2021

# Anal cancer: guidelines for screening

BOSTON UNIVERSITY

SCHOOL OF MEDICINE

Thesis

# ANAL CANCER: GUIDELINES FOR SCREENING

by

**JAMES ALAN GARDNER**

B.S., Georgia College & State University, 2013

Submitted in partial fulfillment of the

requirements for the degree of

Master of Science

2021

Approved by

First Reader _____

Elizabeth Stier, M.D.
Professor of Obstetrics & Gynecology

Second Reader _____

Mina Moussavi, Ph.D.
Assistant Professor of Physiology & Biophysics

## DEDICATION

I would like to dedicate this work to my wonderful dog. She was my rock for the past 15 years. May you forever happily adventure and chase those furry critters in the sky mountains. You are dearly missed by all who met you sweet Dezi-boo-bear Marie.

Adopted: Summer of 2016

Passed: 6/19/2021

**ANAL CANCER: GUIDELINES FOR SCREENING**

**JAMES ALAN GARDNER**

ABSTRACT

Squamous Cell Carcinoma of the Anus (SCCA) is a rare cancer that is heavily associated with high-risk human papillomavirus infection (HRHPV) of the squamocolumnar junction (SCJ) of the anus. Treatment of SCCA ranges from chemotherapy and radiation for early stage cancer, and surgical interventions such as abdominoperineal resection for later stage cancer. Patients who present with late-stage metastatic SCCA have a five-year survival rate of 32%, emphasizing the crucial need for early detection. Given its rarity in the general population (approximately 1 to 2 cases per 100,000 people), screening guidelines to allow for early detection of SCCA have not been fully established, and remains the subject of continuous debate amongst clinicians, researchers, and public health practitioners.

A major challenge in establishing SCCA screening guidelines is slow progression of symptoms. 20-33% of patients diagnosed with SCCA were clinically asymptomatic at the time of their diagnosis. Patients who reported symptoms usually noted mild symptoms, which mimicked ones found in other anal disorders. For instance, early stage cases of SCCA frequently manifest as bleeding in the anus, but in the absence of other serious symptoms, patients and clinicians often assume hemorrhoids as a cause.

As SCCA is a rare disease with that frequently presents with seemingly benign symptoms, if any, few studies have addressed the complexities of concerns in regards to preventive screening of SCCA. Using “Principles and Practice of Screening for Disease”

by Wilson and Jungner, this thesis intends to discuss known screening strategies for SCCA and explore knowledge gaps in need of further study before definitive guidelines for SCCA screening can be established.

Wilson and Jungner do not specifically address the issue of SCCA; rather, they provide a framework for establishing guidelines for disease screening. This thesis will examine the current understanding of SCCA gained in literature and will apply them to the ten tenets that Wilson and Jungner uphold as necessary criteria that should be considered in order to craft an appropriate screening methodology for a specific disease. These tenets address issues ranging from the severity of the disease in question, available treatments for the disease, and the economic perspective relating the cost of screening to the cost of treatment and management.

Analysis of the ten tenets of Wilson and Jungner in relation to SCCA has revealed the need for the cancer research community to gain a better understanding of the role of high-grade intraepithelial lesions, which may act as a precursor to the development of SCCA; however, a significant portion of persons afflicted with HSIL have demonstrated the ability to spontaneously clear them. In addition, this thesis identified a need to gain a better understanding of HPV, especially in chronic variants. Further research to develop SCCA screening guidelines should also evaluate and weigh the effectiveness and practicality of different screening techniques; certain techniques such as anal cytology may be easily implemented on a massive scale, but may be less accurate.

Though a rare disease, the progressive yearly increase in incidence (2.2% per year) of SCCA indicates that comprehensive screening guidelines are urgently needed. Using an

analysis of a tried and true framework for establishing disease screening guidelines set by Wilson and Jungner, this thesis intends to contribute to the development of a standardized set of screening guidelines for SCCA. In doing so, we hope to allow SCCA to be managed in a manner that minimizes the impact on patients' quality of life in a cost-effective manner.

## TABLE OF CONTENTS

## LIST OF TABLES

## LIST OF FIGURES

## LIST OF ABBREVIATIONS

AIN ..... Anal Intraepithelial Neoplasm

ANCHOR.....Anal Cancer HSIL Outcomes Research

ASCUS.....Atypical Squamous Cells of Undetermined Significance

ASCH.....Atypical Squamous Cells cannot exclude High-grade

CI.....Confidence Interval

CIN..... Cervical Intraepithelial Neoplasm

CT ..... Computed Tomography

DARE..... Digital Anal Rectal Exam

DNA..... Deoxyribonucleic Acid

GBM .....Gay and Bisexual Men

HIV .....Human Immunodeficiency Virus

HPV.....Human Papilloma Virus

HRA ..... High Resolution Anoscopy

HRHPV ..... High Risk Human Papilloma Virus

HSIL..... High-grade Squamous Intraepithelial Lesion

IR..... Incidence Ratio

LSIL .....Low-grade Squamous Intraepithelial Lesion

MRI .....Magnetic Resonance Imaging

MSM ..... Men who have Sex with Men

PET .....Positron Emission Tomography

SCCA ..... Squamous Cell Carcinoma of the Anus

SCJ .....Squamocolumnar Junction

SIL.....Squamous Intraepithelial Lesion

SOTR ..... Solid Organ Transplant Recipients

SPANC..... Study of the Prevention of Anal Cancer

# INTRODUCTION

Determining guidelines for screening for any particular disease is a challenging and complex task. However, screening guidelines are often necessary in the prevention, diagnosis, and follow-up of disease. When determining guidelines, one must also account for the individual, community, and population level determinants of disease, the available infrastructure, and the acceptability of said screening test by patients and providers, alike. Without considering all of these facets, the guidelines will be subject to noncompliance, which could result in a null effect towards the patients' health or worse. This thesis will focus on the above concerns in relation to one specific disease, squamous cell cancer of the anus (SCCA).

SCCA is considered a rare cancer (1 to 2 cases per 100,000 people) in the general population (Bray et al., 2018). But, the incidence [or rate] is increasing by about 2.2% per year (Bray et al., 2018). For rare cancers, it is important to know the risk factors of the disease to have a better chance at screening the appropriate people and not wasting resources blindly screening the masses. Although there is a low incidence in the general population, certain specific populations have a much higher incidence of SCCA. (Eng, 2016).

For example, human immunodeficiency virus (HIV) is associated with an astounding increase of risk for SCCA by over 30 times that of those not living with HIV (Grulich et al., 2007). Most alarmingly, in the subset of the general population of men who have sex with men (MSM) and are living with HIV, there is an incidence ratio of 85 per 100,000 person-years, with a 95% confidence interval equal to 82-89 (Clifford et al., 2020).

Transplant recipients are another high-risk, immunocompromised group that also show an increased risk of SCCA (Eng et al., 2019). Transplant recipients have over 10 times the risk of developing anal cancer than that of non-transplant recipients (Eng et al., 2019).

Approximately ninety-percent of anal cancers are associated with high-risk human papillomavirus (HR-HPV) infection of the anus (Poynten et al., 2020). This human papillomavirus (HPV) infection occurs at the anal transformation zone where the squamous anal epithelium transitions to columnar rectal epithelium. This transitional zone is referred to as the squamocolumnar junction (SCJ) (Clarke & Wentzensen, 2018).

SCCA, is a low incident and high morbidity disease that is frequently diagnosed at an advanced stage. There are many reasons for this, which could include the range of symptoms e.g. simply avoiding care due to the nature of the symptoms and/or potential stigma associated with the symptoms or the disease. However, it is interesting to note that of those who are diagnosed, roughly 20% - 33% of patients with SCCA will present initially as clinically asymptomatic, when diagnosed (Osborne et al., 2014).

The majority of individuals who do have symptoms, will have a range of symptoms that tend to mimic other anal disorders or are similar enough to cause the diagnosis to oftentimes be delayed beyond their initial seeking of care. The largest group of people experiencing symptoms will present with bleeding, which is frequently falsely attributed to hemorrhoids. (Osborne et al., 2014).

The next largest group of individuals experiencing symptoms, will show signs of anal pain and/or discomfort, especially from palpation of any existing anal mass. Furthermore, the range of symptomatology can cause other individuals to display

symptoms from bowel movements disorders such as diarrhea or incontinence, to more physically structural based symptoms such as fissure or a fistula (Osborne et al., 2014). Yet, some individuals may simply be suffering from an experience of anal itching, termed anal pruritus (Tanum et al., 1991). Each of these symptoms could be tell-tale of any range of anal disorders, most commonly hemorrhoids, and those disorders will likely be investigated before a provider will consider SSCA, as part of their differential diagnosis.

Once anal cancer is diagnosed by histology on biopsy, the appropriate treatment will be determined, from the stage of the disease. The process of staging anal squamous cell cancer begins with a range of different imaging modalities to determine certain aspects of the disease progression such as the size of the tumor, or the existence of any loco-regional disease (Morton et. al, 2018).

The imaging methods often used for varying regions of the body of concern for metastasis of anal cancer are as follows: for the rectum, imaging methods may include translational ultrasound and/or magnetic resonance imaging (MRI); for nearby regional areas such as the pelvis, the abdomen, and/or the chest, computed tomography (CT) and positron emission tomography (PET) will occur to investigate distant disease (Morton et. al, 2018).

Guidelines for staging an SCCA tumor involve size, nodal status, and metastatic disease. For instance, a stage I tumor will be less than 2 cm in diameter and will not have any lymph node involvement or distant disease present (Morton et. al, 2018). A stage II tumor will be similar to a stage one tumor, but will be larger. In more specific terms, it will be greater than 2 cm in diameter, will not involve any nearby organs, or lymph nodes, and

will not have any distant disease present (Morton et. al, 2018). Beyond a stage two tumor, the staging of anal cancer will involve more than the size of the tumor and will begin to involve regional disease. For example, a stage III tumor will invade nearby organs and/or will involve regional lymph nodes, but will not have any distant disease (Morton et. al, 2018). A stage IV tumor is the point at which an anal cancer tumor will have distant disease present (Morton et al., 2018).

Despite the delays in the diagnosis of SCCA due to the symptomology mimicking other anal disorders such as external or internal hemorrhoids, metastatic disease will be present in less than 20% of cases, at time of diagnosis (Eng et al., 2019). The standard treatment of anal cancer involves chemotherapy, with the use of Mitomycin-C and radiotherapy, which is generally effective in lower stage cancers, but is frequently associated with substantial short-term and long-term toxicity to the patient (Morton et. al, 2018). The shorter term side effects may include dermatitis, weakness, swelling, pain, or tenesmus, which is an inaccurate feeling of needing to pass stool (Morton et. al, 2018).

Longer-term side effects may include problems such as anal stenosis, infertility, painful intercourse, lymphedema, fistula, or radiation proctitis (Morton et. al, 2018). Furthermore, radiation of the anal canal is contraindicated in patients who have received radiation of the pelvis as a treatment before and therefore, alternative treatments must be considered. Sometimes these alternative treatments result in an initial abdominoperineal resection (Morton et al., 2018). Unfortunately, 20 to 30% of these cancers will relapse within the next two years or will fail to respond to the treatment from the onset. This standard of treatment is also not as effective in later stage cancer (Eng et al., 2019).

