

THE ADDED VALUE OF RESCREENING CYTOLOGY NORMAL SAMPLES WITH POSITIVE HPV mRNA

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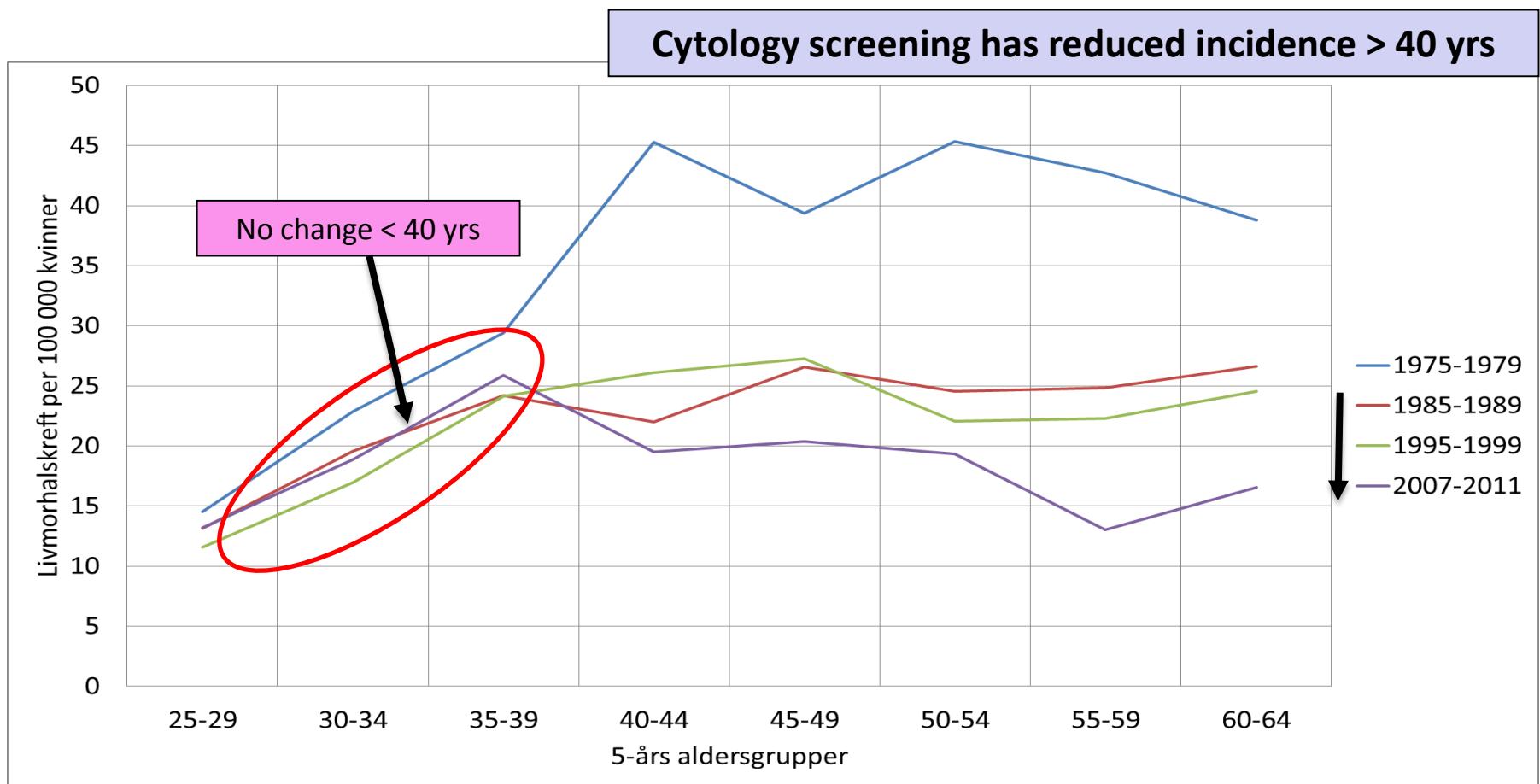
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Incidence CC in Norway 1975-2011

