Who do we (not) have to treat?

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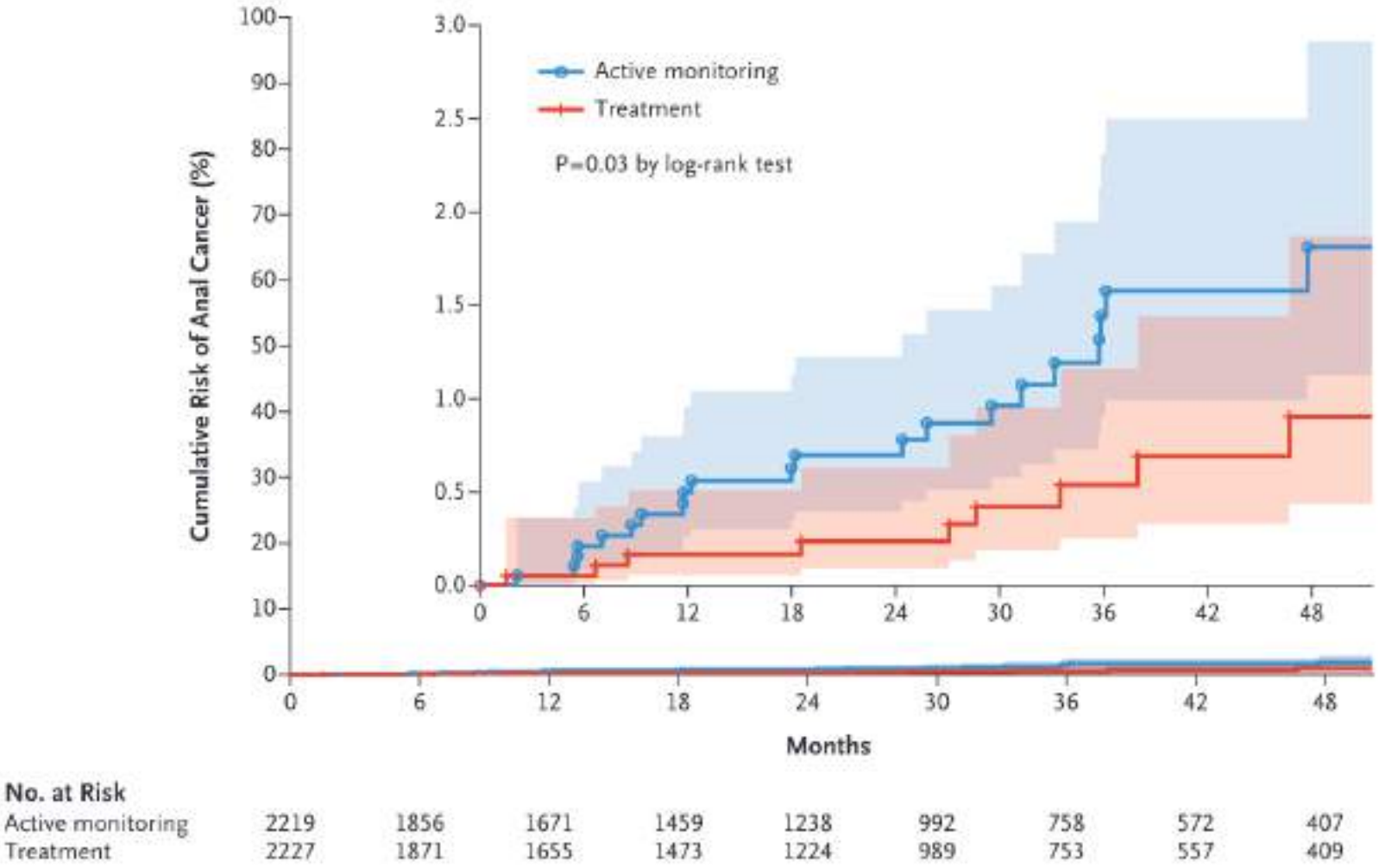
ENFERMEDADES INFECCIOSAS
H.U RAMÓN Y CAJAL

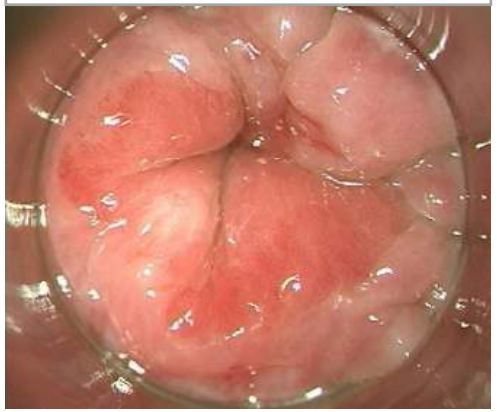
To Treat or Not to Treat?



Palefsky JM et al. Treatment of Anal High-Grade Squamous Intraepithelial Lesions to Prevent Anal Cancer. N Engl J Med. 2022 Jun 16;386(24):2273-2282.

Natural history of anal dysplasia

Normal / LSIL



40%

After 1y: 22-30%

HSIL

- **MSM, HIV-**:
  - 1/4196 per y (0.02%/y)
- **MSM, HIV+:**
  - 1/263 per y (1.72%/y)
  - 2.3% over 3 y

Cancer

Tong W, *et al.* Progression to and spontaneous regression of high-grade anal squamous intraepithelial lesions in HIV-infected and uninfected men. AIDS 2013

Mathews WC, *et al.* Natural History of Anal Dysplasia in an HIV-Infected Clinical Care Cohort: Estimates Using Multi-State Markov Modeling. PLoS ONE. 2014. 9(8):e104116

Jongen VW et al. Anal Squamous Intraepithelial Lesions (SILs) in Human Immunodeficiency Virus-Positive Men Who Have Sex With Men: Incidence and Risk Factors of SIL and of Progression and Clearance of Low-Grade SILs. J Infect Dis. 2020;222(1):62.

Machalek DA, *et al.* Lancet Oncol. 2012;13(5):487.

Goldstone S, *et al*. Five-year cumulative incidence of invasive anal cancer among HIV-infected patients according to baseline anal cytology results: an inception cohort analysis. HIV Med 2015; 16:191–5.

Fazendin EA, *et al*. Condyloma acuminatum, anal intraepithelial neoplasia, and anal cancer in the setting of HIV: do we really understand the risk? Dis Colon Rectum 2017; 60:1078–82

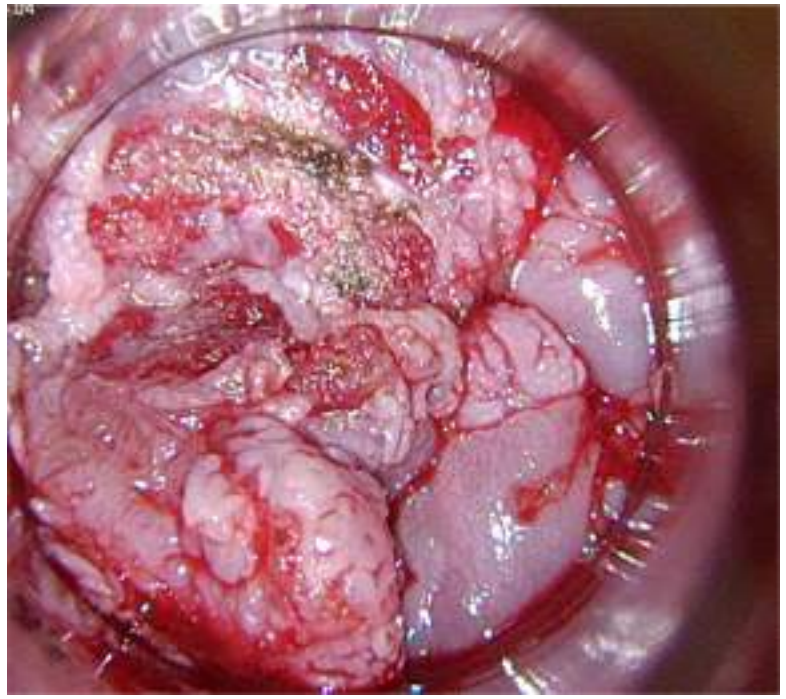
Mette T. Faber *et a*l. Risk of Anal Cancer Following Benign Anal Disease and Anal Cancer Precursor Lesions: A Danish Nationwide Cohort Study, Cancer Epidemiol Biomarkers Prev 2020

Poynten *et al*. The Natural History of Anal High-grade Squamous Intraepithelial Lesions in Gay and Bisexual Men. Clin Infect Dis. 2021 Mar 1;72(5):853-861.

Case 1

40 year-old transgender woman.
HIV+, on ART, CD4 >500, HPV16+, 18+, other HR +.

June 2020: Condylomatosis



November 2021: Verroucous carcinoma

Case 2

53 yo MSM with HIV on ART.
Recurrent circunferential condilomatosis (surgery x3).
HPV16+, 18-, other HR+.