Later stage cancer commonly requires treatments that have a higher negative impact on quality of life and that have an associated higher morbidity, like surgical abdominoperineal resection, requiring the future use of a colostomy bag (Leeds & Fang, 2016). Also, while early stage SCCA generally has a decent prognosis, later stage anal cancer does not. When patients present with metastatic disease, even with chemotherapy and radiation, SCCA has a five-year survival rate of 32% (Morton et. al, 2018).

With such high morbidity for late stage anal cancer, prevention or detection of early cancers may save at-risk individuals significant hardship. A real emphasis is necessary for screening the appropriate patients to diagnose the disease earlier or even potentially prevent anal cancer in as many individuals as possible.

Because cervical cancer and SCCA both share many similarities in natural disease progression (Schiffman et al., 2011), as we will discuss later in **Subsection 3,** it has been proposed that given the similarities between cervical and anal cancers, measures used to prevent cervical cancer may also work to prevent anal cancer.

Let us take a moment to consider screening in the context of prevention. Currently, there are different levels of possible prevention for SCCA, the first being primary prevention. Primary prevention methods target the prevention of HPV infection or persistence of the virus, the same as in cervical cancer prevention. This may occur via the usage of vaccines, which could prevent the initial infection with HPV. These prophylactic vaccines are most effective when administered prior to the onset of sexual activity (Eng et al., 2019).

Usage of just such vaccines have shown success in reducing HPV in Australia, with reports showing as much as a 77% reduction in the HPV subtypes specific to cervical cancer. Unfortunately, HPV vaccine rates have been much lower in the United States. Only 49% of the 66% of U.S. adolescents, who receive the vaccine, completed the vaccination dosage series (*Human Papillomavirus (HPV) and Cancer | CDC*, 2020).

Secondary prevention would target the precancerous lesions caused by HPV and treat them. These lesions are Anal Intraepithelial Neoplastic lesions (AIN) (Eng et al., 2019). The idea is that treating the lesions may help prevent their progression into tumors, similar to treating Cervical Intraepithelial Neoplastic lesions (CIN). Currently, secondary prevention methods (if they occur at all) only happen for a small fraction of people who fall into one or more of the aforementioned high-risk categories, such as MSM living with HIV (Eng et al., 2019).

The main management methods for AIN mentioned in this thesis are both for the cancer itself and for the AIN lesions. The general workup includes a digital anal rectal examination (DARE), anal cytology (i.e. anal Pap test), and high resolution anoscopy, described in detail in **Subsection 3**. If any potential lesions are noted, they will be biopsied with management considerations based on biopsy results. (Goldstone et al., 2011).

Now that background on squamous cell cancer of the anus and the main prevention/evaluation methods have been discussed, we can move forward into the specific aims of this thesis in regards to screening for the disease, the information required to better understand what knowledge gaps exist -in regards to the possibility of setting guidelines in screening for anal cancer, and how we can address them.

## Specific Aims

Few detailed papers have been written on the complexities of concerns in regards to screening for disease. A commonly cited article by Wilson and Jungner, "Principles and Practice of Screening for Disease" is one such article that outlines considerations that should be made when creating screening protocol for any disease (Wilson & Jungner, 1968).

This thesis will use the considerations outlined by Wilson and Jungner, to discuss what is known about screening for squamous cell carcinoma of the anus, with the intention of finding areas that need further research, thought, or infrastructure before considering the possibility of official guidelines in anal cancer screening. More explicitly, official guidelines do not currently exist for screening for squamous cell anal cancer. Through this review, knowledge gaps that need to be addressed before such guidelines should be considered will be highlighted (Nyitray et al., 2020).

## Methods

Wilson and Jungner highlight ten main criteria that need to be considered before determining the most appropriate screening methodology for any specific disease. (Wilson & Jungner, 1968). In this paper, these ten tenets will be addressed in regards to squamous cell cancer of the anus. However, they will be slightly modified. These changes will include subsections one through nine, one subsection for each tenet except that two have been combined. Also, the order in which some of these tenets have been addressed have been

altered, from the original Wilson & Jungner text, as an adaptation to explain more on the natural history/disease progression of squamous cell anal cancer to the reader more promptly, and to improve the flow of information in regards to SCCA.

The original tenet, "The disease should be well understood, specifically the manner of disease progression or the natural history of the disease, this includes the development or transition from latent stage to a stage of declared disease" and the original tenet, "In the disease progression, there should be a feasible point screening and/or treatment such as a latent or early symptomatic period" have been combined to streamline the analysis.

This resulted in the following nine subsections: 1. Principles of Early Disease Detection (Screening); 2. The natural history of squamous cell cancer of the anus & recognizable latent or early symptomatic stage(s) of the disease for screening/intervention/treatment; 3. Suitable test or diagnostic; 4. Screening tests should be acceptable to the population; 5. There should be an accepted treatment for people with disease; 6. There should be an agreed upon policy on whom to treat for disease; 7. Facilities for diagnosis and treatment should be available; 8. There should be an economic balance between case-finding diagnostics & treatment in comparison to medical care on a whole; and 9. Screening should remain a continuous process.

Lastly, information for the analysis was found via searching peer reviewed articles on Google Scholar and PubMed, through the Boston University Alumni Medical Library portal, and from the websites of various studies specific to anal cancer, anal cancer screening, or anal cancer prevention. Also, some information was found via organizations that present information on anal cancer data as detailed later in the analysis, i.e. the Anal

Cancer HSIL Outcomes Research (ANCHOR) and Study of the Prevention of Anal Cancer (SPANC) studies.

One should note that screening for anal cancer is a relatively new concept and many of the gaps in knowledge are due to this, but this thesis should help to provide insight on the next steps in establishing considerations for screening protocol in the future. This paper shall accomplish this by highlighting not only areas that need to be addressed, but also areas of knowledge that are in the midst of being addressed -and for those areas, the studies which are currently being conducted and/or analyzed have been specifically mentioned, i.e. the ANCHOR study. For the purposes of this thesis, their results have been assumed non-concluded and therefore are not included in the analysis beyond mentioning what the study is specifically intending to address and how they help address current gaps in knowledge.

## LITERATURE REVIEW

### Subsection One: Principles of Early Disease Detection (Screening)

We will begin as the process is described in "Principles and Practice of Screening for Disease" by Wilson and Jungner. First and foremost, the specific condition or disease of interest should be an important health problem to the population at large (Wilson & Jungner, 1968). When considering what is "important" it helps to clarify that term in regards to disease.

Being designated as an important health problem does not necessarily mean that the disease must have a high prevalence or high rates of mortality, but there does need to

be serious consequences for those who contract said disease (Wilson & Jungner, 1968). These consequences could be in the form of time required for treatment, negative effects on quality of life, expenses for treatment or travel related to diagnosis and treatment, or any of a myriad of considerations that ultimately have the potential to significantly alter one's life in a negative manner (Wilson & Jungner, 1968).

To better explain the important health problem considerations for anal cancer we will begin with the epidemiology of the disease and then continue into further detail as the paper continues. We will approach this tenet in that manner because many of the concerning aspects of the disease that also categorize it as an important health problem will fall into future tenets as well and will be better explained in those categories.

In the case of anal squamous cell carcinoma, there are approximately 1-2 new cases per 100,000 person-years (Clifford et al., 2020). This amounts to approximately 29,000 cases of squamous cell anal cancer worldwide, per year (de Martel et al., 2020). Furthermore, the incidence of anal cancer is currently on the rise (Poynten et al., 2020).

More specifically, the incidence is highest in gay and bisexual men (GBM) living with HIV. There are recent reports that show incidence rates that have exceeded 100 per 100,000 person-years for those living with HIV and MSM or GBM (Poynten et al., 2020). This is a stark increase from the previously mentioned, recognized incidence rate of one to two cases per 100,000 person-years. Other studies also support this claim and further the special population considerations to specifically MSM (Machalek et al., 2012) and are living with HIV (Clifford et al., 2020) (Grulich et al., 2007), MSM not living with HIV, Non-MSM males living with HIV, Females living with HIV, women with HPV related

gynecological cancers or precancerous lesions, and Iatrogenically immunosuppressed patients (Clifford et al., 2020). For many of these special populations, differences in incidence by age were noted, with older ages associated with higher incidence.

Because age appears to correlate with anal cancer incidence, MSM living with HIV was subcategorized by age so that those with an age less than 30 years had an anal cancer incidence rate (IR) of 16.8 per 100,000 person-years with a 95% confidence interval (CI) of 11.5-23.8. Those with an age between 30 and 44 years had an IR of 66.2 with a 95% CI of 60.7-72.0 per 100,000 person-years. Those with an age between 30 and 44 years had an IR of 99.7 with a 95% CI of 92.5-107.4 per 100,000 person-years. Those with an age equal to 60 or above had an IR of 107.5 with a 95% CI of 89.3-128.2 per 100,000 person-years (Clifford et. al, 2020).

Non-MSM males living with HIV were also subcategorized by age and those less than 30 years of age showed an anal cancer IR of 2.0 with a 95% CI of 0.2-7.3 per 100,000 person years. Those between the ages of 30 and 44 had an IR of 26.6 with a 95% CI of 22.2-31.6 per 100,000 person-years. Those aged 45 to 59 had an IR of 36.5 with a 95% CI between 32.1-41.3 per 100,000 person-years. Finally, those equal to or above the age of 60 showed an IR of 34.0 with a 95% CI of 25.1-44.9 per 100,000 person-years (Clifford et. al, 2020).

For females living with HIV, those with an age less than 30 years of age showed an anal cancer IR of 4.7 with a 95% CI of 1.9-9.6 per 100,000 person years; those between the ages of 30 and 44 had an IR of 17.1 with a 95% CI of 13.8-21.0 per 100,000 person-years; those aged 45 to 59 had an IR of 29.7 with a 95% CI between 24.9-35.1 per 100,000

person-years; and Finally, those equal to or above the age of 60 showed an IR of 23.0 with a 95% CI of 13.9-36.0 per 100,000 person-years (Clifford et. al, 2020).

Pooled IRs for women with CIN3 were subcategorized by age as well and for women between the ages of 18 and 39 the anal cancer IR was 1.3 with a 95% CI of 0.8-2.0 per 100,000 person years. For those aged 40 to 59, the IR was 8.1 with a 95% CI of 6.8-9.7 per 100,000 person years. Finally, for those age 60 and above the anal cancer IR was 15.0 with a 95% CI of 11.4-19.4 per 100,000 person years (Clifford et. al, 2020).

Women with HPV related gynecological cancers or precancerous lesions (Gilbert et al., 2019) were subcategorized into three main groups based on the type of gynecological cancer, those with vulvar cancer, those with cervical cancer, and those with vaginal cancer and precancerous lesions (Clifford et. al, 2020). In women with vulvar cancer, the IR of anal cancer was 48 per 100,000 person-years (95% C.I. = 38 - 61). In women with cervical cancer, the IR of anal cancer was 9 per 100,000 person-years (95% C.I. 8 - 12). And in women with vaginal cancer and precancerous lesions, the IR of anal cancer was 10 per 100,000 person-years (95% C.I. = 3 - 30) (Clifford et. al, 2020).

