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Cost-effectiveness of primary human papillomavirus triage approaches among vaccinated women in Norway: A model-based analysis

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Abstract

As Norway considers revising triage approaches following their first adolescent cohort with human papillomavirus (HPV) vaccination entering the cervical cancer screening program, we analyzed the health impact and cost-effectiveness of alternative primary HPV triage approaches for women initiating cervical cancer screening in 2023. We used a multimodeling approach that captured HPV transmission and cervical carcinogenesis to evaluate the health benefits, harms and cost-effectiveness of alternative extended genotyping and age-based triage strategies under five-yearly primary HPV testing (including the status-quo screening strategy in Norway) for women born in 1998 (ie, age 25 in 2023). We examined 35 strategies that varied alternative groupings of high-risk HPV genotypes ("high-risk" genotypes; "medium-risk" genotypes or "intermediate-risk" genotypes), number and types of HPV included in each group, management of HPV-positive women to direct colposcopy or active surveillance, wait time for re-testing and age at which the HPV triage algorithm switched from less to more intensive strategies. Given the range of benchmarks for severity-specific cost-effectiveness thresholds in Norway, we found that the preferred strategy for vaccinated women aged 25 years in 2023 involved an age-based switch from a less to more intensive follow-up algorithm at age 30 or 35 years with HPV-16/18 genotypes in the "high-risk" group. The two potentially cost-effective strategies could reduce the number of colposcopies compared to current guidelines and simultaneously improve health benefits. Using age to guide primary HPV triage, paired with selective HPV genotype and follow-up time for re-testing, could improve both the cervical cancer program effectiveness and efficiency.

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

What's new?

With its first human papillomavirus (HPV)-vaccinated cohorts now reaching the cervical cancer screening age, Norway may design strategies to follow up women who test positive on primary HPV testing more efficiently. Here, the authors used a multimodeling approach to evaluate the health benefits, harms and cost-effectiveness of alternative extended genotyping and age-based triage strategies. Using age to guide triage ensures balancing resource use among vaccinated women, who face a lower risk of cervical cancer compared to unvaccinated women. Examining the choice of genotypes and follow-up time for re-testing for each level of triage could improve both program effectiveness and efficiency.

1 | INTRODUCTION

Age-specific cervical cancer screening guidelines, for example, primary cytology screening for younger women with a switch to primary human papillomavirus (HPV) screening for older women, have often been used to minimize unnecessary referrals for younger women who have a general higher HPV prevalence and are more likely to have a transient HPV infection. However, several countries are currently transitioning away from primary cytology-based cervical cancer screening toward uniformly recommending primary HPV screening for all target ages, for example, ages 25–69 years in Norway.[1,2] Simultaneously, girls vaccinated against HPV infections in their adolescence (facing a >70% reduction in their risk of cervical cancer) are now entering screen-eligible ages in many countries. These paradigm shifts necessitate consideration of new triage approaches to maintain both the harm-benefit tradeoffs and cost-effectiveness of screening. Previous research has demonstrated that the choice of triage strategy within a primary HPV-based program can have considerable impact.[3]

There are several opportunities to tailor triage strategies for HPV-positive results to limit screening harms by controlling unnecessary referrals (≤cervical intraepithelial neoplasia [CIN] 1) to colposcopy. New technologies that enable HPV genotype stratification can contribute to more efficient screening algorithms by differentiating triage based on the genotype's carcinogenicity, known as partial or extended genotyping. For example, HPV types 16 and 18 are associated with the highest risk of cervical cancer and, therefore, with partial genotyping, women who test HPV-16 or -18 positive may be referred directly to colposcopy, as in the United States.[4,5] In addition, age can be introduced into triage management to capture genotype- and age-specific interactions in risks of precancer and cancer. Age-specific triage algorithms may contribute to important efficiency gains by selectively intensifying triage as women age where additional genotypes contribute to a higher proportion of invasive cancers.

Following their first adolescent-vaccinated cohort entering screening in 2022, Norway is considering extended HPV genotyping and age-specific triage approaches. To our knowledge, although extended genotyping has been examined,[6–8] there are no cost-effectiveness analyses or harm–benefit evaluations that combine both age and multiple extended genotyping triage algorithms. Therefore, the aim of this study was to estimate the health impact, harms and cost-effectiveness of novel primary HPV triage approaches for a highly vaccinated cohort of women initiating screening in 2023.

