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Switching clinic-based cervical cancer screening programs to human papillomavirus self-sampling: A cost-effectiveness analysis of vaccinated and unvaccinated Norwegian women

Kine Pedersen[1] | Allison Portnoy[2] | Stephen Sy[2] | Bo T. Hansen[3] | Ameli Tropé[3] | Jane J. Kim[2] | Emily A. Burger[1,2]

[1]Department of Health Management and Health Economics, University of Oslo, Oslo, Norway

[2]Center for Health Decision Science, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

[3]Cancer Registry of Norway, Oslo, Norway

Correspondence
Emily A. Burger, Department of Health Management and Health Economics, University of Oslo, Oslo, Norway.
Email: eburger@hsph.harvard.edu

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Abstract

Several countries have implemented primary human papillomavirus (HPV) testing for cervical cancer screening. HPV testing enables home-based, self-collected sampling (self-sampling), which provides similar diagnostic accuracy as clinician-collected samples. We evaluated the impact and cost-effectiveness of switching an entire organized screening program to primary HPV self-sampling among cohorts of HPV vaccinated and unvaccinated Norwegian women. We conducted a model-based analysis to project long-term health and economic outcomes for birth cohorts with different HPV vaccine exposure, that is, preadolescent vaccination (2000- and 2008-cohorts), multiage cohort vaccination (1991-cohort) or no vaccination (1985-cohort). We compared the cost-effectiveness of switching current guidelines with clinician-collected HPV testing to HPV self-sampling for these cohorts and considered an additional 44 strategies involving either HPV self-sampling or clinician-collected HPV testing at different screening frequencies for the 2000- and 2008-cohorts. Given Norwegian benchmarks for cost-effectiveness, we considered a strategy with an additional cost per quality-adjusted life-year below $55 000 as cost-effective. HPV self-sampling strategies considerably reduced screening costs (ie, by 24%-40% across cohorts and alternative strategies) and were more cost-effective than clinician-collected HPV testing. For cohorts offered preadolescent vaccination, cost-effective strategies involved HPV self-sampling three times (2000-cohort) and twice (2008-cohort) per lifetime. In conclusion, we found that switching from clinician-collected to self-collected HPV testing in cervical screening may be cost-effective among both highly vaccinated and unvaccinated cohorts of Norwegian women.

Abbreviations: 2vHPV, bivalent human papillomavirus vaccine; 4vHPV, quadrivalent human papillomavirus vaccine; CIN2/3, cervical intraepithelial neoplasia grade 2 or 3; HPV, human papillomavirus; HPV-CC, human papillomavirus clinician-collected sample/sampling; HPV-SS, human papillomavirus self-sample/sampling; NCCSP, Norwegian Cervical Cancer Screening Program; NOK, Norwegian kroner; QALY, quality-adjusted life year.

KEYWORDS
cervical cancer, cost-effectiveness, human papillomavirus, prevention, screening

What's new?

Human papillomavirus (HPV)-based testing offers unique opportunities to improve cervical cancer screening. Among these opportunities is self-sampling, in which samples can be collected at home and sent for laboratory analysis. Here, health and cost outcomes of program-wide use of alternative HPV self-sampling strategies were evaluated among birth cohorts of Norwegian women of varying HPV vaccination exposure. Among highly vaccinated and unvaccinated cohorts, self-sampling was associated with lower screening costs and considered cost-effective compared with clinician-collected testing. The findings suggest that broader application of HPV self-sampling can reduce costs with similar health benefits, though further studies are needed to assess the diagnostic accuracy of of population-based self-sampling and compliance behaviors among women offered self-sampling.

1 | BACKGROUND

Organized cervical cancer screening programs are continuously adapted to improve program effectiveness and efficiency, particularly following the emergence of new technologies, such as human papillomavirus (HPV) testing, which detects the virus that is associated with nearly all cervical cancers and several other anogenital and oropharyngeal cancers,[1] and HPV vaccination, which has proven effective in preventing HPV infections and precancers.[2] In recent years, several organized screening programs have switched (or are in the process of switching) from primary cytology-based (ie, Pap smear) screening to HPV-based testing starting at age 30 years or older.[3] In Norway, implementation of primary HPV testing for women aged 34 to 69 years (with preceding cytology for women aged 25-33 years) is ongoing and complete national rollout is expected by 2023. HPV testing provides opportunities to improve screening; in addition to prolonged screening intervals due to a higher sensitivity compared with cytology,[4] HPV testing allows for self-collection of samples at home instead of the conventional approach involving a health provider collecting the sample at a clinic. Self-collected tests may help overcome barriers to screening participation such as the time or discomfort associated with a clinician visit.[5] A recent systematic review and meta-analysis[6] concluded that HPV self-sampling (HPV-SS) using polymerase chain reaction (PCR)-based methods have comparable diagnostic accuracy as clinician-collected samples (HPV-CC), although specificity was slightly lower. Moreover, studies have found that HPV-SS is generally acceptable among women eligible for screening,[5,7,8] providing opportunities for integration within organized screening.

Previous studies have evaluated use of HPV-SS as an approach to improve screening participation rates among under-screened women who are at higher risk of developing cancer. For example, two Norwegian randomized studies documented improved screening participation rates by offering HPV-SS to women with no screening test in the last 5 to 10 years.[9,10] Several cost-effectiveness analyses, which are increasingly used as part of decision-making processes to address allocation and effectiveness of healthcare services, have found that HPV-SS can be a cost-effective approach to target under-screened women, both in Norway[11] and elsewhere.[12] However, there is a paucity of studies that have evaluated HPV-SS as the primary approach to deliver screening to all women within an organized program, particularly in settings that include cohorts of vaccinated women.