A figure created by Clifford et. al, 2020, for their paper "A Meta-Analysis of Anal Cancer Incidence by Risk Group: Toward a Unified Anal Cancer Risk Scale" does a great job is showing visually the differences in incidence of anal cancer by different risk categories. As you can see in **Figure 1**, MSM who are living with HIV and above the age of 30 -especially above the age of 45, show a much greater incidence rate than is seen for any other risk category. For non-MSM males and all females, those living with HIV also show the highest incidence of anal cancer. It is also interesting to note that for females with

gynecological cancers and pre-cancers and for non-HIV immunocompromised organ transplant recipients of over ten years, the incidence of anal cancer is higher than it is for non-MSM males and females living with HIV (Clifford et al., 2020).

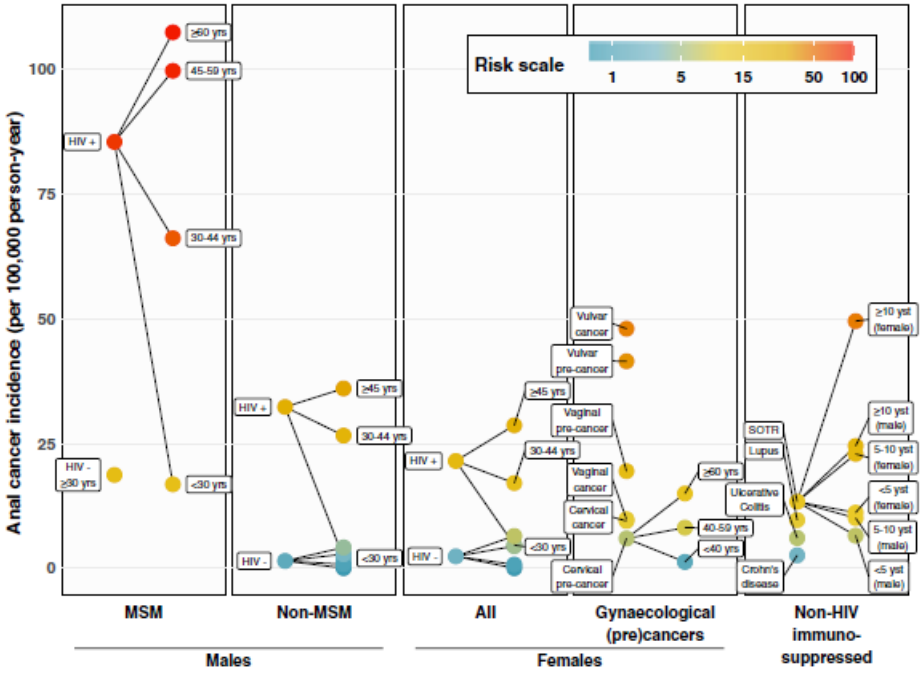


**Figure 1 Incidence by Risk Category:** This figure depicts the varying levels of incidence for anal cancer in different risk group categories for both males and females (Clifford et. al, 2020).

Other higher risk groups included iatrogenically immunosuppressed patients such as solid organ transplant recipients (SOTRs) (Grulich et al., 2007), patients with systemic lupus erythematosus, and patients with ulcerative colitis. The iatrogenically immunosuppressed patients overall showed an anal cancer incidence of 13 per 100,000 person-years (95% C.I. = 12-15), but when broken down by gender and by the amount of time that had passed since their organ transplant, the anal cancer incidence was up to 24.5

per 100,000 person-years for males who had an organ transplant over ten years prior. For females, the anal cancer incidence was up to 49.6 per 100,000 person-year when their organ transplant occurred over ten years prior.

This information showed that the number of years that had passed since the organ transplant was more relevant to this high-risk category than other factors such as age alone (Clifford et al., 2020). Also, squamous cell carcinoma of the anus had an incidence of 10 per 100,000 person-years (95% C.I. = 5 - 19) for patients with systemic erythematosus, 6 per 100,000 person-years (95% C.I. = 3 - 11) for patients with ulcerative colitis, and 3 per 100,000 person-years (95% C.I. = 2 - 4) for patients with Crohn's disease (Clifford et al., 2020).

## Subsection Two: The Natural History of Squamous Cell Cancer of the Anus and Recognizable Latent or Early Symptomatic Stage(s) of the Disease for Screening/Intervention/Treatment

Wilson and Jungner continue to describe that, in regards to formulating screening guidelines, the natural history of a said condition and the development of the disease from a latent stage to a declared state of disease should be understood. Furthermore, there should be a recognizable latent stage or recognizable early symptomatic stage of the disease (Wilson & Jungner, 1968). In regards to anal cancer, the disease progression is from normal mucosa to HPV infection, which may cause low-grade squamous intraepithelial lesions (LSIL). Then the LSIL progresses to high-grade squamous intraepithelial lesions (HSIL). In SCCA, HSIL is the recognizable latent stage of disease.

Eighty-five percent of anal cancer in those not living with HIV, occurs due to HPV 16. For those living with HIV, seventy percent of anal cancers occur due to HPV 16 and of these, approximately one-third were co-infected by other HR-HPV types. Following these persistent infections, progression occurs to pre-cancer or HSIL also known as High-grade Anal Intraepithelial Neoplasia (AIN2/AIN3). These precancerous lesions can then progress to anal cancer (Clarke & Wentzensen, 2018). Finally, HSIL progresses to anal squamous cell carcinoma. But, many aspects of this disease progression are still not very well understood.

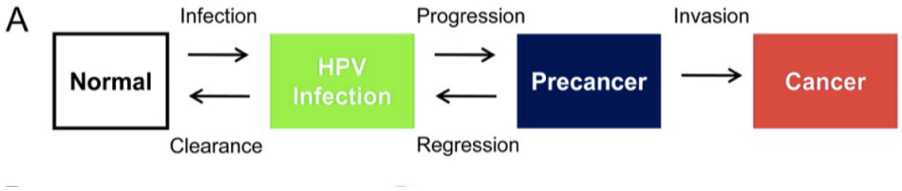


**Figure 2: SCCA Progression:** This figure displays the natural disease progression from normal mucosa to SCCA and how at each stage in between, both progression and regression can occur (Clarke & Wentzensen, 2018).

A large consideration towards this is in the sense that it is not a strictly linear forward progression from LSIL, to HSIL, and then to anal cancer, as can be seen in **Figure 2**. Also, the anal mucosa is known to clear HSIL at a high enough rate that only a small minority of those with squamous intraepithelial lesions (SIL) will have lesions that progress all of the way to anal squamous cell carcinoma. The exact rate at which anal mucosa clears HSIL is not well understood and the analyses of data from the Study of the Prevention of Anal Cancer (SPANC) is underway in Sydney, Australia to help determine the anal mucosa clearance rate for LSIL and HSIL. This study was intended to further describe the natural history of HPV infections including describing the progression and

regression between normal anal mucosa and anal intraepithelial lesions (Poynten et al., 2020).

Some more information on the SPANC study would be beneficial in showing the progress that it has made and the direction of their research. The SPANC study enrolled 617 GBM ages 35 and older. Of their cohort, 220 (35.7%) were living with HIV. During the study, anal cytology and high-resolution anoscopy were performed at baseline and for three consecutive visits, with year-long intervals between the visits (Poynten et al., 2020).

In the SPANC study, the diagnosis of HSIL utilizes both the anal cytology and HRA results histologic results. If either the anal cytology or histology was read as HSIL, then the patient was considered to have composite High-grade Squamous Intraepithelial Lesions (cHSIL). The SPANC study determined the incidence rates and clearance rates of cHSIL. Along with this data, a Cox regression analysis was performed by their team to determine hazard ratios associated with predictors of cHSIL. For all of the analysis above, 95% confidence intervals were also determined (Poynten et al., 2020).

The resulting analysis concluded that 124 cases of composite HSIL occurred over 1097.3 person-years of follow-up or 11.3 cases per 100 years of follow-up, with a 95% confidence interval of 9.5 to 13.5 per 100 person-years. When Cox regression analysis of significant higher incidence predictors was performed, age less than 45 years, living with HIV, a prior SIL diagnosis, and HPV were identified as significant predictors. Also, 153 cases of cHSIL were cleared over 695.3 person-years of follow-up or 22.0 cases of clearance per 100 person-years, with a 95% confidence interval of 18.8 - 25.8 person-years of follow-up. Significant predictors of cHSIL clearance were found by Cox regression

analysis to be: age less than 45 years, AINII instead of AINIII, not having persistent HPV16, and having smaller lesions. Of the whole study, there was only 1 patient whose lesions progressed to cancer (Poynten et al., 2020).

The results of this study suggested that not all anal HSIL requires treatment. It was hypothesized by the investigators that those who did not have persistent HPV were also those who were less likely to benefit from HSIL treatment, because they had higher rates of HSIL clearance than those with persistent HPV (Poynten et al., 2020). It is interesting to note that while the SPANC study determined younger age (35 to 44 years of age) to be associated with the incidence of HSIL, two prior studies reported that age was not associated with HSIL incidence (Burgos et al., 2015; de Pokomandy et al., 2011).

Wilson and Jungner also recommend that it should be known what changes should be considered normal physiological variation versus pathological change (Wilson & Jungner, 1968). When considering changes to the anal canal, physiological variation exists in the forms of surface area and anal mucosa folds. Pathological changes include condyloma, hemorrhoids, and treatment related scar tissue (Clarke & Wentzensen, 2018).

Next, it is recommended that when determining screening guidelines, that it be known whether or not early pathological variations are progressive (Wilson & Jungner, 1968). In anal cancer, HSIL is progressive and shares similarities with cervical cancer. The main difference at the anus in comparison to the cervix deals predominantly in prevalence and oncogenic potential. There is a twenty-two percent prevalence of anal HSIL in GBM persons not living with HIV and twenty-nine percent anal HSIL prevalence in GBM persons living with HIV. There is a less than two percent prevalence of cervical HSIL in

the general population (Poynten et al., 2020). Of these, roughly 1 in 80 will progress to cancer (McCredie et al., 2008) whereas, most anal HSIL will never progress to anal cancer (Poynten et al., 2020). More specifically, approximately 1 in 377 of those living with HIV and MSM will progress to anal cancer compared to approximately 1 in 4196 in men not living with HIV (Machalek et al., 2012).

### Subsection Three: Suitable Test or Diagnostic

Much of what is known about the natural history of anal squamous cell cancer has been adopted from the much more well understood natural history of cervical cancer. This disease progression also occurs at the cervix and is generally due to HPV infection. Seventy-five percent of cervical cancers arise from infection with HPV 16 and 18 and another fifteen percent of cervical cancers arise from one of the other five carcinogenic HPV strains (Clarke & Wentzensen, 2018).

