743	169	152
7	1,157	864	248	214
8	1,379	980	344	285
9	1,607	1,093	458	367
10	1,841	1,202	592	458
11	2,078	1,306	744	557
12	2,317	1,406	917	666
13	2,557	1,501	1,109	782
14	2,796	1,593	1,321	907
15	3,034	1,680	1,554	1,039
16	3,271	1,762	1,805	1,179
17	3,504	1,841	2,077	1,325
18	3,735	1,916	2,368	1,478
19	3,961	1,987	2,678	1,637
20	4,184	2,055	3,006	1,802

Credit: Adapted from Ehrenpreis ED and Smith DG. *Papillomavirus Research. 2018;5:38-45*: https://www.ncbi.nlm.nih.gov/pubmed/29272853 Licensed under:: https://creativecommons.org/licenses/by/4.0/

Model estimates for cost-effectiveness of the anal cancer screening intervention (all values are assumed to be in US dollars, although this was not explicitly stated in the study)

	Costs in the unscreened group (cancer care)	Costs in the screen group (screening and treatment costs)	Cost difference	Cost per anal cancer prevented	Cost per anal cancer death prevented	Cost per quality of life year saved
5 years	$54,418,071	$73,650,033	$19,231,962	$291,409	$3,205,127	$71,229
10 years	$165,859,480	$194,217,145	$28,357,665	$168,796	$210,057	$9,785
20 years	$536,526,508	$567,969,558	$31,463,030	$98,631	$26,133	$1,687

Credit: Adapted from Ehrenpreis ED and Smith DG. *Papillomavirus Research. 2018;5:38-45*: https://www.ncbi.nlm.nih.gov/pubmed/29272853 Licensed under: https://creativecommons.org/licenses/by/4.0/

Results of sensitivity analysis comparing different cure rates of anal high-grade squamous intraepithelial lesions with electrocautery techniques (all values are assumed to be in US dollars, although this was not explicitly stated in the study)

"In summary, woman with a new diagnosis of cervical cancer that are screened for anal HPV infection, monitored for anal cytology, and treated for anal HSIL will benefit from prevention of anal cancer and anal cancer deaths and will have decreased cost of care. Clinical trials are needed to validate these findings. Healthcare providers are encouraged to be diligent in evaluating patients with cervical cancer having anorectal complaints. It is critical to appreciate their risk for anal HPV infection and to prevent the potential consequences of these infections."[21] (p. 44)

Table 11: Summary of Findings of Included Economic Evaluations

Main Study Findings	Authors' Conclusion

Cure rate of anal high-grade dysplasia	Cost per life year saved		
	5 years	10 years	20 years
0.38	$321,194.20	$66,579.65	$27,398.40
0.48	$209,408.02	$41,747.47	$16,634.34
0.58	$150,733.67	$28,669.60	$10,862.67
0.78	$91,251.41	$15,320.73	$4,869.95
0.88	$74,457.50	$11,504.29	$3,128.97
0.98	$64,371.75	$8,806.70	$1,518.24

Credit: Adapted from Ehrenpreis ED and Smith DG. *Papillomavirus Research. 2018;5:38-45*: https://www.ncbi.nlm.nih.gov/pubmed/29272853 Licensed under: https://creativecommons.org/licenses/by/4.0/

Cromwell et al., 2016[22]

Economic evaluation that estimated the cost-effectiveness of adding anal cancer screening with anal cytology to routine follow-up for women in British Columbia with a history of cervical intraepithelial neoplasia (CIN). In the base care, screening occurred in year one and year two, followed by every three years until year 20. Alternative screening strategies (i.e., screening every year for the first five years and screening only once as the populations entered the model) were also considered in the analysis.

Model estimates of cost-effectiveness for the base case and alternative screening strategies versus the unscreened population (all values are expressed in 2014 Canadian dollars)

	Incremental cost	Life years gained	QALYs	Mean ICER	Cost per cancer avoided
Baseline	$82.17	0.004	−0.0364	$20,561/LYG	$67,933
Scenario A (5 years of screening)	$68.25	0.002	−0.0195	$29,673/LYG; dominated	$148,532
Scenario B ("One-off" screening)	$13.06	0.0007	−0.0037	$52,602/LYG; dominated	$102,806

Credit: Adapted from Cromwell I, et al. *BMC Health Services Research. 2016;16:206*: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4924299/ Licensed under: https://creativecommons.org/licenses/by/4.0/

In order to account for the uncertainty in model parameters, sensitivity analyses were conducted by adjusting model inputs to 50 and 150% of their base case values. The parameter changes which resulted in the greatest increases to the resulting cost per LYG were time horizon, likelihood of early stage anal squamous cell carcinoma, and sensitivity of Pap test.

The cost-effectiveness acceptability curves suggested that screening became cost-effective at a willingness-to-pay threshold of C$45,500 per life-year gained.

"The addition of anal Pap cytology to regular follow-up for women with detected CIN II/III lesions was shown to be 95 % cost-effective at a WTP threshold of $45,500/LYG. The low incremental effectiveness in terms of LYG is matched by low incremental costs. The analysis did not find a difference in terms of quality-adjusted survival, suggesting that it may not be cost-effective when QALYs are considered."[22] (p. 9)

CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesions; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year; WTP = willingness-to-pay.

Appendix 5: Additional References of Potential Interest

Randomized Controlled Trials

Alternative Comparator

Wiley DJ, Hsu HK, Ganser MA, et al. Comparison of nylon-flocked swab and Dacron swab cytology for anal HSIL detection in transgender women and gay, bisexual, and other men who have sex with men. *Cancer Cytopathol*. 2019 Apr;127(4):247-257.
PubMed: PM30913381

Review Articles

Diefenthaler VL, de Fatima Pavan Zanella J, Coser J. Screening anal cancer in women living with HIV/AIDS. *J Coloproctol (Rio J).*2018;38(3):233-239:
http://www.scielo.br/pdf/jcol/v38n3/2237-9363-jcol-38-03-0233.pdf

Gosens KC, Richel O, Prins JM. Human papillomavirus as a cause of anal cancer and the role of screening. *Curr Opin Infect Dis*. 2017 Feb;30(1):87-92.
PubMed: PM27845952

Wasserman P, Rubin DS, Turett G. Review: Anal Intraepithelial Neoplasia in HIV-Infected Men Who Have Sex with Men: Is Screening and Treatment Justified? *AIDS Patient Care STDS*. 2017 Jun;31(6):245-253.
PubMed: PM28530494

Leeds IL, Fang SH. Anal cancer and intraepithelial neoplasia screening: A review. *World J Gastrointest Surg*. 2016 Jan 27;8(1):41-51.
PubMed: PM26843912

Long KC, Menon R, Bastawrous A, Billingham R. Screening, Surveillance, and Treatment of Anal Intraepithelial Neoplasia. *Clin Colon Rectal Surg*. 2016 Mar;29(1):57-64.
PubMed: PM26929753

Wells JS, Holstad MM, Thomas T, Bruner DW. An integrative review of guidelines for anal cancer screening in HIV-infected persons. *AIDS Patient Care STDS*. 2014 Jul;28(7):350-357.
PubMed: PM24936878

Environmental Scans

Patel J, Salit IE, Berry MJ, et al. Environmental scan of anal cancer screening practices: worldwide survey results. *Cancer medicine*. 2014 Aug;3(4):1052-1061.
PubMed: PM24740973