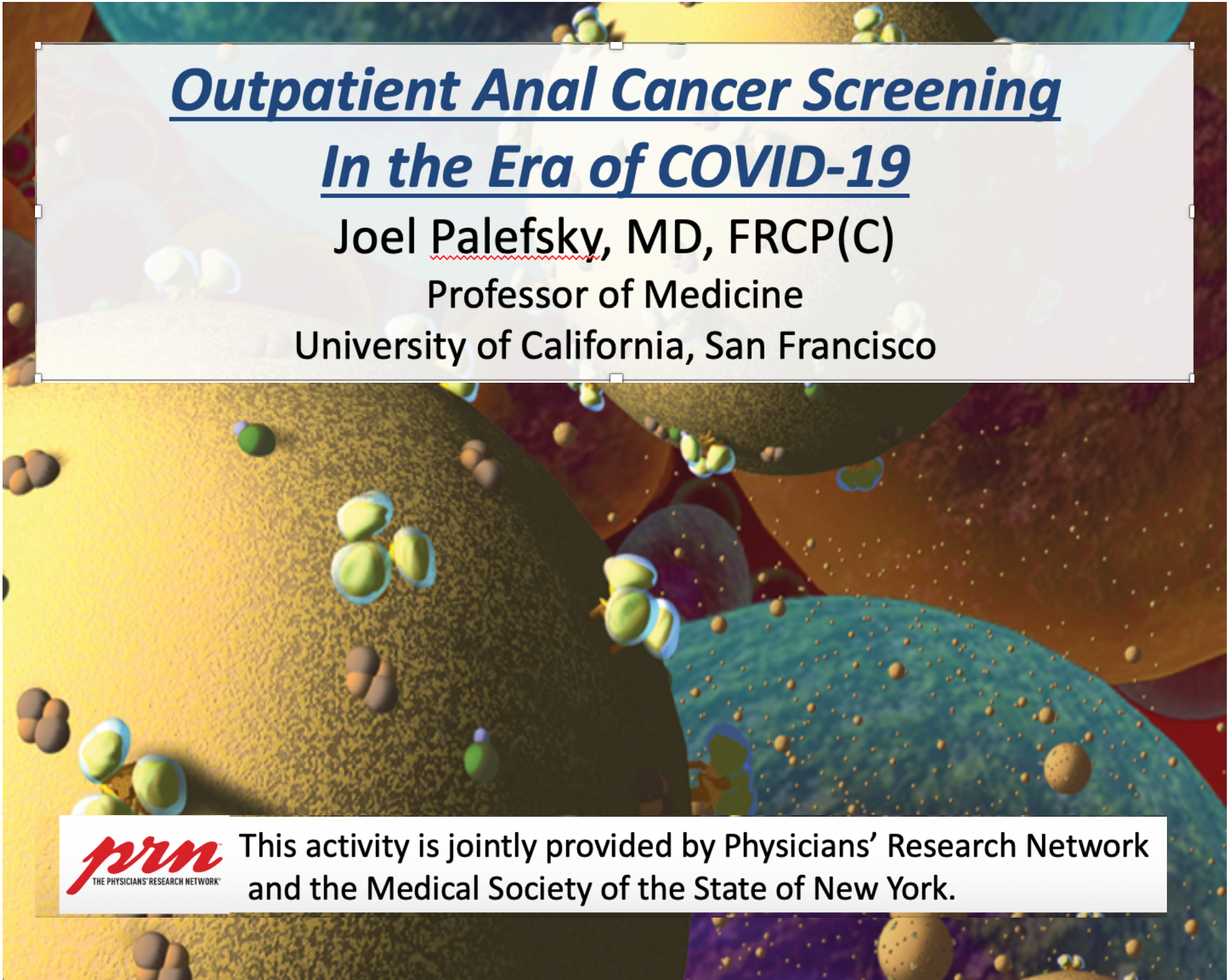

Outpatient Anal Cancer Screening In the Era of COVID-19

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Professor of Medicine
University of California, San Francisco

This activity is jointly provided by Physicians' Research Network and the Medical Society of the State of New York.

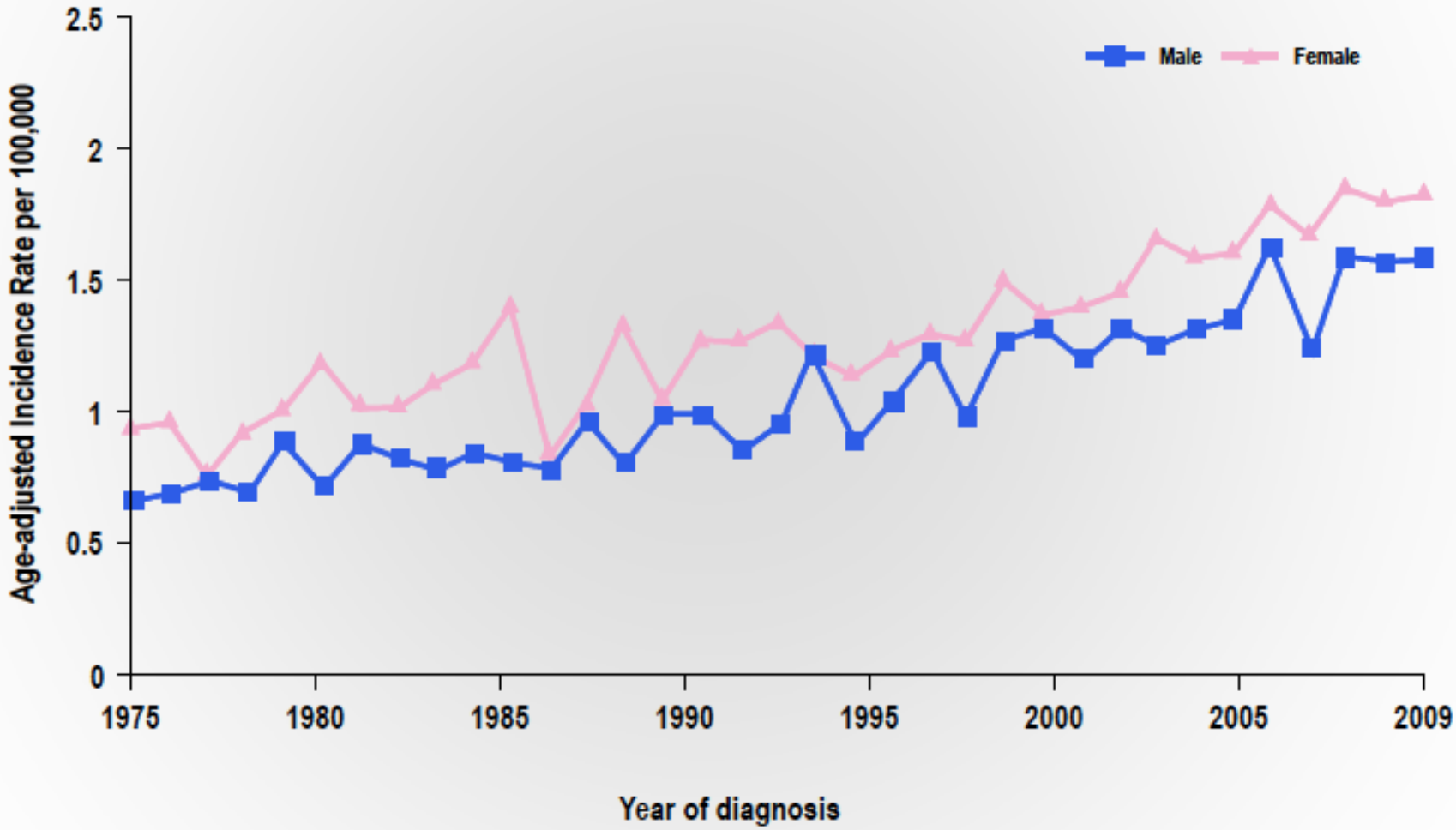
Disclosures

- Merck and Co- research and travel support
- Vir Biotechnologies- consultant, stock options
- Virion Therapeutics- stock options
- Vaccitech- consultant

