Technical Report

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

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No. HHSA-290-2012-00015-I

Prepared by:
Harvard T.H. Chan School of Public Health
Center for Health Decision Science
Boston, MA

Investigators:
Jane J. Kim, PhD
Emily A. Burger, PhD
Catherine Regan, BA
Stephen Sy, MS

Table of Contents

Figures

Tables

Appendix Tables

Chapter 1. Introduction

Despite dramatic reductions in cervical cancer since the introduction of Papanicolaou (Pap) cytology testing in the United States, roughly 12,820 women are expected to develop and 4,210 women are expected to die from cervical cancer in 2017.[1] Information on the natural history of human papillomavirus (HPV) and its causal role in cervical disease, coupled with technologies to improve detection of precancerous lesions, continue to emerge and have prompted revisions to screening guidelines. In 2012, cervical cancer screening guidelines were harmonized across several major guidelines-making organizations, including the US Preventive Services Task Force (USPSTF),[2-4] with recommendations for 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. Screening end age is recommended at age 65, provided a history of regular screening without abnormalities in the past 10-20 years.[2-4] Since 2012, new evidence on primary human papillomavirus (HPV) testing has emerged, contributing to the FDA-approval of the first stand-alone HPV test for primary screening in women ages 25 and older.

While empirical studies such as randomized clinical trials provide high-quality evidence on the effectiveness of screening, outcomes are usually based on intermediate endpoints after a limited number of rounds of screening. Mathematical disease simulation models can complement such evidence by extrapolating data beyond the trial period to project the benefits and harms of screening in the long-term, over multiple rounds. Models can also explore the impact of alternative scenarios that have not been examined in empirical studies.

This decision analysis using a cervical cancer disease simulation model accompanies the systematic review that is being conducted by the Kaiser Permanente Evidence Based Practice Center (EPC) to update the evidence and address gaps in the expected benefits and harms of cervical cancer screening strategies in primary care.[5] The key questions for the decision analysis center around the long-term impact of primary HPV screening, with or without cytology, compared to currently recommended screening strategies in terms of health benefits and harms in the general population:

1. How does the effectiveness of primary HPV screening in reducing cervical cancer incidence and mortality vary by (1) age to start HPV screening, (2) rescreening interval (following an HPV-negative result), and (3) age to stop HPV screening?
2. How do the harms of primary HPV screening vary by (1) age to start HPV screening, (2) rescreening interval, and (3) age to stop HPV screening?
3. Which cervical cancer screening strategies are considered efficient in terms of the additional number of colposcopies required per additional life-year gained?

Two variations of triage of HPV-positive women were included in the base case. In addition to the key questions above, sensitivity analysis was conducted to assess the impact of uncertainty in the data and alternative screening scenarios.

Chapter 2. Methods

Model

An overview of the decision model in terms of model attributes, natural history, and screening strategies are provided below and summarized in **Table 1**. The model is a microsimulation (i.e., individual-based) model of HPV-induced cervical carcinogenesis, in which individual women enter the model at an early age (i.e., age 9 years) and are followed over their lifetimes.[6,7] The main health states of the model comprise HPV infection (by genotype), precancer (i.e., cervical intraepithelial neoplasia or CIN, grades 2 and 3) and invasive cancer (by stage) (**Figure 1**). The model focuses on squamous cell carcinoma, the most common histologic subtype of cervical cancer.

The current analysis was conducted using a single hypothetical birth cohort assumed to be born in year 1996 that would begin screening at age 21 in year 2017. Screening is used to detect the presence of high-grade precancers, which may resolve spontaneously or can be treated and removed before progressing to cancer; therefore, reductions in cervical cancer morbidity and mortality due to screening result from both the prevention and the earlier detection of invasive cancer. The effectiveness of screening strategies depends on coverage by age, interval, test characteristics, treatment efficacy, and compliance to follow-up visits. The model was used to project estimates of both benefits and harms, including life-years gained, cervical cancer cases and deaths, screening tests, diagnostic procedures, and false positive results under various scenarios of primary screening tests, screening start and end ages, and screening intervals. These measures are calculated as the cumulative number of events or time spent in the different health states, which are then modified by the interventions, over the selected time horizon (e.g., lifetime). These measures in totality capture the benefits and harms for the strategies being considered. To examine the relative tradeoff of harms versus benefits among the strategies, we calculated three efficiency outcomes in terms of the incremental number colposcopies per life-year gained, incremental number of screening tests per life-year gained, and incremental number of colposcopies per cervical cancer case averted.

Natural History

Upon entry into the model, each woman faces monthly transitions between health states that describe underlying true health, including HPV infection, precancer (i.e., CIN2, CIN3), and invasive cancer (i.e., local, regional, distant). CIN2 and CIN3 are modeled as non-sequential precancerous health states with distinct probabilities of regression to normal or progression to cancer, whereas CIN1 is interpreted as a microscopic manifestation of acute HPV infection and is therefore incorporated into the HPV-infected state. States are further stratified into oncogenic HPV types 16, 18, 31, 33, 45, 52, and 58, each considered separately; pooled other high-risk types; and pooled low-risk HPV types. Transition probabilities can vary by age, HPV type, duration of infection or lesion status, and a woman's history of prior HPV infection and CIN treatment. Cancer detection can occur through symptoms or screening. Each month, all women are subjected to hysterectomy rates and background mortality,[8,9] as well as excess mortality from

cervical cancer.[10]

Screening, Diagnosis, and Precancer Treatment

Screening assumptions in the model can vary by screening start age, stop age, frequency, coverage, triage testing, compliance to recommended follow-up. Tests for primary screening and triage include cytology (conventional or liquid-based), high-risk HPV DNA testing (pooled or genotyping), as well as cytology and HPV cotesting. Management of screen-positive women can vary by age, follow-up test, time to follow-up test(s), number of negative follow-up tests required to return to routine screening.

Cancer Treatment and Survival

Cancer staging (i.e., local to regional to distant) and progression is modeled, accounting for symptomatic detection and the possibility of downstaging at diagnosis due to screening. In addition to background mortality, women with cervical cancer are subject to excess mortality, based on 5-year survival estimates depending on cancer stage, age, and time since diagnosis according to *Surveillance, Epidemiology, and End Results* (SEER) data.[10]

Model Calibration

A process of model calibration and validation was undertaken to ensure fit to observed data. Calibrated parameters included HPV incidence (by age and genotype), CIN progression and regression, and HPV natural immunity following type-specific HPV infection and clearance. 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. To capture uncertainty in the natural history parameters, the 50 best-fitting sets were used in all analyses; the results are reported as the mean value across the 50 sets (the minimum and maximum values are also reported for the base case analysis).

For calibration target data, the data sources were selected on the basis of representativeness of the general population, sampling methods, and sample size. All data were from populations prior to HPV vaccination. Age-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.[11] The model was fitted to prevalence of HPV types 16, 18, 31, 33, 45, 52, and 58 separately, as well as other pooled high-risk HPV types. HPV type distribution in cases of CIN and cancer were also included as calibration target data. For CIN 2 and CIN 3, HPV type distribution was based on data from the NMHPVPR;[12] for cancer, HPV type distribution in SCC was based on a recent study by the US Centers for Disease Control and Prevention (CDC) using tissue samples from US population-based cancer registries.[13] Model fit to calibration targets are displayed in **Figures 2-4**.

Model Validation

Age-specific cervical cancer incidence rates under an assumption of no intervention (i.e., natural history) were projected by the model and compared against cancer registry data from the 1950s and early 1960s, before Pap smear screening was widely performed (**Figure 5**).[14,15] 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 model but instead were used to assess predictive validity for overall underlying risk.

In addition, model-projected outcomes of cervical cancer incidence and mortality rates were compared against those reported in SEER cancer registries in recent years (i.e., 2000-2012), under assumptions of screening practice patterns reported in the NMHPVPR (**Figure 6**).[16-18] Screening practice patterns included estimated proportions of women never screened and screened at different intervals (e.g., annual, biennial) and proportions of women who do not comply to follow-up diagnostic testing and/or precancer treatments.

Additional model validation exercises included simulating the protocol from the HPV FOCAL trial and comparing model projections against reported outcomes.[19] We simulated three screening scenarios involving switching to primary HPV testing at ages 27, 34 and 52 to reflect women that switch from cytology-based routine screening to primary HPV testing under the trial screening protocol. We projected the baseline and cumulative 12-month CIN2+, CIN3+ and colposcopy rates per 1,000 women in the first round of the HPV and control arms of the HPV FOCAL trial for ages 25-29, 30-34 and 35-65 years (**Figure 7**). Comparisons of model-projections against observational data have been previously reported.[7]

Screening Strategies

The analysis focused on the three key questions assessing the comparative effectiveness and harms of primary HPV testing, with or without cytology, compared to currently recommended screening strategies. **Table 2** summarizes the 19 main strategies evaluated.

The primary HPV testing strategies were varied by three main attributes: (1) age to switch from cytology to HPV screening, (2) rescreening interval (following an HPV-negative result), and (3) age to stop HPV screening. For the base case, *age to switch to HPV screening* was evaluated at ages 25, 27, and 30 years, following cytology-only screening starting at age 21. Age 25 was selected to reflect the FDA-approved age threshold for primary HPV testing; age 27 was selected to coincide with timing of 3-year cytology testing (at ages 21 and 24); and age 30 was selected to be consistent with the age threshold to begin cotesting. The *rescreening interval* for primary HPV testing was evaluated at every 3 years and every 5 years, consistent with current US guidelines for cytology-only and cotesting. In the base case analysis, *age to stop screening* was 65 years, assuming no recent history of abnormal results, consistent with current guidelines; we evaluated the impact of extending the age threshold at which to terminate screening to ages 70 and 75 years. These three main attributes were assessed in a univariate manner, as well as simultaneously.

In the base case, two triage strategies for HPV-positive screening results were examined (**Figure 8**): (a) assuming HPV-16/18 genotype information is available, 16/18-positive women are referred to colposcopy, whereas women positive for other high-risk HPV types receive cytology triage (cytology ≥ ASCUS are referred to colposcopy; cytology-negative receive a follow-up test in 12 months); (b) all women with high-risk HPV receive cytology triage (cytology ≥ ASCUS are referred to colposcopy; cytology-negative receive a follow-up test in 12 months). A referral threshold of cytology ≥ LSIL was also evaluated, and the interval for follow-up testing was varied (e.g., 6 or 24 months) in sensitivity analysis. An additional triage strategy in which all women with high-risk HPV are referred for immediate colposcopy was also included in sensitivity analysis.

Guideline-based screening strategies comprised (1) cytology alone every 3 years from ages 21-65 years, and (2) cytology alone every 3 years from ages 21-29 years, with a switch to cytology and HPV cotesting every 5 years from ages 30-65 years.[2-4] Management of women with equivocal or abnormal tests were assumed to follow established guidelines.[3,20] For cotesting, HPV-positive/cytology-negative women were managed by repeat cotesting at 12 months, with referral to colposcopy for any positive result. We assumed full compliance to screening initiation, rescreening interval, and follow-up for both diagnostic and pre-cancer treatment referrals. Furthermore, the base-case analysis focused on women who did not receive HPV vaccination.

Screening Inputs

Screening Test Characteristics

Test sensitivity and specificity values, defined at a disease threshold of CIN2 or worse (CIN2+), were required as model inputs and were informed from the studies reviewed by the EPC,[5] as well as from the published literature (**Table 3**).[21-26] For strategies involving cytology testing, we applied estimates of test sensitivity and specificity assuming a positivity threshold of ASC-US, with base-case values obtained from a meta-analysis conducted by Koliopoulos et al.[21] These pooled estimates of sensitivity and specificity of cytology for detection of CIN2+ (72.7% and 91.9%, respectively) were based on 18 studies identified in a systematic review. The ranges of test performance values for cytology were informed by the Koliopolous study, as well as estimates reported in the recent US-based Addressing the Need for Advanced HPV Diagnostics (ATHENA) study.[22]

The model also required data on the distribution of abnormal cytology results (e.g., proportion of women with ASC-US, LSIL, and HSIL result) conditional on histologic diagnosis (**Table 4**). These estimates were based on data from the ATHENA study, which reported the baseline cytology results by central pathology review diagnosis of 8,000 women age 25 years and older.[23]

The main inputs of test performance for primary HPV testing, alone and as part of cotesting, were based on ATHENA and studies that were included in EPC review.[22,24-26] 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+) (**Table 3**). Our base-case estimates were anchored on the ATHENA study,[22] which provided verification-bias adjusted estimates and included both HPV (cobas HPV test (Roche)) and cotesting strategies with similar follow-up algorithms as what is evaluated in this analysis. The worst- and best-case values for sensitivity and specificity for all screening test modalities were informed by data reported in ATHENA,[22] a meta-analysis by Arbyn et al.,[24] and the New Technology in Cervical Cancer (NTCC) trial,[25,26] which reflect variations across testing modalities that include cobas HPV test (Roche), Hybrid Capture 2 (Qiagen), and PCR-based tests.

Colposcopy/Biopsy and Precancer Treatment

The sensitivity and specificity of colposcopy and biopsy were assumed to be perfect (100%) in the base case, although we explored the impact of error in histologic diagnosis using data from the NMHPVPR in sensitivity analysis.[27] We assumed that, with active surveillance of women who receive precancer treatment, the effectiveness of treatment in removing a CIN2 or CIN3 lesion (e.g., via loop electrosurgical excisional procedure (LEEP)) is ultimately 100%, but also explored a lower treatment effectiveness of 82%.[28] The model assumes that HPV infections are also removed with precancer treatment; and therefore, treated women return to an uninfected state.

Outcomes

The model generated a number of outcomes associated with each screening strategy, reflecting both health effects and harms over the lifetime of the screening cohort (i.e., ages 20 to 100 years): total number of cytology and HPV tests (including screening, triage, and surveillance), colposcopies, CIN2 and CIN3 detected, CIN3+ detected (including CIN3 and cervical cancers detected through screening), false positive screening results (defined as total number of colposcopies without underlying CIN2, CIN3 or cancer), cervical cancer cases, cervical cancer deaths, and life-years.

Analogous to cost-effectiveness analysis, the relative efficiency of each screening strategy was evaluated and expressed as the incremental number of colposcopies per life-year gained, defined as the additional number of colposcopies divided by the additional life-years of a specific strategy (strategy x) compared to the strategy with the next fewer colposcopies (strategy y):

$$\frac{Colposcopies_{\,Strat\,x} - Colposcopies_{\,Strat\,y}}{Life\text{-}years_{\,Strat\,x} - Life\text{-}years_{\,Strat\,y}}$$

Strategies with a higher number of colposcopies and lower life-years than an alternative strategy were considered “inefficient” and eliminated from the calculation; all other strategies were considered “efficient.” Because there is no consensus on the appropriate metric to assess efficiency, we also presented results in terms of the incremental number of total screening tests per life-year gained and the incremental number of colposcopies per cervical cancer case averted.

Scenario Analysis

For primary HPV testing, the different options for triaging HPV-positive women are not equally available or preferred; therefore, analyses to determine the relative efficiency of the screening strategies were conducted under four different scenarios of triage availability:

- Scenario A: included only 16/18 genotype triage option for HPV-positive women (strategies 3-8)
- Scenario B: included only cytology triage option for HPV-positive women (strategies 9-14)
- Scenario C: included both 16/18 genotyping and cytology triage options for HPV-positive women (strategies 3-14)
- Scenario D: included both 16/18 genotyping and cytology triage options for HPV-positive women, plus additional cotesting strategies (strategies 3-19)

Each scenario analysis above also included the current guidelines-based strategies of cytology testing alone every 3 years, without or with a switch to cotesting every 5 years at age 30 (strategies 1 and 2).

Sensitivity Analysis

We assessed the impact of uncertainty in the data, alternative screening management protocols, and screening in HPV-vaccinated women. Data uncertainty focused on the underlying natural history of disease (i.e., transition probabilities), screening test characteristics, colposcopy/biopsy performance, and precancer treatment effectiveness. Alternative screening scenarios included variations in management of HPV-positive women, including cytology triage with a referral threshold of LSIL (base-case assumed ASC-US), varying intervals for follow-up testing from 6 months to 24 months (base-case assumed 12 months), and immediate colposcopy for all HPV-positive women. To reflect a low-risk population, we evaluated screening in HPV-vaccinated women. We assumed women were vaccinated with the three-dose HPV-16/18 vaccine in pre-adolescence and that vaccination conferred 100% protection against HPV-16 and -18 infections over the lifetime.

Chapter 3. Results

Health Benefits and Harms

In the absence of screening, the lifetime risk of cervical cancer was 1.9% (range across 50 best-fitting sets, 1.3-2.4%) and lifetime mortality from cervical cancer was 0.83% (range, 0.58-1.08%), resulting in a life expectancy of 63.921 years (63.845-64.006 years) for 20-year-old women. Under scenarios of screening, model outcomes of screening tests (cytology, HPV, total), colposcopies, CIN2/3 detected, CIN3+ detected, false positives, cervical cancer cases, cervical cancer deaths, and life-years per 1,000 women were projected, separately for screening end ages of 65, 70, and 75 (**Tables 5-7**). Compared to no screening, all cervical cancer screening strategies led to substantial reductions in cancer cases and deaths, and gains in life-years. Compared to the current guidelines-based strategies of cytology alone every 3 years starting at age 21, with or without a switch to cotesting every 5 years starting at age 30, all new alternative strategies were more effective. For example, when screening ended at age 65 (**Table 5**), cervical cancer deaths associated with the guidelines-based strategies (strategies 1 and 2) ranged from 0.30-0.76 deaths per 1,000 women, whereas the new alternative strategies involving primary HPV testing or cotesting (strategies 3-19) had fewer cervical cancer deaths, ranging from 0.23-0.29 deaths per 1,000 women.

Earlier switch age, more frequent interval and cotesting strategies generally led to a greater number of lifetime total tests. The proportion of tests that were cytology versus HPV test depended on the particular strategy. Screening strategies that involved switching to primary HPV testing alone (strategies 3-14) were associated with a substantially lower total number of cytology tests – 3 to 8 times fewer cytology tests than cytology alone or cotesting. In contrast, strategies involving HPV testing alone with 16/18 genotype triage (strategies 3-8) had the highest number of HPV tests, followed closely by HPV testing alone with cytology triage (strategies 9-14) and cotesting (strategies 2, 15-19); cytology only, which utilizes HPV testing only for triage of ASC-US had the lowest number of HPV tests. In total, the cotesting strategies had nearly double the total tests of the primary HPV testing strategies. The HPV testing strategy with cytology triage (strategies 9-14) led to a slightly higher number of tests than HPV with 16/18 genotyping (strategies 3-8). Continually screening with cytology alone every 3 years (strategy 1) had the fewest number of total tests than other HPV and cotesting strategies involving 3-year screening.

Cytology testing alone every 3 years also yielded the lowest number of lifetime colposcopies (i.e., 645 per 1,000 women). All other strategies increased colposcopies substantially, ranging from 1,452-2,535 per 1,000 women – up to four-fold higher when screening with primary HPV testing or cotesting every 3 years starting at age 25. All else equal, colposcopies were generally highest for cotesting (strategies 2, 15-19), followed closely by primary HPV testing with 16/18 genotype triage (strategies 3-8). HPV testing with 16/18 genotype triage had 12-14% greater colposcopies than HPV testing with cytology triage.

Likewise, the lowest numbers of CIN2/3 detected and CIN3+ detected were from cytology testing alone every 3 years, for example 160 CIN2/3 detected per 1,000 women (strategy 1)

versus 198-223 CIN2/3 detected per 1,000 women for the strategies involving primary HPV testing and cotesting (strategies 2-19). Cotesting strategies (strategies 2, 15-19) yielded the highest numbers of CIN2/3 and CIN3+ detected, but only marginally higher than primary HPV testing with 16/18 genotype triage (strategies 3-8), followed by primary HPV testing with cytology triage (strategies 9-14). Mimicking the trend of colposcopies, the number of false positives increased dramatically from cytology testing every 3 years to HPV testing or cotesting, irrespective of screening switch age or interval, up to five-fold greater with cotesting or HPV testing every 3 years starting at age 25 (strategies 3, 9, 15).