Cervical HPV can lead to squamous-cell intraepithelial lesions (SIL), also known as Cervical Intraepithelial Neoplasia (CIN), more specifically CIN3 can progress to cancer. Without intervention, approximately one-third of untreated CIN3 lesions will progress to cancer after 20-30 years, which is a much higher rate of progression than is seen from high-grade anal SIL to SCCA (Clarke & Wentzensen, 2018).

Both cancers frequently form at a squamocolumnar junction, a location of epithelial transition where there is a high-turnover of epithelial cells. These areas, at the cervix and at the anus, are both vulnerable to genetic mutations (Schiffman et al., 2011). It

is currently thought that HPV causes DNA mutations in the cells of each cancer's respective regions and they both frequently coexist (Darragh et al., 2012).

As mentioned previously for anal cancer, immunosuppression is an important risk factor, and the same is true for cervical cancer. Also, they both have a very different prognosis for treatment at an early stage of disease versus treatment at a later stage disease (Saslow et al., 2012).

However, the two diseases do differ in respective epidemiology in many regards. Particularly in regards to their incidence in the general population. For example, SCCA and cervical cancer both differ in their trends in diagnosed cases over the past few decades. For example, cervical cancer has shown a decreasing trend since 1976 from 15.1 to 8.6 cases per 100,000 people (Yang et al., 2018). The reduction in cervical cancer cases is attributable to the progressively more routine use of cervical cancer screening, primarily the cervical Papanicolaou (Pap) test which detects cervical precancers, which when treated prevents cervical cancer (Oortmarssen & Habbema, 1995). Therefore, an attempt to swap the trend in anal cancer to be a decreasing trend, as seen in cervical cancer, would likely need to begin with showing an increased emphasis on screening for SCCA. This could potentially decrease the incidence of SCCA, if treatment of high grade lesions is found to be effective in preventing SCCA.

The US Prevention Task Force (USPTF) recommends that screening for cervical cancer women ages 25 to 29 should include cervical cytology every three years, with hrHPV every 5 years, and hrHPV/cervical cytological cotesting every 5 years for women ages 30 to 65. They also do not recommend cervical cancer screening in women below the

age of 21 or above the age of 65 (if they have had appropriate prior screening and are not at high-risk for the disease). The USPTF also recommends against screening women that do not have a history of high-grade cervical SIL or cervical cancer, have had a hysterectomy, and have had their cervix removed (Curry et al., 2018). Screening for cervical cancer has been effective in aiding decreasing cervical cancer by allowing providers to locate high-grade CIN early in the disease process and provides an opportunity to treat the precancerous lesions prior to the development of cervical cancer. Treatment of lesions may proceed by ablative or excisional therapies and if early stage cervical cancer is found at screening, it may be treated with hysterectomy (Curry et al., 2018).

Since much of what is known and/or thought to be true of anal cancer stems from knowledge about cervical cancer, many of the anal cancer evaluation methods also stem from screening methods used in cervical cancer. The main evaluation methods such as digital anorectal exam (DARE) and high-resolution anoscopy (HRA), should be discussed for clarity. This will help to determine what each method is precisely evaluating for and will help to provide background information on how each method functions in determining the presence of anal intraepithelial neoplasms one, two, three, (AIN I, II, or III) or anal cancer itself (Steele et al., 2012).

First, we will cover the digital anorectal exam or DARE, as can be seen in **Figure 3**. DARE involves palpation of the anal canal via a digital exam. During this exam, a clinician will assess sphincter tone and potential lesions, which can present as irregular thickenings in the anal canal, small ulcerated lesions, or as a large exophytic mass(es) (Morton et al., 2018). Historically, studies on DARE suggest a low sensitivity but,

considering the low risks of the exam to patients, it has been added to the existing leading guidelines for those living with HIV, that also have other high-risk criterion for anal cancer (Papillon et al., 1983; Leeds & Fang, 2016).

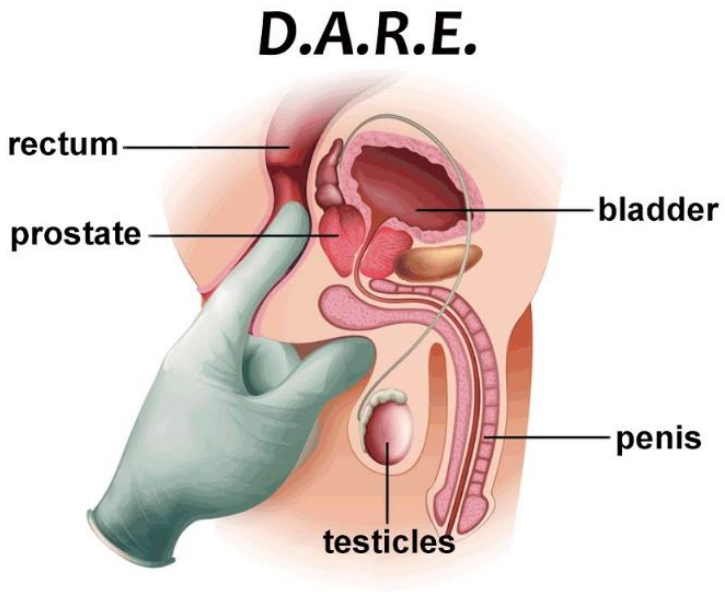


**Figure 3:** This cartoon depicts a cross-sectional view of how a digital anorectal exam is performed. Image (Seventh Planet, 2016).

Second, we will consider the anal pap or anal cytology test. The anal pap test was introduced in the 1990s and shares many of the aspects of design and interpretation as the cervical pap test which is used in screening for premalignant cervical dysplasia (Palefsky et al., 1997). The anal pap test, in similarity with the cervical pap test, functions in a manner where a cellular sample is collected and spread upon a microscope slide for interpretation by a pathologist (Darragh et al, 2012). Most pathologists use the Bethesda System of classification, although many classification systems have been developed (Darragh et al., 2012). In regards to sensitivity and specificity, the anal pap test generally performs similar

to the cervical pap test, but with less accuracy in the high-risk groups for anal cancer (Fox et al., 2005).

Both DARE and anal cytology suffer from their low sensitivity, and therefore another evaluation method, the aforementioned high-resolution anoscopy (HRA), was developed (Palefsky, 2012). It is a variation of standard anoscopy, in which a clear anoscope is inserted into the anus. The anoscope contains a central guidepost that is removed post insertion. Once removed, there is a circular viewing hole to see the mucosa. As the anoscope is removed, in a circular fashion, the mucosa is examined for any masses or lesions (Malik, 2020).

Like anal cytology, high-resolution anoscopy was developed with screening for cervical cancer in mind. In essence, it is similar to colposcopy in many ways. High-resolution anoscopy utilizes a high-magnification microscope in conjunction with a clear anoscope for inspection of both perianal skin and the entire anal canal. To identify anal intraepithelial lesions, 5% acetic acid is used because it turns abnormal cells white (Palefsky, 2012). This color change is termed “acetowhite epithelium.” The application of 5% acetic acid also stems from colposcopy, where it is used to locate cervical SIL. Acetowhite cells do not have to be lesions, however nearly all lesions will show acetowhite characteristics, with the use of 5% acetic acid. Generally, the intensity of whitening is associated with higher-grade SIL (Li et al., 2009).

To aid the usage of 5% acetic acid in determining high-grade anal intraepithelial lesions from low-grade lesions, Lugol’s solution is used after the 5% acetic acid because it is not absorbed well by the higher-grade lesions. This will leave the lesions a lighter color,

while lower grade lesions and non-lesion tissue are stained by the Lugol's solution. This can help a provider distinguish between the low- and higher-grade dysplasia, that is aided in identification by the acetic acid (Palefsky, 2012).

To better understand how high-resolution anoscopy functions, we will take a more detailed look at the process. **Figure 4**, shows an example of the provider's view through a high-resolution microscope used for colposcopy/anoscopy. This image includes designations for the commonly recognized fields of view. These regions can be utilized for noting lesion locations that can be compared to prior imaging, for understanding lesion progression/regression in a patient. These fields are necessary because HRA can be performed on patients that are in different positions such as supine, prone, or laying in the left or right lateral recumbent. Therefore, the orientation of the imaging can change from patient to patient or provider to provider, and the fields act as a method of navigation in an image (Cornall et al., 2015).

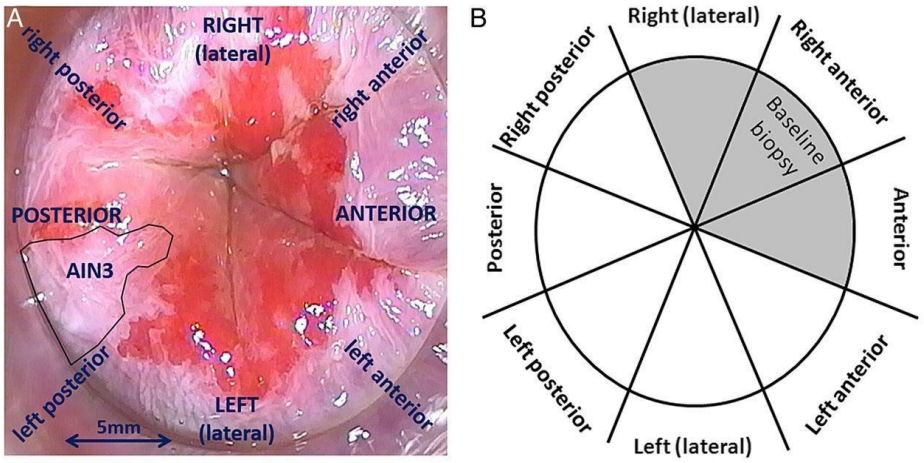


**Figure 4:** A. This image shows the field of view during a high resolution anoscopy. The anal canal's directional fields have been labelled and an AIN3 lesion is notable between the left posterior and posterior fields. B. This image describes the aforementioned directional fields without a high-resolution anoscopy view in the background.

In regards to screening, a suitable test or diagnostic should exist. But, one must consider what makes a good screening test. First, validity is important and can be measured via the metrics of sensitivity and specificity. Essentially, sensitivity is a measure of the false-negative rate and is defined as the accuracy in a screening test for classifying those who are positive for disease as positive for disease. Higher sensitivity is better for screening because you want to capture as many people with the specific disease as possible. With that being stated, a relatively high proportion of false positives can be accepted when screening. Specificity is the metric that is defined as accurately classifying those negative for disease as negative and is a measure of the false-positive rate. Specificity and sensitivity can be varied reciprocally. This means that as sensitivity increases, specificity decreases and vice versa (Wilson & Jungner, 1968).

Considerations towards the reliability and/or efficiency of a screening test should also be considered. For example, when measuring blood pressure, the true arterial pressure may differ from the sphygmometer reading due to variations in the observer's readings. The design of a screening test should be as simple as possible, be able to be carried out rapidly, acceptable to the population of interest, and should cause only minimal pain or discomfort. Another consideration for a screening test is in regards to cost, and they should be minimal (Wilson & Jungner, 1968).