Peak incidence 35-39 years



Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis

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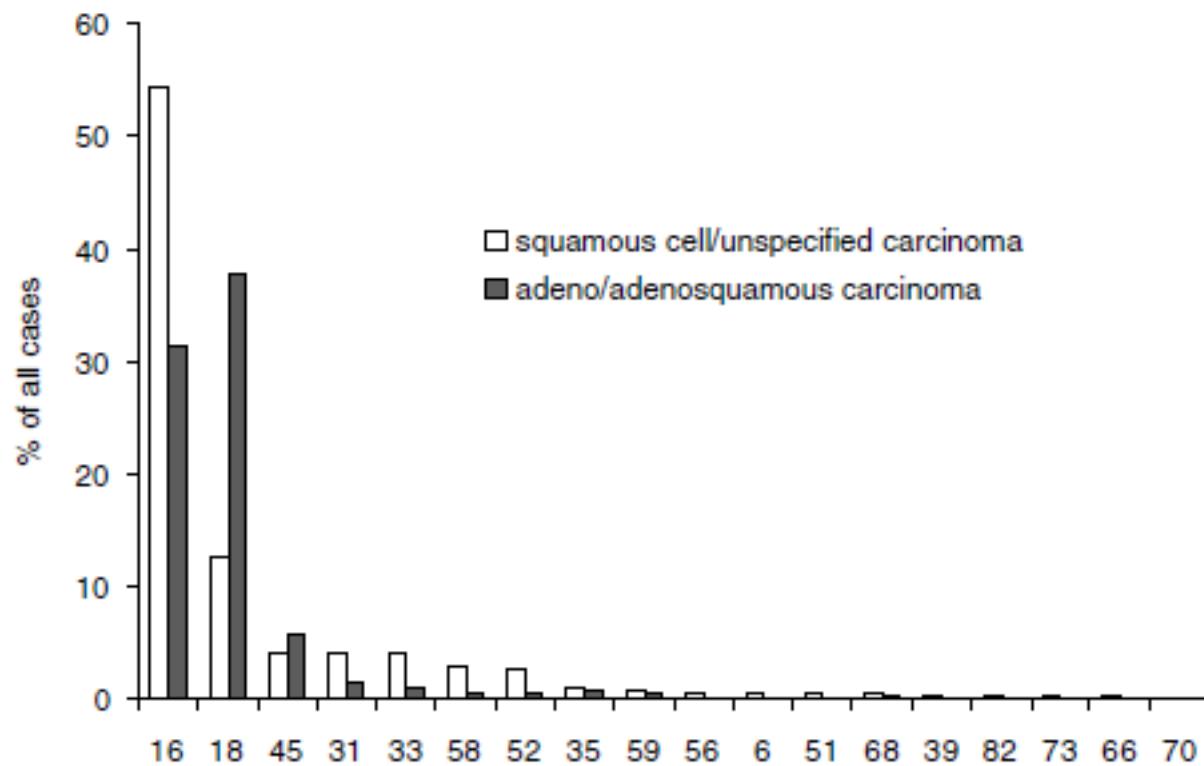
Table I Region- and histology-specific distribution of included studies and ICC cases

Region	No. of studies	Countries represented	No. of cases	Number (%) of cases with histology-specific HPV data		
				SCC	ADC	Unspecified
Africa	6	Algeria, Benin, Guinea, Mali, Morocco, Senegal, South Africa, Tanzania, Uganda	609	204 (33.5)	21 (3.4)	384 (63.1)
Asia	28	Mainland China, India, Indonesia, Japan, Korea, Malaysia, Philippines, Taiwan, Thailand	3091	2273 (73.5)	381 (12.3)	437 (14.1)
Europe	32	Austria, Czech Republic, Denmark, Finland, France, Germany, Greece, Greenland, Holland, Hungary, Ireland, Italy, Norway, Poland, Russia, Sweden, UK	3336	2010 (60.3)	603 (18.1)	723 (21.7)
North America and Australia	13	Australia, Canada, USA	1562	914 (58.5)	450 (28.8)	198 (12.7)
South and Central America	12	Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Honduras, Mexico, Panama, Paraguay, Peru	1460	424 (29.0)	53 (3.6)	983 (67.3)
Total	85					

