Anal Cancer Screening: Is it Time for Cytology and High-risk HPV Co-testing?

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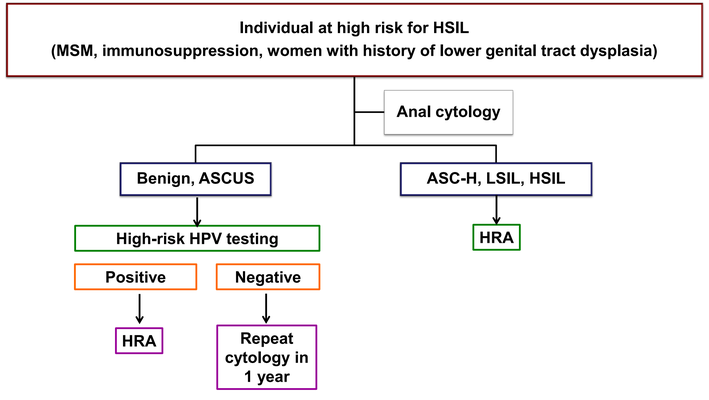
INTRODUCTION

- Anal cancer screening targets high-grade squamous intraepithelial lesions (HSIL), the immediate precursors to anal cancer.
- Current guidelines suggest an anal cytology (AC) severity grade of atypical squamous cells of undetermined significance or greater (≥ASCUS) as referral threshold for high-resolution anoscopy (HRA).
- The performance of AC has been inconsistent, as demonstrated by its wide range of sensitivity (69%-93%) and relatively low specificity (32%-59%), underscoring its deficiencies as a sole screening test for anal cancer.

OBJECTIVES

- To determine whether co-testing AC for high-risk human papillomavirus (hrHPV) improves screening performance.
- To compare the efficiency of two novel HRA referral thresholds to current clinical practice: **Novel algorithm A and B.**

Novel algorithm A (currently used by the Mount Sinai Anal Dysplasia Program): Threshold for HRA referral at any hrHPV or AC LSIL or greater (≥ LSIL)

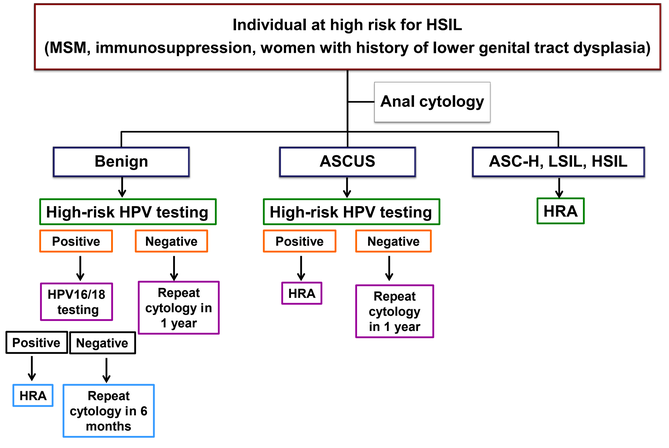


METHODS

- Anal swabs were obtained simultaneously or within 3 months of HRA-guided biopsies and used for AC and Cobas® hrHPV DNA co-testing.
- **1,947 paired AC and hrHPV results from 1,268 individual patients were analyzed (89% HIV-positive, 90% MSM and 9.5% women).**
- Using biopsy-proven HSIL as an endpoint, sensitivity, specificity, and relative risk (RR) of HSIL for various AC/HPV co-testing combinations were calculated.
- Test characteristics were then compared between screening strategies using an efficiency frontier method.



Novel algorithm B (proposed in: Dis Colon Rectum 2018;61:1364-1371)



RESULTS

Anoscopy Referral Threshold	Sensitivity (95% CI)	Specificity (95% CI)	Relative Risk (95% CI)*
Cytology alone			
≥ ASCUS Cytology (Current Guideline)	80.4 (77.6-82.9)	37.6 (34.8-40.5)	8.0 (4.1-15.6)
≥ LSIL Cytology	43.6 (40.4-46.9)	76.1 (73.5-78.6)	9.3 (4.7-18.3)
HSIL Cytology	11.1 (9.1-13.3)	97.9 (96.9-98.7)	13.5 (6.8-26.5)
HPV testing alone			
Any hrHPV	95.9 (94.5-97.1)	23.2 (20.8-25.8)	7.0 (4.0-15.5)
HPV 16/18	51.7 (48.4-54.9)	73.8 (71.1-76.3)	9.7 (4.9-18.9)
Cytology and HPV co-testing			
≥ ASCUS Cytology and any hrHPV	77.5 (74.7-80.1)	48.6 (45.6-51.5)	8.6 (4.4-16.8)
≥ ASCUS Cytology and HPV16/18	47.4 (44.1-50.8)	80.5 (78.0-82.8)	10.4 (5.3-20.5)
Novel Algorithm A**	97.2 (95.9-98.2)	19.8 (17.5-22.3)	4.9 (3.3-7.2)
Novel Algorithm B (Sambursky et al.)***	86.9 (84.5-89.1)	35 (32.2-38.0)	8.2 (4.2-16.0)

- Adding hrHPV testing to the current referral threshold of ≥ASCUS increased specificity from 37.6% to 48.6% (p<0.001).
- Requiring HPV16/18 positivity for referral improved specificity even more, but decreased sensitivity.
- When comparing the current guideline approach with novel algorithms A and B, sensitivity was 80.4%, 97.2%, and 86.9%, while specificity was 37.6%, 19.8%, and 35%, respectively.
- When calculating number of missed HSILs versus number of unnecessary HRAs for a hypothetical cohort of 10,000 persons with 30% HSIL prevalence, all strategies including co-testing were found to be more efficient than those without.

CONCLUSIONS

- Compared with the current screening approach, both novel algorithms A and B improve sensitivity to detect anal HSIL (A>B); A decreases specificity significantly more than B.
- Positivity for any hrHPV, especially types 16/18, implies a significant risk for anal HSIL.
- Both algorithms A and B may improve efficiency of anal cancer screening.
- Further evaluation of harms, benefits and cost-effectiveness of screening strategies is needed.

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