IS CO-TESTING WITH A 3-TYPE HPV MRNA TEST A BETTER STRATEGY FOR WOMEN 21-29 YEARS THAN CYTOLOGY ONLY?

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Disclosures

- SWS has nothing to disclose
- FES has received compensation from PreTect AS for participation at Advisory Board meetings during the previous 2 years
- BMF and SH: Employed by PreTect AS

Background

- Women in their 20's represent a challenge in screening algorithms when it comes to **when** and **how** to test:
  - The prevalence of HPV is high in young women (ca. 30% < 30 years)
  - The prevalence of CIN2+ is high but most cases regress within 1-2 years
  - Cervical cancer is at rise; peaking at 35-39 years in the Nordic countries
- Women < 30 years are advised to have only their PAP done, as HPV DNA test generates too many false positives

Prevention by cytology

- Screening with cytology has shown age dependent sensitivity ranging from 20 – 50% for women < 40 years

- Up to 50% of cervical cancer incidences are missed by cytology; despite attendance in screening (Norwegian Cancer Registry)

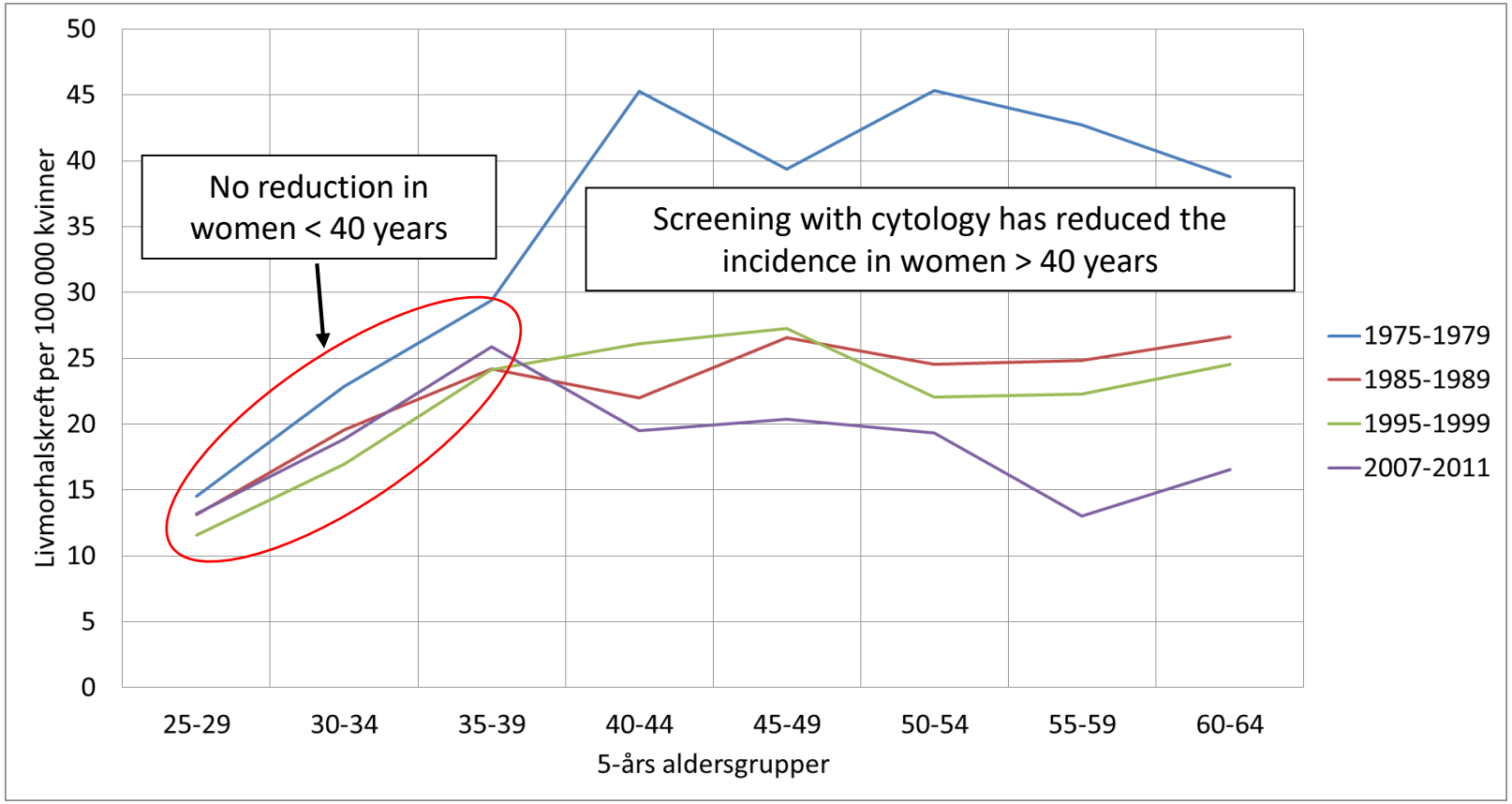
- To prevent more cases of cervical cancer **focus** has to be on young women

