Long term risk prediction of p16/Ki-67 dual stain in triage of HPV-positive women

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Disclosures

- No financial relationships or conflict of interest to disclose

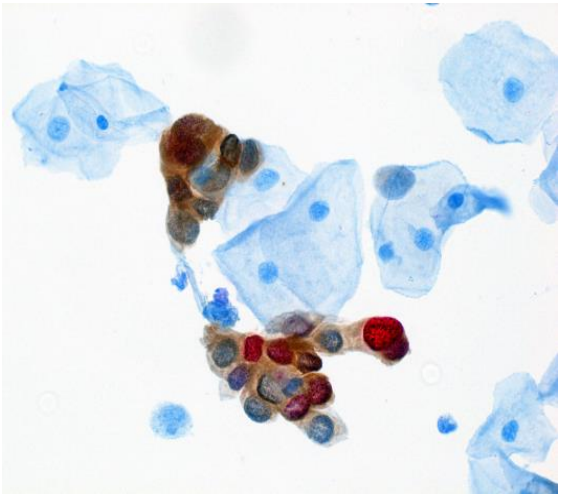
Primary HPV Screening

- Highly sensitive for cervical precancer, but limited specificity
- Requires triage to reduce the colposcopy referral and minimize overtreatment, but maintain high sensitivity for cervical precancer
- Currently approved strategies:
  - HPV16/18 genotyping with reflex cytology
- Other candidate strategies:
  - p16/Ki-67 dual stain
  - Automated cytology
  - Methylation
  - Deep learning

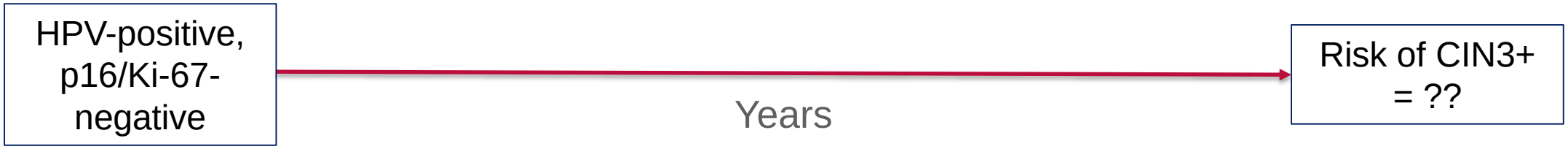
Huh et al., Gynecol Oncol 2015; Cuschieri et al., Int. J Cancer 2018

p16/Ki-67 Dual Stain Triage

- Highly reproducible
- Higher accuracy for detecting precancer compared to cytology
- Risk of precancer in HPV-positive, p16/Ki-67-positive women warrants immediate colposcopy
- Need longitudinal data to determine how long to extend follow-up intervals in women testing HPV-positive, p16/Ki-67-negative



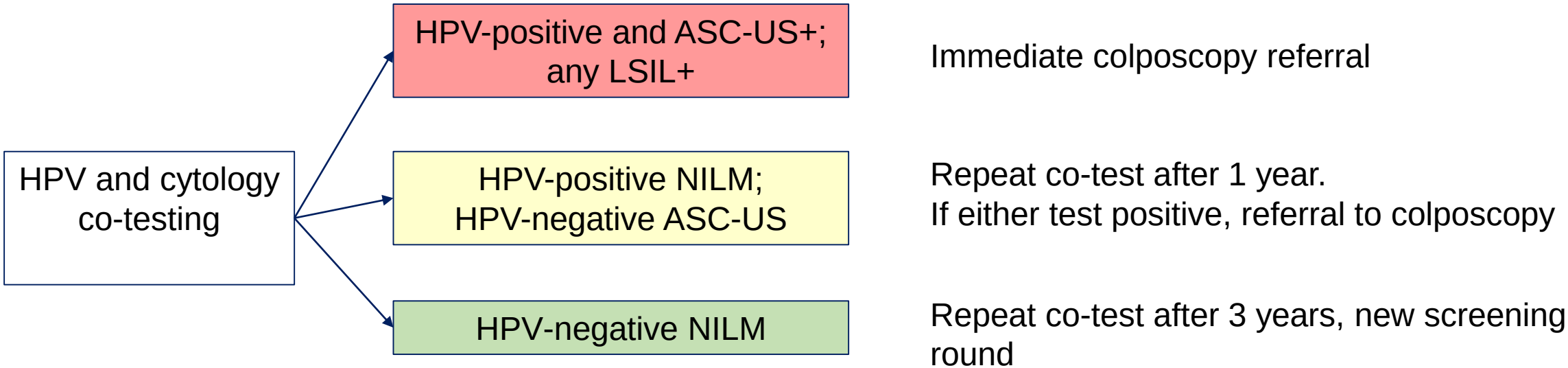
p16 (brown) + Ki-67 (red)



