Screening for Cervical Cancer in Primary Care: A Draft Decision Analysis for the U.S. Preventive Services Task Force

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Structured Abstract

Importance: The US Preventive Services Task Force (USPSTF) is updating its 2018 cervical cancer screening recommendations.

Objective: To provide the USPSTF with updated model-based estimates of the benefits and harms of cervical cancer screening strategies that varied by five main attributes: (1) screening test (cytology, human papillomavirus (HPV) testing, and cytology and HPV cotesting), (2) age to start screening, (3) age to switch to primary HPV testing or cotesting if preceded by cytology, (4) rescreening interval (following a screen-negative result), and (5) age to stop screening.

Design: Comparative modeling using four microsimulation models that produce outcomes with and without cervical cancer screening in a hypothetical cohort of US 21-year-old female persons (all race) born in 2002 who begin the simulation prior to sexual initiation (e.g., age 9). Three separate base-case analyses were conducted to reflect HPV vaccination status: (1) not HPVvaccinated; (2) fully vaccinated with either the bivalent (2vHPV) or quadrivalent (4vHPV) vaccines, providing protection against HPV-16/18; and (3) fully vaccinated with the nonavalent (9vHPV) vaccine, providing protection against HPV-16/18/31/33/45/52/58. Analyses were repeated with a single model to evaluate strategies among female persons of Black race.

Exposures: Age to start screening was evaluated at ages 21 (cytology only), 25, 30, 35 and 40 years. Age to switch from cytology to HPV testing or cotesting was evaluated at ages 25 or 30 years. The rescreening interval was evaluated at every 3 years (cytology only), 5 years or 10 years (HPV and cotesting). Age to stop screening was evaluated at 60, 65, or 70 years. Full adherence to screening initiation, rescreening interval, and follow-up for both diagnostic and precancer treatment referrals was assumed. Scenario analyses included imperfect screening and follow-up adherence, alternative triage management, and the health impacts of a one-time screen at ages 35, 45, 55, and 65 years with HPV self-collection among previously unscreened female persons.

Main Outcome and Measures: Estimated lifetime benefits (life-years gained [LYG], cervical cancer cases and deaths), harms (number of screening tests, colposcopy referrals, false-positive screens), and detected CIN2 or worse for a cohort of 1,000 21-year-old female persons. Efficiency ratios were calculated to measure the harm-benefit tradeoff of screening strategies; we selected strategies that were efficient or near-efficient on both metrics of colposcopies per LYG and total tests per LYG. We repeated the efficiency analysis for each of the three separate basecase cohorts and used efficiency ratios associated with current US guidelines-based cervical cancer screening strategies in the unvaccinated population as indicative benchmarks for identifying potentially efficient strategies in the vaccinated populations.

Results: In the unvaccinated (all race) population, three US guidelines-based strategies involving HPV testing and cotesting were on the efficiency frontier for most models, while the guidelinesbased strategy of 3-year cytology alone from ages 21 to 65 years was not efficient for any model. Several cotesting scenarios were also on the efficiency frontier but were on the upper, flat (less efficient) part of the frontier. Other efficient strategies involved mostly 5-year HPV testing starting at ages 25 or 30 years with a later end age of 70 years.

In the vaccinated cohorts, the models estimated that equal or greater levels of health benefit can be achieved at similar levels of efficiency with less intensive screening. In 2vHPV/4vHPV vaccinated cohorts, strategies of 5-year or 10-year HPV testing starting at age 30 to 40 years were efficient and had ratios that were comparable to current guidelines-based strategies in the unvaccinated population. In 9vHPV vaccinated cohorts, strategies identified as efficient according to the current guidelines-based benchmarks almost universally involved 10-year HPV testing with start ages of 30 to 40 years (and variable end ages).

The analysis of Black female persons using a single model estimated lower absolute benefits and harms associated with screening, compared to female persons of all races; however, strategies identified as efficient under assumptions of perfect screening adherence were nearly identical for both populations and by vaccination status. Assuming imperfect screening and follow-up adherence resulted in reduced health benefits, as well as harms, in each of the three cohorts by vaccination status. Under imperfect adherence, the gap in health benefits between female persons of Black race and female persons of all races widened, although the disproportionate impact of imperfect adherence by race was somewhat attenuated by HPV vaccination.

The base-case findings were generally stable when we assumed HPV-16/18 triaging and when HPV test sensitivity was varied. When the models were used to explore HPV self-collection for single lifetime screening of previously unscreened female persons, screening benefit was estimated to be generally greater when the screen occurred at younger ages (ages 35, 45 years) and when adherence was higher.

Limitations: Simulations assumed perfect screening adherence and fully unvaccinated or vaccinated cohorts with no herd immunity benefits. Alternative strategies or criteria to determine when to stop screening were not explored.

Conclusions: This collaborative modeling analysis suggests that routine cervical cancer screening is effective in reducing cervical cancer cases and deaths and improving life expectancy, even in fully HPV-vaccinated populations. Primary HPV-based testing strategies were found to be efficient irrespective of vaccination status. For the HPV-vaccinated populations, the models estimated that equal or greater levels of health benefit can be achieved efficiently with less intensive screening.

Table of Contents

Figures

- 1. Model Schematic
- 2. Prevalence of HPV by Age and Type
- 3. Type Distribution of HPV in CIN1, CIN2, and CIN3
- 4. Type Distribution of HPV in Cancer
- 5. Cervical Cancer Incidence per 100,000, by Age and Model (Natural History)
- 6. Cervical Cancer Incidence and Mortality by Age (With Screening)
- 7. Model-Estimated Outcomes Compared Against Independent Empirical Studies
- 8. Flow Diagrams for Management of Screen-Positive Results
- 9. Colposcopies per Life-Year Gained for All Strategies Among Unvaccinated Female Persons by Model
- 10. Tests per Life-Year Gained for All Strategies Among Unvaccinated Female Persons by Model
- 11. Colposcopies per Life-Year Gained for All Strategies Among 2vHPV or 4vHPV Vaccinated Female Persons by Model
- 12. Tests per Life-Year Gained for All Strategies Among 2vHPV or 4vHPV Vaccinated Female Persons by Model
- 13. Colposcopies per Life-Year Gained for All Strategies Among 9vHPV Vaccinated Female Persons by Model
- 14. Tests per Life-Year Gained for All Strategies Among 9vHPV Vaccinated Female Persons by Model
- 15. Colposcopies per Life-Year Gained for All Strategies Among Unvaccinated Black Female Persons in the Harvard Model
- 16. Tests per Life-Year Gained for All Strategies Among Unvaccinated Black Female Persons in the Harvard Model
- 17. Colposcopies per Life-Year Gained for All Strategies Among 2vHPV or 4vHPV Vaccinated Black Female Persons in the Harvard Model
- 18. Tests per Life-Year Gained for All Strategies Among 2vHPV or 4vHPV Vaccinated Black Female Persons in the Harvard Model
- 19. Colposcopies per Life-Year Gained for All Strategies Among 9vHPV Vaccinated Black Female Persons in the Harvard Model
- 20. Tests per Life-Year Gained for All Strategies Among 9vHPV Vaccinated Black Female Persons in the Harvard Model
- 21. Colposcopies per Life-Year Gained for All Strategies Among Unvaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model
- 22. Tests per Life-Year Gained for All Strategies Among Unvaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model
- 23. Colposcopies per Life-Year Gained for All Strategies Among 2vHPV or 4vHPV Vaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model
- 24. Tests per Life-Year Gained for All Strategies Among 2vHPV or 4vHPV Vaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model
- 25. Colposcopies per Life-Year Gained for All Strategies Among 9vHPV Vaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model
- 26. Tests per Life-Year Gained for All Strategies Among 9vHPV Vaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model
- 27. Colposcopies per Life-Year Gained for All Strategies Among Unvaccinated Black Female Persons Assuming Imperfect Screening and Follow-up Adherence in the Harvard Model
- 28. Tests per Life-Year Gained for All Strategies Among Unvaccinated Black Female Persons Assuming Imperfect Screening and Follow-up Adherence in the Harvard Model
- 29. Colposcopies per Life-Year Gained for All Strategies Among 2vHPV or 4vHPV Vaccinated Black Female Persons Assuming Imperfect Screening and Follow-up Adherence in the Harvard Model
- 30. Tests per Life-Year Gained for All Strategies Among 2vHPV or 4vHPV Vaccinated Black Female Persons Assuming Imperfect Screening and Follow-up Adherence in the Harvard Model
- 31. Colposcopies per Life-Year Gained for All Strategies Among 9vHPV Vaccinated Black Female Persons Assuming Imperfect Screening and Follow-up Adherence in the Harvard **Model**
- 32. Tests per Life-Year Gained for All Strategies Among 9vHPV Vaccinated Black Female Persons Assuming Imperfect Screening and Follow-up Adherence in the Harvard Model
- 33. Cervical Cancer Cases Averted from a Single Lifetime Screen with HPV Self-Collection Among Unvaccinated Female Persons by Screen Age and Follow-Up Adherence by Model
- 34. Cervical Cancer Cases Averted from a Single Lifetime Screen with HPV Self-Collection Among Unvaccinated Black Female Persons by Screen Age and Follow-Up Adherence in the Harvard Model

Tables

- 1. Key Model Attribute Comparisons
- 2. Screening Strategies Modeled for Validation Exercise
- 3. Base Case Screening Strategies
- 4. Screening Test Characteristics
- 5. Current Screening Practice by Race
- 6. Lifetime Number of Cervical Cancer Cases, Deaths and Life-Years Gained Among Unvaccinated Female Persons for Screening Strategies by Model
- 7. Lifetime Number of Total Tests and Colposcopies Among Unvaccinated Female Persons for Screening Strategies by Model
- 8. Lifetime Number of CIN2+ Detected and False Positives Among Unvaccinated Female Persons for Screening Strategies by Model
- 9. Lifetime Number of Cervical Cancer Cases, Deaths and Life-Years Gained Among 2vHPV or 4vHPV Vaccinated Female Persons for Screening Strategies by Model
- 10. Lifetime Number of Total Tests and Colposcopies Among 2vHPV or 4vHPV Vaccinated Female Persons for Screening Strategies by Model
- 11. Lifetime Number of CIN2+ Detected and False Positives Among 2vHPV or 4vHPV Vaccinated Female Persons for Screening Strategies by Model
- 12. Lifetime Number of Cervical Cancer Cases, Deaths and Life-Years Gained Among 9vHPV Vaccinated Female Persons for Screening Strategies by Model
- 13. Lifetime Number of Total Tests and Colposcopies Among 9vHPV Vaccinated Female Persons for Screening Strategies by Model
- 14. Lifetime Number of CIN2+ Detected and False Positives Among 9vHPV Vaccinated Female Persons for Screening Strategies by Model
- 15. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among Unvaccinated Female Persons by Model
- 16. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 2vHPV or 4vHPV Vaccinated Female Persons by Model
- 17. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 9vHPV Vaccinated Female Persons by Model
- 18. Lifetime Outcomes Among Unvaccinated Black Female Persons for Screening Strategies in the Harvard Model
- 19. Lifetime Outcomes Among 2vHPV or 4vHPV Vaccinated Black Female Persons for Screening Strategies in the Harvard Model
- 20. Lifetime Outcomes Among 9vHPV Vaccinated Black Female Persons for Screening Strategies in the Harvard Model
- 21. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among Unvaccinated Black Female Persons in the Harvard Model
- 22. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 2vHPV or 4vHPV Vaccinated Black Female Persons in the Harvard Model
- 23. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 9vHPV Vaccinated Black Female Persons in the Harvard Model
- 24. Lifetime Number of Cervical Cancer Cases, Deaths and Life-Years Gained Among Unvaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model
- 25. Lifetime Number of Total Tests and Colposcopies Among Unvaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model
- 26. Lifetime Number of CIN2+ Detected and False Positives Among Unvaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model
- 27. Lifetime Number of Cervical Cancer Cases, Deaths and Life-Years Gained Among 2vHPV or 4vHPV Vaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model
- 28. Lifetime Number of Total Tests and Colposcopies Among 2vHPV or 4vHPV Vaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model
- 29. Lifetime Number of CIN2+ Detected and False Positives Among 2vHPV or 4vHPV Vaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by **Model**
- 30. Lifetime Number of Cervical Cancer Cases, Deaths and Life-Years Gained Among 9vHPV Vaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model
- 31. Lifetime Number of Total Tests and Colposcopies Among 9vHPV Vaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model
- 32. Lifetime Number of CIN2+ Detected and False Positives Among 9vHPV Vaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model
- 33. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among Unvaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model
- 34. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 2vHPV or 4vHPV Vaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by **Model**
- 35. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 9vHPV Vaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model
- 36. Lifetime Outcomes Among Unvaccinated Black Female Persons Assuming Imperfect Screening and Follow-up Adherence in the Harvard Model
- 37. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among Unvaccinated Black Female Persons Assuming Imperfect Screening and Follow-up Adherence in the Harvard Model
- 38. Lifetime Outcomes Among 2vHPV or 4vHPV Vaccinated Black Female Persons Assuming Imperfect Screening and Follow-up Adherence in the Harvard Model
- 39. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 2vHPV or 4vHPV Vaccinated Black Female Persons Assuming Imperfect Screening and Follow-up Adherence in the Harvard Model
- 40. Lifetime Outcomes Among 9vHPV Vaccinated Black Female Persons Assuming Imperfect Screening and Follow-up Adherence in the Harvard Model
- 41. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 9vHPV Vaccinated Black Female Persons Assuming Imperfect Screening and Follow-up Adherence in the Harvard Model

Appendix Figures

- 1. HPV Vaccine Completion (2 or More Doses) Among Female Persons Aged 15 Years, by Year of Report, Birth Cohort and Current Age
- 2. Share of HPV Vaccine Doses Among Female Persons Aged 15 Years, by Year of Report, Birth Cohort and Current Age
- 3. Flow Diagrams for Management of Screen-Positive Results: HPV-16/18 Genotype Triage

Appendix Tables

- 1. Model Input Values
- 2. Lifetime Number of Cervical Cancer Cases, Deaths and Life-Years Gained Among Unvaccinated Female Persons Assuming HPV-16/18 Genotype Triage of HPV-Positive Results by Model
- 3. Lifetime Number of Total Tests and Colposcopies Among Unvaccinated Female Persons Assuming HPV-16/18 Genotype Triage of HPV-Positive Results by Model
- 4. Lifetime Number of CIN2+ Detected and False Positives Among Unvaccinated Female Persons Assuming HPV-16/18 Genotype Triage of HPV-Positive Results by Model
- 5. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among Unvaccinated Female Persons Assuming HPV-16/18 Genotype Triage of HPV-Positive Results by Model
- 6. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among Unvaccinated Female Persons Assuming Lower-Bound Relative Test Sensitivity for HPV Testing by Model
- 7. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 2vHPV or 4vHPV Vaccinated Female Persons Assuming Lower-Bound Relative Test Sensitivity for HPV Testing by Model
- 8. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 9vHPV Vaccinated Female Persons Assuming Lower-Bound Relative Test Sensitivity for HPV Testing by Model
- 9. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among Unvaccinated Female Persons Assuming Upper-Bound Relative Test Sensitivity for HPV Testing by Model
- 10. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 2vHPV or 4vHPV Vaccinated Female Persons Assuming Upper-Bound Relative Test Sensitivity for HPV Testing by Model
- 11. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 9vHPV Vaccinated Female Persons Assuming Upper-Bound Relative Test Sensitivity for HPV Testing by Model

Chapter 1. Introduction

Roughly 13,960 female persons^{*} are expected to develop and 4,310 female persons are expected to die from cervical cancer in the United States in 2023 , despite over 60 years of widespread screening with Papanicolaou (Pap) cytology testing, and more recently testing for human papillomavirus (HPV), the causative agent of cervical cancer. Regular reviews of the most recent data, using the best available analytic tools, provide evidence on which to base screening recommendations. Described here is a decision analysis using the Cancer Intervention and Surveillance Modeling Network (CISNET) cervical cancer models to accompany a systematic evidence review describing current gaps in the expected benefits and harms of cervical cancer screening strategies in primary care.² The key questions for the decision analysis center around the long-term health benefits and harms of various cervical cancer screening strategies after multiple rounds of screening. For the first time, this analysis includes consideration of HPV vaccination and its impact on cervical cancer screening outcomes and efficiency.

Progress to reduce cervical cancer incidence has been uneven by race. For example, the Surveillance, Epidemiology, and End Results Program (SEER) cancer registry shows that Hispanic, non-Hispanic Black, and American Indian/Alaskan Native populations have consistently higher annual age-adjusted incidence and mortality from cervical cancer than non-Hispanic White populations.³ For Black female persons, cervical cancer incidence in 2020 was 10% higher, and mortality was 40% higher, than the US average. Reasons for these differences are multifactorial but are fundamentally related to historic and contemporary discrimination. Among the measurable impacts of this discrimination is differences in access to cervical cancer screening and appropriate follow-up from abnormal findings.⁴

Evidence of the short-term risks of cervical precancerous lesions associated with HPV alongside the development of new technologies to improve detection of precancer and cancer have motivated updated screening recommendations. In 2012, for the first time, cervical cancer screening recommendations were consistent across several major guidelines-making organizations, including the US Preventive Services Task Force (USPSTF), which recommended routine cytology screening every 3 years starting at age 21, with an option to switch to cytology and HPV "cotesting" every 5 years starting at age 30 and ending at age 65, for those with adequate screening history and not at high risk.⁵⁻⁷ In 2018, with newer evidence on – and FDA approval of – primary HPV testing among female persons ages 25 years and older, the USPSTF updated their recommendations to add an option after cytology screening every 3 years starting at age 21, to switch to primary HPV testing every 5 years between ages 30 and $65.^8$ The American Cancer Society (ACS) issued updated recommendations in 2020, with a recommendation to initiate screening at age 25 years with a preferred option for 5-year primary HPV testing without preceding cytology screening.⁹ Though the recommendations between the two guidelines-making organizations vary some, both reflect an important shift towards primary HPV testing.

^{*} Throughout this report, we use the term "female persons" to refer to individuals with a cervix, regardless of gender identity (consistent with Caughey AB, Krist AH, Wolff TA, et al. USPSTF Approach to Addressing Sex and Gender When Making Recommendations for Clinical Preventive Services. *JAMA* 2021;326(19):1953-1961).

The availability and uptake of HPV vaccination has further changed the cervical cancer landscape, as a growing number of female persons who were vaccinated starting in year 2006 – and therefore face lower cervical cancer risks – are now age-eligible for screening.¹⁰ According to NIS-TEEN,¹¹ HPV vaccine completion of at least two doses among 15-year-old female persons of all races in year 2013 (i.e., those born in year 1998 and currently age 25 years) was nearly 50% (**Appendix Figure 1**); in 2017, HPV vaccine completion at age 15 years (i.e., those born in 2002 and currently age 21 years) was 58.9% for all-race and 52.8% for Black-race female persons. In 2021, HPV vaccine completion among 15-year-olds increased to 73.0% for all and Black female persons. Additionally, the share of doses that are 9vHPV (nonavalent) compared to 4vHPV (quadrivalent) or unknown has increased over time, suggesting a higher level of protection against cervical disease among rising birth cohorts (**Appendix Figure 2**).¹¹ For example, in 2015, the share of HPV vaccine doses that were 9vHPV was 5.7% among allrace and 2.6% among Black-race 15-year-old female persons (i.e., birth year 2000, current age 23 years), but by year 2017, the share of 9vHPV vaccine doses increased to 38.9% for all-race and 34.9% for Black-race 15-year-old female persons. In year 2021, the share of 9vHPV vaccine doses was 85.1% for all-race and 79.6% for Black-race 15-year-old female persons.¹¹

Empirical evidence typically reflects only intermediate endpoints, usually over a limited number of screening rounds, as the prolonged natural history of HPV to cervical cancer is generally beyond the scope of randomized clinical trials and observational studies. Decision analyses using mathematical models that simulate the natural history of disease and extrapolate outcomes to project long-term benefits and harms with repeated screening have been recently used to accompany evidence reviews in USPSTF cancer screening recommendations.¹²⁻¹⁵ Importantly, these models can explore what-if scenarios and the impact of alternative assumptions on the harm-benefit trade-off of screening. The model-based decision analyses that accompanied the 2018 USPSTF cervical cancer screening recommendations found that strategies involving 3 yearly cytology screening with a subsequent switch to 5-yearly primary HPV-based screening were equally or more effective and efficient than 3-yearly cytology, with or without a switch to 5-yearly cotesting.¹⁵ The 2020 ACS recommendations for cervical cancer screening also included modeling results as part of the evidence to shift towards primary HPV-based screening in the United States.⁹

This decision analysis using the CISNET cervical cancer models accompanies the systematic review² and addresses the following Key Questions:

- 1. How does the effectiveness of cervical cancer screening strategies in reducing cervical cancer incidence and mortality vary by (1) test, (2) age to start screening, (3) age to switch to HPV primary or cotesting, if preceded by cytology, (4) rescreening interval (following a negative result), and (5) age to end screening?
- 2. How do the harms of different cervical cancer screening strategies in reducing cervical cancer incidence and mortality vary by (1) test, (2) age to start screening, (3) age to switch to HPV primary or cotesting, if preceded by cytology, (4) rescreening interval (following a negative result), and (5) age to end screening?
- 3. Which cervical cancer screening strategies are considered efficient in terms of the additional number of (1) colposcopies required per additional life-year gained, and (2) tests required per life-year gained?

Unlike the 2018 modeling report, three separate base-case analyses were conducted to reflect female persons who are expected to face differential levels of baseline cervical cancer risk depending on HPV vaccination status: (1) not HPV-vaccinated; (2) fully vaccinated with bivalent (2vHPV) or quadrivalent (4vHPV) vaccines, providing protection against HPV-16/18; and (3) fully vaccinated with the nonavalent (9vHPV) vaccine, providing protection against HPV-16/18/31/33/45/52/58.

Each of the Key Questions was reassessed using a model that reflects Black US female persons, as well as imperfect screening and follow-up adherence, to examine the impact of screening on cervical cancer disparities in the context of real-world practice. In addition, we conducted sensitivity analyses to explore the impact of alternative triage management, variation in HPV test performance, and opportunities for HPV self-collection.

Chapter 2. Methods

Overview of Models

Four decision models from the Harvard T.H. Chan School of Public Health (Harvard), Erasmus Medical Center (MISCAN-Cervix) from The Netherlands, University of Sydney/Daffodil Centre (Policy1-Cervix) from Australia, and University of Minnesota (UMN) were used for comparative modeling to address the key questions. The four modeling teams are part of the CISNET Cervical Working Group, and the Harvard and UMN teams have led the decision analysis for previous USPSTF recommendations.5,8 Descriptions of the decision models in terms of model attributes, natural history, vaccination, and screening strategies are provided below; key similarities and differences between the models are summarized in **Table 1**. The Harvard and Policy1-Cervix models were programmed in C++, MISCAN-Cervix in Python, and UMN in Java.