2 | METHODS

2.1 | Model overview

To capture the impacts of alternative primary HPV triage strategies on long-term cervical cancer outcomes, we used a multimodeling approach involving linked outputs from an individual-based dynamic transmission model (Harvard-HPV)[9] and an individual-based model of HPV-induced cervical carcinogenesis (Harvard-CC) that tracks a hypothetical cohort of individual women through a series of monthly transitions over their lifetimes.[10] In a previous Norwegian analysis,[9] both models were adapted to reflect sexual behavior and the epidemiological burden of HPV and cervical cancer in Norway before 2009, the initial year of routine vaccination introduction.[11–13]

To inform levels of direct and indirect vaccine protection against HPV infections for the women aged 25 years in 2023 (ie, born in 1998) over their lifetime (the analytic cohort), we used the Norwegian-adapted Harvard-HPV model simulating multiple cohorts assuming observed historical vaccination coverage rates from 2009 to 2019 for girls in the routine and catch-up programs and from 2018 to 2019 for boys.[9] We assumed that the 2019 routine vaccination coverage rates in Norway (90% and 89% for girls and boys, respectively) applied to subsequent cohorts, including the 1998 birth cohort entering the screening program in 2023 examined in this analysis. We assumed the bivalent vaccine currently recommended in Norway provided a vaccine efficacy of 100% against HPV-16/18 infections and cross-protection of 93.8%, 79.1% and 82.6% against HPV types 31, 33 and 45, respectively, over the lifetime.[14] To achieve stochastic stability across the individuals in the Harvard-HPV model, the strategy modeling the current Norwegian vaccination program was simulated for a population size of 10 million individuals.

For Harvard-CC, the calibration process involved randomly drawing 2 million unique combinations of uncertain parameter inputs across natural history parameter inputs. From these parameter sets, we identified the 50 best-fitting natural history parameters sets that fit to the epidemiological outcomes from Norway, that is, calibration targets, as previously described.[11–13] Progression to cervical cancer

required an infection with a high-risk genotype (HPV-16, -18, -31, -33, -45, -52, -58 individually or pooled other high-risk genotypes). Cancer detection occurs at either the local, regional or distant stage through symptoms or screening.[10] Each screening strategy was simulated for a single simulation cohort of 10 million 25-year-old women eligible for primary HPV-based screening starting in year 2023. Additional details regarding model structure, inputs and calibration are provided in a previous publication.[9]

2.2 | Screening strategies

We compared 35 alternative triage strategies assuming routine screening of 5-yearly primary HPV testing, including a status-quo scenario for women born in 1998 (ie, age 25 in 2023). The analyzed strategies varied the triage management threshold by: (a) the number of HPV classification groups to be managed (two groups: "high-risk" and "medium-risk" groups, or three groups: "high-risk," "medium-risk" and "intermediate-risk" groups); (b) the number and genotypes of HPV included in each group; (c) the management of HPV-positive women to prompt direct colposcopy or active surveillance; (d) the wait time for re-testing (varied by HPV genotype risk group) and (e) the age at which the HPV triage algorithm switched from less to more intensive strategies (no switch age, age 30 or age 35; Table 1; Appendix S1). In the case of three classification groups, "medium-risk" HPV types refer to vaccine-preventable oncogenic types whereas "intermediate-risk" HPV types refer to non-vaccine-preventable oncogenic types. For the age-specific triage algorithms, all wait times and genotype groupings remained constant by age, except the expedited management of women in the "intermediate-risk" group. For younger women with an HPV genotype classified as "intermediate-risk," HPV genotype persistence was required to prompt colposcopy (no reflex cytology) in 36 months, while for older women with an HPV genotype classified as "intermediate-risk," reflex cytology was used immediately to guide colposcopy management in an expedited manner. The status-quo scenario was defined as the current Norwegian recommended screening strategy of 5-yearly primary HPV-based screening for women aged 25–69 years with no age-specific triage and specifying only two HPV genotype groups: "high-risk" and "medium-risk" (Appendix S2). A summary of how the triage algorithm varied is presented in Table 1 and a full list of analytic scenarios is presented in Appendix S3. All scenarios were conducted in the context of perfect screening adherence in line with recommendations from a recent analysis.[15]

