Supplementary Appendix

Accompanying the manuscript:

Adapting cervical cancer screening for women vaccinated against human papillomavirus infections: The value of stratifying guidelines

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1. SUPPLEMENTARY METHODS

1.1. Model calibration and analysis

We used a likelihood-based calibration approach to identify multiple natural history parameter values that achieved good-fit with Norwegian epidemiologic data from Norway, which has been (described previously (10, 16, 19), Supplementary Appendix). In the primary analysis, analytic outcomes reflect the average value across 50 good-fitting parameter sets. We used these parameter sets to explore the probability that each strategy was cost-effective under the Norwegian willingness-to-pay threshold. For uncertainty analyses, we selected a parameter set that represents the average parameter input values across all 50 parameter sets.

1.2. Cost-effectiveness framework

We identified efficient prevention strategies for HPV-vaccinated women using the incremental cost-effectiveness ratio (ICER), defined as the additional cost per additional QALY, of a strategy compared to the next most costly strategy (**Equation 1**). Strategies with higher costs and lower QALYs (or a higher ICER) than more effective strategies were excluded from further consideration. We identified the most cost-effective strategy as the strategy with an ICER just below the amount society is willing-to-pay for an additional health benefit (e.g. QALY), using a commonly-cited Norwegian willingness-to-pay threshold of a €75,000 per QALY gained. The threshold can be considered as a benchmark for what constitutes 'good value for money' (1, 2). The additional benefits of a strategy multiplied by the willingness-to-pay threshold generate the monetary value of the health benefits. The additional costs of the strategy can then be subtracted from the monetized health benefits, yielding a metric referred to as the incremental net monetary benefit (INMB) (**Equation 2**). A positive INMB (i.e. >0) indicates that the health benefits cost less than what decision-makers would be willing-to-pay. We calculated the INMB (per vaccinated woman) of each strategy compared to no intervention, and used this metric to identify the efficiency gain of stratifying screening guidelines according to HPV vaccination status. Specifically, we calculated the efficiency gain as the INMB of the optimal screening strategy for a vaccinated woman minus the INMB associated with the current (or proposed) Norwegian guidelines, for a woman vaccinated with either the bivalent/quadrivalent vaccine (2/4vHPV) or the nonavalent vaccine (9vHPV) (**Equation 3**). We interpreted the efficiency gain as the maximum value that could be spent (per vaccinated woman) to identify women's vaccination status and stratifying screening guidelines, while remaining cost-effective. We subsequently enumerated the maximum amount that could be allocated to identify an individual's vaccination status and stratify the screening programme for a cohort of vaccinated women over their lifetime. This was done by multiplying the efficiency gain per woman with the number of women in a birth cohort who received the vaccine (i.e. a total of ~30,000 women per birth cohort in Norway, multiplied with the vaccine coverage for that cohort). For example, for the first cohort of women in Norway who received the quadrivalent vaccine at age 12 years in 2009 (i.e. born in 1997), the 3-dose vaccine coverage was 67% (3), which implies that ~22,000 women were fully vaccinated.

$$(\boldsymbol{Equation\ 1})\ ICER_{A_i} = \frac{Cost_{A_i} - Cost_{B_i}}{QALYs_{A_i} - QALYs_{B_i}} = \frac{\Delta Cost_{A_i}}{\Delta QALYs_{A_i}}$$

$$(\boldsymbol{Equation\ 2})\ INMB_i = (\Delta QALYs_i * \lambda) - \Delta Cost_i$$

$$(\boldsymbol{Equation\ 3})\ Efficiency\ gain_{\ i} = INMB_{Optimal_i} - INMB_{Current_i}$$

Where,
A and *B* indicate any two strategies under evaluation, where *B* is the next most costly strategy compared to *A*.
i = vaccination status (either 2/4vHPV or 9vHPV-vaccinated)

λ = willingness-to-pay threshold (e.g. in Norway, a €75,000 per QALY gained)

$INMB_{Optimal_i}$ = the INMB of the optimal strategy for a woman with vaccination status *i*, where ΔQALYs and ΔCost are calculated for this strategy compared to no intervention.

$INMB_{Current_i}$ = the INMB of the current Norwegian guidelines for a woman with vaccination status *i*, where ΔQALYs and ΔCost are calculated for this strategy compared to no intervention.

Of note, since this analysis is conditioned on women who have received the vaccine, the price of the vaccine will remain constant across all competing screening strategies in the analysis. Subsequently, variations in the cost of the vaccine (e.g. due to a 2-dose schedule, tender price or booster doses) will only affect the total cost per woman and will not change the incremental cost between the strategies.

1.3. Vaccine assumptions

For 2/4vHPV, we assumed a 3-dose schedule and 100% lifelong efficacy (4-6) against vaccine-targeted HPV types; for 9vHPV we assumed 100% efficacy for HPV16/18 infections and 96% efficacy for the five additional high-risk HPV types included in the vaccine (2). In uncertainty analysis, we used 90% efficacy against all HPV types targeted by the vaccines as a lower bound. In addition, we performed a scenario analysis that reflected the 2vHPV with lifelong cross-protection against non-vaccine-targeted HPV types, using estimates from a recent meta-analysis

Supplementary Table 1. Vaccine efficacy under base-case, uncertainty and scenario analysis.

HPV genotype	Base-case analysis vaccine efficacy (%) against persistent infection		Uncertainty analysis vaccine efficacy (%) against persistent infection		Scenario analysis vaccine efficacy (%) against persistent infection for non-vaccine-targeted genotypes
	2/4vHPV	**9vHPV**	**2/4vHPV**	**9vHPV**	**2vHPV**
16/18	100	100	90	90	100
31	0	96	0	90	77.1
33	0	96	0	90	43.1
45	0	96	0	90	79.0
52	0	96	0	90	18.9
58	0	96	0	90	0*

* We assumed 0% vaccine efficacy; the meta-analysis reported a negative estimate of vaccine efficacy.

We assumed a cost per vaccine dose of €132 for the 2/4vHPV and €147 for the 9vHPV based on current market prices in Norway (i.e. the pharmacy retail price excluding value added tax) (7, 8) and including administration cost. The administration cost per dose was based on a previous Norwegian analysis (9), and assumes nurses' travel between schools (60 minutes of travel time per day) and approximately 20 minutes to administer the vaccine per student (30 students per day). The cost of nursing time was valued using an annual wage for "non-speciality nurses" of approximately NOK423,000 per year (10). We assumed 1870 work hours per year with 40% fringe costs, resulting in an administration cost of ~€14 per dose.