Natural History Component

Overview

The four CISNET individual-based models describe the natural history of cervical cancer in an unscreened and unvaccinated population, based on the reasonably well-understood natural history pathway of HPV infection to cervical cancer. Three of the models reflect all cervical cancers, while the Harvard model reflects the natural history of squamous cell carcinomas (SCC), which accounts for over 70% of cervical cancers.¹⁶ For all models, simulated female persons enter the model at an early age (e.g., age 9 years), in a disease-free health state and are followed over their lifetimes. Each female person undergoes transitions between health states that describe underlying true health, including HPV infection (by genotype), pre-cancer (e.g., cervical intraepithelial neoplasia or CIN, grades 1 to 3) and invasive cancer (by stage) (**Figure 1**). Transition probabilities can vary by HPV type, age or duration of infection or lesion status, and history of prior HPV infection or CIN treatment. Natural immunity is modeled as a level of protection against future type-specific HPV infection that can be applied uniformly or to a proportion of previously infected female persons. Cancer detection can occur through symptoms or screening. In all four models, individuals are subject to background mortality and hysterectomy (after which they are no longer at risk for cervical cancer), as well as excess mortality from cervical cancer by stage.

Risk of HPV Acquisition and Clearance

In all four models, risk of acquiring an HPV infection varies stochastically across individuals and by age. HPV-16 and -18 are stratified separately in all four models. The MISCAN-Cervix and UMN models pool the five other high-risk HPV types (HPV-31, -33, -45, -52, -58) targeted by the 9vHPV vaccine into a single category, whereas the Harvard and Policy1-Cervix models stratify these five high-risk types individually. All models pool the remaining high-risk HPV genotypes into a single category. HPV clearance in all models varies by HPV genotype. For the MISCAN-Cervix, Policy1-Cervix and UMN models, clearance from HPV is age-specific, while

for the Harvard model, HPV clearance is a function of HPV persistence (i.e., time since infection) rather than age.

Progression and Regression of Precancer

The UMN, MISCAN-Cervix, and Policy1-Cervix models capture HPV, CIN1, CIN2, and CIN3 as separate states (noting that HPV and CIN1 are interpreted as separate states relating to productive HPV infection), whereas the Harvard model combines HPV and CIN1 into a single state (i.e., CIN1 is interpreted as a microscopic manifestation of acute HPV infection and is therefore incorporated into the HPV-infected state^{17,18}). Progression from HPV to precancer and regression from precancer to HPV (or no lesion) are functions of individual or groups of HPV genotypes. Similar to HPV clearance, the models differ in how transitions between health states are defined. For example, transitions to and from CIN health states in the Harvard model are a function of infection or lesion duration, whereas in all other models, the transitions are invariant by time-in-state but may vary by a woman's age. For the Harvard and MISCAN-Cervix models, CIN lesions can develop in the absence of a high-risk HPV infection (i.e., due to low-risk HPV genotypes), while the Policy1-Cervix and UMN models assumed CIN develops due to high-risk HPV only.

Progression to Cancer

In all four models, cervical cancer can only develop if a high-risk HPV infection is present. All models allow multiple precancers within individuals (due to different HPV genotypes or genotype groups) and allow the time from precancer onset to progression to preclinical invasive cancer to vary stochastically across individuals and across precancers within individuals. Cervical cancer groupings vary by staging according to SEER (i.e., local, regional, distant) for Harvard, MISCAN-Cervix, and Policy1-Cervix, or the International Federation of Gynecology and Obstetrics (FIGO) (I to IV) for UMN; MISCAN-Cervix additionally includes a microinvasive cancer stage. Similar to the progression and regression of HPV infections and precancer, the Harvard model captures the probability of progression to cancer as a function of the duration of the precancerous lesion, whereas in all other models, the progression to cancer is invariant by time-in-state but may vary by a woman's age. However, the MISCAN-Cervix model allows for two types of CIN3; non-progressive CIN3 has a shorter duration than progressive CIN3. In addition, for the Harvard model, CIN2 and CIN3 are modeled as non-sequential precancerous health states with distinct probabilities of progression to cancer.

Progression to Clinically-Detected Cervical Cancer

All models allow sojourn time (i.e., the time from preclinical cancer onset to cancer detection via symptoms rather than screening) to vary stochastically across individuals. Median sojourn time varies among the models from 2.3 to 5.3 years.¹⁹

HPV Vaccination

HPV vaccination effect is modeled as a reduction in the incidence of vaccine-type HPV infections, which is a function of model inputs on age at vaccine receipt, vaccine efficacy, and duration of vaccine protection. In addition, vaccine impact on cervical precancer and cancer

burden is proportional to the cervical disease and cancers attributable to infections with specific HPV genotypes, i.e., HPV type distribution.

Screening, Diagnosis, and Treatment of Precancer

Screening is used for early detection of invasive cancer, as well as to detect the presence of highgrade precancers (CIN2 and CIN3), which may resolve spontaneously or, if screen-detected, can be treated and removed before progressing to cancer. The population-level effectiveness of screening over repeated screening rounds depends on uptake by age, interval, test characteristics, treatment efficacy, and adherence to follow-up visits. Screening assumptions in the model can vary by primary screening test, start age, stop age, interval between negative screens, triage testing following screen-positive results, uptake, and adherence to recommended follow-up. Management of screen-positive female persons can vary by age, follow-up test, time to followup test(s), and number of negative follow-up tests required to return to routine screening. Colposcopy and biopsy are used to diagnose precancer or cancer. Precancer treatment involves primarily loop electrosurgical excision procedure (LEEP) but may include other types, such as conization or ablation therapies.

Following successful precancer treatment, two of the models (MISCAN-Cervix and UMN) return female persons to a healthy, uninfected state, while the Harvard and Policy1-Cervix models assume that a proportion of female persons who receive treatment retain their HPV infection. Furthermore, the Policy1-Cervix model incorporates a more aggressive post-treatment natural history to capture the documented increased risk of development of new cervical precancer and cancer in female persons previously treated for precancer.²⁰⁻²²

Cancer Treatment and Survival

Preclinical cancers can progress through stages (e.g., local to regional to distant) until detection through either symptoms or screening. The likelihood of cancer detection due to symptoms rather than screening increases with increasing cancer stage. Once detected, female persons with cancer are subject to excess mortality as a function of cancer stage, age, and time since diagnosis, based on 5-year conditional relative survival estimates in SEER.³ All models assume no excess mortality due to cervical cancer in survivors, from 15 years after initial cancer detection.

Model Calibration

A process of model calibration was undertaken to ensure fit to observed data from the US population. The models calibrate highly uncertain parameters, which include HPV incidence (by age and genotype), CIN progression and regression, and HPV natural immunity following typespecific HPV infection and clearance.

Calibration approaches varied by model. For example, for the Harvard model, baseline values for each of the uncertain parameters were randomly selected from a pre-determined plausible range, creating a unique natural history parameter set. Goodness of fit was ascertained by calculating the likelihood of model-projected outcomes from each parameter set against corresponding

calibration targets. For the Harvard model, uncertainty in the natural history parameters was captured by using the 50 best-fitting parameter sets in all analyses; the base-case results were reported as the mean value across the 50 sets; sensitivity analysis employed a single top-fitting set. For the MISCAN-Cervix model, a genetic algorithm was adapted to identify a single topfitting parameter set that fit well to the observed target data, while the UMN model used a stochastic optimization algorithm (i.e., simulated annealing) and manual fine-tuning. The Policy1-Cervix model similarly used an optimization algorithm (i.e., differential evolution method) to calibrate to the target data, identifying a best-fitting parameter set. The calibrated model parameter values used in this analysis are summarized in **Appendix Table 1**.

Sources for the calibration target data were selected on the basis of representativeness of the general US population, sampling methods, and sample size. All data were from populations prior to widespread HPV vaccination. Age- and type-specific prevalence of HPV infections was based on data from the New Mexico HPV Pap Registry (NMHPVPR), the only statewide screening registry in the United States.²³ HPV type distribution in cases of CIN and cancer (by cancer histology) were also included as calibration target data. For CIN2 and CIN3, HPV type distribution was based on data from the NMHPVPR;²⁴ for cancer, HPV type distribution was based on a study by the US Centers for Disease Control and Prevention (CDC) using tissue samples from US population-based cancer registries.²⁵ Model fit to calibration targets are displayed in **Figures 2–4**.

Model Validation

Model validation exercises were conducted to assess model fit to data not used as direct inputs or as part of the calibration process. First, age-specific cervical cancer incidence rates under an assumption of no intervention (i.e., natural history) were projected by the models and compared against cancer registry data from the 1950s and early 1960s, before cytology-based screening was widely performed (**Figure** 5).^{26,27} Given the limited data from only a few states (Connecticut, New York, Hawaii) – and the potential changes in sexual behavior and other risk factors since the pre-screening era – these data were not used directly to calibrate the models but instead were used to assess predictive validity for overall underlying risk.

Next, model-projected outcomes of age-specific cervical cancer incidence and mortality rates were compared against those reported in the SEER cancer registries in recent years (i.e., 2000- 2013) (**Figure 6**), under assumptions of cervical cancer screening practice patterns based on data from sites involved in the METRICS Center, a multi-site cervical cancer screening group that examines the effects of screening practice on outcomes as part of the PROSPR II consortium.^{4,28-} ³⁰ Screening practice patterns included estimated proportions of female persons never screened, based on data from the National Health Interview Survey (NHIS),³¹ and screened at different intervals (e.g., annual, biennial) and proportions of female persons who do not comply to followup diagnostic testing and/or precancer treatments (see section on Imperfect Screening Adherence below for further detail).

Lastly, we simulated the protocols of empirical studies included in the EPC report 2 and compared model-estimated outcomes to the empirical outcomes. Specifically, we compared the relative risks (RRs) of colposcopy referral, CIN2+ detection, and CIN3+ detection reported in

randomized controlled trials of primary HPV testing compared to cytology-based screening and, separately, cotesting to cytology-based screening (**Figure 7**). 32-37 The empirical studies varied in terms of study population, age ranges, screening history, and test performance; thus, we assumed the range of the relative performance of the HPV testing and cotesting strategies provided bounds for comparison with our model generated outcomes. **Table 2** summarizes the screening strategies modeled for the validation exercise; the model predicted RRs were calculated based on counts of colposcopy referral, CIN2+ detected, and CIN3+ detected at ages 30 and 31 years.

Screening Strategies

The primary analysis will focus on the three Key Questions assessing the comparative effectiveness and harms of different cervical cancer screening strategies. Given the high uptake of HPV vaccination among current and incoming screen-eligible female persons, three separate base-case analyses were conducted to reflect HPV vaccination status, and thereby differential levels of baseline cervical cancer risk: (1) not vaccinated; (2) fully vaccinated with either the 2vHPV or 4vHPV vaccines, providing protection against HPV-16/18; and (3) fully vaccinated with the 9vHPV vaccine, providing protection against HPV-16/18/31/33/45/52/58. Unvaccinated individuals were modelled as a population in the complete absence of HPV vaccination.

For each of the three populations stratified by vaccination status, we evaluated 73 strategies that varied by five main attributes: (1) screening test, (2) age to start screening, (3) age to switch to primary HPV testing or cotesting if preceded by cytology, (4) rescreening interval (following a screen-negative result), and (5) age to stop screening (**Table 3**). Screening tests included cytology, primary HPV testing, and cytology and HPV cotesting. Age to start screening was evaluated at ages 21 (cytology only), 25, 30, 35 and 40 years. Age to switch, from cytology to either HPV testing or cotesting or from a shorter interval to longer interval, was evaluated at ages 25, 30, 35, 40, and 45 years. The rescreening interval was evaluated at every 3 years (cytology only), 5 years or 10 years (HPV and cotesting), given the lower cervical cancer risk in the vaccinated cohorts. Age to stop screening included 60, 65, or 70 years, assuming a final negative routine screen at each end age.

Guideline-based screening strategies included: (1) cytology alone every 3 years from ages 21 to 65 years; (2) cytology alone every 3 years from age 21 years, with a switch to primary HPV testing every 5 years from ages 30 to 65 years; (3) cytology alone every 3 years from age 21 years, with a switch to cotesting every 5 years from ages 30 to 65 years; and (4) primary HPV testing every 5 years from ages 25 to 65 years.^{8,9} Management of female persons with abnormal tests was based on guidelines revised in 2019 by the ASCCP (formerly known as the American Society for Colposcopy and Cervical Pathology)³⁸ (**Figure 8**) and included: for cytology testing, reflex HPV testing for female persons with atypical squamous cells of undetermined significance (ASC-US) and referral to colposcopy for those with more severe abnormal results; for HPV testing, cytology triage for female persons with high-risk HPV positive results with referral to colposcopy for those with ASC-US or worse and repeat HPV testing in 12 months for those with cytology-negative, HPV-positive results; for cotesting, immediate referral to colposcopy of female persons with cytology worse than ASC-US (irrespective of HPV test result) or cytology-ASC-US, HPV-positive results, and repeat cotesting in 12 months for female persons with cytology-negative, HPV-positive results with referral to colposcopy for those with HPV-positive

and/or ASC-US or worse. Those with histologically-confirmed CIN2+ are then referred for excisional precancer treatment (e.g., LEEP), after which there is a series of follow-up testing prior to return to routine screening; female persons with lower-grade or no lesions from colposcopy undergo less intensive follow-up testing. The base-case analysis assumed full adherence to screening initiation, rescreening interval, and follow-up for both diagnostic and precancer treatment referrals, consistent with prior analyses.

Inputs

Screening Test Characteristics

The models vary in how they incorporate screening test characteristics, but all used values that were consistent with data reported in randomized controlled trials and meta-analyses, which report the absolute and relative sensitivity and specificity of cytology, HPV testing, and cotesting. Test sensitivity and specificity values were defined at a disease threshold of CIN2 (i.e., CIN2 or worse is considered disease "positive"; less than CIN2 is considered disease "negative") $(Table 4).^{39-49}$

For cytology testing, two models (Harvard and UMN) input test characteristics directly, while for MISCAN-Cervix and Policy1-Cervix, the models are fitted either to data on the distribution of cytology test results (e.g., cytology-histology correlations) (Policy1-Cervix)^{50,51} or to precancer detection rates and interval cancers among screened female persons (MISCAN-Cervix).⁵² MISCAN-Cervix differentiates between lesions missed either randomly or systematically over time. For strategies involving cytology testing, we applied estimates of test sensitivity and specificity from a meta-analysis conducted by Koliopoulos et al, ³⁹ which pooled estimates of sensitivity and specificity (ASC-US cut-off) for detection of CIN2+ based on 15 studies (sensitivity 72.9% (95% confidence interval (CI): 70.7-75.0%) and specificity 90.3% (95% CI, 90.1-90.5%)).

For HPV testing, all models directly input a test positivity matrix as a function of HPV positivity given true presence of HPV infection for a given disease health state based on RCTs and clinical studies.⁴¹⁻⁴⁹ We then ensured that the implied test sensitivity and specificity of HPV testing given presence and absence of CIN2+ were consistent with those reported in RCTs and metaanalyses.40,49 Given the wide variation in absolute test characteristics across studies due to differences in protocols and populations, we elected to utilize relative sensitivity and specificity values, compared with cytology testing (positivity threshold of ASC-US or worse). Our basecase estimates were anchored on the U.S.-based ATHENA study, 40 which provided verificationbias adjusted estimates and included both HPV testing and cotesting strategies with similar follow-up algorithms as what was evaluated in the current analysis, but we explored the impact of test performance of HPV testing in sensitivity analysis.

Colposcopy/Biopsy and Precancer Treatment

There is known variation in the performance of histologic diagnosis of precancer in clinical practice in the United States.⁵³ In order to isolate the impacts of primary screening in our analysis, we made the simplifying assumption that colposcopy and biopsy were perfectly

accurate for identifying underlying precancer status (i.e., sensitivity and specificity values were both 100%); sensitivity analysis in the 2018 USPSTF decision analysis showed that conclusions were not influenced by this assumption.¹⁵ We assumed that the effectiveness of treatment in removing a CIN2 or CIN3 lesion (e.g., via LEEP) was 93%.⁵⁴

Cervical Cancer Death, Non-Cervical Cancer Death, and Hysterectomy

All four models applied common inputs for relative stage-specific cervical cancer survival conditional on age at and time since diagnosis (surviving to year 1, 3, 5 and 10) from the Surveillance, Epidemiology, and End Results (SEER) program.³ Simulated individuals faced age-specific background mortality rates reflecting the 2000 birth cohort from the Berkeley Mortality Database (data for the 2002 birth cohort not available) to capture death from all causes.⁵⁵ Finally, all models applied common age- and birth cohort-specific hysterectomy rates, based on smoothed estimates from Simms/Yuill et al.⁵⁶

HPV Vaccination

In the vaccinated cohorts, all four models assumed complete (100%) coverage of girls at age 12 years with 100% protection against high-risk HPV genotypes targeted by either the 2vHPV/4vHPV (HPV-16/18) or 9vHPV (HPV-16/18/31/33/45/52/58) vaccines. We assumed protection was over the lifetime but did not assume any cross-protection against HPV types not targeted by the vaccines.

Outcomes

Each of the models has the capability to produce a common set of analytic outcomes associated with each strategy. These model-generated outcomes reflect both health effects and harms over the lifetime of the screening cohorts (i.e., ages 21 to 100 years): total number of tests, colposcopy referrals, detected CIN2 or worse (i.e., CIN2, CIN3, and cervical cancers), false positive cases, cervical cancer cases, cervical cancer deaths, and life-years gained (LYG) compared to no screening (from age 21 years). These measures were calculated as the cumulative number of events or time spent in the different health states of the lifetime of the cohort, which were then modified by the screening process. These measures in totality captured the benefits and harms of the strategies being considered. Analytic outcomes were presented as ranges across the 4 models, as well as the median estimate (reflecting the average of the two middle models).

Benefits

The models estimated LYG (compared to no screening) as the primary outcome for the benefits of screening in each of the base-case cohorts (unvaccinated, 2vHPV/4vHPV vaccinated, 9vHPV vaccinated). Additional measures of benefit included cervical cancer cases and deaths.

Harms

The total lifetime number of tests (i.e., including both cytology and HPV tests) and colposcopy referrals represented the primary harms and burden of cervical cancer screening. Both measures included tests or colposcopies that resulted from screening, follow-up, and surveillance. An additional measure of harm included the total number of false positive cases (i.e., colposcopies without underlying CIN2, CIN3 or cancer).

Ratio of Harms (Burden) to Benefit

Similar to a traditional incremental cost-effectiveness analysis, we calculated an efficiency ratio of incremental harms to incremental benefits of one strategy compared to the next less harmful strategy. Strategies deemed "efficient" formed an efficiency frontier with the measure of harm on the x-axis and health benefit on the y-axis; the efficiency ratio is equal to the inverse of the slope of two neighboring strategies along the frontier and represents the additional number of harms required to increase the measure of benefit by one unit. On the lower, steep end of the frontier, the ratios are lowest and more efficient; in contrast, on the upper, flat part of the frontier, the ratios are highest and less efficient, reflecting diminishing marginal returns. This ratio reflects a strategy's "value" in terms of the harm-benefit tradeoff.

Two distinct measures of efficiency that had been used in prior USPSTF decision analyses for cervical cancer screening^{15,57} were selected to evaluate the harm-benefit tradeoffs associated with the screening strategies: (1) the incremental number of colposcopies per life-year gained (LYG), and (2) the incremental number of total tests per LYG. The efficiency ratios were therefore defined as the additional number of colposcopies (or tests) divided by the additional LYG of a specific strategy (strategy x) compared to the strategy associated with the next fewer colposcopies (or tests) (strategy y). For example:

$$
Efficiency ratio = \frac{Colposcopies_{Strat\,x} - Colposcopies_{Strat\,y}}{LYG_{Strat\,x} - LYG_{Strat\,y}}
$$

Strategies with a higher number of colposcopies or tests and lower LYG than an alternative strategy were strongly dominated and were thereby considered "inefficient." Additionally, strategies that provided lower LYG than another and had a higher efficiency ratio were weakly dominated and also deemed inefficient. All other strategies were considered "efficient" and formed the efficiency frontier (noting that strategies on the upper, flat part of the frontier may be less efficient and may not necessarily represent good value). In addition to efficient strategies, we also identified "near-efficient" strategies, which we defined as a strategy within 2% of the efficiency frontier (i.e., any strategy whose actual benefits were within 98% of the expected benefits, given the increase in harms and ratio of the next best strategy). For each model, we selected strategies that were efficient or near-efficient on both metrics of colposcopies per LYG and tests per LYG for further consideration since each measure of harm indicates a different valuation of burden.

We repeated the efficiency and near-efficiency calculations for each of the three separate basecase analyses for female persons who are: (1) not vaccinated; (2) fully vaccinated with 2vHPV or 4vHPV vaccines; and (3) fully vaccinated with the 9vHPV vaccine. Because there is no consensus on the appropriate harm-benefit tradeoffs using these metrics, we used efficiency ratios associated with current US guidelines-based cervical cancer screening strategies in the unvaccinated population as indicative benchmarks for identifying potentially efficient strategies in the vaccinated populations.

Scenario and Sensitivity Analyses

We evaluated alternative scenarios and uncertainty in the data, including assessing the impact of the screening strategies in a race-specific model for Black female persons, imperfect screening and follow-up adherence, triage approach using HPV-16/18 genotyping for primary HPV and cotesting, test performance for HPV testing, and the potential benefits of HPV self-collection among previously unscreened female persons.

Race-Specific Analysis

The Harvard all-race model, which was previously adapted to reflect Black female persons, captures observable differences in factors related to cancer risk (mortality, hysterectomy rates) as well as cervical cancer survival data from SEER among Black female persons.⁵⁸ Importantly, this model does not assume any differences in the natural history of HPV infection and cervical cancer by race; rather it reflects the impact of larger societal inequities on burden of cervical cancer for those of Black race, including but not limited to differences in access to screening as well as timely follow up and treatment of cervical cancer precursors.⁵⁸ We used the Harvard Black-race model to replicate the base-case analyses conducted using the all-race model for each of the three cohorts by vaccination status, and compared benefits, harms, and efficiency within the Black-race model, as well as against the Harvard all-race model.

Imperfect Screening and Follow-up Adherence

Because the analysis is intended to support national recommendations, we assumed in the base case that adherence to screening and all follow-up visits, including triage of screen-positive results, surveillance testing, colposcopy/biopsy, and precancer treatment, was 100%. However, cervical cancer screening practice in the United States is not perfect and known to be quite variable by race, geography, and health care systems, with loss to follow up at every step in the screening process.^{4,59-61} Using data from health networks that are part of the PROSPR II consortium (i.e., METRICS), we assessed the impact of imperfect screening practice on our findings.⁴ We assessed under-screening, timely screening, and over-screening using data on individuals continually enrolled in the METRICS cohort, regardless of vaccination status. We adjusted these data using self-reported estimates of the totally unscreened population from the 2019 National Health Interview Survey.⁶² We also used data from the METRICS consortium to estimate the proportion of patients receiving follow-up to colposcopy from an indicated abnormal finding within six months. We did not have data on the rate of follow-up to excisional treatment, however we assumed the same rate as follow-up to colposcopy. We assumed that estimates of imperfect screening practice were applicable to vaccinated populations. Estimation of screening patterns was repeated specifically assessing outcomes for those of self-identified Black race, which was used in the Harvard Black-race model to assess the differential impact of imperfect screening and follow-up (**Table 5**).