Feb 2020: condilomatosis, LSIL, hyperkeratosis

July 2022:
Scamous cell carcinoma

Case 3

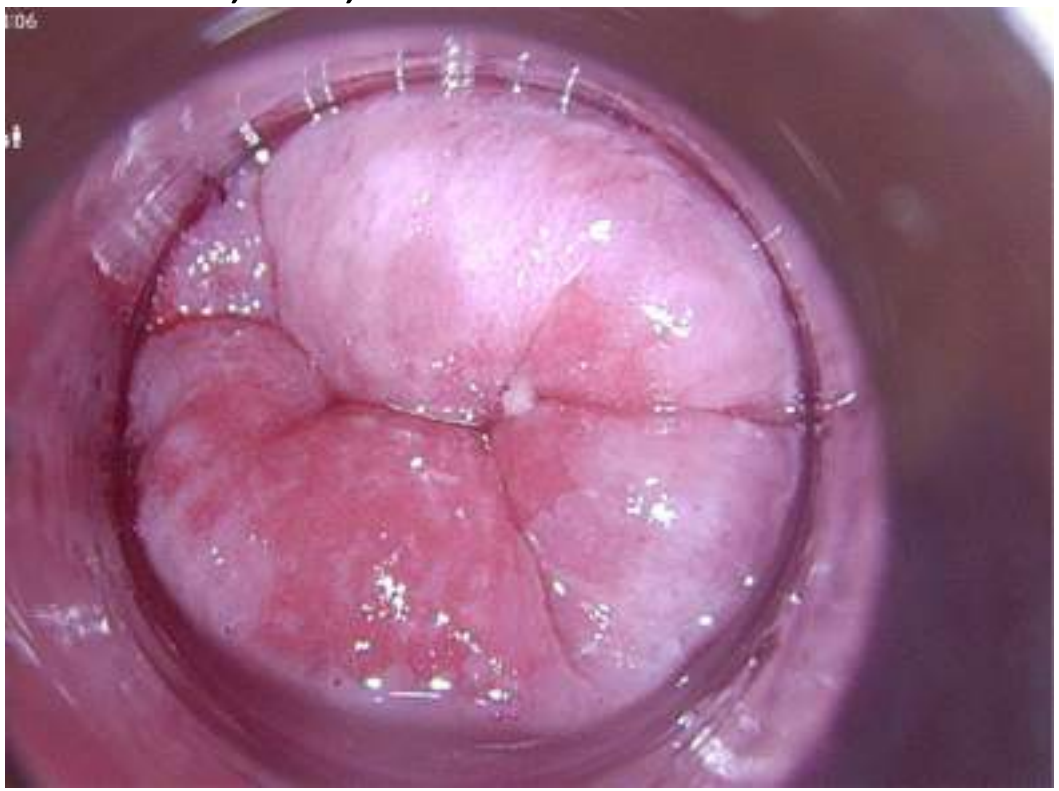
69 yo MSM with HIV, on ART, CD4 900/uL.
HPV16+, 18+, other HR+.

August 2022: First visit, anal complaints

Biopsies: Scamous cell carcinoma

Case 4

53 yo MSM on ART
HPV16+, 18-, other HR+

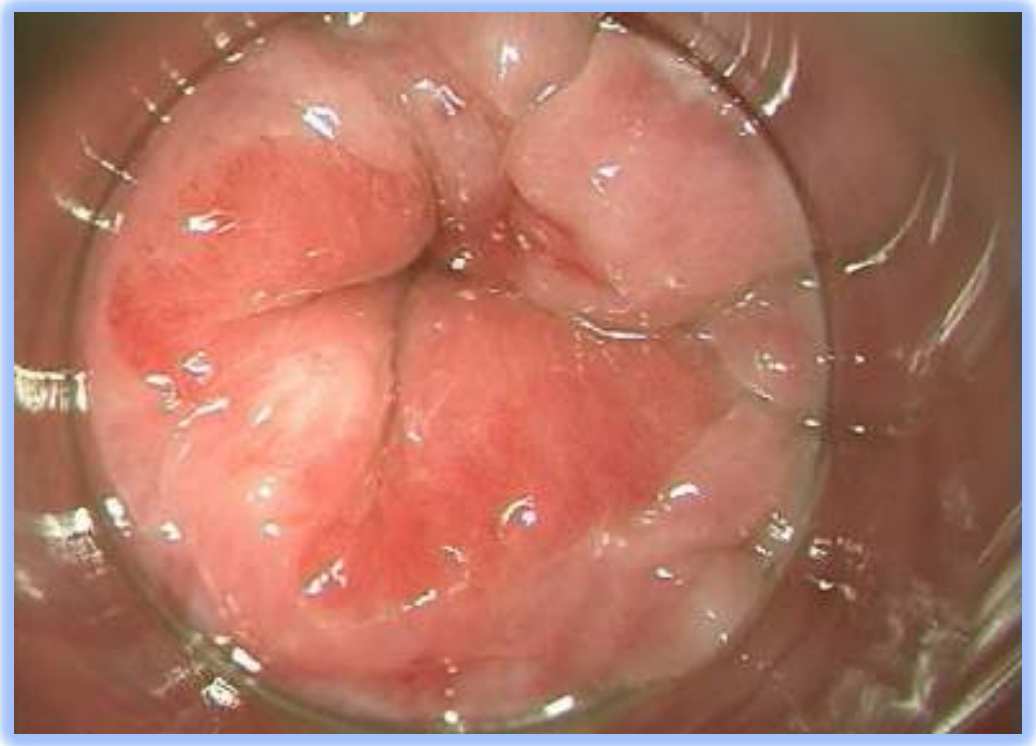


August 2022: Condyloma exeresis, Bx at 11: HSIL extension down to rectal glands. Cannot rule out infiltration

Surgery: Scamous cell carcinoma

Case 5

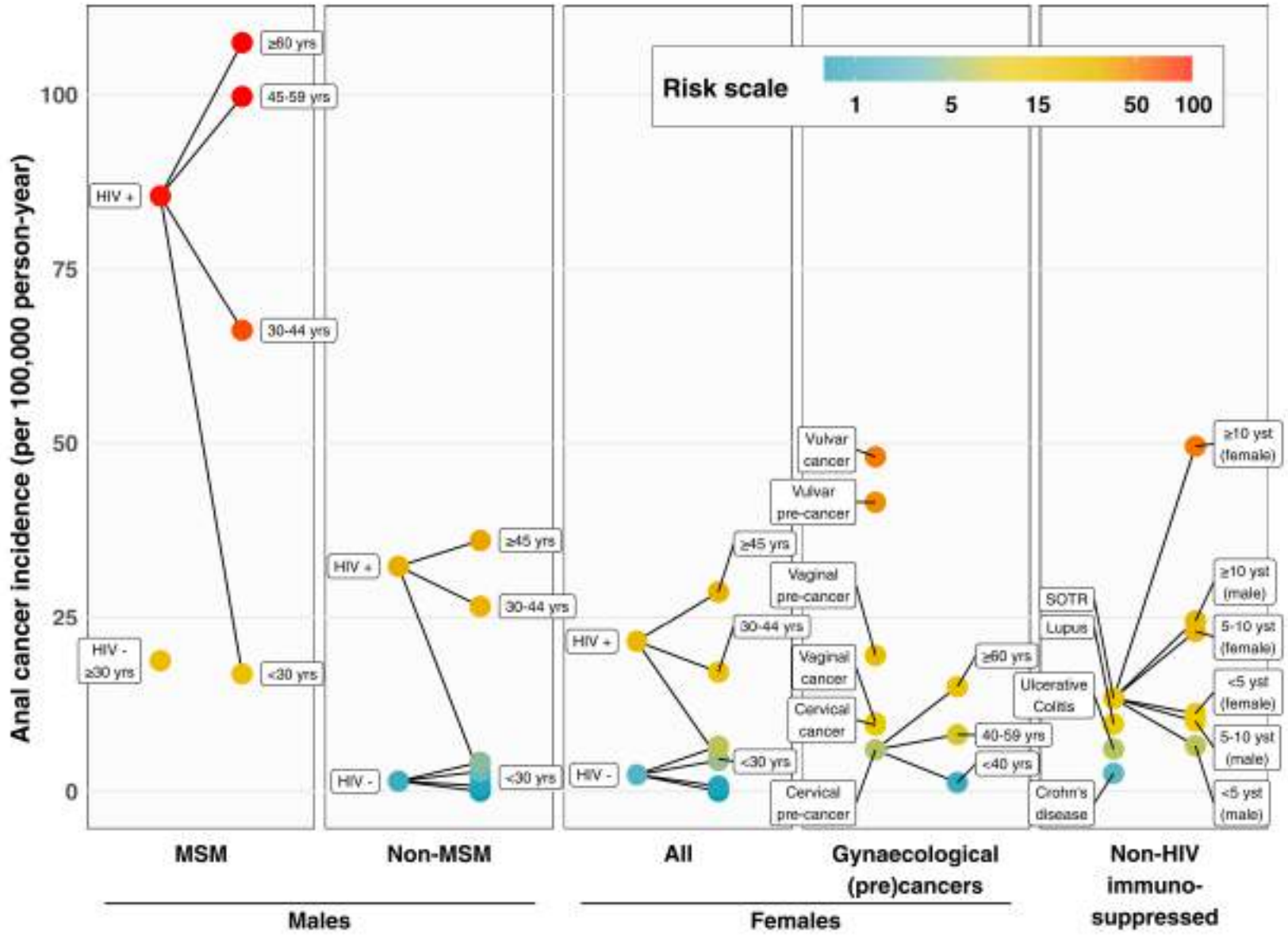
- 75 yo woman, not sexually active, referred from GI specialist.
- Follow-up colonoscopy due to past history of colononic polyps reveals intranal HSIL.
- No comorbidities
- No prior history of anogenital HPV disease.
- HPV 33+, anal cytology: LSIL
- Normal HRA



The majority of anal cancers occur in persons without pre-defined risk factors, and a large retrospective cohort study of a Kaiser Permanente database found previous HSIL to be one of the strongest risk factors for subsequent development of SCC.

Tomassi MJ, Abbas MA, Klaristenfeld DD. Expectant management surveillance for patients at risk for invasive squamous cell carcinoma of the anus: a large US healthcare system experience. Int J Colorectal Dis 2019; 34:47–54.