1.4. Screening strategies

We included a total of 74 candidate screening strategies. Among these, 8 strategies involved HPV testing once-only or twice per lifetime with 15 years apart, starting at ages 25, 30, 35, and 40 years. The remaining 66 strategies involved either primary cytology only, primary HPV only, or triennial cytology until age 33 years and primary HPV testing starting at age 34 years. For these strategies, we varied the age to start screening (i.e. ages 25, 28, 31 and 34 years) and screening frequency (i.e. every 5, 7, 10, 15 or 20 years). Screening ended at age 69 years, yet the implied age to stop screening was earlier for some strategies depending on screening frequency, and subsequently, the implied number of lifetime screens varied across strategies (**Supplementary Table 1**).

Supplementary Table 2. Implied number of lifetime screens and age to stop screening for the candidate screening strategies.

Cytology only or HPV only

Implied number of lifetime screens

Start age	Screening frequency: 3y	5y	7y	10y	15y	20y
25	15	9	7	5	3	3
28	14	9	6	5	3	3
31	13	8	6	4	3	2
34	12	8	6	4	3	2

Implied age to stop screening

Start age	Screening frequency: 3y	5y	7y	10y	15y	20y
25	67	65	67	65	55	65
28	67	68	63	68	58	68
31	67	66	66	61	61	51
34	67	69	69	64	64	54

Switching at age 34 years

Implied number of lifetime screens

Start age	Screening frequency: 3y	5y	7y	10y	15y	20y
25	15	11	9	7	6	5
28	14	10	8	6	5	4
31	13	9	7	5	4	3

Implied age to stop screening

Start age	Screening frequency: 3y	5y	7y	10y	15y	20y
25	67	69	69	64	64	54
28	67	69	69	64	64	54
31	67	69	69	64	64	54

The heat map is formatted using conditional formatting in Excel, ranging from dark red (indicating lowest values) to dark green (indicating highest values). 'Switching at age 34 years' indicate triennial cytology-based screening until age 33 years with primary HPV-based screening starting at age 34 years.

1.5. Diagnostic test accuracy

We assume that the sensitivity (specificity) of HPV DNA assays, defined as the probability of HPV DNA-positive (-negative) given HPV DNA is present (absent), is 1 (to correspond to the accuracy methods used for HPV typing in many epidemiological studies); thus, the sensitivity (and specificity) is modelled as the ability of the HPV test to detect the presence (or absence) of HPV infection. Clinical HPV sensitivity (and specificity) for detecting presence (and absence) of CIN2+ is a model output. While the model assumes that high-risk HPV is a necessary condition for progression to cancer, it also accounts for high-grade precancers attributable to low-risk HPV that may be detected by cytology but would not be detected by high-risk HPV testing. The model calculated sensitivity of HPV reflects the fact that there will be missed high-grade lesions due to low-risk HPV types; but in terms of progression to cancer, HPV testing will detect these clinically important high-risk infections. The resulting clinical detection of HPV positivity among women with CIN offers us a validation step in which we compare this model output to HPV test performance data from clinical studies (11), which often report test characteristics conditioned on disease (i.e., not infection) status. For example, for women vaccinated with the 2/4vHPV, the "implied" HPV test sensitivity and specificity for detecting lesions is 89% and 85%, respectively. This is slightly lower than what we have previously reported for unvaccinated women (12) due to the greater contribution of low-risk HPV types in HPV-vaccinated women.

1.6. Screening compliance

In our primary analysis, we assumed perfect compliance to screening and follow-up procedures as future screening behaviour is highly uncertain. However, in uncertainty

analysis, we evaluated the impact of imperfect screening behaviour to reflect current practice patterns in Norway, on the optimal screening strategy for vaccinated women. We assumed an 80% probability of attending a primary screening test, 72.3% probability of attending follow-up procedures, and 82.8% probability of attending diagnostic colposcopy w/biopsy. If a woman did not attend the procedure, her next chance of attending was at the next recommended primary screen.

2. SUPPLEMENTARY RESULTS FROM PRIMARY ANALYSIS

Outcomes associated with cost-efficient strategies for women vaccinated with 2/4vHPV and 9vHPV are presented in **Supplementary Tables 3 and 4**, respectively. For both vaccine types, the rank order of the efficient strategies remained the same across all 50 good-fitting parameter sets. For the 9vHPV, 100% of the parameter sets identified HPV testing at age 40 years as the most cost-effective strategy under the Norwegian willingness-to-pay threshold. For 2/4vHPV-vaccinated women, HPV testing at ages 31 and 51 was optimal in 50% of the simulations, while HPV testing at ages 30 and 45 years was optimal in 44% of the simulations. The remaining simulations identified HPV testing at ages 28, 48 and 68 years, and once-only HPV testing at age 30 years (**Supplementary Tables 3-4**). The efficiency gains of stratifying guidelines according to vaccination status are presented in **Supplementary Table 5**.

Supplementary Table 3. Outcomes associated with cost-efficient strategies for women vaccinated with 2/4vHPV*.