HPV-16/18 Genotype Triage of High-risk HPV-Positive Results

The base-case analysis assumed that management of female persons with high-risk HPV involved triage with a cytology test to determine who is referred immediately to colposcopy versus for follow-up surveillance testing (see **Figure 8**). The ASCCP also recommends HPV genotype testing for HPV-16/18 as a triage option for both primary HPV testing and cotesting where available.³⁸ We therefore examined the impact of the alternative assumption that female persons who test positive for HPV-16/18 are referred directly to colposcopy and those who test positive for other high-risk HPV types undergo cytology triage (see **Appendix Figure 3**).

Test Performance of HPV Testing

We explored the lower- and upper-bound values of relative test sensitivity for HPV testing compared to cytology testing that was used in the prior 2018 USPSTF decision analysis¹⁵, based primarily on data from the US-based ATHENA trial⁴⁰ and a meta-analysis by Arbyn et al.⁴⁹ Three models (Harvard, Policy1-Cervix, UMN) each replicated the base-case analyses using the lower-bound and upper-bound relative HPV test sensitivity values of 1.15 and 1.37, respectively, which reflect variations across HPV tests that include the Cobas HPV test (Roche), Hybrid Capture 2 (Qiagen), and PCR-based tests. Relative HPV test specificity values remained between 0.96 and 0.98, compared to cytology testing, consistent with the empirical data.

Impact of HPV Self-Collection on Unscreened Female Persons

The majority of studies evaluating adherence to HPV self-collection, including the four USbased studies, targeted female persons who were underscreened.² The sparse data on follow-up management and multiple rounds of screening over time among this underscreened population limited our ability to use the models to evaluate HPV self-collection as part of routine screening. In order to explore the potential health gains from HPV self-collection, we elected to conduct an analysis assuming a single lifetime screen among previously unscreened and unvaccinated female persons, occurring at either age 35, 45, 55, or 65 years to understand the range of health benefits by age. Each analysis was conducted under three assumptions of adherence to follow-up visits: (1) "perfect" adherence to colposcopy referral and precancer treatment, (2) "reduced" adherence consistent with the METRICS data for colposcopy referrals and precancer treatment $(72.5\%$ for all races, 65.3% for Black race) (**Table 5**),⁴ and (3) "low" adherence using an estimate from a self-sampling study conducted in the Mississippi Delta (i.e., 28.6%).⁶³ We applied the relative sensitivity and specificity values of HPV self-collected samples versus clinician-collected samples based on a study by Stanczuk et al. ⁶⁴ that was included in the EPC report.² Specifically, we assumed that the relative sensitivity and specificity of self-collected sampling versus clinician-collected sampling were 0.93(CIN2+)/0.95(CIN3+) and 0.98, respectively. The analysis was repeated using the Harvard Black-race model to identify any differential impacts by race.

Chapter 3. Results

Health Benefits and Harms

Overview of Natural History and Impact of Vaccination on Baseline Risk

In the absence of screening and HPV vaccination, estimates of lifetime risk of cervical cancer for US female persons of all races ranged from 1.1% to 2.1% across the four models (median 1.5%) and lifetime risk of cervical cancer mortality ranged from 0.51% to 0.86% (median 0.73%).

Baseline risks of cervical cancer incidence and mortality decreased considerably in populations vaccinated fully with the 2vHPV, 4vHPV, or 9vHPV vaccines. In the absence of screening, the models predicted that the lifetime risk of cervical cancer decreased by 60% to 77% (median 70%) to 0.37% to 0.65% (median 0.43%) for female persons vaccinated against HPV-16/18 infections (with either 2vHPV or 4vHPV) and by 79% to 93% (median 88%) to 0.14% to 0.34% (median 0.15%) for female persons vaccinated against HPV-16/18/31/33/45/52/58 infections (with 9vHPV). Cervical cancer mortality decreased by 58% to 77% (median 69%) to 0.20% to 0.25% (median 0.21%) for individuals vaccinated with 2vHPV or 4vHPV, and by 76% to 91% (median 88%) to 0.07% to 0.12% (median 0.09%) for individuals vaccinated with 9vHPV. Lifeyears gained (LYG) across the models ranged from 112 to 165 (median 127) per 1,000 21-yearold female persons fully vaccinated with 2vHPV or 4vHPV vaccines, and 145 to 198 (median 159) per 1,000 21-year-old female persons fully vaccinated with the 9vHPV vaccines, compared to no vaccination or screening.

Impact of Screening

Model-estimated outcomes of cervical cancer cases, cervical cancer deaths, LYG, total tests, colposcopies, CIN2+ detected, and false positive cases per 1,000 female persons projected under scenarios of screening are shown separately for the three base-case cohorts of female persons unvaccinated (**Tables 6-8**), vaccinated fully with the 2vHPV or 4vHPV vaccines (**Tables 9-11**), and vaccinated fully with the 9vHPV vaccine (**Tables 12-14**).

The overall gain in health benefits associated with the different screening strategies was considerable, irrespective of vaccination status, although the absolute magnitude of benefits due to screening was smaller among the vaccinated cohorts. Compared to no screening, all screening strategies resulted in reductions in cervical cancer cases and deaths, with greater benefits accruing with younger start and switch ages, shorter intervals, and later end ages. Likewise, harms of screening, including number of tests, colposcopies, and false positive results were generally greater among the more intensive strategies, although these outcomes also diminished in the vaccinated cohorts. Strategies with the lowest benefits in all models were those that involved initiating screening at age 35 or 40 years (without preceding cytology testing) and/or at 10-year interval ending at age 60 years. Strategies with the highest benefits involved those that initiate screening at either age 21 (with cytology) or age 25 years (with HPV testing or

cotesting), with 5-yearly intervals ending at age 70 years. All else being equal, cotesting strategies yielded higher benefits than HPV testing strategies, although in most cases the difference was relatively small. In the unvaccinated population, the estimated health benefits in terms of LYG due to screening were generally higher in the Harvard and UMN models compared to the other models; the Harvard model also estimated greater harms in terms of number of colposcopies, while Policy1-Cervix estimated fewer harms. Absolute differences in outcomes across strategies and models tended to decrease in the vaccinated populations.

Unvaccinated Population

Cancer Cases, Deaths, LYG

In the unvaccinated population, across all screening strategies and all models, the lifetime number of cervical cancer cases ranged from 0.7 to 9.5 per 1,000 21-year-old female persons, and lifetime number of cervical cancer deaths ranged from 0.1 to 3.1 per 1,000 21-year-old female persons. Compared to no screening, the reductions in lifetime risk attributable to screening ranged from 50% to 96% for cases, and 62% to 98% for deaths across all strategies considered and all models (**Table 6**).

The three current USPSTF guidelines-based strategies were associated with cancer reductions ranging from 68% to 94% for cases and 77% to 96% for deaths across the models, compared to no screening; the corresponding LYG ranged from 140 to 195 per 1,000 21-year-old female persons (51 to 71 days of life gained per person, 7.4 to 18.7 cervical cancer cases averted per 1,000 21-year-old female persons), compared to no screening. Among the three USPSTF guidelines-based strategies, all models found that 3-year cytology alone from ages 21 to 65 years yielded the lowest health benefit, followed by 3-year cytology at age 21 with a switch to 5-year HPV testing at age 30 to 65 years. The highest health benefit came from the strategy involving switching to 5-year cotesting at age 30 to 65 years (although the difference between cotesting and HPV testing was much smaller than the difference between cytology and HPV testing).

Strategies that were associated with lower LYG than current guidelines-based strategies generally involved later screening start ages (e.g., 30, 35, 40 years) and/or 10-year interval, particularly when in combination with an earlier screening stop age of 60 years. Strategies that were associated with greater LYG in all models than the current USPSTF guidelines-based strategy of 3-yearly cytology alone from ages 21 to 65 years generally involved start or switch age for HPV testing or cotesting of 25 years, 5-year intervals, and/or later end age of 70 years. These more effective strategies resulted in an additional 8 to 10 LYG per 1,000 21-year-old female persons (2.8 to 3.8 days of life gained per person, 0.1 to 1.0 cervical cancer cases averted per 1,000 female persons) among strategies with screening end age of 60 years (combined with HPV testing or cotesting starting at age 25); 5 to 15 LYG per 1,000 21-year-old female persons (1.9 to 5.5 days of life gained per person, 0.7 to 1.6 cases averted per 1,000 female persons) among strategies with screening end age of 65 years; and 1.2 to 17 per 1,000 21-year-old female persons (0.4 to 6.2 days of life gained per person, 0.5 to 1.9 cases averted per 1,000 female persons) among strategies with screening end age of 70 years.

Total Tests and Colposcopies

The number of total tests over the lifetime across all strategies and models ranged from 3,327 to 26,151 tests per 1,000 female persons; US guidelines-based strategies ranged from 10,947 to 23,683 total tests per 1,000 female persons. As expected, strategies involving earlier start or switch age, more frequent intervals, and cotesting were generally associated with a greater number of total tests; end age was less influential on total number of tests (**Table 7**). For example, switching from primary HPV testing to the same strategy with cotesting resulted in at least a 52% increase in total tests (and over 100% with some strategies), and changing the start age from 30 to 25 for the same screening strategy resulted in a 16% to 23% increase in total tests. In contrast, changing the screening end age from 65 years to either 60 or 70 years for the same screening strategy resulted in no more than a 12% change in total tests.

The number of colposcopies over the lifetime across all strategies and models ranged from 114 to 1,821 per 1,000 female persons (US guidelines-based strategies ranged from 449 to 1,480 per 1,000 female persons). Strategies involving cotesting or primary HPV testing at earlier ages (ages 25, 30) and at 5-yearly intervals tended to have the highest number of colposcopies. For example, the guidelines-based 3-year cytology with a switch to 5-year cotesting at ages 30 to 65 years had 36% to 110% (median 53%) higher number of colposcopies across the models, compared to 3-year cytology testing continuously until age 65, and 13% to 70% (median 19%) higher number of colposcopies, compared to 3-year cytology at age 21 with a switch to 5-year HPV testing at ages 30 to 65 years. All else equal, start age and interval had the biggest impact on number of colposcopies; for example, colposcopies decreased by 22% to 34% when start age shifted from age 25 to 30 years, and by 23 to 37% when interval shifted from 5-year to 10-year; in contrast, the impact of end age was smaller with changes in colposcopy ranging from 2 to 11% when shifting from age 65 to either age 60 or 70 years.

CIN2+ Detected, False Positive Cases

The number of CIN2, CIN3 and cancer cases detected via screening were highest among strategies that involved earlier start or switch ages (age 21 or 25) and 5-year HPV testing or cotesting (**Table 8**). For example, all models found that a strategy of cytology starting at age 21 with a switch to 5-year cotesting at ages 25 to 65 had an additional CIN2+ detection of 9 to 47 per 1,000 21-year-old female persons, compared to the guidelines-based strategy of 3-year cytology without switching. Screening end age was less influential on CIN2+ detection; all else equal, shifting from end age of 65 years to either 60 or 70 years resulted in a change of 2 to 5 cases of CIN2+ detected per 1,000 female persons.

The number of colposcopies that did not result in CIN2+ detection was defined as false positive cases. Across the strategies and models, the proportion of colposcopies that were false positive ranged from 67% to 92% (**Table 8**). The trends in false positives cases tracked those of the number of colposcopies and CIN2+ cases detected, with cotesting strategies being associated with the highest number of false positives, and age to start/switch screening and interval having more influence than screening end age.

Population Vaccinated with 2vHPV or 4vHPV Vaccines

Cancer Cases, Deaths, LYG

In female persons fully vaccinated with 2vHPV or 4vHPV, the same screening strategies generally provided fewer absolute benefits, compared with those among unvaccinated female persons. Across all screening strategies and all models, the lifetime number of cervical cancer cases ranged from 0.2 to 1.9 per 1,000 21-year-old female persons, and lifetime number of cervical cancer deaths ranged from 0.04 to 1.0 per 1,000 21-year-old female persons; these estimates corresponded to LYG of 25 to 65 per 1,000 21-year-old female persons (9 to 24 days of life gained per person, 1.9 to 6.2 cervical cancer cases averted per 1,000 21-year-old female persons), compared to no screening in those fully vaccinated with 2vHPV or 4vHPV (**Table 9**).

Despite the lower absolute gains in health benefit from screening in those fully vaccinated with 2vHPV or 4vHPV vaccines, the *relative* reductions in cancer cases and deaths associated with screening were similar to those in the unvaccinated population, with reductions in lifetime risk of cervical cancer ranging from 50% to 96% for cases and 59% to 98% for deaths, compared to no screening in fully 2vHPV or 4vHPV vaccinated female persons across all strategies and all models. Likewise, the three current guidelines-based strategies were associated with cancer reductions ranging from 67% to 95% for cases and 72% to 97% for deaths across the models.

Total Tests, Colposcopies, CIN2+ Detected, False Positive Cases

Compared to screening in the unvaccinated population, corresponding strategies were associated with reductions in the number of lifetime total tests in the population of female persons vaccinated with 2vHPV or 4vHPV vaccines, ranging from 1% to 15% (**Table 10**). Strategies with higher reductions were those that involved HPV testing, which had lower follow-up testing (with cytology triage) given the lower prevalence of HPV due to vaccination in the population.

Likewise, number of colposcopies, CIN2+ detected, and false positive cases were reduced in those who received 2vHPV/4vHPV vaccines, compared to those who are unvaccinated (**Table 11**). For example, for the three current guidelines-based strategies, reductions in colposcopy ranged from 11% to 22% (median 19%) for 3-year cytology testing from ages 21 to 65 years, 25% to 32% (median 26%) for 3-year cytology starting at 21 with a switch to 5-year HPV testing at ages 30 to 65 years, and 17% to 28% (median 24%) for 3-year cytology starting at age 21 with a switch to 5-year cotesting at ages 30 to 65 years, among those who received 2vHPV or 4vHPV compared to those who were unvaccinated. Importantly, the yield of the colposcopies decreased in the population vaccinated against 2vHPV or 4vHPV in terms of a greater proportion of false positives among colposcopies, ranging from 75% to 94%.

Population Vaccinated with 9vHPV Vaccine

Cancer Cases, Deaths, LYG

In female persons fully vaccinated with the 9vHPV vaccine, the same screening strategies provided even fewer absolute benefits compared with those among female persons unvaccinated or vaccinated with 2vHPV or 4vHPV vaccines (**Table 12**). The lifetime number of cervical cancer cases diagnosed ranged from 0.1 to 0.8 per 1,000 21-year-old female persons, and lifetime number of cervical cancer deaths ranged from 0.02 to 0.4 per 1,000 21-year-old female persons,

corresponding to LYG of 9 to 29 per 1,000 21-year-old female persons (3 to 11 days of life gained per person) compared to no screening in those vaccinated with the 9vHPV vaccine.

As with those vaccinated with the 2vHPV or 4vHPV vaccines, the relative reductions of cervical cancer cases and deaths attributable to screening compared to no screening of fully 9vHPV vaccinated female persons were similar to the unvaccinated population, ranging from 49% to 97% for cases, and 58% to 99% for deaths across all strategies considered and all models.

Total Tests, Colposcopies, CIN2+ Detected, False Positive Cases

Reductions in number of tests, colposcopies, CIN2+ detected, and false positives compared to those who are unvaccinated were even more pronounced in the population of female persons vaccinated with 9vHPV (**Tables 13-14**). For example, for the three current guidelines-based strategies, reductions in colposcopy ranged from 21% to 46% (median 33%) for 3-year cytology testing from ages 21 to 65 years, 52% to 58% (median 54%) for 3-year cytology starting at 21 with a switch to 5-year HPV testing at ages 30 to 65 years, and 37% to 52% (median 49%) for 3 year cytology starting at age 21 with a switch to 5-year cotesting at ages 30 to 65 years, among those who received 9vHPV compared to those who were unvaccinated. The yield of colposcopy decreased even further among those who received the 9vHPV vaccine, with the proportion of false positive cases among colposcopies increasing, ranging from 79% to 96% across all strategies and models.

Efficient Strategies by Vaccination Status

Unvaccinated Population

Of the 73 screening strategies evaluated in this analysis, 27 were identified in the Harvard model, 19 in the MISCAN-Cervix model, 11 in the Policy1-Cervix model, and 15 in the UMN model, as being efficient or near-efficient using both measures of colposcopies per LYG and tests per LYG (**Table 15, Figures 9-10**). Three of the current US guidelines-based strategies were identified on or near the efficiency frontier in three models (Harvard, MISCAN-Cervix, UMN): (1) 3-year cytology starting at 21 with a switch to 5-year HPV testing at ages 30 to 65; (2) 3-year cytology starting at 21 with a switch to 5-year cotesting at ages 30 to 65; and (3) 5-year HPV testing at ages 25 to 65 years. In the fourth model (Policy1-Cervix), the same three strategies were identified on or near the efficiency frontier but with screening end age at 70. When considering both efficiency metrics, the guidelines-based strategy of 3-year cytology alone from ages 21 to 65 years was not identified as efficient on any of the four models.

The strategies with the lowest number of colposcopies per LYG and tests per LYG (indicating high efficiency) tended to involve HPV testing at 10-year intervals; however, in the unvaccinated population, most of these strategies provided fewer LYG than the current guidelines-based strategies. Across the models, strategies with health benefit and (near-)efficient ratios that were similar to current recommended strategies included mostly HPV testing in 5-year intervals starting at ages 25 or 30, either with or without preceding cytology. Three models included 5 year HPV testing from age 25 but with a later end of age of 70 (MISCAN-Cervix, Policy1- Cervix, UMN), and three models included strategies involving cytology starting at age 21 with a switch to 5-year HPV at ages 25 or 30 with end ages at either 65 or 70 years (Harvard, Policy1Cervix, UMN). Although several cotesting scenarios were on the efficiency frontier, they were on the upper, flat part of the frontier yielding slightly higher LYG than similar HPV testing strategies, but with disproportionately greater number of colposcopies and tests, resulting in much higher harms-benefits ratios.

2vHPV/4vHPV Vaccinated Population

In general, the efficiency ratios of guidelines-based strategies tended to be higher in the 2vHPV/4vHPV vaccinated populations compared with the unvaccinated population (that is, more colposcopies or tests were required per LYG). For example, in the Harvard model, the USPSTF recommended strategy involving HPV testing requires nearly double the number of colposcopies per LYG in the 2vHPV/4vHPV vaccinated population than the unvaccinated population, and 2.4 times more tests per LYG.

When using the benchmarks associated with current screening recommendations for both colposcopies per LYG and tests per LYG from the unvaccinated cohort and considering which strategies would be similarly efficient in female persons vaccinated with 2vHPV or 4vHPV vaccines, all models generally identified strategies on the efficiency frontiers that involved 10 year screening intervals and/or later start age (**Table 16, Figures 11-12**). The only strategies with efficiency ratios that were equal to or less than those of current guidelines-based strategies in unvaccinated individuals on both efficiency metrics involved HPV testing alone; for example, the strategy of HPV testing every 10 years from ages 30 to 70 years was identified in 3 models, but otherwise the age to start, switch, and end varied across models. The strategy of 10-yearly HPV testing from ages 40 to 60 was identified as efficient (using both metrics) in all the models but had the lowest effectiveness in terms of LYG. Although strategies involving 5-year HPV testing were also identified as efficient or near-efficient strategies, they were generally associated with higher numbers of tests or colposcopies compared to 10-year HPV testing. As in the unvaccinated population, strategies involving cytology alone and cotesting were not selected using these benchmarks because they were either dominated or had much higher numbers of colposcopies and/or tests per LYG.

9vHPV Vaccinated Population

The efficiency ratios of guidelines-based strategies increased even more dramatically among female persons vaccinated with the 9vHPV vaccine, especially with respect to tests per LYG. For example, in the MISCAN-Cervix model, the number of required colposcopies per LYG associated with the guideline-based strategy of 5-year HPV testing from age 25 to 65 years was 2.3 times higher in the 2vHPV/4vHPV vaccinated population, and 2.9 times higher in the 9vHPV vaccinated population, compared to the unvaccinated population. For tests per LYG, the same strategy required 2.8 times more tests per LYG in the 2vHPV/4vHPV vaccinated population and over 6 times more tests per LYG in the 9vHPV vaccination population. Similar increases in ratios were found when using the other models.

When using the combined metrics of efficiency and efficiency ratios of the US recommended strategies in the unvaccinated population as indicators of efficiency, all identified strategies involved HPV testing alone, starting no earlier than age 30, and mostly at 10-year intervals

(**Table 17, Figures 13-14**). All models identified HPV testing every 10 years, either at ages 40 to 60 years (all models), 35 to 65 years (Harvard and MISCAN-Cervix) or 40 to 70 years (Policy1- Cervix and UMN). The strategy of 10-year HPV testing from ages 40 to 60 years was identified in all the models but had the lowest effectiveness but also the lowest efficiency ratio of all screening strategies using both metrics. One model included strategies with 5-year HPV testing at ages 30 to either 65 or 70 (MISCAN-Cervix), although these strategies were associated with relatively higher tests per LYG. Consistent with the 2vHPV/4vHPV vaccinated population, no strategies identified using the benchmarks included cytology or cotesting at any ages.

Scenario and Sensitivity Analyses

Findings by Race

Differences by Black Race Overall

We further analyzed the impact of 73 base-case screening strategies on female individuals of Black race using the Harvard model. The Harvard Black-race cervical cancer model reflects differences in "risk factors" resulting from social factors, including historic and contemporary discrimination, which manifest as differences in access to timely, appropriate care. Among these are differences in all-cause mortality which results in a lower life-expectancy among Black females compared to those of all races. For example, for a 21-year-old female person in the United States, the Harvard model projected life expectancy to be 55.7 years for Black female persons and 62.4 years for female persons of all races. We also identified important differences in hysterectomy rates. Using data from Adam et al, ⁶⁵ we estimated age- and Black-race specific probability of hysterectomy, with Black individuals more likely to ever have a hysterectomy and to have hysterectomies at younger ages. As a result, once we adjusted for hysterectomy in the population, we estimated a smaller proportion of Black females to be at risk for developing cervical cancer relative to the proportion at risk among females of all races. Additionally, we incorporated SEER registry data on cervical cancer survival by stage and age at diagnosis for Black female persons, ³ which show lower survival, likely reflecting differences in the quality and timeliness of care rather than aggressiveness of disease.