Why co-test using a 3-type HPV mRNA test?

- HPV 16, 18 and 45 are aggressive HPV types known to cause a more rapid development of severe lesions
- > 90% of cervical cancer in women younger than 40 years of age are caused by HPV 16, 18, 45
- Up to 94% of adenocarcinomas are associated with HPV 16, 18, 45

Cervical cancer in Norway (1975-2011)

- Highest incidence of cancer in women **35-39 years**
- Screening with cytology **no reduction** of cancer < 40 y



Objectives

- Evaluate if a specific 3-type HPV E6/E7 mRNA test as co-test to cytology may increase detection rate of **CIN3+**
- Estimate the positive predictive value (PPV) for CIN3+ for cytology, HPV mRNA and co-test positives
- Evaluate if co-testing provides better risk stratification in women with minor cervical lesions and hereby reduce over-referrals

Methods

The study was initiated by Clinical Pathology, University Hospital of North Norway

Enrolled: Women attending the Norwegian screening program in the two most northern counties Troms and Finnmark between 2013 and 2017 with follow up until July 2018

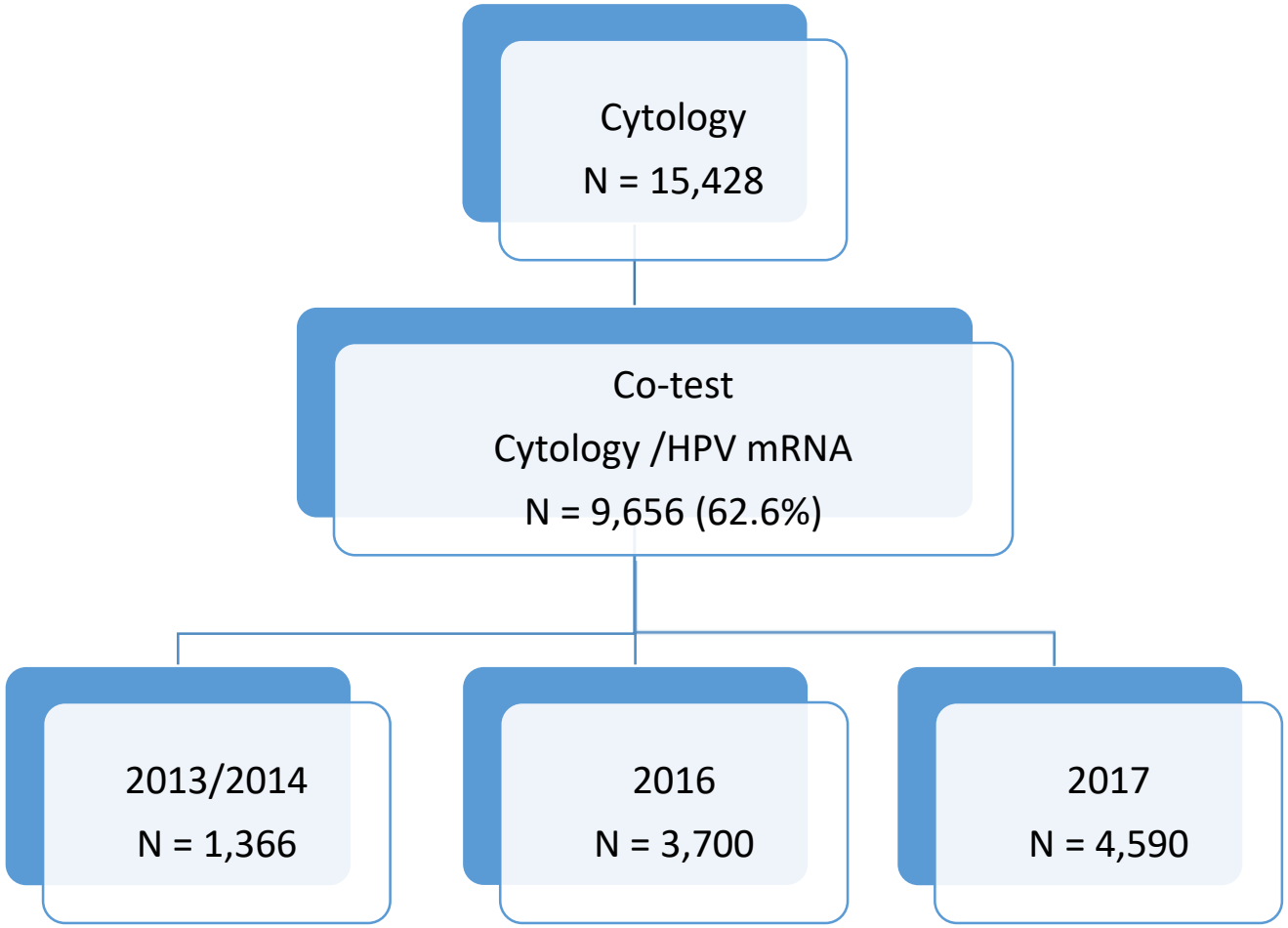
All women were followed up according to national guidelines