Objectives

- Describe the epidemiology of anal HPV infection, high-grade squamous intraepithelial lesions (HSIL) and cancer among people living with HIV (PLWH)
- Describe recent advances in screening for anal cancer and HSIL
- Describe the progress of the ANCHOR Study
- Describe the impact of screening for and treating HSIL in the setting of the COVID pandemic

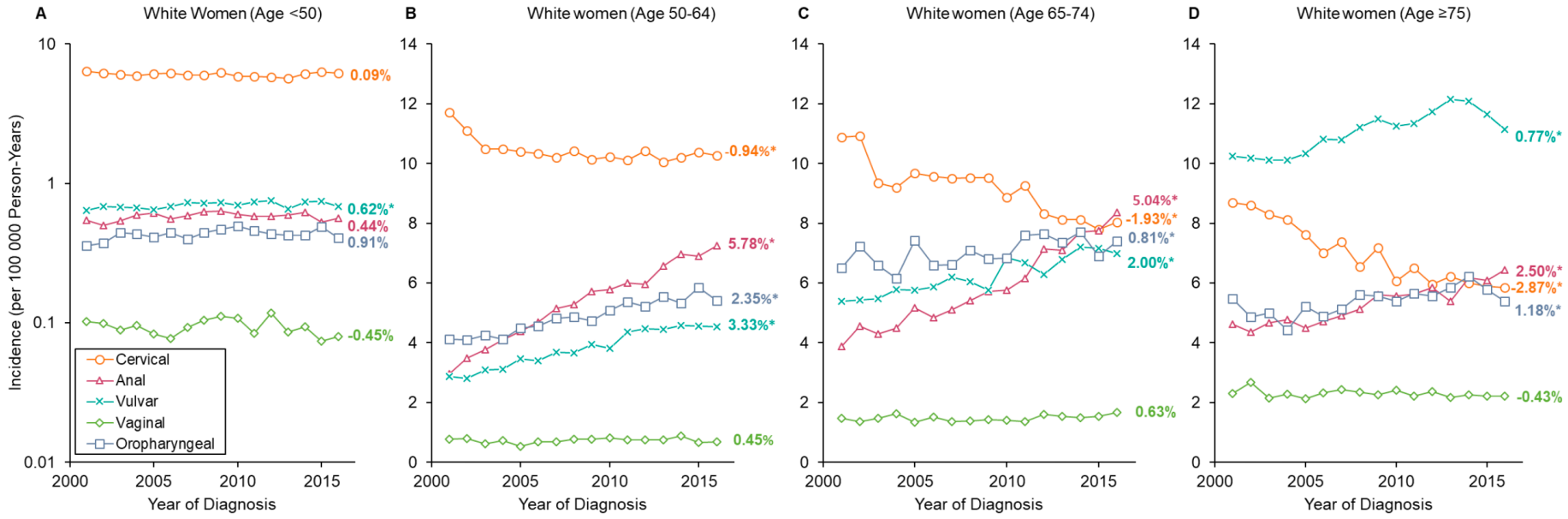
Age-Adjusted Incidence of Invasive Anal Cancer by Gender and Year of Diagnosis: United States



Howlader N et al. (eds). SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations). http://seer.cancer.gov/csr/1975_2009_pops09/. Accessed June 21, 2012.

Anal Cancer Incidence Is Increasing In Women

SCCA among White women



Deshmukh AA, et al. 17th International Conference on Malignancies in HIV/AIDS

Anal cancer rates in North American AIDS Cohort Collaboration on Research and Design) (NA-ACCORD) 1996-2007

	Incidence/100,000 (85% CI)
• HIV-infected	
• MSM	131 (109-157)
• MSW	46 (25-77)
• Women	30 (17-50)