Unvaccinated Population – Black Race

Cancer Cases, Deaths, LYG

The lifetime number of cervical cancer cases, deaths, and LYG were lower among Black female persons compared to all-race female persons, given the lower at-risk population, lower overall life expectancy, and worse cancer survival among Black female persons. For example, in the absence of screening, the lifetime number of cervical cancer cases was 13.1 per 1,000 21-yearold Black female persons, compared to 16.2 per 1,000 21-year-old females of all races (**Table 18**). For unvaccinated Black individuals, the lifetime number of cervical cancer cases across screening strategies ranged from 0.56 to 4.88 per 1,000 21-year-old Black female persons, and of cervical cancer deaths ranged from 0.10 to 1.11 per 1,000 21-year-old Black female persons (compared to 0.69 to 5.84 cervical cancer cases per 1,000 and 0.13 to 1.30 cervical cancer deaths per 1,000 for those of all races). The LYG were lower for each screening strategy (ranging from

99 to 160 per 1,000) for Black estimates as compared to all-race estimates (116 to 184 per 1,000). Importantly, in relative measures, the benefits of screening were very similar for Black versus all-race individuals, with a range across strategies of 63% to 96% reduction in cervical cancer cases (all race; 64% to 96%) and 74% to 98% reduction in cervical cancer deaths (all race; 74% to 98%). Current USPSTF guidelines-based strategies resulted in incidence reductions of 87% to 94% and mortality reductions of 90% to 96% for Black female persons, assuming perfect compliance to screening. Likewise, LYG reflected a similar proportional increase in the Black versus all-race models (ranging from 0.18% to 0.29% for the Black estimates versus 0.19% to 0.29% for all races).

The rank-ordering of strategies by LYG was identical to that of the all-race Harvard model and similar to that of the comparative modeling base-case findings (i.e., characteristics of strategies that are either less or more beneficial than current guidelines-based strategies remained similar). Although life expectancy improved for both groups in all screening scenarios, the life expectancy gap between Black and all-race estimates increased in all screening scenarios. Relative to the baseline gap of 6.71 years per 21-year-old female persons, the gap across screening strategies increased nominally from 6.73 to 6.74 years per person. The gap was wider for the strategies with larger health gains, as these resulted in smaller absolute gains for Black female persons.

Total Tests, Colposcopies, False Positive Cases

Given the lower cervical cancer burden in Black female persons (due to higher hysterectomy rates), we found that Black female persons had a lower total number of tests in all scenarios, ranging from 5.7% to 14.9% fewer tests across the strategies than all-race female persons in the Harvard model. These differences were larger in cotesting strategies (where more tests are generally performed for both groups) and in strategies with later start and stop ages (due to differences in hysterectomy and life expectancy). The total colposcopies and false positive results were also lower in Black individuals (from 5% to 13% for colposcopies and 5% to 14% for false positive results).

2vHPV/4vHPV Vaccinated Population – Black Race

Cancer Cases, Deaths, LYG

In the absence of screening, there was a 61% reduction in cervical cancer incidence and a 59% reduction in cervical cancer deaths from 2vHPV or 4vHPV vaccination among female persons of Black race, when compared to unvaccinated (and unscreened) female persons of Black race. The further proportional reductions in cancer burden when adding screening were similar to those in unvaccinated populations, ranging from 74% to 96% reduction in incidence and 83% to 98% reduction in mortality compared to no screening; these corresponded to LYG of 40 to 56 per 1,000 21-year-old female persons of Black race (14 to 20 days of life per Black female person, 0.20 to 1.33 cervical cancer cases averted per 1,000 21-year-old Black female persons), which were lower than LYG in the unvaccinated Black female persons (**Table 19**). As with the unvaccinated population, the absolute health gain associated with screening was smaller for those of Black race compared to those of all races.

The gap in life expectancy widened between Black and all-race female persons vaccinated with 2vHPV or 4vHPV vaccines, with and without screening, as a result of marginally fewer LYG for each averted cervical cancer case among those of Black race. For example, through 2vHPV or 4vHPV vaccination alone (without screening), LYG per 1,000 21-year-old persons was 107 years for those of Black race compared to 122 years for those of all races. With screening, although the absolute gains were smaller, the additional LYG were still higher among the allrace population (8 to 9 additional LYG per 1,000; 3 days per female persons), compared to the Black-race population.

Total Tests, Colposcopies, False Positive Cases

Black individuals vaccinated with 2vHPV or 4vHPV vaccines had 2% to 15% fewer total tests, 17% to 27% fewer colposcopies, and 7% to 33% fewer false positive findings than unvaccinated Black individuals. The relatively lower testing rates by race remained similar to those estimated in the unvaccinated populations, with roughly 6% to 16% fewer of each measure among female persons of Black race when compared to the corresponding all-race estimates.

9vHPV Vaccinated Population – Black Race

Cancer Cases, Deaths, LYG

In the absence of screening, there was an 81% reduction in cervical cancer incidence and a 78% reduction in cervical cancer deaths from 9vHPV vaccination among female persons of Black race, when compared to unvaccinated female persons of Black race. The further proportional reductions in cancer burden when adding screening ranged from 88% to 97% in lifetime cervical cancer incidence and 91% to 99% in lifetime cervical cancer mortality with screening compared to those without screening (similar to the all-race model); these corresponded to LYG of 20 to 23 per 1,000 21-year-old female persons of Black race (7 to 8 days of life per Black female person, 0.08 to 0.31 cervical cancer cases averted per 1,000 21-year-old Black female persons) (**Table 20**). Similar to unvaccinated and 2vHPV/4vHPV vaccinated female persons, the absolute health gains associated with screening in terms of both cancer cases and LYG were smaller among those of Black race compared to all races while the relative gains were similar by race.

The gap in LYG through 9vHPV vaccination alone (without screening) by race was larger than the gap in LYG through 2vHPV/4vHPV vaccination, with a total gain of 140 years per 1,000 21 year-old female persons of Black race compared to 158 years per 1,000 21-year-old female persons of all races. Adding screening strategies to 9vHPV vaccination further increased the difference in LYG by race by 6 to 7 years per 1,000 21-year-old female persons (approximately 2 days per person).

Total Tests, Colposcopies, False Positive Cases

The total number of tests, colposcopies, and false positive findings were further reduced relative to the same screening strategies in unvaccinated or 2vHPV/4vHPV vaccinated female persons of Black race. Among Black individuals vaccinated with 9vHPV, there were 3% to 27% fewer total tests, 28% to 64% fewer colposcopies, and 14% to 61% fewer false positive findings than for unvaccinated Black individuals. These relative reductions were similar to those estimated in the all-race model, but there were roughly 6% to 16% fewer of each measure when compared to the all-race estimates.

Efficient Strategies – Black Race

Of the 73 screening strategies evaluated by the Harvard Black-race model, 25 were identified as being efficient or near-efficient with respect to both colposcopies per LYG and tests per LYG (**Table 21, Figures 15-16**). Of current guidelines, all 3 strategies identified for female persons of all races were also identified as on or near the efficiency frontier for female persons of Black race: 5-year primary HPV testing from age 25 to age 65, 3-year cytology testing at age 21 followed by 5-year cotesting from age 30 to 65, and 3-year cytology testing at age 21 followed by 5-year HPV testing from age 30 to 65. When constraining the analysis to include only those strategies that had efficiency ratios that were equal or less than the guidelines-based strategies on both metrics of colposcopies per LYG and tests per LYG, strategies mostly involved initiating screening at ages 21 (with cytology) or 25 years with HPV testing every 5 years. Two of the same strategies were selected in both the Black-race and all-race analysis (10-year HPV testing from ages 40 to 60 years, which is less effective than current US guidelines-based strategies, and 3-year cytology at age 21 years, with a switch to 5-year HPV testing from ages 30 to 70 years), with comparable incremental harms and incremental benefits between the Black-race and allrace populations.

In the 2vHPV/4vHPV vaccinated cohort, 31 strategies were identified as being efficient or nearefficient with respect to both colposcopies per LYG and tests per LYG (**Table 22, Figures 17- 18**). The rank ordering of screening strategies by effectiveness was generally similar for vaccinated versus unvaccinated Black female persons; however, the efficiency ratios for corresponding strategies were considerably larger than for unvaccinated Black persons. Similar to the findings from the all-race population, the USPSTF recommended strategy of 3-year cytology followed by 5-year HPV testing from age 30 to 65 would require twice as many colposcopies and 2.5 times the number of total tests for each additional LYG in this vaccinated population, compared to those unvaccinated.

Identifying strategies that were efficient or near-efficient for both measures of colposcopies and total tests per LYG and further restricting to strategies that are at least as efficient as current recommendations (for unvaccinated populations), we identified four efficient or near-efficient strategies which all involved 10-year screening intervals using HPV testing. Of the strategies identified by the all-race model, all but one was also identified by the Black-race model. This strategy involved 10-year HPV testing from ages 30 to 70, which was likely not identified in the Black-race model due to the diminishing marginal returns for later screening among those of Black race, as a result of both hysterectomies and competing mortality.

In the 9vHPV vaccinated cohort, 37 strategies were identified as being efficient or near-efficient with respect to both colposcopies per LYG and tests per LYG (**Table 23, Figures 19-20**). The efficiency ratios for screening strategies increased, particularly for measures of tests per LYG, compared to both 2vHPV/4vHPV vaccinated and unvaccinated Black female persons. When restricting to strategies that were efficient or near efficient for measures of both colposcopies and tests per LYG and were at least as efficient as current recommendations, six strategies were identified. These strategies were similar to those identified for the 2vHPV/4vHPV vaccinated population, and strategies all involved in primary HPV testing at 10-year intervals. All strategies identified by the all-race model were also identified by the Black race model. However, two

additional and more intensive strategies were identified for female persons of Black race, both of which began screening at age 25 and were associated with a high number of tests per LYG.

Imperfect Screening and Follow-up Adherence

In the all-race models, assuming imperfect screening and follow-up adherence resulted in reduced health benefits, as well as harms, in each of the three cohorts by vaccination status (**Tables 24-32**), compared to assuming perfect adherence. Across the screening strategies, the LYG were 82% to 85% (Harvard), 56% to 74% (MISCAN-Cervix), 57% to 82% (Policy1- Cervix) and 72% to 83% (UMN) of the LYG under perfect screening (**Table 24**). Reductions in colposcopy ranged from 17 to 43% in the unvaccinated cohort (**Table 25**), 20% to 44% in the 2vHPV/4vHPV vaccinated cohort (**Table 28**), and 19% to 45% in the 9vHPV vaccinated cohort (**Table 31**).

Because of the reduced outcomes, the efficient and near-efficient strategies - identified using both metrics of colposcopies per LYG and tests per LYG, as well as efficiency ratios that were similar to current US recommended strategies in the unvaccinated cohort - included strategies that were more intensive than in the base-case analysis with perfect adherence. For example, in the unvaccinated cohort, the Harvard model identified additional 10-year HPV testing strategies with earlier start ages (i.e., 25, 30, 35 years) and all models identified additional 5-year HPV testing strategies starting earlier with or without preceding cytology testing (**Table 33, Figures 21-22**). Similarly, additional 5-year HPV testing strategies were included in all 4 models in the 2vHPV/4vHPV vaccinated cohort (**Table 34, Figures 23-24**), and 3 of 4 models (Harvard, MISCAN-Cervix, UMN) in the 9vHPV vaccinated cohort (**Table 35, Figures 25-26**).

Imperfect Screening and Follow-up Adherence in Unvaccinated Population – Black Race

In the Harvard Black-race model, we similarly found that screening was less effective across all measures when accounting for imperfect adherence (**Table 36**). For example, in the unvaccinated cohort, while the screening strategies under an assumption of perfect adherence were projected to reduce lifetime cancer incidence by 63% to 96% and cancer mortality by 74% to 98% in unvaccinated female persons of Black race, we found that the same strategies under imperfect adherence reduced lifetime incidence by 47% to 73% and mortality by 57% to 78%. With imperfect adherence, life-years gained across the screening strategies were 76% to 80% of the LYG under perfect screening.

Under perfect adherence, the models projected that across screening strategies Black female persons derived fewer LYG (due to shorter life expectancy) than female persons of all race, a difference that widened with imperfect adherence. This finding suggests that current adherence patterns in screening and follow-up have a disproportionately negative impact on Black female persons compared to female persons of all races. However, as expected with lower utilization of screening, differences in measures of resource use and screening harms also widened. Compared to those of all races and across all screening strategies, those of Black race received 9% to 18% fewer total tests, 18% to 25% fewer colposcopies, and 20% to 28% fewer false positive tests.

As both benefits and costs of screening were attenuated relative to those in the all-race model, we found substantial overlap in the strategies determined to be efficient or near-efficient by the Black and all-race models (**Table 37, Figures 27-28**). Four strategies were identified by the Black-race model that were not identified as efficient strategies in all-race individuals. These were generally more intensive strategies with screening starting at earlier ages (21 or 25).

Imperfect Screening and Follow-up Adherence in Vaccinated Populations – Black Race

The incremental benefits of screening for a Black population vaccinated with 2vHPV or 4vHPV vaccines were diminished when assuming imperfect screening and follow-up adherence, compared to perfect adherence (**Table 38**). Across the screening strategies, LYG under imperfect adherence was 78% to 81% of the LYG under perfect adherence in the Harvard model for 21 year-old female persons of Black race vaccinated with the 2vHPV, 4vHPV or 9vHPV vaccines.

The disproportionate impact of imperfect screening and follow-up patterns by race was somewhat attenuated by vaccination. For example, in the unvaccinated populations, screening with imperfect adherence was associated with an additional 75 to 128 LYG per 1,000 for female persons of all races, compared to female persons of Black race. However, among those vaccinated with the 9vHPV vaccine, imperfect adherence was associated with a smaller gap in LYG (an additional 21 to 25 LYG for female persons of all races, compared to those of Black race).

Strategies for female persons of Black race were similar to strategies identified under perfect adherence (i.e., HPV testing at either 10-year intervals or a mix of 5- and 10-year intervals) in 2vHPV and 4vHPV vaccinated cohorts, when evaluating strategies identified as efficient or nearefficient for both colposcopies and total tests per LYG performed and at least as efficient as current screening recommendations (**Table 39; Figures 29-30**). We also identified four efficient strategies for female persons of Black race vaccinated with 9vHPV (**Tables 40-41; Figures 31- 32**). Importantly, screening strategies for vaccinated persons of Black race were also generally on the efficiency frontier for imperfect screening and follow-up in all-race individuals.

HPV-16/18 Genotype Triage of High-risk HPV-Positive Results

As observed in the 2018 USPSTF decision analysis, ¹⁵ when using HPV-16/18 genotype testing as the triage approach in unvaccinated female persons, the total number of colposcopies was higher than in the base case, with only slight increases in the health benefits (**Appendix Tables 2-4**). For example, for the current guidelines-based strategies, the increase in number of colposcopies ranged from 6% to 25% (median 15%) across the models for the strategy of cytology every 3 years start at age 21 with a switch to HPV testing every 5 years from ages 30 to 65 years, and 9% to 42% (median 20%) for the strategy of primary HPV testing every 5 years from ages 25 to 65 years. In contrast, when assuming perfect screening adherence, these strategies provided less than a day of life gained per person (no more than 2% increase from the base-case analysis) in all the models. Since the vaccines all target HPV-16/18 with complete efficacy over the lifetime, there were no changes in either health benefits or harms in the 2vHPV/4vHPV vaccinated and 9vHPV vaccinated cohorts compared to those for the base-case (non-genotyping) strategies.

In the unvaccinated population, the majority of strategies that were identified as efficient or nearefficient in the base-case analysis were identified when using HPV-16/18 genotype testing as the triage approach, with additional strategies identified in each model (**Appendix Table 5**). In the Harvard model, two additional strategies involving 10-year HPV testing at age 30 years (end ages 60 and 70 years) with preceding cytology starting at age 21, and 10-year HPV testing from ages 25 to 65 years without preceding cytology were identified. In Policy1-Cervix, one additional strategy of 10-year HPV testing from years 35 to 65 years was included. In MISCAN-Cervix model, two strategies involving 10-year HPV testing with preceding 5-year HPV testing were identified. In the UMN model, two additional strategies involving 5-year HPV testing from ages 25 to 65 years and from ages 30 to 70 years were included in the list of efficient or nearefficient strategies.

Test Performance of HPV Testing

The three models (Harvard, Policy1-Cervix, UMN) found that most of the strategies that were identified as efficient or near efficient in the base-case analysis were also identified when HPV test sensitivity and specificity were varied within observed ranges in empirical studies. A few slightly more intensive strategies were identified as efficient or near-efficient according to both metrics of colposcopies per LYG and tests per LYG when the test sensitivity of HPV testing was assumed to reach the lower-bound value of relative sensitivity compared to cytology (1.2). For example, for strategies that had efficiency ratios close to the current guidelines-based strategies, the Harvard model identified 5-year HPV testing from ages 25 to 70 years, and Policy1-Cervix identified two strategies involving cytology testing at age 21 with a switch to 5-year HPV testing starting at ages 25 or 30 years for the unvaccinated population (**Appendix Table 6**). In the 2vHPV/4vHPV vaccinated population, the efficient and near-efficient strategies with similar efficiency ratios as the current guidelines-based strategies in the unvaccinated population were generally the same as in the base-case analysis for each model with small changes in the ratios themselves (**Appendix Table 7**). Likewise, for the 9vHPV vaccinated cohort, the identified strategies were generally consistent with base-case findings, favoring slightly more intensive strategies in the Harvard and UMN models (**Appendix Table 8**).

When assuming an upper-bound relative sensitivity of HPV testing compared to cytology (1.37), the strategies identified as efficient or near-efficient were even more similar to those identified in the base-case analysis, with the exception that in the unvaccinated cohort, the Harvard model identified less intensive strategies involving 10-year HPV testing (versus 5-year HPV testing) (**Appendix Table 9**). In the 2vHPV/4vHPV and 9vHPV vaccinated populations, most of the same strategies were identified as in the base-case analysis with only slight variations in the efficiency ratios (**Appendix Tables 10-11**).

One-Time Screening with HPV Self-Collection

We used the models to examine the potential health benefits that may be gained with a single lifetime cervical cancer screen using HPV self-collection as an approach to recruit previously unscreened (and unvaccinated) female persons. We varied screening age and adherence to follow-up visits (i.e., colposcopy, precancer treatment) to reflect their impacts on health benefit
in terms of cervical cancer cases averted, compared to no screening (**Figure 33**). Across all four models, screening benefit was generally greater when the single screen occurred at younger ages (ages 35, 45 years) and when adherence was higher; MISCAN-Cervix predicted the lowest absolute benefit, while UMN predicted the highest benefit, for each age group and adherence level.

When follow-up adherence was low (i.e., 28.6%), the models predicted a range of cancer cases averted of 0.08 to 0.39 per 1,000 female persons across the age groups (1% to 2% reduction in lifetime cancer risk, compared to no screening). Cancer cases averted increased substantially when adherence reflected rates observed in the METRICS data (72.5%) by 0.62 to 2.39 per 1,000 female persons across the age groups and models (6% to 16% reduction in lifetime cancer risk, compared to no screening). Under perfect adherence (100%), cancer cases averted increased by an additional 0.70 to 2.58 per 1,000 female persons (12% to 30% reduction in lifetime cancer risk, compared to no screening).

In the Black-race model (Harvard only), cancer cases averted from a one-time screen was lower than in the all-race model across all ages and adherence levels (**Figure 34**). Cases averted were greatest when screening occurred at age 35 years among Black female persons (10 years younger than in the all-race Harvard model). When adherence was low (28.6%), cancer cases averted ranged from 0.08 (screen age 65 years) to 0.25 (screen age 35 years) per 1,000 Black female persons. Increases in cancer cases averted associated with higher adherence to screening follow up using the METRICS data (65.3%) ranged from 0.49 (screen age 65 years) to 1.13 (screen age 35 years) per 1,000 Black female persons; under an assumption of perfect adherence, additional increases in cancer cases averted ranged from 0.83 (screen age 65 years) to 1.92 (screen age 45 years). Compared to the all-race model, cases averted in the Black-race model were 18% to 52% lower, with the highest disparity at older ages and when using the METRICS adherence data, which was differentially lower for Black female persons.⁴

Chapter 4. Discussion

This report provides evidence from a model-based decision analysis on the long-term health effects, harms, and efficiency of cervical cancer screening strategies to inform the USPSTF in updating its recommendations for cervical cancer screening in the United States. Building on the decision analysis conducted in 2018 ,¹⁵ we incorporated several additions in the current analysis, including: (1) results from four established cervical cancer models that are part of the CISNET modeling consortium; (2) extending the analysis to include vaccinated cohorts and thereby a larger number of strategies that involve longer intervals and later screening ages; (3) a race-based analysis to evaluate screening outcomes in Black-race (compared to all-race) female persons; and 4) evaluating the potential impact of a single lifetime screen with HPV self-collection for previously unscreened female persons. Given the marginal benefits of some strategies, especially in the vaccinated populations, and imprecision in model outputs, we elected to be inclusive of strategies that were close to the efficiency frontier ("near-efficient") and evaluated all strategies on the basis of two efficiency metrics to reflect different measures of harm: colposcopies per LYG and tests per LYG.

In the unvaccinated population, we found that the three guidelines-based strategies involving HPV testing and cotesting were on the efficiency frontier for most models. However, other strategies were as effective and had similar or more attractive efficiency ratios in unvaccinated female persons, mostly 5-year HPV testing starting at ages 25 or 30 years and with a later end age of 70 years. The guidelines-based strategy of 3-year cytology alone from ages 21 to 65 years was not efficient for any model. Additionally, strategies involving cotesting were associated with nominal additional benefits but much higher numbers of colposcopies and tests, compared with HPV testing alone, indicating lower efficiency.

In the vaccinated cohorts, the models estimated that equal or greater levels of health benefit can be achieved at similar levels of efficiency with less intensive screening. In this population, where screen-test positivity (and thereby colposcopies) diminishes proportionally with LYG, we observed that tests played an enhanced role in reflecting screening burden (in a similar way to "number needed to screen") since tests are less sensitive to the underlying risk of the population, and thereby we used both measures of colposcopies per LYG and tests per LYG to identify efficient strategies. In 2vHPV/4vHPV vaccinated cohorts, strategies of 5-year HPV testing (without preceding cytology) and 10-year HPV testing starting at age 30 to 40 years were efficient and had ratios that were comparable to current guidelines-based strategies in the unvaccinated population. In 9vHPV vaccinated cohorts, strategies identified as efficient according to the current guidelines-based benchmarks almost universally involved 10-year HPV testing with start ages of 30 to 40 years (and variable end ages).

These base-case findings were generally stable when we assumed HPV-16/18 triaging and when HPV testing sensitivity was varied, though if screening and follow-up adherence were imperfect, we could expect to observe greater differences between strategies. Not surprisingly, the magnitude of the health benefits and harms across all screening strategies decreased under imperfect adherence resulting in similar or slightly more intensive strategies on the frontier, especially with respect to screening interval.

While there are many potential ways to deploy screening with HPV self-collection, we chose to explore one simplified use case because of the limited data on follow-up of screen-positive female persons (e.g., receipt of colposcopy and/or precancer treatment) and screening over multiple rounds. We estimated the potential health gains from a one-time screen with HPV selfcollection among previously unscreened female persons at various screen ages and follow-up adherence levels. The models estimated that a one-time screening with HPV self-collection has the potential to reduce lifetime risk of cervical cancer by 25% to 30% if the screen occurs at age 35 to 45 years (12% to 15% if screening occurs at age 65 years), assuming perfect adherence to follow-up diagnosis and precancer treatment. We found that the health benefits from HPV selfcollection were heavily dependent on adherence to follow-up visits for HPV-positive female person.