Stategy†	Cancer incidence reduction (%)‡	Colposcopy rate (per 1,000 women) §	Screening tests (per 1,000) §	Discounted lifetime cost (EUR) per woman ‖	Discounted QALYs per woman ¶	ICER, € per QALY (% cost-effective*)
No screening, no vaccination	0 (0 - 0)	--	--	159 (93 - 195)	21.46217 (21.45186 - 21.48005)	-
No screening (vaccination only)	58.8 (52.0 – 65.0)	--	--	408 (387 - 419)	21.49111 (21.48828- 21.496675)	8 620 (0)
1-time HPV test, age 40 years	87.8 (85.9 – 89.2)	185 (145 - 230)	1 993 (1 774- 2 256)	498 (483 - 510)	21.49940 (21.49800- 21.501595)	10 900 (0)
1 time HPV test, age 35 years	88.4 (86. 8 – 89.6)	229 (183 - 281)	2 254 (1 996 - 2 561)	538 (520 - 553)	21.50097 (21.49990- 21.502596)	25 220 (0)
1 time HPV test, age 30 years	88.1 (86.2 – 89.4)	295 (240 - 354)	2 637 (2 322 – 2 988)	601 (576 - 624)	21.50242 (21.50173- 21.503563)	43 650 (2)
HPV test (20-year), age 31 years	94.5 (93.8 – 95.3)	383 (307- 464)	4 046 (3 616 – 4 526)	638 (611 - 662)	21.50311 (21.50249- 21.503925)	53 570 (50)
2-times HPV test, ages 30 and 45 years	94.1 (93.3 – 94.8)	407 (329- 489)	4 196 (3 757 – 4 671)	672 (642 - 698)	21.50354 (21.50306- 21.504210)	77 570 (44)
HPV test (20-year), age 28 years	96.4 (96.0 – 96.9)	494 (400- 592)	5 354 (4 841 – 5 911)	717 (683 - 747)	21.50404 (21.50365- 21.504549)	90 810 (4)
HPV test (15-year), age 28 years	96.9 (96.5 – 97.3)	533 (430- 637)	5 836 (5 249 – 6 453)	754 (717 - 787)	21.50429 (21.50396- 21.504715)	146 980 (0)
HPV test (15-year), age 25 years	97.2 (96.9 – 97.5)	628 (513- 743)	6 435 (5 775 – 7 114)	849 (803 - 890)	21.50471 (21.50451- 21.504982)	227 020 (0)
HPV test (10-year), age 25 years	98.6 (98.3 – 98.7)	781 (639- 918)	9 034 (8 231 – 9 832)	966 (915 – 1 014)	21.50500 (21.50488- 21.505167)	408 490 (0)
HPV test (7-year), age 25 years	98.7 (98.5 – 98.8)	909 (747- 1069)	11 485 (10 578 – 12 401)	1 096 (1 040 – 1 149)	21.50504 (21.50492- 21.505196)	2 949 420 (0)
HPV test (5-year), age 25 years	98.7 (98.5 – 98.9)	1038 (857- 1221)	14 336 (13 298 – 15 391)	1 253 (1 191 – 1 312)	21.50506 (21.50494- 21.505209)	9 143 150 (0)
HPV test (3-year), age 25 years	98.8 (98.6 – 99.0)	1278 (1059- 1499)	20 979 (19 776 – 22 204)	1 596 (1 527 - 1 662)	21.50507 (21.50495- 21.505220)	35 974 440 (0)

* Values represent the average value across the 50 parameter sets (with the minimum and maximum values in parenthesis). The table lists strategies identified as cost-efficient (i.e. strategies with higher QALYs and lower cost, or lower ICER, than candidate strategies) in the order of increasing costs. Percent cost-effective refers to the probability that each strategy was cost-effective under the Norwegian willingness-to-pay threshold across the 50 parameter sets. Costs and QALYs are discounted by 4% per year. HPV, human papillomavirus; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; EUR, Euros (2014 values, 1€EUR=8.35NOK). 2/4vHPV refers to the bivalent or quadrivalent HPV vaccines.

† All cost-efficient screening strategies involved primary HPV testing, but varied by the screening frequency (either 1-time or 2-times per lifetime or at the screening interval indicated in parenthesis) and age of screening initiation. In all strategies, except 1-time or 2-times screening per lifetime, screening ends at age 69 years (consistent with current guidelines in Norway). Women who are HPV-positive are managed according to the proposed HPV-based strategy in Norway (i.e. reflex cytology with colposcopy for

women detected with atypical squamous cells of undetermined significance (ASC-US) or more severe, with repeat HPV testing at 12 months for women with a normal cytology result).

‡ The % reduction in lifetime risk of developing cervical cancer incidence compared to no intervention (i.e. no screening and no vaccination).

§ The number of colposcopy referrals and screening tests (i.e. cytology and HPV-tests) per 1,000 women screened over their lifetime (starting at strategy-specific age of screening initiation).

‖ The average lifetime cost per woman is discounted at 4% per year consistent with Norwegian guidelines for economic evaluation. The costs were valued in 2014 Norwegian kroners (NOK) and converted to Euros (€EUR = NOK8.35).

¶ Incremental cost-effectiveness ratios were calculated as the ratio of the average incremental cost divided by the average incremental QALY gained across the 50 parameter sets. Among the total 74 candidate screening strategies, we excluded from further consideration strategies that were more costly and less effective (i.e. strongly dominated) or less costly and less cost-effective (i.e. weakly dominated). Outcomes for dominated strategies are available upon request to the corresponding author.

Supplementary Table 4. Outcomes associated with cost-efficient strategies for women vaccinated with 9vHPV*.

Stategy†	Cancer incidence reduction (%)‡	Colposcopy rate (per 1,000 women) §	Screening tests (per 1,000) §	Discounted lifetime cost (EUR) per woman ‖	Discounted QALYs per woman ¶	ICER, € per QALY (% cost-effective*)
No screening, no vaccination	--	--	--	159 (93 - 195)	21.46217 (21.45186- 21.48005)	--
No screening (vaccination only)	78.6 (71.5– 84.1)	--	--	415 (405 - 423)	21.50028 (21.49827- 21.50268)	6 720 (0)
1-time HPV test, age 40 years	96.6 (95.6 - 97.5)	121 (87 - 160)	1 638 (1 450 – 1 860)	497 (485 - 507)	21.50423 (21.50380- 21.50491)	20 720 (100)
1 time HPV test, age 35 years	96.3 (94.9 - 97.2)	147 (108 - 190)	1 801 (1 582 – 2 053)	527 (511 - 540)	21.50453 (21.50421- 21.50506)	100 530 (0)
HPV test (20-year), age 31 years	98.7 (98.3 – 98.9)	236 (172 - 301)	3 234 (2 870 – 3 615)	607 (583 - 626)	21.50500 (21.50477- 21.50530)	170 320 (0)
HPV test (20-year), age 28 years	99.2 (98.9 – 99.4)	298 (218 - 376)	4 344 (3 906 – 4 783)	663 (635 - 688)	21.50517 (21.50500- 21.50538)	338 320 (0)
HPV test (20-year), age 25 years	99.3 (99.1- 99.4)	333 (245 - 415)	4 661 (4 166 – 5 131)	713 (678 - 742)	21.505278 (21.50515- 21.50543)	454 850 (0)
HPV test (15-year), age 25 years	99.2 (99.1- 99.4)	350 (257 - 434)	4 879 (4 344 – 5 376)	745 (708 - 777)	21.50533 (21.50522 - 21.50545)	631 810 (0)
HPV test (10-year), age 25 years	99.5 (99.4 – 99.6)	428 (312 - 530)	7 108 (6 445 – 7 696)	845 (803 - 882)	21.50538 (21.50528- 21.50548)	2 092 900 (0)
HPV test (7-year), age 25 years	99.6 (99.5 – 99.7)	488 (355 - 606)	9 239 (8 492 – 9 907)	956 (909 - 997)	21.50538 (21.50529 - 21.50549)	19 357 120 (0)
HPV test (5-year), age 25 years	99.6 (99.5- 99.7)	542 (394 - 674)	11 598 (10 737 – 12 375)	1091 (1040 - 1137)	21.50538 (21.50529 - 21.50549)	71 089 020 (0)

