THE ADDED VALUE OF RESCREENING CYTOLOGY NORMAL SAMPLES WITH POSITIVE HPV MRNA TEST FOR THE DETECTION OF CIN2+ IN PRIMARY SCREENING

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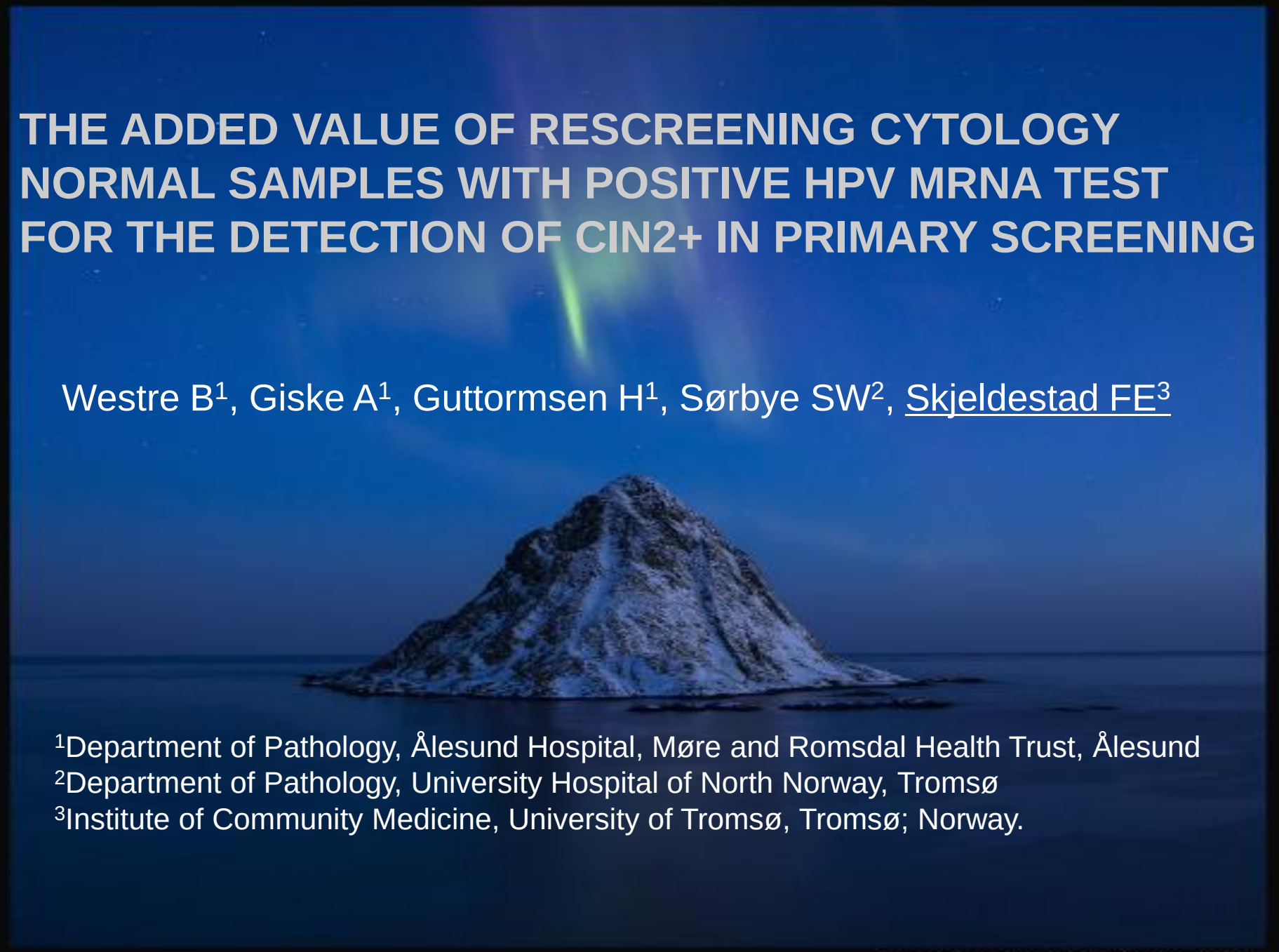


DISCLOSURES

BW, AG, HG and SWS have nothing to disclose.