Several unifying themes emerged from our results, although there was variation in specific strategies selected as efficient or near-efficient across the models: (1) HPV alone was consistently identified as an efficient strategy by all models, cohorts, and metrics; start/switch age, interval, and end ages were influenced by vaccination status; (2) cytology alone was not efficient across any models or cohorts; however, we did not vary start age or screening interval in the same way we explored for HPV and cotesting; (3) cotesting tended to be the least efficient across all models and cohorts; when not dominated, these were clustered at the flat part of the efficiency frontier, indicating diminishing marginal returns with respect to LYG, and (4) overall, interval and screening start age were more influential on outcomes than screening end age.

Differences in the absolute benefits, harms, and (near-)efficient strategies among the models are likely attributable to different assumptions regarding the natural history of HPV. For example, the Harvard model assumes that the transition probabilities between health states depend upon time-in-state rather than age, with longer HPV infection persistence and precancer durations being associated with increasingly higher progression probabilities and lower regression probabilities. A time-in-state model structure that is invariant by age implies that HPV infections acquired at any point over the lifetime are equally risky. In contrast, the MISCAN-Cervix, Policy1-Cervix and UMN models apply age-specific transition probabilities that assume the risk of progression increases with age, which, at a population level, can act as a surrogate marker of time since infection. Age-specific transitions effectively result in dwell times that vary by age (i.e., are longer for female persons who acquire a new HPV infection at a younger age and shorter for those who acquire a new infection at an older age). Consequently, the Harvard model provides a shorter window of time for HPV to be detected in younger ages compared to the other models and therefore tended to favor strategies initiating HPV testing at an earlier age; likewise, the Harvard model estimated lower marginal benefits (all else equal) for ending screening at a later age given it has a comparatively longer window for detection of HPV at older ages compared to the other models. Furthermore, although total dwell times among female persons who developed cervical cancer were similar for the Harvard, UMN and Policy1-Cervix models, ¹⁹ the Harvard model's dwell time in the HPV-infected state for female persons who go on to develop cancer was twice as long as the combined HPV/CIN1 health states for Policy1-Cervix and UMN models (mean duration of 9.9 years (Harvard), 5.2 (Policy1-Cervix), 4.7 years (UMN)). This longer dwell time in the HPV state may contribute to the relatively greater HPVbased screening benefits (and higher colposcopy rates) for female persons in the Harvard model.

The models also differ in their assumptions about the sensitivity of HPV testing for detecting infections in the absence of high-grade disease, with HPV test sensitivity relatively higher in the Harvard model. This contributes to the relatively higher colposcopy numbers and also the relatively larger LYG in the Harvard model at young ages. Other HPV assays shown to improve specificity without compromising sensitivity (e.g., HPV mRNA assays) may reduce colposcopies and follow-up procedures, which would strengthen our overall findings. Other factors, such as cervical cancer burden in the absence of screening (i.e., background risk), may also contribute to differences. For example, the UMN model reflects the largest burden of cervical cancer in the absence of screening across the models, which may impact on the favored strategies and the benefits of continued screening at older ages. All models assumed that all cervical cancers result from high-risk HPV infections. While HPV-negative cancers have been observed among cervical cancer cases, it remains unclear whether these are misclassified cancers, falsely HPV-negative or truly HPV-negative. 66

We observed that the tradeoffs between harms and benefits associated with screening strategies were generally similar for Black and all-race female persons. However, it is important to note that the primary drivers of inequities are not attributable to the differential impact of screening recommendations but rather to structural factors, including differential background mortality, hysterectomy rates, and timely access to screening and cancer treatment. Relative to all-race female persons, we found lower lifetime risk of cervical cancer incidence and mortality for Black female persons in nearly all of our scenarios. While this finding would seem to contradict the presence of a health disparity, the model results reflect (1) the higher hysterectomy rates among Black female persons, which reduce the population at risk for cervical cancer; and (2) the lower life expectancy of Black female persons. Thereby, our findings should not be taken to suggest that Black female persons are actually at lower risk of cervical cancer. In fact, given our comparison to the all-race model that includes Black race, the gap in terms of health benefit may be an underestimate of the true disparities between Black and non-Black female persons.

As in the all-race model, the Harvard model estimated that HPV vaccination provides an opportunity to undertake less intensive screening than current guidelines-based strategies among Black female persons. Furthermore, disparities related to differences in screening practice patterns for Black female persons may be attenuated in HPV-vaccinated populations. However, this attenuation of disparities assumes that the impact of HPV vaccination will be the same for Black individuals; this assumption may not be the case, whether due to differential vaccination uptake or different distribution of causal HPV types in cervical disease.⁶⁷ For example, HPV-35, which is not covered by the available HPV vaccines, is found disproportionately among Black female persons with CIN3.⁶⁸

Although disease simulation models can be powerful tools in projecting long-term outcomes over multiple rounds of screenings and exploring different combinations of screening test modality, intervals, and ages, this analysis is subject to important limitations.

First, as with prior USPSTF decision analyses,^{15,57} our analysis is based on assumptions of perfect adherence to screening intervals and follow-up of screen-positive female persons, including diagnostic colposcopy/biopsy and treatment for precancer; however, it is welldocumented that screening practice is not perfect and quite variable across the United States.²⁹ While we were able to leverage real-world data from the METRICS sites of the PROSPR II consortium, our imperfect adherence assumptions were based on loss-to-follow up in three large health systems, and does not necessarily generalize beyond these health systems. How loss-tofollow up might differ across testing modalities, age, and interval is uncertain – especially in HPV-vaccinated populations – but could impact the overall effectiveness and relative efficiency of the screening strategies modeled. Nonetheless, despite the more realistic representation of current screening practice, basing recommendations under assumptions of imperfect adherence can lead to inefficiencies and excess harms due to over-screening of individuals who adhere to guidelines.⁶⁹

Second, several simplifying assumptions regarding screening were made in the models for tractability or due to a lack of data. For example, while the models attempted to simulate the multitude of pathways of follow-up management according to current recommendations, simplifications around active surveillance post-colposcopy or post-treatment were made with respect to retesting interval and number of repeat tests. Likewise, due to limited data on test performance characteristics in management and follow up, as well as in vaccinated cohorts, we assumed that the test sensitivity and specificity values for cytology and HPV testing remained constant by sub-population (i.e., for those who screened positive or received precancer treatment, based on vaccination status, and across age). As a result of these modeling simplifications, both benefit and harm outcomes may be under- or over-counted on an absolute scale; however, we expect the incremental differences between strategies to be small and therefore unlikely to change overall results or conclusions regarding the efficiency of strategies in any of the three base-case populations.

Third, although we included an extensive number of candidate strategies, there may be alternative strategies that could lead to a more attractive balance of harms and benefits; for example, we restricted our rescreening intervals to be only every 3 years for cytology, and every 5 or 10 years for HPV testing and cotesting, yet there may be combinations of screening test and ages that may make other intervals efficient. Fourth, although we included three different screening end ages (60, 65, 70 years), we did not explore alternative strategies or criteria to determine when to stop screening. Evaluating the impact of screening end age within the context of perfect adherence depends on model assumptions about the natural history of HPV in older female persons. The extent to which newly appearing HPV infections in older female persons are reactivated latent infections, and whether these reactivated infections pose a differential risk of precancer and cancer relative to newly acquired infections in younger female persons, is uncertain. However, evidence from several large cohorts suggests that HPV type and viral persistence (rather than age or reactivation status) are the primary risk determinants.⁷⁰⁻⁷² If earlier birth cohorts (i.e., those born after the 1960s) have elevated HPV prevalence in older ages relative to the cohorts used to calibrate the models or reflected in this analysis, findings may under-estimate the benefits of later screening end ages.

While the number of candidate strategies was extensive, the strategies that were included for consideration influenced the calculated efficiency ratios. For example, by including strategies for unvaccinated individuals that were less effective than current guidelines-based strategies, efficiency ratios for the guidelines-based strategies were higher (less favorable) than they would have been if those strategies were simply compared to no screening. Similarly, the efficiency

ratios for less intensive strategies in vaccinated individuals would likely have been higher had even less intensive strategies been considered (for example, twice lifetime screening). Nevertheless, in general, including sufficient relevant comparator strategies is necessary to prevent underestimation of efficiency ratios, especially for strategies around the acceptability threshold because these strategies are the most policy relevant.⁷³

Additionally, our race-specific analysis used a model that had been previously adapted to reflect HPV natural history in Black female persons.⁵⁸ While we were able to achieve reasonable model fit to currently observed rates of cervical cancer incidence and mortality in SEER, the data to inform the model were more limited than for all races, resulting in greater uncertainty and simplifying assumptions regarding differential underlying risk that may impact the relative benefits of the screening strategies. Although data for other racial and ethnic groups may also be limited, persistent racial disparities in US cervical cancer morbidity and mortality highlight the urgency of more efforts to generate equity-conscious evidence on screening and vaccination in order to guide care delivery interventions to improve outcomes and reduce the disparities in cervical cancer burden.

Better guidance is needed for defining efficiency ratios. Current benchmarks are somewhat arbitrary and, in the absence of evidence on society's "willingness to pay" for colposcopies and tests per LYG, should be used only as general guideposts. For this analysis, we used the efficiency ratios associated with current guidelines-based strategies in the unvaccinated population as indicators for a reasonable and acceptable harm-benefit balance, which enabled us to identify similarly efficient strategies in the vaccinated cohorts. But additional evidence on test harms, societal valuation of different harms, and racial differences in burden of harms will allow future analyses to use better evidence-driven efficiency ratios. Also, the efficiency ratios associated with the guidelines-base strategies were variable across models and sometimes found to be "near efficient" creating non-monotonic patterns in the efficiency ratios; however, this variation – and important advantage of comparative modeling – reflects structural uncertainty across the models, as well as the imprecision and marginal differences between strategies within the models (especially in the vaccinated populations where absolute screening impact is reduced). As a result, we elected to provide general characteristics of efficient strategies that were consistent across the models rather than identifying only one or two strategies that met the technical definition of "most efficient." Reassuringly, broadly similar strategies were identified as the most favorable in vaccinated individuals.

Given the increasing uptake of HPV vaccination and the increasing share of 9vHPV vaccine doses among female persons who are, or will soon be, age-eligible for cervical cancer screening in the United States, we included three base-case analyses to reflect the expected differential risks of cervical cancer by vaccination status. However, our analysis was conducted assuming known vaccination status at the individual level with vaccine completion in early adolescence, rather than assuming a mix of vaccination status that changes over time and varies by age at the population level. Although the United States does not have a universal vaccination registry to readily identify vaccination status for individuals, we elected to avoid conducting the analysis to find a "one size fits all" population-based strategy that would be optimized according to the population average but may not be optimized to specific individuals. A population-average strategy would be ever-changing over time, depending on vaccination uptake patterns in the

population, and would likely disadvantage those who reside in communities with lower vaccine uptake and therefore are less likely to benefit from herd immunity.

Likewise, we modeled and evaluated strategies for unvaccinated individuals assuming no HPV vaccination in the population (i.e., no herd immunity effects). Therefore, the unvaccinated individuals in our analysis are likely less similar to younger birth cohorts who, while personally unvaccinated, become sexually active in an environment where HPV vaccination is available, effectively lowering population-level HPV risk. A nationally-representative US survey reported a 74% reduction in HPV-6/11/16/18 infections in unvaccinated sexually-active 14- to 24-yearold female persons in 2015-2018, compared to 2003-2006 (and compared to a 90% reduction in vaccinated sexually active females), showing substantial herd effects which have increased over the period from 2007 to 2018.⁷⁴ The effects were even stronger for the youngest cohorts of sexually-active female persons, aged 14 to 19 years (an 87% decrease among unvaccinated individuals and a 97% decrease among vaccinated individuals). ¹⁰ This finding of substantial herd effects is consistent with previous meta-analyses of both population-level observed data⁷⁵ and model-based estimates.⁷⁶ These data suggest that the risk of vaccine-preventable HPV types in younger birth cohorts is more comparable to their same-age vaccinated counterparts than to same-age unvaccinated counterparts from older birth cohorts. If this is the case, the identified efficient screening strategies in the unvaccinated population in our study are likely too intensive for unvaccinated female persons born in the era of HPV vaccination.

Summary

The results from our comparative modeling decision analysis suggest that routine cervical cancer screening is effective in reducing cervical cancer cases and deaths and improving life expectancy, even in HPV-vaccinated populations. Strategies involving HPV testing have the potential to provide an efficient balance of harms and benefits, irrespective of HPV vaccination status. In the unvaccinated population, strategies involving 5-year HPV testing with screening start ages of 21 (using cytology) to 30 years, including current US guidelines-based strategies, were found to be efficient. The models estimated that for the HPV-vaccinated populations, there are opportunities to increase health benefit and maintain the same harms-to-benefits balance with less intensive screening, including HPV testing every 5 or 10 years, starting at age 30 to 40 years in 2vHPV/4vHPV vaccinated female persons, and HPV testing every 10 years, starting at ages of 30 to 40 years in 9vHPV vaccinated female persons. Across all scenarios and models, when applying the two metrics of efficiency, strategies involving cytology alone or cotesting were either inefficient or had exceedingly high efficiency ratios.

References

- 1. American Cancer Society. Cancer Facts and Figures, 2023. [\(https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and](https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2023/2023-cancer-facts-and-figures.pdf)[statistics/annual-cancer-facts-and-figures/2023/2023-cancer-facts-and-figures.pdf.](https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2023/2023-cancer-facts-and-figures.pdf) Last accessed September 13, 2023).
- 2. Screening for Cervical Cancer with High-Risk Human Papillomavirus Testing: An Evidence Update for the U.S. Preventive Services Task Force: Evidence Synthesis. Report forthcoming. 2024.
- 3. U.S. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. Cancer Stat Facts: Cervical Cancer. [\(https://seer.cancer.gov/statfacts/html/cervix.html.](https://seer.cancer.gov/statfacts/html/cervix.html) Last accessed September 13, 2023).
- 4. Spencer JC, Kim JJ, Tiro JA, et al. Racial and Ethnic Disparities in Cervical Cancer Screening From Three U.S. Healthcare Settings. Am J Prev Med 2023;65(4):667-677.
- 5. Moyer VA, on behalf of the USPSTF. Screening for Cervical Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2012;156(12):880- 891.
- 6. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. Am J Clin Pathol 2012;137(4):516-42.
- 7. American College of Obstetricians and Gynecologists (ACOG). ACOG Practice Bulletin Number 131: Screening for cervical cancer. Obstet Gynecol 2012;120(5):1222-1238.
- 8. Curry SJ, Krist AH, Owens DK, et al. Screening for Cervical Cancer: US Preventive Services Task Force Recommendation Statement. JAMA 2018;320(7):674-686.
- 9. Fontham ETH, Wolf AMD, Church TR, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. CA Cancer J Clin 2020;70(5):321-346.
- 10. Rosenblum HG, Lewis RM, Gargano JW, Querec TD, Unger ER, Markowitz LE. Declines in Prevalence of Human Papillomavirus Vaccine-Type Infection Among Females after Introduction of Vaccine - United States, 2003-2018. MMWR Morb Mortal Wkly Rep 2021;70(12):415-420.
- 11. U.S. Centers for Disease Control and Prevention. National Immunization Survey-Teen (NIS-TEEN). National Center for Health Statistics. [\(https://www.cdc.gov/vaccines/imz](https://www.cdc.gov/vaccines/imz-managers/nis/datasets-teen.html)[managers/nis/datasets-teen.html.](https://www.cdc.gov/vaccines/imz-managers/nis/datasets-teen.html) Last accessed September 13, 2023).
- 12. Knudsen AB, Rutter CM, Peterse EFP, et al. Colorectal Cancer Screening: An Updated Modeling Study for the US Preventive Services Task Force. JAMA 2021;325(19):1998- 2011.
- 13. Mandelblatt JS, Stout NK, Schechter CB, et al. Collaborative Modeling of the Benefits and Harms Associated With Different U.S. Breast Cancer Screening Strategies. Ann Intern Med 2016;164(4):215-25.
- 14. Meza R, Jeon J, Toumazis I, et al. Evaluation of the Benefits and Harms of Lung Cancer Screening With Low-Dose Computed Tomography: Modeling Study for the US Preventive Services Task Force. JAMA 2021;325(10):988-997.
- 15. Kim JJ, Burger EA, Regan C, Sy S. Screening for Cervical Cancer in Primary Care: A Decision Analysis for the US Preventive Services Task Force. JAMA 2018;320(7):706- 714.
- 16. Cohen CM, Wentzensen N, Castle PE, et al. Racial and Ethnic Disparities in Cervical Cancer Incidence, Survival, and Mortality by Histologic Subtype. J Clin Oncol 2023;41(5):1059-1068.
- 17. Campos NG, Burger EA, Sy S, et al. An Updated Natural History Model of Cervical Cancer: Derivation of Model Parameters. Am J Epidemiol 2014;180(5):545-555.
- 18. Kim JJ, Kuntz KM, Stout NK, et al. Multiparameter calibration of a natural history model of cervical cancer. Am J Epidemiol 2007;166(2):137-50.
- 19. Burger EA, de Kok IM, Groene E, et al. Estimating the natural history of cervical carcinogenesis using simulation models: A CISNET comparative analysis. J Natl Cancer Inst 2020;112(9).955-963.
- 20. Melnikow J, McGahan C, Sawaya GF, Ehlen T, Coldman A. Cervical intraepithelial neoplasia outcomes after treatment: long-term follow-up from the British Columbia Cohort Study. J Natl Cancer Inst 2009;101(10):721-8.
- 21. Soutter WP, Sasieni P, Panoskaltsis T. Long-term risk of invasive cervical cancer after treatment of squamous cervical intraepithelial neoplasia. Int J Cancer 2006;118(8):2048- 55.
- 22. Kitchener HC, Walker PG, Nelson L, et al. HPV testing as an adjunct to cytology in the follow up of women treated for cervical intraepithelial neoplasia. Br J Obstet Gynecol 2008;115(8):1001-7.
- 23. Wheeler CM, Hunt WC, Cuzick J, et al. A population-based study of human papillomavirus genotype prevalence in the United States: baseline measures prior to mass human papillomavirus vaccination. Int J Cancer 2013;132(1):198-207.
- 24. Joste NE, Ronnett BM, Hunt WC, et al. Human papillomavirus genotype-specific prevalence across the continuum of cervical neoplasia and cancer. Cancer Epidemiol Biomarkers Prev 2015;24(1):230-40.
- 25. Saraiya M, Unger ER, Thompson TD, et al. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. J Natl Cancer Inst 2015;107(6):djv086-djv086.
- 26. Laskey PW, Meigs JW, Flannery JT. Uterine cervical carcinoma in Connecticut, 1935- 1973: evidence for two classes of invasive disease. J Natl Cancer Inst 1976;57(5):1037- 43.
- 27. International Agency for Research on Cancer. Cancer Incidence in Five Continents, Vol 1 and 2. [\(http://ci5.iarc.fr/Default.aspx.](http://ci5.iarc.fr/Default.aspx) Last accessed September 13, 2023).
- 28. Beaber EF, Kamineni A, Burnett-Hartman AN, et al. Evaluating and Improving Cancer Screening Process Quality in a Multilevel Context: The PROSPR II Consortium Design and Research Agenda. Cancer Epidemiol Biomarkers Prev 2022;31(8):1521-1531.
- 29. Haas JS, Cheng D, Yu L, et al. Variation in the receipt of human papilloma virus cotesting for cervical screening: Individual, provider, facility and healthcare system characteristics. Prev Med 2022;154:106871.
- 30. Barlow WE, Beaber EF, Geller BM, et al. Evaluating Screening Participation, Follow-up, and Outcomes for Breast, Cervical, and Colorectal Cancer in the PROSPR Consortium. J Natl Cancer Inst 2020;112(3):238-246.
- 31. Suk R, Hong YR, Rajan SS, Xie Z, Zhu Y, Spencer JC. Assessment of US Preventive Services Task Force Guideline-Concordant Cervical Cancer Screening Rates and Reasons for Underscreening by Age, Race and Ethnicity, Sexual Orientation, Rurality, and Insurance, 2005 to 2019. JAMA Netw Open 2022;5(1):e2143582.
- 32. Elfstrom KM, Eklund C, Lamin H, et al. Organized primary human papillomavirus-based cervical screening: A randomized healthcare policy trial. PLoS Med 2021;18(8):e1003748.
- 33. Ogilvie GS, Krajden M, van Niekerk D, et al. HPV for cervical cancer screening (HPV FOCAL): Complete Round 1 results of a randomized trial comparing HPV-based primary screening to liquid-based cytology for cervical cancer. Int J Cancer 2017;140(2):440-448.
- 34. Nygård M, Engesæter B, Castle PE, et al. Randomized Implementation of a Primary Human Papillomavirus Testing-based Cervical Cancer Screening Protocol for Women 34 to 69 Years in Norway. Cancer Epidemiol Biomarkers Prev 2022;31(9):1812-1822.
- 35. Kitchener HC, Almonte M, Thomson C, et al. HPV testing in combination with liquidbased cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. Lancet Oncol 2009;10(7):672-82.
- 36. Naucler P, Ryd W, Törnberg S, et al. Human papillomavirus and Papanicolaou tests to screen for cervical cancer. N Engl J Med 2007;357(16):1589-97.
- 37. Ronco G, Giorgi-Rossi P, Carozzi F, et al. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. Lancet Oncol 2010;11(3):249-57.
- 38. Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors. J Low Genit Tract Dis 2020;24(2):102-131.
- 39. Koliopoulos G, Nyaga VN, Santesso N, et al. Cytology versus HPV testing for cervical cancer screening in the general population. Cochrane Database Syst Rev 2017;8(8):Cd008587.
- 40. Cox JT, Castle PE, Behrens CM, Sharma A, Wright TC, Jr., Cuzick J. Comparison of cervical cancer screening strategies incorporating different combinations of cytology, HPV testing, and genotyping for HPV 16/18: results from the ATHENA HPV study. Am J Obstet Gynecol 2013;208(3):184.e1-184.e11.
- 41. Sherman ME, Schiffman M, Cox JT. Effects of age and human papilloma viral load on colposcopy triage: data from the randomized Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study (ALTS). J Natl Cancer Inst 2002;94(2):102-7.
- 42. Rebolj M, Bonde J, Preisler S, Ejegod D, Rygaard C, Lynge E. Differential Detection of Human Papillomavirus Genotypes and Cervical Intraepithelial Neoplasia by Four Commercial Assays. J Clin Microbiol 2016;54(11):2669-2675.
- 43. Xu L, Oštrbenk A, Poljak M, Arbyn M. Assessment of the Roche Linear Array HPV Genotyping Test within the VALGENT framework. J Clin Virol 2018;98:37-42.
- 44. Rijkaart DC, Berkhof J, Rozendaal L, et al. Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial. Lancet Oncol 2012;13(1):78-88.
- 45. Wahlström C, Iftner T, Dillner J, Dillner L. Population-based study of screening test performance indices of three human papillomavirus DNA tests. J Med Virol 2007;79(8):1169-75.
- 46. Sandri MT, Lentati P, Benini E, et al. Comparison of the Digene HC2 assay and the Roche AMPLICOR human papillomavirus (HPV) test for detection of high-risk HPV genotypes in cervical samples. J Clin Microbiol 2006;44(6):2141-6.
- 47. Zuna RE, Wang SS, Rosenthal DL, Jeronimo J, Schiffman M, Solomon D. Determinants of human papillomavirus-negative, low-grade squamous intraepithelial lesions in the atypical squamous cells of undetermined significance/low-grade squamous intraepithelial lesions triage study (ALTS). Cancer 2005;105(5):253-62.
- 48. Söderlund-Strand A, Rymark P, Andersson P, Dillner J, Dillner L. Comparison between the Hybrid Capture II test and a PCR-based human papillomavirus detection method for diagnosis and posttreatment follow-up of cervical intraepithelial neoplasia. J Clin Microbiol 2005;43(7):3260-6.
- 49. Arbyn M, Ronco G, Anttila A, et al. Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer. Vaccine 2012;30 Suppl 5:F88-F99.
- 50. Lew JB, Simms K, Smith MA, Kang YK, Xu XM, Caruana M. National Cervical Screening Program Renewal: Effectiveness modelling and economic evaluation in the Australian setting (Assessment Report). Canberra: Department of Health. MSAC application number 1276, 2014.
- 51. Lew JB, Simms K, Smith M, Lewis H, Neal H, Canfell K. Effectiveness Modelling and Economic Evaluation of Primary HPV Screening for Cervical Cancer Prevention in New Zealand. PLoS One 2016;11(5):e0151619.
- 52. Kaljouw S, Jansen EEL, Aitken CA, de Kok I. Shift in harms and benefits of cervical cancer screening in the era of HPV screening and vaccination: a modelling study. Br J Obstet Gynecol 2022;129(11):1862-1869.
- 53. Stoler MH, Ronnett BM, Joste NE, Hunt WC, Cuzick J, Wheeler CM. The Interpretive Variability of Cervical Biopsies and Its Relationship to HPV Status. Am J Surg Pathol 2015;39(6):729-36.
- 54. Arbyn M, Redman CWE, Verdoodt F, et al. Incomplete excision of cervical precancer as a predictor of treatment failure: a systematic review and meta-analysis. Lancet Oncol 2017;18(12):1665-1679.
- 55. Berkeley Mortality Database. [\(http://bmd.mortality.org/states.html\)](http://bmd.mortality.org/states.html).
- 56. Simms KT, Yuill S, Killen J, et al. Historical and projected hysterectomy rates in the USA: Implications for future observed cervical cancer rates and evaluating prevention interventions. Gynecol Oncol 2020;158(3):710-718.
- 57. Kulasingam SL, Havrilesky LJ, Ghebre R, Myers ER. Screening for cervical cancer: a modeling study for the US Preventive Services Task Force. J Low Genit Tract Dis 2013;17(2):193-202.
- 58. Spencer JC, Burger EA, Campos NG, Regan MC, Sy S, Kim JJ. Adapting a model of cervical carcinogenesis to self-identified Black women to evaluate racial disparities in the United States. J Natl Cancer Inst Monogr 2023;2023(62):188-195.
- 59. Kinney W, Hunt WC, Dinkelspiel H, Robertson M, Cuzick J, Wheeler CM. Cervical excisional treatment of young women: a population-based study. Gynecol Oncol 2014;132(3):628-35.
- 60. Cuzick J, Myers O, Hunt WC, et al. A population-based evaluation of cervical screening in the United States: 2008-2011. Cancer Epidemiol Biomarkers Prev 2014;23(5):765- 773.
- 61. Cuzick J, Myers O, Hunt WC, et al. Human papillomavirus testing 2007-2012: co-testing and triage utilization and impact on subsequent clinical management. Int J Cancer 2015;136(12):2854-63.
- 62. U.S Centers for Disease Control and Prevention. National Health Interview Survey (NHIS) 2019. National Center for Health Statistics. [\(https://www.cdc.gov/nchs/nhis/2019nhis.htm.](https://www.cdc.gov/nchs/nhis/2019nhis.htm) Last accessed September 13, 2023).
- 63. Campos NG, Scarinci IC, Tucker L, et al. Cost-Effectiveness of Offering Cervical Cancer Screening with HPV Self-Sampling among African-American Women in the Mississippi Delta. Cancer Epidemiol Biomarkers Prev 2021;30(6):1114-1121.
- 64. Stanczuk GA, Currie H, Forson W, et al. Self-sampling as the principal modality for population based cervical screening: Five-year follow-up of the PaVDaG study. Int J Cancer 2022;150(8):1350-1356.
- 65. Adam EE, White MC, Saraiya M. US hysterectomy prevalence by age, race and ethnicity from BRFSS and NHIS: implications for analyses of cervical and uterine cancer rates. Cancer Causes Control 2022;33(1):161-166.
- 66. Pedersen K, Kristiansen IS, Sy S, Kim JJ, Burger EA. Designing Guidelines for Those Who Do Not Follow Them: The Impact of Adherence Assumptions on Optimal Screening Guidelines. Value Health 2023;26(8):1217-1224.
- 67. Giannella L, Di Giuseppe J, Delli Carpini G, et al. HPV-Negative Adenocarcinomas of the Uterine Cervix: From Molecular Characterization to Clinical Implications. Int J Mol Sci 2022;23(23).
- 68. Hirth J, McGrath CJ, Kuo YF, Rupp RE, Starkey JM, Berenson AB. Impact of human papillomavirus vaccination on racial/ethnic disparities in vaccine-type human papillomavirus prevalence among 14-26 year old females in the U.S. Vaccine 2018;36(50):7682-7688.
- 69. Mix J, Saraiya M, Hallowell BD, et al. Cervical Precancers and Cancers Attributed to HPV Types by Race and Ethnicity: Implications for Vaccination, Screening, and Management. J Natl Cancer Inst 2022;114(6):845-853.
- 70. Gage JC, Katki HA, Schiffman M, et al. Age-stratified 5-year risks of cervical precancer among women with enrollment and newly detected HPV infection. Int J Cancer 2015;136(7):1665-71.
- 71. Hammer A, Demarco M, Campos N, et al. A study of the risks of CIN3+ detection after multiple rounds of HPV testing: Results of the 15-year cervical cancer screening experience at Kaiser Permanente Northern California. Int J Cancer 2020;147(6):1612- 1620.
- 72. Rodríguez AC, Schiffman M, Herrero R, et al. Low risk of type-specific carcinogenic HPV re-appearance with subsequent cervical intraepithelial neoplasia grade 2/3. Int J Cancer 2012;131(8):1874-81.
- 73. O'Mahony JF, Naber SK, Normand C, Sharp L, O'Leary JJ, de Kok IM. Beware of Kinked Frontiers: A Systematic Review of the Choice of Comparator Strategies in Cost-Effectiveness Analyses of Human Papillomavirus Testing in Cervical Screening. Value Health 2015;18(8):1138-51.
- 74. Rosenblum HG, Lewis RM, Gargano JW, Querec TD, Unger ER, Markowitz LE. Human Papillomavirus Vaccine Impact and Effectiveness Through 12 Years After Vaccine Introduction in the United States, 2003 to 2018. Ann Intern Med 2022;175(7):918-926.
- 75. Drolet M, Bénard É, Pérez N, Brisson M. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. Lancet 2019;394(10197):497-509.
- 76. Brisson M, Bénard É, Drolet M, et al. Population-level impact, herd immunity, and elimination after human papillomavirus vaccination: a systematic review and metaanalysis of predictions from transmission-dynamic models. Lancet Public Health $2016;1(1):e8-e17.$