* Values represent the average value across the 50 parameter sets (with the minimum and maximum values in parenthesis). The table lists strategies identified as cost-efficient (i.e. strategies with higher QALYs and lower cost, or lower ICER, than candidate strategies) in the order of increasing costs. Percent cost-effective refers to the probability that each strategy was cost-effective under the Norwegian willingness-to-pay threshold across the 50 parameter sets. Costs and QALYs are discounted by 4% per year. HPV, human papillomavirus; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; ; EUR, Euros (2014 values, 1€EUR=8.35NOK). 2/4vHPV refers to the bivalent or quadrivalent HPV vaccines.

† All cost-efficient screening strategies involved primary HPV testing, but varied by the screening frequency (either 1-time or 2-times per lifetime or at the screening interval indicated in parenthesis) and age of screening initiation. In all strategies, except 1-time or 2-times screening per lifetime, screening ends at age 69 years (consistent with current guidelines in Norway). Women who are HPV-positive are managed according to the proposed HPV-based strategy in Norway (i.e. reflex cytology with colposcopy for women detected with atypical squamous cells of undetermined significance (ASC-US) or more severe, with repeat HPV testing at 12 months for women with a normal cytology result).

‡ The % reduction in lifetime risk of developing cervical cancer incidence compared to no intervention (i.e. no screening and no vaccination).

§ The number of colposcopy referrals and screening tests (i.e. cytology and HPV-tests) per 1,000 women screened over their lifetime (starting at strategy-specific age of screening initiation).

‖ The average lifetime cost per woman is discounted at 4% per year consistent with Norwegian guidelines for economic evaluation. The costs were valued in 2014 Norwegian kroners (NOK) and converted to Euros (€EUR = NOK8.35).

¶ Incremental cost-effectiveness ratios were calculated as the ratio of the average incremental cost divided by the average incremental QALY gained across the 50 parameter sets. Among the total 74 candidate screening strategies, we excluded from further consideration strategies that were more costly and less effective (i.e. strongly dominated) or less costly and less cost-effective (i.e. weakly dominated). Outcomes for dominated strategies are available upon request to the corresponding author.

Supplementary Table 5. The efficiency gains of stratifying screening guidelines for a cohort of 30,000 Norwegian women and a willingness-to-pay threshold of a €75,000 per QALY gained, by vaccine type and 3-dose vaccination coverage.*

		Compared to current guidelines				Compared to proposed guidelines			
		2/4vHPV		9vHPV		2/4vHPV		9vHPV	
3-dose vaccine coverage (%)	**Number of vaccinated women in a cohort†**	Efficiency gain per woman (EUR)‡	Efficiency gain for a cohort (EUR)§	Efficiency gain per woman (EUR)‡	Efficiency gain for a cohort (EUR)§	Efficiency gain per woman (EUR)‡	Efficiency gain for a cohort (EUR)§	Efficiency gain per woman (EUR)‡	Efficiency gain for a cohort (EUR)§
50	**15 000**	599	8 985 000	725	10 875 000	477	7 155 000	571	8 565 000
67‖	**20 100**	599	12 039 900	725	14 572 500	477	9 587 700	571	11 477 100
84¶	**25 200**	599	15 094 800	725	18 270 000	477	12 020 400	571	14 389 200
100	**30 000**	599	17 970 000	725	21 750 000	477	14 310 000	571	17 130 000

* Details about calculation of efficiency gains are provided in Supplementary Appendix section 1. 2/4vHPV and 9vHPV indicate the bivalent/quadrivalent and nonavalent vaccine, respectively. Current and proposed guidelines indicate the currently in-use and proposed cervical cancer screening guidelines in Norway, respectively. ; EUR, Euros (2014 values, 1€EUR=8.35NOK).

† The size of a female birth cohort in Norway is ~30,000 women.

‡ The efficiency gain per woman presented in the table is conditioned on vaccine type and a willingness-to-pay threshold of a €75,000 per QALY gained. Efficiency gains for other willingness-to-pay threshold values are presented in Main Manuscript Figure 4.

§ The efficiency gain for a cohort is calculated using the efficiency gain per woman multiplied by the number of vaccinated women in a cohort (conditioned on vaccine coverage).

‖ The 3-dose coverage level for the first cohort of women vaccinated at age 12 years in 2009 (born in 1997) was 67% (3). The actual number of vaccinated women in this cohort was ~22,000 (outcomes presented in the main manuscript).

¶ The 3-dose coverage level for the cohort of women vaccinated at age 12 years in 2014 (born in 2002) was 84% (13).

3. SUPPLEMENTARY RESULTS FROM UNCERTAINTY ANALYSIS

Supplementary Table 6. Outcomes associated with cost-efficient CC screening strategies for women vaccinated with 2/4vHPV*:

a) Assuming cross-protection against non-targeted vaccine genotypes**

Stategy†	Cancer incidence reduction (%)‡	Colposcopy rate (per 1,000 women) §	Screening tests (per 1,000) §	Disc cost per woman (EUR) ‖	Disc QALYs per woman ¶	ICER (€ per QALY)
No screening, no vaccination	0.0 %	-	-	168	21.45955	-
No screening (vaccination only)	73.8 %	-	-	386	21.49710	5 816
1-time HPV test, age 40 years	93.4 %	164	1 876	479	21.50227	17 990
1 time HPV test, age 35 years	93.5 %	198	2 085	515	21.50305	45 982
1 time HPV test, age 30 years	92.9 %	246	2 374	568	21.50372	79 110
HPV test (20-year), age 31 years	97.0 %	327	3 744	607	21.50417	86 252
2-times HPV test, ages 30 and 45 years	96.7 %	343	3 859	637	21.50439	136 138
HPV test (20-year), age 28 years	98.0 %	418	4 978	676	21.50466	142 457
HPV test (15-year), age 28 years	98.2 %	447	5 373	710	21.50480	251 776
HPV test (15-year), age 25 years	98.4 %	510	5 797	784	21.50504	298 082
HPV test (10-year), age 25 years	99.1 %	637	8 277	895	21.50520	697 616
HPV test (7-year), age 25 years	99.2 %	738	10 609	1 017	21.50523	4 968 940
HPV test (5-year), age 25 years	99.2 %	837	13 274	1 165	21.50524	15 099 828
HPV test (3-year), age 25 years	99.3 %	1 032	19 753	1 500	21.50524	216 717 886