FES has received compensation from PreTect AS for participation at Advisory Board meetings during the past two years.

Norway – cervical cancer screening

≤ 1994: opportunistic cytology screening (25-69 yrs)

≥ 1995: organized cytology screening (25-69 yrs)

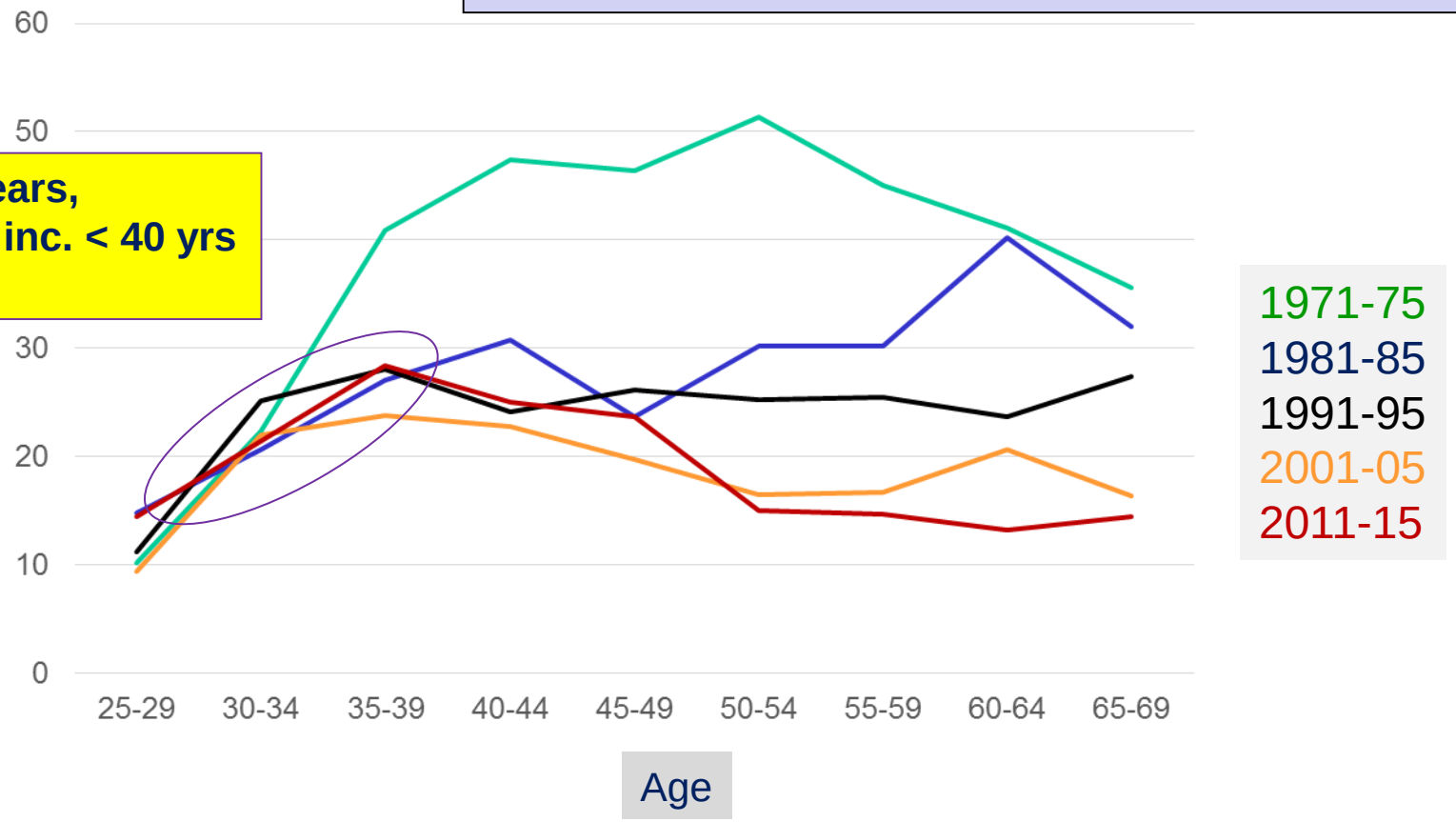
2015 – Age group 25-33: cytology screening
– Age group 34-69: HPV-DNA scr. (3 counties)