Towards a Unified Anal Cancer Risk Scale



Clifford GM, *et al*. A meta-analysis of anal cancer incidence by risk group: Toward a unified anal cancer risk scale. Int. J. Cancer. 2021

Risk factors for HSIL progression

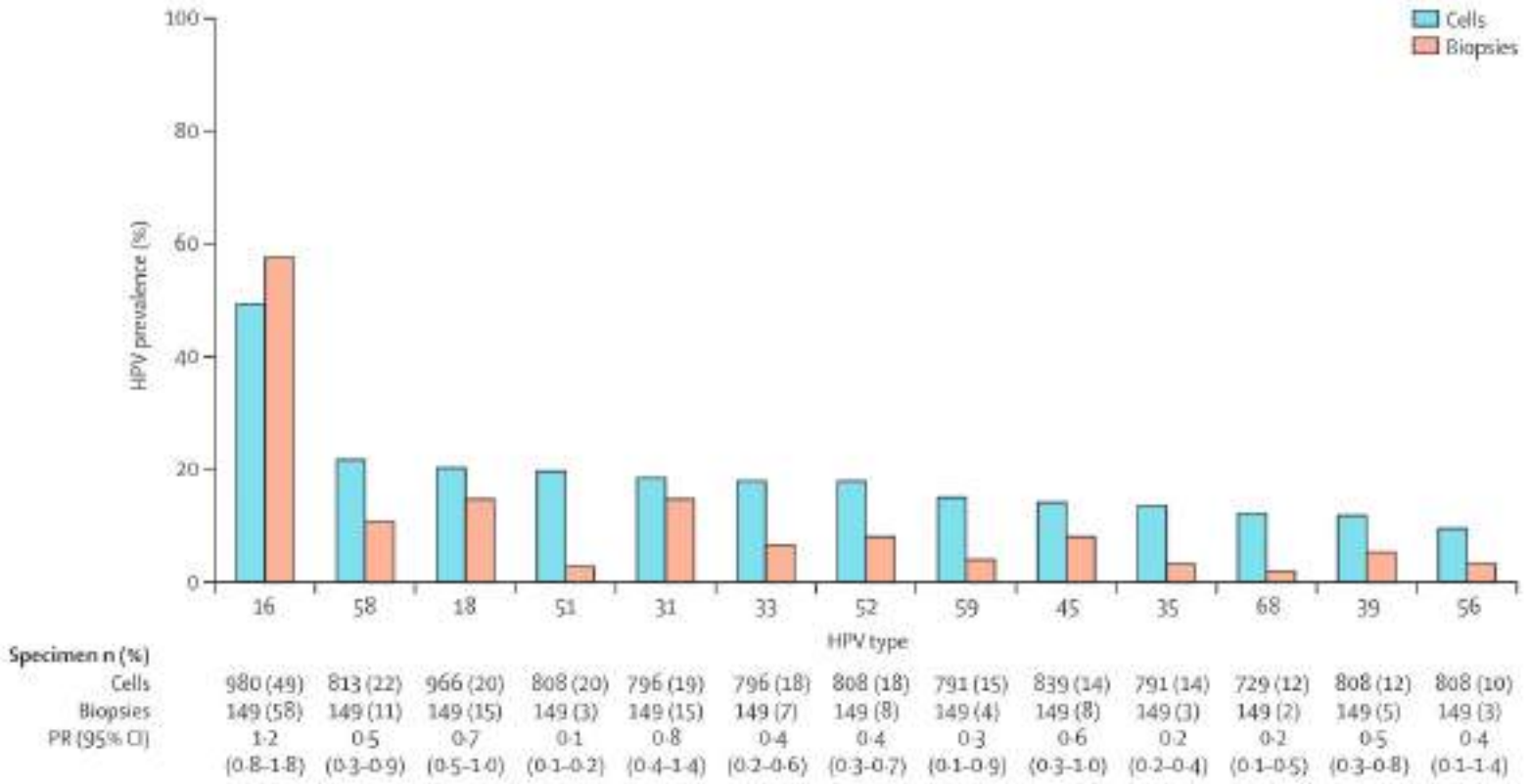
Viral factors

HPV 16

Serrano-Villar, Personal Communication. Generated in biorender.com.

HPV16 is responsible of the largest fraction of anal cancers

- HPV 16 is enriched in HSIL and anal cancer lesions.
- HPV 16 associated with 75-89% of all anal cancers in cross-sectional studies from tissue banking.
- The fraction of anal cancer attributable to HPV16 is smaller in PWH.
- By far the most carcinogenic HPV type.



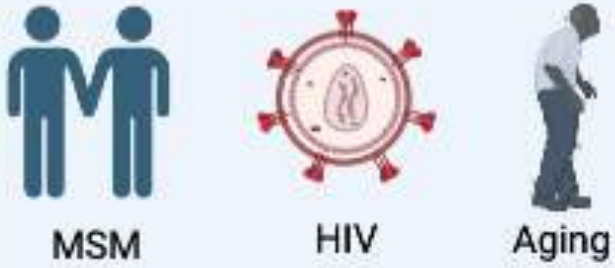
Lin C, Franceschi S, Clifford GM. Human papillomavirus types from infection to cancer in the anus, according to sex and HIV status: a systematic review and meta-analysis. Lancet Infect Dis. 2018 Feb;18(2):198-206. doi: 10.1016/S1473-3099(17)30653-9. Epub 2017 Nov 17. PMID: 29158102; PMCID: PMC5805865.
Roldán Urgoiti GB, et al. The prognostic value of HPV status and p16 expression in patients with carcinoma of the anal canal. PLoS One 2014; 9:e108790. 67. Alemany L, Saunier M, et al.; HPV VVAP Study Group. Human papillomavirus DNA prevalence and type distribution in anal carcinomas worldwide. Int J Cancer 2015; 136:98–107. 68. Valmary-Degano S, et al. Signature patterns of human papillomavirus type 16 in invasive anal carcinoma. Hum Pathol 2013; 44:992–1002.

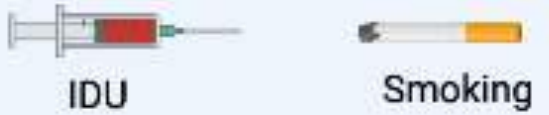
Risk factors for HSIL progression

Viral factors

HPV 16

Environmental factors





Solid-organ transplant

Serrano-Villar, Personal Communication. Generated in biorender.com.

Predictors of HSIL regression

- Age < 45 years old
- HPV16 clearance
- Smaller lesion size
- AIN2 instead of AIN3
- Stronger HPV-specific CD4+ T cell response

Markers of stronger immune responses against HPV

We need markers/an algorithm to distinguish HSIL that requires treatment vs HSIL that can be monitored.

Poynten IM, et al. The natural history of anal high-grade squamous intraepithelial lesions in gay and bisexual men. Clin Infect Dis 2021; 72:853–61.
Tong WW, et al.; Study of the Prevention of Anal Cancer (SPANC) team. Human papillomavirus 16-specific T-cell responses and spontaneous regression of anal high-grade squamous intraepithelial lesions. J Infect Dis 2015; 211:405–15.

Risk factors for HSIL progression

Viral factors

HPV 16

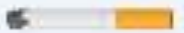
Environmental factors

MSM

HIV

Aging

IDU



Smoking

Solid-organ transplant

Genetic factors

History of anogenital HPV disease

Recalcitrant condylomas (DOCK8 deficiency)

HPV-discordant couples

Serrano-Villar, Personal Communication. Generated in biorender.com.

Recurrent HPV disease and Genetic susceptibility

DOCK8 deficiency

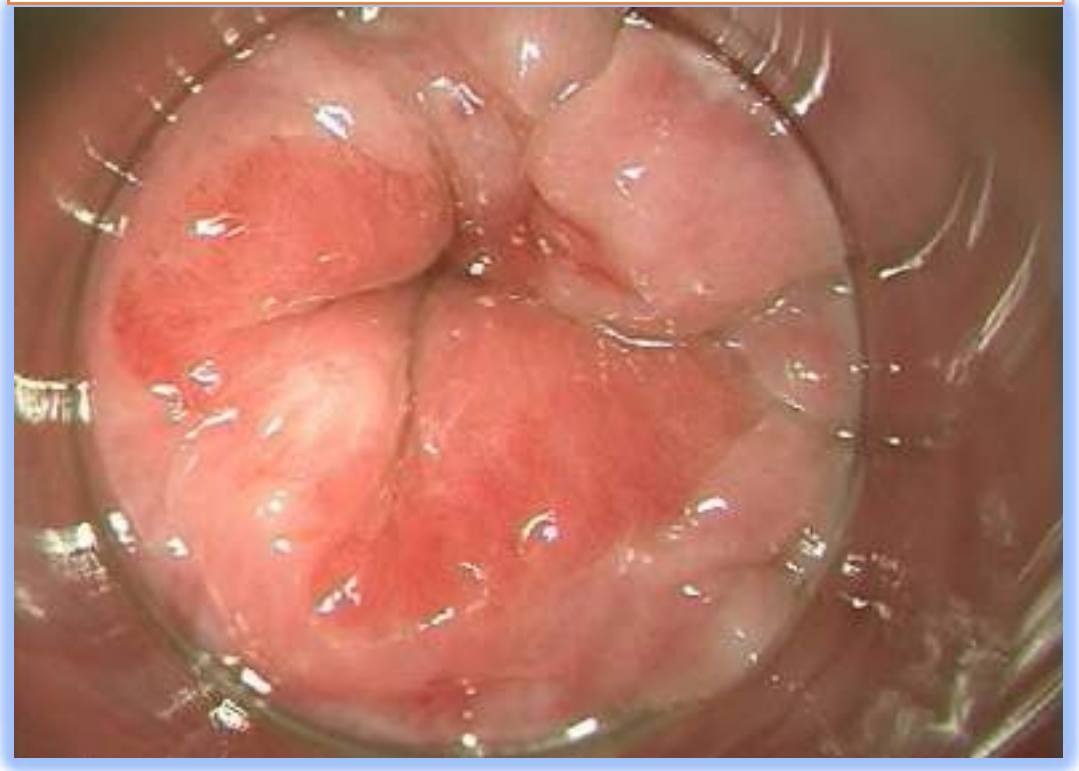
36 y/o African-American man with Hx:

- Recalcitrant genital condylomas (age 20) s/p recurrent hematuria and pyelonephritis requiring urethral diversion.
- Further extension of penile lesions and poor wound healing -→penectomy (age 31)
- HPV-related SCC in situ in upper and lower extremities bilaterally, invasive disease in 4th finger

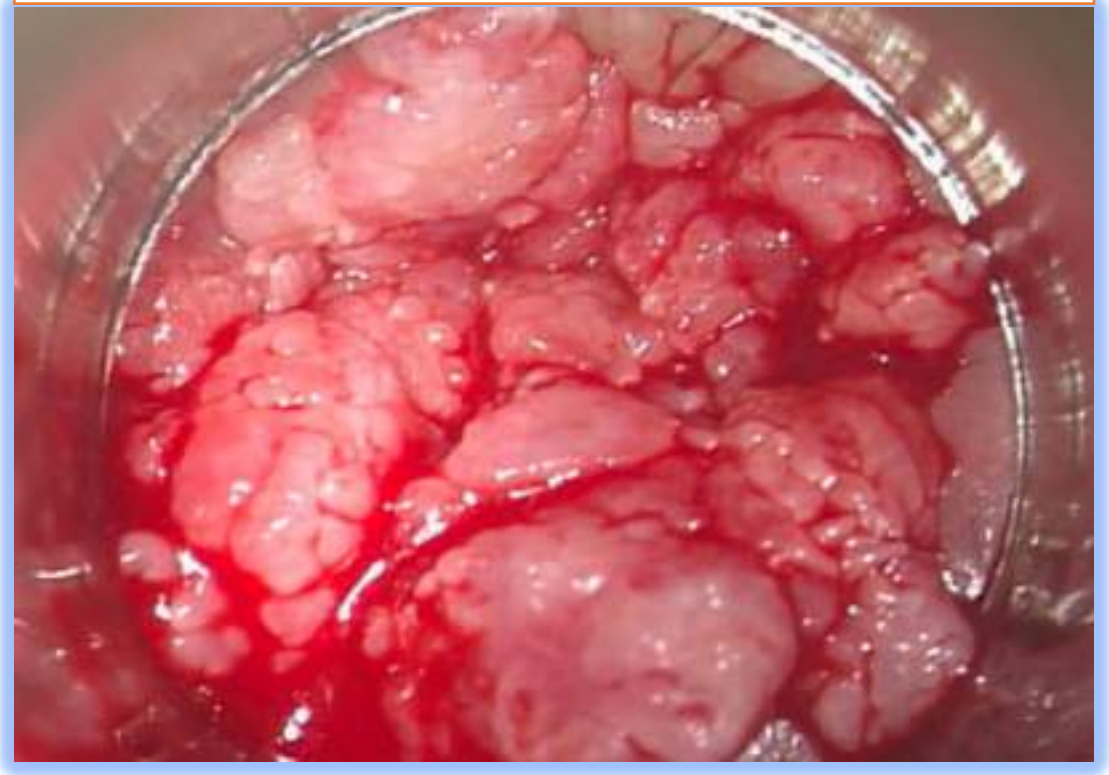
Lisco. Personal Communication. NIH 2017

Clinical discordance between stable sexually active couples: Genetic susceptibility?

Patient 1: MSM with HIV on ART, CD4 >500, HPV 16+



Patient 2 (his partner): MSM with HIV on ART, CD4 >500, HPV 16+



Besides the HPV type and the risk group, how can we better capture the risk of HSIL progression to anal cancer?

Cumulative information

Anal cytologies and HRA repeteadly normal
Absence of high risk HPV over time
Long-term treatment response

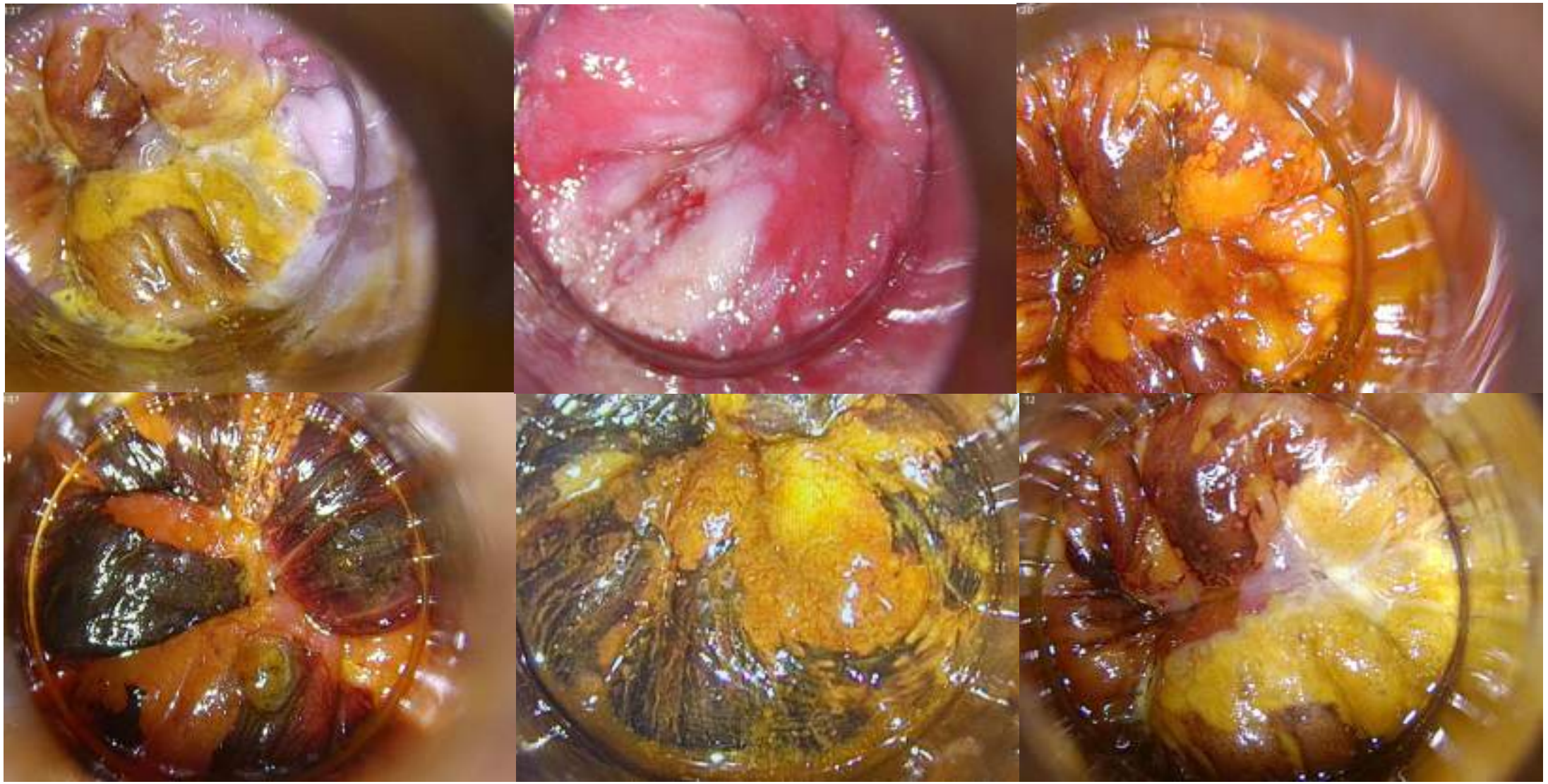
Cytologic HSIL despite “normal” HRA
Persistent HPV16
Refractory/recurrent HSIL

Abnormal HRA

HSIL diagnosed

Successful treatment

HRA patterns: Does a circunferencial HSIL is clinically equivalent to a HSIL diagnosed during random biopsies?



IJC
International Journal of Cancer

2014

Progression of anal high-grade squamous intraepithelial lesions to invasive anal cancer among HIV-infected men who have sex with men

J. Michael Berry[1], Naomi Jay[1], Ross D. Cranston[2], Teresa M. Darragh[3], Elizabeth A. Holly[4], Mark L. Welton[5] and Joel M. Palefsky[1]

[1] Department of Medicine, University of California San Francisco, San Francisco, CA
[2] Department of Medicine, University of Pittsburgh, Pittsburgh, PA
[3] Department of Pathology, University of California San Francisco, San Francisco, CA
[4] Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA
[5] Department of Surgery, Stanford University, Stanford, CA