b) Assuming 90% vaccine efficacy against all vaccine-targeted genotypes**

Stategy†	Cancer incidence reduction (%)‡	Colposcopy rate (per 1,000 women) §	Screening tests (per 1,000) §	Disc cost per woman (EUR) ‖	Disc QALYs per woman ¶	ICER (€ per QALY)
No screening, no vaccination	0.0 %	-	-	168	21.45955	-
No screening (vaccination only)	54.3 %	-	-	420	21.48768	8 961
1-time HPV test, age 40 years	83.8 %	212	2 134	516	21.49716	10 167
1 time HPV test, age 35 years	84.6 %	259	2 410	558	21.49907	21 552
1 time HPV test, age 30 years	84.4 %	328	2 814	624	21.50103	33 822
HPV test (20-year), age 31 years	92.2 %	436	4 328	663	21.50209	36 897
2-times HPV test, ages 30 and 45 years	91.7 %	461	4 476	698	21.50269	57 807
HPV test (20-year), age 28 years	94.8 %	560	5 681	745	21.50337	68 521
HPV test (15-year), age 28 years	95.6 %	607	6 231	784	21.50382	88 625
HPV test (15-year), age 25 years	96.0 %	707	6 857	883	21.50438	175 454
HPV test (10-year), age 25 years	98.1 %	886	9 590	1 006	21.50483	275 396
HPV test (7-year), age 25 years	98.3 %	1 036	12 147	1 141	21.50490	1 988 650
HPV test (5-year), age 25 years	98.3 %	1 188	15 135	1 304	21.50492	9 754 191
HPV test (3-year), age 25 years	98.5 %	1 466	21 941	1 654	21.50493	32 151 039

c) Assuming an HPV test sensitivity (to detect CIN2+) of 90% ††

Stategy†	Cancer incidence reduction (%)‡	Colposcopy rate (per 1,000 women) §	Screening tests (per 1,000) §	Disc cost per woman (EUR) ‖	Disc QALYs per woman ¶	ICER (€ per QALY)
No screening, no vaccination	0.0 %	-	-	168	21.45955	-
No screening (vaccination only)	63.9 %	-	-	420	21.49229	7 700
1-time HPV test, age 40 years	83.2 %	136	1 761	516	21.49840	15 751
1 time HPV test, age 35 years	82.8 %	166	1 957	558	21.49938	42 441
HPV test (20-year), age 34 years	89.7 %	252	3 357	616	21.50072	43 403
HPV test (20-year), age 31 years	90.2 %	286	3 584	663	21.50161	52 769
HPV test (15-year), age 31 years	92.9 %	352	4 866	712	21.50216	90 223
HPV test (15-year), age 28 years	93.7 %	405	5 227	784	21.50294	91 453
HPV test (10-year), age 28 years	95.7 %	514	7 464	885	21.50359	154 953
HPV test (7-year), age 25 years	97.2 %	724	10 650	1 141	21.50437	328 574
HPV test (5-year), age 25 years	97.7 %	847	13 484	1 304	21.50465	579 743
HPV test (3-year), age 25 years	98.3 %	1 082	20 168	1 654	21.50487	1 592 891

d) Assuming imperfect compliance to screening and follow-up procedures ‡‡

Stategy†	Cancer incidence reduction (%)‡	Colposcopy rate (per 1,000 women) §	Screening tests (per 1,000) §	Disc cost per woman (EUR) ‖	Disc QALYs per woman ¶	ICER (€ per QALY)
No screening, no vaccination	0.0 %	-	-	168	21.45955	-
No screening (vaccination only)	63.9 %	-	-	404	21.49229	7 196
1-time HPV test, age 40 years	83.7 %	127	1 615	476	21.49807	12 584
1 time HPV test, age 35 years	84.1 %	155	1 823	506	21.49920	26 560
HPV test (20-year), age 34 years	89.9 %	231	3 046	549	21.50040	35 499
HPV test (20-year), age 31 years	90.7 %	262	3 282	582	21.50131	36 685
2-times HPV test, ages 30 and 45 years	90.9 %	278	3 406	607	21.50178	53 006
HPV test (15-year), age 28 years	93.7 %	364	4 737	670	21.50263	73 521
HPV test (10-year), age 28 years	95.6 %	456	6 638	747	21.50324	125 677
HPV test (10-year), age 25 years	96.4 %	532	7 332	832	21.50385	139 915
HPV test (7-year), age 25 years	97.3 %	626	9 384	937	21.50425	262 757
HPV test (5-year), age 25 years	97.7 %	720	11 711	1 064	21.50451	493 605
HPV test (3-year), age 25 years	98.0 %	894	17 161	1 342	21.50466	1 792 016

e) Scenario including only medical costs (i.e. excluding patient time and transportation costs) §§

Stategy†	Cancer incidence reduction (%)‡	Colposcopy rate (per 1,000 women) §	Screening tests (per 1,000) §	Disc cost per woman (EUR) ‖	Disc QALYs per woman ¶	ICER (€ per QALY)
No screening, no vaccination	0.0 %	-	-	137	21.45955	-
1-time HPV test, age 40 years	89.1 %	195	2 048	448	21.49976	7 735
1 time HPV test, age 35 years	89.6 %	240	2 314	473	21.50117	17 724
1 time HPV test, age 30 years	89.3 %	306	2 702	514	21.50256	29 238
HPV test (20-year), age 31 years	95.0 %	402	4 157	536	21.50321	33 436
2-times HPV test, ages 30 and 45 years	94.6 %	426	4 301	557	21.50361	52 100
HPV test (20-year), age 28 years	96.7 %	518	5 483	585	21.50411	57 637
HPV test (15-year), age 28 years	97.1 %	558	5 985	608	21.50435	92 765
HPV test (15-year), age 25 years	97.4 %	652	6 578	668	21.50474	154 945
HPV test (10-year), age 25 years	98.7 %	814	9 229	739	21.50502	257 460
HPV test (7-year), age 25 years	98.8 %	948	11 713	817	21.50506	1 844 574
HPV test (5-year), age 25 years	98.8 %	1 083	14 604	911	21.50507	5 789 430
HPV test (3-year), age 25 years	98.9 %	1 335	21 307	1 114	21.50508	37 912 238

f) Scenario including both medical, patient time, transportation and productivity costs §§