Clifford et al. Br J Cancer 2003;88:63-73

HPV types in cervical cancer worldwide

GM Clifford et al



Clifford et al. Br J Cancer 2003;88:63-73

Short Communication

Comparison of HPV type distribution in high-grade cervical lesions and cervical cancer: a meta-analysis

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Table I Distribution of SCC and HSIL cases by region and study characteristics

Lesion	No. of studies	No. of cases	Source region (% of cases)	Cervical specimen for HPV testing (% of cases)	PCR primers used (% of cases)
SCC	78	8594	Africa (6.9), Asia (31.7), Europe (32.0), North America/Australia (13.0), South/Central America (16.5)	Biopsies (83.4) Exfoliated cells (16.6)	Broad spectrum ^a (61.9) Narrow spectrum ^b (15.5) Combination/other (16.3) Type-specific only (6.4)
HSIL	53	4338	Africa (1.8), Asia (16.7), Europe (52.4), North America (10.3), South/Central America (18.8)	Biopsies (34.1) Exfoliated cells (65.9)	Broad spectrum ^a (80.8) Narrow spectrum ^b (7.9) Combination/other (7.4) Type-specific only (3.9)

HPV = human papillomavirus; SCC = squamous cell/unspecified carcinoma of the cervix; HSIL = high-grade squamous intraepithelial lesion; PCR = polymerase chain reaction;

^aBroad-spectrum PCR primers include MY09/11, GP5+/6+ and SPF10. ^bNarrow-spectrum PCR primers include GP5/6, L1/C1/C2 and PU1M/2R.

Table 2 Comparison of overall and type-specific HPV prevalence between SCC and HSIL cases

HPV type	SCC		HSIL		SCC:HSIL	
	n	HPV (%)	n	HPV (%)	prevalence ratio*	
All	8550	87.6	4338	84.2	1.04	(1.03, 1.06)
16	8594	54.3	4338	45.0	1.21	(1.16, 1.26)
18	8502	12.6	4338	7.1	1.79	(1.56, 2.10)
33	8449	4.3	4302	7.2	0.59	(0.53, 0.68)
45	5174	4.2	2214	2.3	1.85	(1.35, 2.91)
31	7204	4.2	4036	8.8	0.48	(0.43, 0.54)
58	5646	3.0	2175	6.9	0.43	(0.37, 0.52)
52	5304	2.5	2153	5.2	0.48	(0.40, 0.60)
35	6223	1.0	2690	4.4	0.22	(0.18, 0.27)
59	4488	0.8	1636	1.5	0.55	(0.38, 0.97)
56	4493	0.7	2110	3.0	0.23	(0.18, 0.31)
51	4580	0.6	2171	2.9	0.20	(0.16, 0.27)
68	4148	0.5	1763	1.0	0.50	(0.33, 1.04)
39	3899	0.4	1941	1.1	0.35	(0.24, 0.66)
66	4799	0.2	1778	2.1	0.10	(0.08, 0.15)

HPV = human papillomavirus; SCC = squamous cell/unspecified carcinoma of the cervix; HSIL = high-grade squamous intraepithelial lesion. *With 95% confidence intervals.

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	

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

TABLE II – COMPARISON OF HUMAN PAPILLOMA VIRUS (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)

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

Invasive cervical cancer audit: why cancers developed in a high-risk population with an organised screening programme

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Table 4. Presentation/stage of cancer and screening history according to age band

	Age band (years)				
	20–34	35–49	50–64	65 +	All ages
Presentation/stage					
Screen-detected IA	21	16	4	0	41
Screen-detected IB+	6	13	5	0	24
Symptomatic	13	26	14	15	68
All cancers	40	55	23	15	133
% screen-detected	67.5	52.7	39.1	0.0	48.9
Screening history					
No cytology record	7	14	9	11	41
Cytology more than 5 years before	6	9	3	3	21
Cytology within 0.5–5.0 years	27	32	11	1	71
All cancers	40	55	23	15	133
% screened within 5 years	67.5	58.2	47.8	6.7	53.4