The current guidelines-based strategy of cytology alone every 3 years (strategy 1) was the least effective in terms of cervical cancer cases, deaths, and life years. Across the testing modalities, the most effective strategy was primary HPV testing with 16/18 genotype triage (strategies 3-8); the lowest number of cancer cases and deaths, and highest number of life years, occurred with 3-year screening with a switch age to primary HPV testing of 25 years (strategy 3). However, the difference in benefit between strategies involving primary HPV testing with 16/18 genotype triage compared to HPV testing with cytology triage and cotesting were quite small, especially at earlier switch ages and more frequent intervals.

As the screening end age extended to age 70 years and 75 years (**Tables 6 and 7**), the absolute number of screening tests, colposcopies, CIN2/3 detected, CIN3+ detected, false positives, and life years increased, while the cervical cancer cases and deaths decreased. The trends in outcomes between the strategies (i.e., by screening modality, switch age and interval) remained consistent irrespective of screening end age.

Relative Efficiency Analysis

Three different metrics of colposcopies per life-year gained, screening tests per life-year gained, and colposcopies per cancer case averted were calculated to reflect different tradeoffs in harms and benefits. Each scenario analysis (A-D) representing different assumptions of the availability of triage strategies for primary HPV testing included the current guidelines-based strategies of cytology testing alone every 3 years, with or without a switch to cotesting every 5 years at age 30 (**Figures 9-11** and **Appendix Tables 1-3**). These analyses were repeated assuming extension of the screening end age to 70 and 75 (**Figures 12-14** and **Appendix Tables 4-9**), and a comprehensive analysis included all screening strategies, varying screening test modality, triage approach, age to switch to HPV primary testing, interval, and age to end screening (**Figures 15-17** and **Appendix Tables 10-12**).

Summary by Efficiency Outcome

Colposcopies per Life-Year Gained

In all four scenarios of HPV triage and cotesting availability (**Figure 9** and **Appendix Table 1**), the strategy with the lowest number of colposcopies per life-year gained was the current guidelines-based strategy of cytology testing alone every three years (strategy 1), with 2.5 colposcopies per life-year gained compared to no screening. By comparison, primary HPV and

cotesting strategies increased both life-years and number of colposcopies. Efficient strategies included primary HPV testing, either with 16/18 genotyping or cytology triage, every 5 years with a switch age of 25, 27 and 30 years (strategies 6-8, 12-14). For example, with 16/18 genotype triage availability (Scenario A), number of colposcopies per life-year gained increased from 86 to 297 as the switch age from cytology to HPV primary testing decreased from 30 to 25 years. Switching to 3-year primary HPV testing at age 25 (strategy 3), the most effective strategy, had a substantially higher ratio of 2,082 colposcopies per life-year gained, compared to 5-year screening at the same switch age of 25 (strategy 6). When assuming cytology triage for HPV-positive women (Scenario B), the corresponding ratios were lower for every 5-year screening with HPV primary testing, but slightly higher for every 3-year screening. In both Scenarios C and D, which included both triage strategies for HPV-positive women, follow-up with 16/18 genotype triage was not efficient when compared against cytology triage when HPV primary testing was conducted every 5 years. Screening every 3 years with either triage strategy required a much greater number of colposcopies per life-year gained, ranging from 2,188 (cytology triage, strategy 9) to 3,822 (16/18 genotype triage, strategy 3). The guidelines-based cotesting strategy (strategy 2) and additional cotesting strategies with earlier switch ages (25 and 27) and greater frequency (3-year) were not efficient in any scenario (strategies 15-19).

Tests per Life-Year Gained

When the analysis was expressed in terms of tests (both cytology and HPV) per life-year gained, the only efficient strategies were primary HPV testing at a switch age of 25, with either 5- or 3-year screening (strategies 3, 6, 9, 12; **Figure 10** and **Appendix Table 2**). In Scenario A, HPV primary testing with 16/18 genotype triage every 5 years (strategy 6) was associated with 43 tests per life-year gained; the ratio for this same strategy increased substantially to 22,335 tests per life-year gained with every 3-year screening (strategy 3). In Scenario B, with cytology triage, the corresponding ratios increased slightly to 44 tests per life-year gained with 5-year screening (strategy 12), and 28,636 test per life-year gained with 3-year screening (strategy 9). When both triage options were available (Scenarios C and D), 16/18 genotyping was more efficient than cytology triage. Cytology only and cotesting strategies (strategies 1-2, 15-19) were not efficient in any of the scenarios compared to primary HPV testing.

Colposcopies per Cervical Cancer Case Averted

Efficient strategies were consistent with those identified in the analysis of colposcopies per life-year gained (**Figure 11** and **Appendix Table 3**). Across all scenarios, cytology-only screening every 3 years (strategy 1) had the lowest ratio of 39 colposcopies per case averted. In Scenario A, primary HPV testing every 5 years with a switch age of 30 (strategy 8) was associated with a ratio of 766 colposcopies per case averted; shifting the age of switching from cytology to primary HPV testing required a greater number of colposcopies per case averted (1,432 for switch age 27 and 2,120 for switch age 25). The most effective strategy, HPV testing every 3 years with switch age of 25 (strategy 3), increased the ratio to 8,580 colposcopies per case averted. By comparison, when cytology was the only triage option for HPV-positive women (Scenario B), the corresponding ratios were uniformly lower, ranging from 640 to 1,735 colposcopies per case averted for HPV testing every 5 years at switch ages of 30 to 25, respectively; 3-year primary HPV testing with a switch age of 25 (strategy 9) was associated

with 7,018 colposcopies per case averted. When both triage options were equally available, we found that the strategies involving cytology triage for HPV-positive women were more efficient than 16/18 genotyping; 3-year HPV testing at age 25 with 16/18 genotyping (strategy 3), the most effective strategy, had a much higher ratio of 23,974 colposcopies per case averted. In all scenarios, cotesting strategies (strategies 2, 15-19) were not efficient.

Summary by Screening Modality, Interval, and Ages

Screening Modality and Triage

Across all three efficiency outcomes, strategies involving primary HPV testing, with either 16/18 genotype or cytology triage (depending on the scenario), consistently remained on the efficiency frontier. When the two triage strategies were compared in the same analysis (Scenarios C and D), cytology triage was more efficient than 16/18 genotype triage for the two efficiency metrics that used colposcopy as a measure of harm (per life-year gained and per case averted); however, 16/18 genotype testing was the preferred triage option when using screening tests as the measure of harm (per life-year gained).

Cytology only, reflecting a currently recommended strategy, had the lowest benefit in terms of life years and cancer cases, as well as the lowest number of colposcopies, and therefore yielded the lowest ratios when considering colposcopies as the measure of harm. When instead considering screening tests, cytology only was no longer on the efficiency frontier. Strategies involving cotesting, including one that is current recommended in the U.S., were universally not efficient across any of the measures.

Interval

Strategies involving 5-year screening were much more efficient than strategies with 3-year screening, which either were not on the efficiency frontier or had exceedingly high (i.e., unattractive) harm-to-benefit ratios. For all three efficiency measures, strategies involving switching to primary HPV testing every 5 years remained on the efficiency frontier.

Age to Switch From Cytology-Only Screening

For efficiency outcomes using colposcopies as a measure of harm, switching from cytology only to primary HPV testing at ages 25, 27, and 30 were found to be efficient, and the harm-to-benefit ratios decreased (i.e., became more attractive) as the switch age extended from age 25 to 30. When using screening tests as the measure of harm, only two strategies were efficient, both involving switching to primary HPV testing at age 25 (5-year and 3-year intervals).

Age to End Screening

When the analyses were repeated with the age to end screening extended to 70 and 75 years (base case 65 years), we found that our findings were very robust and that all of the same strategies were on the efficiency frontier as in the base-case analysis for each of the three efficiency outcomes (**Figures 12-14** and **Appendix Tables 4-9**). The corresponding ratios

increased (i.e., became less attractive) as the end age increased, indicating that although screening is more effective when continued to later ages, it also becomes less efficient.

When we conducted a comprehensive analysis with all possible strategies, including varying screening end age, we found that most of the strategies on the efficiency frontier involved extending screening end age to 70 and 75 (**Figures 15-17** and **Appendix Tables 10-12**). When using colposcopies as a measure for harms under Scenario D, screening with cytology alone every 3 years (strategy 1) was efficient when screening ended at 65, 70, and 75 years; ratios for colposcopies per life-year gained were 3, 17, and 26, respectively. Next efficient strategies included switch to 5-year primary HPV testing with cytology triage at age 30 (strategy 14), with screening end ages of 70 and 75, which increased colposcopies per life-year gained to 95 and 99 colposcopies per life-year gained, respectively. Those strategies with earlier switch ages (27 and 25; strategies 13 and 12) increased the number of colposcopies required per life-year gained to 135 and 225, respectively. Three-year HPV testing with 16/18 genotype triage at a switch age of 25 (strategy 3) until age 75 was the most effective strategy with the highest ratio of 6,239 colposcopies per life-year gained. When considering colposcopies per case averted, nearly all of the same strategies were efficient, except that the screening end age for primary HPV testing was 75 years. Strategies with a switch to HPV testing younger than age 30 required greater than 1,000 colposcopies per case averted; strategies with a switch age of 25 had ratios ranging from 2,064 to 25,112 colposcopies per case averted depending on triage strategy and interval.

When using screening tests as a measure of harms, we again found that the only efficient strategies involved primary HPV testing with 16/18 genotype triage at a switch age of 25 (strategies 3, 6). Extending the end age of screening increased efficiency ratios dramatically, from 43 to 707 to 1,497 screening tests per life-year gained when screening occurred every 5 years up to ages 65 to 70 to 75, respectively. This same strategy occurring every 3 years up to age 75 required 69,064 screening tests per life-year gained.

Sensitivity Analysis

Because of the inherent uncertainty in key model parameters, we undertook several sensitivity analyses to explore the robustness of results. The range (minimum and maximum) of base-case results across the 50 best-fitting parameter sets are presented in **Appendix Table 13** to show the variation in outcomes when taking into account the uncertainty in the natural history parameters. Despite these variations, the rank order of the strategies according to each outcome was stable over the multiple sets.

Test Characteristics

We undertook several analyses to assess the impact of test performance characteristics on base-case results (Scenario D) (**Tables 8-10** and **Appendix Tables 14-18**). When test sensitivity for cytology was increased to the upper-bound, best-case value (81.5%), with a corresponding decrease in specificity (88.0%), we found that both cervical cancer cases and deaths decreased for all strategies, with the biggest decrease in the cytology-only strategy (decrease of 15% cervical cancer cases and 13% cervical cancer deaths; strategy 1) (**Appendix Table 14**).

Nonetheless, because of the lower specificity, both numbers of colposcopies and false positives increased considerably, whereas the number of tests only increased marginally. For all three efficiency metrics, the efficient strategies remained the same as in the base case, but the ratios generally increased (i.e., became less attractive) given the increase in resource use. For example, ratios associated with a switch to 5-year primary HPV testing at ages 30, 27 and 25 increased to 80, 167, and 323 colposcopies per life-year gained (strategies 12-14; **Table 8**); switching to 3-year primary HPV testing at age 25 (strategies 3, 9) were still associated with ratios over 2,000 colposcopies per life-year gained. The increase in ratios in terms of tests per life-year gained (**Table 9**) and colposcopies per cancer case averted (**Table 10**) was not as pronounced.

When cytology specificity was increased (93.6%), with a decrease in sensitivity (51.4%) (**Appendix Table 15**), the effectiveness of all strategies decreased – especially for screening with cytology alone – but given the corresponding decrease in colposcopies, the ratios using this measure decreased (became more attractive) for all strategies. Efficiency ratios that used colposcopies as a measure of harm decreased by up to 60% for the HPV testing strategies (**Tables 8** and **10**). While switching to 5-year primary HPV testing with 16/18 genotype triage at age 25 (strategy 6) became an efficient strategy in terms of colposcopies per life-year gained (873 colposcopies per life-year gained; **Table 8**); the same strategy with cytology triage was associated with a far lower ratio (104 colposcopies per life-year gained; strategy 12). Since screening tests changed only marginally, the ratios using tests per life-year gained were stable (**Table 9**), switching to 5-year primary HPV testing starting at age 25 at 43 tests per life-year gained; this same strategy at 3-year intervals remained exceedingly high.

We explored the lower-bound (worst-case) relative sensitivity of HPV testing, which impacted both HPV testing alone and cotesting, and found that despite a decrease in the effectiveness of the primary HPV testing strategies, they still provided greater benefits than the current guidelines-based strategies (**Appendix Table 16**). Since the decrease in effectiveness was also accompanied by a decrease in colposcopies, the ratios among efficient strategies improved and more strategies involving 3-year screening with HPV testing alone (strategies 3, 9, 10; **Tables 8** and **10**) became efficient, likely to offset the lower sensitivity value.

When we introduced error in the performance of colposcopy/biopsy in classifying a woman's true histologic status, we found that the number of lifetime colposcopies decreased by up to 16% for the HPV and cotesting strategies; this decrease in colposcopies was also accompanied by a decrease in false positive results, but also an increase in cancer cases and deaths (**Appendix Table 17**). When the effectiveness of precancer treatment (i.e., LEEP) was decreased to 82%, we found only small changes in the number of tests and colposcopies, but 12-17% increase in cervical cancer cases and 4-7% increase in cervical cancer deaths across all strategies (**Appendix Table 18**). Despite these variations in outcomes, the base-case results of the efficiency analyses remained stable under both sensitivity analyses, with slight decreases in the ratios due to the relatively greater reductions in harms (i.e., colpscopies and test) than benefits (i.e., life-years and cases averted).

Follow-Up of HPV-Positive Women

Given that the effectiveness and efficiency of HPV testing depends heavily on the management of screen-positive women, we examined alternative follow-up algorithms based on protocols from empirical studies (**Tables 8-10** and **Appendix Tables 19-22**). In either primary HPV testing strategy, for women who receive cytology triage (i.e., non-16/18, high-risk positive women in 16/18 triage option; all high-risk positive women in cytology triage option), we explored a more stringent cutoff of LSIL or worse as the threshold to refer women directly to colposcopy (versus ASC-US or worse in the base case). Overall, all HPV testing strategies had lower effectiveness, as well as decreases to number of tests, colposcopies, and false positive results (**Appendix Table 19**). Since the change in the measures of harms was slightly larger than the change in measures of benefit, the ratios for all strategies across the three efficiency outcomes marginally decreased (i.e., became more attractive).

We also varied the time to repeat testing for women who receive a normal results upon cytology triage (in both 16/18 genotype and cytology triage options for HPV testing), as well as those who receive HPV-positive and cytology-negative result on cotesting (12 months in the base case). In one scenario, we decreased the time to follow-up to 6 months, and in another scenario, we increased the time to follow-up to 24 months. We found that varying the follow-up interval had a large impact on number of colposcopies and false positives and a smaller impact on effectiveness, especially for HPV testing with cytology triage and cotesting which send greater proportions of women to repeat testing. When follow-up was 6 months (**Appendix Table 20**), both colposcopies and effectiveness increased; this result led to similar efficient strategies as in the base-case analysis, but overall higher ratios indicating lower efficiency. Additionally, switching to 3-year cotesting at age 25 (strategy 15) became the most effective strategy, although with relative high ratios for all three efficiency outcomes. In contrast, when time to follow-up was extended to 24 months (**Appendix Table 21**), HPV testing and cotesting strategies were less effective, but were more efficient in terms of colposcopies per life-year gained and per cancer case averted. For example, colposcopies per life-year gained associated with switching to 5-year HPV testing at ages 30, 27 and 25 decreased to 48, 109, and 114 (72, 143, and 195 in the base case; strategies 14, 13, 12), respectively.

We evaluated a third alternative triage option in which all HPV-positive women are referred directly to colposcopy. Not surprisingly, the number of colposcopies and false positives was much greater (25-29% higher than with 16/18 genotype triage; 40-48% higher than with cytology triage) with only a nominal increase in effectiveness (**Appendix Table 22**). For ratios that used colposcopies as a measure of harm, all strategies that referred HPV-positive women to colposcopy without further testing were not efficient, and the base case strategies and ratios remained the same. Because the number of tests decreased given the removal of repeat testing for HPV-positive women, when defining efficiency in terms of tests per life-year gained, the efficient strategies of 16/18 genotype triage in the base case were replaced by the same strategies of referring all HPV-positive women to colposcopy (i.e., switching to primary HPV testing at age 25); as in the base-case analysis, ratios associated with 3-year HPV testing (>29,000 tests per life-year gained) were much higher than with 5-year testing (42 tests per life-year gained).

HPV-16/18 Vaccinated Women

We evaluated the screening strategies in women assumed to be completely protected from HPV-16/18 infections over the lifetime due to vaccination, to reflect a low-risk population (**Tables 8-10** and **Appendix Table 23**). When protection against HPV-16/18 is complete, the 16/18 genotype and cytology triage options become equivalent and therefore our analysis set reduced to cytology alone, HPV primary testing with cytology triage, and cotesting. Women in this low-risk group faced significant reductions in cervical cancer cases and deaths, as well as high reductions in colposcopies and false positive results. The same strategies were identified as efficient as in the base case; however, their ratios for all efficiency outcomes increased considerably, likely because these strategies (targeted to unvaccinated women in our base-case analysis) remain too intensive in women with considerably lower cervical cancer risk. For example, in terms of colposcopies per life-year gained, the ratio for switching to 5-year HPV testing at age 30 (strategy 14) increased from 73 to 113; ratios for switching to 5-year HPV testing at younger ages, 27 and 25, more than doubled, to 402 and 463, respectively (143 and 195 in the base case; strategies 13 and 12). A similar trend was observed in terms of colposcopies per cancer case averted. When testing was used as a measure of harm, the ratios associated with 5-year HPV testing at age 25 also doubled; ratios associated with 3-year screening ranged from 159,953 per life-year gained (primary HPV testing, strategy 9) to 429,590 per life-year gained (cotesting; strategy 15).

Chapter 4. Discussion

This report summarizes the findings from a model-based decision analysis on the long-term health effects, harms, and efficiency of primary HPV testing strategies to inform the 2017 USPSTF recommendations for cervical cancer screening in the United States. This analysis extends the 2012 decision analysis, which primarily evaluated cytology-based strategies,[29] by focusing specifically on HPV testing for primary screening and including variations in age to switch from cytology-only screening to HPV testing, the rescreening interval, triage options for HPV-positive women, and screening end age. For strategies that overlapped in both reports (e.g., 3-year cytology alone; strategy 1), our results were quite similar to the findings from the previous report.

Consistent with short-term evidence from clinical studies on the effectiveness of HPV testing relative to cytology testing alone, we found that strategies employing primary HPV testing (alone or with cotesting) were associated with greater health benefits compared to current guidelines-based strategies of 3-year cytology alone, with or without a switch to 5-year cotesting at age 30, but come at a harm of greater testing, colposcopies, and false positives. In all analyses, across three different efficiency measures, primary HPV testing strategies occurring at 5-year intervals were efficient; by comparison, the more effective strategies involving 3-year HPV testing, generally had exceedingly high ratios. Which HPV testing triage option was efficient depended on the measure of harm used: in terms of colposcopies per life-year gained or per cancer case averted, cytology triage for HPV-positive women was uniformly more attractive and efficient than 16/18 genotyping triage; most of the efficient strategies when using colposcopies as a measure of harm consistently involved 5-year HPV testing (switching at ages 25, 27, and 30). In contrast, in terms of screening tests per life-year gained, 16/18 genotyping triage was more efficient, mostly involving switching to primary HPV testing at age 25 (5-year and 3-year intervals).

Cotesting strategies were predominantly inefficient and appeared on the efficiency frontier only under two scenarios (repeat follow-up HPV testing at 6 months and in low-risk women), but in both of those cases were associated with much higher ratios compared to strategies involving HPV testing alone. When colposcopies was used as the measure of harm, cytology testing alone every 3 years was associated with very low (i.e., attractive) ratios; however, when using total tests as the measure of harm, cytology testing was inefficient across all analyses.

These findings were robust when varying age to end screening from age 65 to 70 and 75 (assuming no recent abnormal results) with only slight increases in each of the ratios due to decreased efficiency of screening in older ages. When competing all strategies, including end ages for screening, we found that most of the efficient strategies across the three outcomes involved extending the screening age to 70 or 75. However, given the vast uncertainties regarding the natural history of HPV infection and screening effectiveness in older women – which were not extensively explored in the current analysis – our findings of screening end age should be interpreted with caution.