2.3 | Cost-effectiveness analysis

For each of the 35 strategies considered, including the current Norwegian recommended screening strategy, we evaluated model outcomes including total lifetime cost per woman, lifetime number of colposcopies performed, total quality-adjusted life years (QALYs) per woman, lifetime risk of developing cervical cancer and number of cervical cancer cases and deaths projected for the number of estimated 25-year-old women in 2023 (35,702) according to the 2019 World Population Prospects.[16] These outcomes were aggregated to capture the discounted (4% annually)[17] costs and benefits of women entering the screening program in 2023 (over their lifetimes).

We used a limited societal perspective (ie, including women's time and travel costs associated with screening and treatment procedures but excluding productivity losses as recommended in Norway).[18] Costs were measured in 2020 Norwegian krone (NOK) and converted to US dollars (USD) using the average annual 2020 exchange rate (USD1 = NOK9.4004; Appendix S4).[19] In line with Norwegian

TABLE 1 Alternative assumptions for primary HPV triage algorithm.

Analytic lever varied	Variations assumed		
Number of genotype groups to be managed	2	3	
HPV genotypes in "high-risk" group	16/18 ("g2")	16/18/45 ("g3")	16/18/31/33/45/52/58 ("g7")
HPV genotypes in "medium-risk" group	31/33/52/58	31/33/45/52/58	31/33/35/39/45/51/52/56/58/59/66/68
Follow-up of "high-risk" genotype group following reflex cytology	Repeat HPV	Direct colposcopy	
Variations in wait time for re-testing of "high-risk" HPV genotype group and normal cytology (months)	12	18	
Variations in wait time for re-testing of "medium-risk" HPV genotype group and normal cytology (months)	12	24	36
Variations in wait time for re-testing of "intermediate-risk" HPV genotype group and normal cytology (months)	36	60	
Variations in age to switch triage algorithm	None	30	35

Note: All strategies assumed primary HPV-based testing beginning at age 25, except we included a strategy that assumed a switch from cytology to HPV-based testing at age 34 as the recommended screening strategy before 2023.

guidelines for economic evaluation,[17] 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.

For the cost-effectiveness analysis, we ranked the strategies from least to most costly to calculate the incremental cost-effectiveness ratio (ICER), defined as the additional cost of a particular strategy divided by the additional health benefits (ie, QALYs) compared to the next less-costly strategy. Strategies that were more costly and less effective ("strongly dominated"), or having higher ICERs than more effective strategies ("weakly dominated"), were removed from further consideration. According to Norwegian priority setting guidelines, the thresholds for a disease such as cervical cancer in Norway should be determined based on the severity of disease, recommended to be measured by the absolute shortfall in quality-adjusted life expectancy, that is, the average expected remaining QALYs for the general population at the mean age of treatment initiation.[20,21] The severity-based cost-effectiveness thresholds range from $30,000 per QALY gained as the minimum and $90,000 per QALY gained as the maximum in Norway. In addition to cost-effectiveness, we evaluated a second measure of efficiency, that is, the incremental harm–benefit ratio (IHBR), which expresses the amount of harms one has to "accept" for "gaining" one additional unit of benefit (eg, number of additional colposcopies per averted cancer case). Similar to calculating ICERs, we ranked the strategies by the number of colposcopy referrals to calculate the IHBR. Strongly and weakly dominated strategies were removed. Although empirical thresholds do not exist to identify the optimal strategy, we used the projected IHBR of the new adopted 2023 guidelines compared to the <2023 guidelines as a benchmark for the number of colposcopies that health authorities are willing to accept to prevent an additional cancer case.

2.4 | Sensitivity analysis

We conducted several sensitivity analyses regarding our analytic assumptions. First, we examined a scenario with imperfect adherence to reflect the current Norwegian screening program. We assumed that Norwegian women would comply with the recommended 5-yearly screening interval at a proportion of 50.8%, over-screen at a proportion of 28.2% (3-yearly), under-screen at a proportion of 15.0% (10- to 15-yearly) and never attend screening at a proportion of 6.0%.[9,12,22] Additionally, re-testing follow-up compliance (not including reflex testing) was assumed to be 72.3%, diagnostic verification with colposcopy/biopsy compliance was assumed to be 82.8% and precancer treatment compliance was assumed to be 97%. Second, we examined a scenario in which the cohort of women aged 25 years in 2023 was unvaccinated rather than vaccinated. Third, we conducted several alternative cost specifications: (a) doubling the costs of colposcopy; (b) halving the costs of colposcopy; (c) doubling all testing and treatment costs and (d) halving all testing and treatment costs (Appendix S4).

