

SUPPLEMENTARY APPENDIX:
ADDITIONAL RESULTS

Accompanying the manuscript:

**Cost-effective management of women with minor cervical lesions:
Revisiting the application of HPV DNA testing**

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Content:

1. Additional results from primary analysis
2. Additional results from one-way sensitivity analyses
3. Additional results when assuming primary HPV testing

4. ADDITIONAL RESULTS FROM PRIMARY ANALYSIS

Table S1. Discounted health benefits and costs: Average, minimum and maximum values across 50 good-fitting parameter sets. The strategies are ranked by increasing costs (\$).

Management of women with ASC-US/LSIL and high-risk HPV		Cost (\$) per screened woman			QALYs			Life-expectancy		
Screening procedure	Follow-up wait (months)	Average	Min	Max	Average	Min	Max	Average	Min	Max
No screening	-	180	148	214	21.4689	21.4614	21.4758	23.9751	23.9686	23.9810
HPV testing	18	1,249	1,224	1,275	21.5014	21.5007	21.5021	24.0047	24.0041	24.0052
Co-testing	18	1,253	1,227	1,279	21.5014	21.5007	21.5021	24.0047	24.0041	24.0052
HPV testing	12	1,264	1,239	1,291	21.5016	21.5010	21.5024	24.0049	24.0044	24.0054
Genotyping	18	1,268	1,241	1,295	21.5017	21.5011	21.5024	24.0049	24.0044	24.0053
Co-testing	12	1,268	1,242	1,295	21.5016	21.5010	21.5024	24.0049	24.0044	24.0053
Genotyping	12	1,276	1,250	1,304	21.5018	21.5012	21.5025	24.0050	24.0045	24.0055
HPV testing	6	1,285	1,258	1,313	21.5018	21.5012	21.5025	24.0049	24.0045	24.0054
Genotyping	6	1,288	1,261	1,317	21.5019	21.5013	21.5026	24.0050	24.0045	24.0054
Co-testing	6	1,289	1,261	1,317	21.5018	21.5012	21.5025	24.0049	24.0045	24.0054
Colposcopy	-	1,293	1,265	1,321	21.5020	21.5014	21.5026	24.0051	24.0046	24.0055

ASC-US: Atypical squamous cells of undetermined significance, HPV: high-risk human papillomavirus, ICER: incremental cost-effectiveness ratio, LSIL: low-grade squamous intraepithelial lesion, Lys: life-years, QALYs: quality-adjusted life-years.

Health benefits and costs are discounted by 4% per year. All costs are expressed in 2014 US dollars (US\$ = NOK6.30).

Table S2. Costs, health benefits, and cost-effectiveness of alternative triage strategies for women detected with ASC-US/LSIL and high-risk HPV: Undiscounted results ranked by increasing costs (\$).

Management of women with ASC-US/LSIL and high-risk HPV		Costs	Health benefits		Cost-effectiveness
Screening procedure	Follow-up wait (months)	Undiscounted lifetime costs (\$) per woman	Undiscounted QALYs	Undiscounted life-years	ICER (\$ per QALY)
No screening	-	873	63.92257	74.99232	-
HPV testing	18	4,377	64.20811	75.28346	12,272
Co-testing	18	4,387	64.20824	75.28360	-
HPV testing	12	4,414	64.20996	75.28516	20,314
Co-testing	12	4,425	64.20992	75.28516	-
Genotyping	18	4,428	64.21037	75.28514	-
Genotyping	12	4,449	64.21115	75.28591	28,928
HPV testing	6	4,478	64.21092	75.28552	-
Genotyping	6	4,485	64.21156	75.28602	-
Co-testing	6	4,488	64.21082	75.28543	-
Colposcopy	-	4,495	64.21220	75.28662	44,471

ASC-US: Atypical squamous cells of undetermined significance, HPV: high-risk human papillomavirus, ICER: incremental cost-effectiveness ratio, LSIL: low-grade squamous intraepithelial lesion, Lys: life-years, QALYs: quality-adjusted life-years.

Rows highlighted in bold reflect strategies on the efficiency frontier (i.e., strategies providing health benefits in terms of QALYs at lower costs, or lower ICER, than alternative strategies). All costs are expressed in 2014 US dollars (US\$ = NOK6.30).

Table S3. Costs, health benefits, and cost-effectiveness of alternative triage strategies for women detected with ASC-US/LSIL and high-risk HPV under the assumption of imperfect screening compliance: Discounted results ranked by increasing costs (\$).