When multiple strategies are identified as efficient, selecting the “optimal” strategy depends on a

threshold ratio that would be considered a reasonable balance of harms and benefits. The desired thresholds for each of the three efficiency measures is not clear when using intermediate metrics such as colposcopies or screening tests as a proxy for harm as it is difficult to compare head-to-head against other (non-cervical cancer) health interventions. Although costs were not considered in this analysis, the relative efficiency with respect to costs per life-year gained, a standard metric in traditional cost-effectiveness analysis, can provide another dimension of the tradeoff of harms and benefits that can more easily be benchmarked against other health interventions. In the absence of such a standard metric in this report, we elected to express results using three different metrics of efficiency to help interpret results in the context of different potential tradeoffs that might be considered important by decision-makers.

Strengths and Limitations of Modeling

Disease simulation models, when paired with robust data on disease burden and intervention effects, can be powerful tools in projecting long-term outcomes to inform decision-making in a timely manner.[30] While most empirical studies on screening effectiveness report findings after only one or two rounds of screening, we can use the model to evaluate the implications of multiple screenings over an extended period and under different combinations of ages to switch, intervals, and management algorithms of screen-positive women. As with all model-based analyses, however, this analysis is subject to important limitations.

First, our analysis is based on assumptions of perfect compliance to screening intervals and management of screen-positive women; however, it is well-documented that screening practice is not perfect and quite variable across the United States. How loss-to-follow up might differ across testing modalities, age, and interval is uncertain but could impact the overall effectiveness and relative performance of the screening strategy. Also, although we examined a number of unique strategies, there may be other strategies that could lead to a more attractive balance of harms and benefits; for example, we restricted our rescreening interval to be no less frequent than every 5 years, but extending intervals to be even longer (e.g., 7 or 10 years) may be more efficient without compromising on effectiveness. Additionally, as mentioned previously, we did not explore different assumptions regarding the natural history of HPV infection in older women, nor did we examine other strategies or criteria to determine when to stop screening. There is much uncertainty regarding the prevalence and clinical importance of a newly-acquired HPV infection versus re-activation of a previously-acquired infection in older ages, which may impact the optimal age at which to stop screening. Furthermore, recent studies indicate that the incidence and mortality rates from cervical cancer are grossly underestimated by Surveillance, Epidemiology, and End Results Program (SEER) given high rates of hysterectomies in US women, and suggest that the current recommendation for terminating screening may not be optimal.[31,32] The findings from our model, which do correct for hysterectomy rates by age in the population, indicate efficiency and greater effectiveness by extending the screening end age to 70 or 75; however, other screening exit criteria and strategies should be further explored in future analyses under various assumptions of disease risk and screening effect at older ages.

We did not fully explore the recent issues regarding HPV-negative cancers and the implications on the relative effectiveness of HPV testing alone versus cytology alone or cotesting.[33] However,

we explored uncertainty in the screening test characteristics, and we found that our base case results were robust even when decreasing HPV relative test sensitivity (compared to cytology) to a lower bound estimate. In our assessment of screening in a low-risk population, we only represented one very specific subset of low-risk women, those who receive protection against HPV-16/18 infection and disease from vaccination. While there are other low-risk segments of the population, this question will become increasingly more pertinent as vaccinated women enter screening age. Finally, it is important to underscore that the results from the model represent average outcome across whole population and is intended to inform guidelines at the population level not at an individual level.

Summary

In summary, the results from the model indicate that primary HPV screening has the potential to increase the effectiveness of screening compared to current US guidelines-based strategies and may represent a reasonable balance of harms and benefits when administered every 5 years. The optimal age at which to switch from cytology to HPV testing, the optimal management of HPV-positive women, and the optimal screening end age depends on which outcome (colposcopies or tests) is used as the proxy for harms.

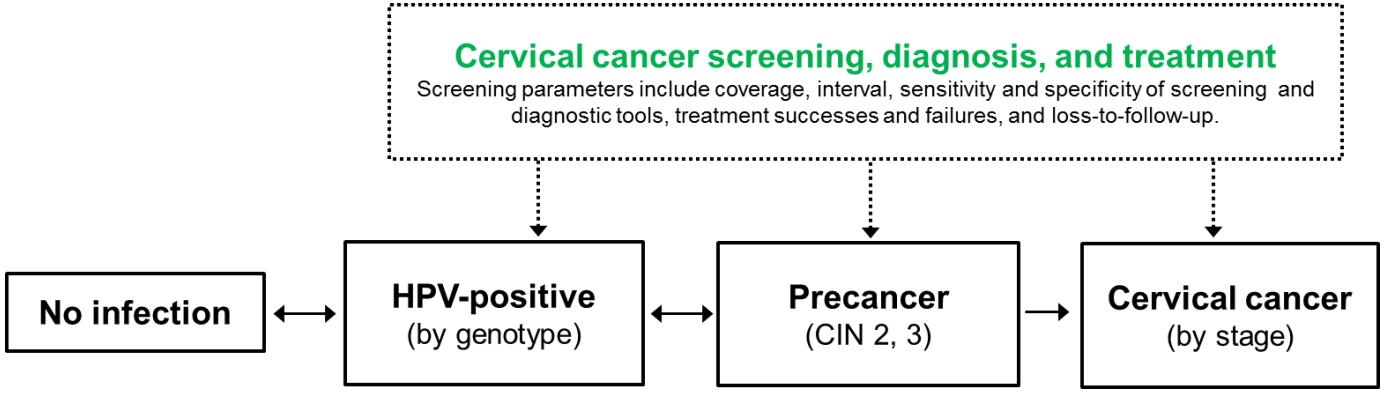
References

1. Cancer Facts and Figures 2017. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2017/cancer-facts-and-figures-2017.pdf. (Last accessed January 31, 2017).
2. U.S. Preventive Services Task Force. Screening for cervical cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2012;156:880-91.
3. 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. *CA Cancer J Clin*. 2012;62:147-72.
4. ACOG Practice Bulletin Number 131: screening for cervical cancer. *Obstet Gynecol*. 2012;120:1222-38.
5. Melnikow J, Henderson JT, Burda BU, et al. Screening for Cervical Cancer With High-Risk Human Papillomavirus Testing: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 158. AHRQ Publication No. 17-05231-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2017.
6. Campos NG, Burger EA, Sy S, et al. An updated natural history model of cervical cancer: derivation of model parameters. *Am J Epidemiol*. 2014;180:545-55.
7. Kim JJ, Campos NG, Sy S, et al. Inefficiencies and high-value improvements in U.S. cervical cancer screening practice: a cost-effectiveness analysis. *Ann Intern Med*. 2015;163:589-97.
8. National Center for Health Statistics. 2010 National Hospital Discharge Survey (NHDS) Public Use Micro-Data File and Documentation. Available at https://www.cdc.gov/nchs/nhds/nhds_questionnaires.htm. (Last accessed January 31, 2017).
9. University of California Berkeley. Berkeley Mortality Database. Available at http://demog.berkeley.edu/~bmd. (Data downloaded on August 2, 2016).
10. U.S. National Cancer Institute. Surveillance, Epidemiology, End Results (SEER) Cancer Statistics Review, 1975-2013. Available at https://seer.cancer.gov/csr/1975_2013/. (Last accessed January 31, 2017).
11. 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;132:198-207.
12. 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;24:230-40.
13. 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:djv086.
14. 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;57:1037-43.
15. International Agency for Research on Cancer. Cancer in Five Continents, Volume 1. Available at http://ci5.iarc.fr/Default.aspx. (Last accessed January 31, 2017).
16. 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;23:765-73.

17. 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;136:2854-63.
18. Kinney W, Hunt WC, Dinkelspiel H, et al. Cervical excisional treatment of young women: a population-based study. *Gynecol Oncol*. 2014;132:628-35.
19. 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;140:440-8.
20. Massad LS, Einstein MH, Huh WK, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis*. 2013;17:S1-S27.
21. Koliopoulos G, Arbyn M, Martin-Hirsch P, Kyrgiou M, Prendiville W, Paraskevaidis E. Diagnostic accuracy of human papillomavirus testing in primary cervical screening: a systematic review and meta-analysis of non-randomized studies. *Gynecol Oncol*. 2007;104:232-46.
22. 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;208:184 e1- e11.
23. Wright TC, Stoler MH, Behrens CM, Sharma A, Zhang G, Wright TL. Primary cervical cancer screening with human papillomavirus: end of study results from the ATHENA study using HPV as the first-line screening test. *Gynecol Oncol*. 2015;136:189-97.
24. Arbyn M, Ronco G, Anttila A, et al. Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer. *Vaccine*. 2012;30(Suppl 5):F88-99.
25. Ronco G, Giorgi-Rossi P, Carozzi F, et al. Human papillomavirus testing and liquid-based cytology in primary screening of women younger than 35 years: results at recruitment for a randomised controlled trial. *Lancet Oncol*. 2006;7:547-55.
26. Ronco G, Segnan N, Giorgi-Rossi P, et al. Human papillomavirus testing and liquid-based cytology: results at recruitment from the new technologies for cervical cancer randomized controlled trial. *J Natl Cancer Inst*. 2006;98:765-74.
27. Stoler MH, Ronnett BM, Joste NE, et al. The interpretive variability of cervical biopsies and its relationship to HPV status. *Am J Surg Pathol*. 2015;39:729-36.
28. Ghaem-Maghami S, Sagi S, Majeed G, Soutter WP. Incomplete excision of cervical intraepithelial neoplasia and risk of treatment failure: a meta-analysis. *Lancet Oncol*. 2007;8:985-93.
29. 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;17:193-202.
30. Kim JJ, Tosteson AN, Zauber AG, et al. Cancer models and real-world data: better together. *J Natl Cancer Inst*. 2016;108.
31. Beavis AL, Gravitt PE, Rositch AF. Hysterectomy-corrected cervical cancer mortality rates reveal a larger racial disparity in the United States. *Cancer*. 2017 Jan 23.
32. Rositch AF, Nowak RG, Gravitt PE. Increased age and race-specific incidence of cervical cancer after correction for hysterectomy prevalence in the United States from 2000 to 2009. *Cancer*. 2014;120:2032-8.

33. Blatt AJ, Kennedy R, Luff RD, Austin RM, Rabin DS. Comparison of cervical cancer screening results among 256,648 women in multiple clinical practices. *Cancer Cytopathol*. 2015;123:282-8.

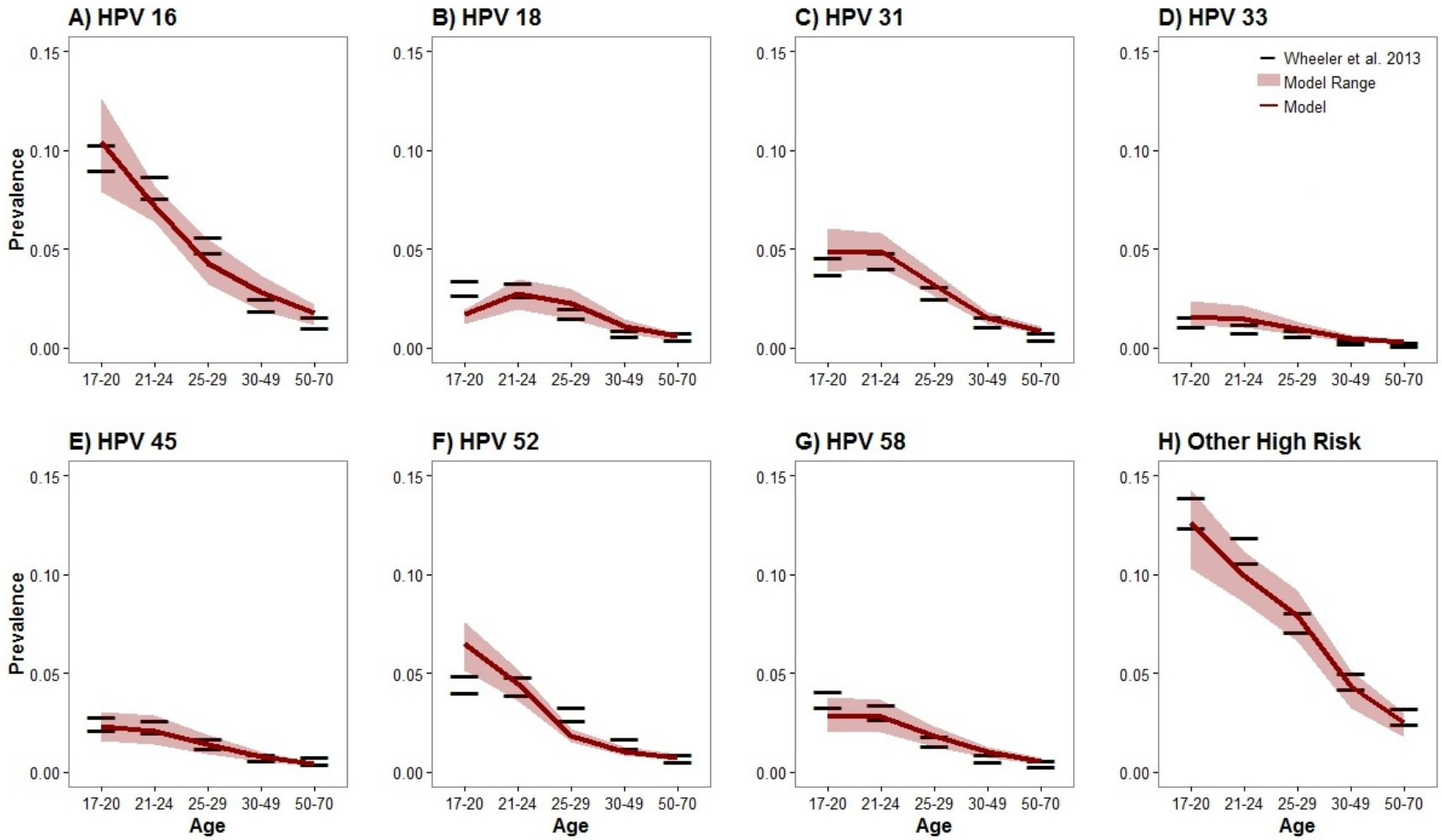
Figure 1. Model Schematic



The main health states of the model comprise HPV infection (by genotype), precancer (e.g., cervical intraepithelial neoplasia or CIN, grades 2 and 3) and invasive cancer (by stage). The model focuses on squamous cell carcinoma, the most common histologic subtype of cervical cancer.

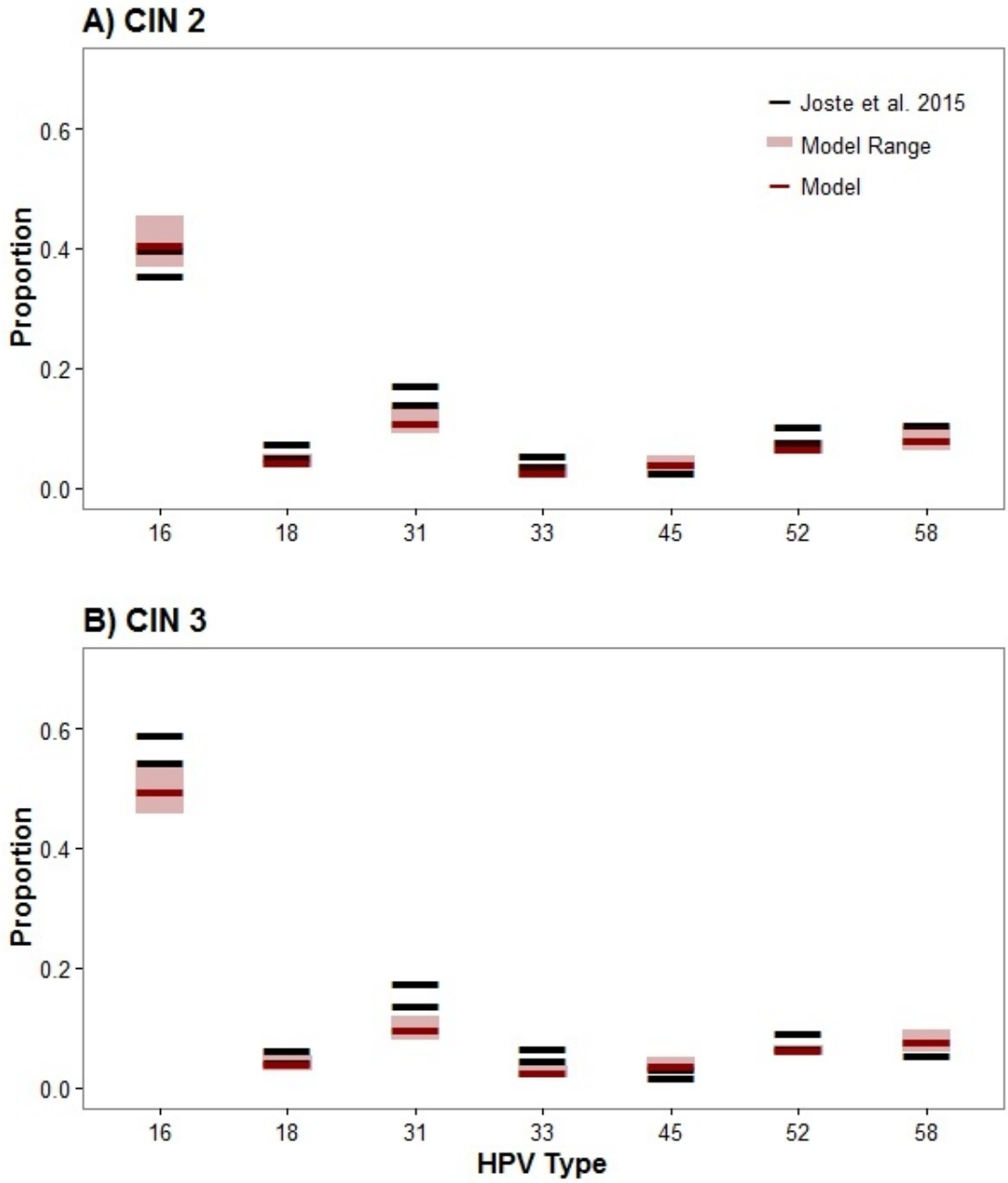
Screening is used to detect the presence of high-grade precancers, which may resolve spontaneously or can be treated and removed before progressing to cancer, as well as for early detection of invasive cancer. The effectiveness of screening strategies depends on coverage by age, interval, test characteristics, treatment efficacy, and compliance to follow-up visits.

Figure 2. Prevalence of HPV by Age and Type



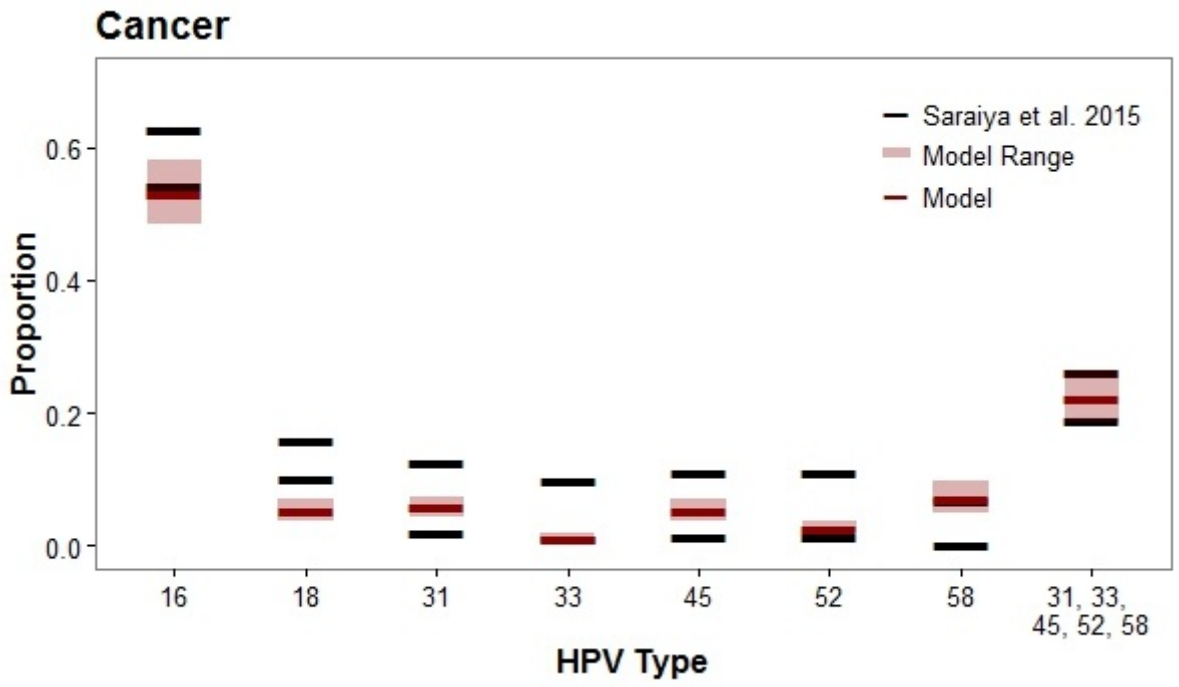
These graphs show post-calibration model fit to age- and type-specific HPV prevalence from the New Mexico HPV Pap Registry.[11] The model range shows the variation in model fit across the 50 best-fitting parameter sets; the red line shows the mean fit across the 50 sets.