- Cytology: Bethesda system: Liquid Based (LBC)
- Histology: CIN classification - Outcome: **CIN3+**
- HPV mRNA: PreTect SEE

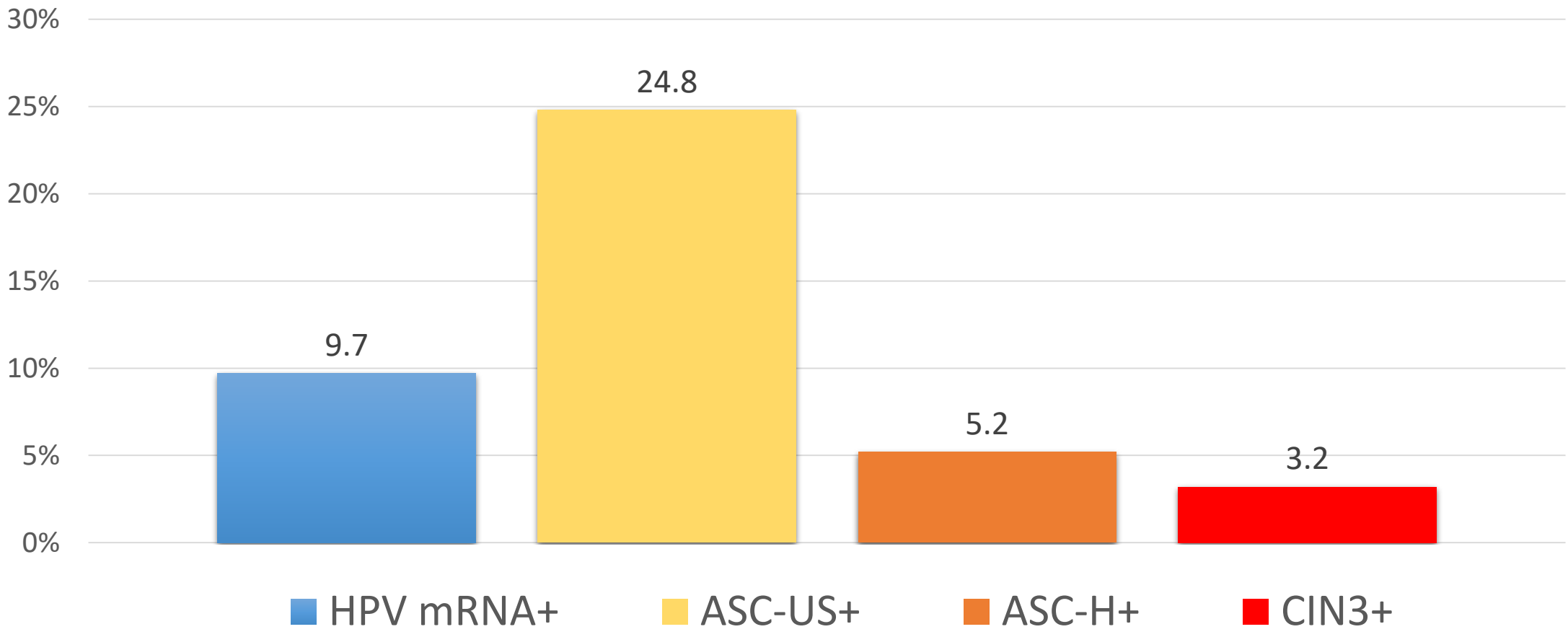
  Individual genotyping of HPV E6/E7 mRNA 16, 18 and 45 incl. ISC

