

**Anal intraepithelial neoplasia (AIN):
Diagnosis, treatment, and follow-up**

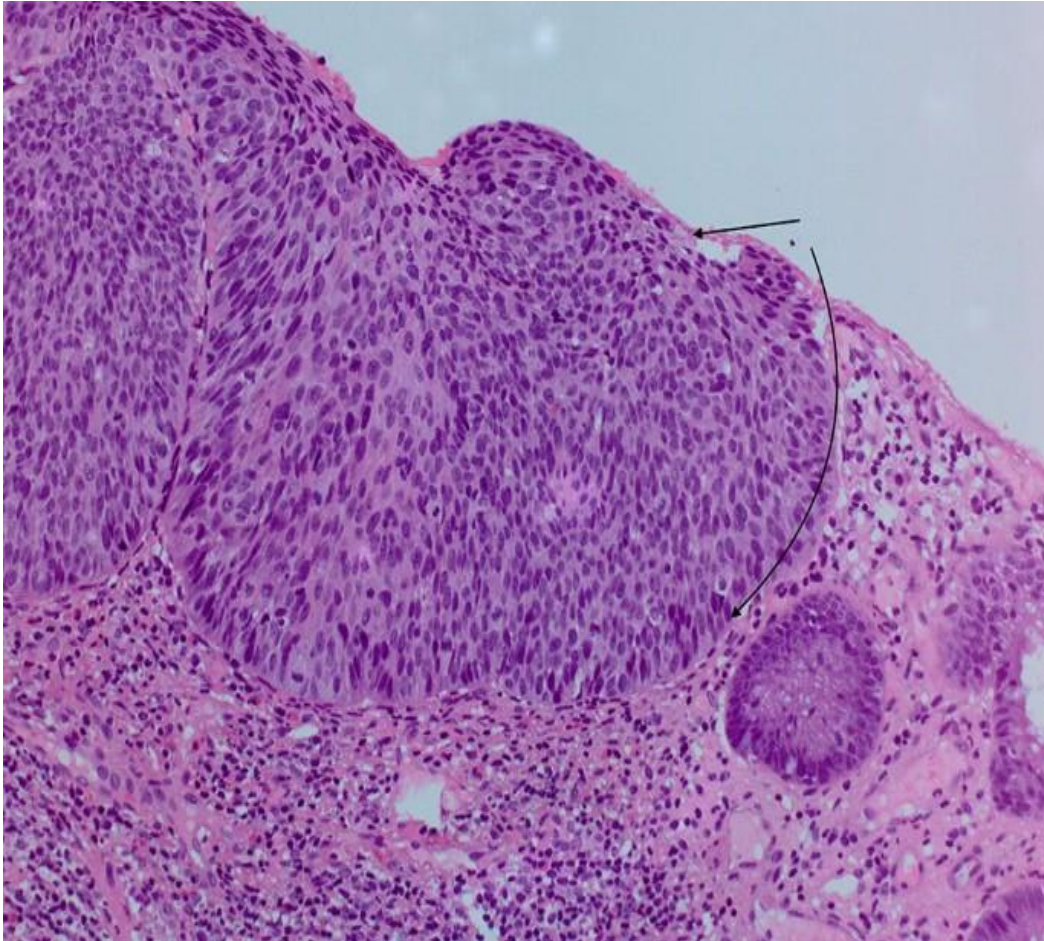


**Dr. Stephan Baumeler
Co-Chefarzt Gastroenterologie**

What is anal intraepithelial neoplasia (AIN) or anal squamous intraepithelial lesion (ASIL)?



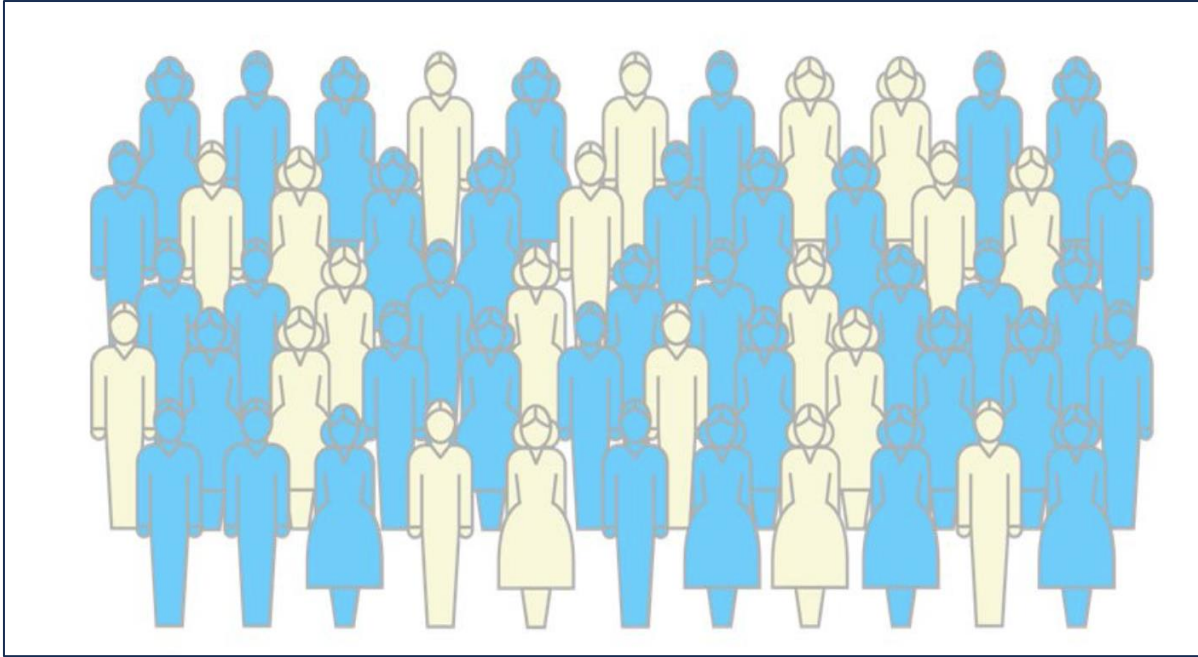
What is anal intraepithelial neoplasia (AIN) or anal squamous intraepithelial lesion (ASIL)?



ASIL is a **neoplastic change** secondary to **chronic infection** with the human papillomavirus (**HPV**) in a **susceptible host**.

ASIL is classified into two groups based on the degree of dysplasia: **low-grade SIL (LSIL)** and **high-grade SIL (HSIL)**

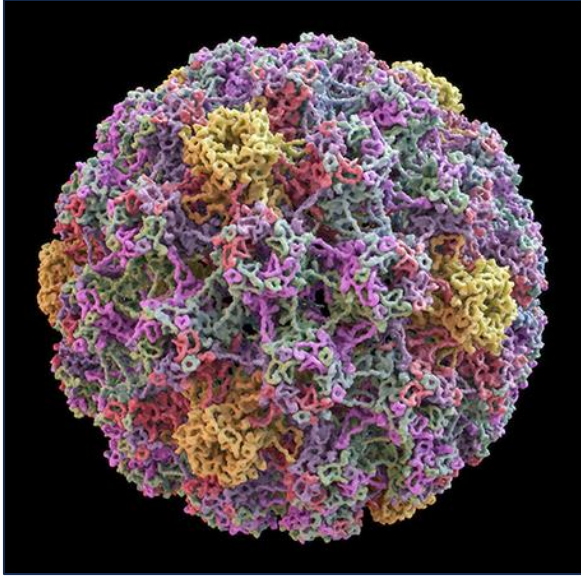
Human Papilloma Virus



in industrialized countries, 70% of the population already had an HPV infection

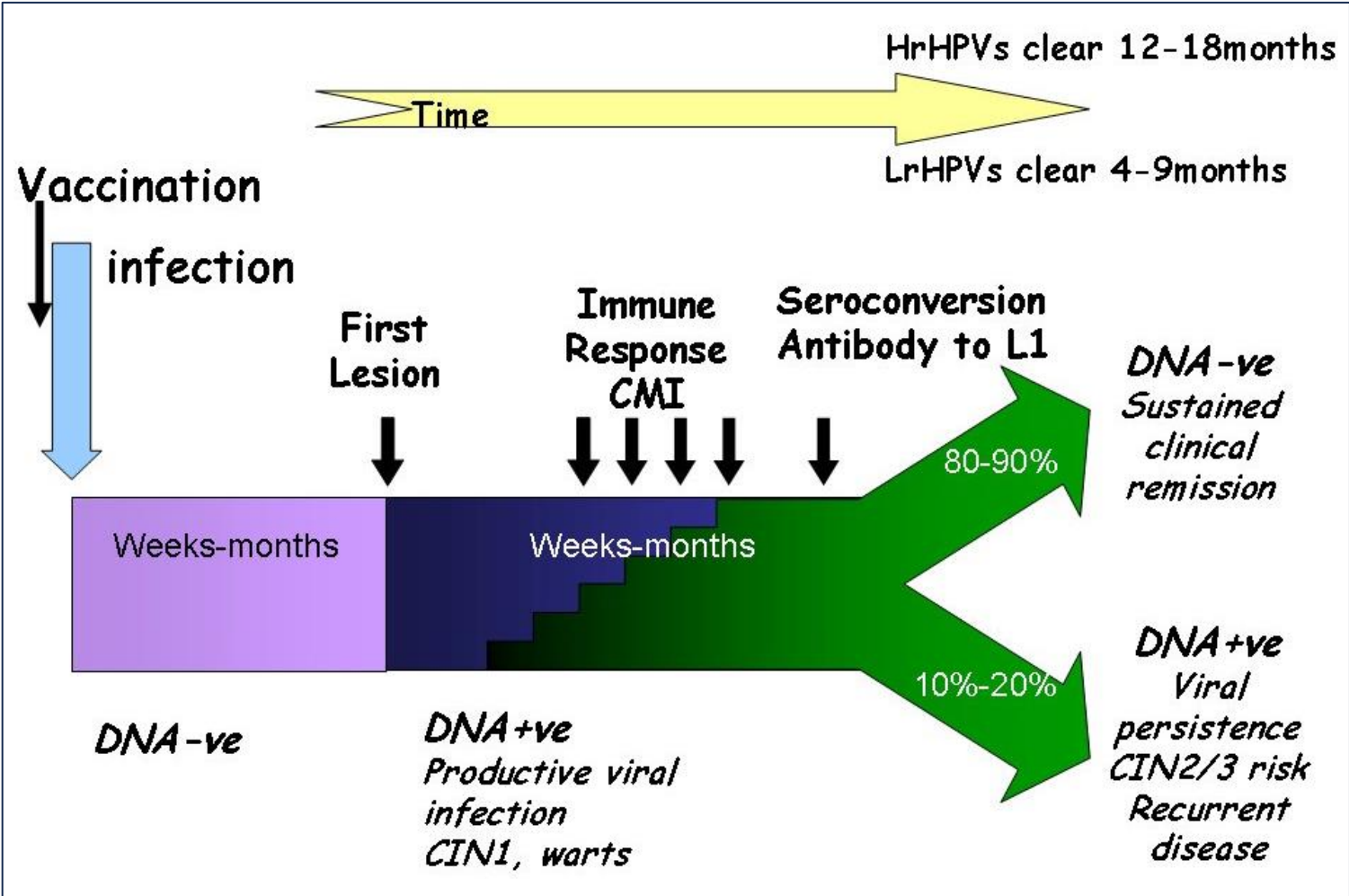
- HPV is the most common family of viruses
- HPV is the most common sexually transmitted infection
- Chances are YOU will contract some form of the HPV virus in your lifetime and not have any signs or symptoms
- At least 80% of women and 50% of men will have been infected by genital HPV by the time they turn 50.

Human Papilloma Virus



- Over 100 different types of HPs. Over 30 types are sexually transmitted
- There are a number of conditions that HPV can cause
 - Common, plantar or flat warts
 - Genital warts
 - Precancerous changes
 - Laryngeal & esophageal papillomas
 - Cervical cancer
 - Anal cancer