≥ 2019 – Age group 25-33: cytology screening
– Age group 34-69: national HPV-DNA screening

Incidence CC Norway 1971 – 2015 by age

Cytology screening has reduced incidence > 40 yrs

**Peak 35-39 years,
no change in inc. < 40 yrs
after 1981**



Data source: Nordcan database

Data from annual reports NCR

N cervical cancers among women < 70, < 25, and < 40 yrs., number of women < 40 yrs. with smears within 4 years of cancer diagnosis, and proportion (%) of women with normal last smear before start of cascade of smears leading to a cancer diagnosis, Norway, 2007-2016, and total.

Year	N CC < 70 yrs.	N CC < 25 yrs.	N CC 25-39 yrs.	N women < 40 yrs., smears < 4 yrs. cancer diag.	% women < 40 yrs., normal last smear before cancer diagnosis
2007	206	2	64	43	48.8
2008	243	5	93	65	55.4
2009	260	6	94	62	46.7
2010	278	4	106	67	65.7
2011	259	5	107	66	51.5
2012	278	1	100	56	48.2
2013	243	6	74	40	55.0
2014	306	6	133	75	56.0
2015	338	5	126	67	58.0
2016	301	**13**	108	62	53.2
Total	2 712	**53**	**1 005**	**603**	**57.0**

2007-16: 344 w. < 40 yrs., false neg. last smear < 4 yrs. Prior a ca. diag.

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Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: A meta-analysis update

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TABLE I – GEOGRAPHIC DISTRIBUTION OF STUDIES AND CASES WITH TYPE SPECIFIC HUMAN PAPILLOMAVIRUS DNA TYPING FOR INVASIVE CERVICAL CARCINOMA (ICC) AND HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESIONS (HSIL)

CONTINENT	ICC		HSIL		Countries represented
	N studies	*N* cases	*N* studies	*N* cases	
Africa	13	1,339	5	296	Algeria,[1] Benin, Ethiopia,[2] Guinea, Ivory Coast,[3] Kenya,[3] Mali, Morocco, Mozambique,[2] Senegal,[1] South Africa,[1] Tanzania, Uganda, Zimbabwe[2]
Asia	51	5,652	22	1,364	China,[1] India,[1] Indonesia,[1] Japan,[1] South Korea,[1] Malaysia, Philippines, Taiwan,[1] Thailand,[1] Iran[2]
Europe	41	4,373	37	3,494	Austria,[1] Belgium,[1] Croatia,[3] Czech Republic, Denmark, Finland, France, Germany, Greece, Greenland, The Netherlands,[1] Hungary, Ireland, Italy,[1] Latvia,[2] Lithuania,[2] Norway, Poland,[1] Portugal,[2] Russia, Sweden,[1] UK
North America	13	1,354	10	1,059	Canada,[1] USA[1]
Oceania	5	450	1	48	Australia[1]
South/Central America	13	1,427	11	833	Argentina,[1] Bolivia, Brazil,[1] Chile, Colombia, Costa Rica,[1] Cuba, Honduras, Jamaica,[3] Mexico, Panama, Paraguay, Peru
Total	130[4]	14,595	85[4]	7,094	

[1]Country for which additional ICC cases have been gained since Clifford *et al.*, 2003 [ref. 4].–[2]Country not previously represented with ICC cases in Clifford *et al.*, 2003 [ref. 4].–[3]Country for which HSIL data only is available.–[4]Continents do not add up to total due to multi-centric studies.