Widespread HPV vaccination warrants new approaches to cervical cancer screening. Currently available HPV vaccines protect against HPV types that contribute to approximately 75% (ie, bivalent and quadrivalent vaccines) and approximately 90% (ie, nonavalent vaccine) of all cervical cancers.[13] Most high-income countries have implemented HPV vaccination in their national immunization programs and have achieved high coverage rates.[14,15] The first cohorts of women who were offered preadolescent vaccination are beginning to reach the age to initiate screening. For example, in Norway, HPV vaccination for 12-year-old girls was implemented in 2009, and the first routinely vaccinated cohort becomes eligible for screening (ie, at age 25 years) in 2022. Several countries have also offered multiaged cohort (sometimes referred to as "catch-up") vaccination programs targeting young adult women up to age 26 years, which typically achieve lower coverage than routine vaccination.[2] Consequently, the population of screen-eligible women will consist of both HPV-vaccinated and HPV-unvaccinated birth cohorts, with differing levels of direct and indirect benefits (ie, herd immunity effects) from vaccination, depending on how direct coverage, the type of vaccine and eligible populations vary over time. Although the risk of developing cervical cancer is expected to decline with increasing vaccination coverage, screening may remain an important preventive measure, because many screen-eligible women will still be unvaccinated, and the current HPV vaccines do not protect against all oncogenic HPV types. Thus, for the next few decades, organized screening programs will be targeting women with different levels of cervical cancer risk, leading to questions on how to optimize program efficiency. Several studies have already suggested that vaccinated women may be screened less intensively (eg, only once or twice a lifetime) to reduce the harms of screening and maintain the cost-effectiveness of the

program[16,17]; however, these studies evaluated the optimal clinician-collected HPV testing strategy and did not consider HPV-SS.

To our knowledge, there are no studies that explore multiple HPV-SS strategies within a high-income setting among birth cohorts of mixed HPV-vaccination status, including evaluation of novel triage approaches using partial HPV genotyping.[12] Therefore, we conducted an exploratory analysis to evaluate the long-term health and economic consequences of switching an organized, clinic-based screening program to self-sampling with HPV testing. Specifically, we evaluated the cost-effectiveness of alternative HPV-SS screening approaches among multiple birth cohorts that faced different direct and indirect protection provided by HPV vaccination programs.

2 | METHODS

2.1 | Analytic overview

We conducted a model-based cost-effectiveness analysis using a previously developed microsimulation model of HPV and cervical carcinogenesis,[18] adapted to reflect Norwegian epidemiologic and costing data.[19,20] The study setting was within the Norwegian Cervical Cancer Screening Program (NCCSP), which currently involves three-yearly cytology-based screening for women aged 25 to 33 years and ongoing implementation of a switch from primary cytology to five-yearly primary HPV testing for women aged 34 to 69 years. Since the resource-demanding switch to primary HPV testing is ongoing, decision-makers are unlikely to introduce major changes to the NCCSP before implementation is complete. Consequently, we considered the hypothetical introduction of candidate screening strategies for women eligible for screening under the current guidelines (ie, aged 25-69 years) from year 2025.

We selected birth cohorts to represent groups of women with different vaccine exposure (ie, preadolescent routine vaccination, multiaged cohort [MAC] "catch-up" vaccination or no vaccination) and protection against HPV infections (ie, direct or indirect vaccine protection). Direct vaccine protection is experienced by vaccinated individuals; the benefit is greatest when the vaccine is given at younger ages (ie, prior to sexual debut).[2] Indirect vaccine protection, or herd effects, occurs when unvaccinated individuals are protected by vaccinated individuals in the population; these benefits are greater among birth cohorts with high vaccine coverage.[2] Specifically, for this analysis, women born in 1985 ("the 1985-cohort"), aged 40 years in 2025, represent women with "low HPV protection," as these women have not been offered routine or catch-up HPV vaccination, and therefore have low direct and indirect protection against HPV infections. Women born in 1991 ("the 1991-cohort"), aged 34 years in 2025, reflect women with "intermediate HPV protection." These women were offered the bivalent HPV vaccine (2vHPV) at age 25 to 27 years during the temporary MAC campaign in 2016 to 2018, and therefore, received a limited amount of direct and indirect protection against HPV infections. Finally, we selected two birth cohorts to reflect "high HPV protection": women born in 2000 and 2008 ("the 2000-cohort" and "the 2008-cohort," aged 25 and 17 years in 2025, respectively). The 2000-cohort was offered routine vaccination with the quadrivalent HPV vaccine (4vHPV) at age 12 years and will be the first cohort with an opportunity to be screened under revised screening guidelines at age 25 years. The 2008-cohort was offered routine 2vHPV at age 12 years (in 2020), reflecting the most recently vaccinated cohort.[20] Cohort-specific coverage rates are available in Appendix E in Supporting Information.

We evaluated screening outcomes over the lifetime of each birth cohort, which included simulation of five million individual women per cohort to reduce stochastic noise. Model outcomes included total cost per woman, total quality-adjusted life expectancy per woman, lifetime risk of developing cervical cancer and number of cancer cases per 30 000 women (ie, the average size of a female birth cohort in Norway). We used a restricted societal analytic perspective (ie, including women's time and travel costs associated with screening and treatment procedures but excluding productivity losses) and discounted costs and health benefits by 4% per year, according to Norwegian guidelines for economic evaluation.[21] All costs were valued in 2020 Norwegian kroner (NOK) and converted to US dollars (USD) using the average annual 2020 exchange rate (USD1 = NOK9.4004).[22]

To evaluate the cost-effectiveness of candidate strategies, we calculated the incremental cost-effectiveness ratio (ICER), defined as the additional cost per additional quality-adjusted life year (QALY) of one strategy compared to the next least costly strategy. Strategies that were either more costly and less effective (ie, strongly dominated), or more effective but with a higher cost per QALY gained (ie, weakly dominated), were considered cost inefficient. In Norway, willingness-to-pay for additional QALYs depends on disease severity. In a previous study, we identified a range of NOK385 000 and NOK495 000 to reflect willingness-to-pay for preventive efforts targeting cervical cancer,[20] corresponding to a range of approximately US$40 000 to 55 000 per QALY. Subsequently, we considered the strategy with an ICER below $55 000 per QALY to represent the most cost-effective (ie, optimal) strategy. We conducted a probabilistic sensitivity analysis to identify the probability of each strategy being cost-effective given this benchmark. In uncertainty analyses, we also considered a lower willingness-to-pay of $40 000 per QALY as well as a maximum willingness-to-pay of $90 000 per QALY.