Genital HPV: natural course

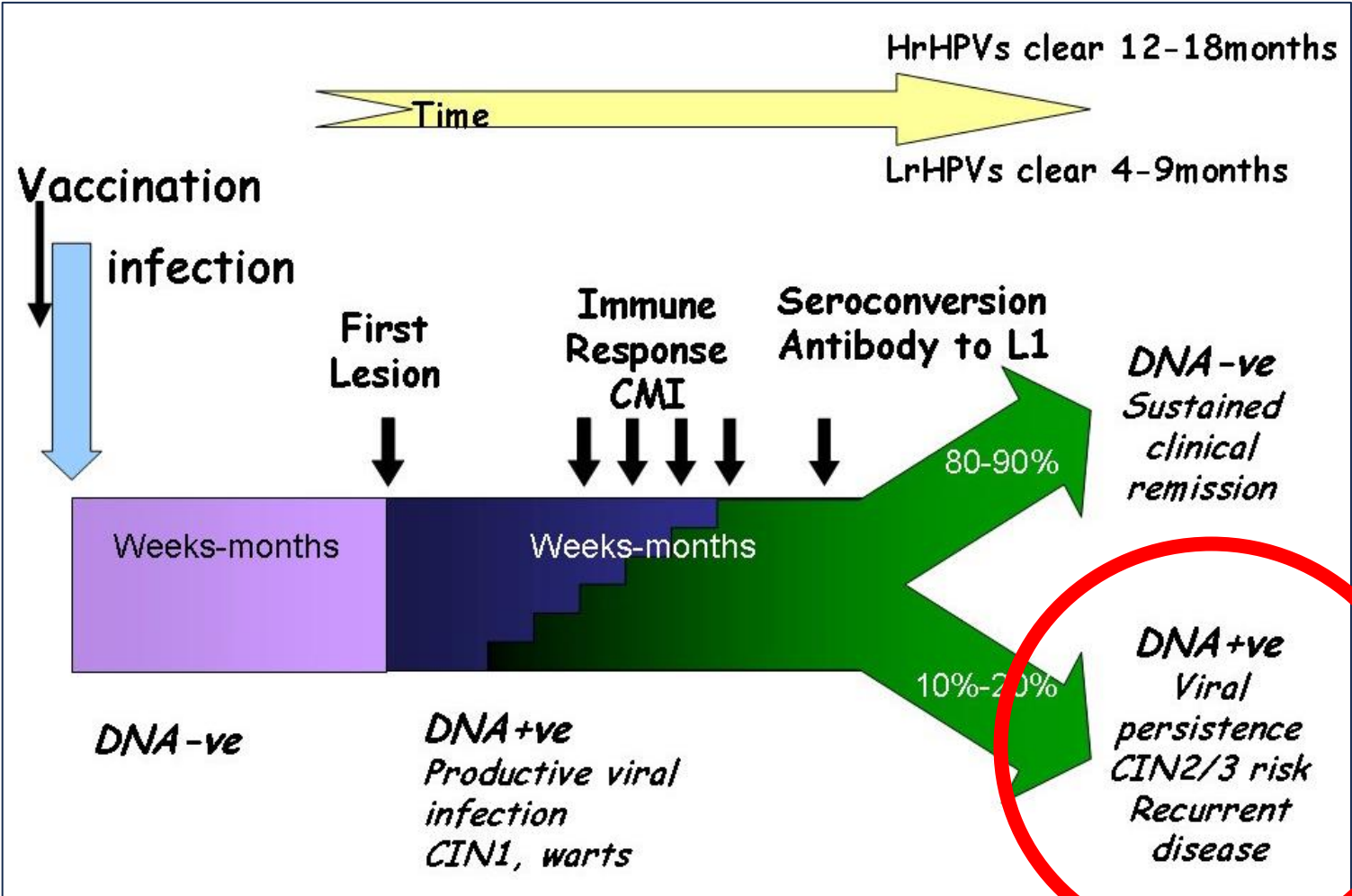


80 – 90% sustained clinical remission

10-20% viral persistence, risk for CIN/ASIL recurrent disease

- susceptible hosts
- and other (?) factors

Genital HPV: natural course

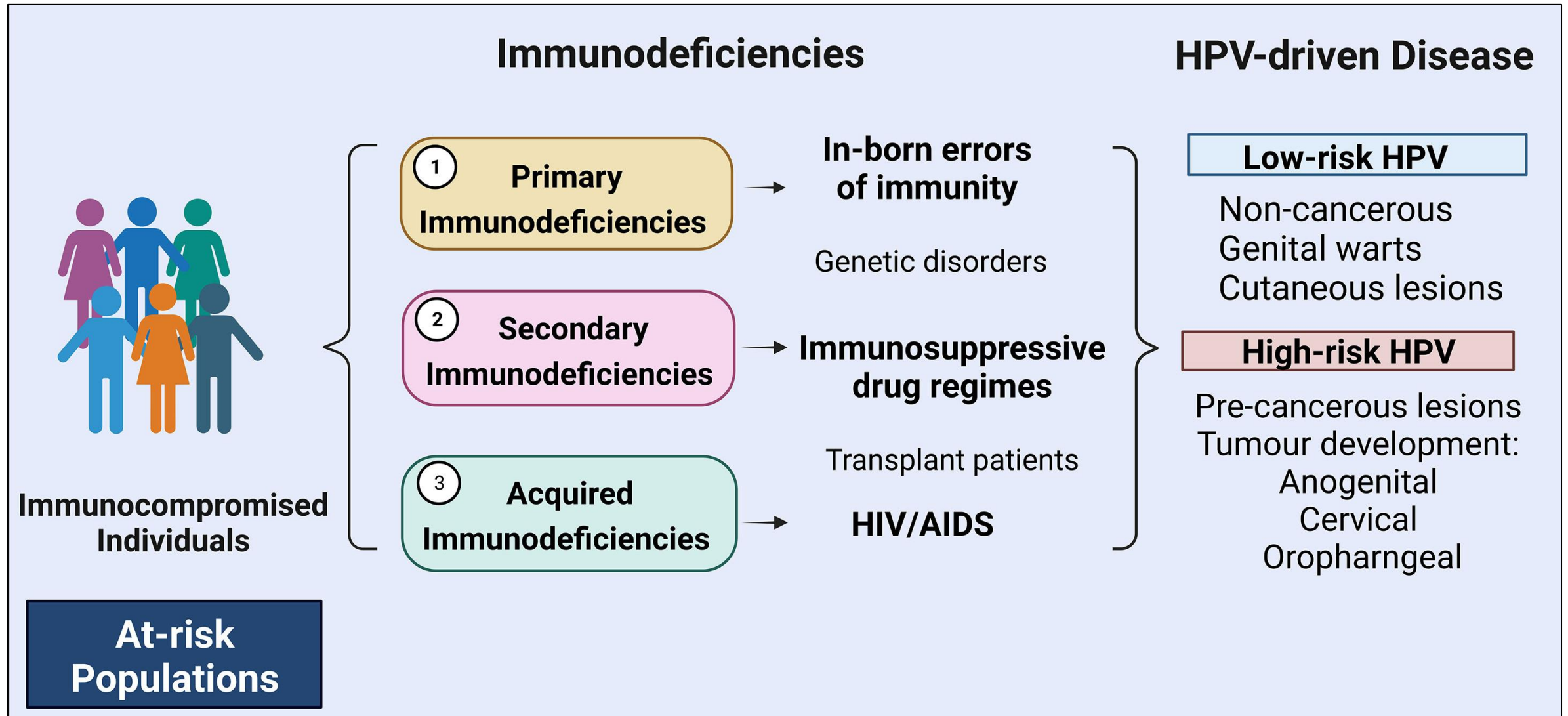


80 – 90% sustained clinical remission

10-20% viral persistence, risk for CIN/ASIL recurrent disease

What are the susceptible hosts?

HPV: What are susceptible hosts?



Are all HPV the same?

Low risk types

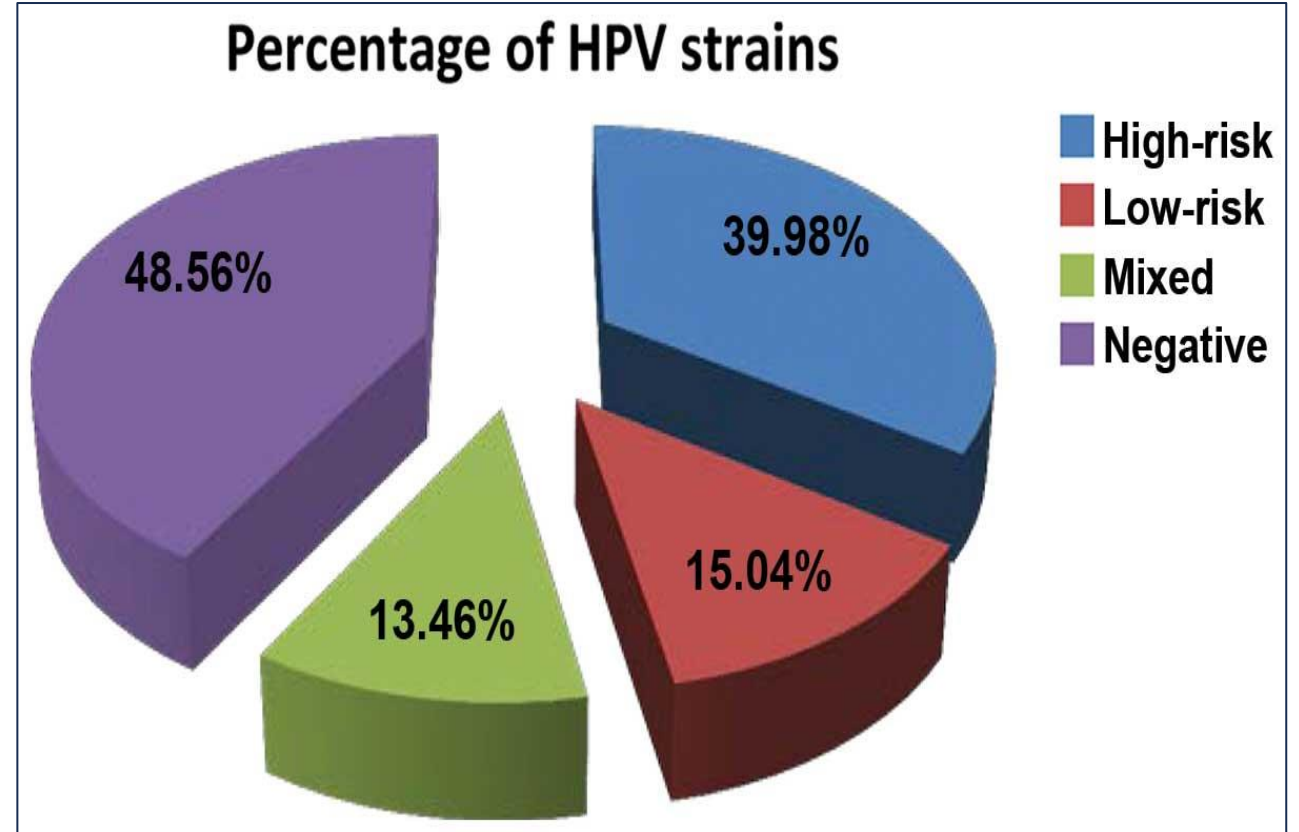
6, 11, 42, 44, 54, 40, 13, 32, 62, 72, 2, 55, 57

High risk types

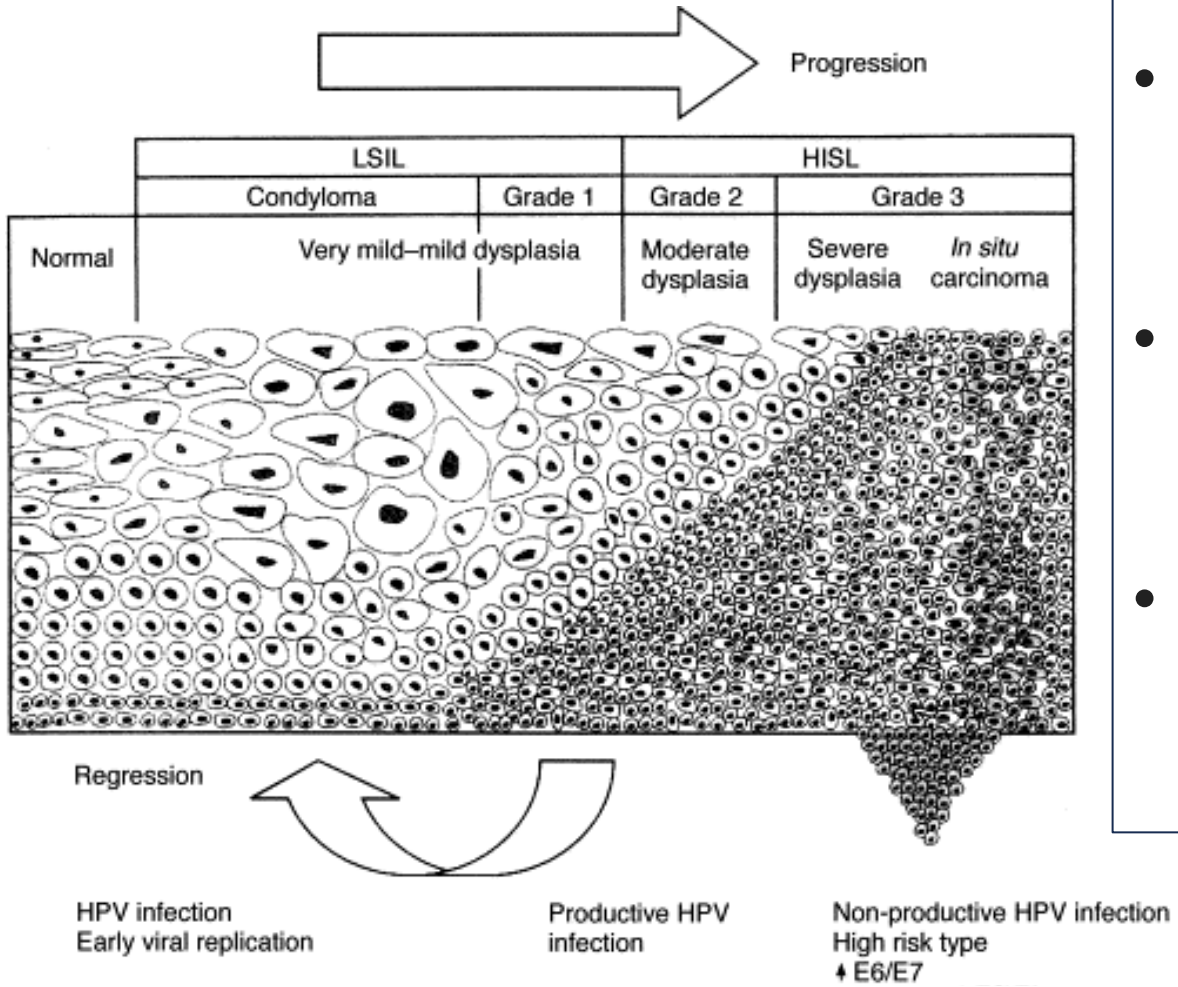
16-like (16, 31, 33, 35, 52, 58, and 67)

18-like (18, 39, 45, 59, 68, 70, 26, 69, and 51)

56-like (56, 53, and 66)



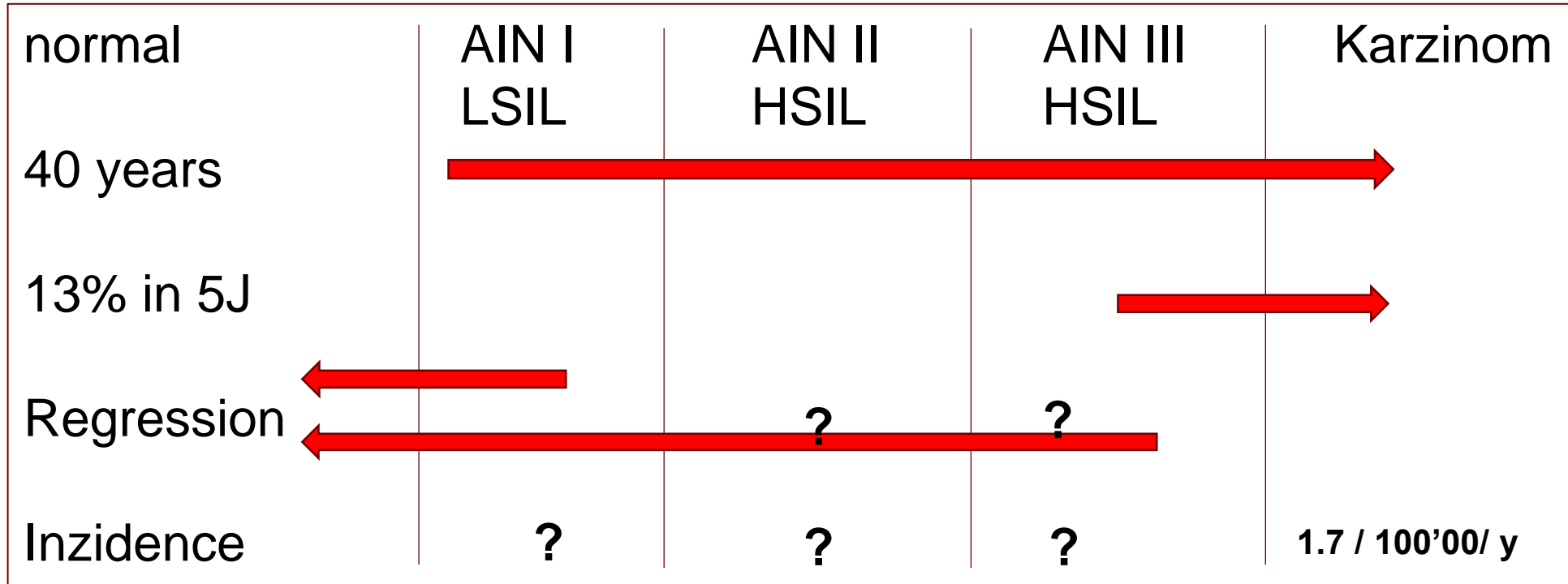
Viral persistence: ASIL Progression



- The natural history is largely unknown
- Historical accounts of progression from premalignant disease to invasive disease rate of 6%
- More contemporary series described rates of 13 to 50% (immunocompromised patients managed expectantly)
- Several case reports of anal SCC arising in areas of HSIL supporting the theory of malignant progression