Study population

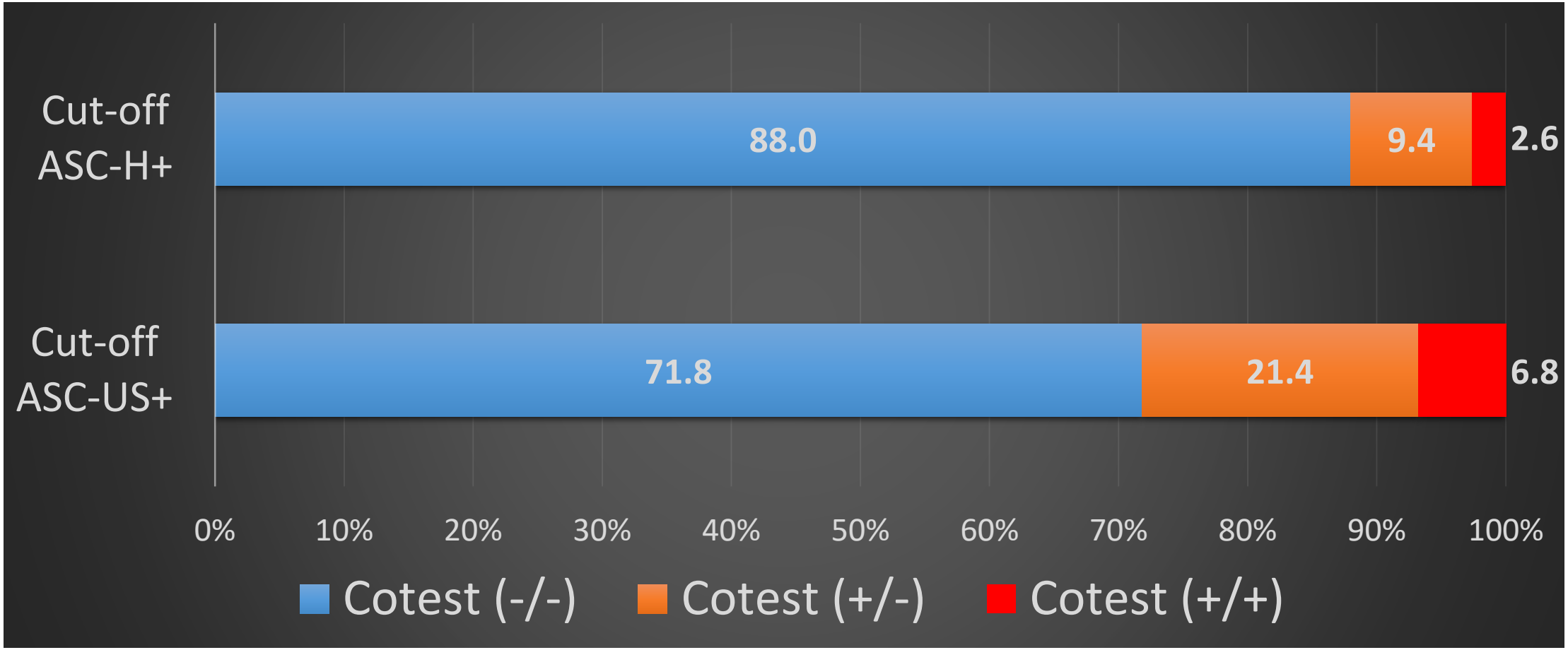
Women 21-29 years during (2013-2017) with follow up until July 2018