Carozzi et al., Lancet Oncol 2013; Wentzensen et al. Cancer Cytopathol 2014; Wentzensen et al. JNCI 2015

Study Design

- Prospective study of 1,549 women aged 30+ years undergoing routine screening at Kaiser Permanente Northern California (KPNC), March 2012
- Baseline: HPV (HC2) and cytology co-testing; p16/Ki-67 dual stain with CINtec-Plus
- Follow-up: Co-test and histology data through May 2017
- Clinical management according to KPNC clinical guidelines



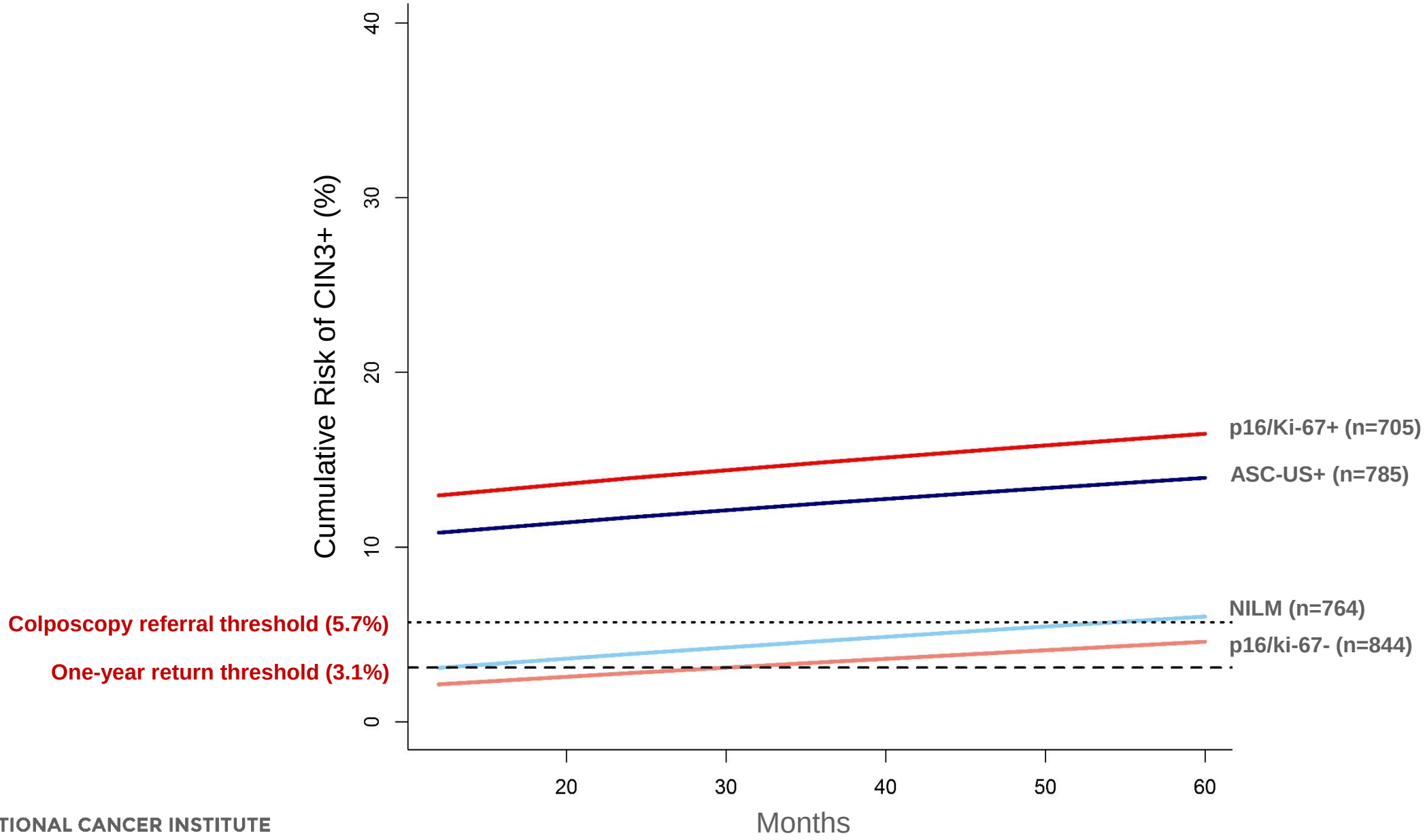
Methods

- Estimated 5-year cumulative risks of CIN3+ using Logistic Weibull models
  - p16/Ki-67 Dual Stain
    - Positive, negative
    - Semi-quantitative assessment of p16/Ki-67+ cells (0, 1, 2-5, 6-50, >50)
  - Cytology
    - ASC-US+, NILM
    - HSIL, LSIL, ASC-US, NILM
- Evaluated in the context of clinical management risk thresholds (KPNC)
  - HPV-positive, ASC-US risk of CIN3+ = 5.7% → Immediate colposcopy referral
  - HPV-positive, NILM risk of CIN3+ = 3.1% → One year repeat co-test