Figure 3. Type Distribution of HPV in CIN2 and CIN3



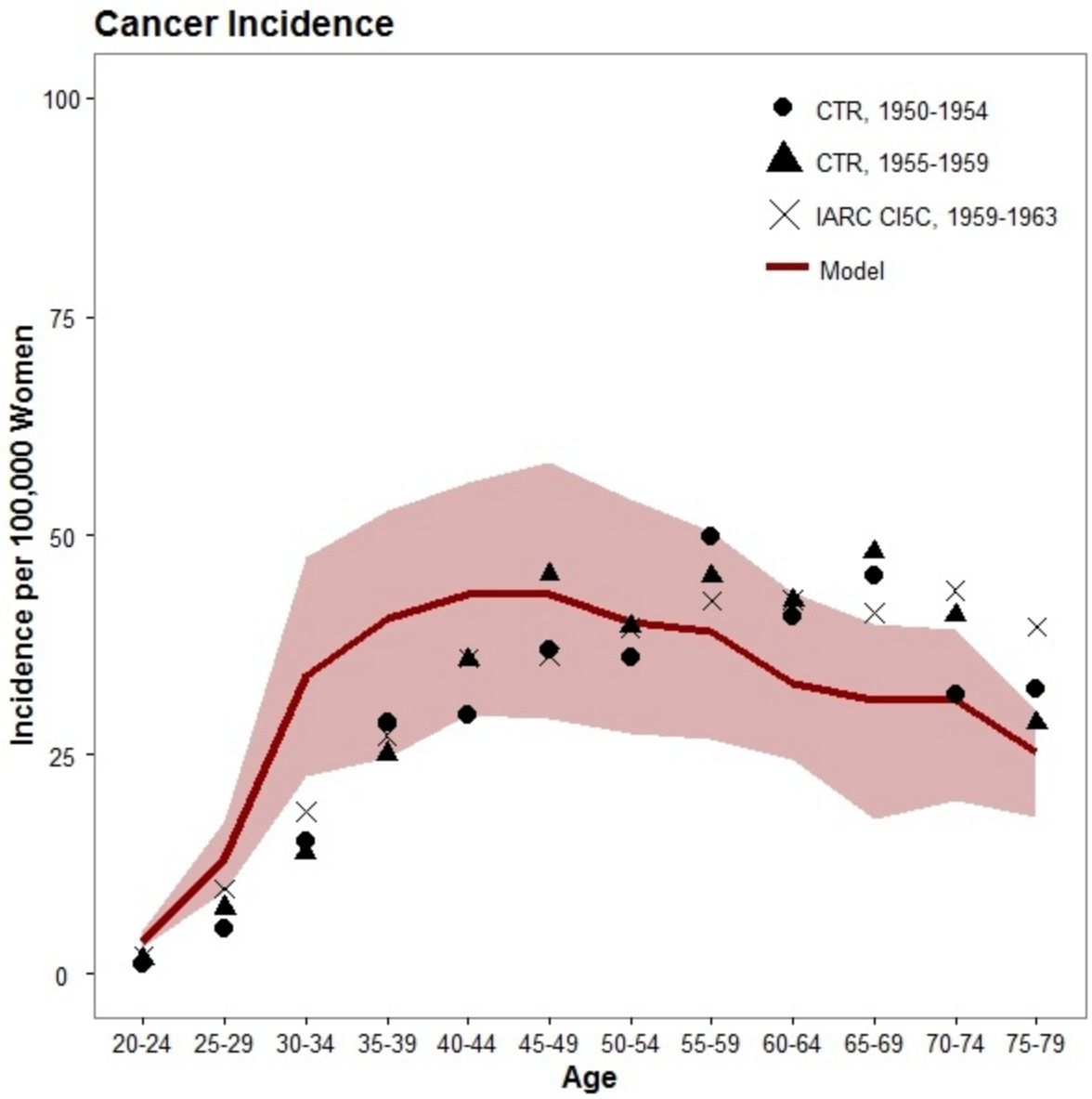
These graphs show post-calibration model fit to HPV type distribution in CIN 2 and CIN 3 from the New Mexico HPV Pap Registry.[12] The model range shows the variation in model fit across the 50 best-fitting parameter sets; the red line shows the mean fit across the 50 sets.

Figure 4. Type Distribution of HPV in Cancer



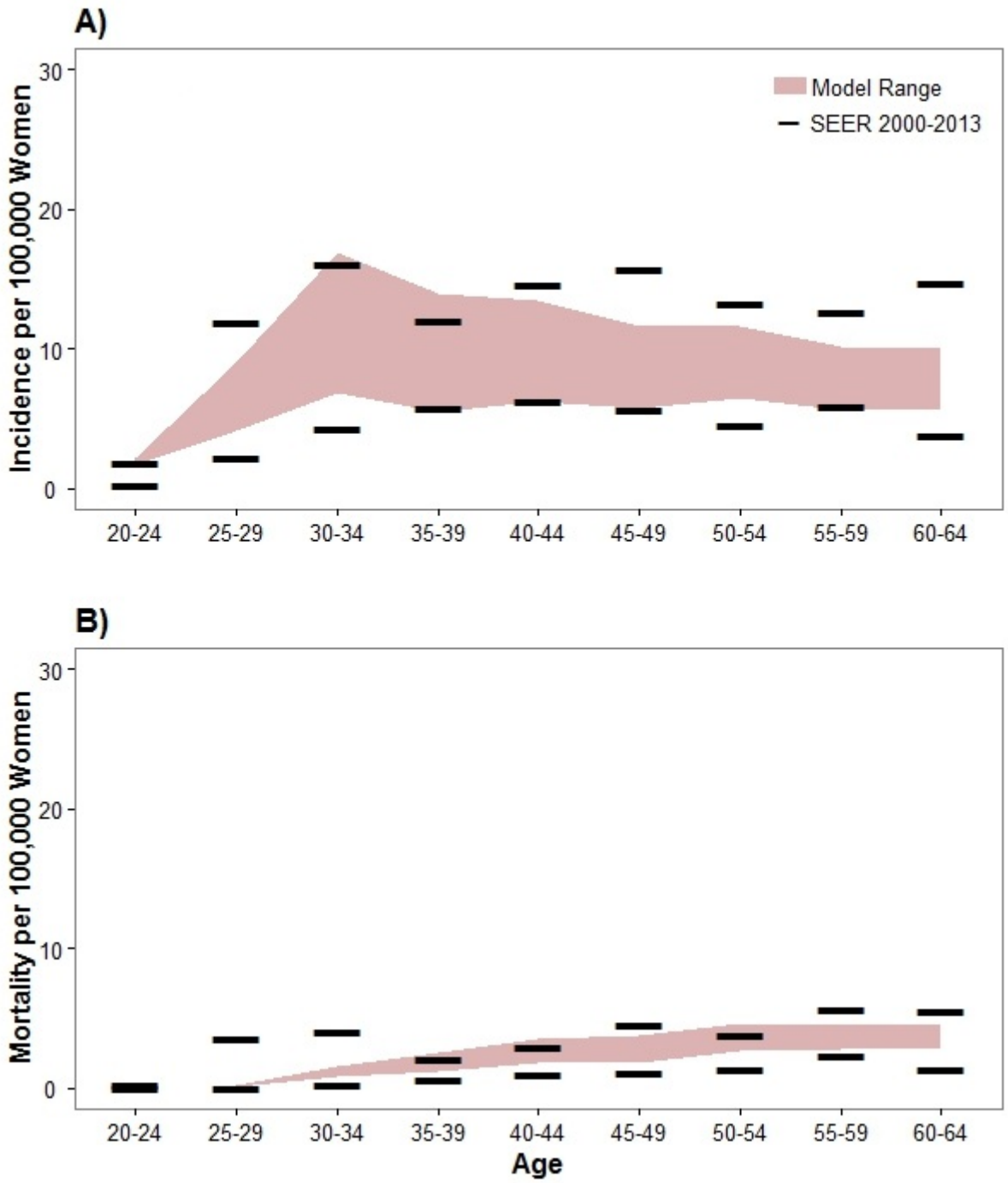
This graph shows post-calibration model fit to HPV type distribution in cancer from U.S. population-based cancer registries.[13] The model range shows the variation in model fit across the 50 best-fitting parameter sets; the red line shows the mean fit across the 50 sets.

Figure 5. Cervical Cancer Incidence per 100,000, by Age and Model (Natural History)



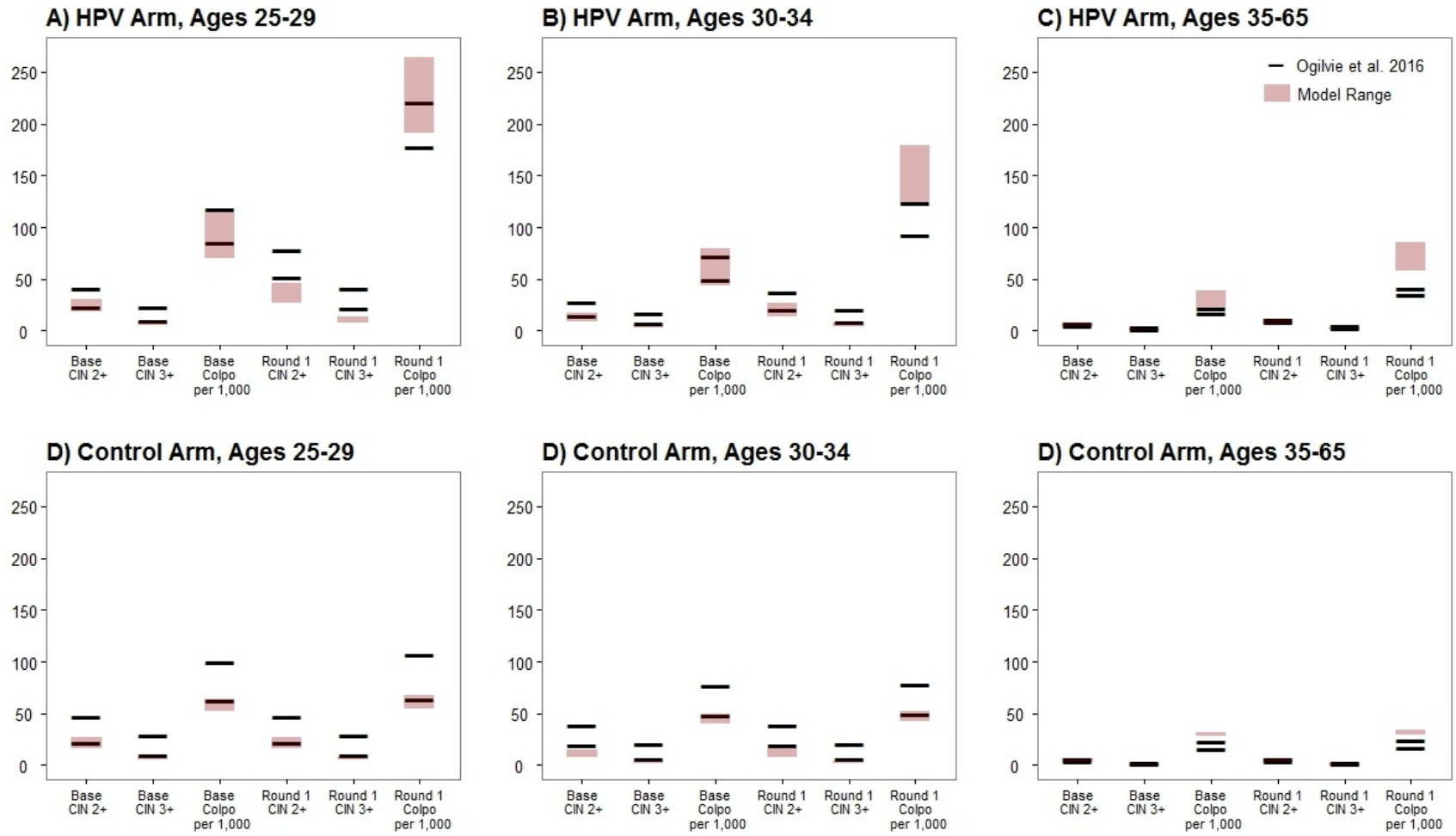
This graph shows model-projected cervical cancer incidence rates under a scenario of no intervention (i.e., natural history) compared against cancer registry data from the 1950s and early 1960s, before Pap smear screening was widely available in the U.S. Data were from the Connecticut Tumor Registry (CTR) and IARC Cancer in Five Continents (volume 1), which included data from Connecticut, New York, Hawaii.[14,15] 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 either model but instead were used to assess predictive validity for overall underlying risk. The model range shows the variation in model projections across the 50 best-fitting parameter sets; the red line shows the mean projection across the 50 sets. [Note: Both incidence and mortality rates from the model were calculated using the number of women alive as the denominator, not adjusting for women with hysterectomy, to match the estimates from the cancer registries.]

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



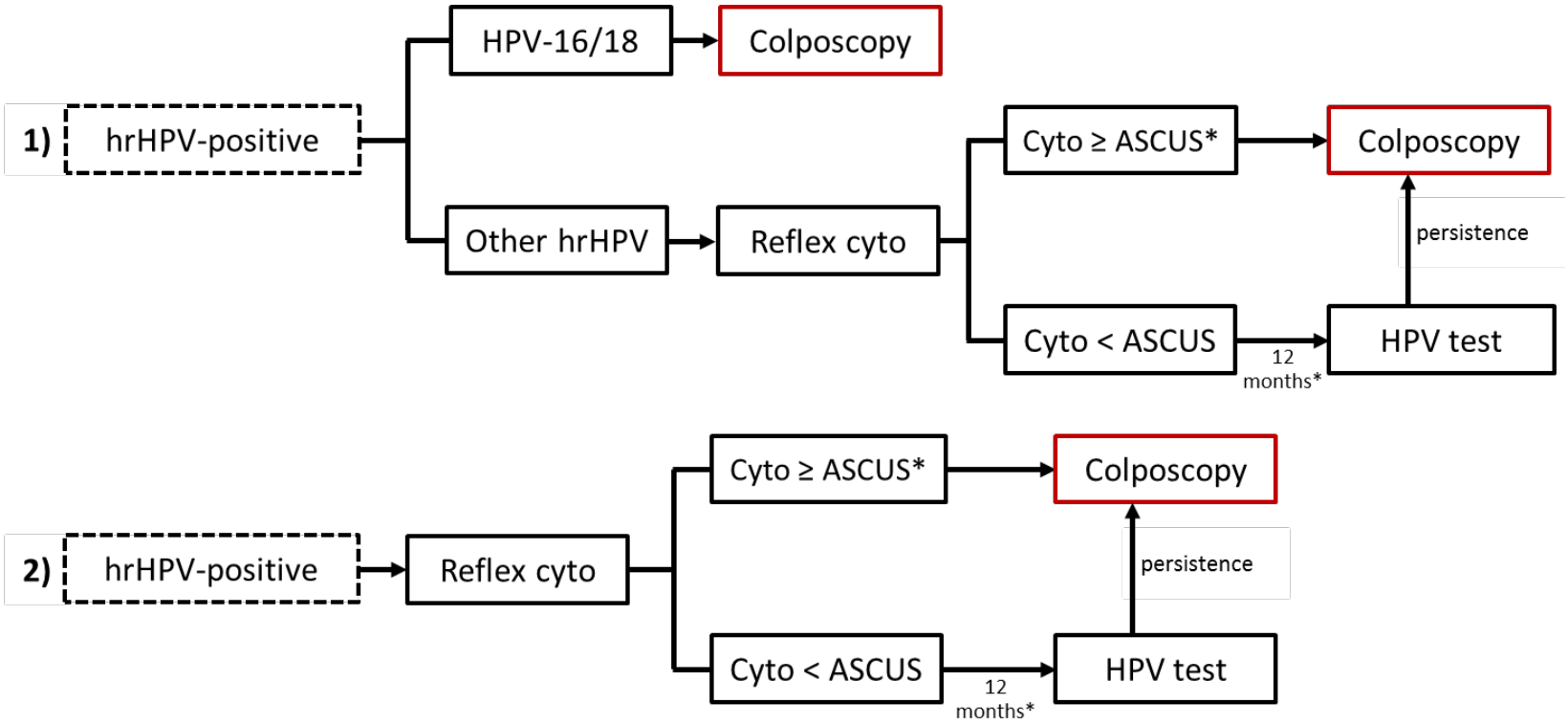
This graph shows model-projected cervical cancer incidence and mortality rates under assumptions of screening practice patterns reported in the New Mexico HPV Pap Registry,[16-18] compared against those reported in SEER cancer registries in recent years (i.e., 2000-2012).[10] The model range shows the variation in model projections under different assumptions of non-compliance to follow-up diagnostic testing and/or precancer treatments. [Note: Both incidence and mortality rates from the model were calculated using the number of women alive as the denominator, not adjusting for women with hysterectomy, to match the estimates from SEER.]

Figure 7. Outcomes From HPV FOCAL Trial (With Screening)



This graph shows model validation against baseline and 12-month outcomes reported in the HPV FOCAL trial.[19] We simulated the trial protocol including three screening scenarios involving switching to primary HPV testing at ages 27, 34 and 52. The model range shows the variation in projections across the 50 best-fitting parameter sets.

Figure 8. Flow Diagram for Alternative Triage Strategies for (hr)HPV-Positive Women



* These variables were varied in sensitivity analysis.

Two triage strategies for HPV-positive screening results were examined: (a) assuming HPV-16/18 genotype information is available, 16/18-positive women are referred to colposcopy, whereas women positive for other high-risk HPV types receive cytology triage (cytology ≥ ASCUS are referred to colposcopy; cytology-negative receive a follow-up test in 12 months); (b) all women with high-risk HPV receive cytology triage (cytology ≥ ASCUS are referred to colposcopy; cytology-negative receive a follow-up test in 12 months). A referral threshold of cytology ≥ LSIL was also evaluated, and the interval for follow-up testing was varied (e.g., 6 or 24 months) in sensitivity analysis.

