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Performance of a 7-type HPV mRNA test compared to Liquid-Based Cytology in triage of HPV-DNA primary screen positive women.

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Disclosures

- I have nothing to declare
- This study had nonfinancial support from PreTect AS, which provided reagents for free

HPV-based screening- a recommended public health policy

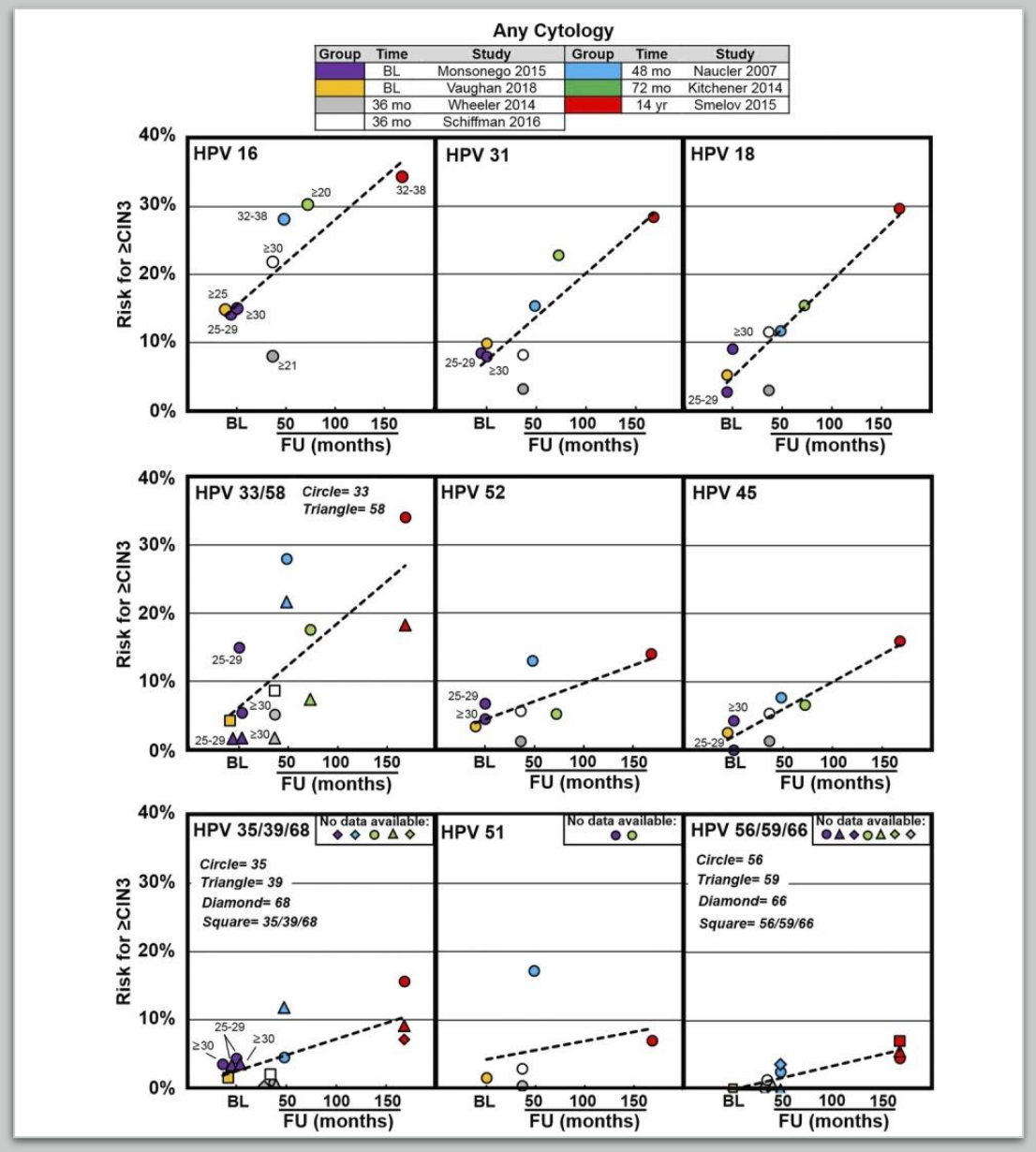
- HPV-based primary screening is the preferred strategy for cervical cancer prevention
- The shift to a more sensitive first line test brings the need of effective triage up for discussion:
  - to reduce the risk of overdiagnosis and overtreatment of transient HPV-infections
- Currently, most countries apply cytology as triage of HPV-DNA positive women
- Various molecular triage alternatives are being evaluated