Furthermore, when considering a good screening test for a disease, one should take time to consider its yield, or the amount of previously unrecognized disease that will be brought to treatment. This is most often in relation to the prevalence of the disease in the population of interest, but can also be concerned with the use of medical centers that will need to occur. Yield can also be related to the efficiency of the test itself (Wilson & Jungner, 1968).

Wilson and Jungner bring to light here a concern for the “border-line” problem in which for diseases that have a continuous measurement scale i.e. when measuring blood glucose levels for determining diabetes or blood pressure in determining hypertension status, there will be patients who fall into a gray area where they do not qualify as diseased, yet also are not fully well. Lastly, a screening test may possess a higher margin of error and may be less valid than a diagnostic test (Wilson & Jungner, 1968).

**Table 1. Sensitivity & Specificity of Abnormal Screening Results in the Detection of AIN-II or Greater**

| **Sensitivity & Specificity of Abnormal Screening Results in the Detection of AIN-II or Greater. Data from Clarke & Wentzensen, 2018.** | | | | |
|---|---|---|---|---|
| **Test** | **Risk Category** | **Test Result** | **Pooled Sensitivity** | **Pooled Specificity** |
| **Cytology** | All | ASCUS/ASCH | **77.3%** (95% C.I. = 64.9% - 86.3%) | **55.5%** (95% C.I. = 45.5% - 65.2%) |
| | | LSIL | **60.7%** (95% C.I. = 41.6% - 77.0%) | **74.2%** (95% C.I. = 61.6% - 83.8%) |
| | | HSIL | **26.9%** (95% C.I. = 10.0% - 52.4%) | **94.7%** (95% C.I. = 85.4% - 98.2%) |
| | HIV+ MSM | ASCUS/ASCH | **80.8%** (95% C.I. = 68.7% - 89.0%) | **54.0%** (95% C.I. = 42.1% - 65.5%) |
| | | LSIL | **75.0%** (95% C.I. = 55.4% - 87.8%) | **68.2%** (95% C.I. = 50.5% - 86.8%) |
| | | HSIL | **40.0%** (95% C.I. = 15.1% - 71.5%) | **92.5%** (95% C.I. = 76.0% - 97.8%) |
| | HIV- MSM | ASCUS/ASCH | **43.5%** (95% C.I. = 14.2% - 78.3%) | **75.9%** (95% C.I. = 61.0% - 86.4%) |
| | | LSIL | **23.6%** (95% C.I. = 6.0% - 60.1%) | **88.1%** (95% C.I. = 74.4% - 95.0%) |
| | | HSIL | **6.0%** (95% C.I. = 0.2% - 63.5%) | **98.3%** (95% C.I. = 78.4% - 99.9%) |
| **HR-HPV** | All | Positive | **91.3%** (95% C.I. = 78.9% - 96.7%) | **33.1%** (95% C.I. = 22.4% - 46.3%) |
| | HIV+ MSM | Positive | **95.4%** (95% C.I. = 84.6% - 98.7%) | **23.8%** (95% C.I. = 16.3% - 33.4%) |

| | | | | |
|---|---|---|---|---|
| | Other Risk Groups | Positive | **Insufficient Data** | **Insufficient Data** |
| **Genotyping for HPV16/18 & HR-HPV** | All | Positive | **39.9%** (95% C.I. = 22.4% - 60.5%) | **74.3%** (95% C.I. = 67.3% - 80.1%) |
| | HIV+ MSM | Positive | **41.3%** (95% C.I. = 22.2% - 63.3%) | **68.5%** (95% C.I. = 63.5% - 73.0%) |
| | Other Risk Groups | Positive | **Insufficient Data** | **Insufficient Data** |
| **p16/Ki67 Immunostaining** | All | Positive | **56.6%** (95% C.I. = 27.9% - 81.5%) | **62.3%** (95% C.I. = 47.8% - 74.9%) |
| | Other Risk Groups | Positive | **Insufficient Data** | **Insufficient Data** |
| | | | | |

When looking at **Table 1**, one can see that for all risk categories, the pooled sensitivity of anal cytology decreased as AIN grade increased and pooled specificity decreased. For each grade of AIN, the 95% confidence levels for pooled specificity overlapped for each risk category, respectively (Clarke & Wentzensen, 2018). It is interesting to note that for HIV- males, the 95% confidence intervals of pooled sensitivity for a HSIL test result nearly included zero with a 0.20% result. The 95% confidence intervals for the pooled specificity values of anal cytology for each test result in each risk category respectively, also overlapped (Clarke & Wentzensen, 2018).

For HR-HPV, the test did not differentiate on the grade of AIN, but showed a high pooled sensitivity and low pooled sensitivity for all risk categories and for MSM living with HIV. The 95% confidence levels for each of these overlapped, respectively as well. Of note, there was not sufficient data available in the literature for HR-HPV testing in other

high-risk categories (Clarke & Wentzensen, 2018). Genotyping for HPV16/18 in combination with HR-HPV did not differentiate between grade of AIN, but did show low pooled specificity with overlapping 95% confidence intervals and moderate pooled sensitivity with overlapping 95% confidence intervals for all risk categories and for MSM living with HIV. Genotyping for HPV16/18 in combination for HR-HPV also had insufficient data when evaluating other risk groups. Interestingly, genotyping for HPV16/18 in combination with HR-HPV showed lower pooled specificity and higher pooled sensitivity than HR-HPV testing alone (Clarke & Wentzensen, 2018).

In regards to p16/ki67 immunostaining, it did not differentiate between AIN grade in the manner that anal cytology did. It was the only test with overlapping 95% confidence levels with a positive result for both pooled specificity and pooled sensitivity values in respect to each other (Clarke & Wentzensen, 2018). These results were for all risk categories and there was not sufficient data available to evaluate high risk categories individually. In addition to the insight brought about by the table above, DNA methylation has shown promise in screening for cervical cancer, but not enough studies have been performed for knowing the sensitivity or specificity in anal cancer (Clarke & Wentzensen, 2018).

Most of the difficulty in effective screening occurs due to the difficulty that lies in continuity and communication between those initiating the screening and the personal physicians responsible for the health of said patient. Also, screening exams do not need to be perfect, and a clean screen does not mean a clean bill of health but new symptoms still need to be reported when they arise. Lastly, well organized records can help auxiliary and

laboratory personnel determine who is at risk and needs to be screened (Wilson & Jungner, 1968).

### Subsection Four: Screening Tests Should Be Acceptable to the Population

For a screening test to be useful, it must be acceptable to the population of interest (Wilson & Jungner, 1968). For squamous cell anal cancer, one such screening test is the digital anorectal examination (DARE) (Clifford et al., 2020). DARE is considered essential, but not sufficient in screening for anal cancer (Leeds & Fang, 2016). DARE is suggested by the American Society of Colon and Rectal Surgeons in the initial workup for any patient with a medical history or symptoms concerning for anal cancer (Steele et al., 2012). Abnormal DARE findings necessitate biopsy due to its low sensitivity. However, DARE does have minimal risk (Leeds & Fang, 2016).

Anal cytology via anal pap are often used in screening for anal HSIL and anal cancer as well as diagnostic High Resolution Anoscopy (Clifford et al., 2020). HRA is significantly more invasive than DARE or anal cytology and often causes mild discomfort among those who experience it, however it is the gold standard for its diagnostic capability (De-Masi et. al, 2018).

In an effort to determine how acceptable HRA is, a study of 404 people that received HRA answered a follow up survey to determine acceptability of the exam. 158 patients (39.1%) had greater than or equal to 1 biopsy during the exam (De-Masi et al., 2018). The survey asked them to rate the experience in two main categories, pain and patient satisfaction, and to respond if they would repeat the exam. For pain, the patients

used a 10-point rating scale with 0 being no pain and 10 being severe pain. In men, the median score was 2 (Interquartile Range (IQR) = 3) with n = 261 and 4 (IQR = 3) in women with n = 119 (De-Masi et. al, 2018).

For patient satisfaction, also rated from 0 to 10, the median score was 10 with 76% of respondents answering with a 10. In reference to whether or not they would repeat the exam, 98% of women and 99% of men in this cohort determined that they would be willing to repeat the exam (De-Masi et al., 2018). Although, if the results had been different and with considerations towards the specific high risk populations for anal cancer, HRA could still be used as a screening tool, because examinations that are generally unacceptable, for example proctosigmoidoscopy, can be acceptable for special populations (Wilson & Jungner, 1968).

### Subsection Five: There Should be an Accepted Treatment for People with Disease

For a screening test to be useful in early disease detection and treatment there should be an accepted treatment for said disease and therefore, screen only when prospects for treatment are at least reasonable (Wilson & Jungner, 1968). When speaking on anal cancer one should include that treatment equates to the management of disease and without results from studies indicating that treatment of anal HSIL is efficacious in preventing anal cancer, monitoring the lesions is also optional appropriate management of disease.

The ongoing ANCHOR study will address the current lack of knowledge on the efficacy of treating HSIL in preventing anal cancer. Approximately 5000 people living with HIV age 35 and older with biopsy proven anal HSIL are being enrolled and

randomized to treatment or active monitoring. The study participants are followed every 6 months with anal cytology and directed biopsy. The outcome of interest is diagnosis of SCCA. The study, initiated in 2014 is ongoing and enrollment is continuing at this time (*About the Study*, 2014). Knowledge gained from the ANCHOR study will help determine potential best management practices, especially when combined with knowledge gained from studies such as SPANC, however currently there is not a standardized management for anal HSIL (Clarke & Wentzensen, 2018).

For practitioners who treat anal HSIL, management options depend upon lesion size, provider skills, or the equipment that they have available. Options for treatment include but are not limited to ablation with a Hyfrecator, infrared coagulation, or via patient applied topical therapies such as 5-fluorouracil or imiquimod 5%. Surgical excision is required for larger lesions, but often is not treated due to morbidity associated with said treatment. Specifically, in regards to circumferential intra-anal lesions due to potential pain, anal stenosis, and incontinence (Clarke & Wentzensen, 2018). Therefore, when circumferential or large lesions exist, patients are often recommended for repeat HRA every 4 - 6 months for early detection of progression to anal cancer. These concerning larger lesions more common in persons living with HIV (Clarke & Wentzensen, 2018).

Furthermore, one should consider whether or not treatment at an earlier disease stage than when one would likely seek medical intervention due to symptomatology, will improve the prognosis (Wilson & Jungner, 1968). DARE screens for early cancer and the prognosis for early treatment is much better than in the advanced cancer that would likely be found due to symptomology based visits alone (Abbas et al., n.d.). Treatment of anal

HSIL could prove an earlier preventative treatment for squamous cell anal cancer (Clifford et al., 2020). The ANCHOR study will be a key study to determine the effectiveness in treating such lesions.

### Subsection Six: There Should be an Agreed upon Policy on Whom to Treat for Disease

An important consideration to make when considering screening for a disease is that there should be an agreed upon policy on whom to treat for disease, especially in reference to the "borderline" patients described earlier (Wilson & Jungner, 1968). There does not seem to be consensus on whom to treat at the borderline stage, or of those with anal HSIL i.e. the treatment of AIN3 versus AIN2 or even AIN1 (Macaya et al., 2012).