TABLE II – COMPARISON OF HUMAN PAPILLOMAVIRUS (HPV) TYPE DISTRIBUTION IN SQUAMOUS CELL CARCINOMA (SCC) VERSUS HIGH-GRADE INTRAEPITHELIAL LESIONS (HSIL)

HPV type	SCC		HSIL		SCC vs HSIL Prevalence ratio[2] (95% CI)
	N	% HPV positive[1]	*N*	% HPV positive[1]	
Any	9,494	89.7	7,094	84.9	1.06 (1.05–1.07)
16	9,494	55.2	7,094	45.3	1.30 (1.26–1.34)
18	9,402	12.8	6,978	6.9	1.76 (1.58–1.95)
45	6,215	4.6	3,726	2.3	1.54 (1.20–1.98)
31	7,565	3.8	6,282	8.6	0.53 (0.45–0.61)
33	8,803	3.7	6,418	7.3	0.52 (0.45–0.60)
52	6,431	2.9	3,945	5.1	0.44 (0.36–0.54)
58	6,873	2.8	4,181	7.0	0.30 (0.25–0.35)
35	6,982	1.5	4,739	3.8	0.38 (0.29–0.49)
59	5,160	1.1	2,933	0.8	0.88 (0.53–1.47)
51	5,706	1.0	3,509	3.6	0.21 (0.15–0.30)
56	5,605	1.0	3,465	2.9	0.29 (0.20–0.42)
39	5,578	0.9	3,067	2.0	0.40 (0.27–0.60)
68	5,224	0.5	2,563	1.1	0.44 (0.24–0.82)
6	7,523	0.5	3,728	2.2	0.17 (0.11–0.25)
66	5,427	0.4	2,840	1.9	0.20 (0.12–0.34)
73	4,717	0.4	1,464	1.8	0.45 (0.23–0.87)
70	4,925	0.1	1,105	1.3	0.11 (0.04–0.29)
82	4,776	0.1	1,183	1.2	0.06 (0.02–0.18)
11	6,874	0.1	3,762	1.3	0.09 (0.05–0.18)

[1]Type-specific prevalence includes that in single or multiple infections.–[2]Prevalence ratio adjusted for continent. CI = confidence interval.

Smith et al. Int J Cancer 2007;121:6:621-31

HPV prevalence CC – Norway

Kraus I, Molden T, Lie KA, et al. JCM 2006;44:1310-7.

	mRNA	mRNA	DNA	DNA	Gp5+/Gp6+	ISH	All
	N=204	N	N=204	N	N	N	N
Neg.	16	16	16	16	17		6
16		121		122			
18	89%	21	88%	21		78%	93%
31		10		8			
33		11		12			
45		18		17			
35	93%	3	92%	5	92%		97%
52		4		5			
58		2		2			
6, 26					2		
66, 69					2		
73					3		
51		1		1			

HPV 16, 18, 45 ~ 80%

Quality control of cytology in cervical cancer screening

a) Rescreen all
b) Rescreen a random sample
c) Rescreen samples positive for another detection method / mRNA or DNA test-positive samples

Retesting - program sensitivity

	CIN 2+	**CIN <=1**	
>= ASC-US	TP	FP	**PPV**
Normal	FN	TN	**NPV**
	Sensitivity	Specificity	

Retest all cytology-negative smears with mRNA test –
Rescreen all smears mRNA-positive

Ålesund Hospital,
Møre and Romsdal Health Trust,
Ålesund

Study outline

- Examine all normal smears with a mRNA-test if liquid based sampling
- Rescreen all mRNA-positive women
- Age-group 23-39 yrs

PreTect SEE, mRNA test, targeting HPV 16, 18, 45

Inclusion period: April 5th, 2013 thru Sept. 15, 2014
Follow-up: one screening round thru Dec. 31, 2017

Outcomes:
- Workload – need for rescreening
- Increase in screening sensitivity of CIN 2+

Index smear and mRNA HPV positivity

Normal		ASC-US	LSIL	HSIL	ASC-H	AGUS	ACIS	Total
Not mRNA tested	mRNA tested							
n	n	n	n	n	n	n	n	N
2 401	1 444	370	82	35	32	1	1	4 366
55.0%	33.1%	8.5%	1.9%	0.8%	0.7%	0.02%	0.02%	100.0%
mRNA (+)	**28**	**23**	**2**		**2**	**1**		
	1.9%							
HPV 16		**19**	**1**		**1**			
HPV 18		**5**			**1**	**1**		
HPV 45		**1**						