3 | RESULTS

3.1 | Cost-effectiveness of primary HPV triage strategies

The current 2023 screening guidelines, as well as screening guidelines before 2023, were dominated by other strategies providing greater benefits for less costs and, therefore, they do not appear along the efficiency frontier (Figure 1). Given benchmarks for severity-specific cost-effectiveness thresholds in Norway, we found that strategies that incorporate age-specific triaging would be considered optimal, with the preferred strategy depending on the exact "willingness-to-pay" threshold. At a threshold of $30,000–$65,000 per QALY gained, the preferred strategy involved direct colposcopy for high-risk HPV-positive tests for types 16/18 and extended wait times for "medium-risk" (24 months) and "intermediate-risk" (60 months) groups with a switch from the "less intensive" to the "more intensive" follow-up algorithm (Appendix S1) at age 35 (at $25,700 per QALY). At a threshold of $75,000–90,000 per QALY gained, the preferred strategy remained similar in management of positive tests but involved a switch to the "more intensive" follow-up algorithm earlier (at age 30 years rather than age 35 years). The two least costly and least beneficial strategies relied on triage approaches without age-specific triage and would not be considered cost-effective given a minimum "willingness-to-pay" threshold of $30,000 USD in Norway. In contrast, the mostly costly strategies (strategies on the right-hand side of the efficiency frontier) involved age-specific triage with shorter wait times for re-testing and/or a greater number of genotypes selected for the "high-risk" group, but yielded ICERs exceeding the maximum threshold in Norway ($90,000 per QALY gained).

3.2 | Health impact and resource trade-offs

For the seven strategies identified as cost-efficient (ie, strategies on the efficiency frontier in Figure 1) under perfect screening adherence assumptions, the health benefits (cases and deaths averted) varied less between the strategies compared to the implication in colposcopy referrals (Table 2). For example, the most intensive cost-efficient strategy (a30, g3, t3) averted 3% more cervical cancer cases compared to the least intensive cost-efficient strategy (repeat, g2, t2); however, the most intensive strategy would require over 50% more colposcopies to achieve those health gains. Furthermore, adding HPV-45 to the "high-risk" group increased colposcopies by 7% (holding other aspects of the algorithms constant, ie, switching at age 30 with wait time for re-testing requiring 12 months for the "high-risk" genotype group, 24 months for the "medium-risk" genotype group and 36 months for the "intermediate-risk" genotype group). In contrast, a younger triage switch age (from age 35 to 30 years) yielded a smaller impact on colposcopy referrals (holding other aspects of the algorithm constant). When examining age-specific triage algorithms, the two potentially cost-effective strategies could reduce the number of colposcopies by 0.7%–1.3% compared to current guidelines and simultaneously improve health benefits (Appendix S5).