Table 5. Screening history according to presentation/stage

Herbert et al. BJOG 2010;117:736-45

Screening history	Presentation/Stage			
	Total (% SD)	SD-IA	SD-IB+	Sym
	133 (48.9)	41	24	68
Category 1 (no cytology record in UK)	41 (24.4)	3	7	31
No record of previous cytology test	35	3	5	27
Previously screened outside UK	6	0	2	4
Category 2 (cytology more than 5 years before)	21 (38.1)	5	3	13
Negative cytology	18	5	2	11
Abnormal cytology and/or CIN treatment	3	0	1	2
Categories 3–6 interval cancers (screened within 5 years)	71 (66.2)	33	14	24
% screened within 5 years	53.4	80.5	58.3	35.5
Category 3 (negative cytology only)	27 (51.9)	10	4	13
Latest test within 0.5–3.5 years	17 [6]	7 [2]	2 [1]	8 [3]
Latest test within 3.5–5.0 years	10 [2]	3	2 [1]	5 [1]
[n] = one negative test within 10 years				
Category 4 (early repeat(s) advised)	8 (62.5)	5	0	3
Repeat cytology as recommended	3	2	0	1
Delayed or no follow-up cytology	5	3	0	2
Category 5 (previous referral advised)	22 (86.4)	12	7	3
Delay diagnosis as the only factor	8	6	0	2
Other factors (negative and/or repeats)	14	6	7	1
Category 6 (previous CIN treatment)	14 (64.3)	6	3	5
Negative follow-up as recommended	1	0	0	1
Insufficient follow-up ± delays	6	2	1	3
Incomplete excision, CIN persists	7	4	2	1

SD, screen-detected; sym, symptomatic.

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

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

Study outline

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

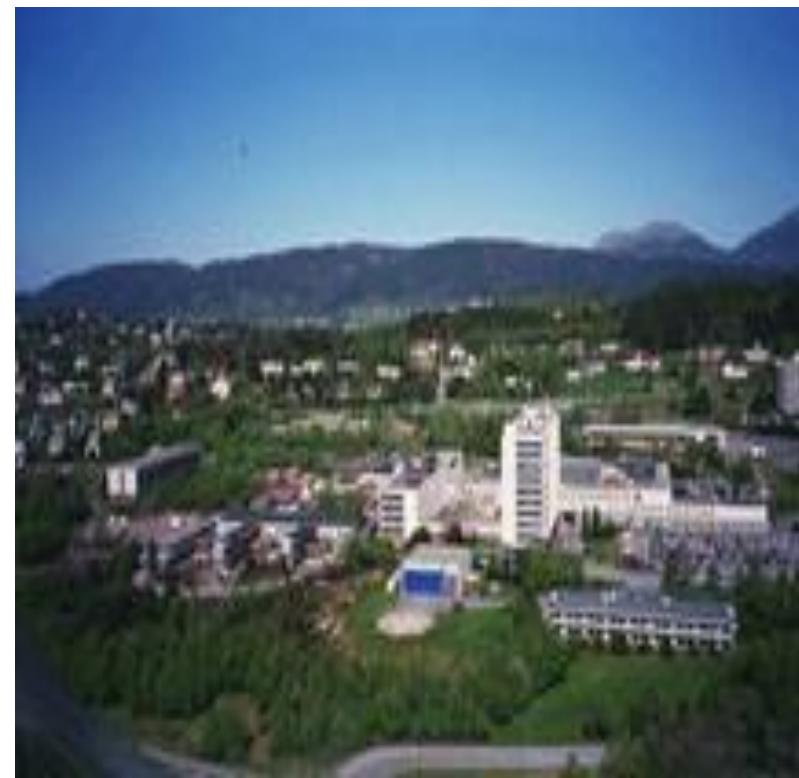
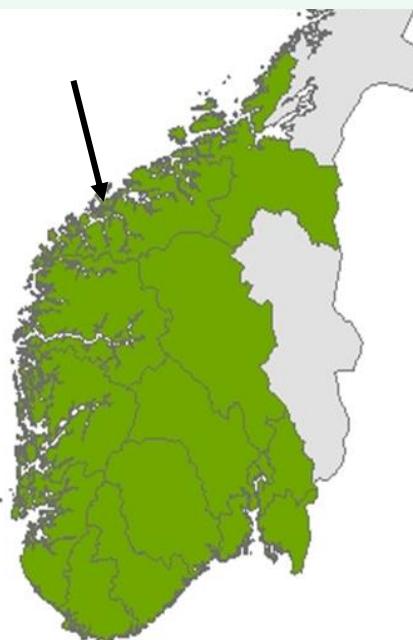
PreTect SEE, mRNA test, targeting HPV 16, 18, 45