Silverberg M et al. CID 2012; 54:1026-34

Recent trends in anal cancer incidence
AIDS and cancer registry match study

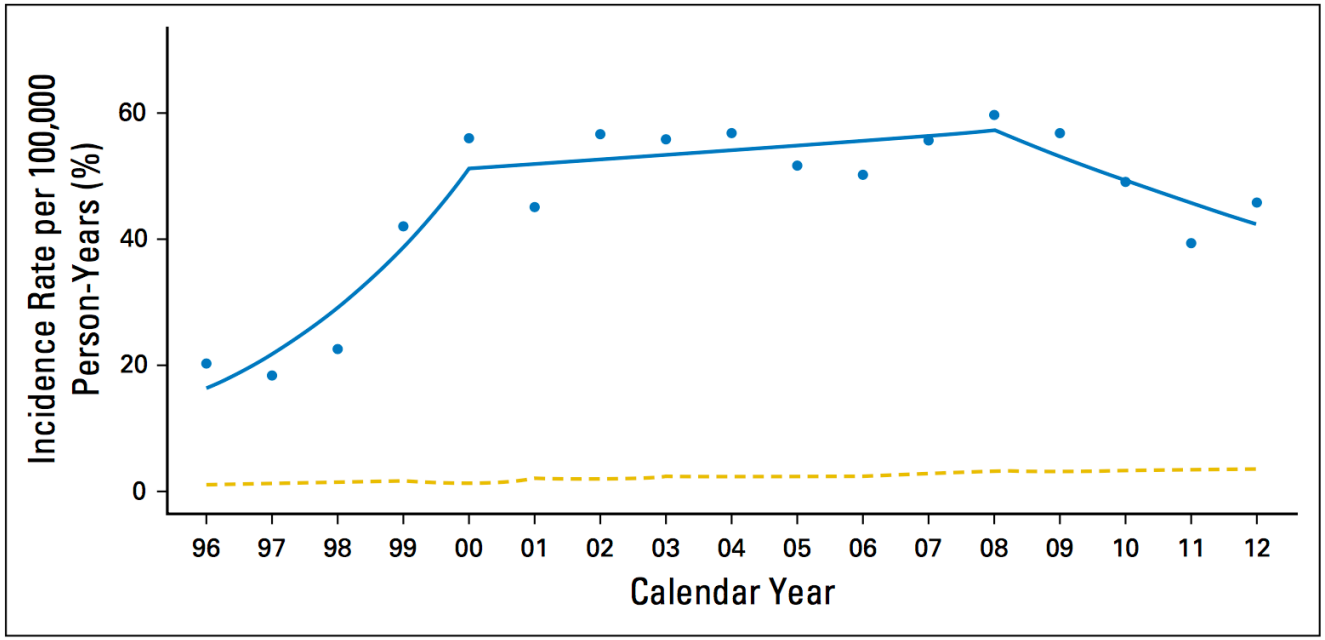


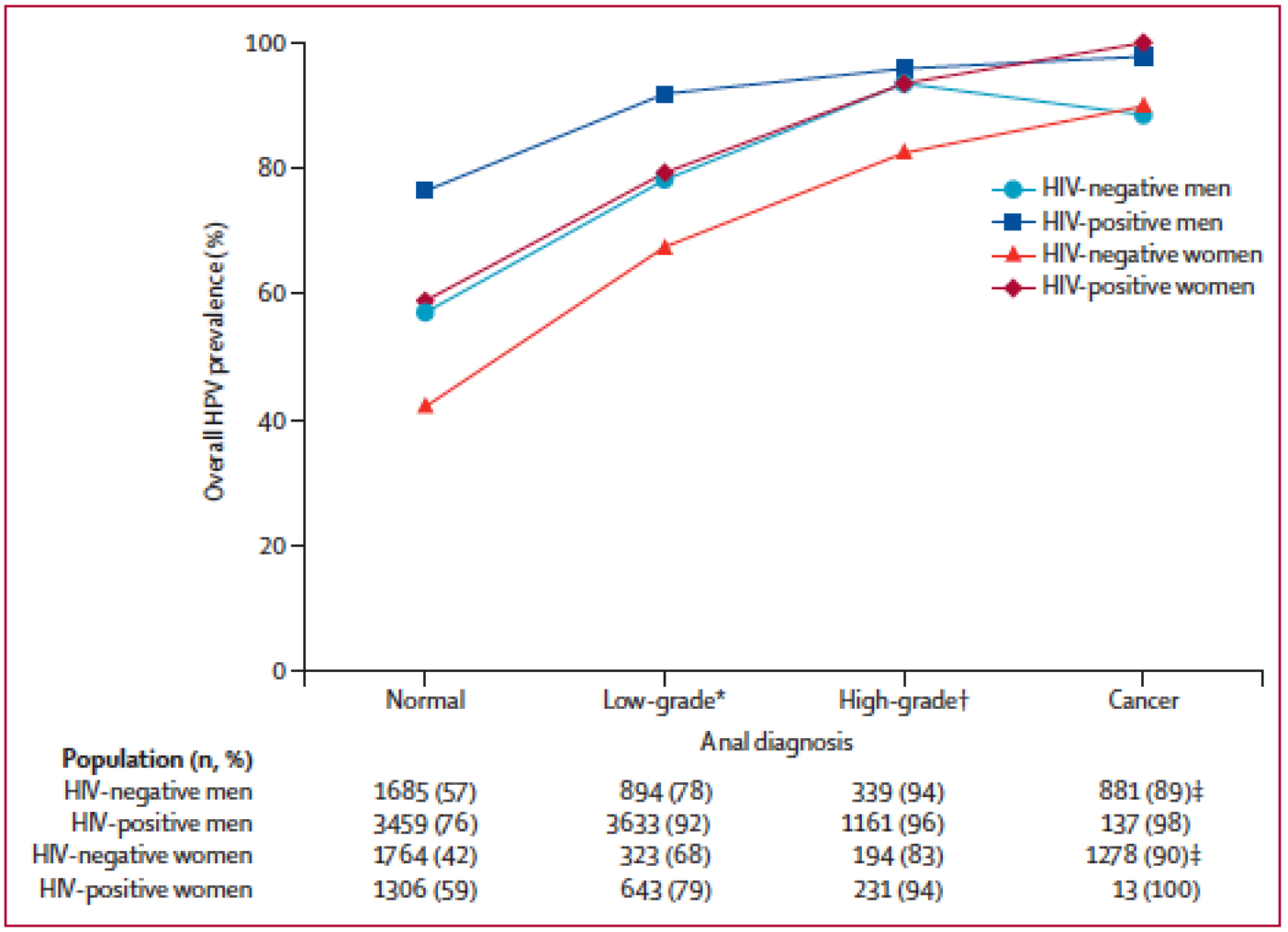
Fig 1. Trend in anal cancer incidence among people with HIV infection and the general population in the United States, 1996 to 2012. Dots indicate the observed incidence of anal cancer among people with HIV in the study population as a function of calendar year. The solid line is the model fitted by Joinpoint, with changes in slope for the incidence trend indicated in 2000 and 2008. The dashed line is the expected incidence in the general population standardized to reflect the demographic characteristics of the HIV population.

Colon-Lopez V. et al J Clin Oncol 2018; 36:68-75

The future of HPV-related cancer in HIV-infected men and women

	Increased incidence of cancer	Decreased incidence of cancer
Increasing age	Possibly	
Accelerated biological aging	Possibly	
Lower nadir CD4 level	Likely	
Lower current CD4 level	Possibly	
Time on effective ART		Possibly
Earlier initiation of ART		Possibly
Screening for and removal of HSIL		Definitely (cervical) Possibly (anal)
HPV vaccination		Likely (in the future)

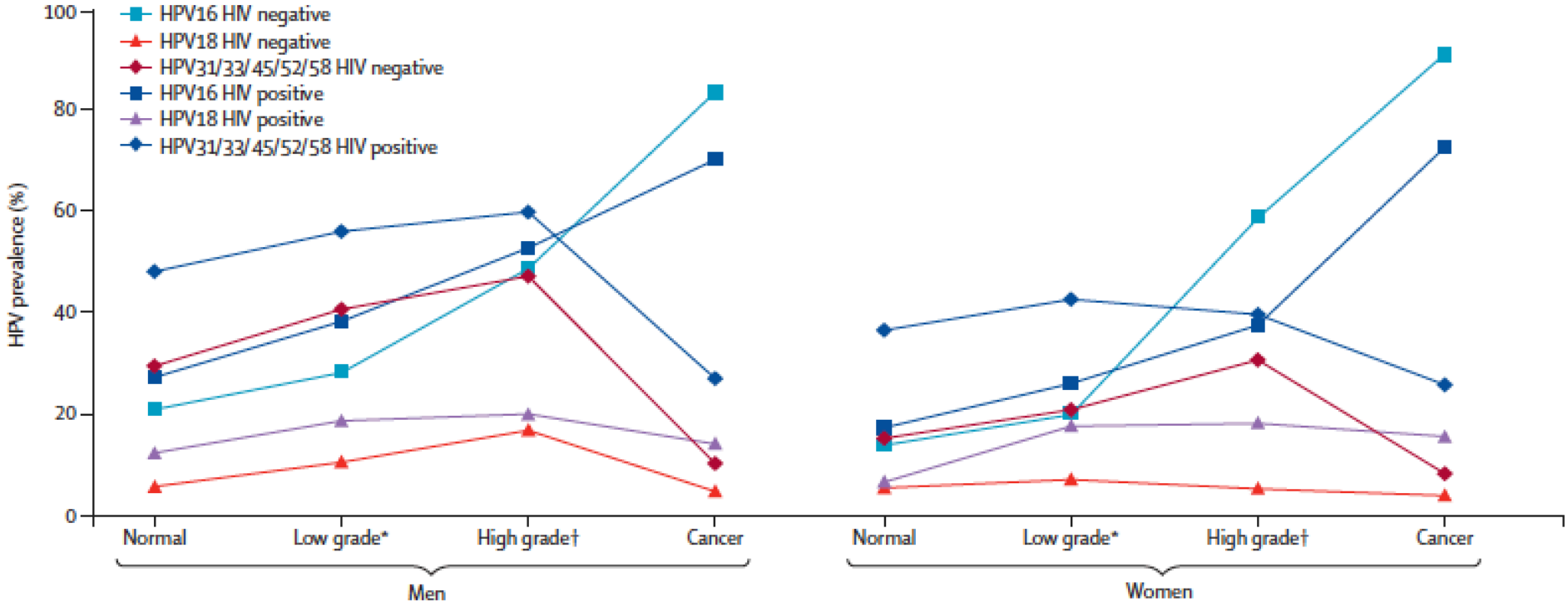
Overall HPV prevalence by sex, anal diagnosis and HIV status