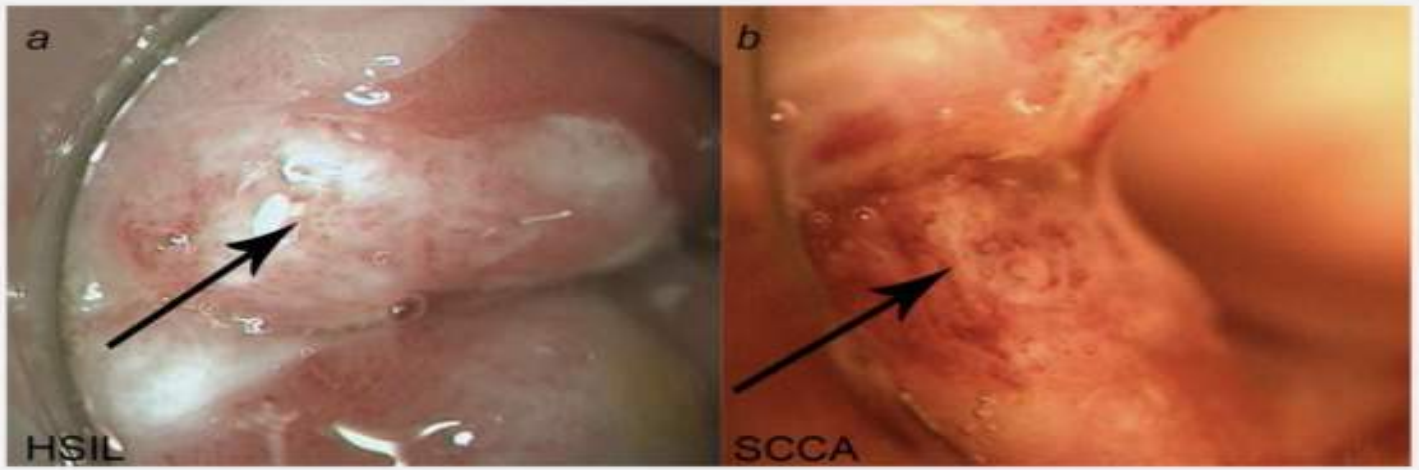


Figure 2. (*a*) Case 6. Arrow indicates anal high-grade squamous intraepithelial lesion (HSIL) biopsied in May 2001 at the end of Anal Neoplasia Study. Patient lost to follow-up. (*b*) The same man presented with a palpable mass in June 2002 in exactly the same area as previously biopsied HSIL; arrow indicates invasive squamous cell carcinoma (SCCA). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

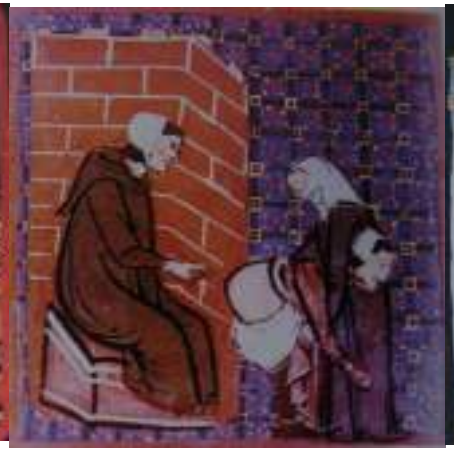
- Retrospective study of **138 cases of anal cancer** (1997-2011).
- Although diffuse multifocal HSIL was present in 21 **(15%)** men, only three men developed simultaneous multifocal cancers.
- Six of 27 study participants had discrete lesions

Current algorithm to capture the risk of HSIL progression

Fiat secundum artem

Enema, Galenic texts
129 dC

Hemorrhoidectomy
Salerno school
XII century



DARE
Middle age

Hemorrhoid
cauterization
XV century

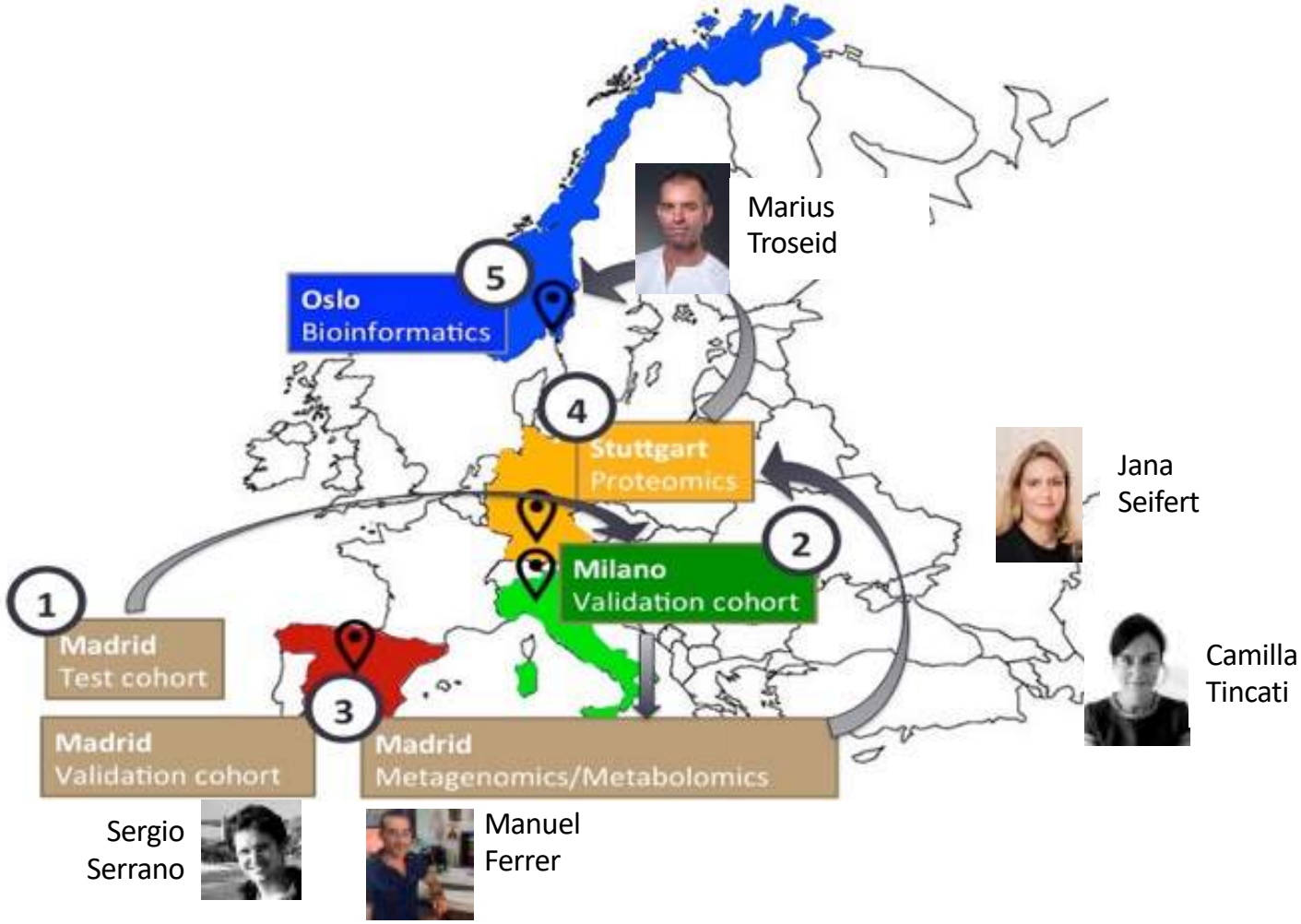
Delfos oracle
2022

Wishlist - #1 – Biomarkers of HSIL progression

Microbiota-based SCReening of Anal Cancer in PWH (SCRATCH)

TRANSCAN-2
ERA-NET: Aligning national/regional translational cancer research programmes and activities
TRANSCAN-2

- **Study period: 2018-2022**
- **N=300, test and validation cohorts**
- **Primary aim:**
  - Identify in MSM with HIV anal-associated bacterial biomarkers to improve the accuracy of anal cytology for the diagnosis of biopsy-proven HSIL.
  - Potential bacterial biomarkers: bacteria, proteins and metabolites**.**



https://www.transcanfp7.eu/index.php/abstract/scratch.html

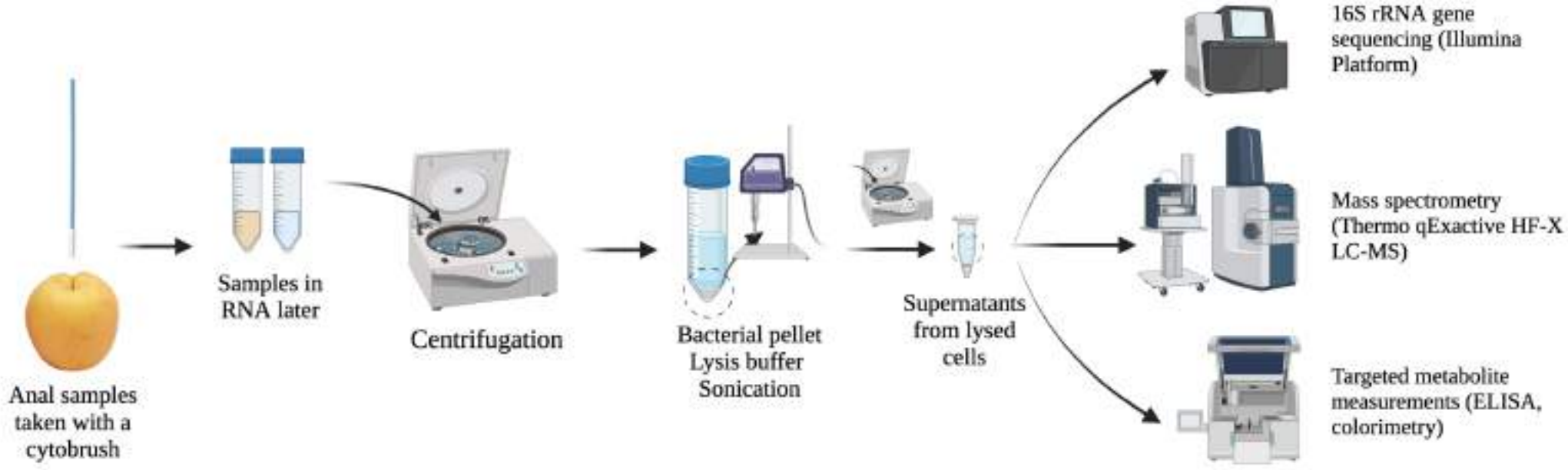
Wishlist - #1 – Biomarkers of HSIL progression

Microbiota-based SCReening of Anal Cancer in PWH (SCRATCH)

METHODS

Population: 213 MSM with HIV undergoing HSIL screening in 4 clinical sites in Spain and Italy