That having been said, for those meeting definitive disease descriptions, i.e. anal cancer, there is agreement on treatment for anal cancer. There also needs to be a clear policy about treatment in place (Wilson & Jungner, 1968). Currently, there is a lack of knowledge on efficacy for treatment of anal HSIL (Macaya et al., 2012). The ANCHOR study plans to address this knowledge gap and the SPANC trial seeks to determine the occurrence and clearance of anal HSIL, as well as anal cancer in GBM (Poynten et al., 2020).

### Subsection Seven: Facilities for Diagnosis and Treatment Should Be Available

If the proceeding considerations are met, there need be available facilities for diagnosis and treatment of the disease or borderline stage of said disease. Services will

need to be available for definitive diagnosis and treatment if mass screening produces positive results (Wilson & Jungner, 1968). Currently, only 24 out of the 50 U.S. states have HRA providers (*HRA Provider List | Anal Cancer Information*, n.d.).

Barriers to HRA include determinants of disease at the patient-level, provider level, and systems level. Patient-level determinants include beliefs about HPV-related disease or HRA, the ability to engage in care, the internalized stigma associated with anal cancer or potentially comorbidities, and physical discomfort (Apaydin et al., 2018).

At the provider-level, determinants of squamous cell anal cancer include knowledge and expertise in the natural history of the disease and its management, communication skills in reference to a potentially uncomfortable topic and its associated stigmatized comorbidities, and the necessary relationship-building with patients that must occur for success in communication and appropriate follow up (Apaydin et al., 2018).

At the systems-level, societal stigma plays a large role in preventing potential patients from seeking screening or treatment at an early stage of the disease progression. This can also be combined with the lack of available locations for adequate screening and/or treatment along with common healthcare system inefficiencies which lead to a greatly increased burden of disease (Apaydin et al., 2018).

### Subsection Eight: There Should be an Economic Balance Between Case-finding Diagnostics and Treatment in Comparison to Medical Care on a Whole

When looking at the costs of case-finding, including diagnostics and treatment, there should be an economic balance in relation to costs of medical care on a whole. When

considering this, one should address it with two ideas in mind, the medical aim and the economic aim. The medical aim is to improve the overall health of a population through early detection of disease via screening and also through early treatment of said disease (Wilson & Jungner, 1968).

The economic aim consists of a short term and a long term goal. The short term goal is to decrease the associated burden on specialist providers by allowing generalist providers to perform the screening tests. The long term goal is to decrease the burden or existence of said disease through early detection and treatment, thus allowing for more productive years of life for members in the population (Wilson & Jungner, 1968).

A consideration should be made that screening may save a specialist physician's time, especially if it is being allocated as a responsibility to a primary care professional, but said screening measures may also increase the medical workload on the system due to finding more disease. (Wilson & Jungner, 1968).

Applying these thoughts to SCCA one can turn to a study conducted by Assoumou et al. This specific study was conducted to assess the cost effectiveness of different assessments for recurrence, after treatment for HSIL, in high-risk patients. They found that combining HRA and cytology at the six and twelve-month time gaps was the most cost effective strategy in ninety-one percent of their simulations. This also maintained the costs of care well below the one-hundred thousand dollars per quality adjusted life year (QALY) threshold (Assoumou et al., 2013).

### Subsection Nine: Screening Should Remain a Continuous Process:

Finally, Wilson and Jungner make a point that the case-finding process, or screening, should remain an active process and should not be completed in a once-and-for-all sense. They make this argument to highlight that single screening exams only catch individuals with disease at that time point and do not account for future incidence in that same person (Willson & Jungner, 1968).

This is important to highlight in regards to squamous cell anal cancer because of the unknowns surrounding anal HSIL clearance. As the current ANCHOR and SPANC trials draw to an end, we may have more light to shed on these unknown facets of anal cancer progression, but for now it is important to remember that high-risk patients who screen negative may have had anal HSIL in the past and may very well have it again in the future.

## DISCUSSION

Above in subsection one, it was determined that squamous cell carcinoma of the anus does qualify as an important health problem because there are serious consequences for those who contract the disease (Wilson & Jungner, 1968). Also, recent trends suggest that anal cancer incidence will continue to increase, ultimately meaning that more people will suffer the disease (Poynten et al., 2020). Previous reports showed roughly 29,000 cases of anal cancer per year worldwide, with the highest incidence occurring in GBM living with HIV (de Martel et al., 2020) (Clifford et al., 2020). Therefore, considerations should likely be made towards the groups with the highest individual risk if considering screening

guidelines. As shown in Figure **1**, the highest risk cohort is MSM living with HIV and ages 30 and older (with age 45 and older having a higher risk of SCCA).

In subsection two, squamous cell cancer of the anus was discussed. To meet the Wilson and Jungner criteria, a disease should be reasonably well understood and have notable latent or early symptomatic periods where an intervention could occur (Wilson & Jungner, 1968). Squamous cell anal cancer does meet these criteria in most ways. As mentioned before, the cellular changes that lead to the cancer are recognizable as low-grade SIL, then high-grade SIL, then cancer (Poynten et. al, 2020). And therefore, there are early recognizable disease stages that can be targeted for treatment. But, it is interesting to note that these changes are not solely a forward type progression and it is not well understood why and or how some people manage to clear HSIL on their own without intervention (Poynten et. al, 2020).

Having more knowledge in this area would benefit any potential plan for guidelines to screening for anal cancer because understanding this may prove portions of the currently accepted screening population do not actually necessitate screening (Poynten et. al, 2020). As the SPANC trial described, it is likely that anal HSIL does not need treatment in those without persistent HPV (Poynten et. al, 2020).

Also, it is important to mention that there is no current evidence that treatment of HSIL is effective in the prevention of squamous cell anal cancer. The ANCHOR study has the aim of determining if treatment of HSIL is effective at preventing anal cancer (Macaya et. al, 2012) (*About the Study*, 2014). More studies should be performed to investigate this aspect of the disease before guidelines for screening for anal cancer are created.

In subsection 3, tests and diagnostics were discussed including what makes a test or diagnostic suitable and also what options are available for the screening of anal cancer. The concepts of sensitivity and specificity were described and the reliability of a test was discussed. Much like the differing values that can be obtained for a blood pressure reading, anal cytology, in particular, does not always show the higher level lesions that can be found with higher diagnostic tests like high-resolution anoscopy with biopsy (Clarke & Wentzensen, 2018).

Therefore, considerations should be taken towards the inherent weaknesses of the anal pap exam. For instance, the anal pap test often reports low-grade atypia in lesions that are reported as higher-grade lesions by more diagnostic methods such as HRA biopsy with laboratory confirmations (Betancourt et al., 2013). Also, it has been shown that sensitivity tends to decrease for the higher risk, high-risk groups. So much so that among MSM not living with HIV and in MSM living with HIV, false negative results can be as high as 23% and 45%, respectively. Thus, it is recommended that the anal pap test be combined with high-resolution anoscopy and biopsy in higher-risk groups. (Betancourt et al., 2013).

But, anal cytology is simple, fast, fairly inexpensive, and causes less pain or discomfort compared with HRA. Perhaps most importantly screening with anal cytology can be done by a primary care provider, thereby referring only patients with abnormal screenings for HRA. Test characteristics for anal cytology are also fairly well described, whereas for HR-HPV, genotyping, and p16/Ki67 immunostaining all have deficiencies in data available for interpreting their respective pooled sensitivities and specificities for most high-risk patient populations (Clarke & Wentzensen, 2018).

In subsection 4, the acceptability of a screening exam was discussed. For anal cancer, there are several different screening exams. And the consensus is often that several of them should be combined to gain the most effective result (Leeds and Fang, 2016). The digital anal rectal exam, for instance, is suggested to be combined with biopsy for anyone that has a medical history or symptoms that are concerning for anal cancer. But, DARE is a low risk exam that is generally tolerated fairly well (Leeds & Fang, 2016).

Diagnostic high-resolution anoscopy is more invasive, but is the most accurate exam for the detection of anal HSIL. A study conducted using patients who experienced HRA was performed to determine the acceptability of the exam and ultimately 98% of the women and 99% of the men in the study reported that they would be willing to repeat the exam (De-Masi et al., 2018).

Treatment for early stages in the disease progression were discussed in the fifth subsection above. Currently, there are treatments for pre-cancer, or neoplastic, stages of the anal cancer disease progression. But, their efficacy is still unknown and there is no standardized treatment plan (Clifford et. al, 2020). Studies like ANCHOR are currently being performed in an effort to determine just this and combining knowledge gained from them with other studies, like the SPANC trial are likely to yield interesting results.

Under this subsection, considerations towards the treatment being effective at an earlier stage is yet to be seen in regards to the anal intraepithelial lesions. But, it is known that the prognosis for early treatment of squamous cell anal cancer is better than the prognosis at a later time (Abbas et al., n.d.). Depending on the results of the ANCHOR

study it could be found that treating the precancerous lesions may prevent progression to anal cancer.

Unfortunately, there does not seem to be consensus on agreed upon policy of who to treat in reference to the "borderline" patients. There are variations in methods concerning the treatment of AIN2 or AIN3, sometimes even AIN1. Therefore, if screening for anal intraepithelial neoplasms were to be designated as the most appropriate method, then more research would need to occur that would allow for an agreement to be met upon. Considering screening for anal cancer itself though is slightly different in this domain because there is an agreed upon treatment plan for it (Macaya et al., 2012).

Furthermore, there are the concerns that exist with the availability of locations for treatment, if screening guidelines to be set. This was described above in subsection seven. Only about half of the states in the U.S. currently have high-resolution anoscopy providers (*HRA Provider List | Anal Cancer Information*, n.d.). Therefore, it is likely that an increase in the number of available providers will be necessary to handle larger volumes of screening and treatment of disease.

There are other barriers than just access to providers as well. Specifically, at the patient-level disease determinants, beliefs about HPV-related disease, self-efficacy in the management of the disease, and/or stigma associated with anal cancer or other comorbidities surrounding the disease may prevent people from seeking care. Barriers to care at the provider level can include the provider's specific training or expertise as well as their communication capabilities with their patient (Apaydin et al., 2018). Further

barriers to care for providers may include financial shortages, insurance coverage, and provider availability (Apaydin et al., 2018; Allen et al., 2017).

On the broader systems-level, societal stigma can have a large impact on preventing at-risk patients from seeking screening or treatment early enough to catch the disease at an early stage when it is most easily treatable. Furthermore, many of the common healthcare inefficiencies and simple lack of existence of high resolution anoscopy infrastructure or providers will increase the noticeable effect from the increasing incidence of anal cancer (Apaydin et al., 2018).

Continuing with the broader themes from above, in subsection 8 we discussed the economic implications towards the costs associated with screening, or "case-finding." In this discussion, these costs should be compared with those of treatment and further medical costs associated with treating the disease. The medical aim here is towards improving the overall health of the population. This occurs via screening and early detection, to limit the chronicity of disease (Wilson & Jungner, 1968).