Marfing T E, et al. Perianal Bowen's disease and associated malignancies. Results of a survey. *Dis Colon Rectum*. 1987
 Devaraj B, Cosman B C. Expectant management of anal squamous dysplasia in patients with HIV. *Dis Colon Rectum*. 2006
 Scholefield J H, Castle M T, Watson N F. Malignant transformation of high-grade anal intraepithelial neoplasia. *Br J Surg*. 2005
 Pineda C E et al HRA in the planned staged treatment of ASIL in HIV-negative patients. *J Gastrointest Surg*. 2007

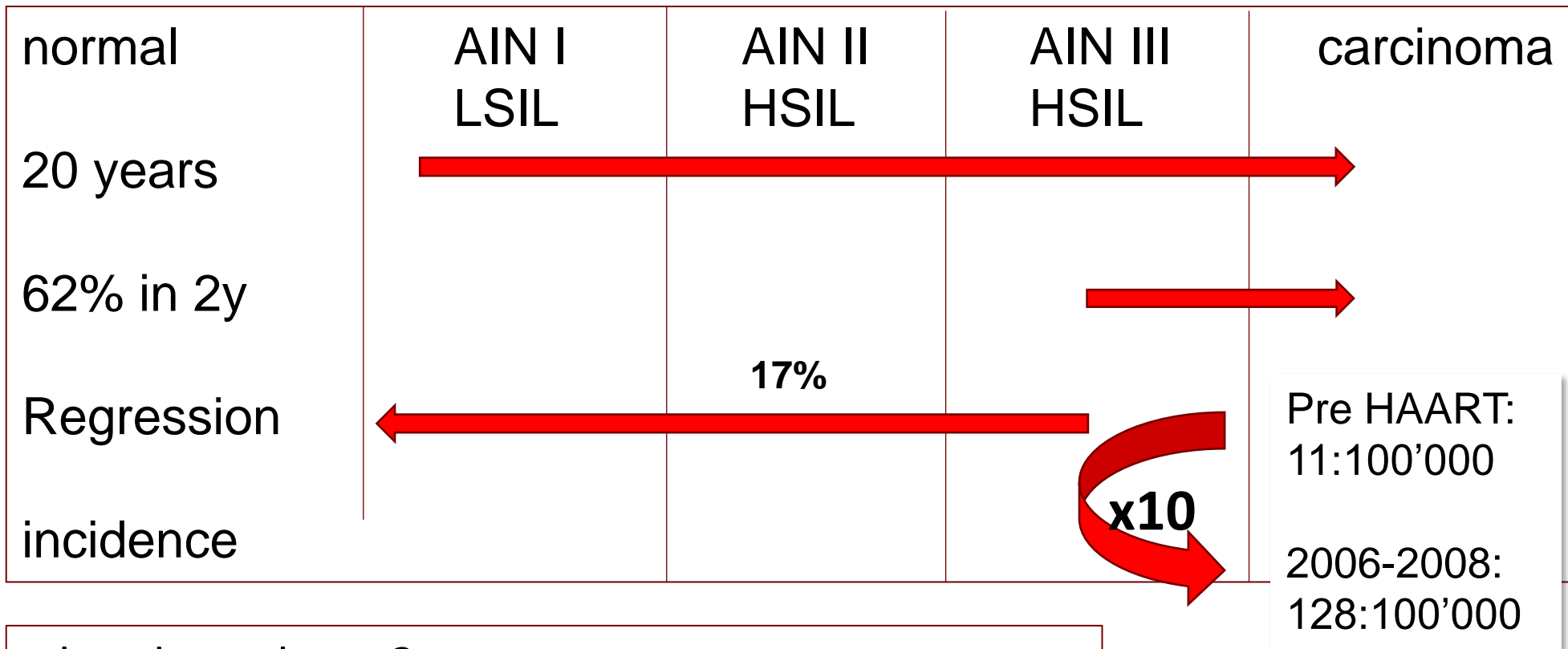
Progression in overall population



What do we know?

- few!!
- It takes a long time from LSIL to HSIL
- Regression happens

Progression in case of HIV+ und MSM



what do we know?

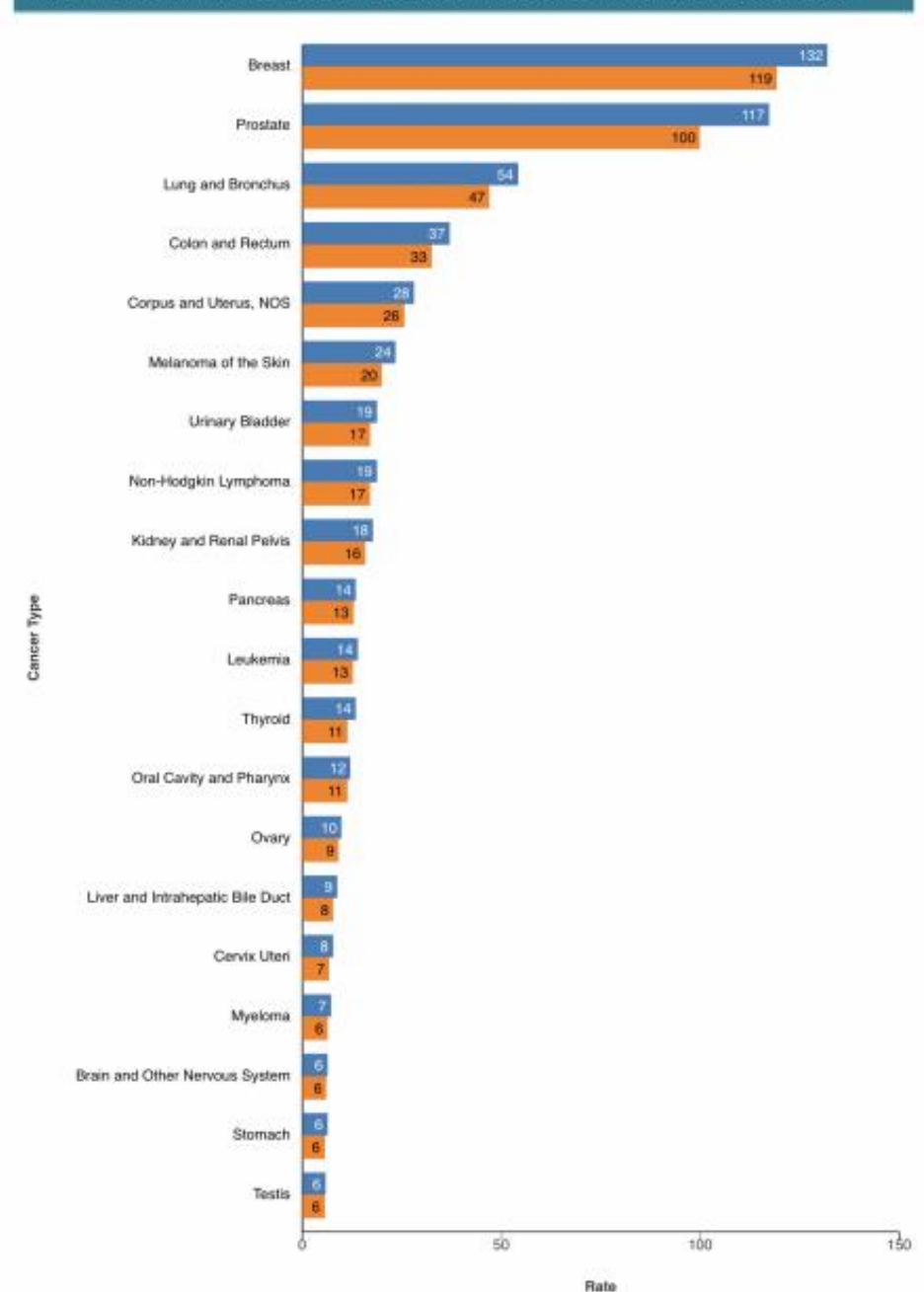
- few!!
- It takes a shorter time from LSIL to HSIL
- incidence rising
- regression is possible

Incidence and who should we screen?

what do we need for screening programm?

- Frequent tumor
- Deadly tumor
- Detectable precursor lesion
- Curable precursor lesion

Figure 4. Annual Cancer Incidence and Percentage Change in Rates by Cancer Type, United States, 2019 and 2020



Incidence and who should we screen?

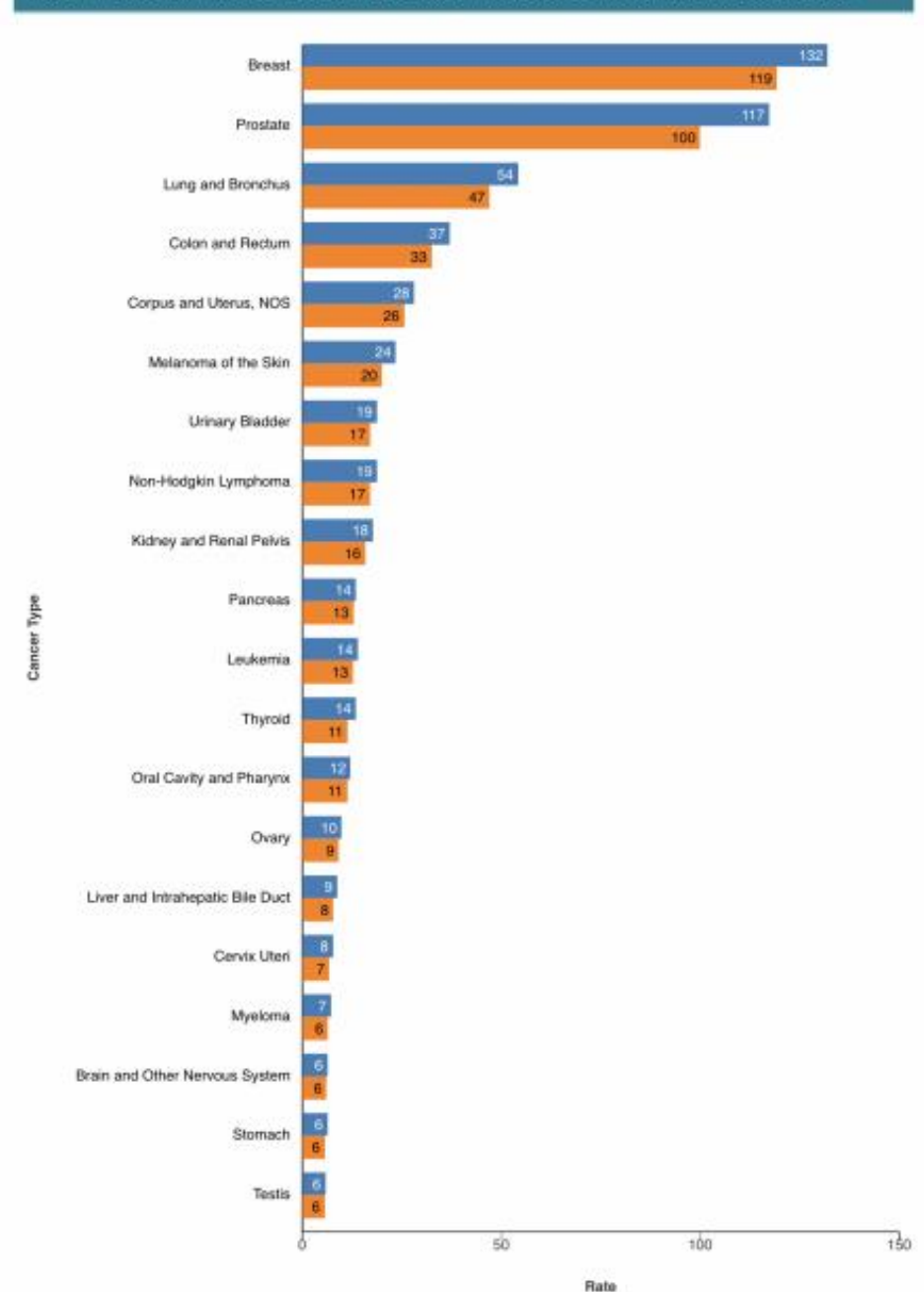
what do we need for screening programm?

- Frequent tumor
- Deadly tumor
- Detectable precursor lesion
- Curable precursor lesion

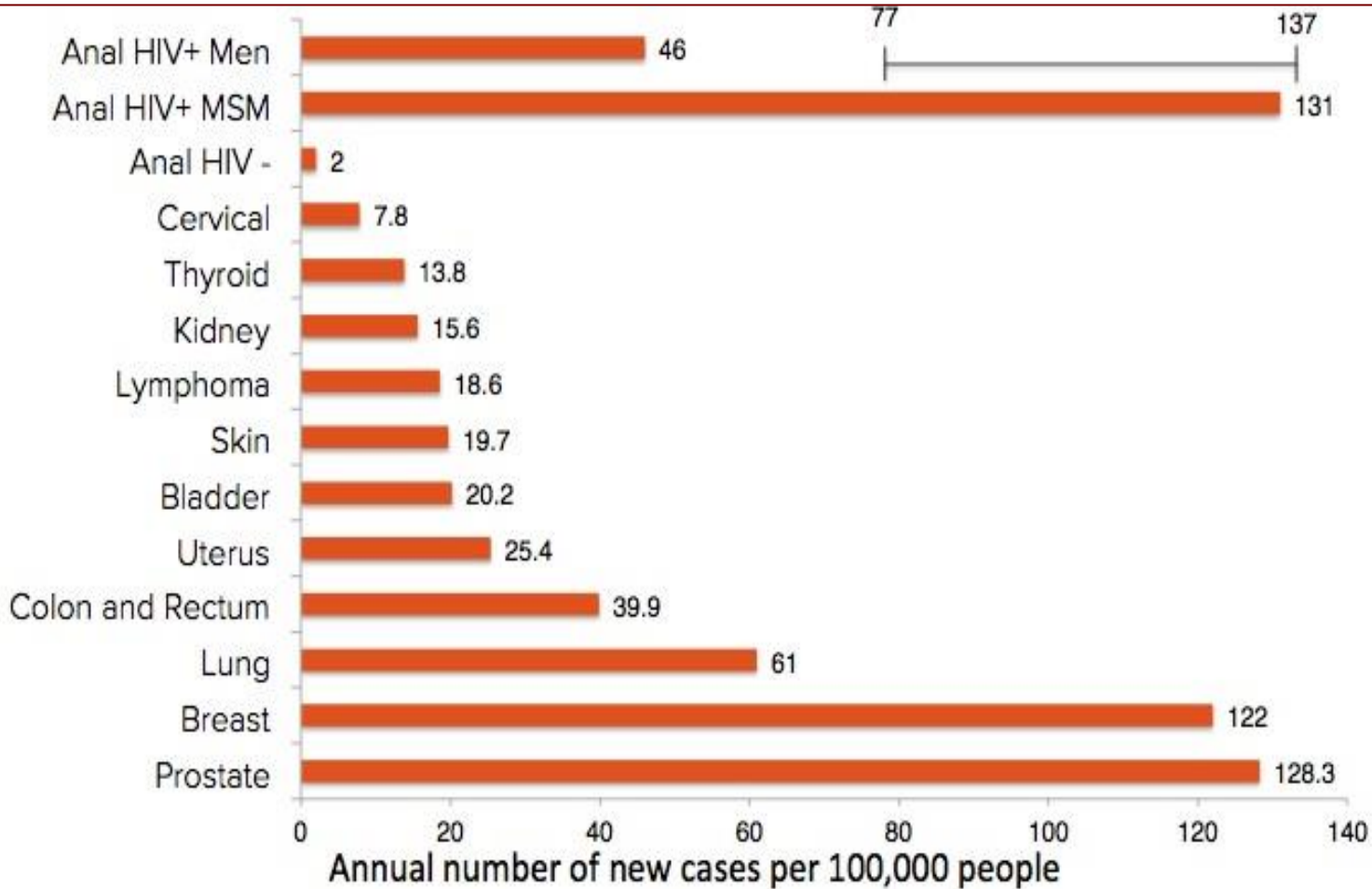
Who do we screen?

	incidence	CH
• Cervix carcinoma	4 :	100'000
• Colon carcinoma	29 :	100'000
• Breast carcinoma	113 :	100'000
• Prostata carcinoma	123 :	100'000

Figure 4. Annual Cancer Incidence and Percentage Change in Rates by Cancer Type, United States, 2019 and 2020



Incidence and who should we screen? Anal Carcinoma?