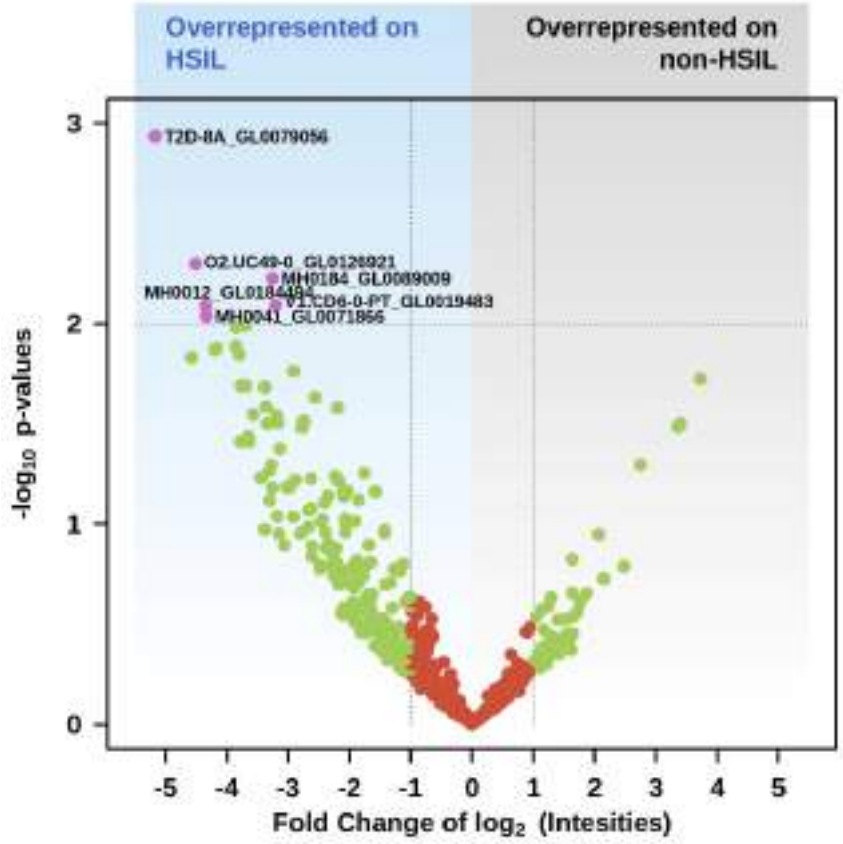
- Discovery cohort: 167 (70 with confirmed HSIL)
- Validation cohort: 46 (25 with confirmed HSIL)

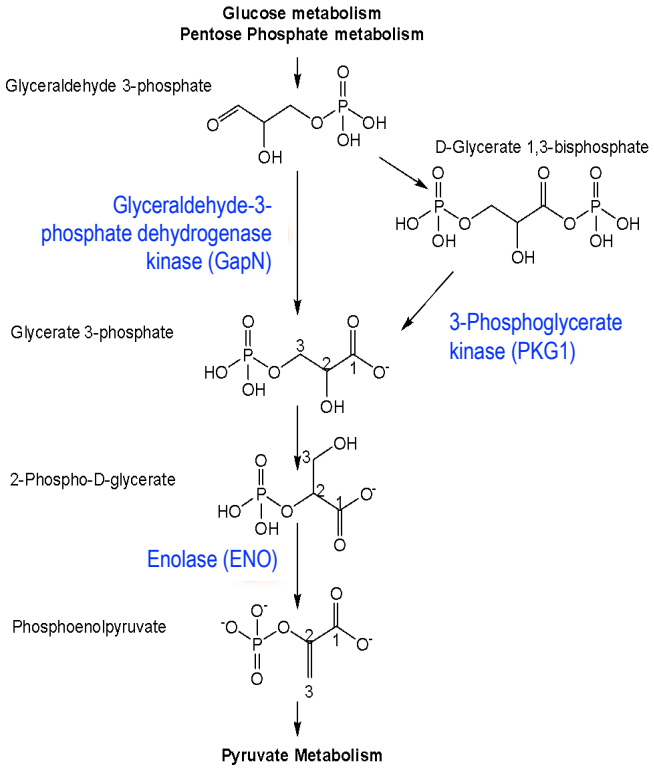


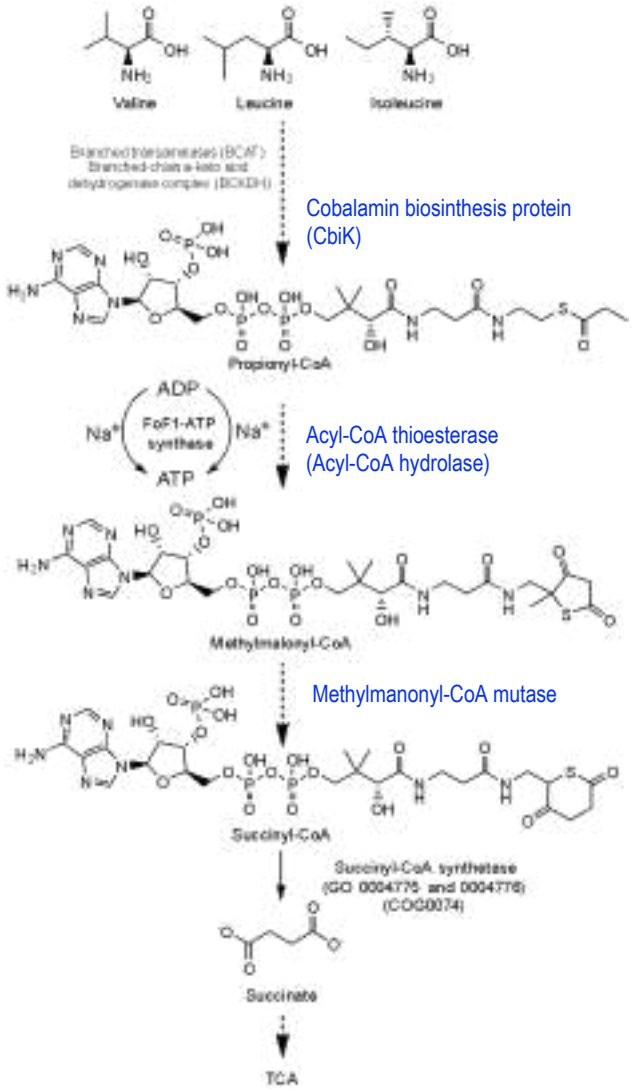
Wishlist - #1 – Biomarkers of HSIL progression

Microbiota-based SCReening of Anal Cancer in PWH (SCRATCH)