Population (n, %)				
HIV-negative men	1685 (57)	894 (78)	339 (94)	881 (89)‡
HIV-positive men	3459 (76)	3633 (92)	1161 (96)	137 (98)
HIV-negative women	1764 (42)	323 (68)	194 (83)	1278 (90)‡
HIV-positive women	1306 (59)	643 (79)	231 (94)	13 (100)

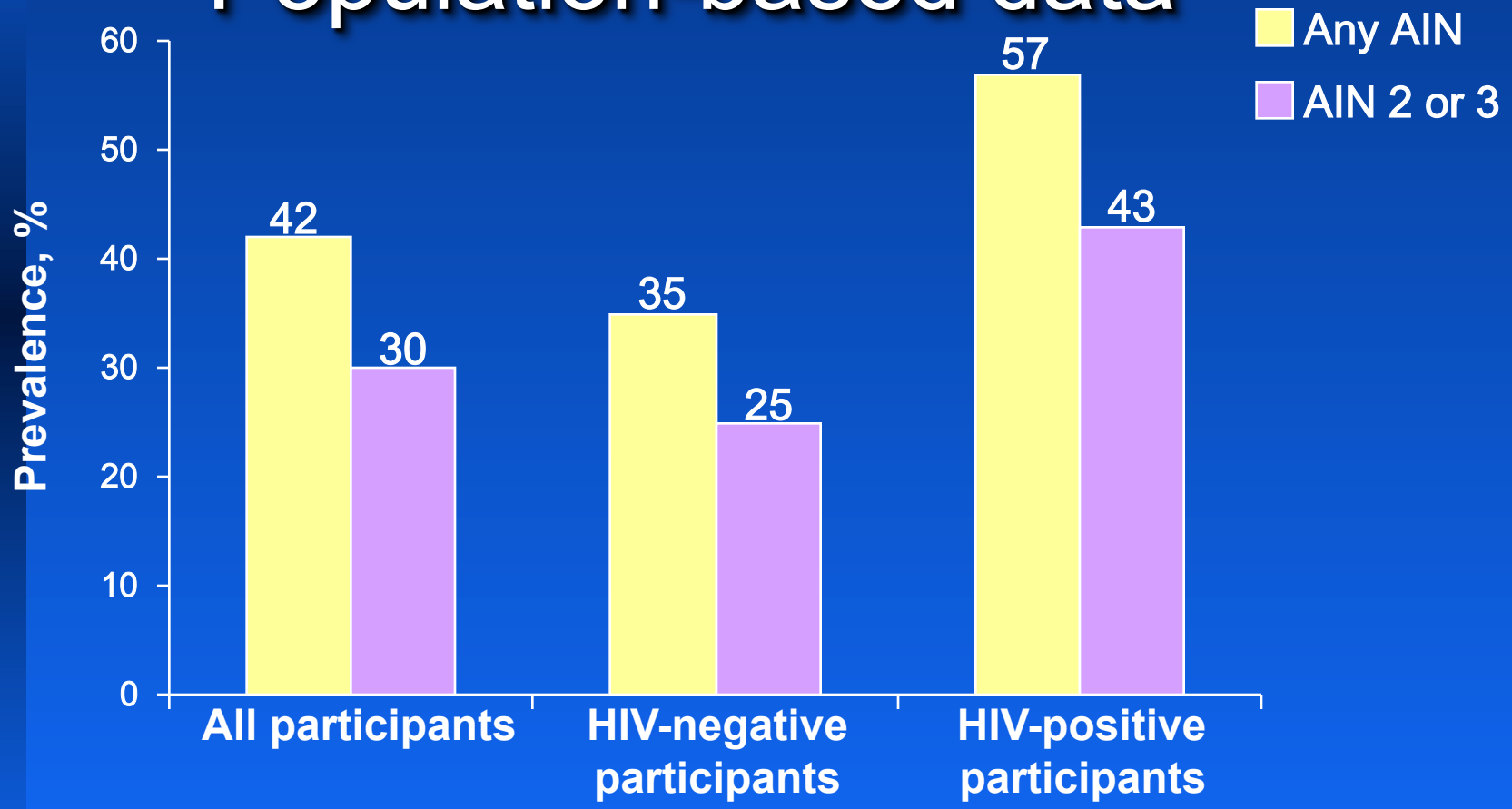
Lin C et al. Lancet Infect Dis 2018;18: 198–206

Prevalence of HPV16, HPV18, and HPV31/33/45/52/58 by anal diagnosis and HIV status, in HPV-positive men and women



Lin C et al. Lancet Infect Dis 2018;18: 198–206

Future indicators: prevalence of AIN among MSM Population-based data



Chin-Hong et al. *Ann Int Med.* 2008;149;300-6.

AMC-072
HPV vaccination among HIV+ MSM 18-26 years

- 34% had HSIL at screening
- 93% had at least one anal HPV type
- 23/47/47/63% of participants were naïve at baseline to HPV 6/11/16/18, respectively