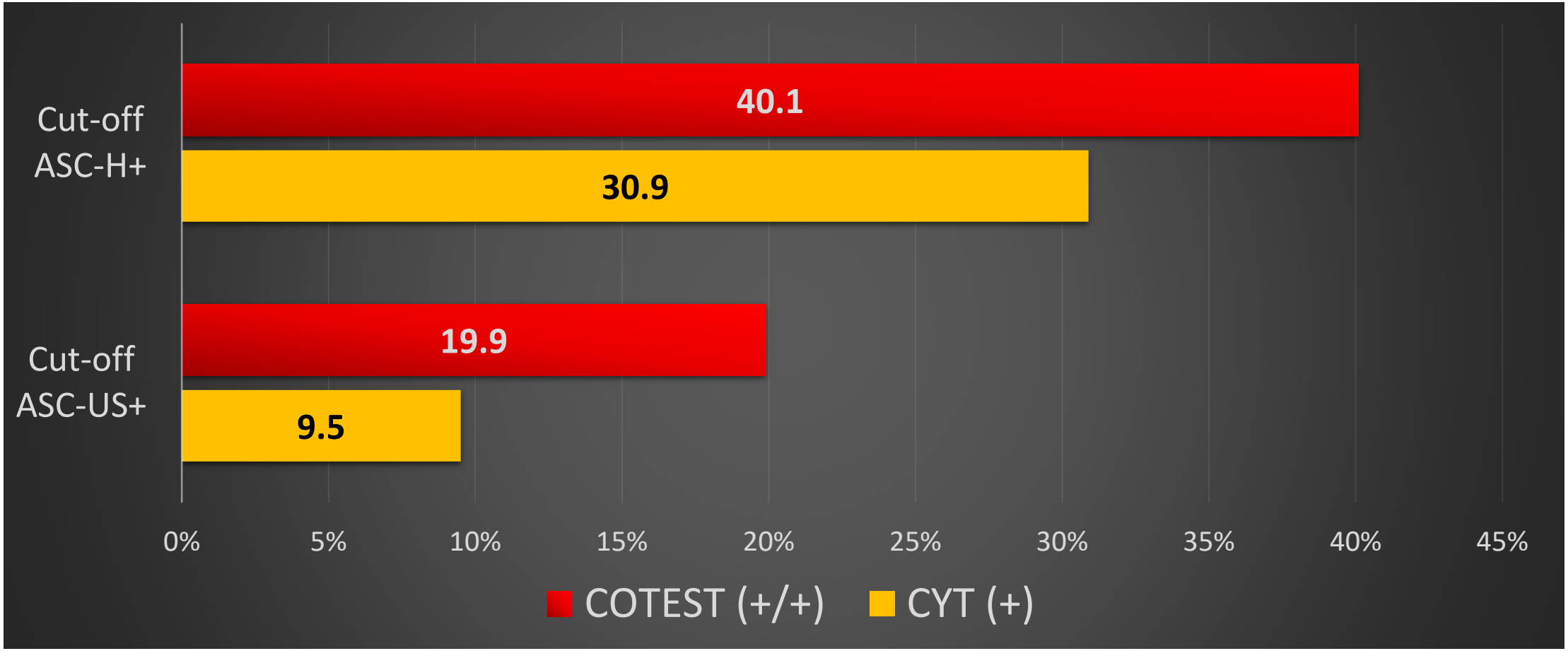
Positivity rates at baseline in women 21-29 years
Detection of CIN3+ during follow-up