Figure 1. Model Schematic

The main health states of the model comprise HPV infection (by genotype), precancer (cervical intraepithelial neoplasia or CIN, grades 1, 2 and 3) and invasive cancer (by stage). The MISCAN-Cervix, Policy1-Cervix, and UMN models reflect all cervical cancers; the Harvard model focuses on squamous cell carcinoma, the most common histologic subtype.

HPV vaccination is modeled as a reduction in the incidence of vaccine-type HPV infections, which is a function of model inputs on age at vaccine receipt, vaccine efficacy, and duration of vaccine protection. Screening is used for early detection of invasive cancer, as well as to detect the presence of high-grade precancers (CIN2 and CIN3), which may resolve spontaneously or, if screen-detected, can be treated and removed before progressing to cancer. The effectiveness of screening strategies depends on coverage by age, interval, test characteristics, treatment efficacy, and compliance to follow-up visits.

These graphs show post-calibration model fit to age- and type-specific HPV prevalence from the New Mexico HPV Pap Registry. ²³

Figure 3. Type Distribution of HPV in CIN1, CIN2 and CIN3

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.

These graphs show post-calibration model fit to HPV type distribution in CIN1, CIN2 and CIN3 from the New Mexico HPV Pap Registry. ²⁴

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; SCC, squamous cell carcinoma.

These graphs show post-calibration model fit to HPV type distribution in cancer (Harvard calibrated to SCC only) from US population-based cancer registries.²⁵

Figure 5. Cervical Cancer Incidence by Age (Natural History)

This graph shows model-projected cervical cancer incidence rates under a scenario of no intervention (i.e., natural history) compared against cancer registry data from the 1950s and early 1960s, before Pap smear screening was widely available in the United States. Data were from the Connecticut Tumor Registry (CTR) and IARC Cancer Incidence in Five Continents (volumes 1 and 2), which included data from Connecticut, New York, Hawaii. ^{26,27} Given the limited data from only a few states – and the potential changes in sexual behavior and other risk factors since the pre-screening era, these data were not used directly to calibrate the models but instead were used to assess predictive validity for overall underlying

Figure 6. Cervical Cancer Incidence and Mortality by Age (With Screening)

Abbreviations: SCC, squamous cell carcinoma.

These graphs show model-projected cervical cancer incidence (All (Panel A), squamous cell carcinoma (SCC) only (Panel B) and mortality rates (All (Panel C), SCC only (Panel D) under assumptions of screening practice patterns reported in the METRICS sites, ²⁹ compared against those reported in SEER cancer registries in recent years (i.e., 2000-2013). ³ Model projections from Harvard show the mean, minimum and maximum values across 50 good-fitting natural history parameter sets. [Note: Both incidence and mortality rates from the model were calculated using the number of female persons alive as the denominator, not adjusting for hysterectomy, to match the

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Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus.

Model-estimated outcomes were compared to those reported in empirical studies summarized in the evidence synthesis.² Specifically, we compared the relative risks (RRs) of colposcopy referral, CIN2+ detection, and CIN3+ detection reported in randomized controlled trials of primary HPV testing compared to cytology-based screening and, separately, cotesting to cytology-based screening. 32-37,44

Figure 8. Flow Diagrams for Management of Screen-Positive Results

A. Primary cytology testing (HPV testing for ASC-US)

C. Primary cotesting (repeat cotesting for HPV-positive/cytology-negative)

Figure 9. Colposcopies per Life-Year Gained for All Strategies Among Unvaccinated Female Persons by Model

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Figure 10. Tests per Life-Year Gained for All Strategies Among Unvaccinated Female Persons by Model

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Figure 18. Tests per Life-Year Gained for All Strategies Among 2vHPV or 4vHPV Vaccinated Black Female Persons in the Harvard Model

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Figure 19. Colposcopies per Life-Year Gained for All Strategies Among 9vHPV Vaccinated Black Female Persons in the Harvard Model

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Figure 20. Tests per Life-Year Gained for All Strategies Among 9vHPV Vaccinated Black Female Persons in the Harvard Model

Figure 21. Colposcopies per Life-Year Gained for All Strategies Among Unvaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model

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Figure 22. Tests per Life-Year Gained for All Strategies Among Unvaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model

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Figure 24. Tests per Life-Year Gained for All Strategies Among 2vHPV or 4vHPV Vaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model

Cervical Cancer Screening Decision Analysis ϵ EPC> ϵ 63

Figure 25. Colposcopies per Life-Year Gained for All Strategies Among 9vHPV Vaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model

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Figure 26. Tests per Life-Year Gained for All Strategies Among 9vHPV Vaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model

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Figure 27. Colposcopies per Life-Year Gained for All Strategies Among Unvaccinated Black Female Persons Assuming Imperfect Screening and Follow-up Adherence in the Harvard Model

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Figure 28. Tests per Life-Year Gained for All Strategies Among Unvaccinated Black Female Persons Assuming Imperfect Screening and Follow-up Adherence in the Harvard Model

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Figure 29. Colposcopies per Life-Year Gained for All Strategies Among 2vHPV or 4vHPV Vaccinated Black Female Persons Assuming Imperfect Screening and Follow-up Adherence in the Harvard Model

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Figure 30. Tests per Life-Year Gained for All Strategies Among 2vHPV or 4vHPV Vaccinated Black Female Persons Assuming Imperfect Screening and Follow-up Adherence in the Harvard Model

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Figure 31. Colposcopies per Life-Year Gained for All Strategies Among 9vHPV Vaccinated Black Female Persons Assuming Imperfect Screening and Follow-up Adherence in the Harvard Model

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Figure 33. Cervical Cancer Cases Averted from a Single Lifetime Screen with HPV Self-Collection Among Unvaccinated Female Persons by Screen Age and Follow-Up Adherence by Model

Figure 34. Cervical Cancer Cases Averted from a Single Lifetime Screen with HPV Self-Collection Among Unvaccinated Black Female Persons by Screen Age and Follow-Up Adherence in the Harvard Model

Abbreviations: CIN, cervical intraepithelial neoplasia; FIGO, International Federation of Gynecology and Obstetrics; HPV, Human papillomavirus; SEER, Surveillance, Epidemiology, and End Results.

Table 2. Screening Strategies Modeled for Validation Exerciseᵃ

Abbreviations: ASC-US, atypical squamous cells of undetermined significance; CYTO, cytology; HPV, Human papillomavirus.

aValidation exercise involved simulating the protocols of clinical studies included in the evidence synthesis² and comparing model-predicted outcomes against the empirical outcomes.

Table 3. Base-Case Screening Strategies

Abbreviations: CYTO, cytology; HPV, Human papillomavirus.

a Strategies (bolded) represent current US recommended strategies.

Table 4. Screening Test Characteristics^a

Abbreviations: HPV, Human papillomavirus.

a Sensitivity (specificity) for all tests defined as probability to detect presence (absence) of cervical

intraepithelial neoplasia, grade 2 or worse (CIN2+).

ᵇ For cytology testing, positivity threshold is atypical squamous cells of undetermined significance (ASC-US).

ᶜ For HPV testing and cotesting, sensitivity and specificity are relative to cytology test characteristics.

Table 5. Current Screening Practice by Race^a

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, Human papillomavirus.

ᵃ The table shows the distribution of screening intervals for all-race and Black-race female persons when adherence is imperfect under different recommended screening intervals of either 3-year, 5-year or 10-year. For example, when the recommended interval is 10-year, then a "very early" screener is assumed to screen at an 8-year interval, whereas an "early" screener screens at a 9-year interval.

Table 6. Lifetime Number of Cervical Cancer Cases, Deaths and Life-Years Gained Among Unvaccinated Female Persons for Screening Strategies by Model^a

Abbreviations: CYTO, cytology; HPV, Human papillomavirus; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

ᵃ Outcomes calculated from age 21 to 100 years.

b Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30.

ᶜ Median outcome across the four models.

^d End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

ᵉ Strategies (bolded) represent current US recommended strategies.

Table 7. Lifetime Number of Total Tests and Colposcopies Among Unvaccinated Female Persons for Screening Strategies by Modelᵃ

Abbreviations: CYTO, cytology; HPV, Human papillomavirus; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

a Outcomes calculated from age 21 to 100 years.

b Total number of tests including cytology and HPV tests, irrespective of primary, triage or surveillance context.

ᶜ Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30. ᵈ Median outcome across the four models.

ᵉ End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female

persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

ᶠ Strategies (bolded) represent current US recommended strategies.

Table 8. Lifetime Number of CIN2+ Detected and False Positives Among Unvaccinated Female Persons for Screening Strategies by Model^a

Abbreviations: CIN, cervical intraepithelial; CYTO, cytology; HPV, Human papillomavirus; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

ᵃ Outcomes calculated from age 21 to 100 years.

D CIN2+ detected includes CIN2s, CIN3s and cervical cancers detected through screening (excludes clinically detected cancers).

ᶜ Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

ᵈ Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30. ᵉ Median outcome across the four models.

ᶠ End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment. ᵍ Strategies (bolded) represent current US recommended strategies.

Table 9. Lifetime Number of Cervical Cancer Cases, Deaths and Life-Years Gained Among 2vHPV or 4vHPV Vaccinated Female Persons for Screening Strategies by Modela

Abbreviations: CYTO, cytology; HPV, Human papillomavirus; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

ᵃ Outcomes calculated from age 21 to 100 years.

b Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30.

ᶜ Median outcome across the four models.

^d End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

ᵉ Strategies (bolded) represent current US recommended strategies.

Table 10. Lifetime Number of Total Tests and Colposcopies Among 2vHPV or 4vHPV Vaccinated Female Persons for Screening Strategies by Modelᵃ

Abbreviations: CYTO, cytology; HPV, Human papillomavirus; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

a Outcomes calculated from age 21 to 100 years.

ᵇ Total number of tests including cytology and HPV tests, irrespective of primary, triage or surveillance context.

ᶜ Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30. ᵈ Median outcome across the four models.

ᵉ End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

ᶠ Strategies (bolded) represent current US recommended strategies.

Table 11. Lifetime Number of CIN2+ Detected and False Positives Among 2vHPV or 4vHPV Vaccinated Female Persons for Screening Strategies by Model^a

Abbreviations: CIN, cervical intraepithelial; CYTO, cytology; HPV, Human papillomavirus; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

ᵃ Outcomes calculated from age 21 to 100 years.

ᵇ CIN2+ detected includes CIN2s, CIN3s and cervical cancers detected through screening (excludes clinically detected cancers).

ᶜ Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

ᵈ Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30. ᵉ Median outcome across the four models.

ᶠ End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

ᵍ Strategies (bolded) represent current US recommended strategies.

Table 12. Lifetime Number of Cervical Cancer Cases, Deaths and Life-Years Gained Among 9vHPV Vaccinated Female Persons for Screening Strategies by Modela

Abbreviations: CYTO, cytology; HPV, Human papillomavirus; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

ᵃ Outcomes calculated from age 21 to 100 years.

b Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30.

ᶜ Median outcome across the four models.

^d End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

ᵉ Strategies (bolded) represent current US recommended strategies.

Table 13. Lifetime Number of Total Tests and Colposcopies Among 9vHPV Vaccinated Female Persons for Screening Strategies by Modela

Abbreviations: CYTO, cytology; HPV, Human papillomavirus; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

ᵃ Outcomes calculated from age 21 to 100 years.

ᵇ Total number of tests including cytology and HPV tests, irrespective of primary, triage or surveillance context

ᶜ Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30. ᵈ Median outcome across the four models.

ᵉ End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

ᶠ Strategies (bolded) represent current US recommended strategies.

Table 14. Lifetime Number of CIN2+ Detected and False Positives Among 9vHPV Vaccinated Female Persons for Screening Strategies by Model^a

Abbreviations: CIN, cervical intraepithelial; CYTO, cytology; HPV, Human papillomavirus; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

a Outcomes calculated from age 21 to 100 years.

^b CIN2+ detected includes CIN2s, CIN3s and cervical cancers detected through screening (excludes clinically detected cancers).

ᶜ Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

^d Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30. ᵉ Median outcome across the four models.

ᶠ End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

ᵍ Strategies (bolded) represent current US recommended strategies.

Table 15. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among Unvaccinated Female Persons by Model^a

Abbreviations: CYTO, cytology; HPV, Human papillomavirus; LYG, life-years gained; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

ᵃ Near-efficient (i.e., within 2% of the efficiency frontier) are indicated by *. Strategies are ordered by increasing colposcopies in the Harvard model. Ratios were calculated against the next-less effective, non-dominated strategy within each model. Ratios in grey font indicate strategies that had lower LYG than the guidelines-based strategy of 3-yearly cytology from ages 21 to 65 years in each model. Yellow highlighted ratios indicate strategies that were most efficient on both metrics among the current guidelines-based strategies and whose efficiency ratios served as benchmarks for efficiency in the vaccinated populations in each model. Strategies that were dominated by both efficiency metrics in all 4 models are not shown. **b** Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, HPV-10Y, 40, 60 indicates HPV testing every 10 years starting at age 40 years and ending at age 60 years, and HPV-5Y, 35/HPV-10Y, 40, 60 indicates HPV testing every 5 years starting at age 35 years with a switch to HPV testing every 10 years starting at age 40 years and ending at age 60 years. ᶜ Strategies (bolded) represent current US recommended strategies.

Table 16. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 2vHPV or 4vHPV Vaccinated Female Persons by Model^a

Abbreviations: CYTO, cytology; HPV, Human papillomavirus; LYG, life-years gained; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

a Near-efficient (i.e., within 2% of the efficiency frontier) are indicated by *. Strategies are ordered by increasing colposcopies in the Harvard model. Ratios were calculated against the next-less effective, non-dominated strategy within each model. Yellow highlighted ratios indicate strategies with efficiency ratios that were equal to or less than those from the current guidelines-based strategies in the unvaccinated population on both efficiency metrics of colposcopies per LYG and tests per LYG in each model. The efficiency ratios used as benchmarks in each model were: 78-133 colposcopies per LYG and 1,509-2,663 tests per LYG in the Harvard model; 48-54 colposcopies per LYG and 291-4,279 tests per LYG in the MISCAN-Cervix model; 17-32 colposcopies per LYG and 688-1,052 tests per LYG in the Policy1-Cervix model; 92 to 134 colposcopies per LYG and 229-2,016 tests per LYG in the UMN model (see **Table 15**). Strategies that were dominated by both efficiency metrics in all 4 models are not shown. **b** Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, HPV-10Y, 40, 60 indicates HPV testing every 10 years starting at age 40 years and ending at age 60 years, and HPV-5Y, 35/HPV-10Y, 40, 60 indicates HPV testing every 5 years starting at age 35 years with a switch to HPV testing every 10 years starting at age 40 years and ending at age 60 years. ᶜ Strategies (bolded) represent current US recommended strategies.

Table 17. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 9vHPV Vaccinated Female Persons by Modelᵃ

Abbreviations: CYTO, cytology; HPV, Human papillomavirus; LYG, life-years gained; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

a Near-efficient (i.e., within 2% of the efficiency frontier) are indicated by *. Strategies are ordered by increasing colposcopies in the Harvard model. Ratios were calculated against the next-less effective, non-dominated strategy within each model. Yellow highlighted ratios indicate strategies with efficiency ratios that were equal to or less than those from the current guidelines-based strategies in the unvaccinated population on both efficiency metrics of colposcopies per LYG and tests per LYG in each model. The efficiency ratios used as benchmarks in each model were: 78-133 colposcopies per LYG and 1,509-2,663 tests per LYG in the Harvard model; 48-54 colposcopies per LYG and 291-4,279 tests per LYG in the MISCAN-Cervix model; 17-32 colposcopies per LYG and 688-1,052 tests per LYG in the Policy1-Cervix model; 92-134 colposcopies per LYG and 229-2,016 tests per LYG in the UMN model (see **Table 15**). Strategies that were dominated by both efficiency metrics in all 4 models are not shown.

b Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, HPV-10Y, 40, 60 indicates HPV testing every 10 years starting at age 40 years and ending at age 60 years, and HPV-5Y, 35/HPV-10Y, 40, 60 indicates HPV testing every 5 years starting at age 35 years with a switch to HPV testing every 10 years starting at age 40 years and ending at age 60 years. ᶜ Strategies (bolded) represent current US recommended strategies.