Who should we screen?

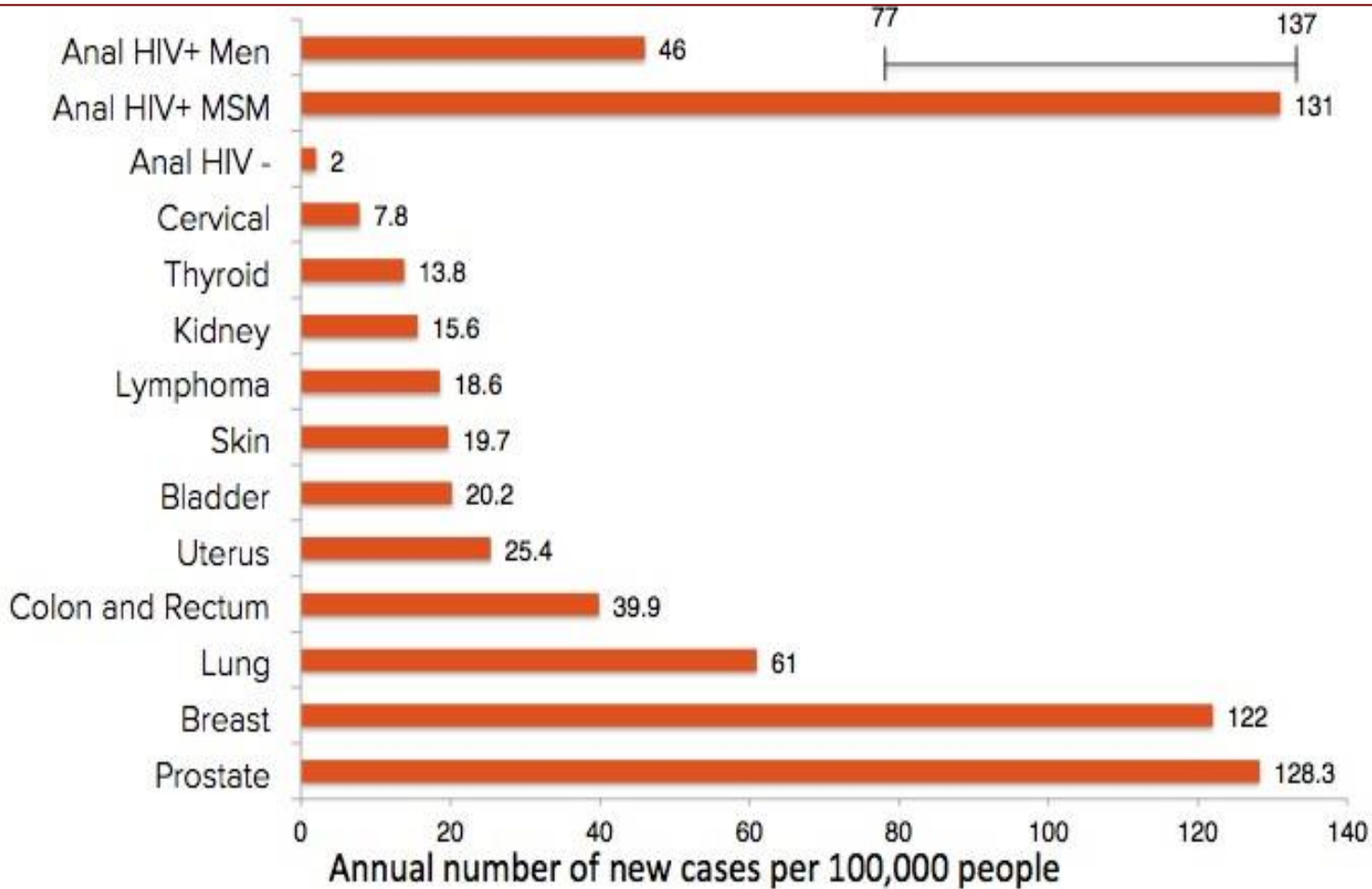
Anal cancer

Overall	1.7 :100'000
HIV + men	46 :100'000
HIV + MSM	131 :100'000

Who do we screen?

	incidence CH
• Cervix ca	4 :100'000
• Colon ca	29 :100'000
• Breast ca	113 :100'000
• Prostata ca	123 :100'000

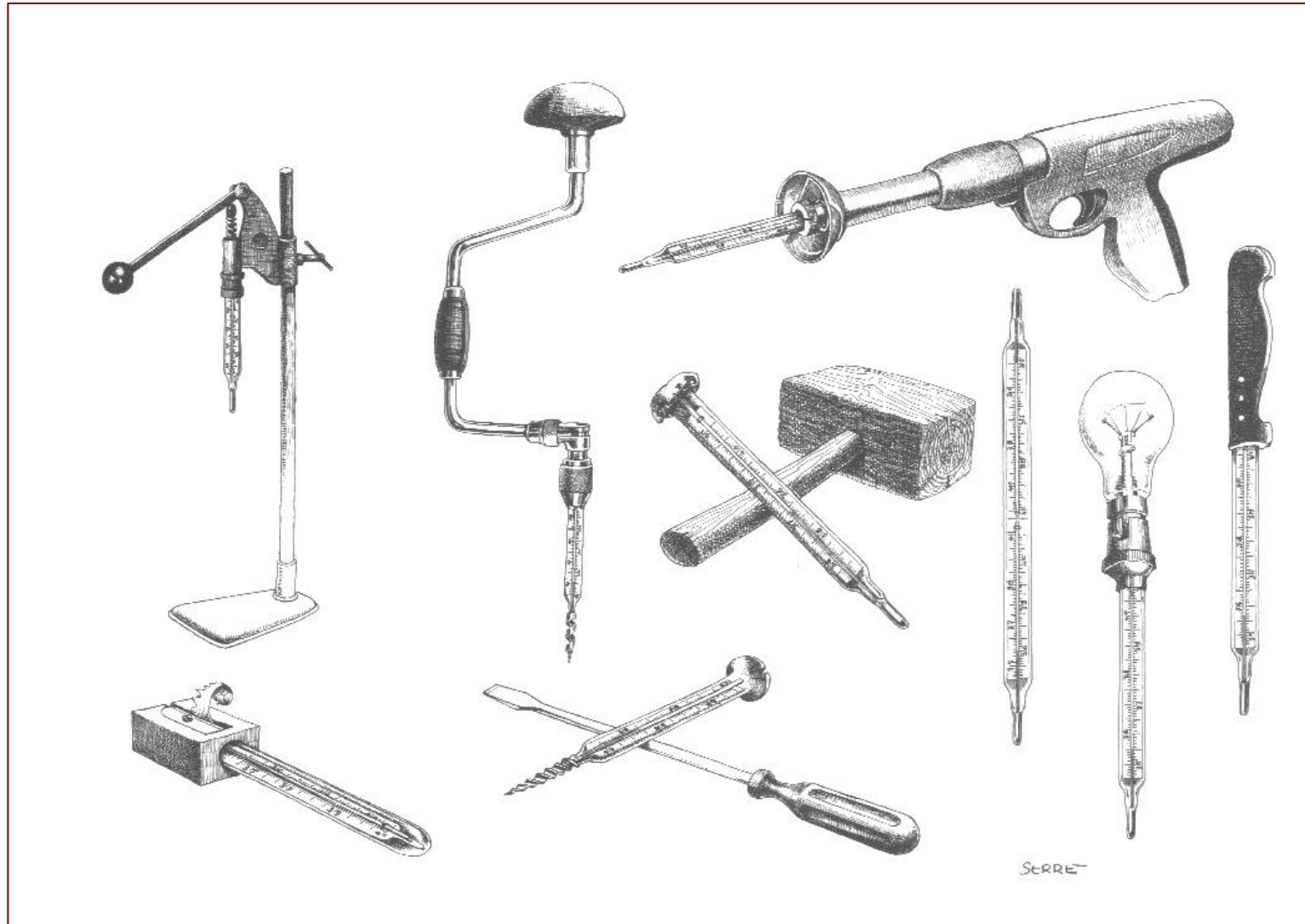
Incidence and who should we screen? Anal Carcinoma?



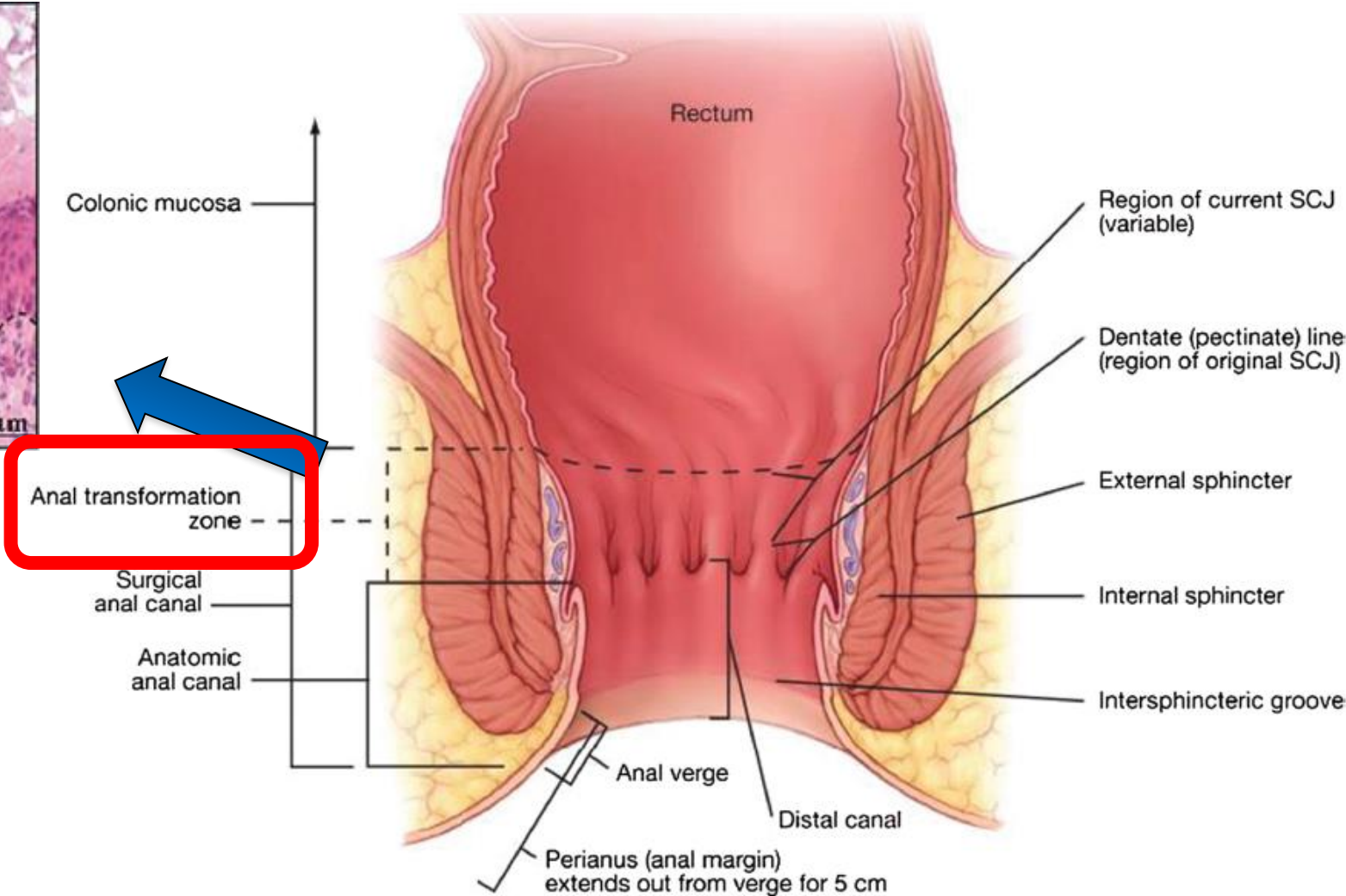
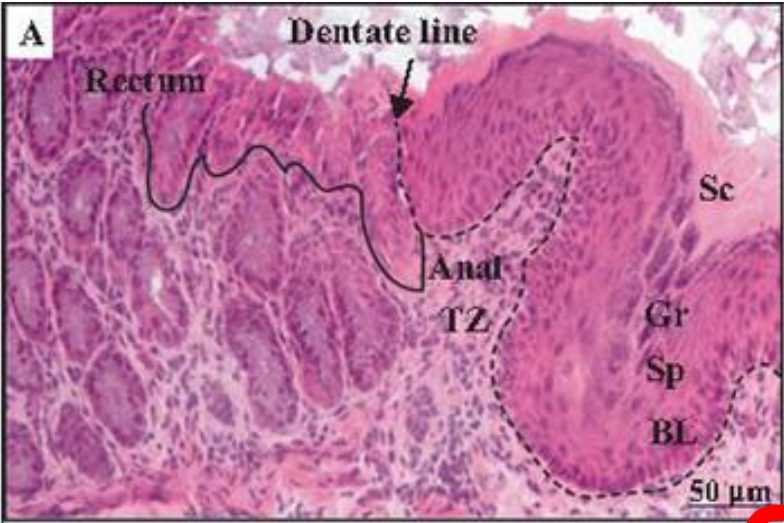
Who should we screen for anal cancer?