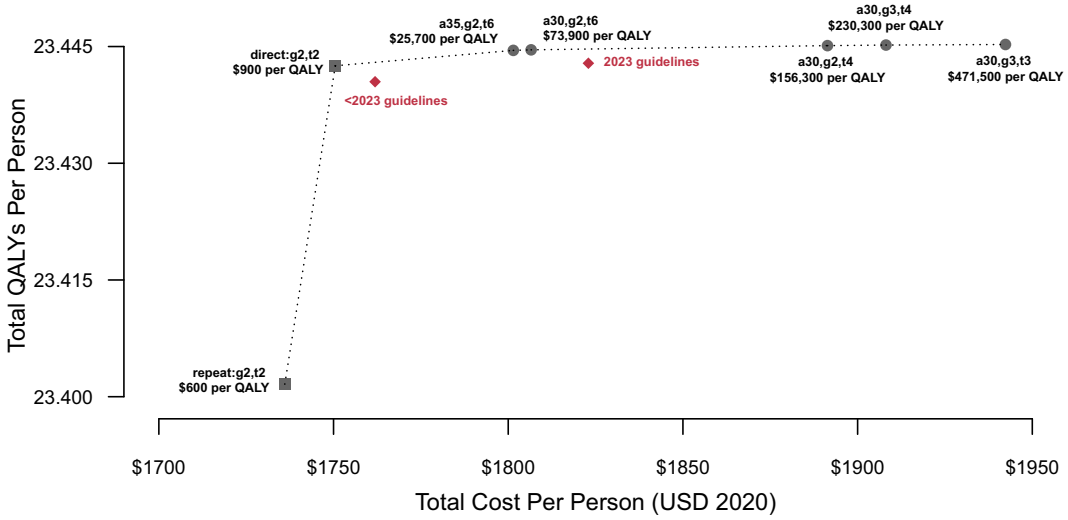

FIGURE 1 Cost-effectiveness results for alternative HPV triage strategies for women vaccinated against HPV infections in adolescence, assuming perfect screening adherence. Strategies along the efficiency frontier are the efficient strategies; all non-efficient strategies are excluded with the exception of <2023 screening guidelines and 2023 screening guidelines in red diamonds. All strategies assumed primary HPV-based testing beginning at age 25, except <2023 screening guidelines assumed a switch from cytology to HPV-based testing at age 34. The first strategy on the lefthand side of the frontier is compared to no intervention, that is, natural history, but no intervention is excluded from the graph. ICERs are rounded to the nearest hundred. All costs are discounted (4% annually) and expressed in 2020 USD (USD1 = NOK9.4004). Squares represent strategies in which there is no algorithm switch by age; dots represent strategies in which there is a switch from a less to more intensive triage algorithm and risk groups are differentiated into three groups of genotypes, as detailed in Appendix S1 (no reflex cytology in this strategy). a, age that women switch from less to more intensive primary HPV triage algorithm; direct, strategies in which HPV-positive results in the "high-risk" genotype group with normal or low-grade cytology are referred to direct colposcopy; g, number of genotypes included in "high-risk" genotype group; HPV, human papillomavirus; QALY, quality-adjusted life-years; repeat, strategies in which HPV-positive 16/18 genotypes with normal cytology and HPV-positive non-16/18 genotypes receive repeat HPV test; select, strategies with direct colposcopy for HPV- 16/18 and repeat HPV test for HPV-positive non-16/18 genotypes; t, wait time for re-testing if HPV-positive: (t1) 12 months for "high-risk" genotype group and 24 months for "medium-risk" genotype group, (t2) 18 months for "high-risk" genotype group and 36 months for "medium-risk" genotype group, (t3) 12 months for "high-risk" and "medium-risk" genotype groups and 36 months for "intermediate-risk" genotype group, (t4) 12 months for "high-risk" genotype group, 24 months for "medium-risk" genotype group and 36 months for "intermediate-risk" genotype group, (t5) 12 months for "high-risk" and "medium-risk" genotype groups and 60 months for "intermediate-risk" genotype group, (t6) 12 months for "high-risk" genotype group, 24 months for "medium-risk" genotype group and 60 months for "intermediate-risk" genotype group.

In our harm-benefit analysis, the number of colposcopy referrals required to avert one additional cervical cancer case increased with more intensive screening strategies (Figure 2). Importantly, the only strategies considered efficient (on the frontier) were those strategies that involved age-based triage (apart from the <2023 guidelines). The IHBRs ranged from 11 additional colposcopy referrals per cancer case averted to 2650 additional colposcopy referrals to avert one additional cancer case. Compared to an IHBR threshold of 266 additional colposcopies to avert one additional cancer case according to the recent change in Norwegian screening guidelines, the harm-benefit frontier identified the same two strategies considered potentially cost-effective, which could indicate that the same strategies would be considered optimal under harm–benefit considerations.

3.3 | Sensitivity analysis

Importantly, when we assumed imperfect screening adherence based on current adherence estimates in Norway, we found that strategies that incorporate age-specific triaging would no longer be considered cost-effective (Appendix S6). At a range of cost-effectiveness thresholds, the preferred strategies instead involved greater use of reflex cytology to manage triage of results to direct colposcopy to avoid repeat HPV testing (potential opportunities for loss to follow-up given imperfect adherence).