Primary HPV-DNA Challenges

- Generates a lot of screen positives (10-20%)
- Causes substantial increased number of colposcopies/biopsies
- Most women with a positive HPV-DNA test do not have clinically significant disease
- HPV DNA tests with 14 genotypes have a lower specificity than cytology
- Effective Triage & Risk stratification is crucial to reduce the number of unnecessary colposcopies

HPV Genotype Specific CIN3+ Risks - Regardless of Cytology

- **HPV 16**
- **HPV 18, 31, 33, 45, 52, 58**
- **HPV 35, 39, 51, 56, 59, 66, 68**
- Risks lower than colposcopy threshold



***Bonde, J. et al.** Clinical Utility of Human Papillomavirus Genotyping in Cervical Cancer Screening: A Systematic Review. J Low Genit Tract Dis. 2020 Jan;24(1):1-13. Fig 1.

A risk-based approach: 7-type HPV E6/E7 mRNA-test

- Detects HPV mRNA E6/E7; precursors of the oncoproteins known to disturb normal cell cycle
- Genotypes the 7 most prevalent HPV-types causing 90% of all cervical cancer cases
  - HPV 16, 18, 31, 33, 45, 52 and 58
- Holds low positivity rate in general population
- Only 1/3 of HPV-DNA positives show mRNA expression from the 7 types

HPV-DNA primary screening Norway

Implemented in 2019:

- ❑ Women 34-69 years of age screened by HPV
- ❑ Women 25-33 yrs. screened by cytology

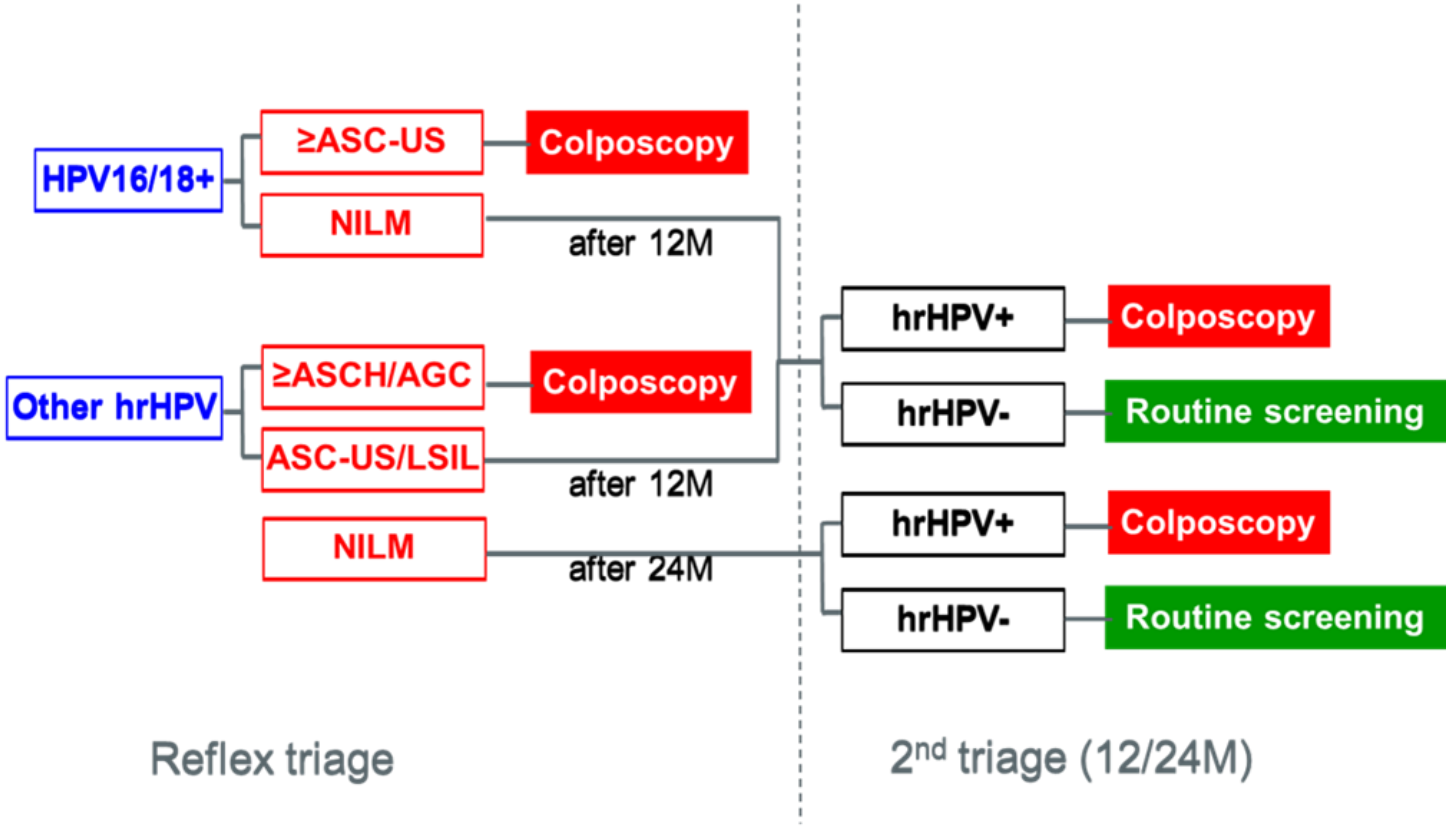
Starting in July 2023:

- ❑ All women 25-69 years of age HPV-tested

Follow up of test positives:

- ❑ More intense follow up of HPV16/18+

Follow-up HPV primary screen positives Norway



*Marc Arbyn, illustration of the Norwegian HPV-Primary screening algorithm

Performance of a 7-Type HPV mRNA Test in Triage of HPV DNA Primary Screen Positive Women Compared to Liquid-Based Cytology*

HPV DNA Primary Screening

- ❑ Women 34-69 yrs. (2019-2021)
- ❑ HPV DNA test: Cobas 4800, Roche

Triage of all DNA positives by

- ❑ Cervical Cytology (LBC)
- ❑ HPV mRNA test (PreTect HPV-Proofer`7)
  Individual genotyping (16,18,31,33,45,52,58)

Study endpoint:

- ❑ Histologically confirmed CIN2+
- ❑ Follow-up: December 2022

*Data published:

- ❑ J. Mol. Pathol. 2023, 4, 69–8
  https://doi.org/10.3390/jmp4020008

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Study Objectives

- ❑ Compare performance of 7-type HPV-mRNA to LBC in triage of HPV primary pos.
  - Sensitivity, Specificity, Diagn. Accuracy, PPV, NPV
  - Cut-off ASC-US+/ASC-H+/5-type/7-type mRNA
- ❑ Establish the risk of CIN2+ at specific branching points in screening (primary test and triage)
- ❑ Assess the rate of colposcopies per CIN2+ detected per strategy
- ❑ Calculate the absolute risk of CIN2+ by HPV genotype for DNA versus mRNA detection