HIV positive (women & men)
MSM and HIV +
People with immunosuppression
Women with CIN 2-3

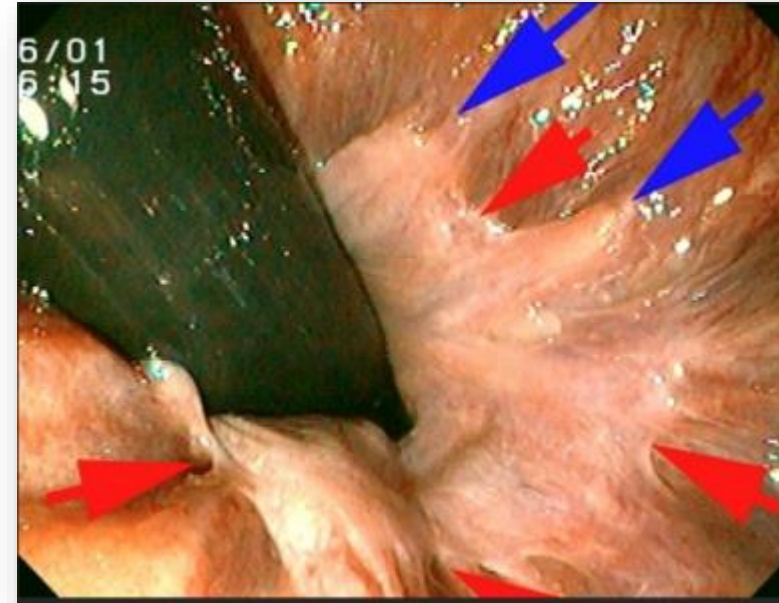
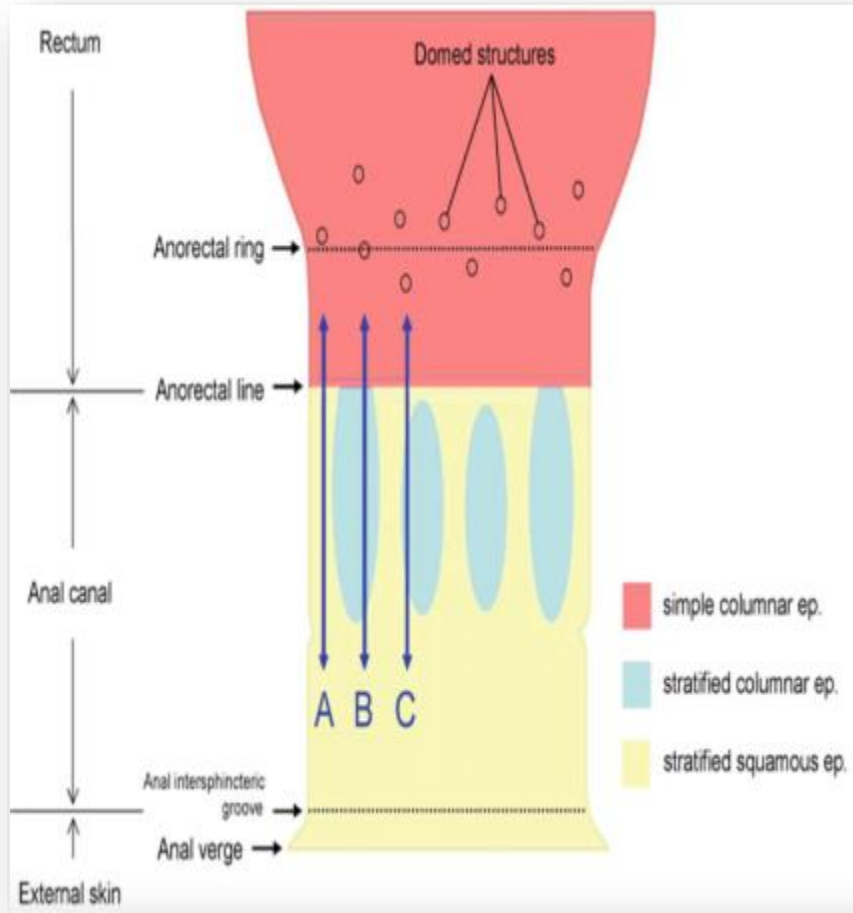
Diagnostics



Region of Interest



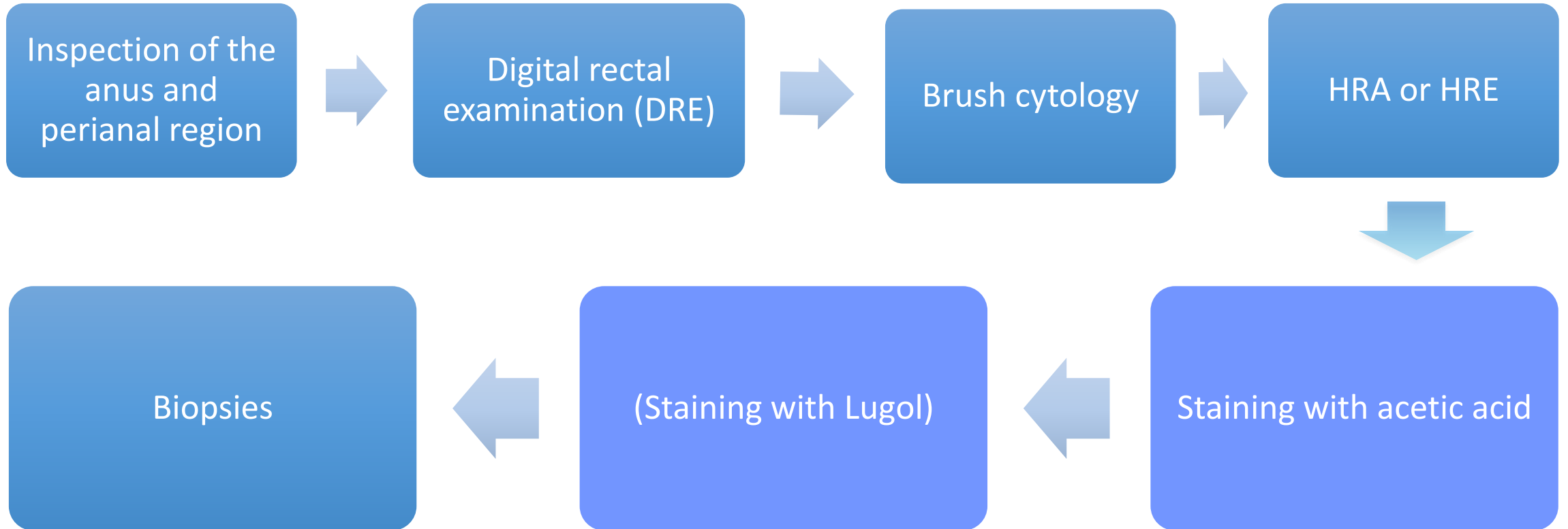
Transformations Zone



➡ Morgani Krypten

➡ Basis der Columnae anales

The Screening Procedure



The Tools



The Tools



High Resolution Anoscopy (HRA)



Advantages:

- large magnification
- good image
- well-established



Disadvantages:

- small depth of field
- often not available, expensive
- often no direct digital image processing

High Resolution Endoscopy (HRE)



Advantages:

- large depth of field
- direct digital image processing
- readily accessible
- extreme close-up possible

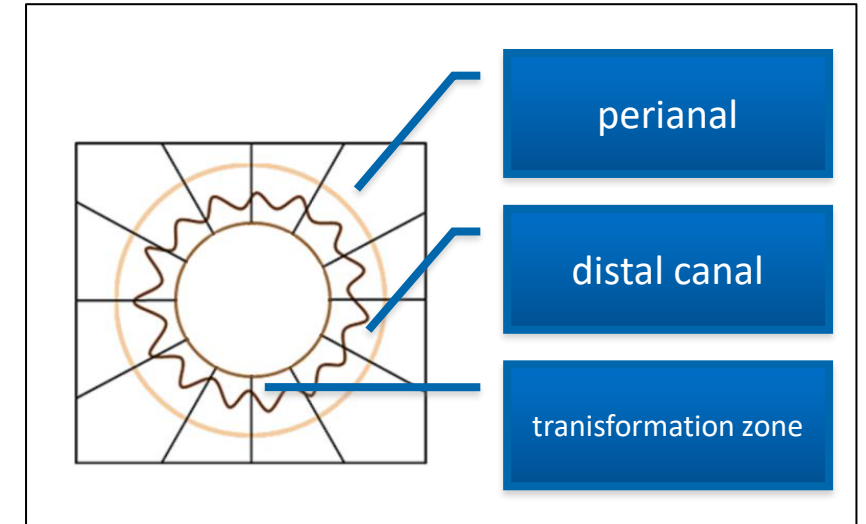
Disadvantages:

- costly maintenance
- not well-established yet, no data
- orientation difficult



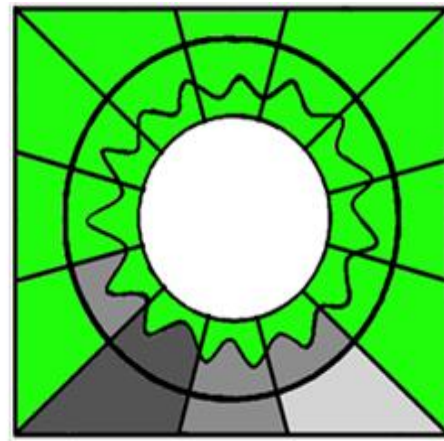
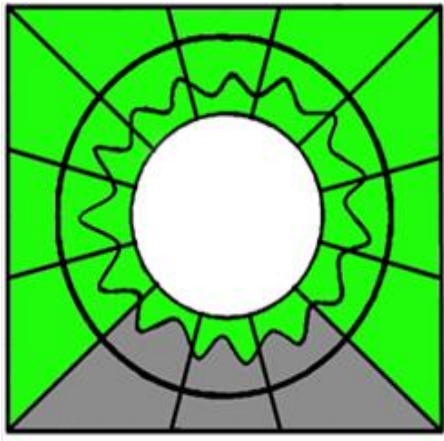
Performance of High resolution anoscopy

Performance analysis with anal mapping biopsies
Protocoll 28 biopsies/ patient



HRA

Mapping Biopsies



■ normal ■ AIN II
■ AIN I ■ AIN III

Performance of High resolution anoscopy

Performance analysis with anal mapping biopsies
Protocoll 28 biopsies/ patient

Per lesion analysis:

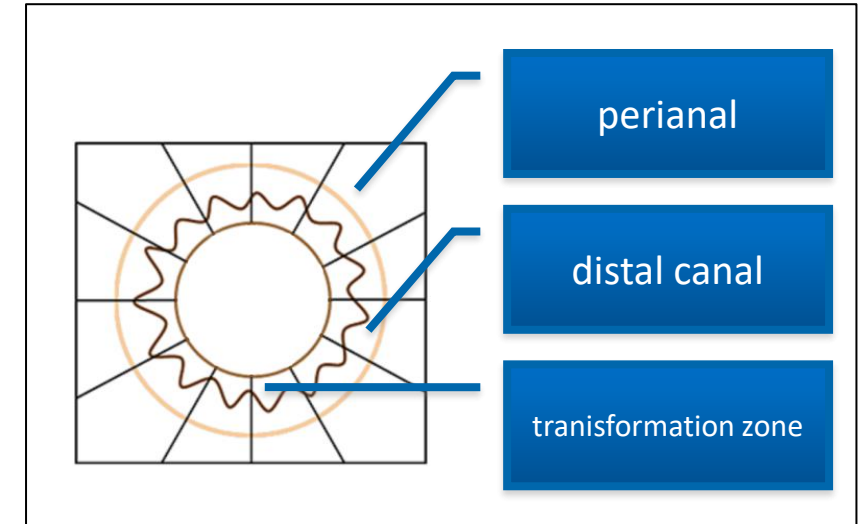
Per field analysis

Sensitivity: 86%

Sensitivity: 44%

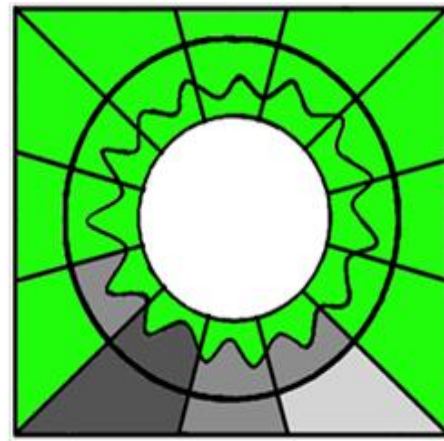
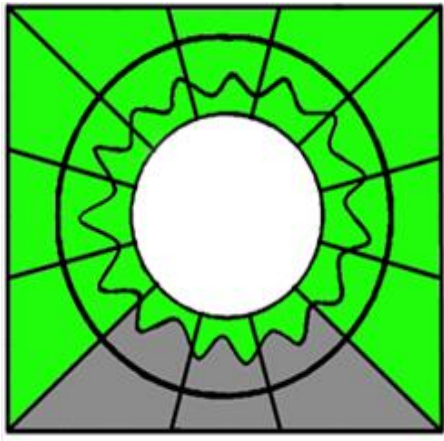
Specificity: 60%