Economically speaking there are often two additional goals: the short term goal, and the long term goal. These two goals often function independently; the shorter term economic goals focus more on the direct effects of decreasing the provider burden, whereas the longer term goals focus more on the net effect of decreasing the burden of disease from the population (Wilson & Jungner, 1968).

A study examining just this for anal cancer by Assoumou et. al determined that likely, these goals could be met with screening for anal cancer and in over ninety percent

of their simulations, they maintained that they could achieve costs for care below the one-hundred-thousand-dollar cap per quality adjusted life year (Assoumou et. al, 2013).

Lastly, in subsection 9 it was brought to light how anal HSIL clearance has a large part to do with why a simple one-and-done type screening approach is not the best method and should be avoided (Willson & Jungner, 1968). With screening for HSIL it is likely that an approach with interval frequencies would alert providers to more HSIL existence and thus, more potential lesions that could progress to cancer could be found and could be treated -if this is found to be efficacious.

## CONCLUSION

In conclusion, considering that screening for anal cancer is relatively new, much has already been determined about the process and a significant more is currently under way to be determined. Currently, there are many areas of knowledge that need to be elucidated before successful guidelines for screening for anal cancer can be considered.

Specifically, more studies should be conducted to assess the clearance rate of HSIL. This attribute about the anal canal seems to be a large part of what makes it different from cervical cancer other than its incidence. Understanding more about this specific phenomenon would address more than just tenet two, where the disease progression was discussed. Many nuances to the self-clearance of HSIL may apply in a set of guidelines for screening, but there is a knowledge deficit on just what allows certain people to clear HSIL. Although the SPANC study suggests that it is the non-detection of persistent HPV, it begs the question of "could there be more?" Perhaps there is a genetic difference in those who

have persistent HPV v. those who do not have persistent HPV. Could this genetic difference be a way to determine who is at higher risk for anal cancer as well? Could there be an environmentally related implication like a mutagen, toxin, or carcinogen that is similar exposure amongst a great portion of those with difficulty clearing HPV?

If future research is conducted and results confirm that it is just those who suffer persistent HPV, then persistent HPV could be included in the algorithm and could be a main determining factor in who receives screening for anal cancer. Perhaps others in the main risk groups described throughout this paper do not necessitate screening, and they could be spared their time, money, and the experience of anal cancer screening. It would also decrease the strain on providers. Especially, if these factors mitigated a drastic increase in the need for an increase in providers and healthcare resources.

However, there could be something further to look into in regards to HPV persistence. Generally, the risk factors for persistent HPV are risk factors that give one a decreased immunity to the virus, like HIV. But, there could be other reasons that someone has persistent HPV. These other reasons may also make them more susceptible to the progression to anal cancer. Not, in the general sense of the risk factors above, but in a manner such as diet.

For example, one study determined that diet, specifically being in the upper two quartiles of ingestion of β-cryptoxanthin and lutein / zeaxanthin, often found in mangos, was associated with lower rates of persistent HPV (Giuliano et al., 2003). This may or may not be directly relevant to the potential of screening guidelines, but if the ultimate goal is prevention, then it is an area that could use further research.

Also, when considering guidelines, it could be mentioned that the current methods of screening often have their own individual strengths and weaknesses and that the manner of combining them could be to incorporate their strengths. For instance, anal cytology does not seem to perform as well in the highest risk groups, but that does not mean that it would not be a useful tool for finding HSIL in large populations of people. DARE too could be incorporated rather easily. Both exams are associated with some discomfort, but the need for HRA could be saved for those in higher high-risk groups, where anal cytology tends to underperform.

For many of the other screening methodologies here, more research needs to be conducted. Particularly, HR-HPV genotyping and p16/Ki67 immunostaining because they both lack the data on their pooled sensitivity and specificity when looking at the higher high-risk groups.

Furthermore, in screening for anal cancer, there is the cancer itself and then there are the precancerous lesions. As is discussed above, these precancerous lesions are commonly treated, but there is a lack of information on the effectiveness of this treatment. There is also a lack of unanimity in regards to the specific methods of treating HSIL and who to treat. Especially for those who lie in the "gray" area as described by Wilson and Jungner. The ANCHOR study is being conducted currently to address these deficits in knowledge. But, without said treatment being effective and without agreement upon how to treat the neoplasms, the tenets have not been properly addressed for setting guidelines for screening for anal cancer, at least in respect to screening for anal cancer by screening for anal neoplasms.

Finally, if guidelines were to be set there would need to be further research conducted to examine the exact infrastructure requirements such guidelines might impose and a real effort should be conducted to address these shortages. With only half of the U.S. states possessing providers capable of high-resolution anoscopy, there will be new strain on the system when guidelines are unveiled. Ultimately, this strain is going to be felt by providers and patients, but it will be felt the most by the patients themselves. Patients are likely already suffering from underserved societal stigma towards their disease(s) and with guidelines established, the medical community will need to ask many of them to travel away from loved ones, friends, family, and support nets to receive invasive medical exams.

Guidelines in screening for anal cancer could be important for specific high-risk groups, and are likely becoming more important as anal cancer incidence increases. But, there are still large aspects of the disease and potential screening parameters that need to be investigated before potential official guidelines can be established.

## REFERENCES


Abbas, A., Yang, G., & Fakih, M. G. (n.d.). *Management of Anal Cancer in 2010 Part 1: Overview, Screening, and Diagnosis*. Cancer Network. Retrieved February 5, 2021, from https://www.cancernetwork.com/view/management-anal-cancer-2010-part-1-overview-screening-and-diagnosis

*About the Study*. (2014, June 18). https://anchorstudy.org/about

Allen, E. M., Call, K. T., Beebe, T. J., McAlpine, D. D., & Johnson, P. J. (2017). Barriers to Care and Healthcare Utilization among the Publicly Insured. *Medical Care*, *55*(3), 207–214. https://doi.org/10.1097/MLR.0000000000000644

Apaydin, K. Z., Nguyen, A., Panther, L., Shtasel, D. L., Dale, S. K., Borba, C. P. C., Lathan, C. S., Mayer, K., & Keuroghlian, A. S. (2018). Facilitators of and barriers to high-resolution anoscopy adherence among men who have sex with men: A qualitative study. *Sexual Health*, *15*(5), 431–440. https://doi.org/10.1071/SH18029

Assoumou, S. A., Mayer, K. H., Panther, L., Linas, B. P., & Kim, J. J. (2013). Cost-effectiveness of surveillance strategies after treatment for high-grade anal dysplasia in high risk patients. *Sexually Transmitted Diseases*, *40*(4), 298–303. https://doi.org/10.1097/OLQ.0b013e31827f4fe9

Bartelink, H., Roelofsen, F., Eschwege, F., Rougier, P., Bosset, J. F., Gonzalez, D. G., Peiffert, D., van Glabbeke, M., & Pierart, M. (1997). Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: Results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. *Journal of Clinical Oncology*, *15*(5), 2040–2049. https://doi.org/10.1200/JCO.1997.15.5.2040

Betancourt, E. M., Wahbah, M. M., Been, L. C., Chiao, E. Y., Citron, D. R., & Laucirica, R. (2013). Anal cytology as a predictor of anal intraepithelial neoplasia in HIV-positive men and women. *Diagnostic Cytopathology*, *41*(8), 697–702. https://doi.org/10.1002/dc.22941

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, *68*(6), 394–424. https://doi.org/10.3322/caac.21492

Burgos, J., Curran, A., Tallada, N., Guelar, A., Navarro, J., Landolfi, S., Villar, J., Crespo, M., Ribera, E., & Falcó, V. (2015). Risk of progression to high-grade anal

intraepithelial neoplasia in HIV-infected MSM. *AIDS (London, England)*, *29*(6), 695–702. https://doi.org/10.1097/QAD.0000000000000603

*Cancer of the Anus, Anal Canal, and Anorectum—Cancer Stat Facts*. (n.d.). SEER. Retrieved July 12, 2021, from https://seer.cancer.gov/statfacts/html/anus.html

Clarke, M. A., & Wentzensen, N. (2018). Strategies for screening and early detection of anal cancers: A narrative and systematic review and meta-analysis of cytology, HPV testing, and other biomarkers: Review of Anal Cancer Screening Tests. *Cancer Cytopathology*, *126*(7), 447–460. https://doi.org/10.1002/cncy.22018

Clifford, G. M., Georges, D., Shiels, M. S., Engels, E. A., Albuquerque, A., Poynten, I. M., Pokomandy, A., Easson, A. M., & Stier, E. A. (2020). A meta-analysis of anal cancer incidence by risk group: Toward a unified anal cancer risk scale. *International Journal of Cancer*, *148*(1), 38–47. https://doi.org/10.1002/ijc.33185

Cornall, A. M., Roberts, J. M., Molano, M., Machalek, D. A., Phillips, S., Hillman, R. J., Grulich, A. E., Jin, F., Poynten, I. M., Templeton, D. J., Garland, S. M., & Tabrizi, S. N. (2015). Laser capture microdissection as a tool to evaluate human papillomavirus genotyping and methylation as biomarkers of persistence and progression of anal lesions. *British Medical Journal Open*, *5*(8), e008439. https://doi.org/10.1136/bmjopen-2015-008439

Curry, S. J., Krist, A. H., Owens, D. K., Barry, M. J., Caughey, A. B., Davidson, K. W., Doubeni, C. A., Epling, J. W., Kemper, A. R., Kubik, M., Landefeld, C. S., Mangione, C. M., Phipps, M. G., Silverstein, M., Simon, M. A., Tseng, C.-W., & Wong, J. B. (2018). Screening for Cervical Cancer: US Preventive Services Task Force Recommendation Statement. *Journal of the American Medical Association*, *320*(7), 674. https://doi.org/10.1001/jama.2018.10897

Darragh, T. M., Colgan, T. J., Cox, J. T., Heller, D. S., Henry, M. R., Luff, R. D., McCalmont, T., Nayar, R., Palefsky, J. M., Stoler, M. H., Wilkinson, E. J., Zaino, R. J., Wilbur, D. C., Wilbur, D. C., Darragh, T. M., Henry, M. R., McCalmont, T., Luff, R. D., Wilkinson, E. J., … Spires, S. (2012). The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: Background and Consensus Recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *Archives of Pathology & Laboratory Medicine*, *136*(10), 1266–1297. https://doi.org/10.5858/arpa.LGT200570

de Martel, C., Georges, D., Bray, F., Ferlay, J., & Clifford, G. M. (2020). Global burden of cancer attributable to infections in 2018: A worldwide incidence analysis. *The Lancet Global Health*, *8*(2), e180–e190. https://doi.org/10.1016/S2214-109X(19)30488-7

De-Masi, A., Davis, E., Cuming, T., Chindawi, N., Pesola, F., Cappello, C., Chambers, S., Bowring, J., Rosenthal, A. N., Sasieni, P., & Nathan, M. (2018). The acceptability of high resolution anoscopy examination in patients attending a tertiary referral centre. *BioMed Central Cancer*, *18*(1), 554. https://doi.org/10.1186/s12885-018-4475-6

de Pokomandy, A., Rouleau, D., Ghattas, G., Trottier, H., Vézina, S., Coté, P., Macleod, J., Allaire, G., Hadjeres, R., Franco, E. L., & Coutlée, F. (2011). HAART and progression to high-grade anal intraepithelial neoplasia in men who have sex with men and are infected with HIV. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, *52*(9), 1174–1181. https://doi.org/10.1093/cid/cir064

Eng, C. (2016). *Anal Canal Cancers, An Issue of Surgical Oncology Clinics of North America*. Elsevier Health Sciences.