2.2 | Simulation model

The static simulation model has been previously described[18] and adapted to reflect HPV and cervical cancer epidemiology in Norway.[19,20] In short, we applied the model to simulate hypothetical women from age 9 years over their lifetime. Women transition through health states (at monthly intervals) reflecting HPV infection status (no HPV infection, HPV types 16, 18, 31, 33, 45, 52, 58, pooled other high-risk HPV types and pooled low-risk types), cervical precancer (by cervical intraepithelial neoplasia grade 2 or 3 [CIN2 or CIN3]) and squamous cell carcinoma (by stages local, regional and

distant cancer). We reflected uncertainty in the natural history of disease using 50 good-fitting parameter sets, which were previously fit using a likelihood-based calibration approach. Model outcomes reflected the average across 50 parameter sets, with uncertainty bounds reflecting the lower and upper value across the 50 sets.

To capture the direct and indirect protection from HPV vaccination, we used estimates of age- and birth cohort-specific HPV incidence that were previously derived from an agent-based dynamic model of HPV transmission.[20] The agent-based model simulated both current and historic Norwegian vaccination coverage and policies that varied by target population, vaccine type, dosing schedule and vaccination coverage over time (ie, the immunization program at that given point in time). Vaccine efficacy was assumed 100% against HPV-16/18 infections[23-25] for both the 2vHPV and 4vHPV, with different assumptions around cross-protection against HPV types 31, 33 and 45 for the two vaccine types. Specifically, we assumed cross-protection against these types were 89.3%, 47.8% and 53.7% for the 4vHPV, and 93.8%, 79.1% and 82.6% for the 2vHPV.[26,27] In uncertainty analysis, we assumed 2vHPV cross-protection was equal to observed 4vHPV levels. We also included a scenario assuming no herd immunity benefit from vaccination.

2.3 | Screening strategies and assumptions

For the 1985- and 1991-cohorts (with low and intermediate vaccine protection), we restricted the analysis to include current guidelines with HPV-CC, duplicated to also reflect HPV-SS (Table 1). Given the ongoing implementation of primary HPV testing within the Norwegian screening program, we assumed primary HPV testing started at age 40 years for the 1985-cohort and at age 34 years for the 1991-cohort, with preceding cytology starting at age 25 years for both cohorts. For the 2000- and 2008-cohorts (with high vaccine protection), we first considered 23 HPV-CC strategies, including the current guidelines, that varied by primary test modality (cytology with a switch to HPV testing vs HPV testing with no preceding cytology), age to start and stop screening and primary screening frequency. These strategies were subsequently duplicated replacing HPV-CC with HPV-SS, resulting in 23 "pairs" of strategies, such that one pair reflected the same algorithm (ie, same age to start and stop screening, and primary screening frequency) with either HPV-CC or HPV-SS as the primary test, resulting in a total of 46 unique strategies for each birth cohort (Table 1).

Relevant strategies were identified based on previous Norwegian cost-effectiveness studies[16,28] and discussions with the NCCSP and decision-makers in Norway. We considered de-intensified screening strategies (eg, once or twice per lifetime) for women vaccinated against HPV infections during adolescence, as suggested by previous cost-effectiveness studies, due to the lower risk of developing cervical cancer among HPV vaccinated women.[16,17] All candidate strategies involved follow-up of HPV-positive women according to current guidelines (Figure 1). For the HPV-SS strategies, we assumed that women identified positive by HPV-SS were referred for clinician-collected cytology prior to determining further follow-up, whereas women identified positive by HPV-CC receive immediate reflex cytology. We assumed HPV-SS strategies were delivered as an opt-in service, such that women were sent an invitation letter to self-order a screening kit (with 100% of women ordering the kit in our base-case analysis). In scenario analyses, we evaluated all 23 algorithm-pairs as a hybrid approach in which, for each algorithm-pair, 50% of women opted for HPV-SS and 50% of women opted for HPV-CC. We also considered an alternative algorithm that involved repeat HPV-CC for women identified positive by HPV-SS (Appendix D in Supporting Information).

We assumed equal diagnostic sensitivity and specificity of HPV-CC and HPV-SS in line with a recent meta-analysis[6] that found that the clinical sensitivity to detect CIN2+ was similar for HPV-CC and HPV-SS, with comparable specificity (0.98 relative specificity). In uncertainty analysis, we considered a lower relative specificity of 0.98 (Appendix B in Supporting Information).

Consistent with our previous model-based analyses evaluating optimal screening guidelines,[16,19,28] we assumed 100% screening coverage and follow-up compliance in our base-case analysis. In uncertainty analyses, we considered two scenarios reflecting imperfect

TABLE 1 Candidate screening algorithms considered in the analysis

Primary screening test	Age to start (stop) screening	Screening frequency	Implied number of lifetime screens	Birth cohorts considered
Cytology with a switch to HPV testing at age 34 y[a]	25 (69)	3-yearly cytology 5-yearly HPV testing	11 (3 + 8)	1985, 1991, 2000, 2008
HPV testing with no preceding cytology	25, 30, 35 (69)	5-, 7-, 10-yearly	4-9	2000, 2008
	25 (55), 30 (60)	15-yearly	3	
	25 (65)	20-yearly	3	
	25 (40), 30 (45), 35 (50), 30 (50), 40 (60)	Twice-only	2	
	30 (30), 35 (35), 40 (40)	Once-only	1	

Note: All strategies are considered for both self- and clinician-collection, resulting in 46 unique screening strategies.
Abbreviation: HPV, human papillomavirus.
[a]The 1985-cohort was assumed to switch at age 40 years (ie, their age in analysis Year 2025), while the other cohorts switched at age 34 years.