Specificity: 96%



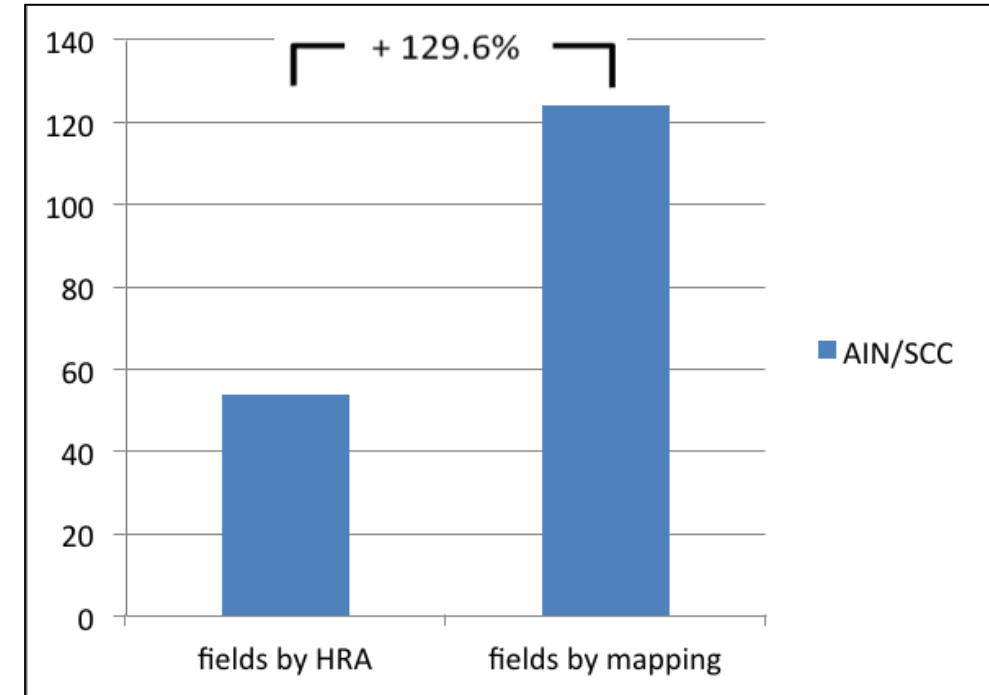
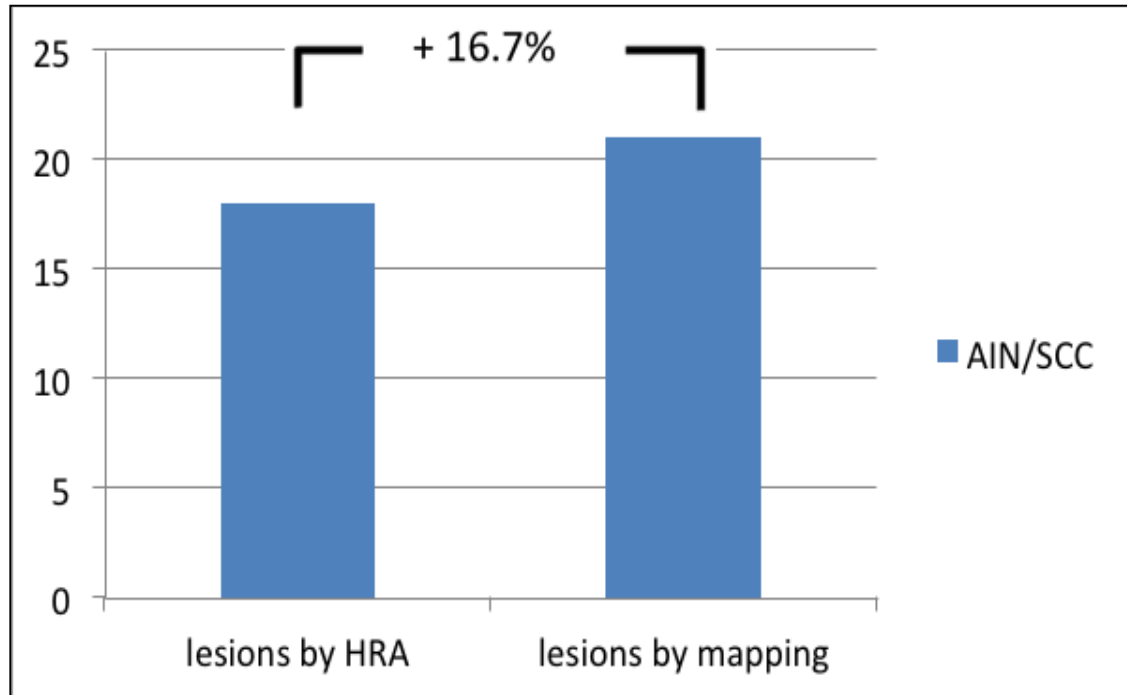
HRA

Mapping Biopsies



■ normal ■ AIN II
■ AIN I ■ AIN III

Can HRA estimate the extent of the lesion?



HRA finds the lesions but,
HRA underestimates lesions extent !

The Staining



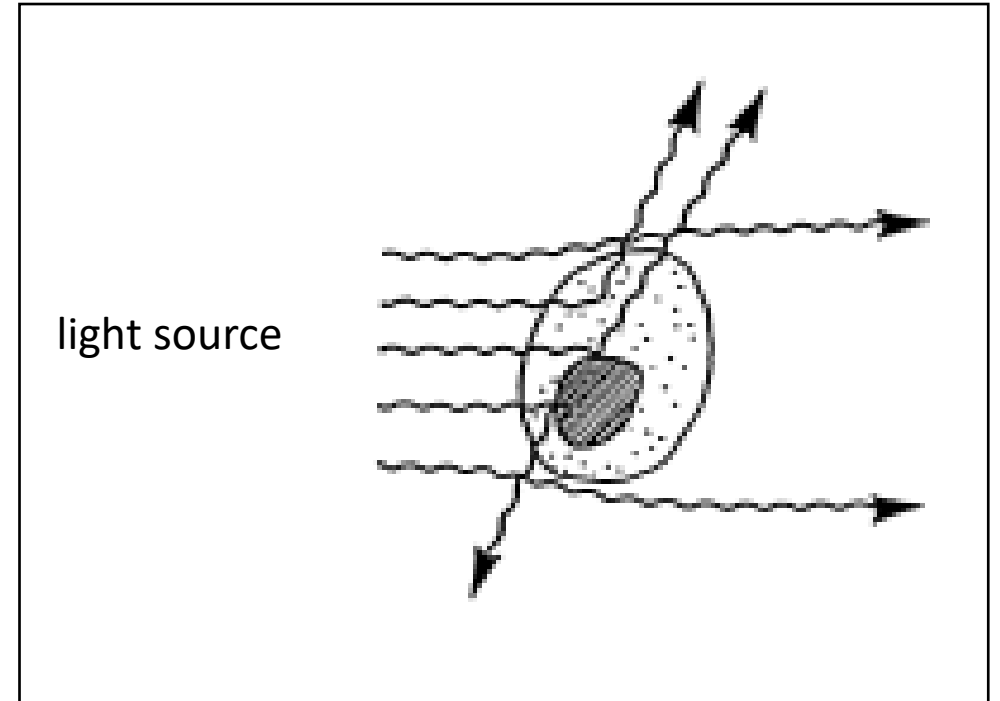
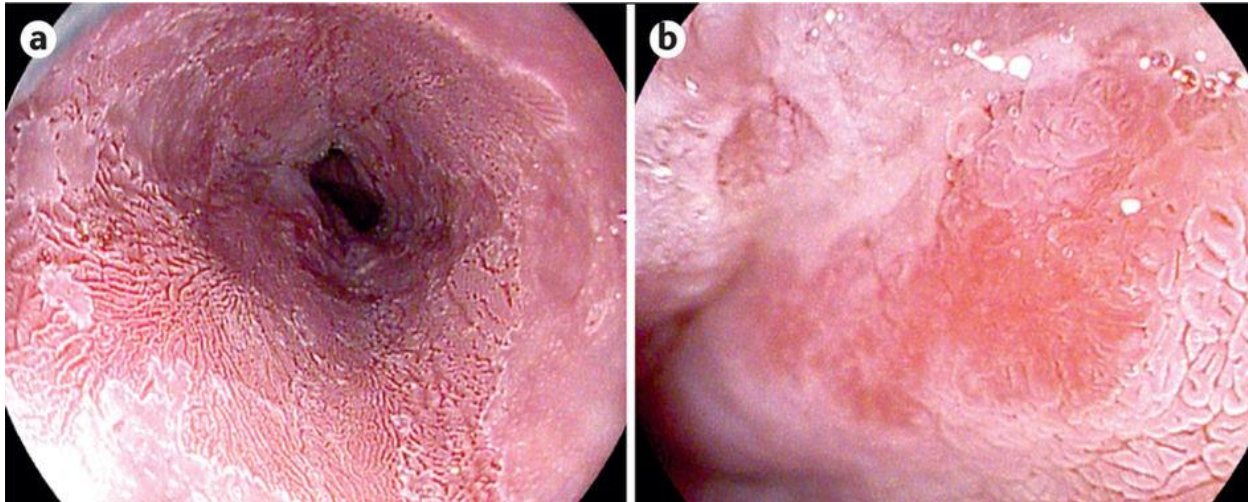
The Staining



Acetic Acid 5%

Effect

Wide angle side scattering from nucleus and cytoplasm increases when acetic acid is applied to the cell

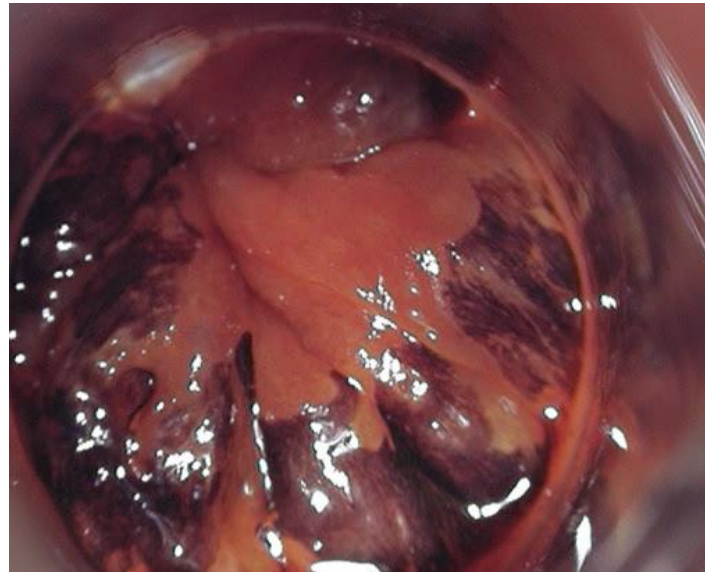
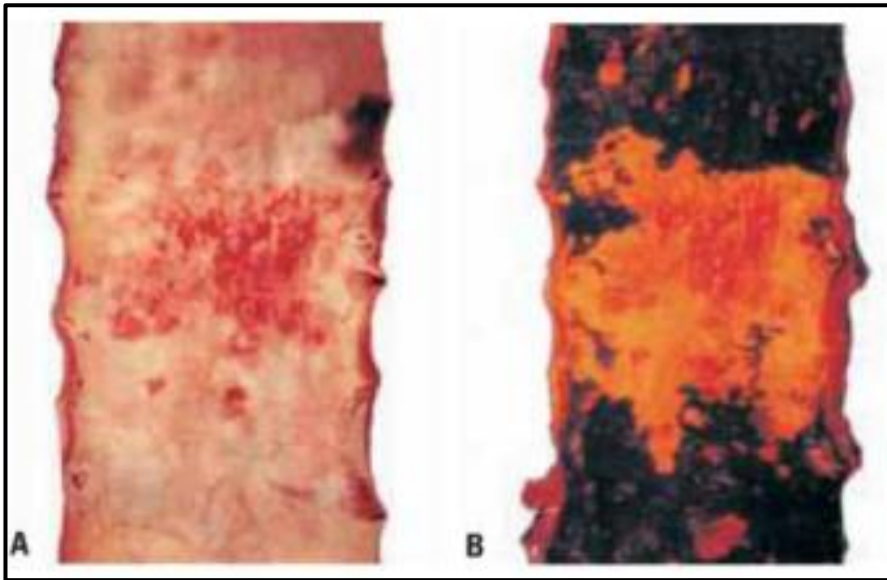


Lugol's Solution 2% (Iodine)

Effect

Brown staining of superficial glycogen.
No/partial staining in dysplasia

Starch granule



Lugol's Solution 2% (Iodine)

Effect

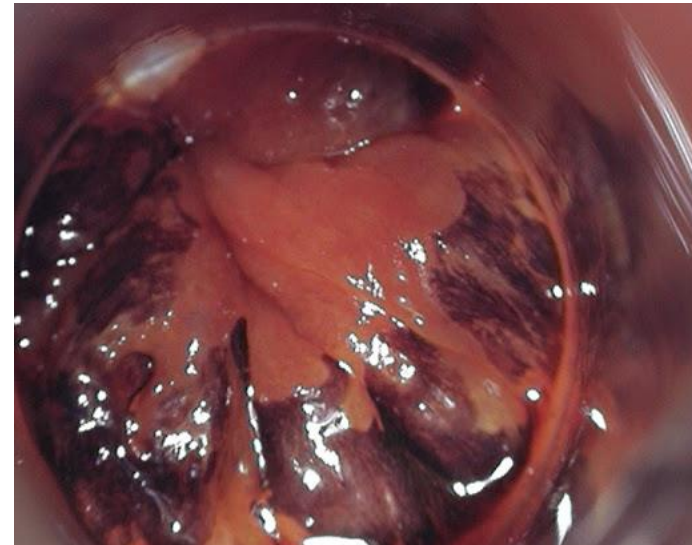
Brown staining of superficial glycogen.
No/partial staining in dysplasia

Application with

- Cotton swab
- Acetic acid soaked gauze
- spray catheter

Wait 2 minutes!!

Starch granule



Lugol's Solution 2% (Iodine)

Effect

Brown staining of superficial glycogen.
No/partial staining in dysplasia

Application with

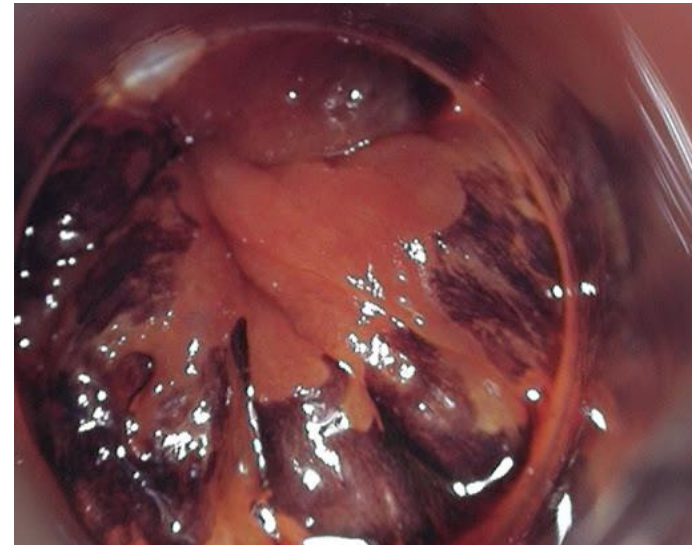
- Cotton swab
- Acetic acid soaked gauze
- spray catheter

Wait 2 minutes!!