RESULTS





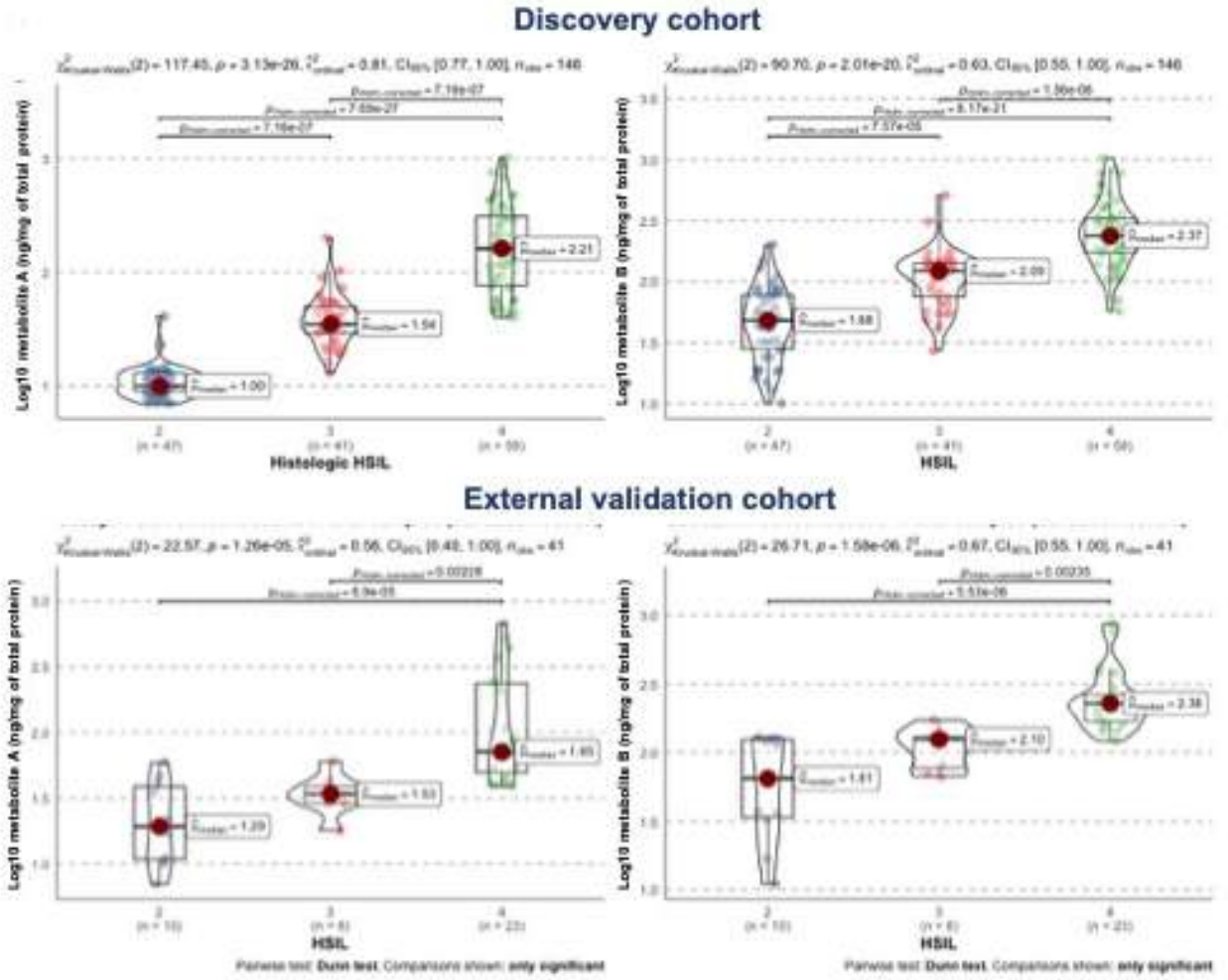


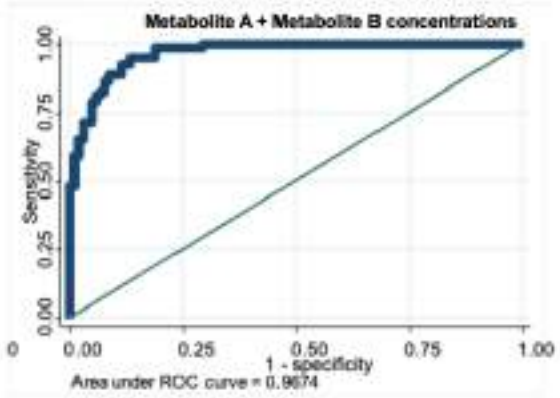
Scratch study. Unpublished

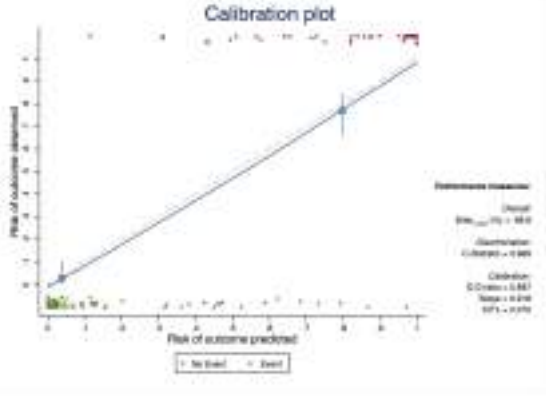
Wishlist - #1 – Biomarkers of HSIL progression

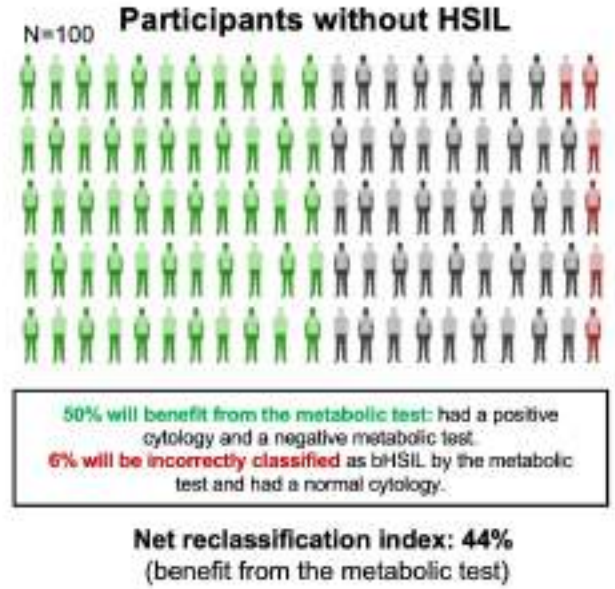
Microbiota-based SCReening of Anal Cancer in PWH (SCRATCH)

RESULTS





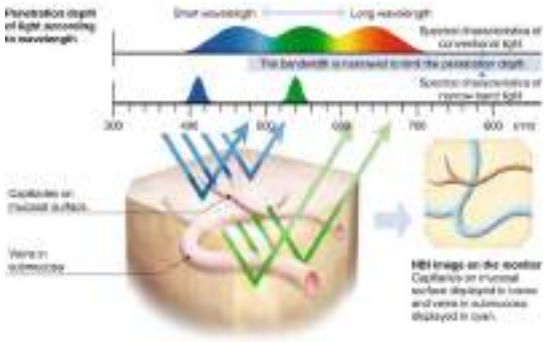




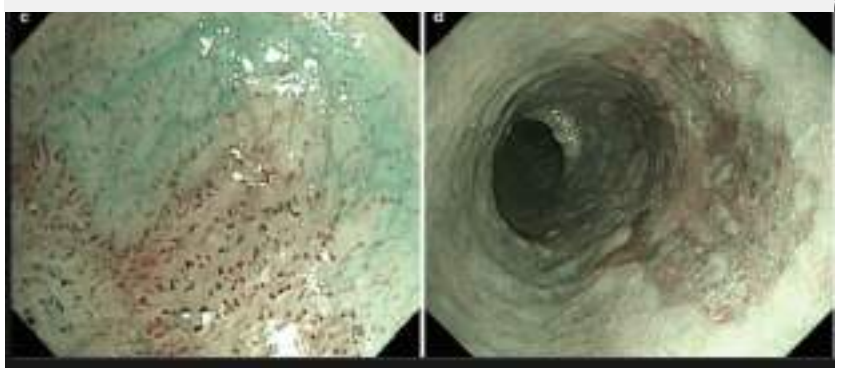
Net reclassification index: 44%
(benefit from the metabolic test)

Wishlist - #2 – Move beyond acetic and Lugol staining

Narrow Band Imaging (NBI)



Esophagus

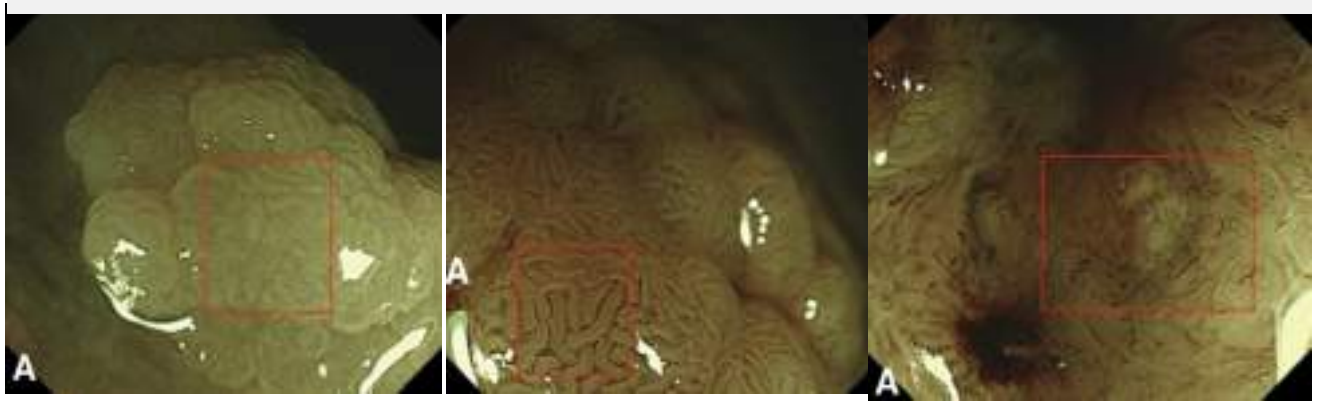


Origin of ectocervix glycogen staining with iodine

Paul Erlich
1854 – 1915
Physiologis
Nobel Price 1908

Walter Schiller
(1887-1960)
Pathologist

Colon



The computer-aided classification system yielded a detection accuracy of 97.8% (363/371); sensitivity and specificity of types B-C3 lesions for a diagnosis of neoplastic lesion were 97.8% (317/324) and 97.9% (46/47), respectively

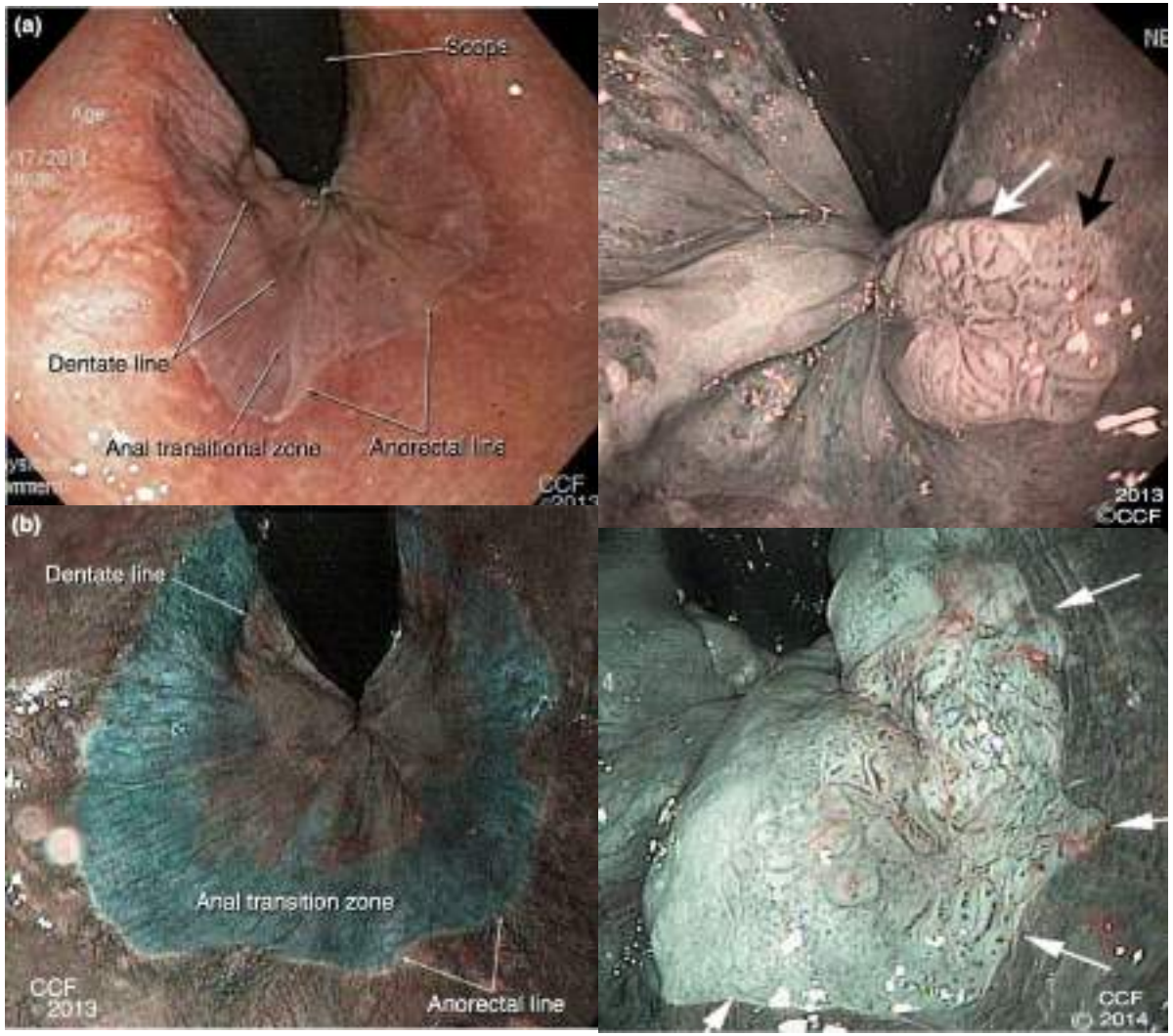
Takemura Y et al. Computer-aided system for predicting the histology of colorectal tumors by using narrow-band imaging magnifying colonoscopy. Gastrointestinal endoscopy 2012; 75: 179-185.