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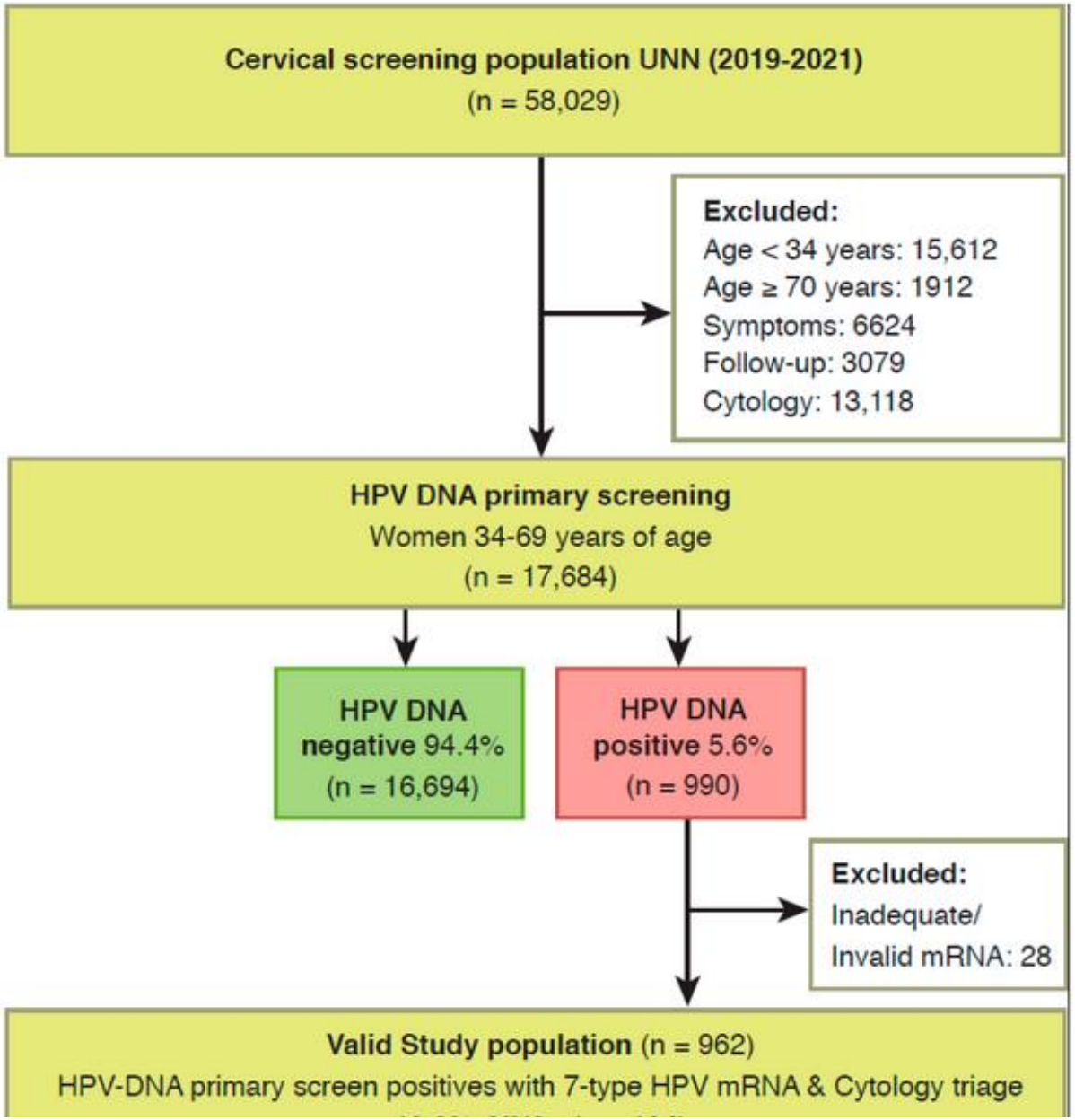
Selection Study Population



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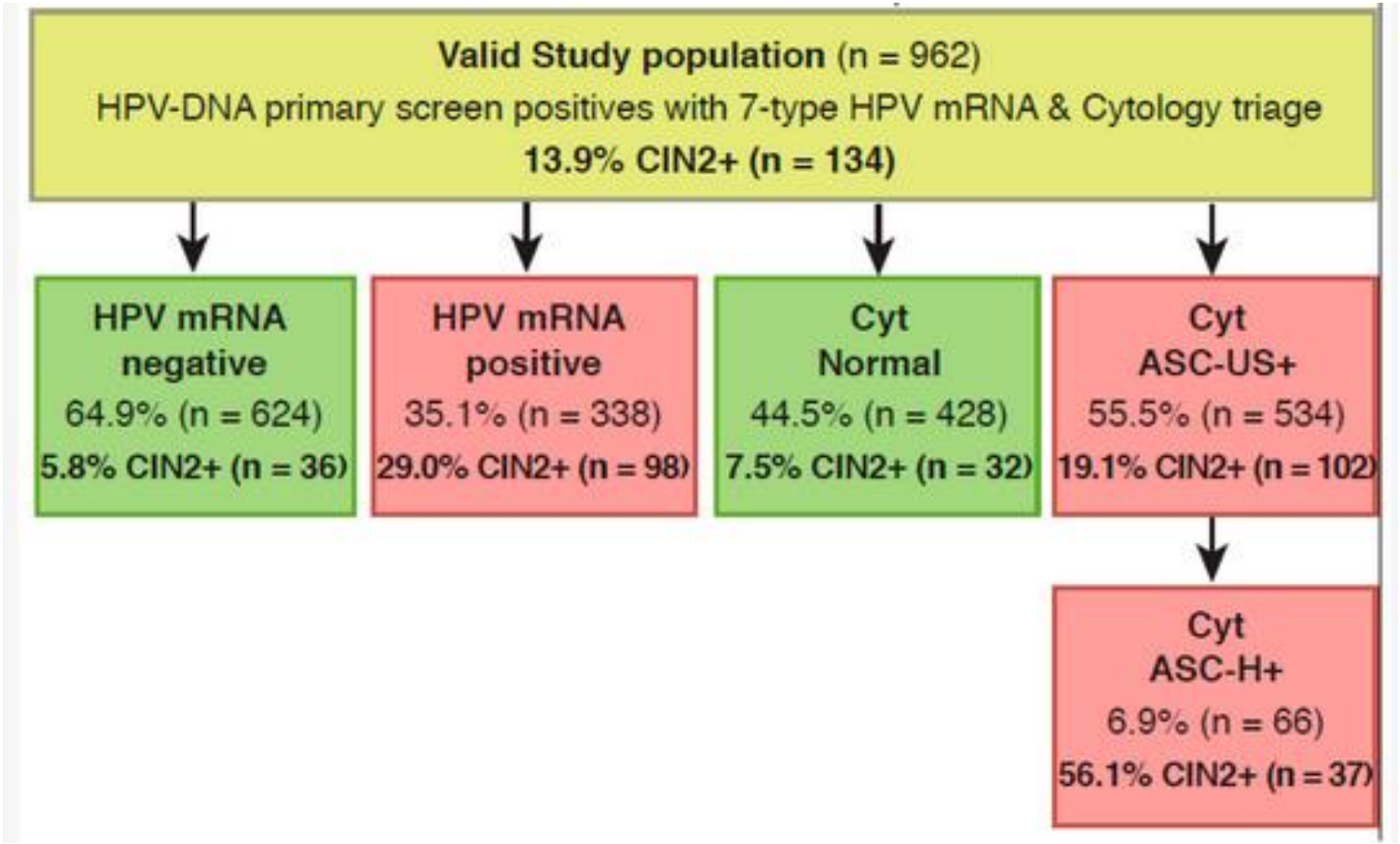
Results 1. Test positivity rates and CIN2+ prevalence