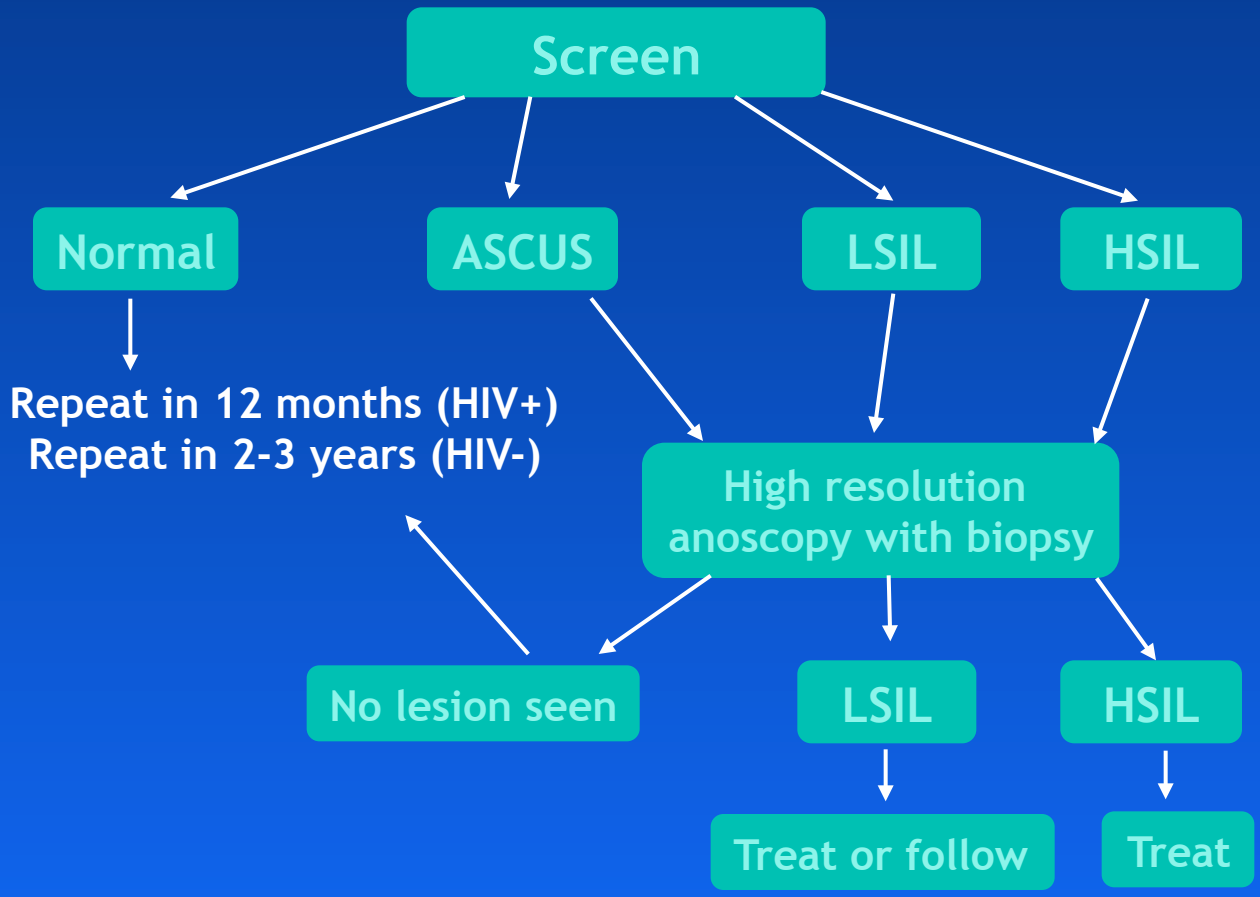
J. Palefsky, personal communication
Kahn J et al. Papillomavirus Research 7 (2019) 52–61

High prevalence of anal HSIL in HIV+ women

- AMC-084- 27% of HIV+ women

Stier EA et al. Clin Infect Dis. 2019 Jul 11.

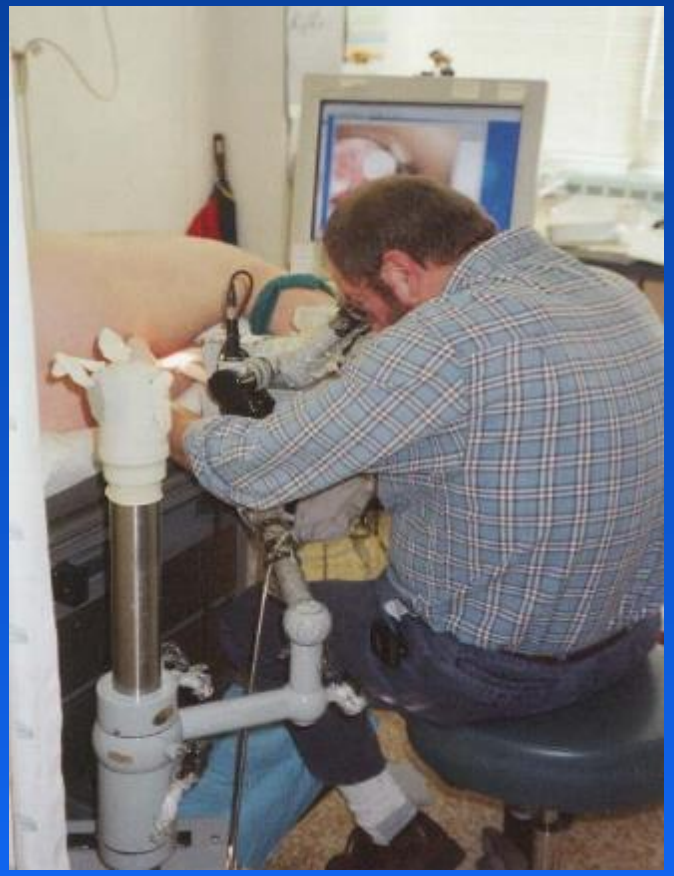
Anal cytology screening for ASIL



Chin-Hong PV et al. *J Infect Dis.* 2004;90:2070-2076.

High resolution anoscopy (HRA)

HRA is an *office-based* procedure examining the anus, anal canal and perianus using a colposcope or operating microscope with 5% acetic acid and Lugol's solution



Who should be screened?

- All HIV-positive men regardless of sexual orientation
- All HIV-negative MSM
- Women with high-grade cervical or vulvar lesions or cancer
- All HIV+ women
- All men and women with perianal condyloma
- Solid organ transplant recipients
- Over 25 years if immunosuppressed, inc. HIV
- Over 40 years if immunocompetent

Digital anorectal exam (DARE!)

Challenges of anal cancer screening

- Limited sensitivity of anal cytology
- Undercalls severity of lesions

Cytology testing to screen for anal HSIL

	Sensitivity (%)	Specificity (%)	Absolute risk (%)
ASC-US	37/308 (12.0, 8.8 to 16.1)	400/634 (63.1, 59.3 to 66.8)	12/241 (5.0, 2.9 to 8.5)
LSIL	49/308 (15.9, 12.2 to 20.4)	463/634 (73.0, 69.4 to 76.3)	37/271 (13.7, 10.1 to 18.3)
ASC-H	66/308 (21.4, 17.2 to 26.3)	634/634 (100.0, 99.4 to 100.0)	49/220 (22.3, 17.3 to 28.2)
HSIL	143/308 (46.4, 40.9 to 52.0)	634/634 (100.0, 99.4 to 100.0)	66/66 (100.0, 94.5 to 100.0)
SCCA	1/308 (0.3, 0.1 to 1.8)	634/634 (100.0, 99.4 to 100.0)	143/143 (100.0, 97.4 to 100.0)

J. Palefsky, personal communication

Sensitivity, specificity and positive predictive value for detection of anal HSIL

	Sensitivity (%)	Specificity (%)	Absolute Risk (%)
Aptima HPV	231/309 (74.8, 69.6 to 79.3)	440/634 (69.4, 65.7 to 72.9)	231/425 (54.4, 49.6 to 59.0)
Aptima HPV 16	96/309 (31.1, 26.2 to 36.4)	599/634 (94.5, 92.4 to 96.0)	96/131 (73.3, 65.1 to 80.1)
Aptima HPV 18/45	39/309 (12.6, 9.4 to 16.8)	600/634 (94.6, 92.6 to 96.1)	39/73 (53.4, 42.1 to 64.4)

J. Palefsky, personal communication

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J. Palefsky, personal communication

HPV testing for anal screening

- “Basket” tests have good sensitivity but low specificity
- Specific types such as HPV 16 have low sensitivity but high specificity