Figure 9. Efficiency Frontiers: Colposcopies per Life-Year Gained Varying HPV Testing Switch Age and Interval (Screening End Age 65), Under Different Scenarios of Triage Options for HPV-Positive Women (Scenarios A-D)

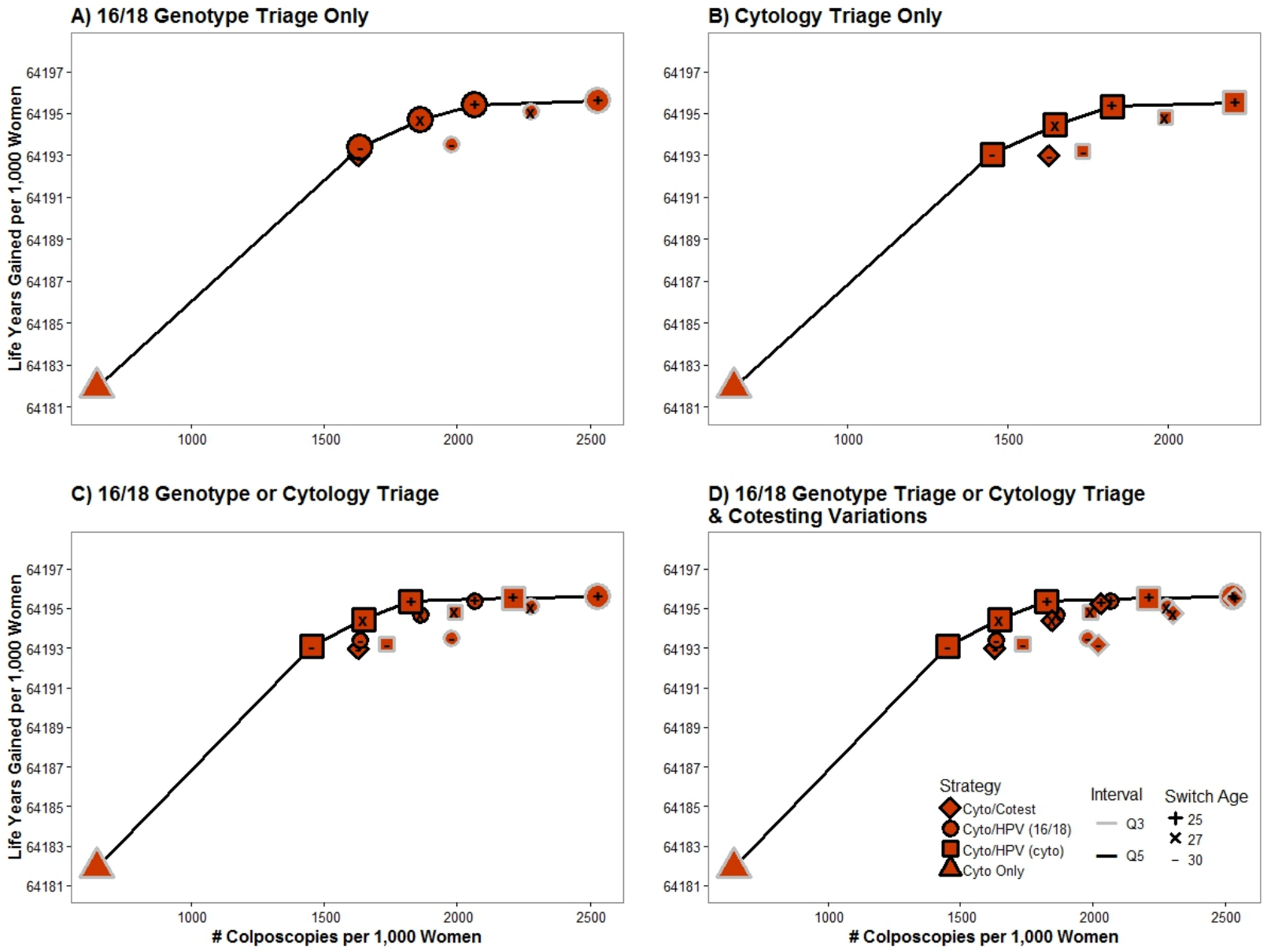


Figure 10. Efficiency Frontiers: Tests per Life-Year Gained Varying HPV Testing Switch Age and Interval (Screening End Age 65), Under Different Scenarios of Triage Options for HPV-Positive Women (Scenarios A-D)

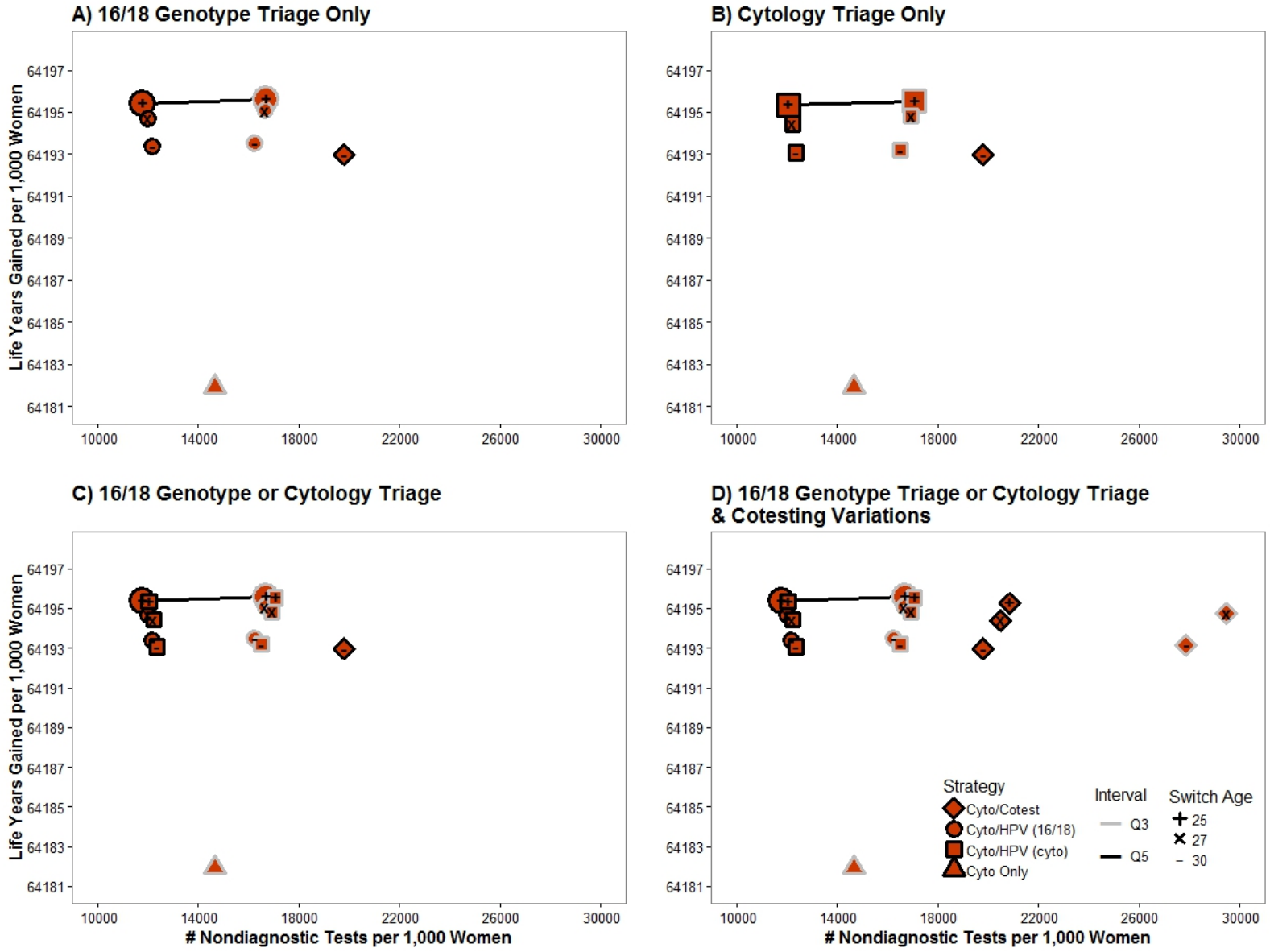


Figure 11. Efficiency Frontiers: Colposcopies per Cervical Cancer Case Averted Varying HPV Testing Switch Age and Interval (Screening End Age 65), Under Different Scenarios of Triage Options for HPV-Positive Women (Scenarios A-D)

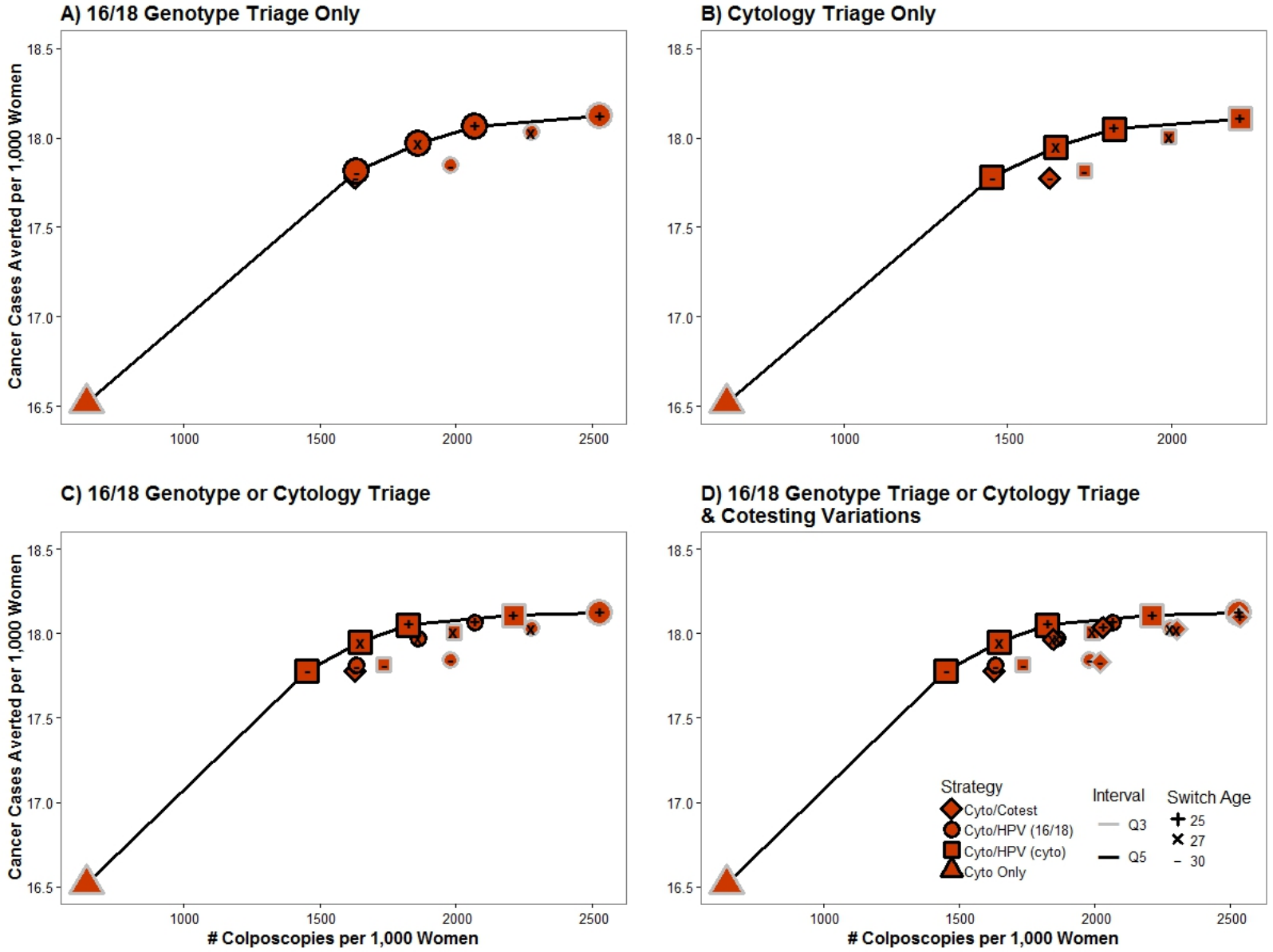


Figure 12. Efficiency Frontiers: Colposcopies per Life-Year Gained When Varying Screening End Age (65, 70, 75 Years), Under Different Scenarios of Triage Options for HPV-Positive Women (Scenarios A-D)

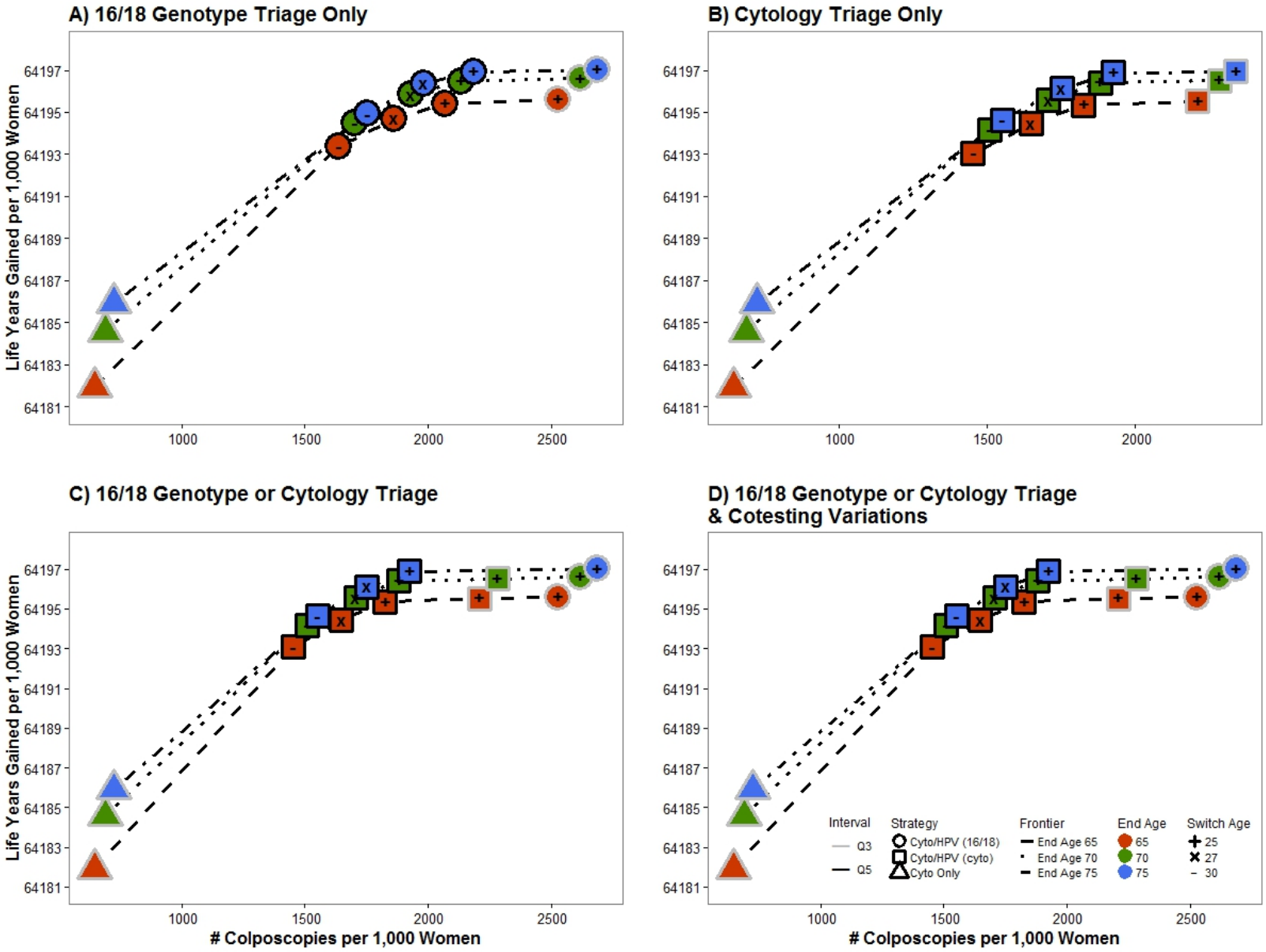


Figure 13. Efficiency Frontiers: Tests per Life-Year Gained When Varying Screening End Age (65, 70, 75 Years), Under Different Scenarios of Triage Options for HPV-Positive Women (Scenarios A-D)

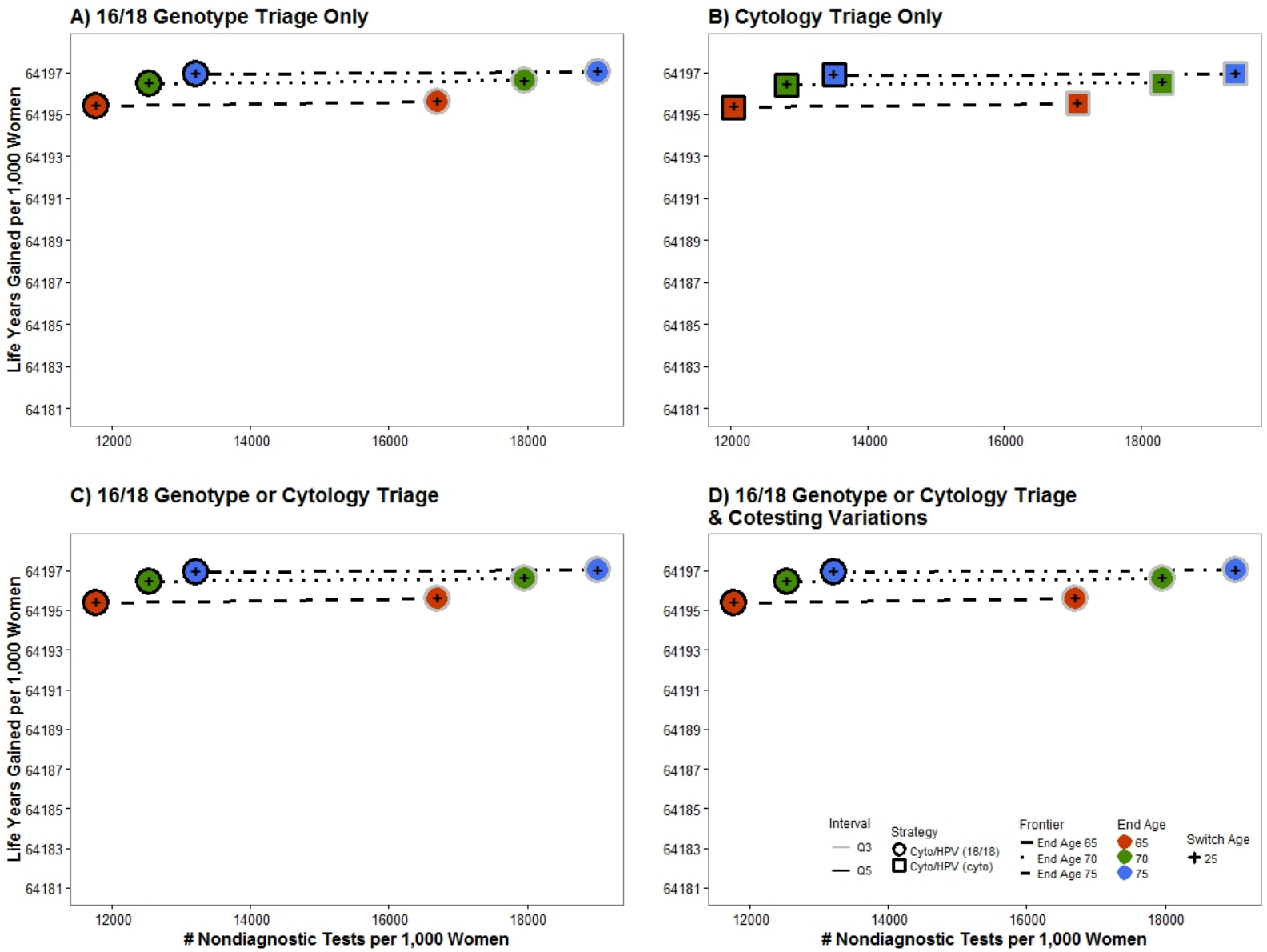


Figure 14. Efficiency Frontiers: Colposcopies per Cervical Cancer Case Averted When Varying Screening End Age (65, 70, 75 Years), Under Different Scenarios of Triage Options for HPV-Positive Women (Scenarios A-D)