Outcomes:

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



Ålesund Hospital,
Møre and Romsdal Health Trust,
Ålesund



Selection of study population

Sympathy		
	Smears	
	n	N
Total database		168 209
1999	2 303	
Missing information date	29	
Only follow-up diagnosis	116	
Not a valid smear diagnosis	4 973	
Duplicate registrations	26	
> 1 smear calendar month	<u>296</u>	
	<u>7 743</u>	
Valid smears 01.01.2000-30.09.2014		160 466

Selection of study population

Sympathy				
	Women	Smears	Women	Smears
	n	n	N	n
01.01.2000-30.09.2014			47 926	160 466
No smear after 04.04.2013	34 129	98 828		
Age index smear: 14-24	195	293		
40-92	<u>8 855</u>	<u>44 339</u>		
	<u>43 179</u>	<u>143 460</u>		
Eligible study participation 23-39 yrs			4 747	17 006
CIN 1+ before index	339	2 473		
HSIL before index	<u>42</u>	256		
Normal smears before index		<u>9 477</u>		
	381	12 204		
Study population			4 366	4 802

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
2 407	1 444	366	80	35	32	1	1	4 366
55.1%	33.1%	8.4%	1.8%	0.8%	0.7%	0.02%	0.02%	100.0%
mRNA (+)	27	23	1		2	1		
	1.9%							
HPV 16	19	1		1				
HPV 18	5			1	1			
HPV 45	1							