Compliance with triage/follow-up

	SEE-positive-arm	ASCUS/LSIL-arm	HSIL-arm
Index smear	N=28	N=452	N=69
	%	%	%
No follow-up	0	8	3
Incomplete follow-up	0	4	3
Back to screening	29	44	0
Biopsies – not indicated	0	8	0
Biopsies - indicated	71	36	94

Status referral to biopsy/outcome biopsy

Screening cytology	SEE-positive-arm	ASCUS/LSIL-arm		HSIL-arm
Outcome referral to biopsy	Screening indication for biopsy			
	Yes	Yes	No	Yes
	N=20	N=164	N=36	N=69
Not met for biopsy	0	0	0	2
Cytology follow-up	0	61	0	2
Highest histology	N=20	N=103	N=36	N=65
Normal	5	18	6	2
CIN 1	6	25	5	2
CIN 2	1	8	9	6
CIN 3	8	51	15	53
Sq. CC	0	1	1	1
Adenonc.	0	0	0	1
CIN2+ (%)	45.0	61.2		93.9

Detection rates of CIN2+/CIN3+ in study population from

a) Indicated referrals
b) As practiced
c) As practiced + rescreening + assumption that SEE-positivity (1.9%) was similar in untested women with normal cytology

Outcome	Biopsy collected	Normal cytology – not HPV tested	See-positive-arm	ASC-US/ LSIL-arm		HSIL-arm	Total	Detection rate (95% CI)
		N=2 401	N=1 444	N=416	N=36	N=69	N=4 366	
CIN 2+	As indicated			60		61	121	2.8 (2.3-3.2)
	As practiced			60	25	61	146	3.3 (2.8-3.9)
	+ rescreening	15*	9	60	25	61	170	3.9 (3.3-4.4)
CIN3+	As indicated			52		55	107	2.5 (2.0-2.9)
	As practiced			52	16	55	123	2.8 (2.3-3.3)
	+ rescreening	13.3*	8	52	16	55	144.3	3.3 (2.8-3.8)

Detection rates and increase in program sensitivity

Age 23-39 yrs	**Detection rates**		**Difference**	**95% (CI)**
	As practiced	+Rescreening		
N=4 366	Per 100 w.	Per 100 w.	%	
CIN 2+	3.3	3.9	16.4	15.3-17.5
CIN 3+	2.8	3.3	17.3	16.2-18.4

Age 23-33 yrs	**Detection rates**		**Difference**	**95% (CI)**
	As practiced	+Rescreening		
N=2 701	Per 100 w.	Per 100 w.	%	
CIN 2+	4.5	5.4	19.8	18.6-20.9
CIN 3+	3.4	4.2	21.2	20.0-22.4

Follow-up of the 2 401 women not screened with SEE

	Normal cytology – not HPV tested
	N=2 401
Not met for screening	701
Incomplete f-up	83
Back to screening	1570
Histology	
Normal	18
CIN 1	6
CIN 2	4
CIN 3	19