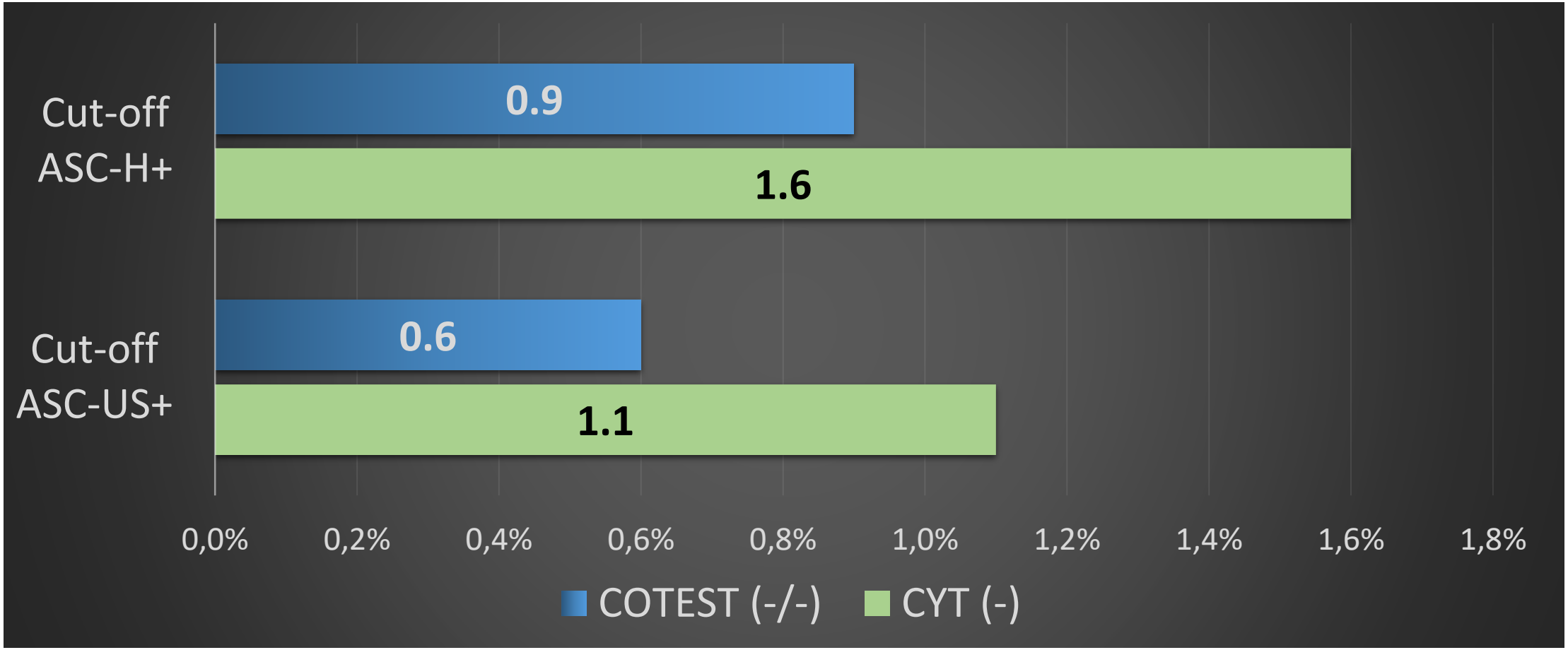
Co-test results (N=9,656) by cut-off: ASC-US+ versus ASC-H+



PPV CIN3+ for Cytology and Co-test positive (+/+) by cut-off: ASC-US+ versus ASC-H+



Risk of CIN3+ in cytology and co-test negative (-/-)
Cut-off: ASC-US+ versus ASC-H+