Compliance with triage/follow-up

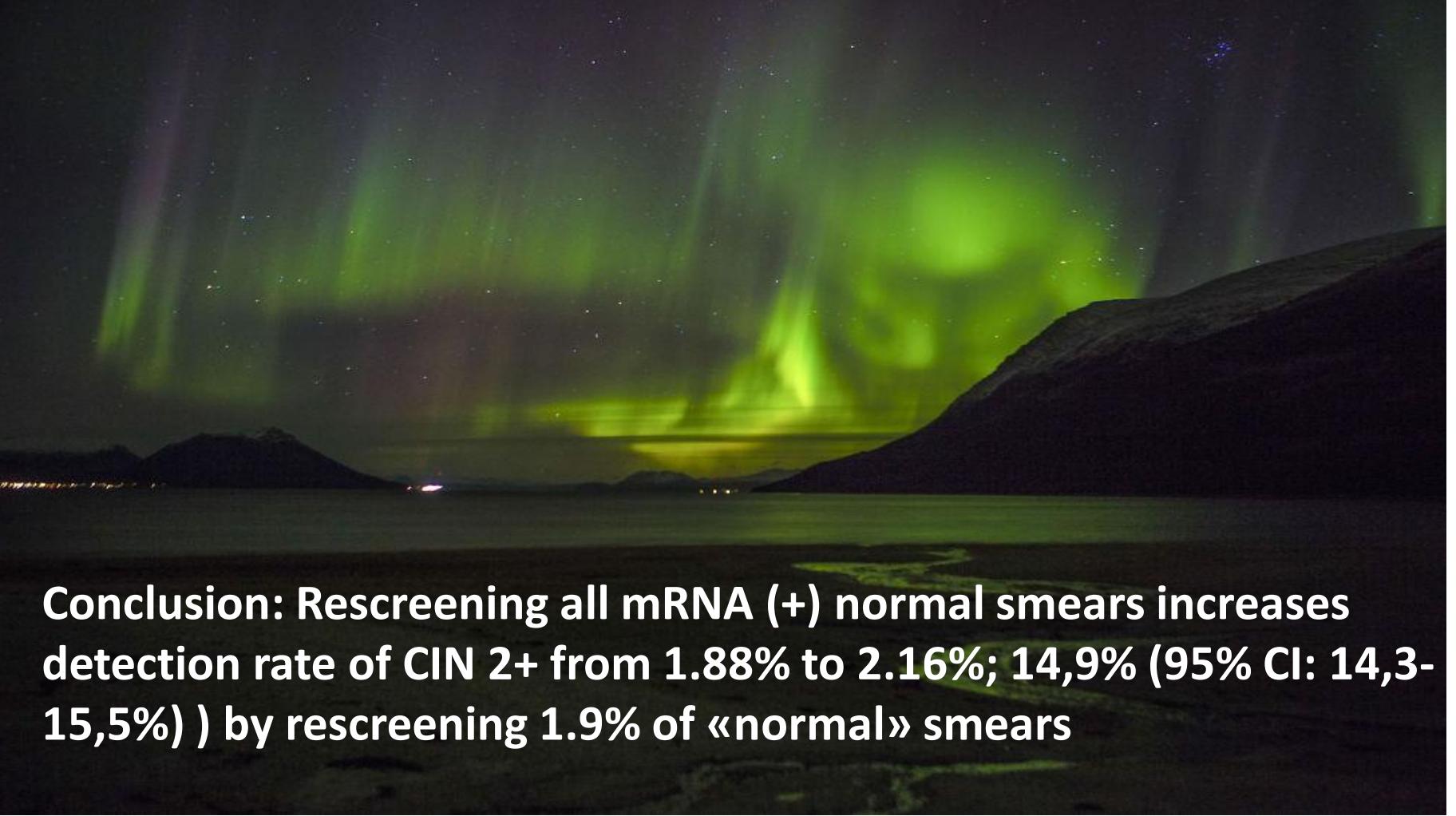
	mRNA (+)	ASC-US/ LSIL	HSIL	Total
	N=27	N=446	N=69	N=542
Not resolved	5	265	8	278
Back to screening	7	126	0	133
To biopsy	15 (56%)	55 (21%)	61 (88%)	131 (48%)