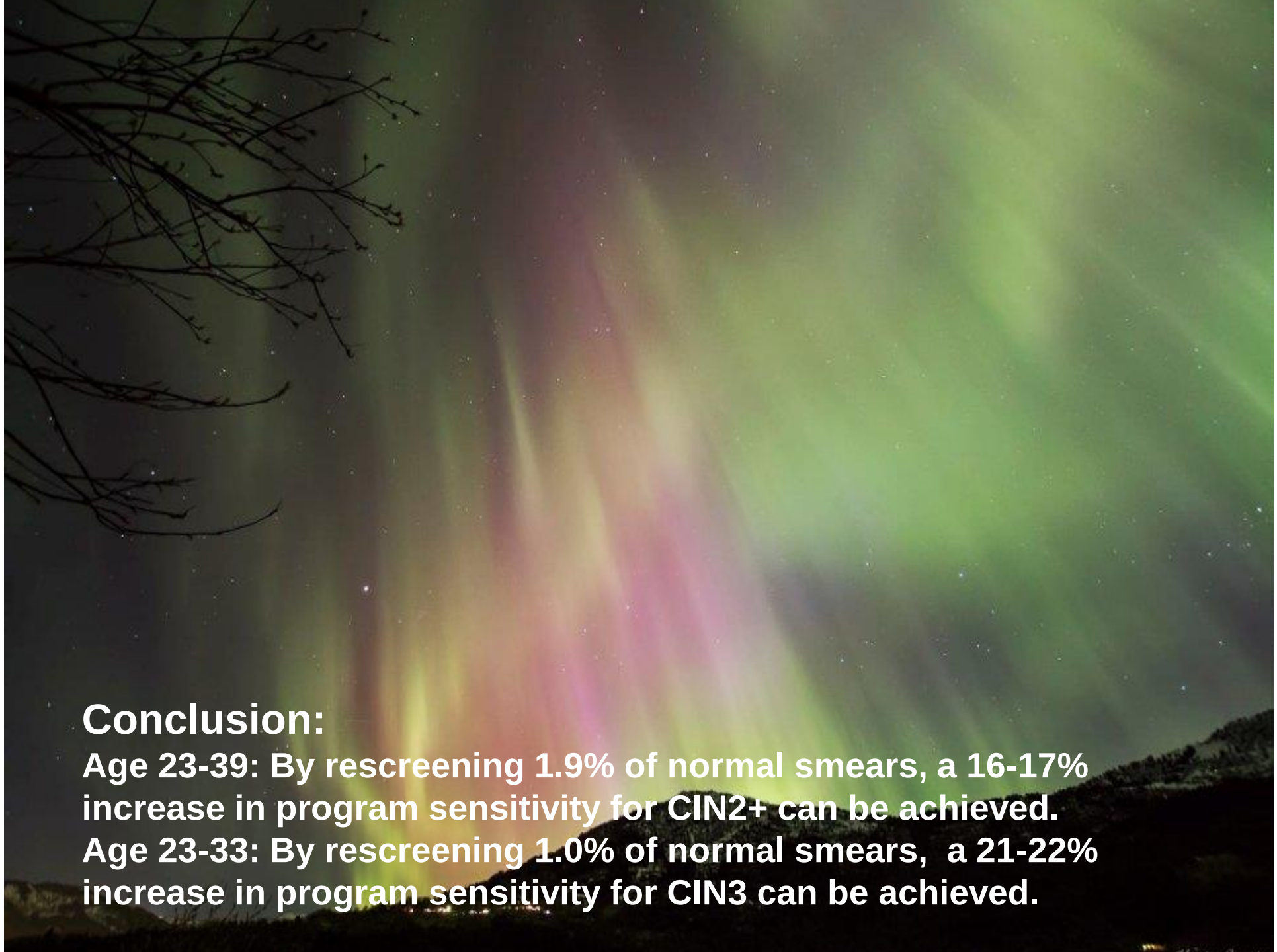
Estimated 13.3 cases of CIN3 with HPV-16/-18/-45 among 2401 women.
Observed 13 cases with CIN3 with HPV-16/-18/-45 among 1700 women

Strengths:

- **Population-based study**
- **In a laboratory with high focus on quality assurance**
- **Follow-up as practised**
- **Studying the 3 most important HPV-types in cervical cancer (16,18,45)**

Limitations:

- **Assessing only 1444 of 3845 (38%) of women with normal smears with the mRNA test at study start (compensated with HPV-status in lesions in subsequent screening round)**



Conclusion:

Age 23-39: By rescreening 1.9% of normal smears, a 16-17% increase in program sensitivity for CIN2+ can be achieved.

Age 23-33: By rescreening 1.0% of normal smears, a 21-22% increase in program sensitivity for CIN3 can be achieved.

Implication:

The Ålesund Hospital has implemented rescreening of all mRNA (+) smears as part of quality control of cytology in primary cervical cancer prevention for the age-group 25-39 years old women


Thank you!
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