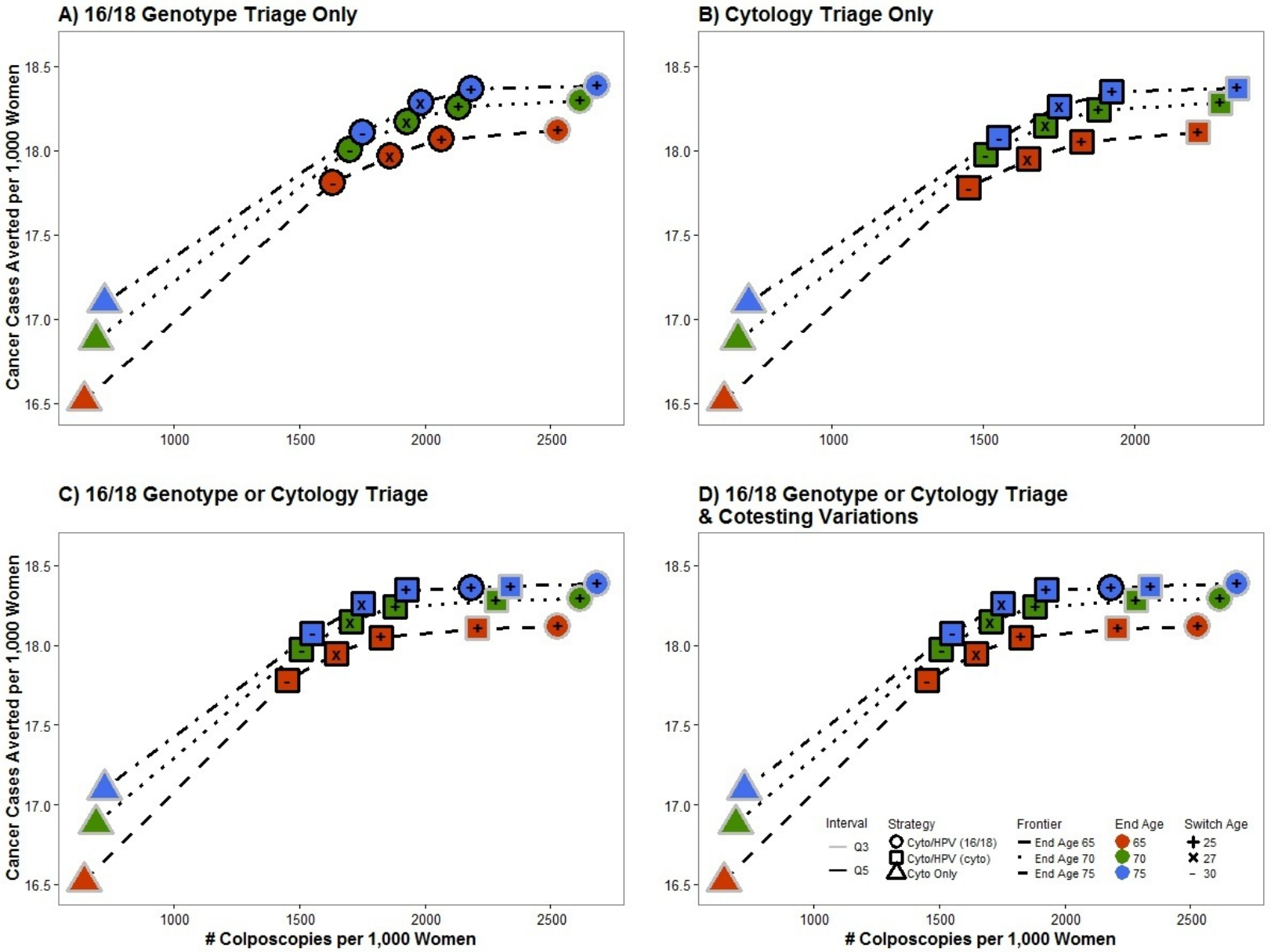


Figure 15. Efficiency Frontiers: Colposcopies per Life-Year Gained for All Strategies, Varying HPV Testing Switch Age, Interval, and Screening End Age, Under Different Scenarios of Triage Options for HPV-Positive Women (Scenarios A-D)

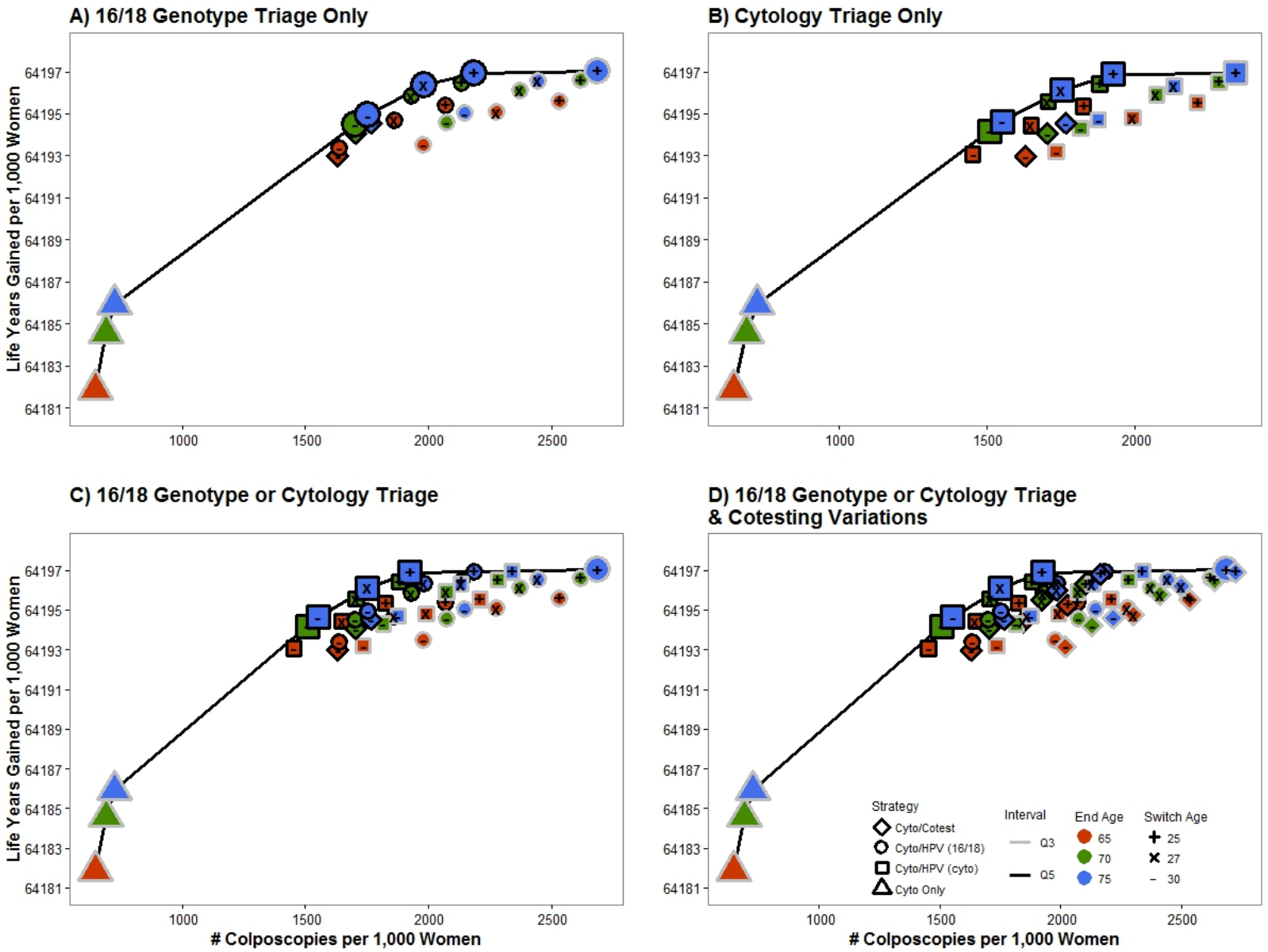


Figure 16. Efficiency Frontiers: Tests per Life-Year Gained for All Strategies, Varying HPV Testing Switch Age, Interval, and Screening End Age, Under Different Scenarios of Triage Options for HPV-Positive Women (Scenarios A-D)

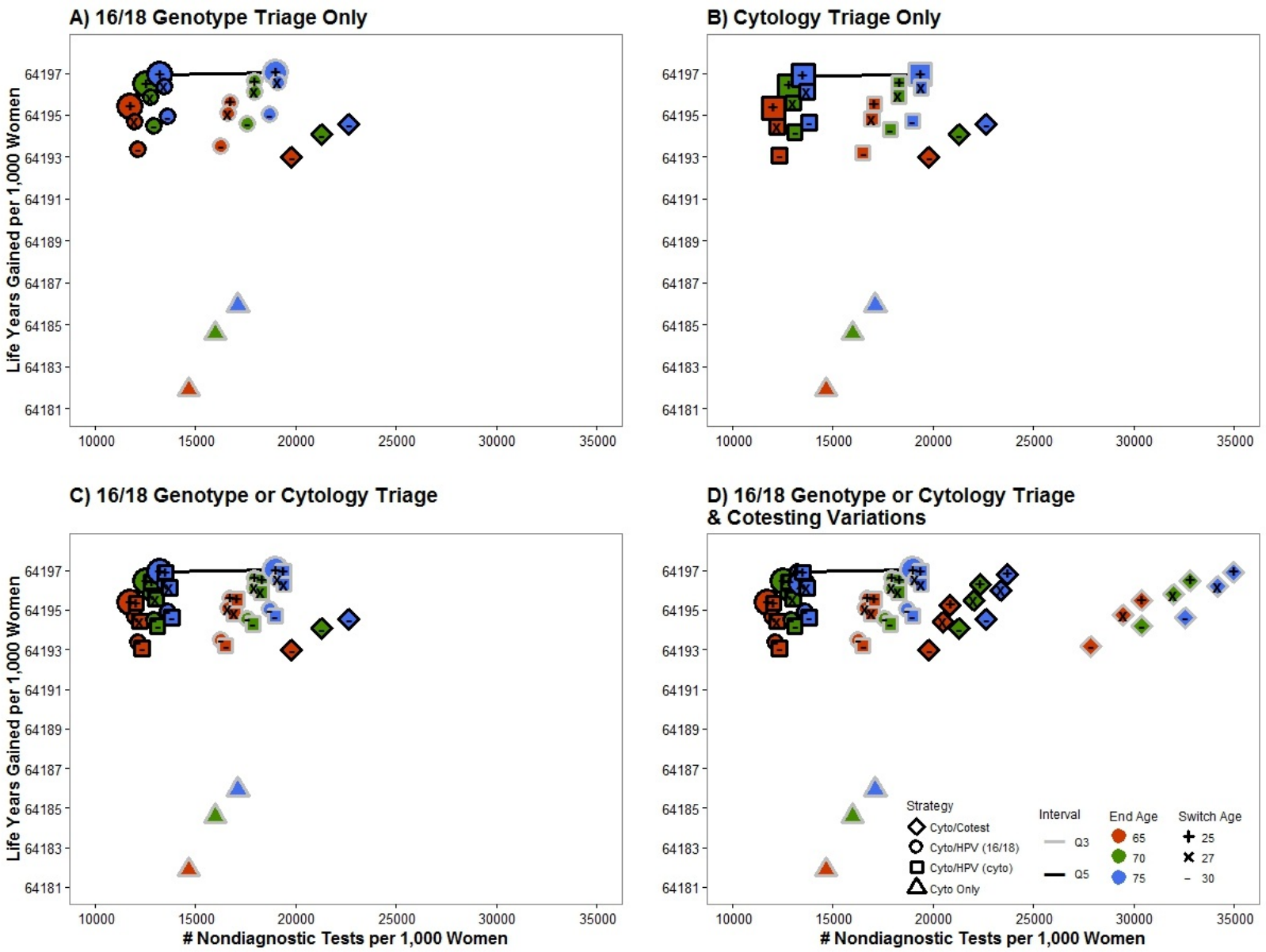


Figure 17. Efficiency Frontiers: Colposcopies per Cervical Cancer Case Averted for All Strategies, Varying HPV Testing Switch Age, Interval, and Screening End Age, Under Different Scenarios of Triage Options for HPV-Positive Women (Scenarios A-D)

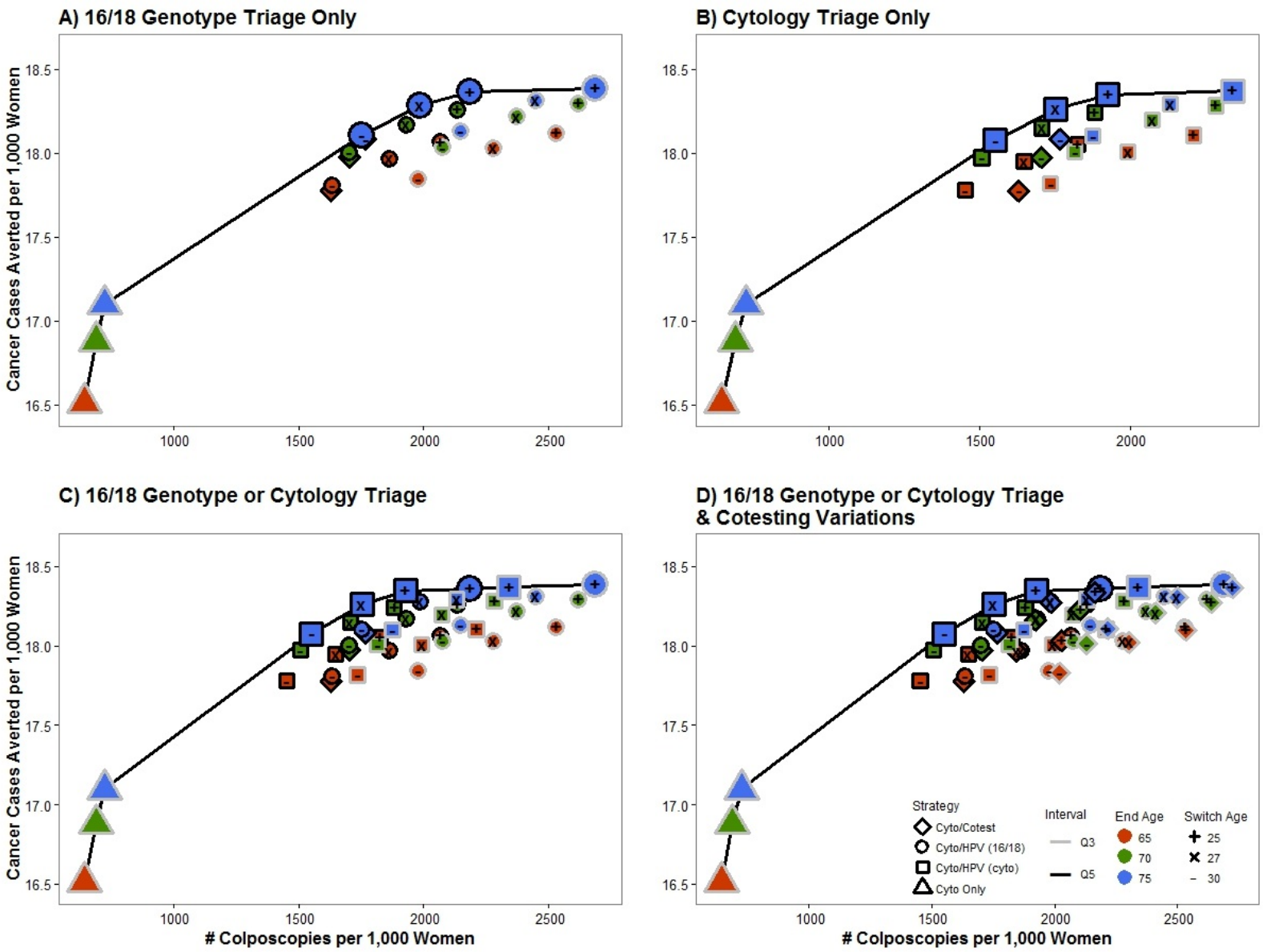


Table 1. Key Model Attributes

Attribute	Model
Mode of analysis, simulating life histories	Individual-based
Cycle length	Monthly
HPV types included	HPV-16; HPV-18; HPV-31; HPV-33; HPV-45; HPV-52; HPV-58; pooled HPV other high-risk; pooled HPV low-risk
Natural immunity	Reduced probability of future type-specific infection
Health states included	Healthy, HPV, CIN2, CIN3, Cancer*
Progression and regression probabilities	Age-specific, function of HPV persistence
Cancer staging	Local, regional, distant
Screening	Yes
Diagnosis	Yes
Precancer treatment	Yes
Vaccination	Yes

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

* The model focuses on squamous cell carcinoma, the most common histologic subtype of cervical cancer.

Table 2. Cervical Cancer Screening Strategies*

#	Strategy Name	Screen (1) test, interval	Screen (1) start age	Screen (2) test, interval	Screen (2) start age	Triage strategies for HPV-pos results
1	CYTO-3Y, 21	Cytology, 3y	21	--	--	HPV for ASC-US
2	CYTO-3Y, 21/COTEST-5Y, 30	Cytology, 3y	21	Cotest, 5y	30	Repeat cotest, 12 mos
3	CYTO-4Y, 21/HPV-3Y (16/18), 25	Cytology, 4y	21	HPV, 3y	25	HPV-16/18 genotype
4	CYTO-3Y, 21/HPV-3Y (16/18), 27	Cytology, 3y	21	HPV, 3y	27	HPV-16/18 genotype
5	CYTO-3Y, 21/HPV-3Y (16/18), 30	Cytology, 3y	21	HPV, 3y	30	HPV-16/18 genotype
6	CYTO-4Y, 21/HPV-5Y (16/18), 25	Cytology, 4y	21	HPV, 5y	25	HPV-16/18 genotype
7	CYTO-3Y, 21/HPV-5Y (16/18), 27	Cytology, 3y	21	HPV, 5y	27	HPV-16/18 genotype
8	CYTO-3Y, 21/HPV-5Y (16/18), 30	Cytology, 3y	21	HPV, 5y	30	HPV-16/18 genotype
9	CYTO-4Y, 21/HPV-3Y (cyto), 25	Cytology, 4y	21	HPV, 3y	25	Cytology triage
10	CYTO-3Y, 21/HPV-3Y (cyto), 27	Cytology, 3y	21	HPV, 3y	27	Cytology triage
11	CYTO-3Y, 21/HPV-3Y (cyto), 30	Cytology, 3y	21	HPV, 3y	30	Cytology triage
12	CYTO-4Y, 21/HPV-5Y (cyto), 25	Cytology, 4y	21	HPV, 5y	25	Cytology triage
13	CYTO-3Y, 21/HPV-5Y (cyto), 27	Cytology, 3y	21	HPV, 5y	27	Cytology triage
14	CYTO-3Y, 21/HPV-5Y (cyto), 30	Cytology, 3y	21	HPV, 5y	30	Cytology triage
15	CYTO-4Y, 21/COTEST-3Y, 25	Cytology, 4y	21	Cotest, 3y	25	Repeat cotest, 12 mos
16	CYTO-3Y, 21/COTEST-3Y, 27	Cytology, 3y	21	Cotest, 3y	27	Repeat cotest, 12 mos
17	CYTO-3Y, 21/COTEST-3Y, 30	Cytology, 3y	21	Cotest, 3y	30	Repeat cotest, 12 mos
18	CYTO-4Y, 21/COTEST-5Y, 25	Cytology, 4y	21	Cotest, 5y	25	Repeat cotest, 12 mos
19	CYTO-3Y, 21/COTEST-5Y, 27	Cytology, 3y	21	Cotest, 5y	27	Repeat cotest, 12 mos

Abbreviations: Cyto: cytology; HPV: human papillomavirus.

* Management of women with abnormal screening results was assumed to follow clinical guidelines[3,20] and includes: for cytology testing, reflex HPV testing for women with atypical squamous cells of undetermined significance (ASC-US) and referral to colposcopy for women with more severe abnormal results; for cotesting, repeat cotesting in 12 months for women with cytology-negative, HPV-positive results; for HPV testing, two triage options were evaluated: "HPV (16/18)" strategies involved referral to colposcopy for women positive on HPV-16/18 genotype testing and cytology triage for women positive for other (non-16/18) high-risk HPV, and "HPV (cyto)" strategies involved cytology triage for all high-risk HPV-positive women. Strategies were evaluated in context of screening end age of 65, 70, and 75 years in separate analyses.

Table 3. Screening Test Characteristics

Test characteristic*	Base-Case Value	Source	Worst-Case Value	Best-Case Value	Source
Cytology †		[21]			[21,22]
Sensitivity	0.727		0.514	0.815	
Specificity	0.919		0.880	0.936	
HPV ‡		[22]			[22,24-26]
Relative sensitivity	1.24		1.15	1.37	
Relative specificity	0.97		0.96	0.98	
Cotest ‡		[22]			[22,24-26]
Relative sensitivity	1.31		1.20	1.42	
Relative specificity	0.93		0.93	0.94	

* Sensitivity (specificity) for all tests defined as probability to detect presence (absence) of CIN2+.
† For cytology testing, positivity threshold is ASC-US.
‡ For HPV testing and cotesting, sensitivity and specificity are relative to cytology test characteristics.