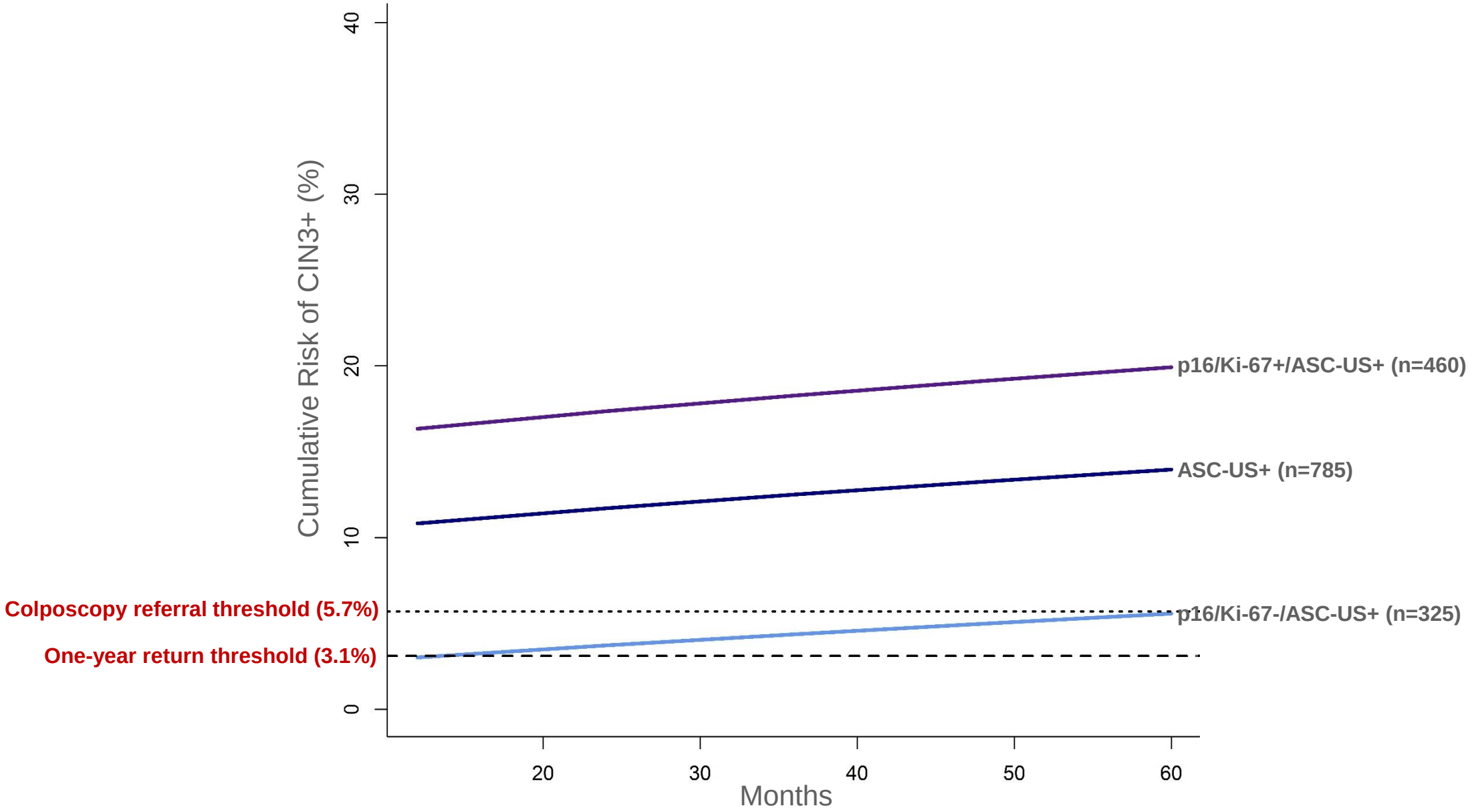
Study Population

	Total n	col %	p16/Ki-67+ n	row%
Total	1,549	100.0	705	45.5
Cytology				
NILM	764	49.3	245	32.1
ASC-US	374	24.1	183	48.9
LSIL	309	19.9	193	62.5
HSIL+	102	6.6	84	82.4
Histology				