J. Palefsky, personal communication

HPV testing for anal screening

Relative risk of anal HSIL for selected HPV result comparisons, by cytology

Cytology	HPV result comparison	Absolute risks (%)	Relative risk (95% CI)
Normal	Aptima+ vs. Aptima-	16.7 vs. 1.6	10.4 (2.9 to 37.0)
ASC-US	Aptima+ vs. Aptima-	26.2 vs. 8.0	3.3 (1.8 to 6.0)
LSIL	Aptima+ vs. Aptima-	30.4 vs. 11.6	2.6 (1.4 to 4.9)
Normal	Aptima 16+ vs. Aptima 16-	40.0 vs. 4.2	9.4 (2.8 to 32.4)
ASC-US	Aptima 16+ vs. Aptima 16-	35.3 vs. 12.2	2.9 (1.4 to 6.0)
LSIL	Aptima 16+ vs. Aptima 16-	44.7 vs. 17.6	2.5 (1.6 to 4.1)

J. Palefsky, personal communication

Sensitivity, specificity and positive predictive value for detection of anal HSIL

	Sensitivity (%)	Specificity (%)	Absolute Risk (%)
Aptima HPV	231/309 (74.8, 69.6 to 79.3)	440/634 (69.4, 65.7 to 72.9)	231/425 (54.4, 49.6 to 59.0)
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Aptima HPV 18/45	39/309 (12.6, 9.4 to 16.8)	600/634 (94.6, 92.6 to 96.1)	39/73 (53.4, 42.1 to 64.4)
Screening combo	235/309 (76.1, 71.0 to 80.5)	599/634 (94.5, 92.4 to 96.0	235/270 (87.0, 82.5 to 90.5

Screening combo: (Normal cytology and HPV 16+) or (ASC-US and HPV 16+) or (LSIL and HPV 16+) or (cytology > LSIL)

J. Palefsky, personal communication

Cytology and HPV testing for screening

- HSIL/ASC-H on cytology → refer
- Anything other than HSIL → test for HPV 16
- HPV 16+ → refer
- HPV 16- → repeat
  - Normal- repeat in 2-3 years?
  - ASC-US-repeat in 1 year?
  - LSIL- repeat in 6 months?

Other approaches

- Methylation
- P16/INK4A

Screening for anal cancer

Yes or no?

IDSA
Oct 5, 2019

Joel Palefsky
Department of Medicine
University of California, San Francisco

Does screening for anal cancer and its precursors meet current screening standards?

- Dobrow MJ et al. CMAJ 2018 April 9;190:E422-9.
  - Wilson and Jungner's 10 principles of screening

    Principles and practice of screening for disease. Geneva: World Health Organization; 1968.

#10 “..overall benefit of the screening program outweighs its potential harms”

- **Incidence of anal cancer is high in well-defined at-risk populations**
- **Treatment of cervical HSIL is proven to reduce the incidence of cervical cancer**
- **Treating anal HSIL will therefore reduce the incidence of anal cancer and so we should be screening for anal HSIL**

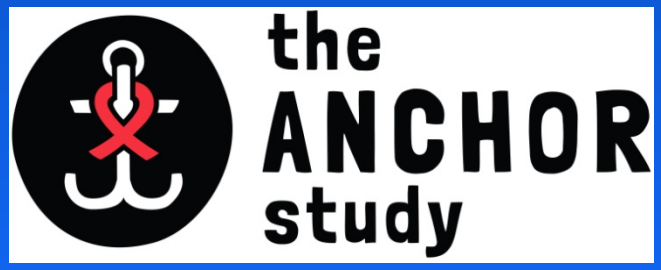
Here's why not

- Anal and cervical HSIL are very similar- treatment should work: Here's why not:
  - In many at-risk people lesions are large and multifocal
  - Clinicians may miss lesions
  - Clinicians may inadequately treat lesions
  - New lesions often arise- anal whack-a-mole!

"I just want to apologize beforehand if you miss."

ANCHOR study

- **Aim 1:** To determine whether treating anal high-grade squamous intraepithelial lesions (HSIL) is effective in reducing the incidence of anal cancer in HIV-infected men and women



NCI UM1CA121947 and OAR

ANCHOR study

- **Aim 2:** To determine the safety of infrared coagulation (IRC), electrocautery, imiquimod, laser and 5- fluorouracil treatments for anal HSIL

- **Aim 3:** To develop and implement an instrument to measure the impact of ANCHOR procedures on QoL (ANCHOR Health-Related Symptom Index (A-HRSI)

NCI UM1CA121947 and OAR

ANCHOR study

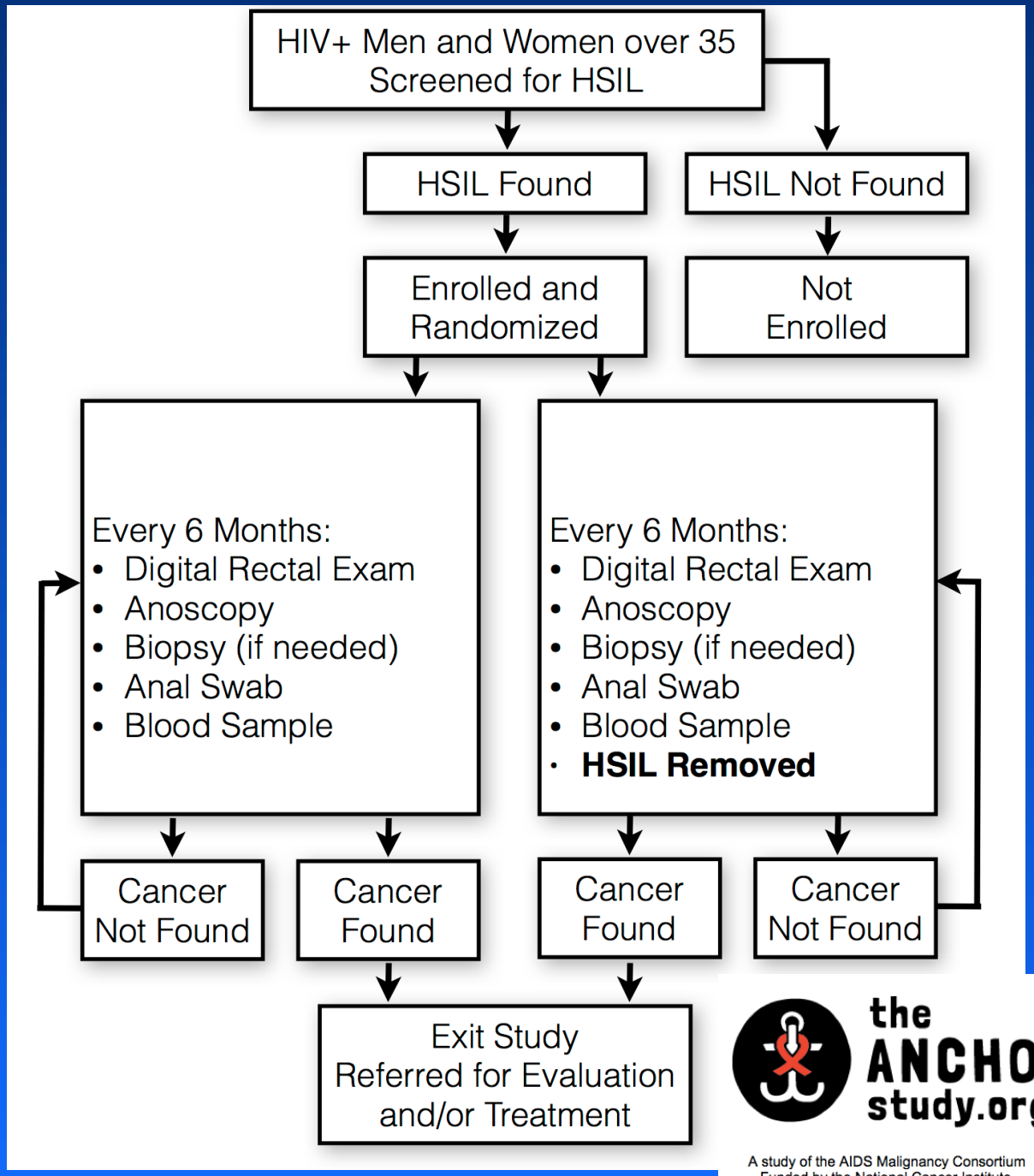
- **Aim 4:** Collect clinical specimens and data to create a bank of well-annotated specimens that will enable correlative science:
  - Identify host and viral factors in HSIL progression to cancer;
  - Identify host and viral biomarkers of progression from HSIL to cancer;
  - Identify medical history and behavioral risk factors for HSIL progression to cancer