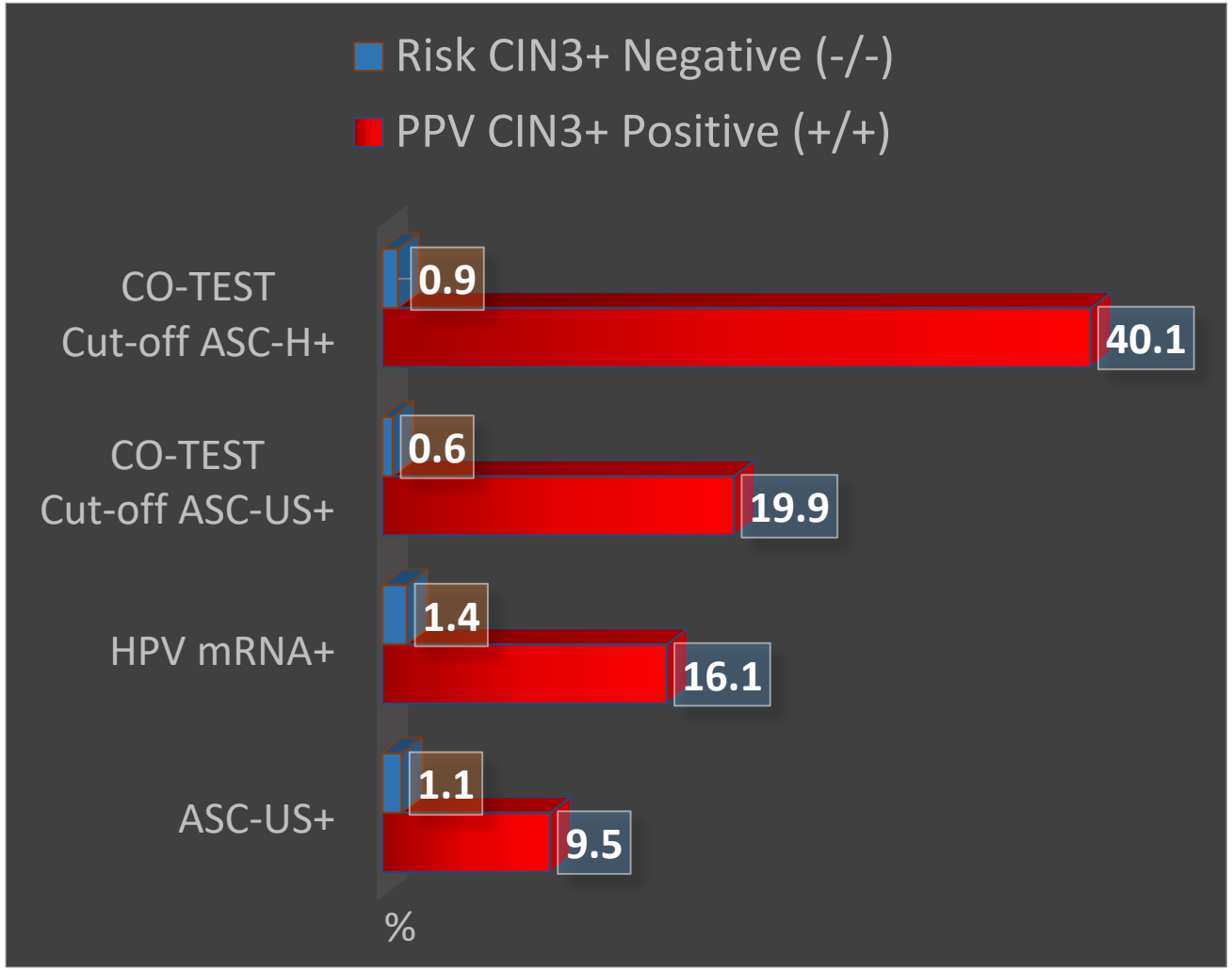


A risk based approach using ASC-H+ as cut-off

Double co-test positives **(+/+)** can be referred directly to colposcopy and biopsy (2.6%)

Single co-test positives **(+/-)** can be followed up in 12 months (9.4%)

Co-test negatives **(-/-)** have low risk of CIN3+ and may return to screening (88.0%)



May co-testing be a better approach for women in their 20's?

	Current practice Cytology ASC-US+ (%)	Co-test HPV mRNA /ASC-H+ (%)
Return to screening	75.2	88.0 (-/-)
Risk CIN3+ in test negative	1.1	0.9 (-/-)
Follow-up of test positive Direct colpo/biopsy Repeat/triage	24.8 5.2 (ASC-H+) 19.6 (ASC-US/LSIL)	12.0 2.6 (+/+) 9.4 (+/-)
PPV CIN3+ test positive	9.5 30.9 (ASC-H+) 3.2 (ASC-US/LSIL)	19.9 40.1 (+/+) 10.1 (+/-)

Conclusion

- Double co-test positives have substantial higher risk of CIN3+ targeting the right women for colposcopy
- Low HPV mRNA positivity rate result in low referral rate
  - 50% reduction of women 21-29 years to be followed up with equal or less risk of CIN3+ in test negatives
- Improved safety for co-test negatives will reduce future incidents of cancer
- Knowledge of HPV mRNA genotypes enables accurate patient management