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Table 18. Lifetime Outcomes Among Unvaccinated Black Female Persons for Screening Strategies in the Harvard Model^a

Abbreviations: CC, Cervical cancer; CIN, cervical intraepithelial; Colpos, colposcopies; CYTO, cytology; HPV, Human papillomavirus.

^a Outcomes calculated from age 21 to 100 years.

 $^{\rm b}$ Total number of tests including cytology and HPV tests, irrespective of primary, triage or surveillance context.

ᶜ CIN2+ detected includes CIN2s, CIN3s and cervical cancers detected through screening (excludes clinically detected cancers).

ᵈ Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

ᵉ Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30.

ᶠ End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

ᵍ Strategies (bolded) represent current US recommended strategies.

Table 19. Lifetime Outcomes Among 2vHPV or 4vHPV Vaccinated Black Female Persons for Screening Strategies in the Harvard Modela

Abbreviations: CC, Cervical cancer; CIN, cervical intraepithelial; Colpos, colposcopies; CYTO, cytology; HPV, Human papillomavirus.

^a Outcomes calculated from age 21 to 100 years.

 $^{\rm b}$ Total number of tests including cytology and HPV tests, irrespective of primary, triage or surveillance context.

ᶜ CIN2+ detected includes CIN2s, CIN3s and cervical cancers detected through screening (excludes clinically detected cancers).

ᵈ Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

ᵉ Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30.

ᶠ End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

ᵍ Strategies (bolded) represent current US recommended strategies.

Table 20. Lifetime Outcomes Among 9vHPV Vaccinated Black Female Persons for Screening Strategies in the Harvard Model^a

Abbreviations: CC, Cervical cancer; CIN, cervical intraepithelial; Colpos, colposcopies; CYTO, cytology; HPV, Human papillomavirus.

ᵃ Outcomes calculated from age 21 to 100 years.

ᵇ Total number of tests including cytology and HPV tests, irrespective of primary, triage or surveillance context.

ᶜ CIN2+ detected includes CIN2s, CIN3s and cervical cancers detected through screening (excludes clinically detected cancers).

ᵈ Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

ᵉ Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30.

^f End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment. ᵍ Strategies (bolded) represent current US recommended strategies.

Table 21. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among Unvaccinated Black Female Persons in the Harvard Model^a

Abbreviations: CYTO, cytology; HPV, Human papillomavirus; LYG, life-years gained

ᵃ Near-efficient (i.e., within 2% of the efficiency frontier) are indicated by *. Strategies are ordered by increasing colposcopies. Ratios were calculated against the next-less effective, non-dominated strategy. Ratios in grey font indicate strategies that had lower LYG than the guidelines-based strategy of 3-yearly cytology from ages 21 to 65 years in the Harvard model. Yellow highlighted ratios indicate strategies that were most efficient on both metrics among the current guidelines-based strategies and whose efficiency ratios served as benchmarks for efficiency in the vaccinated populations. Strategies that were dominated by both efficiency metrics are not shown. **b** Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, HPV-10Y, 40, 60 indicates HPV testing every 10 years starting at age 40 years and ending at age 60 years, and HPV-5Y, 35/HPV-10Y, 40, 60 indicates HPV testing every 5 years starting at age 35 years with a switch to HPV testing every 10 years starting at age 40 years and ending at age 60 years.

ᶜ Strategies (bolded) represent current US recommended strategies.

Strategyb	Incremental Colposcopies per LYG	Incremental Total Tests per LYG
HPV-10Y, 40, 60	6	81
HPV-10Y, 30, 60	22	132
HPV-10Y, 30, 70	$121*$	$3,130*$
HPV-5Y, 30/HPV-10Y, 35, 65	$76*$	$1,273*$
CYTO-3Y, 21/HPV-10Y, 30, 60	47	$5,078*$
CYTO-3Y, 21/HPV-10Y, 30, 70	112	27,151*
HPV-10Y, 25, 65	$78*$	522
CYTO-4Y, 21/HPV-10Y, 25, 65	86*	$3,855*$
HPV-5Y, 25/HPV-10Y, 30, 60	$1,061*$	661
HPV-5Y, 25/HPV-10Y, 30, 70	$1,123*$	2,987*
CYTO-3Y, 21/HPV-5Y, 30, 60	$167*$	$8,530*$
HPV-5Y, 25/HPV-10Y, 35, 65	556*	2,636
CYTO-3Y, 21/HPV-5Y, 30, 65c	163	7,374*
CYTO-3Y, 21/COTEST-10Y, 30, 70	$717*$	27,051*
CYTO-3Y, 21/HPV-5Y, 30, 70	228	7,362*
HPV-5Y, 25, 60	$314*$	$4,260*$
CYTO-4Y, 21/COTEST-10Y, 25, 65	993*	20,223*
HPV-5Y, 25, 65°	20,867*	4,269*
HPV-5Y, 25, 70	14,924*	4,587*
COTEST-5Y, 25/COTEST-10Y, 30, 70	$1,524*$	27,500*
CYTO-4Y, 21/HPV-5Y, 25, 60	$1,091*$	4,001
CYTO-4Y, 21/HPV-5Y, 25, 65	545*	4,431
CYTO-4Y, 21/HPV-5Y, 25, 70	475	7,554
COTEST-5Y, 25/COTEST-10Y, 35, 65	907*	75,471*
CYTO-3Y, 21/COTEST-5Y, 30, 60	4,128*	17,804*
CYTO-3Y, 21/COTEST-5Y, 30, 65°	$1,931*$	2,957,692*
CYTO-3Y, 21/COTEST-5Y, 30, 70	1,298*	137,556*
COTEST-5Y, 25, 65	93,784*	18,040*
CYTO-4Y, 21/COTEST-5Y, 25, 60	19,744*	768,353*
CYTO-4Y, 21/COTEST-5Y, 25, 65	1,808*	68,566*
CYTO-4Y, 21/COTEST-5Y, 25, 70	1,273	47,851

Table 22. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 2vHPV or 4vHPV Vaccinated Black Female Persons in the Harvard Modelᵃ

Abbreviations: CYTO, cytology; HPV, Human papillomavirus; LYG, life-years gained.

ᵃ Near-efficient (i.e., within 2% of the efficiency frontier) are indicated by *. Strategies are ordered by increasing colposcopies. Ratios were calculated against the next-less effective, non-dominated strategy. Yellow highlighted ratios indicate strategies with efficiency ratios that were equal to or less than those from the current guidelinesbased strategies in the unvaccinated population on both efficiency metrics of colposcopies per LYG and tests per LYG in the Harvard model. The efficiency ratios used as benchmarks were: 75-587 colposcopies per LYG and 1,341-2,604 tests per LYG (see **Table 21**). Strategies that were dominated by both efficiency metrics are not shown.

b Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, HPV-10Y, 40, 60 indicates HPV testing every 10 years starting at age 40 years and ending at age 60 years, and HPV-5Y, 35/HPV-10Y, 40, 60 indicates HPV testing every 5 years starting at age 35 years with a switch to HPV testing every 10 years starting at age 40 years and ending at age 60 years.

ᶜ Strategies (bolded) represent current US recommended strategies.

Table 23. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 9vHPV Vaccinated Black Female Persons in the Harvard Model^a

Abbreviations: CYTO, cytology; HPV, Human papillomavirus; LYG, life-years gained.

a Near-efficient (i.e., within 2% of the efficiency frontier) are indicated by *. Strategies are ordered by increasing colposcopies. Ratios were calculated against the next-less effective, non-dominated strategy. Yellow highlighted ratios indicate strategies with efficiency ratios that were equal to or less than those from the current guidelines-based strategies in the unvaccinated population on both efficiency metrics of colposcopies per LYG and tests per LYG in the Harvard model.

The efficiency ratios used as benchmarks were: 75-587 colposcopies per LYG and 1,341-2,604 tests per LYG (see **Table 21**). Strategies that were dominated by both efficiency metrics are not shown.

b Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, HPV-10Y, 40, 60 indicates HPV testing every 10 years starting at age 40 years and ending at age 60 years, and HPV-5Y, 35/HPV-10Y, 40, 60 indicates HPV testing every 5 years starting at age 35 years with a switch to HPV testing every 10 years starting at age 40 years and ending at age 60 years.

ᶜ Strategies (bolded) represent current US recommended strategies.

Table 24. Lifetime Number of Cervical Cancer Cases, Deaths and Life-Years Gained Among Unvaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model^a

Abbreviations: CYTO, cytology; HPV, Human papillomavirus; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

ᵃ Outcomes calculated from age 21 to 100 years.

b Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30.

ᶜ Median outcome across the four models.

^d End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

ᵉ Strategies (bolded) represent current US recommended strategies.

Table 25. Lifetime Number of Total Tests and Colposcopies Among Unvaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model^a

Abbreviations: CYTO, cytology; HPV, Human papillomavirus; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

^a Outcomes calculated from age 21 to 100 years.

b Total number of tests including cytology and HPV tests, irrespective of primary, triage or surveillance context.

ᶜ Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30. ᵈ Median outcome across the four models.

ᵉ End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

ᶠ Strategies (bolded) represent current US recommended strategies.

Table 26. Lifetime Number of CIN2+ Detected and False Positives Among Unvaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Modelᵃ

Abbreviations: CIN, cervical intraepithelial; CYTO, cytology; HPV, Human papillomavirus; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

ᵃ Outcomes calculated from age 21 to 100 years.

ᵇ CIN2+ detected includes CIN2s, CIN3s and cervical cancers detected through screening (excludes clinically detected cancers).

ᶜ Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

ᵈ Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30. ᵉ Median outcome across the four models.

ᶠ End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

ᵍ Strategies (bolded) represent current US recommended strategies.

Table 27. Lifetime Number of Cervical Cancer Cases, Deaths and Life-Years Gained Among 2vHPV or 4vHPV Vaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Modela

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Abbreviations: CYTO, cytology; HPV, Human papillomavirus; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model. ᵃ Outcomes calculated from age 21 to 100 years.

b Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30.

ᶜ Median outcome across the four models.

^d End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

ᵉ Strategies (bolded) represent current US recommended strategies.

Table 28. Lifetime Number of Total Tests and Colposcopies Among 2vHPV or 4vHPV Vaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Modelᵃ

Abbreviations: CYTO, cytology; HPV, Human papillomavirus; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

ᵃ Outcomes calculated from age 21 to 100 years.

ᵇ Total number of tests including cytology and HPV tests, irrespective of primary, triage or surveillance context.

ᶜ Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30. ᵈ Median outcome across the four models.

e End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

f Strategies (bolded) represent current US recommended strategies.

Table 29. Lifetime Number of CIN2+ Detected and False Positives Among 2vHPV or 4vHPV Vaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Modelᵃ

Abbreviations: CYTO, cytology; HPV, Human papillomavirus; CIN, cervical intraepithelial; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

ᵃ Outcomes calculated from age 21 to 100 years.

ᵇ CIN2+ detected includes CIN2s, CIN3s and cervical cancers detected through screening (excludes clinically detected cancers).

ᶜ Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

ᵈ Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30. ᵉ Median outcome across the four models.

ᶠ End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

ᵍ Strategies (bolded) represent current US recommended strategies.

Table 30. Lifetime Number of Cervical Cancer Cases, Deaths and Life-Years Gained Among 9vHPV Vaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Modelᵃ

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Abbreviations: CYTO, cytology; HPV, Human papillomavirus; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model. ᵃ Outcomes calculated from age 21 to 100 years.

b Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30.

ᶜ Median outcome across the four models.

^d End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

ᵉ Strategies (bolded) represent current US recommended strategies.

Table 31. Lifetime Number of Total Tests and Colposcopies Among 9vHPV Vaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Modela

Abbreviations: CYTO, cytology; HPV, Human papillomavirus; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

ᵃ Outcomes calculated from age 21 to 100 years.

ᵇ Total number of tests including cytology and HPV tests, irrespective of primary, triage or surveillance context.

ᶜ Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30. ᵈ Median outcome across the four models.

e End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

f Strategies (bolded) represent current US recommended strategies.

Table 32. Lifetime Number of CIN2+ Detected and False Positives Among 9vHPV Vaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Model^a

Abbreviations: CIN, cervical intraepithelial; CYTO, cytology; HPV, Human papillomavirus; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

ᵃ Outcomes calculated from age 21 to 100 years.

ᵇ CIN2+ detected includes CIN2s, CIN3s and cervical cancers detected through screening (excludes clinically detected cancers).

ᶜ Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

ᵈ Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30. ᵉ Median outcome across the four models.

ᶠ End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

ᵍ Strategies (bolded) represent current US recommended strategies.

Table 33. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among Unvaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Modela

Abbreviations: CYTO, cytology; HPV, Human papillomavirus; LYG, life-years gained; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

a Near-efficient (i.e., within 2% of the efficiency frontier) are indicated by *. Strategies are ordered by increasing colposcopies in the Harvard model. Ratios were calculated against the next-less effective, non-dominated strategy within each model. Ratios in grey font indicate strategies that had lower LYG than the guidelines-based strategy of 3-yearly cytology from ages 21 to 65 years in each model. Yellow highlighted ratios indicate strategies with efficiency ratios that were equal to or less than those from the current guidelines-based strategies in the unvaccinated population on both efficiency metrics of colposcopies per LYG and tests per LYG in each model, assuming perfect adherence. The efficiency ratios used as benchmarks in each

model were: 78-133 colposcopies per LYG and 1,509-2,663 tests per LYG in the Harvard model; 48-54 colposcopies per LYG and 291-4,279 tests per LYG in the MISCAN-Cervix model; 17-32 colposcopies per LYG and 688-1,052 tests per LYG in the Policy1-Cervix model; 92-134 colposcopies per LYG and 229-2,016 tests per LYG in the UMN model (see **Table 15**). Strategies that were dominated by both efficiency metrics in all 4 models are not shown.

b Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, HPV-10Y, 40, 60 indicates HPV testing every 10 years starting at age 40 years and ending at age 60 years, and HPV-5Y, 35/HPV-10Y, 40, 60 indicates HPV testing every 5 years starting at age 35 years with a switch to HPV testing every 10 years starting at age 40 years and ending at age 60 years. ᶜ Strategies (bolded) represent current US recommended strategies.

Table 34. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 2vHPV or 4vHPV Vaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Modelᵃ

Abbreviations: CYTO, cytology; HPV, Human papillomavirus; LYG, life-years gained; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

ᵃ Near-efficient (i.e., within 2% of the efficiency frontier) are indicated by *. Strategies are ordered by increasing colposcopies in the Harvard model. Ratios were calculated against the next-less effective, non-dominated strategy within each model. Yellow highlighted ratios indicate strategies with efficiency ratios that were equal to or less than those from the current guidelines-based strategies in the unvaccinated population on both efficiency metrics of colposcopies per LYG and tests per LYG in each model, assuming perfect adherence. The efficiency ratios used as benchmarks in each model were: 78-133 colposcopies per LYG and 1,509-2,663 tests per LYG in the Harvard model; 48-54 colposcopies per LYG and 291-4,279 tests per LYG in the MISCAN-Cervix model; 17-32 colposcopies per LYG and 688-1,052 tests per LYG in the Policy1-Cervix model; 92-134 colposcopies per LYG and 229-2,016 tests per LYG in the UMN model (see **Table 15**). Strategies that were dominated by both efficiency metrics in all 4 models are not shown.

ᵇ Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, HPV-10Y, 40, 60 indicates HPV testing every 10 years starting at age 40 years and ending at age 60 years, and HPV-5Y, 35/HPV-10Y, 40, 60 indicates HPV testing every 5 years starting at age 35 years with a switch to HPV testing every 10 years starting at age 40 years and ending at age 60 years. ᶜ Strategies (bolded) represent current US recommended strategies.

Table 35. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 9vHPV Vaccinated Female Persons Assuming Imperfect Screening and Follow-up Adherence by Modela

Incremental Total Tests per LYG

Abbreviations: CYTO, cytology; HPV, Human papillomavirus; LYG, life-years gained; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

a Near-efficient (i.e., within 2% of the efficiency frontier) are indicated by *. Strategies are ordered by increasing colposcopies in the Harvard model. Ratios were calculated against the next-less effective, non-dominated strategy within each model. Yellow highlighted ratios indicate strategies with efficiency ratios that were equal to or less than those from the current quidelinesbased strategies in the unvaccinated population on both efficiency metrics of colposcopies per LYG and tests per LYG in each model, assuming perfect adherence. The efficiency ratios used as benchmarks in each model were: 78-133 colposcopies per LYG and 1,509-2,663 tests per LYG in the Harvard model; 48-54 colposcopies per LYG and 291-4,279 tests per LYG in the MISCAN-Cervix model; 17-32 colposcopies per LYG and 688-1,052 tests per LYG in the Policy1-Cervix model; 92-134 colposcopies per LYG and 229-2,016 tests per LYG in the UMN model (see **Table 15**). Strategies that were dominated by both efficiency metrics in all 4 models are not shown.

b Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, HPV-10Y, 40, 60 indicates HPV testing every 10 years starting at age 40 years and ending at age 60 years, and HPV-5Y, 35/HPV-10Y, 40, 60 indicates HPV testing every 5 years starting at age 35 years with a switch to HPV testing every 10 years starting at age 40 years and ending at age 60 years. $\,^{\rm c}$ Strategies (bolded) represent current US recommended strategies.

Table 36. Lifetime Outcomes Among Unvaccinated Black Female Persons Assuming Imperfect Screening and Follow-up Adherence in the Harvard Modelᵃ

Abbreviations: CC, Cervical cancer; CIN, cervical intraepithelial; Colpos, colposcopies; CYTO, cytology; HPV, Human papillomavirus.

^a Outcomes calculated from age 21 to 100 years.

 $^{\rm b}$ Total number of tests including cytology and HPV tests, irrespective of primary, triage or surveillance context.

ᶜ CIN2+ detected includes CIN2s, CIN3s and cervical cancers detected through screening (excludes clinically detected cancers).

ᵈ Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

e Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30.

ᶠ End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

ᵍ Strategies (bolded) represent current US recommended strategies.

Table 37. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among Unvaccinated Black Female Persons Assuming Imperfect Screening and Follow-up Adherence in the Harvard Modelᵃ

Abbreviations: CYTO, cytology; HPV, Human papillomavirus; LYG, life-years gained.

ᵃ Near-efficient (i.e., within 2% of the efficiency frontier) are indicated by *. Strategies are ordered by increasing colposcopies. Ratios were calculated against the next-less effective, non-dominated strategy. Ratios in grey font indicate strategies that had lower LYG than the guidelines-based strategy of 3-yearly cytology from ages 21 to 65 years in the Harvard model. Yellow highlighted ratios indicate strategies with efficiency ratios that were equal to or less than those from the current guidelines-based strategies in the unvaccinated population on both efficiency metrics of colposcopies per LYG and tests per LYG in the Harvard model. assuming perfect adherence. The efficiency ratios used as benchmarks were: 75-587 colposcopies per LYG and 1,341-2,604 tests per LYG (see **Table 21**). Strategies that were dominated by both efficiency metrics are not shown.

ᵇ Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, HPV-10Y, 40, 60 indicates HPV testing every 10 years starting at age 40 years and ending at age 60 years, and HPV-5Y, 35/HPV-10Y, 40, 60 indicates HPV testing every 5 years starting at age 35 years with a switch to HPV testing every 10 years starting at age 40 years and ending at age 60 years.

ᶜ Strategies (bolded) represent current US recommended strategies.

Table 38. Lifetime Outcomes Among 2vHPV or 4vHPV Vaccinated Black Female Persons Assuming Imperfect Screening and Follow-up Adherence in the Harvard Modelᵃ

Abbreviations: CC, Cervical cancer; CIN, cervical intraepithelial; Colpos, colposcopies; CYTO, cytology; HPV, Human papillomavirus. ^a Outcomes calculated from age 21 to 100 years.

ᵇ Total number of tests including cytology and HPV tests, irrespective of primary, triage or surveillance context.

ᶜ CIN2+ detected includes CIN2s, CIN3s and cervical cancers detected through screening (excludes clinically detected cancers).

d Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

e Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30.

f End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

ᵍ Strategies (bolded) represent current US recommended strategies.

Table 39. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 2vHPV or 4vHPV Vaccinated Black Female Persons Assuming Imperfect Screening and Follow-up Adherence in the Harvard Modelᵃ

Abbreviations: CYTO, cytology; HPV, Human papillomavirus; LYG, life-years gained.

a Near-efficient (i.e., within 2% of the efficiency frontier) are indicated by *. Strategies are ordered by increasing colposcopies. Ratios were calculated against the next-less effective, non-dominated strategy. Yellow highlighted ratios indicate strategies with efficiency ratios that were equal to or less than those from the current guidelines-based strategies in the unvaccinated population on both efficiency metrics of colposcopies per LYG and tests per LYG in the Harvard model. assuming perfect adherence. The efficiency ratios used as benchmarks were: 75-587 colposcopies per LYG and 1,341-2,604 tests per LYG (see **Table 21**). Strategies that were dominated by both efficiency metrics are not shown.

CYTO-3Y, 21/COTEST-5Y, 30, 70 275, 2001 2.469* 2.469* 225,113* CYTO-4Y, 21/COTEST-5Y, 25, 60 292* 292* 17,944* 17,944* COTEST-5Y, 25, 65 803* 803* 803* 48,335* 48,335* CYTO-4Y, 21/COTEST-5Y, 25, 65 286* 286* 17,413* CYTO-4Y, 21/COTEST-5Y, 25, 70 283 283 17,148

b Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, HPV-10Y, 40, 60 indicates HPV testing every 10 years starting at age 40 years and ending at age 60 years, and HPV-5Y, 35/HPV-10Y, 40, 60 indicates HPV testing every 5 years starting at age 35 years with a switch to HPV testing every 10 years starting at age 40 years and ending at age 60 years.

ᶜ Strategies (bolded) represent current US recommended strategies.

Table 40. Lifetime Outcomes Among 9vHPV Vaccinated Black Female Persons Assuming Imperfect Screening and Follow-up Adherence in the Harvard Modelᵃ

Abbreviations: CC, Cervical cancer; CIN, cervical intraepithelial; Colpos, colposcopies; CYTO, cytology; HPV, Human papillomavirus.

^a Outcomes calculated from age 21 to 100 years.

 $^{\rm b}$ Total number of tests including cytology and HPV tests, irrespective of primary, triage or surveillance context.

ᶜ CIN2+ detected includes CIN2s, CIN3s and cervical cancers detected through screening (excludes clinically detected cancers).

ᵈ Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

e Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30.

ᶠ End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include female persons who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

ᵍ Strategies (bolded) represent current US recommended strategies.

Table 41. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 9vHPV Vaccinated Black Female Persons Assuming Imperfect Screening and Followup Adherence in the Harvard Modelᵃ

Abbreviations: CYTO, cytology; HPV, Human papillomavirus; LYG, life-years gained.