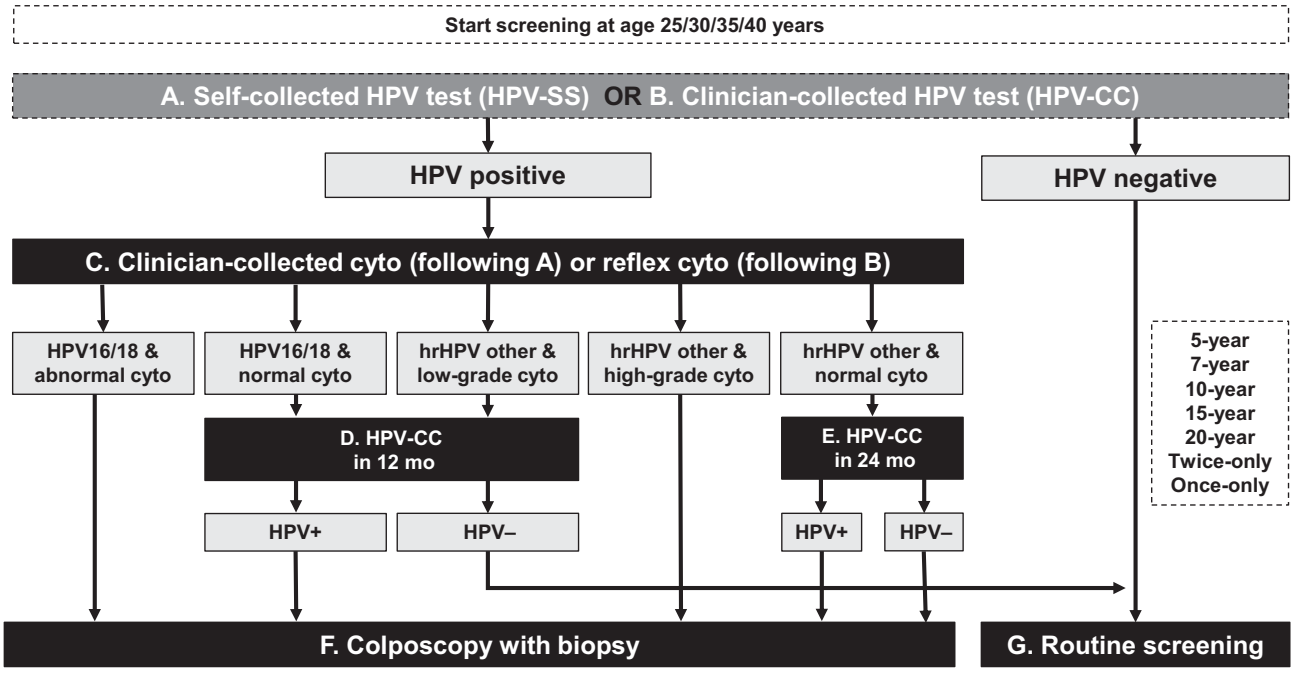

FIGURE 1 Screening algorithms considered in the analysis. We considered 23 pairs of strategies that involved HPV-SS (A) or HPV-CC (B). Women who are HPV positive are referred for clinician-collected cytology (following A) or have a reflex cytology performed (following B). Women receive further follow-up according to their HPV and cytology result. Stapled boxes indicated algorithm variables that varied in strategy. cyto, cytology; HPV-CC, clinician-collected HPV test; HPV-SS, self-collected HPV test; hrHPV other, high-risk HPV other than 16/18-infections; mo, months

screening behavior, using observed compliance rates in Norway[29] (Table 2). A previous study of longitudinal screening adherence in Norway identified 6% of screen-eligible women as never-screeners.[29] Subsequently, in Scenario 1, we assumed 94% of women complied with the recommended screening interval for the HPV-CC strategies, with the remainder of women assumed to never screen. We allowed screening coverage to be slightly higher for HPV-SS strategies (ie, 96%) as this approach has been found to increase participation among under-screened women in Norway.[9,10] We further assumed Norwegian-specific compliance rates of 72% to follow-up procedures, 83% to colposcopy and 97% to precancer treatment,[19] which were assumed equal for HPV-CC and HPV-SS strategies. In Scenario 2, we assumed 100% compliance with primary screening and imperfect compliance to follow-up procedures, colposcopy and treatment (using similar rates as Scenario 1).

2.4 | Costs and health-related quality of life

We included costs associated with screening and treatment procedures (personnel, materials, and laboratory analysis), as well as women's time and travel costs associated with these procedures. Unit costs were identified, quantified and valued for previous analyses,[19,20,28] and updated for this analysis to reflect 2020 values (Table 2 and Appendix A in Supporting Information). We varied cost assumptions in uncertainty analyses (details provided in Table 2). In line with Norwegian guidelines for economic evaluation,[30] we applied health state utility values for the general population from a recent Norwegian study, and reflected utility decrements associated with local, regional and distant cancer stages (Appendix C in Supporting Information). In uncertainty analyses, we did not assume utility decrements associated with health states (ie, we calculated the ICER using the additional cost per life year saved).

2.5 | Analysis

The duplication of strategies with replacement of HPV-CC with HPV-SS allowed pairwise comparison of costs and health benefits associated with HPV-CC vs HPV-SS across the different screening algorithm levers. For each algorithm-pair, we first calculated the percentage change in total costs that could be achieved by switching from HPV-CC to HPV-SS. We subsequently evaluated the cost-effectiveness of candidate screening strategies in two scenarios: (a) a restricted analysis that included only HPV-CC strategies; and (b) an expanded analysis that included consideration of both HPV-CC and HPV-SS strategies. Finally, we compared health benefits for the optimal strategies identified by each scenario.

3 | RESULTS

3.1 | Cohorts with low and intermediate vaccine protection

For the 1985- and 1991-cohorts, current Norwegian guidelines with HPV-CC were associated with a total lifetime cost of $850 and $940 per woman, respectively. Switching to HPV-SS reduced costs by 35% for the 1985-cohort and 38% for the 1991-cohort. Given our base-case assumptions of equal diagnostic accuracy and equal screening compliance between HPV-CC and HPV-SS, the pairwise