NCI UM1CA121947 and OAR

Screen >17,385

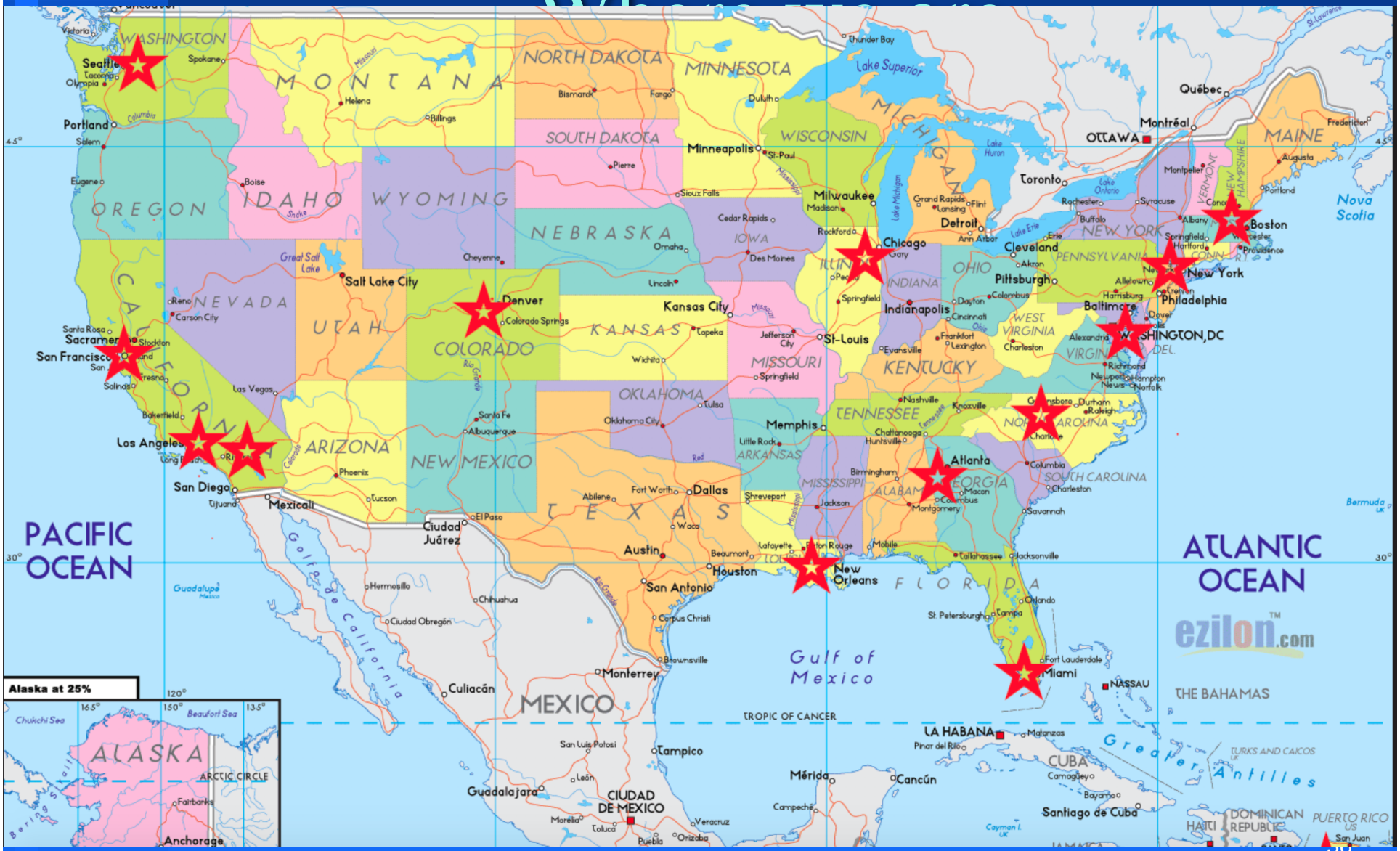
Enroll 5,058

Retain for 5 or more years



the ANCHOR study.org

A study of the AIDS Malignancy Consortium
Funded by the National Cancer Institute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Orlando
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NASSAU
THE BAHAMAS
Bermuda
San Antonio
Corpus Christi
Brownsville
Hermosillo
Chihuahua
Ciudad Obregón
Culiacán
Monterrey
MEXICO
Gulf of Mexico
Golfo de California
Guadalupe
Mexico
Rio Grande
Colorado
Red
Mississippi
Tennessee
PACIFIC OCEAN
ATLANTIC OCEAN
TROPIC OF CANCER
LA HABANA
Matanzas
Pinar del Río
CUBA
Camagüey
Bayamo
Santiago de Cuba
Cancún
Mérida
Campeche
Tampico
San Luis Potosí
León
Guadalajara
CIUDAD DE MEXICO
Morelia
Toluca
Puebla
Veracruz
Orizaba
Cayman I.
Greater Antilles
TURKS AND CAICOS
DOMINICAN REPUBLIC
HAITI
PUERTO RICO
US
San Juan
Alaska at 25%
ALASKA
Chukchi Sea
Beaufort Sea
Bering Sea
ARCTIC CIRCLE
Fairbanks
Anchorage
ezilon.com