When we assumed that the cohort of women aged 25 years in 2023 was unvaccinated, we found that strategies that incorporate age-specific triaging remained optimal but often required a younger switch age or shorter wait times to account for the higher cancer risk among unvaccinated women (Appendix S7). For example, at a threshold of $30,000–$40,000 per QALY gained, the preferred strategy involved direct colposcopy for HPV-positive tests for types 16/18 and extended wait times for "medium-risk" (24 months) and "intermediate-risk" (60 months) groups with a switch to the "more intensive" follow-up algorithm at age 30 (at $33,000 per QALY). At a threshold of $90,000 per QALY gained, the preferred strategy involved direct colposcopy for HPV-positive tests for types 16/18 and extended wait times only for the "medium-risk" (24 months) group with a switch to the "more intensive" follow-up algorithm at age 30 (at $79,700 per QALY).

TABLE 2 Number of colposcopies performed and cervical cancer cases averted, deaths averted and cancer risk reduction over the lifetime of 25-year-old women screened in 2023 compared to no intervention in Norway, by strategy, assuming perfect screening adherence.

Strategy	Colposcopies performed	Cervical cancer cases averted	Cervical cancer deaths averted	Lifetime risk of cervical cancer	Reduction in lifetime risk of cervical cancer
<2023 guidelines	**11,945**	**1037**	**526**	**0.00203**	**92.5%**
repeat:g2,t2	13,584	1047	529	0.00178	93.5%
direct:g2,t2	14,189	1048	530	0.00174	93.6%
2023 guidelines	**16,197**	**1051**	**530**	**0.00167**	**93.9%**
a35,g2,t6	15,991	1072	542	0.00117	95.7%
a30,g2,t6	16,088	1073	542	0.00116	95.7%
a30,g2,t4	17,874	1077	544	0.00105	96.2%
a30,g3,t4	19,241	1078	544	0.00103	96.2%
a30,g3,t3	20,800	1078	545	0.00101	96.3%

Note: Strategies are defined in the legend of Figure 1. Only <2023 and 2023 screening guidelines (in bold) and efficient strategies are included (ie, strategies along the efficiency frontier). repeat = strategies in which HPV-positive 16/18 genotypes with normal cytology and HPV-positive non-16/18 genotypes repeat HPV test; direct = strategies in which HPV-positive results in the "high-risk" genotype group with normal or low-grade cytology sent to direct colposcopy; for all other strategies, there is a switch from a less to more intensive triage algorithm and risk groups are differentiated into three categories of genotypes, as detailed in Appendix S1 (no reflex cytology in this strategy). Strategies appear in order of increasing health benefits (identical to the order of increasing incremental cost-effectiveness ratios in Figure 1, with <2023 and 2023 screening guidelines added in bold). Strategies that fall within the range of cost-effectiveness thresholds in Norway ($30,000–$90,000) are shaded in gray. Reduction in lifetime risk of cervical cancer compared to the no-intervention (ie, natural history) scenario lifetime risk of 0.0272. For reference, unvaccinated women following current screening guidelines assuming perfect adherence face experience a lifetime risk of 0.0043. Colposcopies performed, cases averted and deaths averted estimated assuming the number of estimated 25-year-old women in 2023 (35,702) according to the 2019 World Population Prospects.[17]