No Biopsy	270	17.4	60	22.2
Normal	350	22.6	138	39.4
Atypical	55	3.6	20	36.4
CIN1	633	40.9	300	47.4
CIN2	108	7.0	83	76.9
CIN3	122	7.9	94	77.1
Cancer	11	0.7	10	90.9

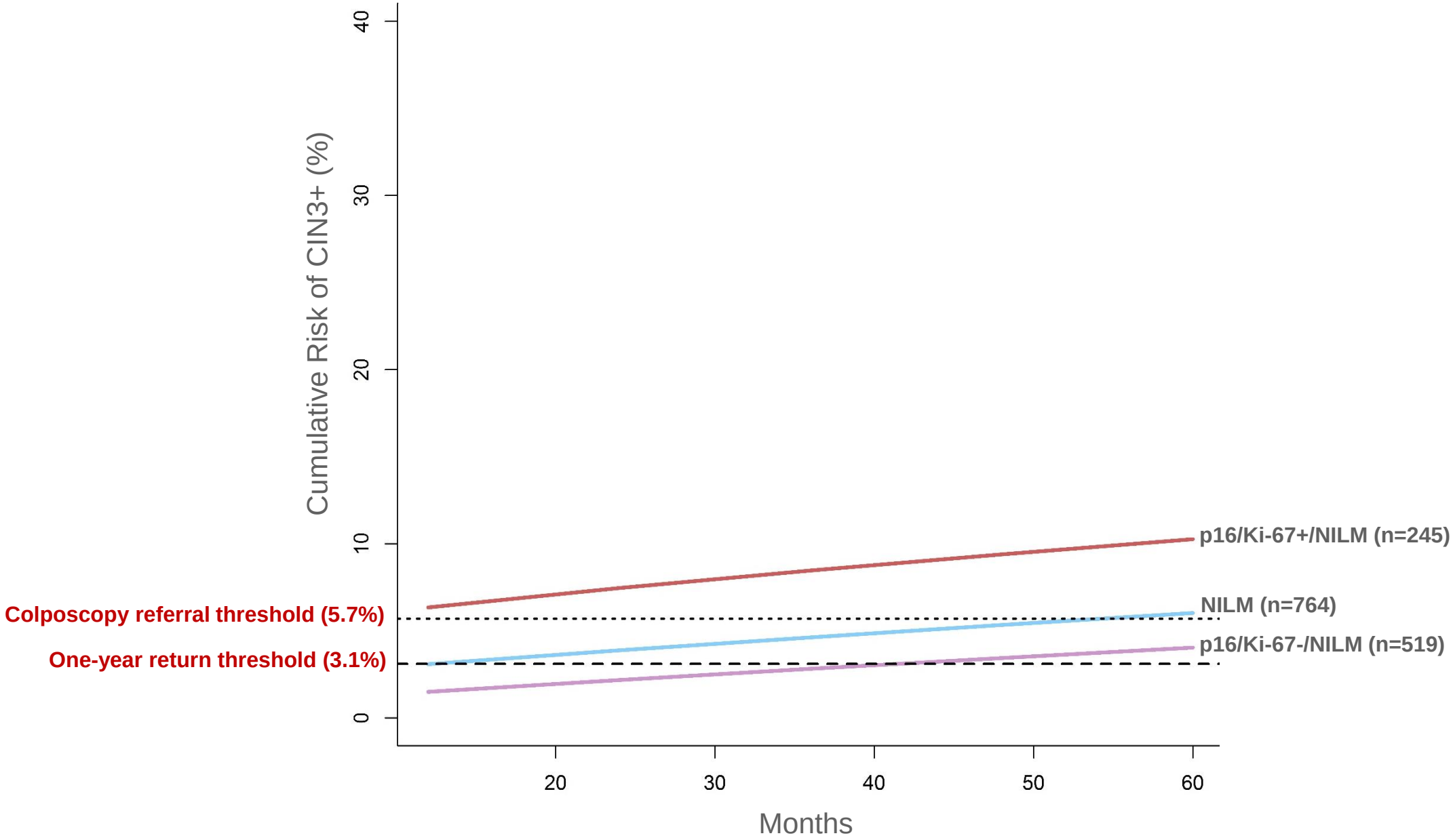
Cumulative risk of CIN3+ by dual stain and cytology