Stategy†	Cancer incidence reduction (%)‡	Colposcopy rate (per 1,000 women) §	Screening tests (per 1,000) §	Disc cost per woman (EUR) ‖	Disc QALYs per woman ¶	ICER (€ per QALY)
No screening, no vaccination	0.0 %	-	-	412	21.45955	-
No screening (vaccination only)	63.9 %	-	-	477	21.49229	1 999
1-time HPV test, age 40 years	89.1 %	195	2 048	550	21.49976	9 781
1 time HPV test, age 35 years	89.6 %	240	2 314	593	21.50117	29 809
1 time HPV test, age 30 years	89.3 %	306	2 702	663	21.50256	51 037
HPV test (20-year), age 31 years	95.0 %	402	4 157	699	21.50321	54 789
2-times HPV test, ages 30 and 45 years	94.6 %	426	4 301	736	21.50361	91 454
HPV test (20-year), age 28 years	96.7 %	518	5 483	786	21.50411	100 797
HPV test (15-year), age 28 years	97.1 %	558	5 985	825	21.50435	162 269
HPV test (15-year), age 25 years	97.4 %	652	6 578	930	21.50474	269 107
HPV test (10-year), age 25 years	98.7 %	814	9 229	1 054	21.50502	449 813
HPV test (7-year), age 25 years	98.8 %	948	11 713	1 190	21.50506	3 193 892
HPV test (5-year), age 25 years	98.8 %	1 083	14 604	1 351	21.50507	9 932 297
HPV test (3-year), age 25 years	98.9 %	1 335	21 307	1 698	21.50508	65 049 006

g) Scenario using life-years gained (rather than QALYs) to calculate the ICER

Stategy†	Cancer incidence reduction (%)‡	Colposcopy rate (per 1,000 women) §	Screening tests (per 1,000) §	Disc cost per woman (EUR) ‖	Disc LYG per woman ¶	ICER (€ per LYG)
No screening, no vaccination	0.0 %	-	-	159	23.96856	-
No screening (vaccination only)	63.9 %	-	-	408	23.99392	9 840
1-time HPV test, age 40 years	89.1 %	195	2 048	498	24.00217	10 957
1 time HPV test, age 35 years	89.6 %	240	2 314	538	24.00347	30 302
HPV test (20-year), age 31 years	95.0 %	402	4 157	638	24.00540	52 086
2-times HPV test, ages 30 and 45 years	94.6 %	426	4 301	672	24.00574	97 477
HPV test (20-year), age 28 years	96.7 %	518	5 483	717	24.00607	137 509
HPV test (15-year), age 28 years	97.1 %	558	5 985	754	24.00628	176 213
HPV test (15-year), age 25 years	97.4 %	652	6 578	849	24.00651	412 295
HPV test (10-year), age 25 years	98.7 %	814	9 229	966	24.00674	511 518
HPV test (7-year), age 25 years	98.8 %	948	11 713	1 096	24.00678	3 234 704
HPV test (5-year), age 25 years	98.8 %	1 083	14 604	1 253	24.00679	15 695 261
HPV test (3-year), age 25 years	98.9 %	1 335	21 307	1 596	24.00680	34 307 898

h) Scenario assuming 0% discounting of costs and QALYs

Stategy†	Cancer incidence reduction (%)‡	Colposcopy rate (per 1,000 women) §	Screening tests (per 1,000) §	Undisc cost per woman (EUR) ‖	Undisc QALYs per woman ¶	ICER (€ per QALY)
No screening (vaccination only)	63.9 %	-	-	734	64.09705	-
1-time HPV test, age 40 years	89.1 %	195	2 048	932	64.19114	2 105
1 time HPV test, age 35 years	89.6 %	240	2 314	984	64.20006	5 777
1 time HPV test, age 30 years	89.3 %	306	2 702	1 071	64.20544	16 085
HPV test (20-year), age 31 years	95.0 %	402	4 157	1 316	64.21861	18 670
2-times HPV test, ages 30 and 45 years	94.6 %	426	4 301	1 351	64.22025	20 779
HPV test (15-year), age 28 years	97.1 %	558	5 985	1 673	64.22675	49 647
HPV test (15-year), age 25 years	97.4 %	652	6 578	1 793	64.22871	61 331
HPV test (10-year), age 25 years	98.7 %	814	9 229	2 317	64.23155	184 071
HPV test (7-year), age 25 years	98.8 %	948	11 713	2 810	64.23193	1 292 086
HPV test (5-year), age 25 years	98.8 %	1 083	14 604	3 378	64.23203	6 206 426
HPV test (3-year), age 25 years	98.9 %	1 335	21 307	4 703	64.23214	11 578 430

* Values represent the value for the one parameter set with input values closest to the average input values for the 50 best-fitting parameter sets. The table lists strategies identified as cost-efficient (i.e. strategies with higher QALYs and lower cost, or lower ICER, than candidate strategies) in the order of increasing costs. Costs and QALYs are discounted by 4% per year. Italicised strategies indicate strategies that were not identified as cost-efficient under base-case assumptions. HPV, human papillomavirus; Disc, discounted; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; EUR, Euros (2014 values). 2/4vHPV refers to the bivalent or quadrivalent HPV vaccines.

† All cost-efficient screening strategies involved primary HPV testing, but varied by the screening frequency (either 1-time or 2-times per lifetime or at the screening interval indicated in parenthesis) and age of screening initiation. All strategies except 1-time or 2-times screening per lifetime ends screening at age 69 years (consistent with current guidelines in Norway). Women who are HPV-positive are managed according to the proposed HPV-based strategy in Norway (i.e. reflex cytology with colposcopy for women detected with atypical squamous cells of undetermined significance (ASC-US) or more severe, with repeat HPV testing at 12 months for women with a normal cytology result).

‡ The % reduction in lifetime risk of developing cervical cancer incidence compared to no intervention (i.e. no screening and no vaccination).

§ The number of colposcopy referrals and screening tests (i.e. cytology and HPV-tests) per 1,000 women screened over their lifetime (starting at strategy-specific age of screening initiation).

‖ The average lifetime cost per woman is discounted at 4% per year consistent with Norwegian guidelines for economic evaluation. The costs were valued in 2014 Norwegian kroners (NOK) and converted to Euros (€EUR = NOK8.35).