Lugo negative

Sensitivity HSIL:	86%
Specificity HSIL:	43%

Starch granule



Cytology and Biopsy



Cytology, how to do it

1. Insert moistened synthetic swab until it bypasses internal sphincter
2. Rotate swab to sample cells from all aspects of the anal canal
3. Swab should bend slightly with gentle pressure for adequate collection of cells
4. Count slowly to 10 before removing swab

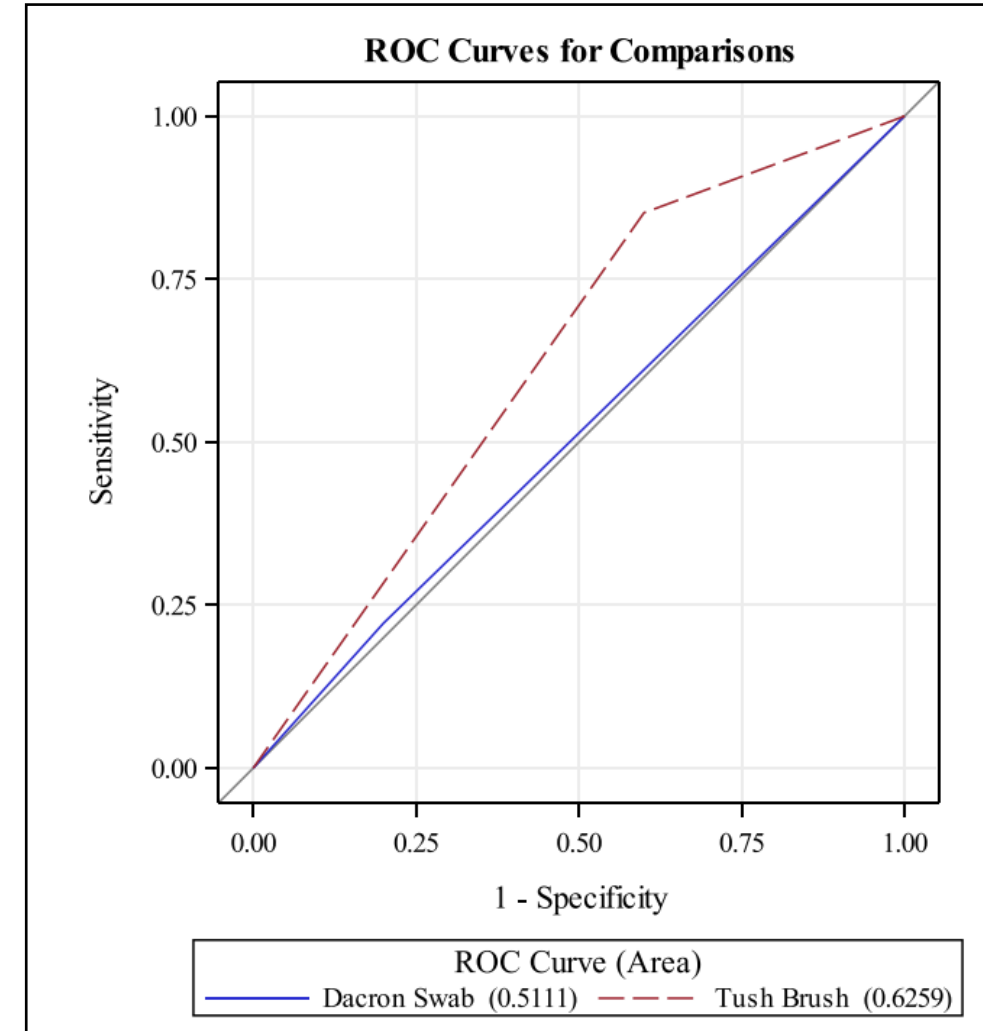


Cytology Performance

Sensitivity for HG-AIN: 63%

Specificity for HG-AIN: 86%

In combination with HPV-PCR: Sensitivity > 90%



Cytology Performance

Sensitivity for HG-AIN: 63%

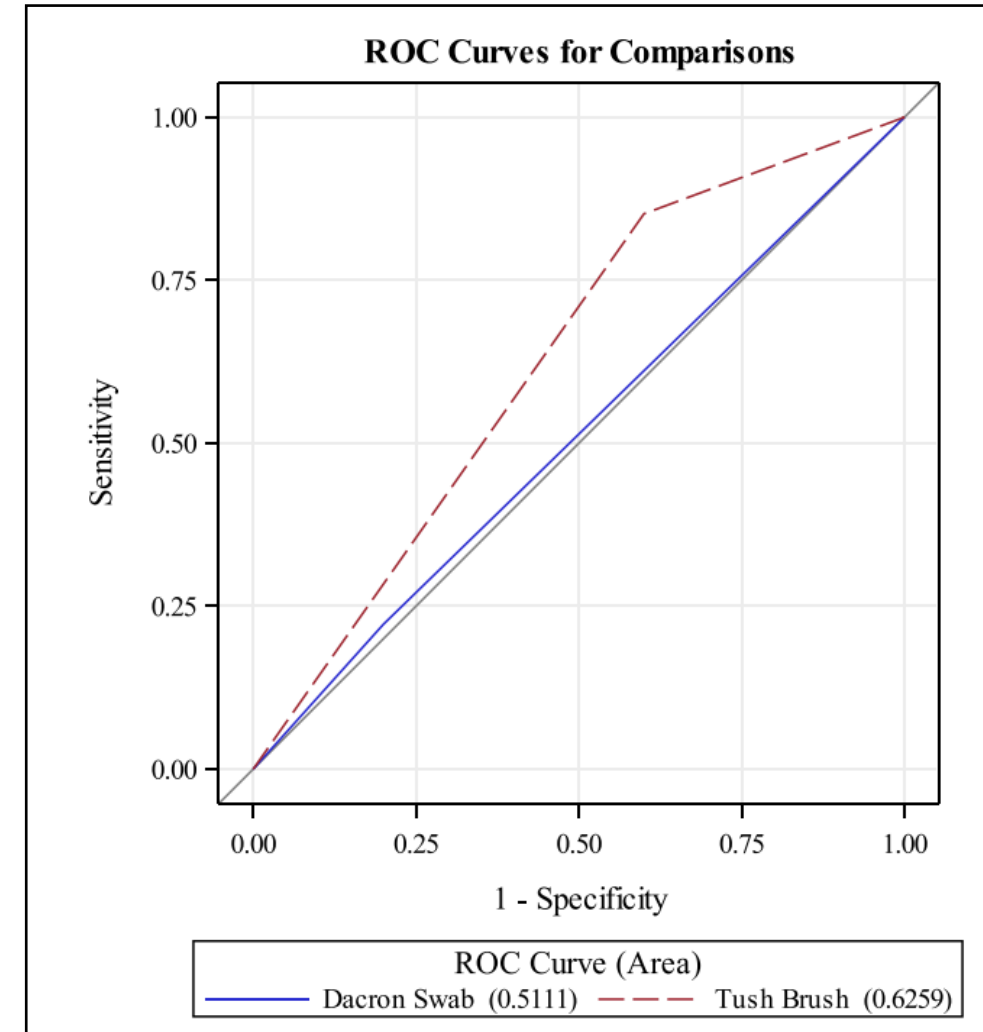
Specificity for HG-AIN: 86%

In combination with HPV-PCR: Sensitivity > 90%

NPV ASIL vs negative: 84%

PPV ASIL vs negative: 54%

Specificity improves with increasing age



Cytology Performance

Sensitivity for HG-AIN: 63%

Specificity for HG-AIN: 86%

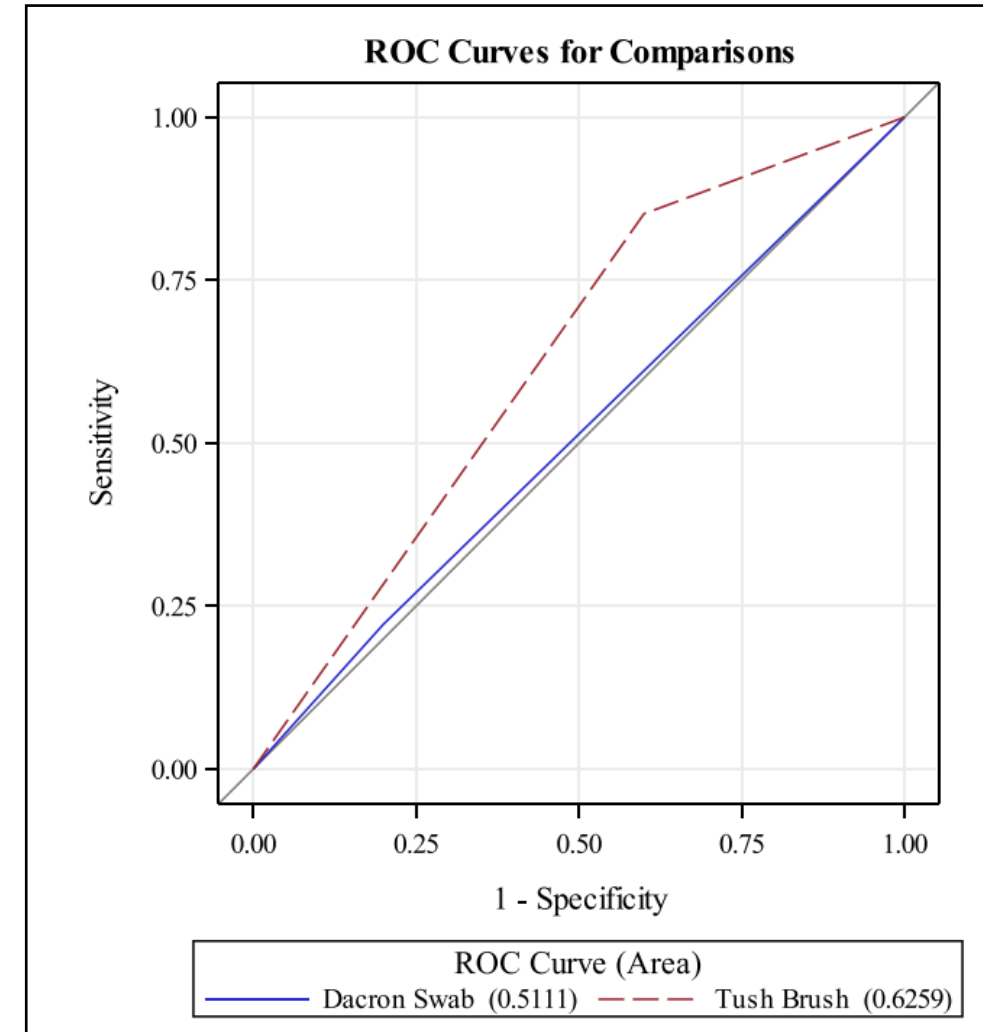
In combination with HPV-PCR: Sensitivity > 90%

Cytology is not a game changer
Cytology is only one part of the entire workup

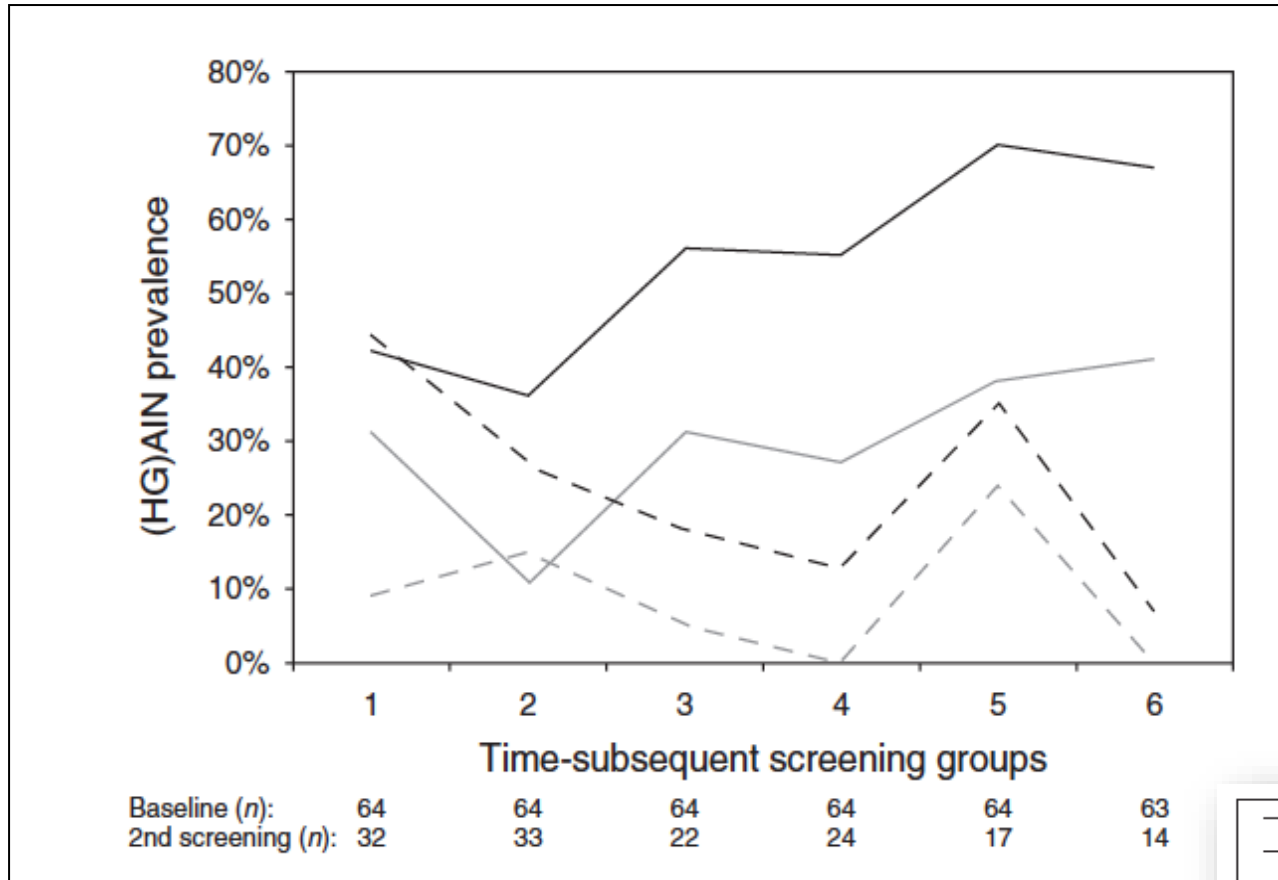
NPV ASIL vs negative: 84%

PPV ASIL vs negative: 54%

Specificity improves with increasing age



Long Learning Curve for AIN Diagnostics



HRA is a complicated procedure, which should not be underestimated.

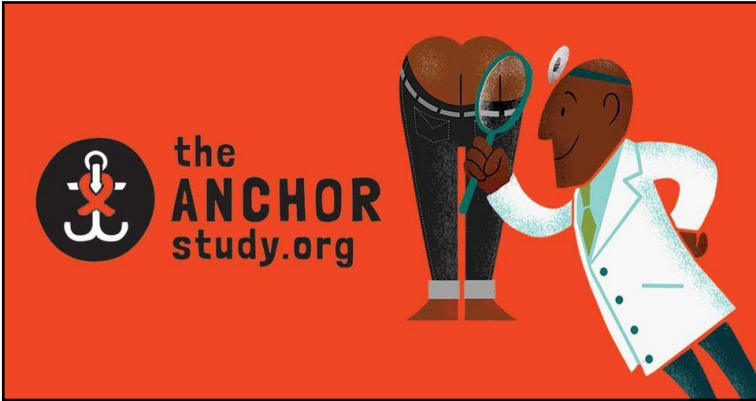
level off the learning curve after 200 examinations

— AIN baseline
- - AIN 2nd screening
— HGAIN baseline
- - HGAIN 2nd screening

Treatment



Should we treat at all ... or observe?