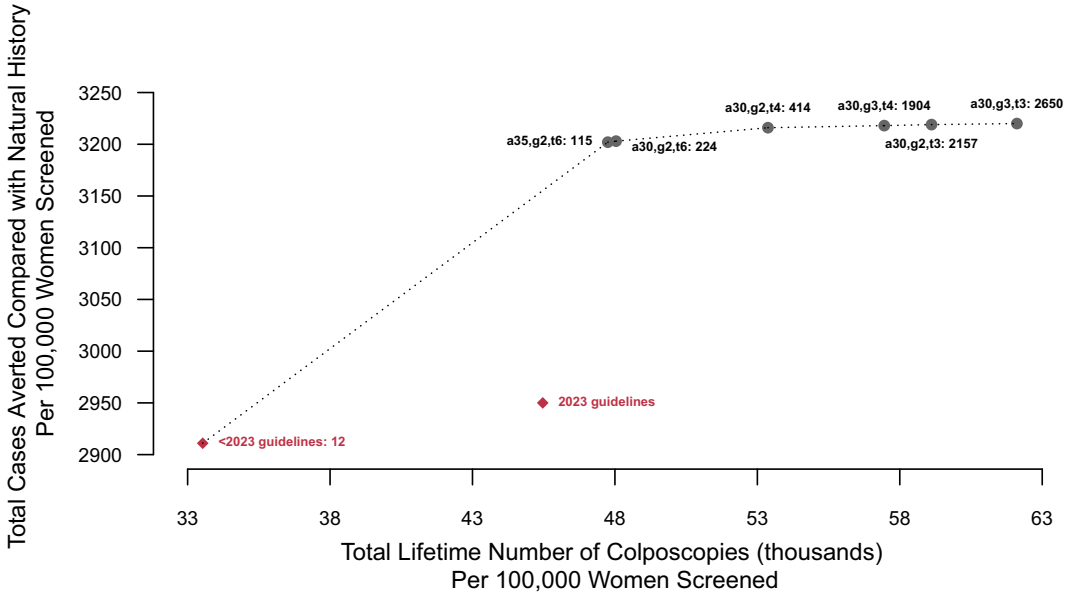

FIGURE 2 Harm–benefit frontier comparing total lifetime number of colposcopies and total cases averted per 100,000 women screened for alternative HPV triage strategies for women vaccinated against HPV infections in adolescence, assuming perfect screening adherence. Strategies are defined in the legend of Figure 1. Strategies along the frontier are the efficient strategies in terms of harms and benefits; all non-efficient strategies are excluded with the exception of 2023 screening guidelines. All strategies assumed primary HPV-based testing beginning at age 25, except <2023 screening guidelines assumed a switch from cytology to HPV-based testing at age 34. The first strategy on the lefthand side of the frontier is compared to no intervention, that is, natural history, but this strategy is excluded from the graph. Numeric values following the strategy name after each colon represent the number of lifetime colposcopies per cervical cancer case averted.

When examining variations in testing and treatment costs, whether colposcopy costs were halved or doubled or all costs were halved or doubled, we found that strategies that incorporate age-specific triaging would still be considered optimal (Appendices S8–S11). At a

threshold of $30,000–$55,000 per QALY, the preferred strategy remained the same strategy as in the base-case scenario, ie, direct colposcopy for HPV-positive tests for types 16/18 and extended wait times for "medium-risk" (24 months) and "intermediate-risk" (60 months) groups with a switch to the "more intensive" follow-up algorithm at age 35; however, ICERs were higher or lower depending on whether costs increased or decreased, respectively. When costs (either colposcopy alone or all testing/treatment costs) were halved, strategies involving shorter wait times for re-testing and/or a greater number of genotypes in the "high-risk" genotype group were still found to be cost-effective at thresholds less than the maximum cost-effectiveness threshold in Norway (ie, $90,000 per QALY).

4 | DISCUSSION

As cohorts of women who were vaccinated against HPV in adolescence are now age-eligible for cervical cancer screening, screening programs have begun to move away from age-based primary screening recommendations. However, age and careful selection of HPV genotype may continue to play a critical role in the management of HPV-positive women. In this model-based analysis, we identified two potential age-based and extended HPV genotype-specific triage algorithms that were preferred (ie, considered cost-effective) over the current recommended strategy in Norway. Similar to current guidelines, we found that HPV-16 and HPV-18, which have the greatest carcinogenic potential, should be referred directly to colposcopy. In contrast to current guidelines that only have two HPV genotype classification groups, we identified value in adding a third HPV genotype group to separately manage those genotypes classified as medium or intermediate risk. For these two risk groups, the optimal strategies involved reflex cytology ("medium-risk" or "intermediate-risk" group for older women) or identifying persistence ("intermediate-risk" group for younger women). Importantly, the health benefits across the alternative triage strategies yielded small net improvements, but we found that alternative age and extended genotyping could impact monetary costs and colposcopy referrals by up to 12% and 53%, respectively.