TABLE 2 Key assumptions in base case and uncertainty analyses

Variable	Description	Base case assumption	Assumption in uncertainty analysis
Costing assumptions[a]			
Clinician-collected HPV test (HPV-CC), excl. laboratory cost	Material, clinician consultation, time and travel cost	$214	$118 in scenario without time and travel costs
Self-collected HPV test (HPV-SS), excl. laboratory cost	Material, time and travel cost	$43	$22-65 in scenario with ±50% of base cost $7 in scenario without time and travel costs
Laboratory analysis HPV-CC	Reflects Norwegian fee schedules	$65	$30 in scenario using micro-costing assumptions
Laboratory analysis HPV-SS	Reflects Norwegian fee schedules	$65	$30 in scenario using micro-costing assumptions
Laboratory analysis cytology		$17	$34 in scenario using micro-costing assumptions
Compliance to screening and follow-up procedures		100% compliance to screening and follow-up procedures	Scenario 1 assuming: • For HPV-CC strategies: 6% of women never-screen, 94% comply with recommended interval • For HPV-SS strategies: 4% of women never-screen, 96% comply with recommended interval • 72% compliance to follow-up • 83% compliance to colposcopy • 97% compliance to treatment Scenario 2 assuming: • 100% compliance to screening • 72% compliance to follow-up • 83% compliance to colposcopy • 97% compliance to treatment
Diagnostic accuracy[b]		Equal diagnostic accuracy of SS and CC	Relative specificity of SS vs CC = 0.98
HPV-SS screening algorithm[c]	See Figure 1	HPV-SS replaces HPV-CC in current algorithm	Alternative algorithm requiring repeat HPV-CC for HPV-SS-positive women (Appendix D in Supporting Information)

Abbreviations: HPV, human papillomavirus; HPV-CC, clinician-collected HPV test; HPV-SS, self-collected HPV test.
[a]All costs were measured in 2020 Norwegian kroner (NOK) and converted to US dollars (USD) using the average annual 2020 exchange rate (USD1 = NOK9.4004). We assumed an equal cost of laboratory analysis for HPV-CC and HPV-SS of $65 per test. In addition to laboratory cost, the cost of HPV-SS included the cost of invitation letter to order a self-sample kit, the self-sample kit itself, postage to return the kit, women's time cost to take the self-sample and return the envelope (45 minutes) and the cost of informing the patient about her test result, resulting in a total cost per HPV-SS (for a woman who returns the self-sampling kit) of $43. The cost of HPV-SS will depend on logistics partner and information technology infrastructure; to reflect this uncertainty, we varied the cost of HPV-SS (excluding laboratory analysis) by ±50% in one-way uncertainty analysis. Additional information and sources are provided in Appendix A in Supporting Information.
[b]Additional information and sources are provided in Appendix B in Supporting Information.
[c]Additional information is provided in Appendix D in Supporting Information.

strategies provided equal health benefits. Consequently, and within a cost-effectiveness framework, HPV-SS would be preferred over HPV-CC for both the 1985- and 1991-cohorts given equal benefits and lower costs, that is, HPV-SS strongly dominated HPV-CC.

3.2 | Cohorts with high vaccine protection

Consistent with projections for the 1985- and 1991-cohorts, switching from HPV-CC to HPV-SS (across strategy pairs) reduced costs by 24% to 40% (24% for current guidelines) for the 2000-cohort and 25% to 42% (25% for current guidelines) for the 2008-cohort, with no impact on health benefits. Cost reductions associated with switching from HPV-CC to HPV-SS were generally higher with higher primary HPV testing frequency. When we first considered the cost-effectiveness of alternative HPV-CC strategies, the optimal strategy involved screening twice per lifetime (at ages 30 and 50 years; ICER = $52 330 per QALY) for the 2000-cohort (Figure 2, dashed line) and once per lifetime (at age 40 years; $23 930 per QALY) for the 2008-cohort. When we broadened the set of alternative strategies to also include HPV-SS strategies, none of the HPV-CC strategies were considered cost-efficient (ie, they were either strongly or weakly dominated), and the entire efficiency frontier shifted to the left, that is, less costly but equally beneficial strategies (Figure 2, solid line).

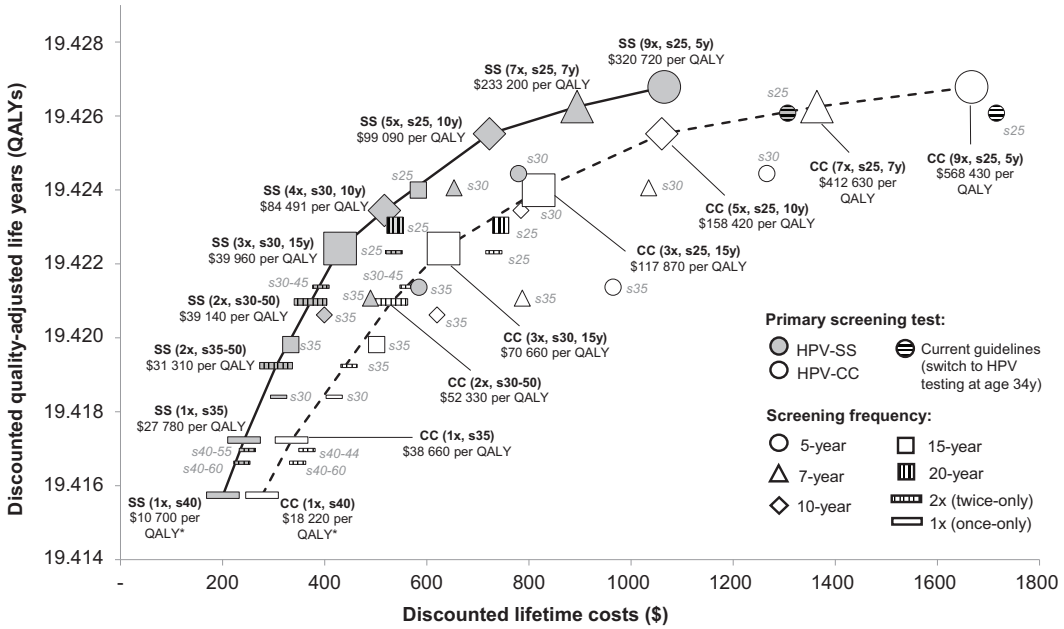

FIGURE 2 Cost-effectiveness plane for analysis reflecting women born in Year 2000. Solid line reflects cost-effectiveness frontier when considering both HPV-SS and HPV-CC strategies. Dashed line reflects cost-effectiveness frontier when considering HPV-CC strategies only. Strategies on either of the frontiers are highlighted with bolded labels and associated ICERs below the strategy label. *Compared to vaccination only. HPV, human papillomavirus; HPV-CC/CC, clinician-collected HPV test; HPV-SS/SS, self-collected HPV test; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; s, screening start age; x, number of lifetime screens; y, yearly (indicating screening frequency)

Importantly, the optimal, that is, cost-effective, strategy when considering HPV-SS involved one additional screening round for both birth cohorts, involving HPV-SS at ages 30, 45 and 60 years for the 2000-cohort ($39 960 per QALY) and HPV-SS at ages 35 and 50 years for the 2008-cohort ($48 360 per QALY).