Eng, C., Messick, C., & Glynne-Jones, R. (2019). The Management and Prevention of Anal Squamous Cell Carcinoma. *American Society of Clinical Oncology Educational Book*, *39*, 216–225. https://doi.org/10.1200/EDBK_237433

Fox, P. A., Seet, J. E., Stebbing, J., Francis, N., Barton, S. E., Strauss, S., Allen-Mersh, T. G., Gazzard, B. G., & Bower, M. (2005). The value of anal cytology and human papillomavirus typing in the detection of anal intraepithelial neoplasia: A review of cases from an anoscopy clinic. *Sexually Transmitted Infections*, *81*(2), 142–146. https://doi.org/10.1136/sti.2003.008318

Geskus, R. B., González, C., Torres, M., Del Romero, J., Viciana, P., Masiá, M., Blanco, J. R., Iribarren, M., De Sanjosé, S., Hernández-Novoa, B., Ortiz, M., & Del Amo, J. (2016). Incidence and clearance of anal high-risk human papillomavirus in HIV-positive men who have sex with men: Estimates and risk factors. *AIDS (London, England)*, *30*(1), 37–44. https://doi.org/10.1097/QAD.0000000000000874

Gilbert, D. C., Wakeham, K., Langley, R. E., & Vale, C. L. (2019). Increased risk of second cancers at sites associated with HPV after a prior HPV-associated malignancy, a systematic review and meta-analysis. *British Journal of Cancer*, *120*(2), 256–268. https://doi.org/10.1038/s41416-018-0273-9

Goldstone, R. N., Goldstone, A. B., Russ, J., & Goldstone, S. E. (2011). Long-term Follow-up of Infrared Coagulator Ablation of Anal High-Grade Dysplasia in Men Who Have Sex with Men. *Diseases of the Colon & Rectum*, *54*(10), 1284–1292. https://doi.org/10.1097/DCR.0b013e318227833e

Grulich, A. E., van Leeuwen, M. T., Falster, M. O., & Vajdic, C. M. (2007). Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant

recipients: A meta-analysis. *The Lancet*, *370*(9581), 59–67. https://doi.org/10.1016/S0140-6736(07)61050-2

Giuliano, A. R., Siegel, E. M., Roe, D. J., Ferreira, S., Luiza Baggio, M., Galan, L., Duarte-Franco, E., Villa, L. L., Rohan, T. E., Marshall, J. R., & Franco, E. L. (2003). Dietary Intake and Risk of Persistent Human Papillomavirus (HPV) Infection: The Ludwig-McGill HPV Natural History Study. The Journal of Infectious Diseases, 188(10), 1508–1516. https://doi.org/10.1086/379197

*HRA Provider List | Anal Cancer Information*. (n.d.). Retrieved January 22, 2021, from https://analcancerinfo.ucsf.edu/hra-provider-list

*Human Papillomavirus (HPV) and Cancer | CDC*. (2020, September 15). https://www-cdc-gov.ezproxy.bu.edu/cancer/hpv/index.htm

Leeds, I. L., & Fang, S. H. (2016). Anal cancer and intraepithelial neoplasia screening: A review. *World Journal of Gastrointestinal Surgery*, *8*(1), 41–51. https://doi.org/10.4240/wjgs.v8.i1.41

Li, W., Venkataraman, S., Gustafsson, U. P., Oyama, J. C., M.d, D. G. F., & Lieberman, R. W. (2009). Using acetowhite opacity index for detecting cervical intraepithelial neoplasia. *Journal of Biomedical Optics*, *14*(1), 014020. https://doi.org/10.1117/1.3079810

Macaya, A., Muñoz-Santos, C., Balaguer, A., & Barberà, M. J. (2012). Interventions for anal canal intraepithelial neoplasia. *The Cochrane Database of Systematic Reviews*, *2012*(12). https://doi.org/10.1002/14651858.CD009244.pub2

Machalek, D. A., Poynten, M., Jin, F., Fairley, C. K., Farnsworth, A., Garland, S. M., Hillman, R. J., Petoumenos, K., Roberts, J., Tabrizi, S. N., Templeton, D. J., & Grulich, A. E. (2012). Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: A systematic review and meta-analysis. *The Lancet Oncology*, *13*(5), 487–500. https://doi.org/10.1016/S1470-2045(12)70080-3

Malik, Z. (2020). *How to Do Anoscopy—Gastrointestinal Disorders*. Merck Manuals Professional Edition. https://www.merckmanuals.com/professional/gastrointestinal-disorders/how-to-do-gastrointestinal-procedures/how-to-do-anoscopy

McCredie, M. R., Sharples, K. J., Paul, C., Baranyai, J., Medley, G., Jones, R. W., & Skegg, D. C. (2008). Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: A retrospective cohort study. *The Lancet Oncology*, *9*(5), 425–434. https://doi.org/10.1016/S1470-2045(08)70103-7

Morton, M., Melnitchouk, N., & Bleday, R. (2018). Squamous cell carcinoma of the anal canal. *Current Problems in Cancer*, *42*(5), 486–492. https://doi.org/10.1016/j.currproblcancer.2018.11.001

Nigro, MD, N., Gunter Seydel, MD, MS, FACR, H., Considine, MD, B., Vaitkevicius, MD, V. K., Leichman, MD, L., & Kinzie, MD, J. J. (n.d.). *Combined preoperative radiation and chemotherapy for squamous cell carcinoma of the anal canal—Nigro—1983—Cancer—Wiley Online Library*. Retrieved July 10, 2021, from https://acsjournals.onlinelibrary.wiley.com/doi/abs/10.1002/1097-0142(19830515)51:10%3C1826::AID-CNCR2820511012%3E3.0.CO;2-L

Nyitray, A. G., D'Souza, G., Stier, E. A., Clifford, G., & Chiao, E. Y. (2020). The Utility of Digital Anal Rectal Examinations in a Public Health Screening Program for Anal Cancer. *Journal of Lower Genital Tract Disease*, *24*(2), 192–196. https://doi.org/10.1097/LGT.0000000000000508

Oortmarssen, G. J. V., & Habbema, J. D. F. (1995). Duration of Preclinical Cervical Cancer and Reduction in Incidence of Invasive Cancer following Negative Pap Smears. *International Journal of Epidemiology*, *24*(2), 300–307. https://doi.org/10.1093/ije/24.2.300

Osborne, M. C., Maykel, J., Johnson, E. K., & Steele, S. R. (2014). Anal squamous cell carcinoma: An evolution in disease and management. *World Journal of Gastroenterology : WJG*, *20*(36), 13052–13059. https://doi.org/10.3748/wjg.v20.i36.13052

Palefsky, J. M. (2012). Practising high-resolution anoscopy. *Sexual Health*, *9*(6), 580–586. https://doi.org/10.1071/SH12045

Palefsky, J. M., Giuliano, A. R., Goldstone, S., Moreira, E. D., Aranda, C., Jessen, H., Hillman, R., Ferris, D., Coutlee, F., Stoler, M. H., Marshall, J. B., Radley, D., Vuocolo, S., Haupt, R. M., Guris, D., & Garner, E. I. O. (2011). HPV Vaccine against Anal HPV Infection and Anal Intraepithelial Neoplasia. *New England Journal of Medicine*, *365*(17), 1576–1585. https://doi.org/10.1056/NEJMoa1010971

Palefsky, J. M., Holly, E. A., Hogeboom, C. J., Berry, J. M., Jay, N., & Darragh, T. M. (1997). Anal cytology as a screening tool for anal squamous intraepithelial lesions. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology: Official Publication of the International Retrovirology Association*, *14*(5), 415–422. https://doi.org/10.1097/00042560-199704150-00004

Papillon, J., Mayer, M., Montbarbon, J. F., Gerard, J. P., Chassard, J. L., & Bailly, C. (1983). A new approach to the management of epidermoid carcinoma of the anal

canal. *Cancer*, *51*(10), 1830–1837. https://doi.org/10.1002/1097-0142(19830515)51:10<1830::aid-cncr2820511013>3.0.co;2-z

Poynten, I. M., Jin, F., Roberts, J. M., Templeton, D. J., Law, C., Cornall, A. M., Molano, M., Machalek, D. A., Carr, A., Farnsworth, A., Tabrizi, S., Phillips, S., Fairley, C. K., Garland, S. M., Hillman, R. J., & Grulich, A. E. (2020). The Natural History of Anal High-grade Squamous Intraepithelial Lesions in Gay and Bisexual Men. *Clinical Infectious Diseases*, ciaa166. https://doi.org/10.1093/cid/ciaa166

Saslow, D., Solomon, D., Lawson, H. W., Killackey, M., Kulasingam, S., Cain, J., Garcia, F. A. R., Moriarty, A., Waxman, A., Wilbur, D., Wentzensen, N., Downs, L., Spitzer, M., Moscicki, A.-B., Franco, E. L., Stoler, M. H., Schiffman, M., Castle, P. E., & Myers, E. R. (2012). American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Screening Guidelines for the Prevention and Early Detection of Cervical Cancer. *CA: A Cancer Journal for Clinicians*, *62*(3), 147–172. https://doi.org/10.3322/caac.21139

Schiffman, M., Wentzensen, N., Wacholder, S., Kinney, W., Gage, J. C., & Castle, P. E. (2011). Human Papillomavirus Testing in the Prevention of Cervical Cancer. *Journal of the National Cancer Institute*, *103*(5), 368–383. https://doi.org/10.1093/jnci/djq562

Seventh Planet. (2016). Performing a Digital Anal Rectal Examination—D.A.R.E. Retrieved July 26, 2021, from https://www.youtube.com/watch?v=KDUcJHdz-Sk

Steele, S. R., Varma, M. G., Melton, G. B., Ross, H. M., Rafferty, J. F., & Buie, W. D. (2012). Practice Parameters for Anal Squamous Neoplasms. *Diseases of the Colon & Rectum*, *55*(7), 735–749. https://doi.org/10.1097/DCR.0b013e318255815e

Tanum, G., Tveit, K., & Karlsen, K. O. (1991). Diagnosis of Anal Carcinoma – Doctor's Finger Still the Best. *Oncology*, *48*(5), 383–386. https://doi.org/10.1159/000226964

Wilson, J. M. G., & Jungner, G. (1968). Principles and Practice of Screening for Disease. *World Health Organization Geneva*, *34*, 168.

Yang, D. X., Soulos, P. R., Davis, B., Gross, C. P., & Yu, J. B. (2018). Impact of widespread cervical cancer screening: Number of cancers prevented and changes in race-specific incidence. *American Journal of Clinical Oncology*, *41*(3), 289–294. https://doi.org/10.1097/COC.0000000000000264.

## CURRICULUM VITAE