¶ Incremental cost-effectiveness ratios were calculated as the ratio of the average incremental cost divided by the average incremental QALY gained across the 50 parameter sets. Among the total 74 candidate screening strategies, we excluded from further consideration strategies that were more costly and less effective (i.e. strongly dominated) or less costly and less cost-effective (i.e. weakly dominated). Outcomes for dominated strategies are available upon request to the corresponding author.

**Explicit assumptions are presented in Supplementary Appendix Table 1.

†† Details about diagnostic accuracy are provided in Supplementary Appendix Section 1.4.

‡‡ Details about screening compliance assumptions are provided in Supplementary Appendix Section 1.5.

§§ Details about costing assumptions for base-case and uncertainty analysis are provided in the Technical Appendix (14).

Supplementary Table 7. Outcomes associated with cost-efficient CC screening strategies for women vaccinated with 9vHPV*:

a) Assuming 90% vaccine efficacy against all vaccine-targeted genotypes**

Stategy†	Cancer incidence reduction (%)‡	Colposcopy rate (per 1,000 women) §	Screening tests (per 1,000) §	Disc cost per woman (EUR) ‖	Disc QALYs per woman ¶	ICER (€ per QALY)
No screening, no vaccination	0.0 %	-	-	168	21.45955	-
No screening (vaccination only)	71.0 %	-	-	431	21.49586	7 230
1-time HPV test, age 40 years	91.3 %	155	1 815	519	21.50152	15 678
1 time HPV test, age 35 years	91.3 %	185	2 002	552	21.50231	41 441
HPV test (20-year), age 31 years	95.8 %	303	3 596	639	21.50380	58 570
2-times HPV test, ages 30 and 45 years	95.3 %	317	3 695	666	21.50408	96 610
HPV test (20-year), age 28 years	97.3 %	384	4 777	701	21.50440	109 106
HPV test (15-year), age 28 years	97.5 %	409	5 137	734	21.50464	136 247
HPV test (15-year), age 25 years	97.7 %	456	5 462	796	21.50494	208 458
HPV test (10-year), age 25 years	98.9 %	570	7 869	904	21.50517	463 830
HPV test (7-year), age 25 years	99.0 %	658	10 137	1 022	21.50521	3 258 576
HPV test (5-year), age 25 years	99.0 %	742	12 694	1 166	21.50521	31 289 050
HPV test (3-year), age 25 years	99.1 %	909	19 052	1 496	21.50521	128 456 109

b) Assuming an HPV test sensitivity (to detect CIN2+) of 90% ††

Stategy†	Cancer incidence reduction (%)‡	Colposcopy rate (per 1,000 women) §	Screening tests (per 1,000) §	Disc cost per woman (EUR) ‖	Disc QALYs per woman ¶	ICER (€ per QALY)
No screening, no vaccination	0.0 %	-	-	168	21.45955	-
No screening (vaccination only)	81.9 %	-	-	431	21.50108	6 339
1-time HPV test, age 40 years	92.8 %	87	1 481	520	21.50362	34 848
2-times HPV test, ages 40 and 55 years	95.9 %	129	2 612	560	21.50403	97 928
HPV test (15-year), age 34 years	97.2 %	190	3 872	641	21.50444	198 374
HPV test (15-year), age 31 years	97.4 %	212	4 063	683	21.50459	280 543
HPV test (10-year), age 34 years	98.0 %	225	5 024	695	21.50463	286 926
HPV test (10-year), age 31 years	98.3 %	251	5 251	746	21.50480	306 674
HPV test (10-year), age 28 years	98.4 %	299	6 308	824	21.50495	504 611
HPV test (10-year), age 25 years	98.6 %	335	6 693	904	21.50507	653 926
HPV test (7-year), age 25 years	99.0 %	397	8 856	1 023	21.50519	1 056 763
HPV test (5-year), age 25 years	99.2 %	459	11 267	1 167	21.50526	2 056 380
HPV test (3-year), age 25 years	99.4 %	585	17 481	1 497	21.50532	5 114 348

c) Assuming imperfect compliance to screening and follow-up procedures ‡‡

Stategy†	Cancer incidence reduction (%)‡	Colposcopy rate (per 1,000 women) §	Screening tests (per 1,000) §	Disc cost per woman (EUR) ‖	Disc QALYs per woman ¶	ICER (€ per QALY)
No screening, no vaccination	0.0 %	-	-	168	21.45955	-
No screening (vaccination only)	81.9 %	-	-	412	21.50108	5 870
1-time HPV test, age 40 years	94.1 %	87	1 341	479	21.50369	25 794
2-times HPV test, ages 40 and 55 years	96.8 %	126	2 302	509	21.50405	80 501
2-times HPV test, ages 35 and 50 years	97.1 %	149	2 501	541	21.50436	104 868
HPV test (20-year), age 31 years	97.2 %	170	2 664	565	21.50450	173 175
2-times HPV test, ages 30 and 45 years	97.1 %	178	2 748	585	21.50461	178 672
HPV test (15-year), age 28 years	98.3 %	227	3 817	634	21.50483	222 972
HPV test (15-year), age 25 years	98.3 %	250	4 030	674	21.50497	282 972
HPV test (10-year), age 25 years	99.1 %	313	5 878	756	21.50514	503 233
HPV test (7-year), age 25 years	99.3 %	363	7 668	847	21.50521	1 237 373
HPV test (5-year), age 25 years	99.3 %	407	9 620	959	21.50526	2 154 539
HPV test (3-year), age 25 years	99.4 %	498	14 641	1 218	21.50528	11 962 094

d) Scenario including only medical costs (i.e. excluding patient time and transportation costs) §§

Stategy†	Cancer incidence reduction (%)‡	Colposcopy rate (per 1,000 women) §	Screening tests (per 1,000) §	Disc cost per woman (EUR) ‖	Disc QALYs per woman ¶	ICER (€ per QALY)
No screening, no vaccination	0.0 %	-	-	137	21.45955	-
No screening (vaccination only)	81.9 %	-	-	408	21.50108	6 521
1-time HPV test, age 40 years	97.2 %	133	1 702	459	21.50442	15 077
1 time HPV test, age 35 years	96.9 %	160	1 874	478	21.50463	90 540
HPV test (20-year), age 31 years	98.9 %	259	3 363	528	21.50504	123 613
HPV test (20-year), age 28 years	99.3 %	327	4 499	564	21.50520	221 639
HPV test (20-year), age 25 years	99.4 %	363	4 833	595	21.50530	303 670
HPV test (15-year), age 25 years	99.4 %	382	5 068	615	21.50534	485 699
HPV test (10-year), age 25 years	99.6 %	470	7 353	675	21.50538	1 565 375
HPV test (7-year), age 25 years	99.6 %	537	9 522	740	21.50538	19 405 174
HPV test (5-year), age 25 years	99.6 %	598	11 932	820	21.50539	55 386 842

e) Scenario including medical, patient time, transportation and productivity costs §§