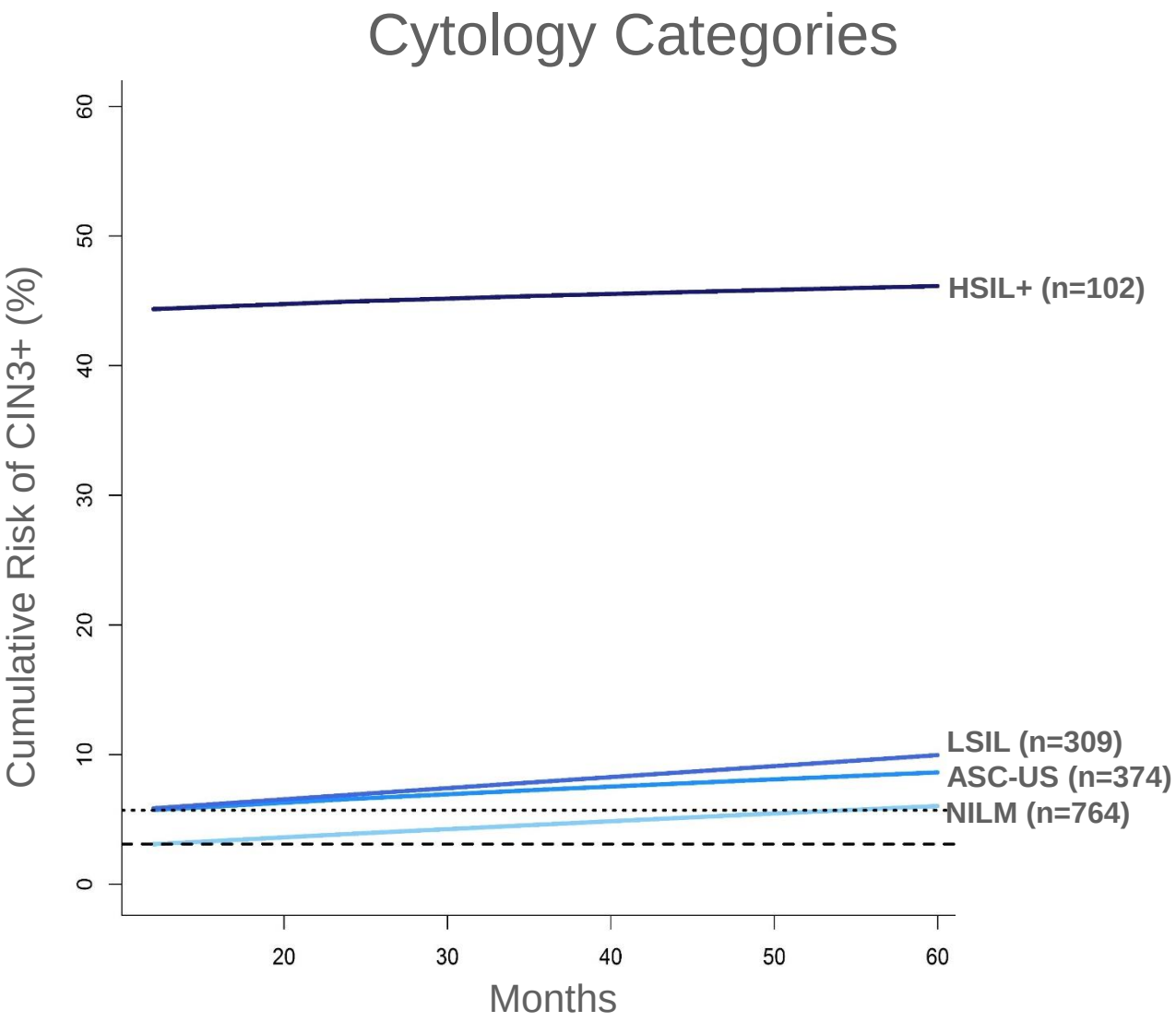
Cumulative risk of CIN3+ by combined dual stain and cytology