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Results 2.
Test characteristics for detection of CIN2+ in HPV DNA pos. women

Triage strategy	TP	TN	FP	FN	SE %	SP %	AU %	PPV %	95% CI	NPV %
Cytology ASC-US+	102	396	432	32	76.1	47.8	62.0	19.1	15.8-22.4	92.5
Cytology ASC-H+	37	799	29	97	27.6	96.5	62.1	56.1	44.1-68.0	89.2
HPV mRNA`5+	86	646	182	48	64.2	78.0	71.1	32.1	26.5-37.7	93.1
HPV mRNA`7+	98	588	240	36	73.1	71.0	72.1	29.0	24.2-33.8	94.2

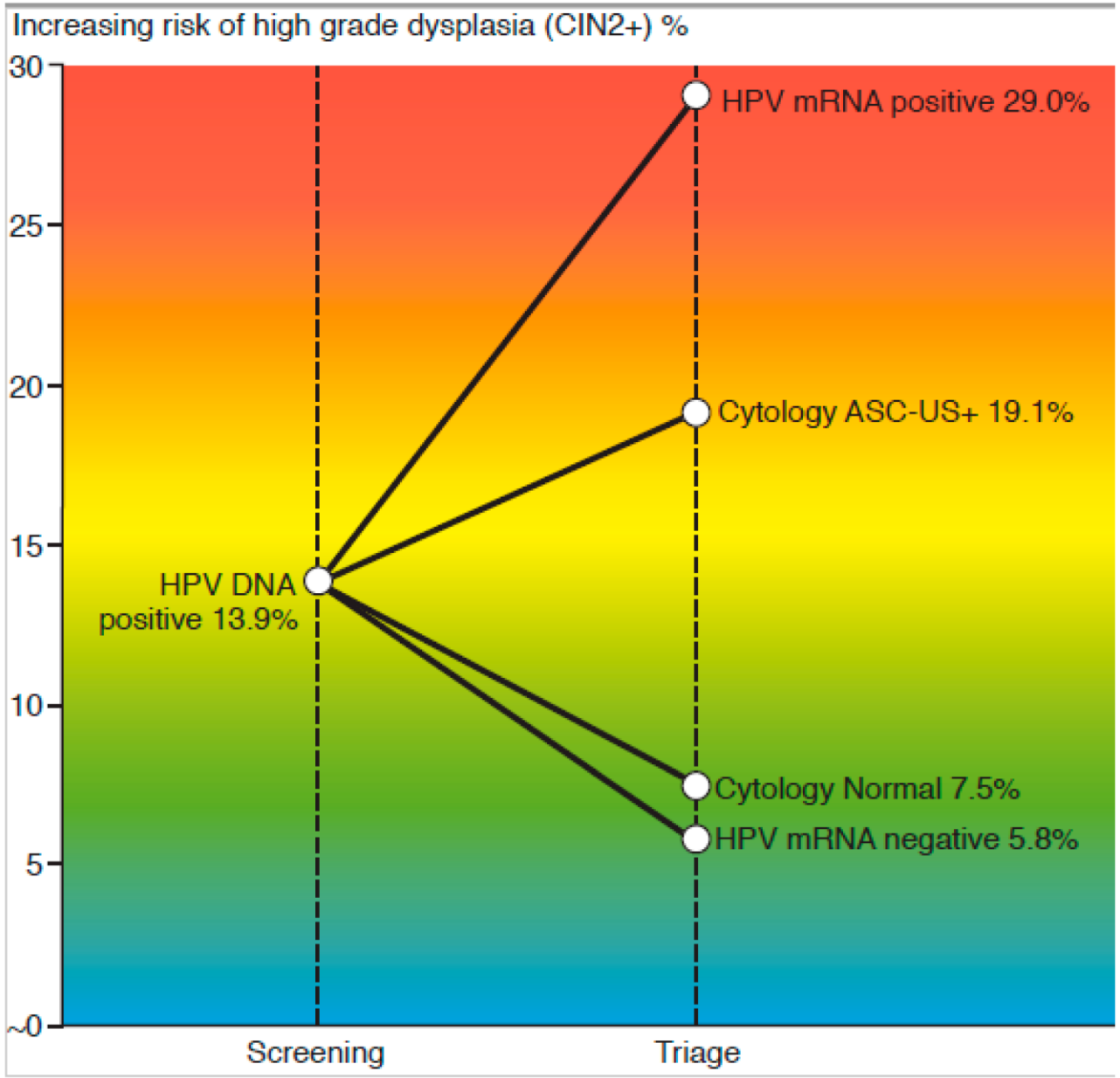
- HPV mRNA`5: 16, 18, 31, 33, 45+
- HPV mRNA`7: 16, 18, 31, 33, 45, 52, 58+