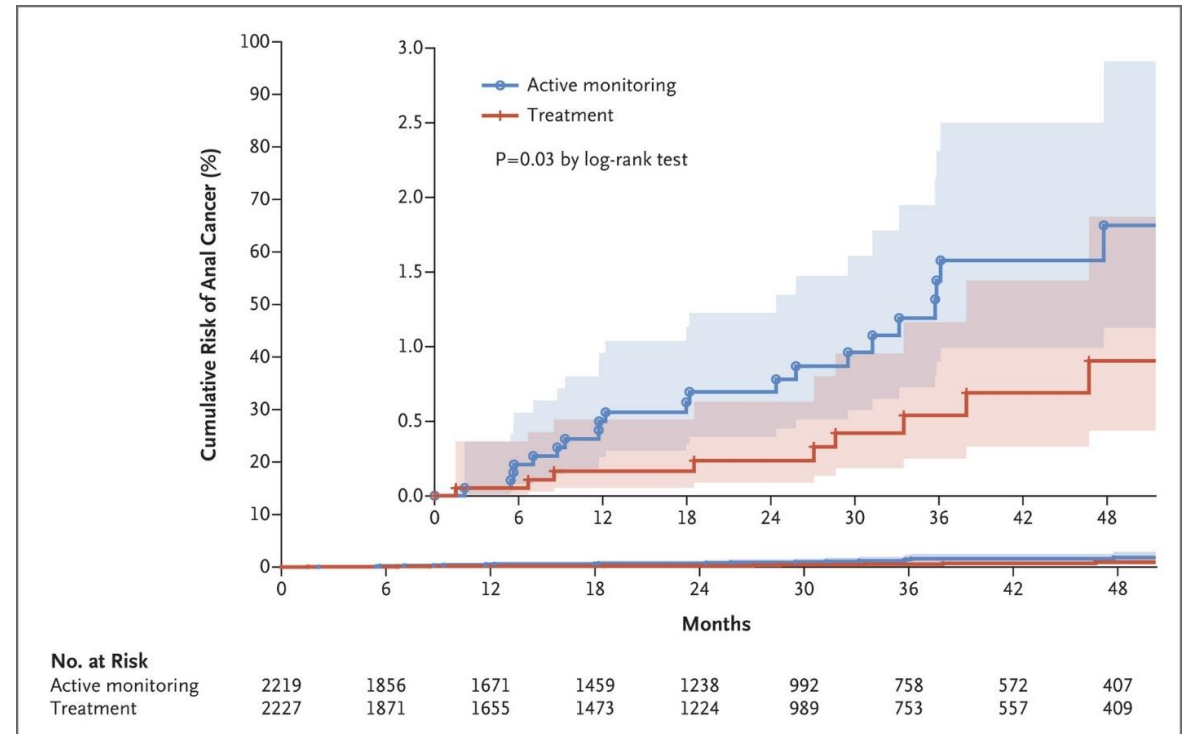
Active Monitoring vs Treatment
4446 participants across 25 cities in USA
Randomized trial
All had biopsy-proven HSIL

progression to cancer

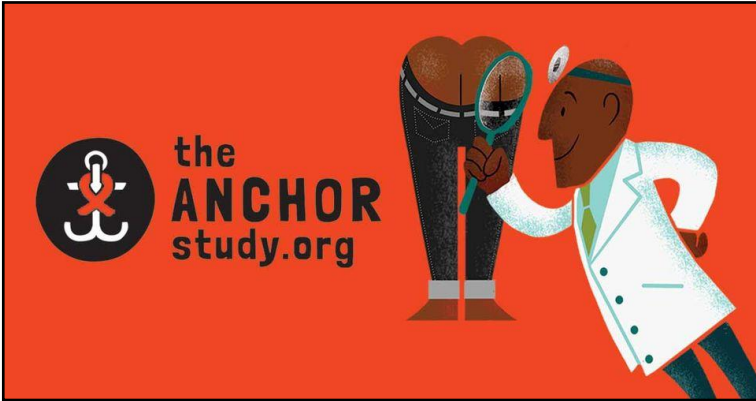
treatment group 173 per 100,000

monitoring group 402 per 100,000

Significant 57% ($p = 0.03$) reduction in cancer with treatment



Should we treat at all ... or observe?

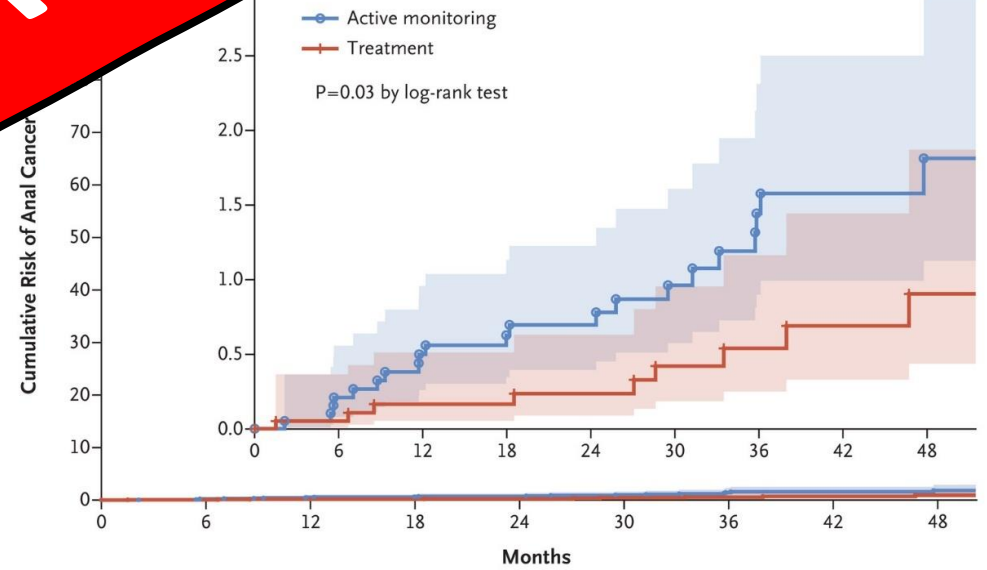


Active Monitoring vs Treatment
4446 participants across 25 cities in USA
Randomized trial
All had biopsy-proven HSIL

TREAT!

progression to cancer
treatment group 173
monitoring group 402

Significant 57% ($p = 0.03$) reduction in cancer with treatment



No. at Risk	0	6	12	18	24	30	36	42	48
Active monitoring	2219	1856	1671	1459	1238	992	758	572	407
Treatment	2227	1871	1655	1473	1224	989	753	557	409

How should we treat?

topic

Imiquamod
Toll-like Receptor 7 (TRL7)
agonist

5-Fluorouracil
pyrimidine analogue

Cidofovir
nucleotide analogue

Trichloroacetic
acid

ablative

Laser

Electrocautery

Infrared
coagulation

Kryoablation

Radiofrequency
ablation

excision

Surgical
excision

others

HPV
Vaccination

How should we treat?

topic

Imiquamod

Toll-like Receptor 7 (TRL7)
agonist

5-Fluorouracil
pyrimidine analogue

Cidofovir

nucleotide analogue

Trichloroacetic
acid

ablative

Laser

Electrocautery

Infrared
coagulation

Kryoablation

Radiofrequency
ablation

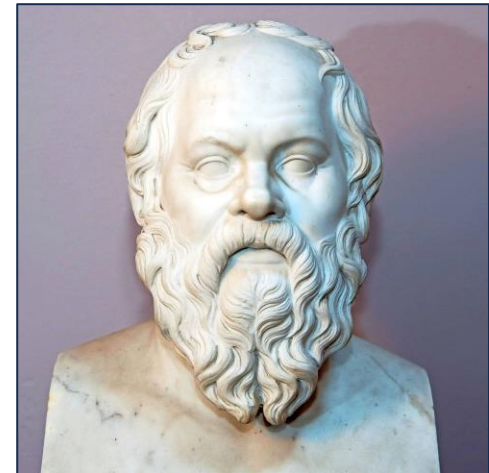
excision

Surgical
excision

I know that I
know nothing

others

HPV
Vaccination



How should we treat?

topic

Imiquamod

Toll-like Receptor 7 (TRL7)
agonist

One randomised double-blind controlled trial (imiquimod vs placebo)
14% complete response, 29% partial response
39% recurrence over median of 36 month

5-Fluorouracil

pyrimidine analogue

7 studies
9 -86% complete response, 0–27% partial response
9 – 58% r recurrence rates

Cidofovir

nucleotide analogue

2 studies
15 resp. 59% complete response, 39% partial response
18% recurrence rate

**Trichloroacetic
acid**

2 studies
28 resp. 72% complete response, 11 reso. 15% partial response
15 resp 28% recurrence rate

How should we treat?

ablative	
Laser	No data
Electrocautery	6 studies complete response between 22 and 78% partial response between 7 and 26%
Infrared coagulation	6 studies complete response between 3 and 71% partial response between 6–69%
Kryoablation	No data
Radiofrequency ablation	1 study 10 patients first treatment: 40% persistent after a further treatment: 0% recurrence at 1 year follow-up

How should we treat?

excision

Surgical
excision

historically used to be a much more widely - only old papers available
Scholefield et al. (1994): 30% recurrence of HSIL
Brown et al. (1999): 18% recurrence of HSIL

How should we treat?

excision

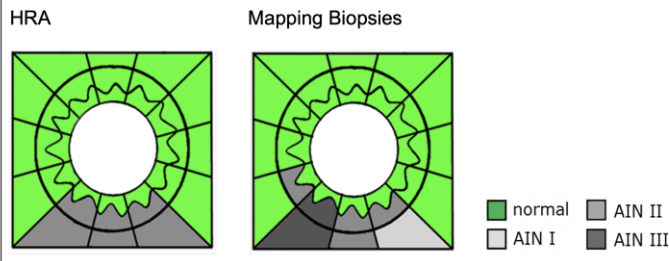
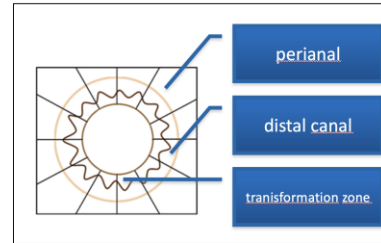
Surgical
excision

historically used to be a much more widely - only old papres available
Scholefield et al. (1994): 30% recurrence of HSIL
Brown et al. (1999): 18% recurrence of HSIL

Performance of High resolution anoscopy

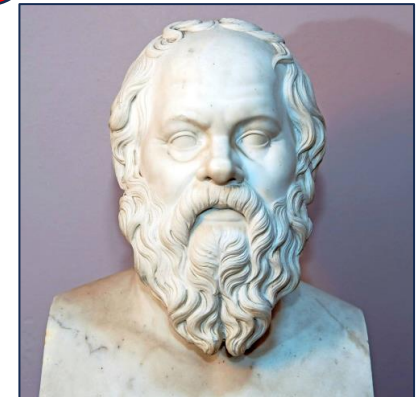
Performance analysis with anal mapping biopsies
Protocoll 28 biopsies/ patient

Per lesion analysis:		Per field analysis	
Sensitivity:	86%	Sensitivity:	44%
Specificity:	60%	Specificity:	96%



Baumeler S, Marti L, Borovicka J, Jochum W, Maurus C, unpublished yet

Maybe they
haven't seen
everything?



How should we treat?

others

HPV
Vaccination

Palefsky 2006 and 2011

- quadrivalent HPV 6, 11, 16 and 18 vaccine has been proposed as a method of secondary prevention for the recurrence of high-grade AIN
- 33% complete or partial response on vaccine

Swedish 2012

quadrivalent vaccination prevents the recurrence of high-grade AIN after targeted destruction.

Wilkin 2018

randomised controlled trial of patients with high-grade AIN receiving quadrivalent vaccine or a placebo. The trial was stopped early due to finding no benefit

How should we treat?

others

HPV
Vaccination

Palefsky 2006 and 2011

- quadrivalent HPV 6, 11, 16 and 18 vaccine has been proposed as a method of secondary prevention of high-grade AIN
- 33% complete or partial response

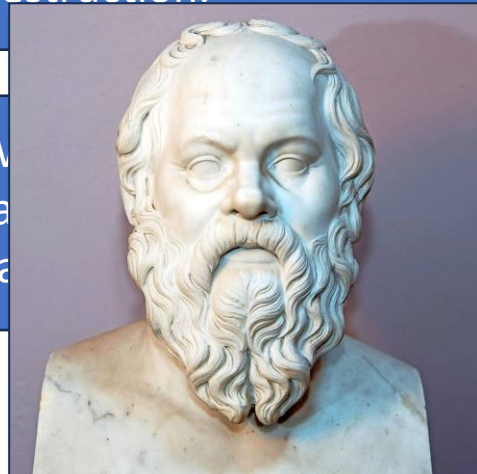
I know that I know nothing

Swedish 2012

quadrivalent vaccination prevented recurrence of high-grade AIN after targeted destruction.

Wilkin
randomized
vaccine

A randomized trial of patients with high-grade AIN receiving quadrivalent vaccine was stopped early due to finding no benefit



Palefsky JM et al. A trial of SGN-00101 (HspE7) to treat high-grade anal intraepithelial neoplasia in HIV-positive individuals. *AIDS*. 2006

Palefsky JM et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *N Engl J Med*. 2011

Swedish KA et al. E. Prevention of recurrent high-grade anal neoplasia with quadrivalent human papillomavirus vaccination *Clin Infect Dis*. 2012

Wilkin TJ et al. A Randomized, Placebo-Controlled Trial of the Quadrivalent Human Papillomavirus Vaccine in Human Immunodeficiency Virus-Infected ...*Infectious* 2018

Follow-up



Brand new guidelines!!!

Received: 3 November 2023 | Revised: 17 December 2023 | Accepted: 21 December 2023

DOI: 10.1002/ijc.34850

SPECIAL REPORT

 INTERNATIONAL
JOURNAL of CANCER 

International Anal Neoplasia Society's consensus guidelines for anal cancer screening

Elizabeth A. Stier¹  | Megan A. Clarke²  | Ashish A. Deshmukh^{3,4}  |
Nicolas Wentzensen²  | Yuxin Liu⁵  | I. Mary Poynten⁶  |
Eugenio Nelson Cavallari⁷ | Valeria Fink⁸ | Luis F. Barroso⁹ |
Gary M. Clifford¹⁰  | Tamzin Cuming¹¹ | Stephen E. Goldstone¹² |
Richard J. Hillman^{6,13} | Isabela Rosa-Cunha¹⁴ | Luciana La Rosa^{15,16} |
Joel M. Palefsky¹⁷ | Rosalyn Plotzker¹⁸ | Jennifer M. Roberts¹⁹  | Naomi Jay¹⁷

Stier EA et al. International Anal Neoplasia Society's consensus guidelines for anal cancer screening. Int J Cancer. 2024

Take Home Messages

- Anal cancer is caused by HPV
- There are people with more risk than others
- Treatment is better than no treatment
- the optimal therapy is unclear