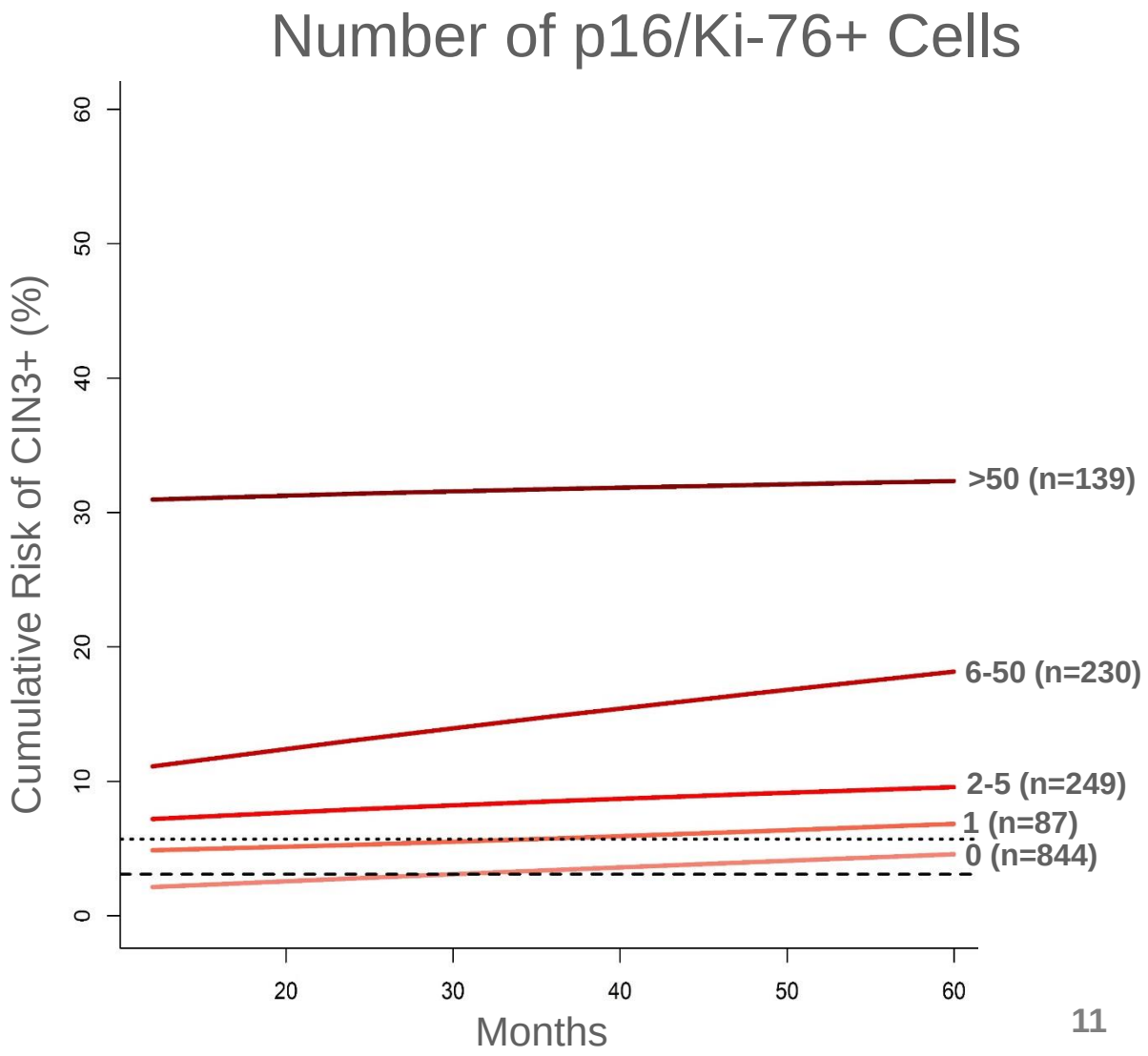


Cumulative risk of CIN3+ by combined dual stain and cytology



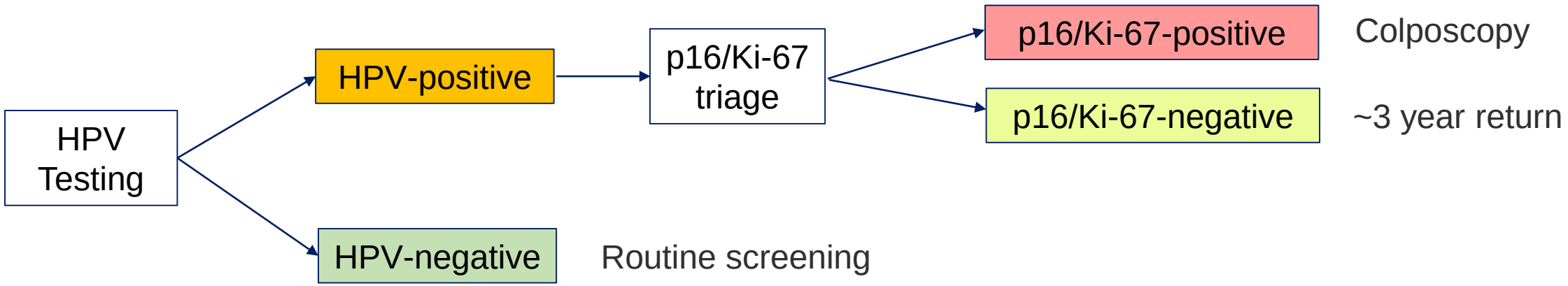
Risk of CIN3+ by Number of p16/Ki-67+ Cells and Cytology





Conclusions

- p16/Ki-67 dual stain provided long-term risk stratification over 5 years
- Fewer women testing p16/Ki-67 positive at baseline compared to cytology
- Repeat screening interval could be extended up to 3 years in HPV-positive, p16/Ki-67-negative women