Outcome biopsies

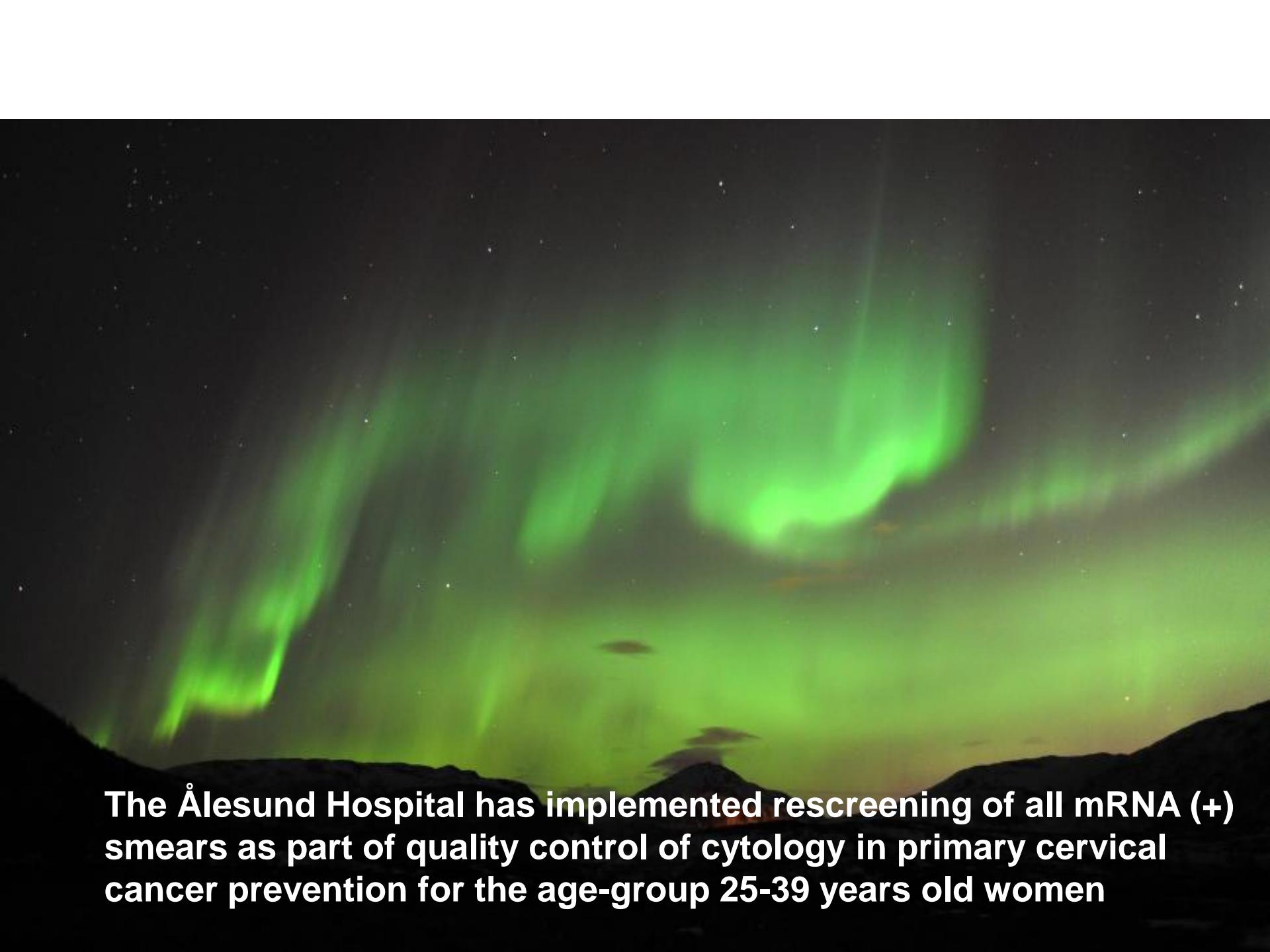
	mRNA (+)	ASC-US/ LSIL	HSIL	Total
	N=15	N=55	N=61	N=131
Normal	5	11	5	21
CIN 1	5	17	2	24
CIN 2	0	6	5	11
CIN 3	4	21	45	70
AGUS	0	0	1	1
ACIS	1	0	3	4
CIN 2+	33.3%	48.2%	80.3%	57.6%

Program sensitivity/detection rate CIN 2+

	ASC-US/ LSIL	HSIL	Total	Normal mRNA tested	Normal Not examined
	N=446	N=61	N=4 366	N=1 444	N=2 407
CIN 2+	27	54	81	5 (0.35%) →	8.4 (0.35%)?
CIN 3+	21	49	70	5 (0.35%)	8.4 (0.35%)?
	CIN 2+ 1.9% (81/4 366) (95% CI: 1.7-2.1%)				
				CIN 2+ 2.2% (94,4/4366) (95% CI: 2.0-2.4%)	



Conclusion: Rescreening all mRNA (+) normal smears increases detection rate of CIN 2+ from 1.88% to 2.16%; 14,9% (95% CI: 14,3-15,5%)) by rescreening 1.9% of «normal» smears

A photograph of the Aurora Borealis (Northern Lights) in a dark night sky. The green lights are visible in various shades across the upper half of the frame, with some faint stars visible. The horizon line is dark, suggesting a silhouette of land or mountains.

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!