The additional lifetime screen by considering HPV-SS for vaccinated women was associated with additional health benefits and lower costs compared with HPV-CC. For example, the cost-effective strategy for the 2000-cohort (ie, involving HPV-SS at ages 30, 45 and 60 years) was projected to reduce lifetime risk of cancer by 90.9% (uncertainty range: 89.7%-92.4%) compared with no intervention, which translates into an expected number of cancer cases of 74 (48-87) over the lifetime for a birth cohort of 30 000 women. These benefits were higher compared with what could be achieved under the optimal strategy when only considering HPV-CC (ie, HPV-CC at ages 30 and 50 years), which was expected to reduce lifetime risk of cancer by 87% (85.2%-89.4%), translating to 106 (70-129) cancer cases. Furthermore, HPV-SS at ages 30, 45 and 60 years was projected to cost $430 ($384-470) per woman, which was lower than the cost per woman for HPV-CC at ages 30 and 50 years of $530 ($495-561).

3.3 | Uncertainty analyses

Cost reductions were generally lower (compared to our base-case analysis) when assuming a lower specificity, or a higher cost of HPV-SS compared to HPV-CC, or when assuming no herd immunity from vaccination (Appendix Table F27 in Supporting Information). Cost reductions were generally higher in the remainder of uncertainty analyses, when assuming imperfect screening compliance or lower cost of HPV-SS, when including direct healthcare costs only or costs based on micro-costing approach, or when considering an alternative HPV-SS screening algorithm (Appendix Table F27 in Supporting Information). However, despite variation in costs, the cost-effectiveness results were generally robust across uncertainty analyses (Table 3 and Appendix Tables F1-F26 in Supporting Information). The only scenario in which HPV-CC strategies were not dominated was when we assumed imperfect screening compliance and when we evaluated an alternative screening algorithm that required a repeat HPV-CC for all HPV-SS-positive women prior to triaging. However, only one to three HPV-CC strategies were on the efficiency frontier (for both the 2000- and the 2008-cohorts) but would not be considered cost-effective as all ICERs exceeded current willingness-to-pay benchmarks in Norway (ie, greater than $300 000 per QALY) (Appendix Tables F5-F8 and F17 in Supporting Information).

Given a willingness-to-pay threshold of $55 000 per QALY, three lifetime screens for the 2000-cohort and two lifetime screens for the 2008-cohort remained cost-effective among most scenarios. For the 2000-cohort, HPV-SS with four lifetime screens was optimal when assuming imperfect compliance (Appendix Tables F5-F8 in Supporting Information). For the 2008-cohort, increasing the number of lifetime HPV-SS screens from two to three was optimal when assuming: (a) costs included direct healthcare costs only (Appendix Table F10 in Supporting Information); (b) laboratory costs of HPV and cytology

TABLE 3 Results from uncertainty analyses [Color table can be viewed at wileyonlinelibrary.com]

Analytic scenario	$40,000 per QALY gained (% cost-effective)	$55,000 per QALY gained (% cost-effective)	$90,000 per QALY gained (% cost-effective)
Women born in 2000			
Base-case assumptions	30, 45 and 60 (44%)	30, 45 and 60 (98%)	30, 40, 50 and 60 (48%)
Relative specificity of 0.98 (HPV-SS vs HPV-CC)	30 and 50 (30%)	30, 45 and 60 (98%)	30, 40, 50 and 60 (38%)
Imperfect coverage and follow-up compliance	30, 45 and 60 (48%)	30, 40, 50 and 60 (80%)	25, 35, 45, 55 and 65 (68%)
Imperfect follow-up compliance	30, 45 and 60 (48%)	30, 40, 50 and 60 (66%)	25, 35, 45, 55 and 65 (68%)
Costs restricted to direct healthcare costs	30, 45 and 60 (100%)	30, 45 and 60 (80%)	25, 35, 45, 55 and 65 (94%)
HPV and cytology cost based on micro-costing	30, 45 and 60 (84%)	30, 45 and 60 (76%)	25, 35, 45, 55 and 65 (58%)
Cost of HPV-SS 50% higher than base-case	35 and 50 (70%)	30, 45 and 60 (68%)	30, 45 and 60 (100%)
Cost of HPV-SS 50% lower than base-case	30, 45 and 60 (68%)	30, 45 and 60 (80%)	30, 40, 50 and 60 (80%)
Alternative HPV-SS screening algorithm	30, 45 and 60 (52%)	30, 45 and 60 (98%)	30, 40, 50 and 60 (60%)
No herd immunity benefit from the vaccine	30, 45 and 60 (90%)	30, 45 and 60 (100%)	30, 40, 50 and 60 (96%)
2vHPV provided 4vHPV cross-protection	30, 45 and 60 (44%)	30, 45 and 60 (98%)	30, 40, 50 and 60 (66%)
Women born in 2008			
Base-case assumptions	40 (98%)	35 and 50 (24%)	30, 45 and 60 (88%)
Relative specificity of 0.98 (HPV-SS vs HPV-CC)	40 (96%)	35 and 50 (42%)	30, 45 and 60 (92%)
Imperfect coverage and follow-up compliance	40 and 55 (90%)	35 and 50 (62%)	30, 40, 50 and 60 (98%)
Imperfect follow-up compliance	40 and 55 (90%)	35 and 50 (70%)	30, 40, 50 and 60 (98%)
Costs restricted to direct healthcare costs	30, 45 and 60 (54%)	30, 45 and 60 (74%)	30, 40, 50 and 60 (98%)
HPV and cytology cost based on micro-costing	40 and 55 (62%)	30, 45 and 60 (44%)	30, 40, 50 and 60 (80%)
Cost of HPV-SS 50% higher than base-case	40 (100%)	35 and 50 (42%)	30, 45 and 60 (96%)
Cost of HPV-SS 50% lower than base-case	40 (100%)	35, 50 and 65 (58%)	30, 40, 50 and 60 (56%)
Alternative HPV-SS screening algorithm	40 and 55 (40)	35, 50 and 65 (38%)	30, 45 and 60 (56%)
No herd immunity benefit from the vaccine	30, 45 and 60 (46%)	30, 45 and 60 (94%)	30, 40, 50 and 60 (68%)
2vHPV provided 4vHPV cross-protection	40 (98%)	30, 45 and 60 (98%)	30, 45 and 60 (48%)