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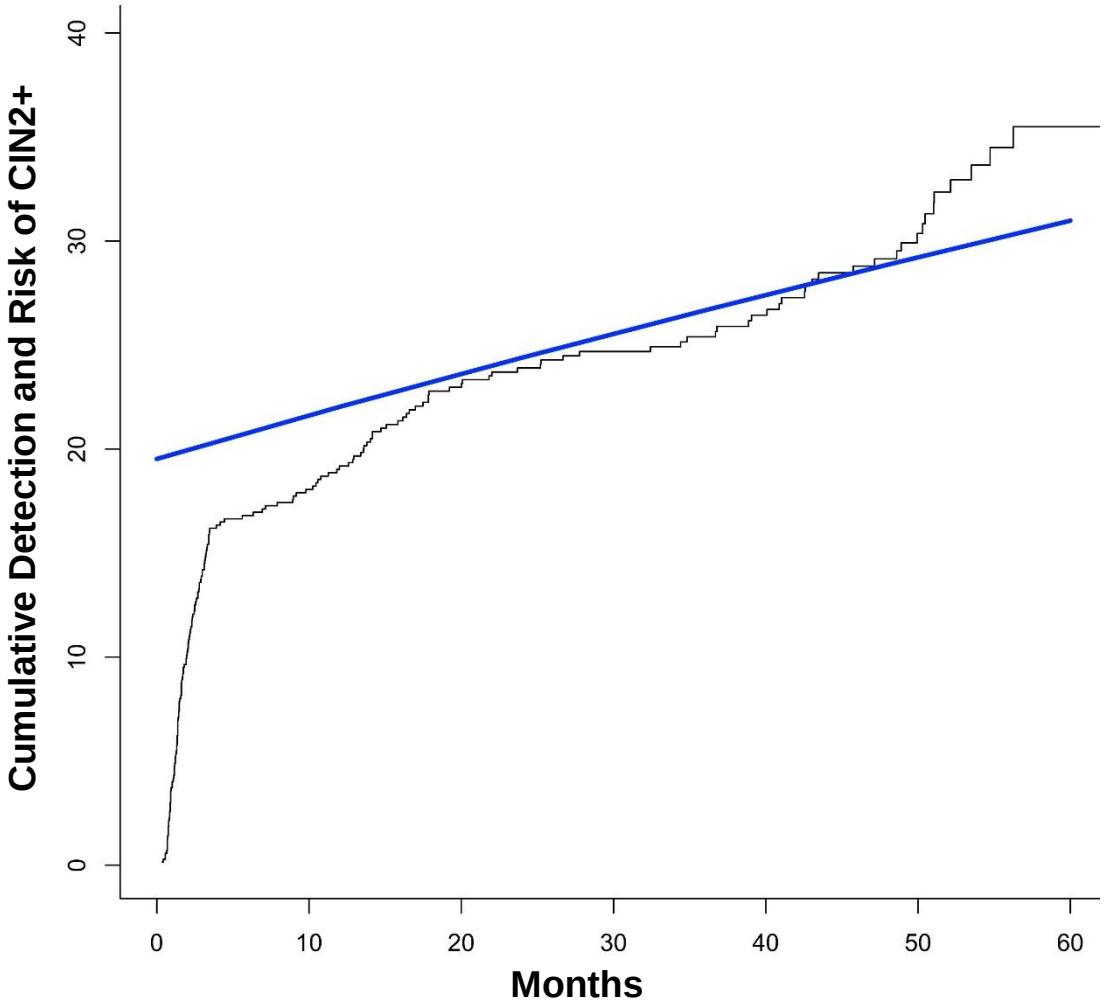
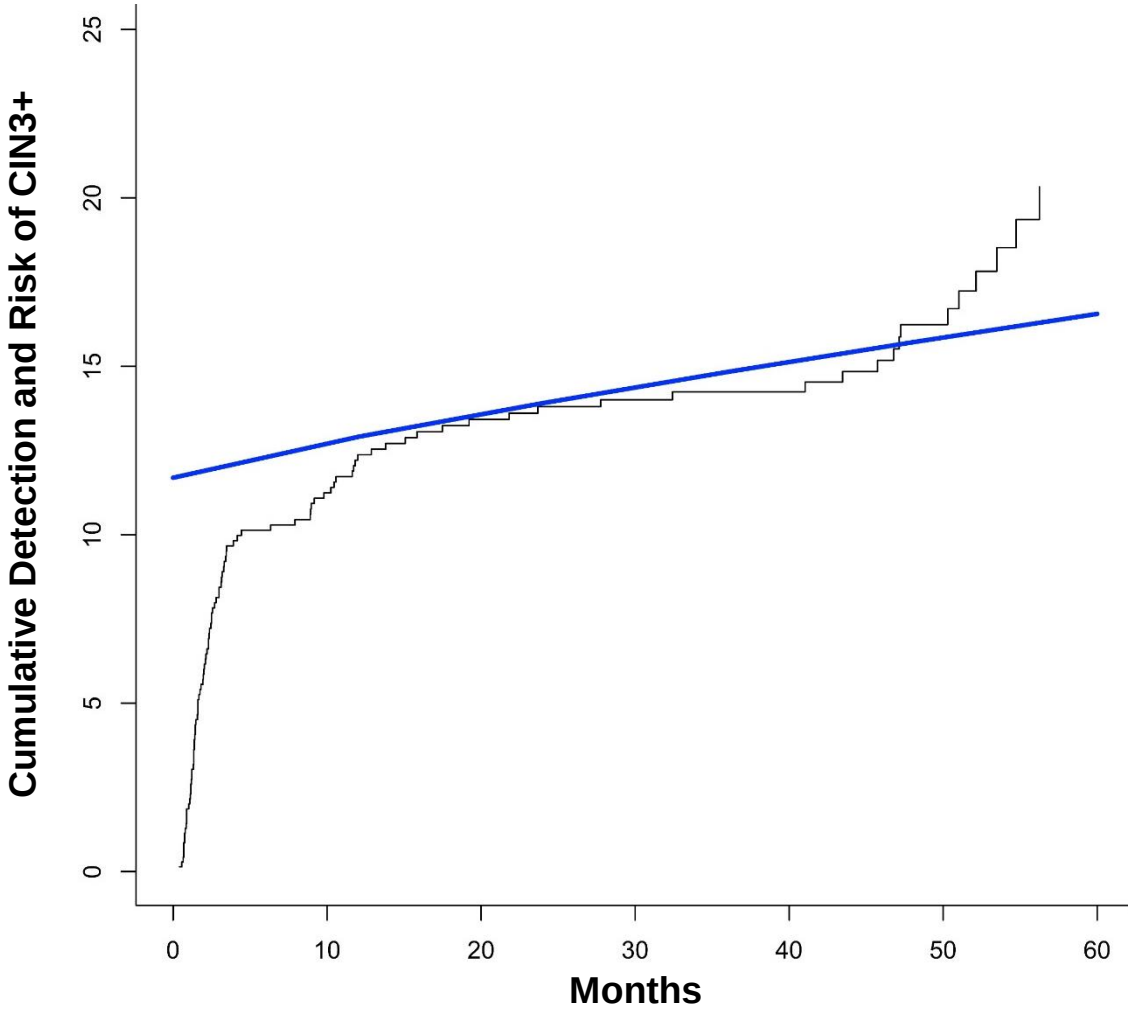


Kaplan Meier	705	420	268	21
No. At Risk				



Kaplan Meier	705	467	307	29
No. At Risk				

Supplementary Figure 4. Cumulative risk of CIN2+ and CIN3+ in women with DS-positive cytology at enrollment. Logistic Weibull curves are shown in blue, Kaplan Meier curves are shown in black.