Management of women with ASC-US/LSIL and high-risk HPV		Costs	Health benefits			Cost-effectiveness
Screening procedure	Follow-up wait (months)	Discounted lifetime costs (\$) per woman	Cancer incidence reduction (%)	Discounted QALYs	Discounted life-years	ICER (\$ per QALY)
No screening	-	180	87.11 %	21.46887	23.97505	-
HPV testing	18	960	72.02 %	21.49633	24.00037	28 421
Co-testing	18	963	72.12 %	21.49633	24.00035	-
HPV testing	12	970	72.52 %	21.49652	24.00050	-
Genotyping	18	972	73.13 %	21.49669	24.00061	32 822
Co-testing	12	973	72.64 %	21.49653	24.00051	-
Genotyping	12	978	73.35 %	21.49676	24.00065	-
HPV testing	6	985	73.36 %	21.49677	24.00065	29 541
Genotyping	6	987	73.79 %	21.49689	24.00075	-
Co-testing	6	988	73.37 %	21.49674	24.00063	-
Colposcopy	-	988	74.08 %	21.49699	24.00082	54 114

ASC-US: Atypical squamous cells of undetermined significance, HPV: high-risk human papillomavirus, ICER: incremental cost-effectiveness ratio, LSIL: low-grade squamous intraepithelial lesion, Lys: life-years, QALYs: quality-adjusted life-years.

Rows highlighted in bold reflect strategies on the efficiency frontier (i.e., strategies providing health benefits in terms of QALYs at lower costs, or lower ICER, than alternative strategies). Health benefits and costs are discounted by 4% per year. All costs are expressed in 2014 US dollars (US\$ = NOK6.30).

5. ADDITIONAL RESULTS FROM ONE-WAY SENSITIVITY ANALYSES

Table S4. One-way deterministic sensitivity analysis of selected model parameters (including additional strategy involving differential management of ASC-US and LSIL): Incremental cost-effectiveness ratios (\$ per QALY gained) of efficient strategies.

Base-case		
HPV testing (18 mn.)		32,914
HPV-16/-18 genotyping (18 mn.)		52,552
HPV-16/-18 genotyping (12 mn.)		78,012
Colposcopy		104,402
Differential management		9,011,895
Sensitivity of cytology		
Parameter range:		40 %
HPV testing (18 mn.)		38,020
HPV-16/-18 genotyping (18 mn.)		49,777
HPV-16/-18 genotyping (12 mn.)		93,340
Colposcopy		113,697
Differential management		4,442,472
Sensitivity of HPV DNA test		
Parameter range:		90 %
<i>HPV & cytology co-test (18 mn.)</i>		33,207
HPV testing (18 mn.)		Not efficient
HPV-16/-18 genotyping (18 mn.)		40,409
HPV-16/-18 genotyping (12 mn.)		Not efficient
Colposcopy		59,635
Differential management		442,069
Perfect diagnostic accuracy of colposcopy w/biopsy		
Parameter range:		100 %
HPV testing (18 mn.)		32,797
HPV-16/-18 genotyping (18 mn.)		59,650
HPV-16/-18 genotyping (12 mn.)		82,504
Colposcopy		119,811
Differential management		3,052,788
Cost of analyzing cytology		
Parameter range:	\$22	\$89
HPV testing (18 mn.)	30,332	38,078
<i>HPV testing (12 mn.)</i>	<i>Not efficient</i>	<i>57,608</i>
HPV-16/-18 genotyping (18 mn.)	49,981	58,047
HPV-16/-18 genotyping (12 mn.)	75,282	83,473
Colposcopy	98,622	115,958
Differential management	8,710,111	9,615,477
Cost of analyzing HPV test		
Parameter range:	\$20	\$79
HPV testing (18 mn.)	32,607	33,528
<i>HPV testing (12 mn.)</i>	<i>52,758</i>	<i>Not efficient</i>
HPV-16/-18 genotyping (18 mn.)	52,851	52,102
HPV-16/-18 genotyping (12 mn.)	76,411	81,217
Colposcopy	105,762	101,677
Differential management	9,077,070	8,881,577
Cost of analyzing biopsy		
Parameter range:	\$62	\$247
HPV testing (18 mn.)	32,683	33,375
<i>HPV testing (12 mn.)</i>	<i>Not efficient</i>	<i>58,232</i>
HPV-16/-18 genotyping (18 mn.)	49,420	61,155
HPV-16/-18 genotyping (12 mn.)	74,855	84,327
Colposcopy	97,086	119,032
Differential management	8,407,105	10,221,522
Cost of physician consultation		
Parameter range:	\$57	\$229
HPV testing (18 mn.)	26,171	46,400
<i>HPV testing (12 mn.)</i>	<i>48,689</i>	<i>Not efficient</i>
HPV-16/-18 genotyping (18 mn.)	57,343	56,817
HPV-16/-18 genotyping (12 mn.)	70,573	92,888
Colposcopy	102,661	107,880
Differential management	8,236,767	10,562,181

Table S4 continued.