Table 4. Distribution of Abnormal Cytology Results Conditioned on Histology Result[23]

Cytology result	<CIN 2	CIN 2	CIN 3+
ASC-US	0.6674	0.3026	0.2518
LSIL	0.2994	0.5395	0.2734
ASC-H	0.0130	0.0395	0.1007
HSIL	0.0202	0.1184	0.3741

Abbreviations: ASC-H: atypical squamous cells, cannot exclude HSIL; ASC-US: atypical squamous cells of undetermined significance; CIN: cervical intraepithelial neoplasia; HSIL: high-grade squamous intraepithelial lesion; LSIL: low-grade squamous intraepithelial lesion.

Table 5. Outcomes for Cervical Cancer Screening Strategies Over the Lifetime of Screening (Screening End Age 65)*

		Per 1,000 women									
#	Strategy	Cyto tests	HPV tests	Total tests†	Colpos	CIN2,3 detected	CIN3+ detected‡	False positives§	CC cases	CC deaths	Life-years
0	No screening	0	0	0	0	0	0	0	18.86	8.34	63921.34
1	CYTO-3Y, 21-65	13877	786	14662	645	160	46	484	2.34	0.76	64181.89
2	CYTO-3Y, 21 / COTEST-5Y, 30-65	11425	8380	19806	1630	201	54	1429	1.08	0.30	64192.97
3	CYTO-4Y, 21 / HPV-3Y (16/18), 25-65	1905	14807	16712	2530	218	57	2312	0.74	0.23	64195.61
4	CYTO-3Y, 21 / HPV-3Y (16/18), 27-65	2876	13772	16648	2278	214	56	2063	0.83	0.25	64195.08
5	CYTO-3Y, 21 / HPV-3Y (16/18), 30-65	3824	12428	16252	1978	205	54	1773	1.01	0.27	64193.51
6	CYTO-4Y, 21 / HPV-5Y (16/18), 25-65	1706	10065	11771	2068	211	55	1857	0.79	0.25	64195.39
7	CYTO-3Y, 21 / HPV-5Y (16/18), 27-65	2697	9290	11987	1861	207	55	1655	0.89	0.28	64194.69
8	CYTO-3Y, 21 / HPV-5Y (16/18), 30-65	3675	8476	12151	1635	199	53	1435	1.05	0.29	64193.38
9	CYTO-4Y, 21 / HPV-3Y (cyto), 25-65	2277	14790	17067	2209	217	56	1992	0.75	0.23	64195.53
10	CYTO-3Y, 21 / HPV-3Y (cyto), 27-65	3205	13738	16943	1992	213	56	1779	0.85	0.25	64194.82
11	CYTO-3Y, 21 / HPV-3Y (cyto), 30-65	4102	12397	16499	1734	203	54	1530	1.04	0.28	64193.19
12	CYTO-4Y, 21 / HPV-5Y (cyto), 25-65	1993	10049	12042	1826	209	55	1617	0.81	0.25	64195.35
13	CYTO-3Y, 21 / HPV-5Y (cyto), 27-65	2950	9273	12223	1648	205	54	1443	0.91	0.28	64194.44
14	CYTO-3Y, 21 / HPV-5Y (cyto), 30-65	3888	8459	12348	1452	198	53	1254	1.08	0.29	64193.07
15	CYTO-4Y, 21 / COTEST-3Y, 25-65	15723	14693	30416	2535	223	57	2312	0.76	0.23	64195.50
16	CYTO-3Y, 21 / COTEST-3Y, 27-65	15765	13723	29488	2303	218	57	2084	0.83	0.25	64194.75
17	CYTO-3Y, 21 / COTEST-3Y, 30-65	15456	12411	27867	2021	209	55	1812	1.03	0.27	64193.17
18	CYTO-4Y, 21 / COTEST-5Y, 25-65	10944	9914	20859	2029	213	55	1816	0.82	0.26	64195.26
19	CYTO-3Y, 21 / COTEST-5Y, 27-65	11275	9233	20508	1846	209	55	1637	0.89	0.27	64194.40

Abbreviations: CC: cervical cancer; CIN: cervical intraepithelial neoplasia; Colpos: colposcopies; Cyto: cytology; HPV: Human papillomavirus.

* Outcomes calculated from age 20 to 100 years.
† Total number of tests, irrespective of primary, triage or surveillance context.
‡ CIN3+ includes CIN3s and cervical cancers detected through screening (excludes clinically detected cancers).
§Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

Table 6. Outcomes for Cervical Cancer Screening Strategies Over the Lifetime of Screening (Screening End Age 70)*

		Per 1,000 women									
#	Strategy	Cyto tests	HPV tests	Total tests†	Colpos	CIN2,3 detected	CIN3+ detected‡	False positives§	CC cases	CC deaths	Life-years
0	No screening	0	0	0	0	0	0	0	18.86	8.34	63921.34
1	CYTO-3Y, 21-70	15149	855	16004	689	166	48	522	1.98	0.55	64184.58
2	CYTO-3Y, 21 / COTEST-5Y, 30-70	12173	9128	21301	1705	207	55	1498	0.88	0.19	64194.07
3	CYTO-4Y, 21 / HPV-3Y (16/18), 25-70	1940	16024	17965	2620	224	58	2395	0.56	0.13	64196.60
4	CYTO-3Y, 21 / HPV-3Y (16/18), 27-70	2914	15055	17968	2373	220	57	2153	0.64	0.14	64196.14
5	CYTO-3Y, 21 / HPV-3Y (16/18), 30-70	3861	13721	17582	2074	210	56	1863	0.82	0.17	64194.60
6	CYTO-4Y, 21 / HPV-5Y (16/18), 25-70	1729	10807	12536	2134	216	56	1917	0.60	0.15	64196.47
7	CYTO-3Y, 21 / HPV-5Y (16/18), 27-70	2722	10049	12771	1930	212	56	1718	0.68	0.17	64195.84
8	CYTO-3Y, 21 / HPV-5Y (16/18), 30-70	3698	9216	12914	1700	204	55	1495	0.85	0.18	64194.50
9	CYTO-4Y, 21 / HPV-3Y (cyto), 25-6570	2327	15979	18306	2283	222	58	2060	0.58	0.13	64196.52
10	CYTO-3Y, 21 / HPV-3Y (cyto), 27-70	3260	15035	18295	2073	218	57	1854	0.66	0.14	64195.91
11	CYTO-3Y, 21 / HPV-3Y (cyto), 30-70	4157	13704	17861	1816	209	56	1606	0.85	0.17	64194.31
12	CYTO-4Y, 21 / HPV-5Y (cyto), 25-70	2028	10790	12818	1881	214	56	1667	0.62	0.15	64196.41
13	CYTO-3Y, 21 / HPV-5Y (cyto), 27-70	2986	10032	13017	1706	210	56	1496	0.71	0.17	64195.57
14	CYTO-3Y, 21 / HPV-5Y (cyto), 30-70	3923	9198	13121	1508	203	55	1304	0.88	0.18	64194.18
15	CYTO-4Y, 21 / COTEST-3Y, 25-70	16929	15899	32829	2640	229	58	2411	0.58	0.14	64196.49
16	CYTO-3Y, 21 / COTEST-3Y, 27-70	17021	14979	32000	2412	224	58	2188	0.65	0.15	64195.78
17	CYTO-3Y, 21 / COTEST-3Y, 30-70	16722	13677	30399	2131	215	56	1916	0.84	0.17	64194.21
18	CYTO-4Y, 21 / COTEST-5Y, 25-70	11696	10666	22361	2105	219	57	1886	0.63	0.15	64196.31
19	CYTO-3Y, 21 / COTEST-5Y, 27-70	12038	9995	22033	1922	215	56	1707	0.69	0.17	64195.50

Abbreviations: CC: cervical cancer; CIN: cervical intraepithelial neoplasia; Colpos: colposcopies; Cyto: cytology; HPV: Human papillomavirus.

* Outcomes calculated from age 20 to 100 years.
† Total number of tests, irrespective of primary, triage or surveillance context.
‡ CIN3+ includes CIN3s and cervical cancers detected through screening (excludes clinically detected cancers).
§ Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

Table 7. Outcomes for Cervical Cancer Screening Strategies Over the Lifetime of Screening (Screening End Age 75)*

		Per 1,000 women									
#	Strategy	Cyto tests	HPV tests	Total tests†	Colpos	CIN2,3 detected	CIN3+ detected‡	False positives§	CC cases	CC deaths	Life-years
0	No screening	0	0	0	0	0	0	0	18.86	8.34	63921.34
1	CYTO-3Y, 21-75	16213	913	17127	724	170	49	554	1.76	0.42	64185.93
2	CYTO-3Y, 21 / COTEST-5Y, 30-75	12848	9803	22651	1767	211	56	1556	0.77	0.13	64194.54
3	CYTO-4Y, 21 / HPV-3Y (16/18), 25-75	1967	17051	19018	2687	228	59	2459	0.47	0.09	64197.01
4	CYTO-3Y, 21 / HPV-3Y (16/18), 27-75	2942	16156	19098	2446	224	58	2222	0.54	0.09	64196.58
5	CYTO-3Y, 21 / HPV-3Y (16/18), 30-75	3890	14825	18715	2147	215	57	1931	0.72	0.12	64195.03
6	CYTO-4Y, 21 / HPV-5Y (16/18), 25-75	1748	11473	13222	2186	220	58	1966	0.49	0.09	64196.93
7	CYTO-3Y, 21 / HPV-5Y (16/18), 27-75	2741	10730	13472	1984	216	57	1768	0.58	0.11	64196.36
8	CYTO-3Y, 21 / HPV-5Y (16/18), 30-75	3717	9880	13597	1752	208	56	1544	0.75	0.13	64194.93
9	CYTO-4Y, 21 / HPV-3Y (cyto), 25-75	2366	17013	19380	2340	226	59	2114	0.49	0.09	64196.93
10	CYTO-3Y, 21 / HPV-3Y (cyto), 27-75	3301	16112	19413	2132	223	58	1910	0.56	0.10	64196.32
11	CYTO-3Y, 21 / HPV-3Y (cyto), 30-75	4198	14784	18983	1876	213	57	1662	0.75	0.12	64194.71
12	CYTO-4Y, 21 / HPV-5Y (cyto), 25-75	2057	11455	13512	1926	218	57	1708	0.51	0.09	64196.89
13	CYTO-3Y, 21 / HPV-5Y (cyto), 27-75	3015	10712	13728	1752	215	57	1537	0.59	0.11	64196.12
14	CYTO-3Y, 21 / HPV-5Y (cyto), 30-75	3952	9861	13813	1552	207	56	1345	0.78	0.13	64194.63
15	CYTO-4Y, 21 / COTEST-3Y, 25-75	18009	16979	34988	2726	233	60	2493	0.49	0.09	64196.92
16	CYTO-3Y, 21 / COTEST-3Y, 27-75	18113	16071	34184	2500	229	59	2271	0.55	0.10	64196.20
17	CYTO-3Y, 21 / COTEST-3Y, 30-75	17813	14768	32581	2218	219	58	1999	0.75	0.12	64194.61
18	CYTO-4Y, 21 / COTEST-5Y, 25-75	12372	11342	23714	2166	223	58	1943	0.52	0.10	64196.81
19	CYTO-3Y, 21 / COTEST-5Y, 27-75	12724	10681	23405	1985	219	57	1766	0.58	0.11	64196.01

Abbreviations: CC: cervical cancer; CIN: cervical intraepithelial neoplasia; Colpos: colposcopies; Cyto: cytology; HPV: Human papillomavirus.

* Outcomes calculated from age 20 to 100 years.
† Total number of tests, irrespective of primary, triage or surveillance context.
‡ CIN3+ includes CIN3s and cervical cancers detected through screening (excludes clinically detected cancers).
§ Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

Table 8. Sensitivity Analysis Summary: Impact of Uncertainty on Colposcopies per Life-Year Gained

#	Strategy*	Base case (end 65)	Base case (end 70)	Base case (end 75)	Cyto sens 81.5%, spec 88.0%	Cyto sens 51.4%, spec 93.6%	HPV sens (rel 1.15)	Imper-fect colpo	Treat effic. 82%	LSIL thres-hold	6-month follow-up	24-month follow-up	Direct colpo referral†	16/18 vacc
0	No Screening‡	--	--	--	--	--	--	--	--	--	--	--	--	--
1	CYTO-3Y, 21 -65	3	3	3	3	2	2	3	3	2	2	2	2	5
14	CYTO-3Y, 21 / HPV-5Y (cyto), 30-65	73	85	95	80	38	66	42	69	71	90	48	72	113
2	CYTO-3Y, 21 / COTEST-5Y, 30-65	x	x	x	x	x	x	x	x	x	x	x	x	x
8	CYTO-3Y, 21 / HPV-5Y (16/18), 30-65	x	x	x	x	x	x	x	x	x	x	x	x	x
13	CYTO-3Y, 21 / HPV-5Y (cyto), 27-65	143	143	135	167	67	116	89	115	128	222	109	143	402
11	CYTO-3Y, 21 / HPV-3Y (cyto), 30-65	x	x	x	x	x	x	x	x	x	x	x	x	x
12	CYTO-4Y, 21 / HPV-5Y (cyto), 25-65	195	208	225	323	104	x	136	212	184	255	114	195	463
19	CYTO-3Y, 21 / COTEST-5Y, 27-65	x	x	x	x	x	x	x	x	x	x	x	x	x
7	CYTO-3Y, 21 / HPV-5Y (16/18), 27-65	x	x	x	x	x	x	x	x	x	x	x	x	x
5	CYTO-3Y, 21 / HPV-3Y (16/18), 30-65	x	x	x	x	x	x	x	x	x	x	x	x	x
10	CYTO-3Y, 21 / HPV-3Y (cyto), 27-65	x	x	x	x	x	127	x	x	x	x	x	x	x
17	CYTO-3Y, 21 / COTEST-3Y, 30-65	x	x	x	x	x	x	x	x	x	x	x	x	x
18	CYTO-4Y, 21 / COTEST-5Y, 25-65	x	x	x	x	x	x	x	x	x	x	x	x	x
6	CYTO-4Y, 21 / HPV-5Y (16/18), 25-65	x	x	x	x	873	x	1,251	x	x	x	x	x	x
9	CYTO-4Y, 21 / HPV-3Y (cyto), 25-65	2,188	3,758	x	2,590	x	234	1,741	2,016	1,789	x	1,369	2,188	8,163
4	CYTO-3Y, 21 / HPV-3Y (16/18), 27-65	x	x	x	x	x	x	x	x	x	x	x	x	x
16	CYTO-3Y, 21 / COTEST-3Y, 27-65	x	x	x	x	x	x	x	x	x	x	x	x	x
3	CYTO-4Y, 21 / HPV-3Y (16/18), 25-65	3,822	4,014	6,239	3,347	2,147	459	2,064	4,661	2,783	x	2,074	3,822	x
15	CYTO-4Y, 21 / COTEST-3Y, 25-65	x	x	x	x	x	x	x	x	x	3,887	x	x	10,884
25	CYTO-3Y, 21 / HPV-5Y (colpo), 30-65	na	na	na	na	na	na	na	na	na	na	na	x	na
24	CYTO-3Y, 21 / HPV-5Y (colpo), 27-65	na	na	na	na	na	na	na	na	na	na	na	x	na
22	CYTO-3Y, 21 / HPV-3Y (colpo), 30-65	na	na	na	na	na	na	na	na	na	na	na	x	na
23	CYTO-4Y, 21 / HPV-5Y (colpo), 25-65	na	na	na	na	na	na	na	na	na	na	na	x	na
21	CYTO-3Y, 21 / HPV-3Y (colpo), 27-65	na	na	na	na	na	na	na	na	na	na	na	x	na
20	CYTO-4Y, 21 / HPV-3Y (colpo), 25-65	na	na	na	na	na	na	na	na	na	na	na	x	na

Abbreviations: Colpo: colposcopy; Cyto: cytology; HPV: Human papillomavirus; LSIL: low-grade squamous intraepithelial lesion; na: not analyzed; rel: relative; sens: sensitivity; spec: specificity; vacc: vaccinated.

* Strategies are list in order of increasing colposcopies in the base-case analysis. “HPV (colpo)” strategies involved direct referral to colposcopy for all HPV-positive women, which were only included in one sensitivity analysis.
† All strategies involving direct colposcopy referral for all HPV-positive women were inefficient.
‡ No screening was the comparator strategy for all analyses.

Table 9. Sensitivity Analysis Summary: Impact of Uncertainty on Tests per Life-Year Gained

#	Strategy*	Base case (end 65)	Base case (end 70)	Base case (end 75)	Cyto sens 81.5%, spec 88.0%	Cyto sens 51.4%, spec 93.6%	HPV sens (rel 1.15)	Imper-fect colpo	Treat effic. 82%	LSIL thres-hold	6-month follow-up	24-month follow-up	Direct colpo referral†	16/18 vacc
0	No Screening‡	--	--	--	--	--	--	--	--	--	--	--	--	--
6	CYTO-4Y, 21 / HPV-5Y (16/18), 25-65	43	46	48	43	43	42	42	43	43	44	41	x	x
7	CYTO-3Y, 21 / HPV-5Y (16/18), 27-65	x	x	X	x	x	x	x	x	x		x	x	x
12	CYTO-4Y, 21 / HPV-5Y (cyto), 25-65	x	x	X	x	x	x	x	x	x	6,359	x	x	107
8	CYTO-3Y, 21 / HPV-5Y (16/18), 30-65	x	x	X	x	x	x	x	x	x	x	x	x	x
13	CYTO-3Y, 21 / HPV-5Y (cyto), 27-65	x	x	X	x	x	x	x	x	x	x	x	x	x
14	CYTO-3Y, 21 / HPV-5Y (cyto), 30-65	x	x	X	x	x	x	x	x	x	x	x	x	x
1	CYTO-3Y, 21 -65	x	x	X	x	x	x	x	x	x	x	x	x	x
5	CYTO-3Y, 21 / HPV-3Y (16/18), 30-65	x	x	X	x	x	x	x	x	x	x	x	x	x
11	CYTO-3Y, 21 / HPV-3Y (cyto), 30-65	x	x	X	x	x	x	x	x	x	x	x	x	x
4	CYTO-3Y, 21 / HPV-3Y (16/18), 27-65	x	x	x	x	x	x	x	x	x	x	x	x	x
3	CYTO-4Y, 21 / HPV-3Y (16/18), 25-65	22,335	41,852	69,063	23,126	23,131	3,111	24,006	24,871	21,594	45,833	25,769	35,241	x
10	CYTO-3Y, 21 / HPV-3Y (cyto), 27-65	x	x	x	x	x	x	x	x	x	x	x	x	x
9	CYTO-4Y, 21 / HPV-3Y (cyto), 25-65	x	x	x	x	x	x	x	x	x	x	x	x	159,953
2	CYTO-3Y, 21 / COTEST-5Y, 30-65	x	x	x	x	x	x	x	x	x	x	x	x	x
19	CYTO-3Y, 21 / COTEST-5Y, 27-65	x	x	x	x	x	x	x	x	x	x	x	x	x
18	CYTO-4Y, 21 / COTEST-5Y, 25-65	x	x	x	x	x	x	x	x	x	x	x	x	x
17	CYTO-3Y, 21 / COTEST-3Y, 30-65	x	x	x	x	x	x	x	x	x	x	x	x	x
16	CYTO-3Y, 21 / COTEST-3Y, 27-65	x	x	x	x	x	x	x	x	x	x	x	x	x
15	CYTO-4Y, 21 / COTEST-3Y, 25-65	x	x	x	x	x	x	x	x	x	134,110	x	x	429,590
23	CYTO-4Y, 21 / HPV-5Y (colpo), 25-65	na	na	na	na	na	na	na	na	na	na	na	42	na
24	CYTO-3Y, 21 / HPV-5Y (colpo), 27-65	na	na	na	na	na	na	na	na	na	na	na	x	na
25	CYTO-3Y, 21 / HPV-5Y (colpo), 30-65	na	na	na	na	na	na	na	na	na	na	na	x	na
22	CYTO-3Y, 21 / HPV-3Y (colpo), 30-65	na	na	na	na	na	na	na	na	na	na	na	x	na
20	CYTO-4Y, 21 / HPV-3Y (colpo), 25-65	na	na	na	na	na	na	na	na	na	na	na	29,184	na
21	CYTO-3Y, 21 / HPV-3Y (colpo), 27-65	na	na	na	na	na	na	na	na	na	na	na	x	na

Abbreviations: Colpo: colposcopy; Cyto: cytology; HPV: Human papillomavirus; LSIL: low-grade squamous intraepithelial lesion; na: not analyzed; rel: relative; sens: sensitivity; spec: specificity; vacc: vaccinated.