Results 3.
The number of colposcopies required per ≥ CIN2 case detected

Triage strategy	Positives (%)	No. CIN2+ (*1*)	No. Colpo (*2*)	Colpo/CIN2+ (*3*)
Cytology ASC-US+	55.5	102	534	5.2
Cytology ASC-H+	6.9	37	66	1.8
HPV mRNA`5+	27.9	86	268	3.1
HPV mRNA `7+	35.1	98	338	3.4

(1) the number of CIN2+ cases detected by each strategy among the total 134 cases.
(2) the estimated number of colposcopies to be performed if all test positives are scheduled to colpo.
(3) the calculated number of colposcopies required to detect one case of CIN2+.

Results 4. Risk of CIN2+ across screening tests



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Results 5.
Absolute risk for CIN2+ per HPV DNA & mRNA genotype

HPV genotype	No. of infections	No. of CIN2+	Risk estimate (%)	95% CI
16_DNA	130	45	34.6	26.4 - 42.8
16_mRNA	73	39	53.4	42.0 - 64.9
18_DNA	39	9	23.1	9.9 - 36.3
18_mRNA	30	10	33.1	16.5 - 50.2
Other_12 DNA*	793	80	10.1	8.0 - 12.2
Other_5 mRNA**	235	49	20.9	15.7 - 26.0
31	88	23	26.1	17.0 - 35.3
33	28	14	50.0	31.5 - 68.5
45	59	8	13.6	4.8 - 22.3
52	59	14	23.7	12.9 - 34.6
58	32	6	18.8	5.2 - 32.3

*12 types DNA (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68)

** 5 types mRNA (31, 33, 45, 52, 58)

Conclusions

7-type mRNA test performance compared to LBC in triage of HPV-DNA positives:

- ❑ Specificity ↑ (71.0% vs. 47.8%)
- ❑ PPV ↑ (29.0% vs. 19.1%)
- ❑ Sensitivity = (73.1% vs. 76.1%)
- ❑ NPV = (94.2% vs. 92.5%)
- ❑ No. of colpo ↓ (3.4 vs. 5.2)

Using this biomarker as a threshold for referral to colposcopy may better balance the benefits and harms of screening, reducing over referrals.

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Take home messages

HPV DNA primary screening provides high sensitivity and improved prevention of CC

Risk stratification is required for accurate patient management of HPV DNA positive women

7 HPV-types are crucial

HPV 16, 18, 31, 33, 45, 52, 58 cause 90% of CC

A 7-type HPV mRNA test might better balance benefits/harms of screening and allows self-sampling

A low mRNA positivity rate gives a low referral rate for colposcopy and might reduce over-treatment

Thank you for your attention!