Hajelssedig *et al*. Diagnostic accuracy of narrow-band imaging endoscopy with targeted biopsies compared with standard endoscopy with random biopsies in patients with Barrett's esophagus: A systematic review and meta-analysisJ Gastroenterol Hepatol. 2021 Oct;36(10):2659-2671

Wishlist - #2 – Move beyond acetic and Lugol staining

Detection of anal dysplasia is enhanced by NBI and acetic acid

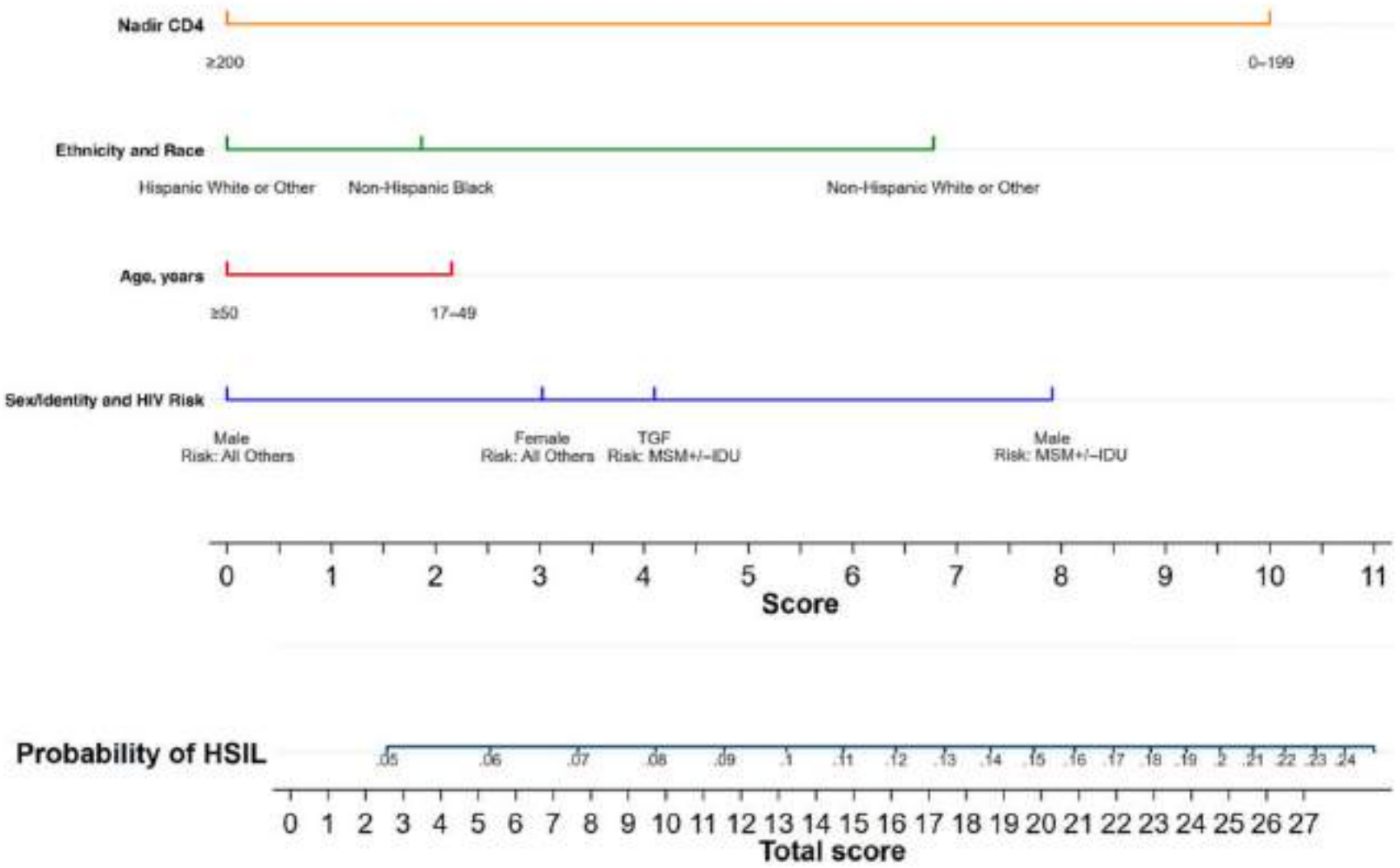
- 60 patients with abnormal anal cytology
- Endoscopic anorectal examination
- Biopsies from abnormal regions in 58 cases.
- SIL 41/60 demonstrated: 28 LSIL, 13 HSIL.
- Acetic acid + NBI was able to detect more lesions than acetic acid or NBI alone.



Inkster *et al.* Detection of anal dysplasia is enhanced by narrow band imaging and acetic acid. Colorectal Dis; 1: O17-21, 2016.

Wishlist - #3 – Nomograms for anal cancer risk

Need nomograms to prioritize patients for anal cancer screening

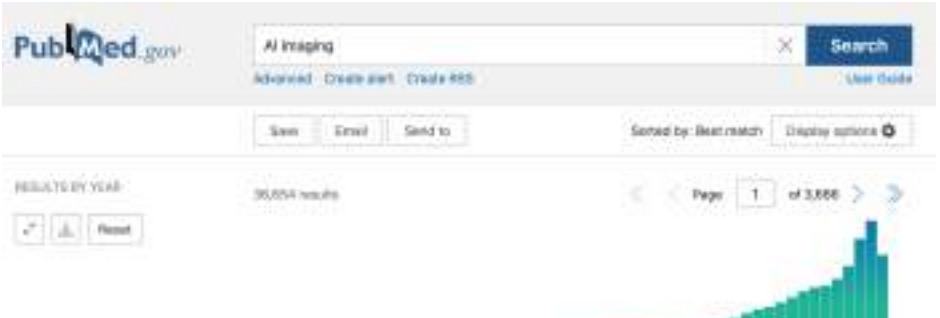


AUC 0.63

Cachay *et al.* Shared decision-making concerning anal cancer screening in persons with HIV. Clin Infect Dis 2022 (ciac491) 2016.

Wishlist - #4 – Facilitate AI takeover

Need to develop for AI-based HRA



Thanks to Dr. Crespillo and Dr. Ron, our next-gen anoscopist taking over

Clinical Gastroenterology and Hepatology

CLINICAL – ALIMENTARY TRACT | ARTICLES IN PRESS

Artificial Intelligence–Assisted Colonoscopy for Colorectal Cancer Screening: A Multicenter Randomized Controlled Trial

Hong Xu • Raymond S.Y. Tang • Thomas Y.T. Lam • ... Zhenshi Ye • Zhang Shutian • Joseph J.Y. Sung

Show all authors • Show footnotes

Conclusions

In this multicenter RCT in asymptomatic patients, AI-assisted colonoscopy improved overall ADR, advanced ADR, and ADR of both expert and nonexpert attending endoscopists. (ClinicalTrials.gov, Number: NCT04422548).

nature COMMUNICATIONS

ARTICLE

OPEN

Accurate recognition of colorectal cancer with semi-supervised deep learning on pathological images

Gang Yu[1], Kai Sun[1], Chao Xu[2], Xing-Hua Shi[3], Chong Wu[4], Ting Xie[1], Run-Qi Meng[5], Xiang-He Meng[6], Kuan-Song Wang[7✉], Hong-Mei Xiao[8✉] & Hong-Wen Deng[6,8✉]

Who do we (not) have to treat?

Treat everyone

Prioritize people for HSIL screening and treatment based on anal cancer incidence

1. PWH: MSM, >45 years, women with previous genital HPV disease
2. Other causes of immunosuppression
3. Use cumulative information: recurrent HSIL lesions, persistent HPV16

Promote highly collaborative research

- Discover markers of HSIL progression: large biobanks in prospective cohorts with enough number of cancers
- Nomograms to stratify anal cancer risk
- Understad better the clinical significance of HSIL patterns
- Facilitate AI: massive prospective image repositories

THANK YOU!!

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