Note: Color shading indicated number of lifetime screens associated with each strategy: orange = one, red = two, light green = three, dark green = four, dark blue = five. See Section 2 for details about each analytic scenario.
Abbreviations: 2v, bivalent; 4v, quadrivalent; HPV, human papillomavirus; HPV-CC, clinician-collected HPV test; HPV-SS, self-collected HPV test; QALY, quality-adjusted life year.

were based on the micro-costing approach rather than fee schedules (Appendix Table F12 in Supporting Information); (c) the cost of HPV-SS was 50% lower than in our base-case scenario (Appendix Table F16 in Supporting Information); (d) when we assumed the alternative screening algorithm for HPV-SS strategies (Appendix Table F18 in Supporting Information); (e) when we assumed the vaccine did not provide herd immunity effects (Appendix Table F20 in Supporting Information) and (f) when we assumed the 2vHPV provided similar levels of cross-protection as the 4vHPV (Appendix Table F22 in Supporting Information). If we assumed 50% of women would choose HPV-SS and 50% would choose HPV-CC, the optimal strategies involved screening at ages 30 and 50 years for the 2000-cohort, and at age 40 years for the 2008-cohort (Appendix Tables F25 and F26 in Supporting Information). Cost-effectiveness results for both birth cohorts generally remained consistent across parameter sets but depended on the willingness-to-pay threshold (Table 3). For example, for the 2000-cohort, HPV-SS at ages 30, 45 and 60 years was optimal across 98% of parameter sets for a threshold of $55 000 per QALY. If we assumed a maximum willingness-to-pay threshold of $90 000 per QALY, the optimal strategies involved HPV-SS four and three times per lifetime for the 2000- and 2008-cohorts, respectively.

4 | DISCUSSION

Our study shows that a switch from clinician-collected to self-collected primary cervical cancer screening may be cost-effective regardless of the extent of vaccine-induced HPV protection in the population. We found that HPV-SS might considerably reduce screening costs among cohorts of women with low, intermediate and high HPV protection. Importantly, screening with HPV-SS among cohorts with high HPV protection generally yielded more health benefits while simultaneously reducing the total cost per screened woman compared to HPV-CC. Specifically, for women with high HPV protection, cost-effective screening involved HPV-SS at ages 30, 45 and 60 years for the 2000-cohort (who received the 4vHPV at age 12 years) and HPV-SS at ages 35 and 50 years for the 2008-cohort (who received the bivalent HPV vaccine at age 12 years). The optimal strategy for the 2000-cohort includes one additional lifetime screen compared to the 2008-cohort, which can be explained in part due to: (a) the additional cross-protection provided by the quadrivalent vaccine compared to the bivalent vaccine, and (b) higher direct and indirect protection in the 2008-cohort (with adjacent vaccinated cohorts on either side). The optimal number of lifetime screens varied between one and four, depending on birth cohort (ie, the 2000- or

2008-cohort), analytic assumptions (eg, screening compliance, unit costs and diagnostic accuracy) and willingness-to-pay for additional health benefits.

Given our base-case assumptions of equal diagnostic accuracy, screening behavior and screening algorithm for HPV-SS and HPV-CC strategies, our analysis shows that cost savings of HPV-SS can be achieved with no loss in health benefits. Moreover, these results proved robust in uncertainty analyses with alternative base-case assumptions. First, our assumption of equal diagnostic accuracy is supported by a recent systematic review and meta-analysis,[6] although the relative specificity of HPV-SS compared to HPV-CC was 0.98 (95% confidence interval = 0.97-0.99). Assuming the lower relative specificity in uncertainty analysis had only minor impact on cost reductions associated with HPV-SS strategies. Furthermore, assuming the lower relative specificity had no impact on the rank order of strategies, which strategies were cost-efficient (ie, on the efficiency frontier), nor did it affect which strategies were optimal (ie, cost-effective according to the willingness-to-pay threshold). Second, the same meta-analysis[6] found that while opt-in HPV-SS did not improve participation rates compared to HPV-CC, opt-out approaches did not. When we assumed differential screening compliance between HPV-SS and HPV-CC (ie, higher screening coverage for HPV-SS strategies) in uncertainty analysis, one additional lifetime screen was optimal for the 2000-cohort, while results for the 2008-cohort did not change. Third, the pairwise screening algorithms of HPV-SS and HPV-CC strategies differed in that women positive by HPV-CC received reflex cytology while women positive by HPV-SS were assumed to require a clinician visit to have a cytology performed, since reflex cytology triage is not recommended for HPV-SS due to poor accuracy.[6,31] The performance of HPV-SS in clinical practice will depend on achieving high compliance with this follow-up procedure, which on average was 81% across studies identified in a systematic review.[6] In our imperfect compliance scenarios, we assumed that follow-up compliance to clinician-collected cytology was 72%, based on observed rates from the NCCSP; in which case HPV-CC strategies was still dominated by HPV-SS strategies (or had ICERs far exceeding current willingness-to-pay benchmarks). With the emergence of self-collected tests that allow reflex testing, HPV-SS strategies will become even more efficient compared with HPV-CC as the additional cost associated with the clinician visit can be avoided.