ANCHOR study as of 8/28/20

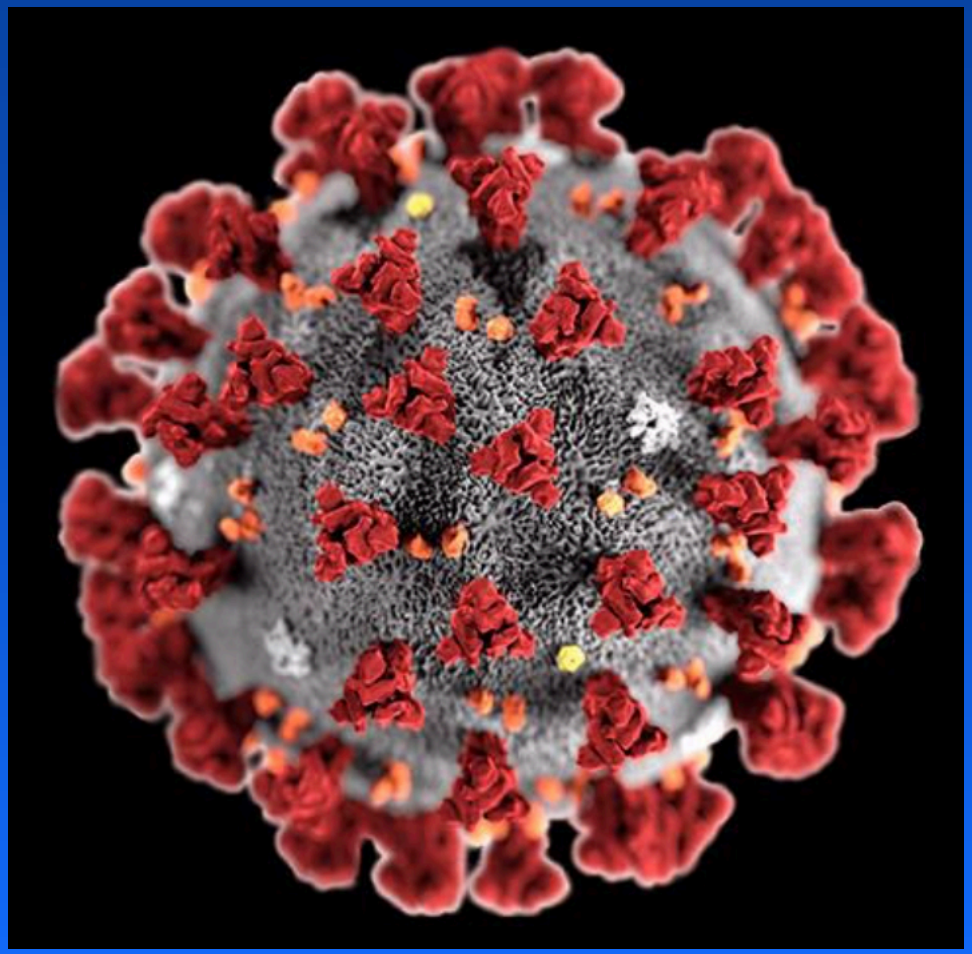
- Screened: 9684
- Enrolled: 3924

- Call 415-353-7443
- www.anchorstudy.org

Until ANCHOR results are available:

- Refer eligible patients to ANCHOR
- For patients ineligible or not interested in ANCHOR: screen with cytology or HPV and refer for HRA

Screening for and treating HSIL in the COVID era



In Memory

Barbara Winkler, MD

IANS guidelines

IANS Guidelines for the practice of HRA in the era of COVID-19

April 8, 2020

Key Points

- COVID-19 responses are rapidly changing and vary considerably with local epidemiology and resources. You can find out about what is happening in other places **here**.
- If resources allow, prioritize patients at highest risk of anal cancer risk – many/most will be able to be deferred for at least three months.
- Assess all patients for COVID-19 risk at time of booking and on day of procedure. HRA only indicated for those with highest risk of anal cancer and low risk of having COVID-19. Consider delaying HRA, even in these individuals, if they fall into any of the highly vulnerable COVID risk groups.
- If HRA is still indicated, then follow local Infection Control guidelines as a minimum.

www.iansoc.org

Do we really need guidelines for HRA during COVID-19 pandemic?

"Consequent to COVID-19 pandemic, all International and National Societies published countless guidelines about the management of patients affected by COVID-19. In spite of this IANS proposed its guidelines for the use of HRA in anal cancer and its precursors. Considering the costs to deal with COVID-19, the deficiency of healthcare professionals and the lack of worldwide evidence consensus on HRA, this examination cannot be considered mandatory during the COVID-19 pandemic. DARE with biopsy of suspicious palpable lesions in symptomatic patients could be considered enough during this period. Probably a latency of 6-12 months is reasonable for these patients without affecting the natural history of AIN."

Mistrangelo M et al. Colorectal Dis. 2020

Yes, we think so

"Many organisations have issued guidelines regarding the management of cancer in the era of COVID-19. In England at least, a new diagnosis of anal cancer would clearly be allocated a "Priority level 1", as there is a curative therapy with a high (>50%) chance of successful treatment. Newly diagnosed anal cancers clearly have better outcomes when diagnosed earlier, with increasing evidence that chemoradiotherapy may be avoided in small cancers such as superficially invasive squamous cell cancers"

Hillman R. et al. Colorectal Dis. 2020

HRA risk prioritization

Risk assessment	Category 1 High	Category 2 Intermediate	Category 3 Low
Priority	**Urgent**	**As soon as possible**	**May be deferred**
Definition	HRA should occur within one month, unless epidemic situation is extreme - in which case, prioritise biopsy of clinically invasive lesions. Prioritized as first to be scheduled.	HRA performed within 6 months, if possible. Symptom check-in by phone or telemedicine, repeat at 3 months.	Defer HRA until resumption of normal clinic scheduling. Symptom check-in by phone or telemedicine, repeat at 3-6 months.
Principal objective			
Clinical cancer assessment	Clinically highly suspicious of cancer. Digital Anal Rectal Examinations are an integral part of such an assessment.	Within 6 months of first cancer treatment and those treated within 2 years ago.	Low risk of cancer (unlikely within one year).
HSIL surveillance	HSIL clinically suspicious for cancer. Cytology or histology suspicious, but not diagnostic of cancer.	Features concerning for progressive disease in previous exam (e.g. lesion characteristics that are very prominent). Cytology HSIL, not yet assessed with HRA.	No current evidence of HSIL. No concerning features in previous exam. Cytology <HSIL or ASC-H (PHSIL).
Investigation of symptoms/signs (lump, bleeding, pain, tenesmus)	Symptoms or signs that have worsened or recurred	Symptoms present but unchanged in 6 months > 1 year since last exam.	No symptoms/signs.

Fecal shedding of SARS-CoV-2

- 28 of 42 (67%) patients with NP shedding tested positive for SARS-CoV-2 RNA in stool specimens,
- not associated with gastrointestinal symptoms
- 18 of 28 (64%) remained positive for viral RNA in the feces after the pharyngeal swabs turned negative.
- duration of viral shedding from the feces after negative conversion in pharyngeal swabs was 6-10 days, regardless of COVID-9 severity

Chen Y et al. J Med Virol 2020 Apr 3.

IANS guidelines
Summary recommendations

- Consider seeing only patients assessed to be at very high risk of anal cancer. DARE may provide a simple and relatively safe means of assessing risk.
- Aerosol-generating procedures such as laser or electrocautery are rarely necessary in an urgent situation. They should only be undertaken with full PPE including FFP3/N95 masks

www.iansoc.org

Screening in the COVID era

- Ongoing assessment of risk:benefit ratio
- Can defer screening of asymptomatic individuals with a negative DARE
- Consider referring symptomatic individuals
- Refer those with a mass on DARE

Summary

- Anal cancer is increasing in general population, remains high in HIV+ population
  - In the long run we can eliminate anal cancer

- The HPV vaccine is highly efficacious and is an Important tool to prevent anal cancer
  - Vaccinate age 26 and under!
  - After age 26= individual decision


Thank You for Your Attendance!
Please visit us at:
www.prn.org