Cost of colposcopy examination		
Parameter range:	\$129	\$516
HPV testing (18 mn.)	32,432	33,877
<i>HPV testing (12 mn.)</i>	<i>Not efficient</i>	<i>62,998</i>
HPV-16/-18 genotyping (18 mn.)	46,018	76,112
HPV-16/-18 genotyping (12 mn.)	71,426	91,185
Colposcopy	89,140	134,924
Differential management	7,750,195	11,535,343
Cost of precancer treatment		
Parameter range:	\$841	\$3364
HPV testing (18 mn.)	31,873	34,996
<i>HPV testing (12 mn.)</i>	<i>Not efficient</i>	<i>66,735</i>
HPV-16/-18 genotyping (18 mn.)	43,088	90,459
HPV-16/-18 genotyping (12 mn.)	69,881	94,273
Colposcopy	88,153	136,898
Differential management	8,926,075	9,183,598
Cost of local cancer treatment		
Parameter range:	\$13,471	\$53,882
HPV testing (18 mn.)	33,614	34 465
HPV-16/-18 genotyping (18 mn.)	54,403	48 851
HPV-16/-18 genotyping (12 mn.)	79,113	75 812
Colposcopy	106,724	99 755
Differential management	9,008,449	9 018 835
Cost of regional cancer treatment		
Parameter range:	\$28,301	\$113,202
HPV testing (18 mn.)	34 238	34,763
HPV-16/-18 genotyping (18 mn.)	53 938	49,781
HPV-16/-18 genotyping (12 mn.)	79 074	75,892
Colposcopy	105 409	102,384
Differential management	9 017 755	9,000,238
Cost of distant cancer treatment		
Parameter range:	\$20,684	\$82,735
HPV testing (18 mn.)	33,176	32,390
HPV-16/-18 genotyping (18 mn.)	52,671	52,314
HPV-16/-18 genotyping (12 mn.)	78,116	77,806
Colposcopy	104,518	104,168
Differential management	9,012,212	9,011,307
Scenario: Only including direct medical costs		
HPV testing (18 mn.)		19,368
<i>HPV testing (12 mn.)</i>		<i>35,554</i>
HPV-16/-18 genotyping (18 mn.)		40,235
HPV-16/-18 genotyping (12 mn.)		51,909
Colposcopy		75,114
Differential management		5,979,879
Scenario: Including indirect costs		
HPV testing (18 mn.)		38,786
<i>HPV testing (12 mn.)</i>		<i>71,784</i>
HPV-16/-18 genotyping (18 mn.)		Not efficient
HPV-16/-18 genotyping (12 mn.)		106,058
Colposcopy		157,540
Differential management		9,307,437

HPV: high-risk human papillomavirus, QALYs: quality-adjusted life-years.

Italicized rows reflect strategies that were not on the efficiency frontier in the base-case scenario. All incremental cost-effectiveness ratios are expressed in 2014 US dollars (US\$ = NOK6.30).

6. ADDITIONAL RESULTS WHEN ASSUMING PRIMARY HPV TESTING

Table S5. Costs, health benefits, and cost-effectiveness of alternative triage strategies for women detected with ASC-US/LSIL and high-risk HPV **when switching to primary HPV testing at age 31.** (Discounted results ranked by increasing costs).

Management of women with ASC-US/LSIL and high-risk HPV		Costs	Health benefits			Cost-effectiveness
Screening procedure	Follow-up wait	Discounted lifetime costs (\$)	Cancer incidence	Discounted QALYs	Discounted life-years	ICER (\$ per QALY)
No screening	-	180	-	21.46887	23.97505	-
HPV testing	18	1,205	92.46 %	21.50311	24.00602	29,940
Co-testing	18	1,207	92.48 %	21.50313	24.00604	-
HPV testing	12	1,213	92.65 %	21.50325	24.00613	-
Genotyping	18	1,214	92.79 %	21.50327	24.00611	54,761
Co-testing	12	1,215	92.66 %	21.50326	24.00614	-
Genotyping	12	1,218	92.84 %	21.50333	24.00616	76,051
HPV testing	6	1,223	92.84 %	21.5033	24.00612	-
Genotyping	6	1,225	92.93 %	21.50335	24.00616	-
Co-testing	6	1,225	92.83 %	21.50329	24.00612	-
Colposcopy	-	1,227	92.99 %	21.50338	24.00618	169,474

Rows in bold indicate cost-efficient strategies. Discount rate = 4% per year.

Table S6. Costs, health benefits, and cost-effectiveness of alternative triage strategies for women detected with ASC-US/LSIL and high-risk HPV **when switching to primary HPV testing at age 34.** (Discounted results ranked by increasing costs).

Management of women with ASC-US/LSIL and high-risk HPV		Costs	Health benefits			Cost-effectiveness
Screening procedure	Follow-up wait	Discounted lifetime costs (\$)	Cancer incidence	Discounted QALYs	Discounted life-years	ICER (\$ per QALY)
No screening	-	180	-	21.46887	23.97505	-
HPV testing	18	1,197	91.59 %	21.50257	24.00563	30,191
Co-testing	18	1,200	91.60 %	21.5026	24.00566	-
HPV testing	12	1,207	91.84 %	21.50276	24.00578	-
Genotyping	18	1,208	92.03 %	21.50279	24.00576	49,485
Co-testing	12	1,209	91.82 %	21.50277	24.00579	-
Genotyping	12	1,214	92.10 %	21.50286	24.00582	80,690
HPV testing	6	1,220	92.12 %	21.50284	24.00579	-
Genotyping	6	1,222	92.22 %	21.50289	24.00582	-
Co-testing	6	1,222	92.10 %	21.50284	24.00579	129,594
Colposcopy	-	1,224	92.32 %	21.50294	24.00585	-

Rows in bold indicate cost-efficient strategies. Discount rate = 4% per year.