Stategy†	Cancer incidence reduction (%)‡	Colposcopy rate (per 1,000 women) §	Screening tests (per 1,000) §	Disc cost per woman (EUR) ‖	Disc QALYs per woman ¶	ICER (€ per QALY)
No screening, no vaccination	0.0 %	-	-	412	21.45955	-
No screening (vaccination only)	81.9 %	-	-	440	21.50108	675
1-time HPV test, age 40 years	97.2 %	133	1 702	519	21.50442	23 615
1 time HPV test, age 35 years	96.9 %	160	1 874	553	21.50463	157 077
HPV test (20-year), age 31 years	98.9 %	259	3 363	639	21.50504	214 346
HPV test (20-year), age 28 years	99.3 %	327	4 499	701	21.50520	381 646
HPV test (20-year), age 25 years	99.4 %	363	4 833	753	21.50530	507 843
HPV test (15-year), age 25 years	99.4 %	382	5 068	788	21.50534	847 836
HPV test (10-year), age 25 years	99.6 %	470	7 353	892	21.50538	2 726 442
HPV test (7-year), age 25 years	99.6 %	537	9 522	1 006	21.50538	33 682 777
HPV test (5-year), age 25 years	99.6 %	598	11 932	1 144	21.50539	96 166 645

f) Scenario using life-years gained (rather than QALYs) to calculate the ICER

Stategy†	Cancer incidence reduction (%)‡	Colposcopy rate (per 1,000 women) §	Screening tests (per 1,000) §	Disc cost per woman (EUR) ‖	Disc LYG per woman ¶	ICER (€ per LYG)
No screening, no vaccination	0.0 %	-	-	159	23.96856	-
No screening (vaccination only)	81.9 %	-	-	415	24.00207	7 645
1-time HPV test, age 40 years	97.2 %	133	1 702	497	24.00603	20 701
1 time HPV test, age 35 years	96.9 %	160	1 874	527	24.00627	126 234
HPV test (20-year), age 34 years	98.8 %	232	3 180	575	24.00654	176 436
HPV test (20-year), age 31 years	98.9 %	259	3 363	607	24.00669	213 032
HPV test (20-year), age 28 years	99.3 %	327	4 499	663	24.00683	405 610
HPV test (15-year), age 25 years	99.4 %	382	5 068	745	24.00694	745 338
HPV test (10-year), age 25 years	99.6 %	470	7 353	845	24.00698	2 494 932

g) Scenario assuming 0% discounting of costs and QALYs

Stategy†	Cancer incidence reduction (%)‡	Colposcopy rate (per 1,000 women) §	Screening tests (per 1,000) §	Undisc cost per woman (EUR) ‖	Undisc QALYs per woman ¶	ICER (€ per QALY)
No screening (vaccination only)	81.9 %	-	-	615	64.17589	-
1-time HPV test, age 40 years	97.2 %	133	1 702	821	64.22514	4 178
1 time HPV test, age 35 years	96.9 %	160	1 874	856	64.22635	29 206
HPV test (20-year), age 31 years	98.9 %	259	3 363	1 134	64.23130	56 132
HPV test (15-year), age 25 years	99.4 %	382	5 068	1 462	64.23337	158 664
HPV test (10-year), age 25 years	99.6 %	470	7 353	1 914	64.23386	912 056
HPV test (7-year), age 25 years	99.6 %	537	9 522	2 345	64.23392	7 050 002
HPV test (5-year), age 25 years	99.6 %	728	18 134	4 057	64.23393	224 436 771

* Values represent the value for the one parameter set with input values closest to the average input values for the 50 best-fitting parameter sets. The table lists strategies identified as cost-efficient (i.e. strategies with higher QALYs and lower cost, or lower ICER, than candidate strategies) in the order of increasing costs. Costs and QALYs are discounted by 4% per year. Italicised strategies indicate strategies that were not identified as cost-efficient under base-case assumptions. HPV, human papillomavirus; Disc, discounted; ICER, incremental cost-

effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life-year; EUR, Euros (2014 values). 2/4vHPV refers to the bivalent or quadrivalent HPV vaccines.

† All cost-efficient screening strategies involved primary HPV testing, but varied by the screening frequency (either 1-time or 2-times per lifetime or at the screening interval indicated in parenthesis) and age of screening initiation. All strategies except 1-time or 2-times screening per lifetime ends screening at age 69 years (consistent with current guidelines in Norway). Women who are HPV-positive are managed according to the proposed HPV-based strategy in Norway (i.e. reflex cytology with colposcopy for women detected with atypical squamous cells of undetermined significance (ASC-US) or more severe, with repeat HPV testing at 12 months for women with a normal cytology result).

‡ The % reduction in lifetime risk of developing cervical cancer incidence compared to no intervention (i.e. no screening and no vaccination).

§ The number of colposcopy referrals and screening tests (i.e. cytology and HPV-tests) per 1,000 women screened over their lifetime (starting at strategy-specific age of screening initiation).

‖ The average lifetime cost per woman is discounted at 4% per year consistent with Norwegian guidelines for economic evaluation. The costs were valued in 2014 Norwegian kroners (NOK) and converted to Euros (€EUR = NOK8.35).

¶ Incremental cost-effectiveness ratios were calculated as the ratio of the average incremental cost divided by the average incremental QALY gained across the 50 parameter sets. Among the total 74 candidate screening strategies, we excluded from further consideration strategies that were more costly and less effective (i.e. strongly dominated) or less costly and less cost-effective (i.e. weakly dominated). Outcomes for dominated strategies are available upon request to the corresponding author.

**Explicit assumptions are presented in Supplementary Appendix Table 1.

†† Details about diagnostic accuracy are provided in Supplementary Appendix Section 1.4.

‡‡ Details about screening compliance assumptions are provided in Supplementary Appendix Section 1.5.

§§ Details about costing assumptions for base-case and uncertainty analysis are provided in the Technical Appendix (14).

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