To our knowledge, this is the first study to evaluate HPV-SS strategies among women with high protection against HPV. Among the six studies[32-37] identified in a recent systematic review that evaluated a broader use of self-sampling,[12] most were set in low- and middle-income countries with screening only once or twice per lifetime, and none evaluated HPV-SS among vaccinated cohorts. Two studies that were set in a high-income setting[32,35] considered only a limited number of HPV-SS strategies and did not consider prolonged screening intervals. A more recent study, not included in the systematic review, also evaluated HPV-SS as a primary screening method for unvaccinated screen-eligible women,[38] yet only considered short-term outcomes from a limited number of strategies included in the randomized-controlled trial and did not use decision-analytic modeling to project longer-term outcomes required by many decision-makers. Although direct comparisons with other studies are not possible, our general findings are consistent: (a) HPV-SS is a cost-effective primary screening approach[12,38]; and (b) women in cohorts with high protection against HPV should be screened less frequently than women in cohorts with no (or lower) vaccine protection for screening to remain cost-effective.[16]

Our study has several limitations. First, the analysis is relevant primarily for high-income countries with organized screening and vaccination programs that have achieved similar program coverage to Norway. Second, we did not explore alternative triage strategies (eg, further genotype-specific management) as we aimed to initially explore whether HPV-SS could have a place in primary screening; however, choosing between candidate triage strategies is important to improve efficiency of the screening program[39] and should be the focus of future analyses. Third, our base-case scenario assumed perfect compliance, while our scenario analyses with imperfect compliance assumed that the same women would attend screening irrespective of screening method. However, average risk may differ; for example, a higher proportion of high-risk women may comply with HPV-SS than HPV-CC if HPV-SS strategies attract relatively more under-screened women. If that is the case, HPV-SS would be even more beneficial compared to HPV-CC. Since we do not have empirical data to support screening behavior under a primary HPV-SS scenario, we did not let behavioral assumptions impact the value of HPV-SS in our base-case scenario. Furthermore, the considerable cost savings provided by HPV-SS compared to HPV-CC could be redirected to maintain and improve screening participation. Fourth, we did not explore candidate strategies for the 1985- and 1991-cohorts; screening guidelines for these cohorts recently underwent revisions and further adaptations are currently unlikely. Finally, our analysis reflects Norwegian-specific vaccination policies, which do not currently include the nine-valent HPV vaccine. For countries with higher vaccine protection than the 2v/4vHPV, even less frequent screening (than suggested in this analysis) may be optimal, as suggested in previous analyses evaluating optimal screening in vaccinated women.[16,17]

There are several potential individual and system-level challenges, or barriers, to address prior to implementing HPV-SS as a primary screening method. On an individual-level, women may feel anxious by the increased responsibility of self-collection compared with clinician-collected sampling and may worry about not performing the test correctly.[7] If women worry about the adequacy of the test, they may have an additional clinician-collected test performed, which would lead to cost-inefficiencies. Prior to implementation, screening organizers will need to provide information to women about the new technology, as well as ensure that the provided tests are easy to perform. One approach to consider would be to give women the choice between HPV-SS and HPV-CC, as is the case in the Netherlands, where a randomized implementation of primary HPV-SS is ongoing.[40] When we assumed that half the screening population would choose HPV-SS, cost-effective screening involved one lifetime screen less than if all women would choose HPV-SS. On a system-level, there are several logistical aspects to consider, for example, whether HPV-SS should be offered as an opt-in (ie, women are invited to order an

HPV-SS) or opt-out (ie, women directly receive an HPV-SS in their mail) approach. In this analysis, we considered HPV-SS as an opt-in approach, which generally has not shown to improve participation rates since it requires women to self-order the screening test.[6] However, a Norwegian study found that opt-in HPV-SS increased coverage considerably compared to reminder letter.[10] Empirical studies have, furthermore, shown that an opt-out approach among under-screened women achieves greater compliance than an opt-in approach,[9,10] but is associated with higher costs and wastage for non-compliers. Norway is currently considering an opt-out approach for women who have not screened in the past 10 years, while an opt-in approach is being considered for women who did not screen during the past 8 or 9 years.[41] Consequently, development of the infrastructure required to offer HPV-SS is underway, offering opportunities for the expansion of the HPV-SS program to the entire target population. Another concern with HPV-SS has been potential harms related to removing office-based exams; however, a recent systematic review showed that there were no additional benefits of these exams other than cervical cancer screening.[42] In Norway, general practitioners are already at capacity and experiencing excess demand; thus, reducing the burden from cervical cancer screening would be beneficial. However, future studies need to evaluate physician acceptability for moving away from pelvic exams and the potential consequences related to loss of knowledge and skills in performing such exams. While there are barriers to implementing HPV-SS as a primary screening method, it may help overcome other barriers associated with the delivery of healthcare services; for example, HPV self-sampling (and home-based cancer screening in general) has been suggested as the way forward for cancer screening following the COVID-19 pandemic.[43,44]

Following implementation of HPV vaccination, women in screening target ages will have increasingly heterogeneous risk of developing cervical cancer, requiring adaptations to the screening program. As screening programs undergo this transitional era, less costly technologies such as HPV-SS provide opportunities to continue offering repeated screening rounds, while remaining a cost-effective prevention approach. Importantly, HPV-SS also has the potential to reduce costs associated with screening unvaccinated women. To support this process, future studies should continue to evaluate the diagnostic accuracy of HPV-SS within a primary screening setting and consider feasible ways of implementing HPV-SS within the healthcare sector to ensure acceptability among screen-eligible women.

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CONFLICT OF INTEREST

Ameli Trope is the leader of the Norwegian Cervical Cancer Screening Program. Ameli Trope, Bo T. Hansen, Emily A. Burger and Kine Pedersen were part of the recent task force, appointed by the Norwegian Directorate of Health, to evaluate HPV self-sampling as an intervention for under-screened women in Norway. All other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Supporting Information contained in the supplementary material of Portnoy et al.[20] provides details on microsimulation model inputs, calibration to epidemiologic data and calibration approach in line with good modeling practice. Access to the raw results data is available upon reasonable request.

ORCID

Kine Pedersen https://orcid.org/0000-0002-4923-0670
Allison Portnoy https://orcid.org/0000-0002-8467-1324
Bo T. Hansen https://orcid.org/0000-0003-2765-4488
Emily A. Burger https://orcid.org/0000-0002-6657-5849

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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