To our knowledge, our study is one of the first to explicitly quantify the efficient gains through age- and genotype-specific algorithms under uniform primary HPV testing for a vaccinated cohort. We identified two studies (the United States and Singapore) that found extended genotyping (three HPV groups) was likely to be considered cost-effective over partial genotyping; however, they did not consider the potential of age-specific algorithms alongside extended genotyping.[7,8]

Under the majority of our sensitivity analyses, including for a vaccine-naive cohort, we found that age-based triage remained preferred, except when we assumed imperfect screening adherence. Although imperfect screening adherence reflects the current screening program in Norway, program evaluations given imperfect adherence can lead to more intensive guideline recommendations, and subsequently more harms, for women who would have adhered according to any guideline.[15] In the imperfect adherence scenario, we found that strategies that incorporate age-specific triaging would no longer be considered optimal, but rather strategies that do not de-intensify the screening program for younger women compared to older women were prioritized. Consideration of age-specific triage or other changes to current screening guidelines must weigh the trade-off between designing guidelines for those who do not adhere to them and potential harms (ie, over-screening) for those who do.[15]

Most countries still rely on one or two HPV genotype groups to manage HPV-positive women. To our knowledge, Sweden is the only country to introduce an age-stratified and extended genotyping triage algorithm in the national screening program.[23] The HPV genotypes are divided into high oncogenic risk (HPV types 16, 18 and 45), middle oncogenic risk (31, 33, 52 and 58) and low oncogenic risk (35, 39, 51, 56, 59 and 68) groups. HPV-positive women's smear is then only analyzed between 23 and 32 years old if the HPV genotypes are positive for high-risk or middle-risk HPV types. All smears are analyzed in women older than 33 years of age. Triage algorithms are further differentiated based on HPV genotype and cytology result. This approach is similar to the optimal strategy found in our Norwegian-based analysis, which likewise involved three genotype risk groups and also involved a switch from less to more intensive triage at age 30 or 35 years of age.

There are several limitations to consider. First, we did not vary the primary screening frequency under the alternative triage strategies. During stakeholder meetings, it was clear that the primary screening frequency would remain unchanged during the implementation of a uniform primary HPV recommendation; however, future program evaluations should consider potential interactions between selecting the primary screening frequency and optimal triage algorithms. As primary screening frequencies are likely lengthened,[12,24,25] the wait time for re-testing within triage algorithms may be shortened to ensure the optimal risk-based management of positive women. We also did not explore combinations of genotype and follow-up length for the age-stratified algorithms. For example, we did not explore direct colposcopy for HPV-16- or HPV-18-positive younger women and direct colposcopy for HPV-16-, HPV-18 or HPV-45-positive older women. Our strategy choice set was informed through stakeholder meetings that did not involve these more complex alternatives. Future analyses can consider a wider range of HPV screening strategies, including the potential role of dual staining, methylation or self-sampling (when reflex cytology testing is not immediately available). Second, regional and other differences in underlying risks of HPV infection and cervical disease in Norway were not considered. Third, we analyzed a single cohort of 25-year-old women eligible for cervical cancer screening in 2023. However, as optimal strategies may differ for women without direct protection from vaccination, we analyzed women without direct protection from vaccination in sensitivity analysis as well as women eligible for both vaccination and screening in the base-case scenario.

As vaccinated cohorts enter screening age in Norway, we have the opportunity to design triage algorithms for primary HPV

screening more effectively and efficiently. Using age to guide triage seems to be an efficient approach, as it ensures balancing resources use among the cohorts of vaccinated women who face a low risk of cervical cancer compared to unvaccinated women. Transitioning away from primary cytology-based screening and examining the choice of genotypes and follow-up time for re-testing to include for each level of triage could improve both program effectiveness and efficiency.

AUTHOR CONTRIBUTIONS

Allison Portnoy: Conceptualized the study; Developed the methodology and conducted the formal analysis with support from Kine Pedersen, Stephen Sy and Emily A. Burger and drafted the original article with input from all authors. **Kine Pedersen:** Conceptualized the study. **Emily A. Burger:** Conceptualized the study. All authors reviewed and edited the article and approved the final article as submitted. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

All authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

Supporting information contained in Portnoy et al (2021) (https://doi.org/10.1016/j.ypmed.2020.106276) and Appendix S1 provides details on model inputs, calibration to epidemiological data and calibration approach in line with good modeling practice. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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