ᵃ Near-efficient (i.e., within 2% of the efficiency frontier) are indicated by *. Strategies are ordered by increasing colposcopies. Ratios were calculated against the next-less effective, non-dominated strategy. Yellow highlighted ratios indicate strategies with efficiency ratios that were equal to or less than those from the current guidelinesbased strategies in the unvaccinated population on both efficiency metrics of colposcopies per LYG and tests per LYG in the Harvard model. assuming perfect adherence. The efficiency ratios used as benchmarks were: 75-587 colposcopies per LYG and 1,341-2,604 tests per LYG (see **Table 21**). Strategies that were dominated by both efficiency metrics are not shown.

b Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, HPV-10Y, 40, 60 indicates HPV testing every 10 years starting at age 40 years and ending at age 60 years, and HPV-5Y, 35/HPV-10Y, 40, 60 indicates HPV testing every 5 years starting at age 35 years with a switch to HPV testing every 10 years starting at age 40 years and ending at age 60 years.

ᶜ Strategies (bolded) represent current US recommended strategies.

HPV vaccine completion of at least two doses among 15-year-old female persons of all races in year 2013 (i.e., those born in year 1998 and currently age 25 years) was nearly 50%; in 2017, HPV vaccine completion at age 15 years (i.e., those born in 2002 and current age 21 years) was 58.9% for all-race and 52.8% for Blackrace female persons. In 2021, 2-dose HPV vaccine uptake among 15-year-olds increased to 73.0% for all and Black female persons.

Source: National Immunization Survey-Teen (NIS-TEEN). 2012-2021. National Center for Health Statistics. Available from: https://www.cdc.gov/vaccines/imz-
managers/nis/datasets-teen.html.

Appendix Figure 2. Share of HPV Vaccine Doses Among Female Persons Aged 15 Years, by Year of Report, Birth Cohort and Current Age

The share of doses that are 9vHPV (nonavalent) compared to 4vHPV (quadrivalent) or unknown has increased over time, suggesting a higher level of protection against cervical disease among younger birth cohorts. For example, in 2015, the share of HPV vaccine doses that were 9vHPV was 5.7% among all-race and 2.6% among Black-race 15-year-old female persons (i.e., birth year 2000, current age 23 years), but by year 2017, the share of 9vHPV vaccine doses increased to 38.9% for all-race and 34.9% for Black-race 15-year-old female persons. In year 2021, the share of 9vHPV vaccine doses was 85.1% for all-race and 79.6% for Black-race 15-year-old female persons.

Source: National Immunization Survey-Teen (NIS-TEEN). 2012-2021. National Center for Health Statistics. Available from: https://www.cdc.gov/vaccines/imz-
managers/nis/datasets-teen.html.

Appendix Figure 3. Flow Diagrams for Management of Screen-Positive Results: HPV-16/18 Genotype Triage

Primary HPV testing

Primary cotesting

Appendix Table 1A. Natural History Model Parameters, Post-Calibration: Harvard Model

Abbreviations: CIN2, cervical intraepithelial neoplasia grade 2; CIN3, cervical

intraepithelial neoplasia grade 3; HPV, human papillomavirus; HR, high-risk.

ᵃ Values represent the range of probabilities across the 50 top-fitting sets; parameters

without a range of values were held constant across the 50 top-fitting sets.

^b Natural immunity represents the percentage reduction in risk of subsequent, typespecific infection after a woman has cleared a carcinogenic infection with the same type. Risk reduction is assumed to be constant across age, time, and genotype.

^c HPV clearance and progression probabilities are a function of time since infection (i.e., persistence).

Precancer regression probabilities decrease by time since lesion onset and are constant across carcinogenic HPV types. Given limited data, we assumed that the monthly CIN3 regression probability is 50% of CIN2 regression; 50% regress to typespecific HPV-infected health states and 50% regress to the Normal health state. ᵉ Precancer progression probabilities increase by time since lesion onset and are constant across carcinogenic HPV types. CIN2 progression is set at 20% of CIN3 progression (for carcinogenic types only).

f In addition to time since diagnosis, cancer mortality was adjusted for age at diagnosis by applying stage-specific multipliers to the baseline probabilities that ranged from 0.49 to 3.28 for local cancer; 0.62 to 1.60 for regional cancer; and 0.71 to 2.99 for distant cancer.

HPV Type	Age	Regression		Probability		Progression	
		From	To	(ever ^a)	From	To	(ever ^a)
HPV 16	15	HPV 16	Cleared	0.920	HPV 16	CIN 1	0.08
HPV 16	25	HPV 16	Cleared	0.941	HPV 16	CIN ₁	0.059
HPV 16	35	HPV 16	Cleared	0.833	HPV 16	CIN ₁	0.167
HPV 16	50	HPV 16	Cleared	0.912	HPV 16	CIN ₁	0.088
HPV 16	75	HPV 16	Cleared	0.982	HPV 16	CIN ₁	0.018
HPV 18	15	HPV 18	Cleared	0.790	HPV 18	CIN ₁	0.21
HPV 18	25	HPV 18	Cleared	0.845	HPV 18	CIN ₁	0.155
HPV 18	35	HPV 18	Cleared	0.562	HPV 18	CIN ₁	0.438
HPV 18	50	HPV 18	Cleared	0.768	HPV 18	CIN ₁	0.232
HPV 18	75	HPV 18	Cleared	0.952	HPV 18	CIN ₁	0.048
HPV 9V	15	HPV 9V	Cleared	0.920	HPV 9V	CIN ₁	0.08
HPV 9V	25	HPV 9V	Cleared	0.941	HPV 9V	CIN ₁	0.059
HPV 9V	35	HPV 9V	Cleared	0.833	HPV 9V	CIN ₁	0.167
HPV 9V	50	HPV 9V	Cleared	0.911	HPV 9V	CIN ₁	0.089
HPV 9V	75	HPV 9V	Cleared	0.982	HPV 9V	CIN ₁	0.018
HPVOHR	15	HPVOHR	Cleared	0.859	HPVOHR	CIN ₁	0.141
HPVOHR	25	HPVOHR	Cleared	0.897	HPVOHR	CIN ₁	0.103
HPVOHR	35	HPVOHR	Cleared	0.707	HPVOHR	CIN ₁	0.293
HPVOHR	50	HPVOHR	Cleared	0.845	HPVOHR	CIN ₁	0.155
HPVOHR	75	HPVOHR	Cleared	0.968	HPVOHR	CIN ₁	0.032
HPV 16	20	CIN ₁	Cleared	0.439	CIN ₁	CIN ₂	0.561
HPV 16	35	CIN ₁	Cleared	0.807	CIN ₁	CIN ₂	0.193
HPV 16	50	CIN ₁	Cleared	0.777	CIN ₁	CIN ₂	0.223
HPV 16	65	CIN ₁	Cleared	0.708	CIN ₁	CIN ₂	0.292
HPV 18	20	CIN ₁	Cleared	0.833	CIN ₁	CIN ₂	0.167
HPV 18	35	CIN ₁	Cleared	0.943	CIN ₁	CIN ₂	0.057
HPV 18	50	CIN ₁	Cleared	0.934	CIN ₁	CIN ₂	0.066
HPV 18	65	CIN ₁	Cleared	0.913	CIN ₁	CIN ₂	0.087
HPV 9V	20	CIN ₁	Cleared	0.643	CIN ₁	CIN ₂	0.357
HPV 9V	35	CIN ₁	Cleared	0.877	CIN ₁	CIN ₂	0.123
HPV 9V	50	CIN ₁	Cleared	0.858	CIN ₁	CIN ₂	0.142
HPV 9V	65	CIN ₁	Cleared	0.814	CIN ₁	CIN ₂	0.186
HPVOHR	20	CIN ₁	Cleared	0.813	CIN ₁	CIN ₂	0.187
HPVOHR	35	CIN ₁	Cleared	0.936	CIN ₁	CIN ₂	0.064
HPVOHR	50	CIN ₁	Cleared	0.926	CIN ₁	CIN ₂	0.074
HPVOHR	65	CIN ₁	Cleared	0.902	CIN ₁	CIN ₂	0.098
NoHPV	20	CIN ₁	Cleared	0.961	CIN ₁	CIN ₂	0.039
NoHPV	35	CIN ₁	Cleared	0.987	CIN ₁	CIN ₂	0.013
NoHPV	50	CIN ₁	Cleared	0.985	CIN ₁	CIN ₂	0.015
NoHPV	65	CIN ₁	Cleared	0.980	CIN ₁	CIN ₂	0.02
HPV 16	20	CIN ₂	Cleared	0.735	CIN ₂	CIN ₃	0.265
HPV 16	35	CIN ₂	Cleared	0.229	CIN ₂	CIN ₃	0.771
HPV 16	50	CIN ₂	Cleared	0.426	CIN ₂	CIN ₃	0.574
HPV 16	65	CIN ₂	Cleared	0.000	CIN ₂	CIN ₃	$\mathbf{1}$
HPV 18	20	CIN ₂	Cleared	0.903	CIN ₂	CIN ₃	0.097
HPV 18	35	CIN ₂	Cleared	0.718	CIN ₂	CIN ₃	0.282
HPV 18	50	CIN ₂	Cleared	0.790	CIN ₂	CIN ₃	0.21
HPV 18	65	CIN ₂	Cleared	0.619	CIN ₂	CIN ₃	0.381

Appendix Table 1B. Transition Probabilities by HPV Genotype and Age: MISCAN-Cervix Model

Abbreviations: CC, cervical cancer; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HPV 9V, HPV-31/33/45/52/58; HPVOHR, other high-risk HPV-35/39/51/56/59/66/68.

^a Values represent the total probability of moving from one health state to another, unless a women undergoes a

hysterectomy or dies before this transition; the probabilities are assumed to be independent of the transition duration. ^b CIN 3 lesions can never transition to cervical cancer without an HPV infection.

Appendix Table 1C. Natural History Model Parameters, Post-Calibration: Policy1-Cervix Model

Abbreviations: CIN2, cervical intraepithelial neoplasia grade 2; CIN3, cervical

intraepithelial neoplasia grade 3; HPV, human papillomavirus; HR, high-risk.

^a Values represent the range of probabilities by age and also treatment status; posttreatment natural history uses a different set of parameters reflecting elevated risk among this group.

Cancer mortality is a function of both time since diagnosis and age at diagnosis.

Appendix Table 1D. Natural History Model Parameters, Post-Calibration: UMN Model

Abbreviations: CIN2, cervical intraepithelial neoplasia grade 2; CIN3, cervical intraepithelial neoplasia grade 3; HPV, human papillomavirus; HR, high-risk. ^a Values represent the range of age-dependent probabilities.

ᵇ Natural immunity represents the percentage reduction in risk of subsequent, type-specific infection after a woman has cleared a carcinogenic infection with the same type. Risk reduction is assumed to be constant across age and time.

Appendix Table 2. Lifetime Number of Cervical Cancer Cases, Deaths and Life-Years Gained Among Unvaccinated Female Persons Assuming HPV-16/18 Genotype Triage of HPV-Positive Results by Modelᵃ

Abbreviations: cyto, cytology; HPV, Human papillomavirus; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

ᵃ Outcomes calculated from age 21 to 100 years.

b Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30.

ᶜ Median outcome across the four models.

^d End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include those women who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

Appendix Table 3. Lifetime Number of Total Tests and Colposcopies Among Unvaccinated Female Persons Assuming HPV-16/18 Genotype Triage of HPV-Positive Results by Modelᵃ

Abbreviations: cyto, cytology; HPV, Human papillomavirus; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

ᵃ Outcomes calculated from age 21 to 100 years.

b Total number of tests including cytology and HPV tests, irrespective of primary, triage or surveillance context.

ᶜ Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30. ᵈ Median outcome across the four models.

ᵉ End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include those women who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

Appendix Table 4. Lifetime Number of CIN2+ Detected and False Positives Among Unvaccinated Female Persons Assuming HPV-16/18 Genotype Triage of HPV-Positive Results by Model^a

Abbreviations: cyto, cytology; HPV, Human papillomavirus; CIN, cervical intraepithelial; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

ᵃ Outcomes calculated from age 21 to 100 years.

ᵇ CIN2+ detected includes CIN2s, CIN3s and cervical cancers detected through screening (excludes clinically detected cancers).

ᶜ Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

ᵈ Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, CYTO-3Y, 21 indicates cytology testing every 3 years starting at age 21, and CYTO-3Y, 21/HPV-5Y,30 indicates cytology testing every 3 years starting at age 21 with a switch to HPV testing every 5 years starting at age 30. ᵉ Median outcome across the four models.

ᶠ End age indicates the age at which the final routine screen should occur, irrespective of age at last screen; exceptions include those women who are recommended to continue screening due to prior abnormal results and/or precancer treatment.

Appendix Table 5. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among Unvaccinated Female Persons Assuming HPV-16/18 Genotype Triage of HPV-Positive Results by Model^a

Abbreviations: cyto, cytology; HPV, Human papillomavirus; LYG, life-years gained; H, Harvard model; M, MISCAN-Cervix model; P, Policy1-Cervix model; U, University of Minnesota model.

- a Near-efficient (i.e., within 2% of the efficiency frontier) are indicated by *. Strategies are ordered by increasing colposcopies in the Harvard model. Ratios were calculated against the next-less effective, non-dominated strategy within each model. Ratios in grey font indicate strategies that had lower LYG than the guidelines-based strategy of 3-yearly cytology from ages 21 to 65 years in each model. Yellow highlighted ratios indicate strategies with efficiency ratios that were equal to or less than those from the current quidelines-based strategies in the unvaccinated population on both efficiency metrics of colposcopies per LYG and tests per LYG in each model in the base-case analysis. The efficiency ratios used as benchmarks in each model were: 78-133 colposcopies per LYG and 1,509-2,663 tests per LYG in the Harvard model; 48-54 colposcopies per LYG and 291-4,279 tests per LYG in the MISCAN-Cervix model; 17-32 colposcopies per LYG and 688-1,052 tests per LYG in the Policy1-Cervix model; 92-134 colposcopies per LYG and 229-2,016 tests per LYG in the UMN model (see **Table 15**). Strategies that were dominated by both efficiency metrics in all 4 models are not shown.
- **b** Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, HPV-10Y, 40, 60 indicates HPV testing every 10 years starting at age 40 years and ending at age 60 years, and HPV-5Y, 35/HPV-10Y, 40, 60 indicates HPV testing every 5 years starting at age 35 years with a switch to HPV testing every 10 years starting at age 40 years and ending at age 60 years.
- ᶜ Strategies (bolded) represent current US recommended strategies.

Appendix Table 6. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among Unvaccinated Female Persons Assuming Lower-Bound Relative Test Sensitivity for HPV Testing by Modelᵃ

Abbreviations: cyto, cytology; HPV, Human papillomavirus; LYG, life-years gained; H, Harvard model; P, Policy1-Cervix model; U, University of Minnesota model.

a Near-efficient (i.e., within 2% of the efficiency frontier) are indicated by *. Strategies are ordered by increasing colposcopies in the Harvard model. Ratios were calculated against the next-less effective, non-dominated strategy within each model. Ratios in grey font indicate strategies that had lower LYG than the guidelines-based strategy of 3-yearly cytology from ages 21 to 65 years in each model. Yellow highlighted ratios indicate strategies with efficiency ratios that were equal to or less than those from the current guidelines-based strategies in the unvaccinated population on both efficiency metrics of colposcopies per LYG and tests per LYG in each model, assuming perfect adherence. The efficiency ratios used as benchmarks in each model were: 78-133 colposcopies per LYG and 1,509-2,663 tests per LYG in the Harvard model; 17-32 colposcopies per LYG and 688-1,052 tests per LYG in the Policy1-Cervix model; 92-134 colposcopies per LYG and 229-2,016 tests per LYG in the UMN model (see **Table 15**). Strategies that were dominated by both efficiency metrics in all 3 models are not shown.

^b Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, HPV-10Y, 40, 60 indicates HPV testing every 10 years starting at age 40 years and ending at age 60 years, and HPV-5Y, 35/HPV-10Y, 40, 60 indicates HPV testing every 5 years starting at age 35 years with a switch to HPV testing every 10 years starting at age 40 years and ending at age 60 years.

Appendix Table 7. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 2vHPV or 4vHPV Vaccinated Female Persons Assuming Lower-Bound Relative Test Sensitivity for HPV Testing by Modela

Abbreviations: cyto, cytology; HPV, Human papillomavirus; LYG, life-years gained; H, Harvard model; P, Policy1-Cervix model; U, University of Minnesota model.

a Near-efficient (i.e., within 2% of the efficiency frontier) are indicated by *. Strategies are ordered by increasing colposcopies in the Harvard model. Ratios were calculated against the next-less effective, non-dominated strategy within each model. Yellow highlighted ratios indicate strategies with efficiency ratios that were equal to or less than those from the current guidelines-based strategies in the unvaccinated population on both efficiency metrics of colposcopies per LYG and tests per LYG in each model. The efficiency ratios used as benchmarks in each model were: 78-133 colposcopies per LYG and 1,509-2,663 tests per LYG in the Harvard model; 17-32 colposcopies per LYG and 688-1,052 tests per LYG in the Policy1-Cervix model; 92-134 colposcopies per LYG and 229-2,016 tests per LYG in the UMN model (see **Table 15**). Strategies that were dominated by both efficiency metrics in all 3 models are not shown. **^b** Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, HPV-10Y, 40, 60 indicates HPV testing every 10 years starting at age 40 years and ending at age 60 years, and HPV-5Y, 35/HPV-10Y, 40, 60 indicates HPV testing every 5 years starting at age 35 years with a switch to HPV testing every 10 years starting at age 40 years and ending at age 60 years.

Appendix Table 8. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 9vHPV Vaccinated Female Persons Assuming Lower-Bound Relative Test Sensitivity for HPV Testing by Modelᵃ

a Near-efficient (i.e., within 2% of the efficiency frontier) are indicated by *. Strategies are ordered by increasing colposcopies in the Harvard model. Ratios were calculated against the next-less effective, non-dominated strategy within each model. Yellow highlighted ratios indicate strategies with efficiency ratios that were equal to or less than those from the current guidelines-based strategies in the unvaccinated population on both efficiency metrics of colposcopies per LYG and tests per LYG in each model. The efficiency ratios used as benchmarks in each model were: 78-133 colposcopies per LYG and 1,509-2,663 tests per LYG in the Harvard model; 17-32 colposcopies per LYG and 688-1,052 tests per LYG in the Policy1-Cervix model; 92-134 colposcopies per LYG and 229-2,016 tests per LYG in the UMN model (see **Table 15**). Strategies that were dominated by both efficiency metrics in all 3 models are not shown.

b Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, HPV-10Y, 40, 60 indicates HPV testing every 10 years starting at age 40 years and ending at age 60 years, and HPV-5Y, 35/HPV-10Y, 40, 60 indicates HPV testing every 5 years starting at age 35 years with a switch to HPV testing every 10 years starting at age 40 years and ending at age 60 years. ᶜ Strategies (bolded) represent current US recommended strategies.

Appendix Table 9. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among Unvaccinated Female Persons Assuming Upper-Bound Relative Test Sensitivity for HPV Testing by Modelᵃ

ᵃ Near-efficient (i.e., within 2% of the efficiency frontier) are indicated by *. Strategies are ordered by increasing colposcopies in the Harvard model. Ratios were calculated against the next-less effective, non-dominated strategy within each model. Ratios in grey font indicate strategies that had lower LYG than the guidelines-based strategy of 3-yearly cytology from ages 21 to 65 years in each model. Yellow highlighted ratios indicate strategies with efficiency ratios that were equal to or less than those from the current guidelines-based strategies in the unvaccinated population on both efficiency metrics of colposcopies per LYG and tests per LYG in each model, assuming perfect adherence. The efficiency ratios used as benchmarks in each model were: 78-133 colposcopies per LYG and 1,509-2,663 tests per LYG in the Harvard model; 17-32 colposcopies per LYG and 688-1,052 tests per LYG in the Policy1-Cervix model; 92-134 colposcopies per LYG and 229-2,016 tests per LYG in the UMN model (see **Table 15**). Strategies that were dominated by both efficiency metrics in all 3 models are not shown.

b Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, HPV-10Y, 40, 60 indicates HPV testing every 10 years starting at age 40 years and ending at age 60 years, and HPV-5Y, 35/HPV-10Y, 40, 60 indicates HPV testing every 5 years starting at age 35 years with a switch to HPV testing every 10 years starting at age 40 years and ending at age 60 years. ᶜ Strategies (bolded) represent current US recommended strategies.

Appendix Table 10. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 2vHPV or 4vHPV Vaccinated Female Persons Assuming Upper-Bound Relative Test Sensitivity for HPV Testing by Modelᵃ

a Near-efficient (i.e., within 2% of the efficiency frontier) are indicated by *. Strategies are ordered by increasing colposcopies in the Harvard model. Ratios were calculated against the next-less effective, non-dominated strategy within each model. Yellow highlighted ratios indicate strategies with efficiency ratios that were equal to or less than those from the current guidelines-based strategies in the unvaccinated population on both efficiency metrics of colposcopies per LYG and tests per LYG in each model. The efficiency ratios used as benchmarks in each model were: 78-133 colposcopies per LYG and 1,509-2,663 tests per LYG in the Harvard model; 17-32 colposcopies per LYG and 688-1,052 tests per LYG in the Policy1-Cervix model; 92-134 colposcopies per LYG and 229-2,016 tests per LYG in the UMN model (see **Table 15**). Strategies that were dominated by both efficiency metrics in all 3 models are not shown.

^b Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, HPV-10Y, 40, 60 indicates HPV testing every 10 years starting at age 40 years and ending at age 60 years, and HPV-5Y, 35/HPV-10Y, 40, 60 indicates HPV testing every 5 years starting at age 35 years with a switch to HPV testing every 10 years starting at age 40 years and ending at age 60 years.

Appendix Table 11. Efficient and Near-Efficient Cervical Cancer Screening Strategies Among 9vHPV Vaccinated Female Persons Assuming Upper-Bound Relative Test Sensitivity for HPV Testing by Modelᵃ

a Near-efficient (i.e., within 2% of the efficiency frontier) are indicated by *. Strategies are ordered by increasing colposcopies in the Harvard model. Ratios were calculated against the next-less effective, non-dominated strategy within each model. Yellow highlighted ratios indicate strategies with efficiency ratios that were equal to or less than those from the current guidelines-based strategies in the unvaccinated population on both efficiency metrics of colposcopies per LYG and tests per LYG in each model. The efficiency ratios used as benchmarks in each model were: 78-133 colposcopies per LYG and 1,509- 2,663 tests per LYG in the Harvard model; 17-32 colposcopies per LYG and 688-1,052 tests per LYG in the Policy1-Cervix model; 92-134 colposcopies per LYG and 229-2,016 tests per LYG in the UMN model (see **Table 15**). Strategies that were dominated by both efficiency metrics in all 3 models are not shown.

b Strategies are denoted by the screening modality, interval, age to begin screening/screening modality after switch age, interval after switch age, switch age for each end age category. For example, HPV-10Y, 40, 60 indicates HPV testing every 10 years starting at age 40 years and ending at age 60 years, and HPV-5Y, 35/HPV-10Y, 40, 60 indicates HPV testing every 5 years starting at age 35 years with a switch to HPV testing every 10 years starting at age 40 years and ending at age 60 years.