* Strategies are list in order of increasing colposcopies in the base-case analysis. “HPV (colpo)” strategies involved direct referral to colposcopy for all HPV-positive women, which were only included in one sensitivity analysis.

† Rank order of efficient strategies differed from base case.

‡ No screening was the comparator strategy for all analyses.

Table 10. Sensitivity Analysis Summary: Impact of Uncertainty on Colposcopies per Cervical Cancer Case Averted

#	Strategy*	Base case (end 65)	Base case (end 70)	Base case (end 75)	Cyto sens 81.5%, spec 88.0%	Cyto sens 51.4%, spec 93.6%	HPV sens (rel 1.15)	Imper-fect colpo	Treat effect 82%	LSIL thres-hold	6-month follow-up	24-month follow-up	Direct colpo referral†	16/18 vacc
0	No Screening‡	--	--	--	--	--	--	--	--	--	--	--	--	--
1	CYTO-3Y, 21 -65	39	41	42	54	33	38	42	41	39	39	39	39	77
14	CYTO-3Y, 21 / HPV-5Y (cyto), 30-65	640	748	847	638	399	551	375	601	624	792	423	624	900
2	CYTO-3Y, 21 / COTEST-5Y, 30-65	x	x	x	x	x	x	x	x	x	x	x	x	x
8	CYTO-3Y, 21 / HPV-5Y (16/18), 30-65	x	x	x	x	x	x	x	x	x	x	x	x	x
13	CYTO-3Y, 21 / HPV-5Y (cyto), 27-65	1,161	1,134	1,081	1,495	647	1,138	681	1,028	1,118	1,601	879	1,161	2,900
11	CYTO-3Y, 21 / HPV-3Y (cyto), 30-65	x	x	x	x	x	x	x	x	x	x	x	x	x
12	CYTO-4Y, 21 / HPV-5Y (cyto), 25-65	1,735	1,914	2,064	2,017	974	x	1,101	1,543	1,682	2,023	1,449	1,735	3,247
19	CYTO-3Y, 21 / COTEST-5Y, 27-65	x	x	x	x	x	x	x	x	x	x	x	x	x
7	CYTO-3Y, 21 / HPV-5Y (16/18), 27-65	x	x	x	x	x	x	x	x	x	x	x	x	x
5	CYTO-3Y, 21 / HPV-3Y (16/18), 30-65	x	x	x	x	x	x	x	x	x	x	x	x	x
10	CYTO-3Y, 21 / HPV-3Y (cyto), 27-65	x	x	x	x	x	1,307	x	x	x	x	x	x	x
17	CYTO-3Y, 21 / COTEST-3Y, 30-65	x	x	x	x	x	x	x	x	x	x	x	x	x
18	CYTO-4Y, 21 / COTEST-5Y, 25-65	x	x	x	x	x	x	x	x	x	x	x	x	x
6	CYTO-4Y, 21 / HPV-5Y (16/18), 25-65	x	x	15,899	x	x	x	x	x	x	x	x	x	x
9	CYTO-4Y, 21 / HPV-3Y (cyto), 25-65	7,018	9,848	19,645	7,240	6,223	1,757	6,261	6,879	6,132	17,353	4,839	7,018	19,066
4	CYTO-3Y, 21 / HPV-3Y (16/18), 27-65	x	x	x	x	x	x	x	x	x	x	x	x	x
16	CYTO-3Y, 21 / COTEST-3Y, 27-65	x	x	x	x	x	x	x	x	x	x	x	x	x
3	CYTO-4Y, 21 / HPV-3Y (16/18), 25-65	23,974	23,361	25,112	37,553	11,659	4,500	16,287	15,224	12,647	x	7,646	23,974	x
15	CYTO-4Y, 21 / COTEST-3Y, 25-65	x	x	x	x	x	x	x	x	x	27,217	x	x	418,870
23	CYTO-4Y, 21 / HPV-5Y (colpo), 25-65	na	na	na	na	na	na	na	na	na	na	na	x	na
24	CYTO-3Y, 21 / HPV-5Y (colpo), 27-65	na	na	na	na	na	na	na	na	na	na	na	x	na
25	CYTO-3Y, 21 / HPV-5Y (colpo), 30-65	na	na	na	na	na	na	na	na	na	na	na	x	na
22	CYTO-3Y, 21 / HPV-3Y (colpo), 30-65	na	na	na	na	na	na	na	na	na	na	na	x	na
20	CYTO-4Y, 21 / HPV-3Y (colpo), 25-65	na	na	na	na	na	na	na	na	na	na	na	x	na
21	CYTO-3Y, 21 / HPV-3Y (colpo), 27-65	na	na	na	na	na	na	na	na	na	na	na	x	na

Abbreviations: Colpo: colposcopy; Cyto: cytology; HPV: Human papillomavirus; LSIL: low-grade squamous intraepithelial lesion; na: not analyzed; rel: relative; sens: sensitivity; spec: specificity; vacc: vaccinated.

* Strategies are list in order of increasing colposcopies in the base-case analysis. “HPV (colpo)” strategies involved direct referral to colposcopy for all HPV-positive women, which were only included in one sensitivity analysis.
† All strategies involving direct colposcopy referral for HPV-positive women were inefficient.
‡ No screening was the comparator strategy for all analyses.

Appendix Table 1. Efficient Cervical Cancer Screening Strategies (Screening End Age 65) in Terms of Colposcopies per Life-Year Gained

#, Strategy	Colpos	Δ Colpos*	Life-years	Δ Life-years*	Efficiency ratio (Δcolpo/ΔLY)
Scenario A					
0, No screening	0		63921.34		
1, CYTO-3Y, 21	645	645	64181.89	260.56	3
8, CYTO-3Y, 21 / HPV-5Y (16/18), 30	1635	990	64193.38	11.45	86
7, CYTO-3Y, 21 / HPV-5Y (16/18), 27	1861	227	64194.69	1.31	173
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25	2068	206	64195.39	0.69	297
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25	2528	461	64195.61	0.22	2,082
Scenario B					
0, No screening	0		63921.34		
1, CYTO-3Y, 21	645	645	64181.89	260.56	3
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30	1452	807	64193.07	11.14	73
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27	1648	196	64194.44	1.37	143
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25	1826	177	64195.35	0.91	195
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25	2209	384	64195.53	0.18	2,188
Scenario C					
0, No screening	0		63921.34		
1, CYTO-3Y, 21	645	645	64181.89	260.56	3
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30	1452	807	64193.07	11.14	73
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27	1648	196	64194.44	1.37	143
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25	1826	177	64195.35	0.91	19
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25	2209	384	64195.53	0.18	2,188
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25	2530	321	64195.61	0.08	3,822
Scenario D					
0, No screening	0		63921.34		
1, CYTO-3Y, 21	645	645	64181.89	260.56	3
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30	1452	807	64193.07	11.14	73
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27	1648	196	64194.44	1.37	143
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25	1826	177	64195.35	0.91	195
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25	2209	384	64195.53	0.18	2,188
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25	2530	321	64195.61	0.08	3,822

Abbreviations: Colpos: colposcopies; Cyto: cytology; HPV: human papillomavirus; LY: life-year.

* Incremental values may be slightly different due to rounding.

Appendix Table 2. Efficient Cervical Cancer Screening Strategies (Screening End Age 65) in Terms of Tests per Life-Year Gained

#, Strategy	Screening tests	∆ Tests*	Life-years	∆ Life-years*	Efficiency ratio (∆tests/∆LY)
Scenario A					
0, No screening	0		63921.34		
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25	11771	11771	64195.39	274.05	43
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25	16712	4942	64195.61	0.22	22,335
Scenario B					
0, No screening	0		63921.34		
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25	12042	12042	64195.35	274.01	44
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25	17067	5025	64195.53	0.18	28,636
Scenario C					
0, No screening	0		63921.34		
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25	11771	11771	64195.39	274.05	43
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25	16712	4942	64195.61	0.22	22,335
Scenario D					
0, No screening	0		63921.34		
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25	11771	11771	64195.39	274.05	43
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25	16712	4942	64195.61	0.22	22,335

Abbreviations: Colpos: colposcopies; Cyto: cytology; HPV: human papillomavirus; LY: life-year.

* Incremental values may be slightly different due to rounding.

Appendix Table 3. Efficient Cervical Cancer Screening Strategies (Screening End Age 65) in Terms of Colposcopies per Cervical Cancer Case Averted*

#, Strategy	Colpos	Δ Colpos†	Cancer cases averted	Δ Cases averted†	Efficiency ratio (Δcolpo/Δcases averted)
Scenario A					
0, No screening	0		0.00		
1, CYTO-3Y, 21	645	645	16.52	16.52	39
8, CYTO-3Y, 21 / HPV-5Y (16/18), 30	1635	990	17.81	1.29	766
7, CYTO-3Y, 21 / HPV-5Y (16/18), 27	1861	227	17.97	0.16	1,432
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25	2068	206	18.07	0.10	2,120
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25	2530	463	18.12	0.05	8,580
Scenario B					
0, No screening	0		0.00		
1, CYTO-3Y, 21	645	645	16.52	16.52	39
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30	1452	807	17.78	1.26	640
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27	1648	196	17.95	0.17	1,161
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25	1826	177	18.05	0.10	1,735
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25	2209	384	18.11	0.05	7,018
Scenario C					
0, No screening	0		0.00		
1, CYTO-3Y, 21	645	645	16.52	16.52	39
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30	1452	807	17.78	1.26	640
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27	1648	196	17.95	0.17	1,161
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25	1826	177	18.05	0.10	1,735
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25	2209	384	18.11	0.05	7,018
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25	2530	321	18.12	0.01	23,974
Scenario D					
0, No screening	0		0.00		
1, CYTO-3Y, 21	645	645	16.52	16.52	39
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30	1452	807	17.78	1.26	640
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27	1648	196	17.95	0.17	1,161
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25	1826	177	18.05	0.10	1,735
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25	2209	384	18.11	0.05	7,018
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25	2530	321	18.12	0.01	23,974

Abbreviations: Colpos: colposcopies; Cyto: cytology; HPV: human papillomavirus.

* Cervical cancer cases averted, compared to no intervention (i.e., natural history).
† Incremental values may be slightly different due to rounding.

Appendix Table 4. Efficient Cervical Cancer Screening Strategies (Screening End Age 70) in Terms of Colposcopies per Life-Year Gained

#, Strategy	Colpos	Δ Colpos*	Life-years	Δ Life-years*	Efficiency ratio (Δcolpo/ΔLY)
Scenario A					
0, No screening	0		63921.34		
1, CYTO-3Y, 21-70	689	689	64184.58	263.24	3
8, CYTO-3Y, 21 / HPV-5Y (16/18), 30-70	1700	1011	64194.50	9.93	102
7, CYTO-3Y, 21 / HPV-5Y (16/18), 27-70	1930	230	64195.84	1.34	172
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-70	2134	203	64196.47	0.63	321
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-70	2620	486	64196.60	0.13	3,747
Scenario B					
0, No screening	0		63921.34		
1, CYTO-3Y, 21-70	689	689	64184.58	263.24	3
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30-70	1508	819	64194.18	9.61	85
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27-70	1706	199	64195.57	1.39	143
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25-70	1881	175	64196.41	0.84	208
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25-70	2283	401	64196.52	0.11	3,758
Scenario C					
0, No screening	0		63921.34		
1, CYTO-3Y, 21-70	689	689	64184.58	263.24	3
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30-70	1508	819	64194.18	9.61	85
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27-70	1706	199	64195.57	1.39	143
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25-70	1881	175	64196.41	0.84	208
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25-70	2283	401	64196.52	0.11	3,758
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-70	2620	337	64196.60	0.08	4,014
Scenario D					
0, No screening	0		63921.34		
1, CYTO-3Y, 21-70	689	689	64184.58	263.24	3
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30-70	1508	819	64194.18	9.61	85
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27-70	1706	199	64195.57	1.39	143
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25-70	1881	175	64196.41	0.84	208
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25-70	2283	401	64196.52	0.11	3,758
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-70	2620	337	64196.60	0.08	4,014

Abbreviations: Colpos: colposcopies; Cyto: cytology; HPV: human papillomavirus; LY: life-year.

* Incremental values may be slightly different due to rounding.

Appendix Table 5. Efficient Cervical Cancer Screening Strategies (Screening End Age 70) in Terms of Tests per Life-Year Gained

#, Strategy	Screening tests	∆ Tests*	Life-years	∆ Life-years*	Efficiency ratio (∆tests/∆LY)
Scenario A					
0, No screening	0		63921.34		
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-70	12536	12536	64196.47	275.14	46
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-70	17965	5428	64196.60	0.13	41,852
Scenario B					
0, No screening	0		63921.34		
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25-70	12818	12818	64196.41	275.07	47
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25-70	18306	5488	64196.52	0.11	51,383
Scenario C					
0, No screening	0		63921.34		
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-70	12536	12536	64196.47	275.14	46
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-70	17965	5428	64196.60	0.13	41,852
Scenario D					
0, No screening	`		63921.34		
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-70	12536	12536	64196.47	275.14	46
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-70	17965	5428	64196.60	0.13	41,852

Abbreviations: Colpos: colposcopies; Cyto: cytology; HPV: human papillomavirus; LY: life-year.

* Incremental values may be slightly different due to rounding.

Appendix Table 6. Efficient Cervical Cancer Screening Strategies (Screening End Age 70) in Terms of Colposcopies per Cervical Cancer Case Averted*

#, Strategy	Colpos	Δ Colpos†	Cancer cases averted	Δ Cases averted†	Efficiency ratio (Δcolpo/Δcases averted)
Scenario A					
0, No screening	0		0.00		
1, CYTO-3Y, 21-70	689	689	16.88	16.88	41
8, CYTO-3Y, 21 / HPV-5Y (16/18), 30-70	1700	1011	18.01	1.13	898
7, CYTO-3Y, 21 / HPV-5Y (16/18), 27-70	1930	230	18.17	0.17	1,391
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-70	2134	203	18.26	0.09	2,375
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-70	2620	486	18.30	0.04	12,631
Scenario B					
0, No screening	0		0.00		
1, CYTO-3Y, 21-70	689	689	16.88	16.88	41
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30-70	1508	819	17.97	1.09	748
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27-70	1706	199	18.15	0.18	1,134
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25-70	1881	175	18.24	0.09	1,914
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25-70	2283	401	18.28	0.04	9,848
Scenario C					
0, No screening	0		0.00		
1, CYTO-3Y, 21-70	689	689	16.88	16.88	41
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30-70	1508	819	17.97	1.09	748
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27-70	1706	199	18.15	0.18	1,134
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25-70	1881	175	18.24	0.09	1,914
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25-70	2283	401	18.28	0.04	9,848
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-70	2620	337	18.30	0.01	23,361
Scenario D					
0, No screening	0		0.00		
1, CYTO-3Y, 21-70	689	689	16.88	16.88	41
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30-70	1508	819	17.97	1.09	748
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27-70	1706	199	18.15	0.18	1,134
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25-70	1881	175	18.24	0.09	1,914
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25-70	2283	401	18.28	0.04	9,848
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-70	2620	337	18.30	0.01	23,361

Abbreviations: Colpos: colposcopies; Cyto: cytology; HPV: human papillomavirus.

* Cervical cancer cases averted, compared to no intervention (i.e., natural history).
† Incremental values may be slightly different due to rounding.

Appendix Table 7. Efficient Cervical Cancer Screening Strategies (Screening End Age 75) in Terms of Colposcopies per Life-Year Gained

#, Strategy	Colpos	Δ Colpos*	Life-years	Δ Life-years*	Efficiency ratio (Δcolpo/ΔLY)
Scenario A					
0, No screening	0		63921.34		
1, CYTO-3Y, 21-75	724	724	64185.93	264.59	3
8, CYTO-3Y, 21 / HPV-5Y (16/18), 30-75	1752	1028	64194.93	9.00	114
7, CYTO-3Y, 21 / HPV-5Y (16/18), 27-75	1984	232	64196.36	1.43	163
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-75	2186	202	64196.93	0.57	353
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-75	2687	501	64197.01	0.08	5,972
Scenario B					
0, No screening	0		63921.34		
1, CYTO-3Y, 21-75	724	724	64185.93	264.59	3
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30-75	1552	827	64194.63	8.71	95
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27-75	1752	200	64196.12	1.49	135
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25-75	1926	174	64196.89	0.77	225
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25-75	2340	414	64196.93	0.04	10,854
Scenario C					
0, No screening	0		63921.34		
1, CYTO-3Y, 21-75	724	724	64185.93	264.59	3
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30-75	1552	827	64194.63	8.71	95
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27-75	1752	200	64196.12	1.49	135
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25-75	1926	174	64196.89	0.77	225
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-75	2687	762	64197.01	0.12	6,239
Scenario D					
0, No screening	0		63921.34		
1, CYTO-3Y, 21-75	724	724	64185.93	264.59	3
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30-75	1552	827	64194.63	8.71	95
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27-75	1752	200	64196.12	1.49	135
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25-75	1926	174	64196.89	0.77	225
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-75	2687	762	64197.01	0.12	6,239

Abbreviations: Colpos: colposcopies; Cyto: cytology; HPV: human papillomavirus; LY: life-year.

* Incremental values may be slightly different due to rounding.

Appendix Table 8. Efficient Cervical Cancer Screening Strategies (Screening End Age 75) in Terms of Tests per Life-Year Gained

#, Strategy	Screening tests	∆ Tests*	Life-years	∆ Life-years*	Efficiency ratio (∆tests/∆LY)
Scenario A					
0, No screening	0		63921.34		
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-75	13222	13222	64196.93	275.59	48
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-75	19018	5796	64197.01	0.08	69,064
Scenario B					
0, No screening	0		63921.34		
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25-75	13512	13512	64196.89	275.55	49
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25-75	19380	5868	64196.93	0.04	153,816
Scenario C					
0, No screening	0		63921.34		
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-75	13222	13222	64196.93	275.59	48
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-75	19018	5796	64197.01	0.08	69,064
Scenario D					
0, No screening	0		63921.34		
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-75	13222	13222	64196.93	275.59	48
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-75	19018	5796	64197.01	0.08	69,064

Abbreviations: Colpos: colposcopies; Cyto: cytology; HPV: human papillomavirus; LY: life-year.

* Incremental values may be slightly different due to rounding.

Appendix Table 9. Efficient Cervical Cancer Screening Strategies (Screening End Age 75) in Terms of Colposcopies per Cervical Cancer Case Averted*

#, Strategy	Colpos	Δ Colpos†	Cancer cases averted	Δ Cases averted†	Efficiency ratio (Δcolpo/Δcases averted)
Scenario A					
0, No screening	0		0.00		--
1, CYTO-3Y, 21-75	724	724	17.10	17.10	42
8, CYTO-3Y, 21 / HPV-5Y (16/18), 30-75	1752	1028	18.11	1.01	1,020
7, CYTO-3Y, 21 / HPV-5Y (16/18), 27-75	1984	232	18.28	0.17	1,333
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-75	2186	202	18.36	0.08	2,479
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-75	2687	501	18.38	0.02	23,138
Scenario B					
0, No screening	0		0.00		
1, CYTO-3Y, 21-75	724	724	17.10	17.10	42
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30-75	1552	827	18.08	0.98	847
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27-75	1752	200	18.26	0.19	1,081
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25-75	1926	174	18.35	0.08	2,064
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25-75	2340	414	18.37	0.02	17,110
Scenario C					
0, No screening	0		0.00		
1, CYTO-3Y, 21-75	724	724	17.10	17.10	42
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30-75	1552	827	18.08	0.98	847
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27-75	1752	200	18.26	0.19	1,081
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25-75	1926	174	18.35	0.08	2,064
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-75	2186	260	18.36	0.02	15,899
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25-75	2340	154	18.37	0.01	19,645
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-75	2687	348	18.38	0.01	25,112
Scenario D					
0, No screening	0		0.00		
1, CYTO-3Y, 21-75	724	724	17.10	17.10	42
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30-75	1552	827	18.08	0.98	847
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27-75	1752	200	18.26	0.19	1,081
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25-75	1926	174	18.35	0.08	2,064
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-75	2186	260	18.36	0.02	15,899
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25-75	2340	154	18.37	0.01	19,645
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-75	2687	348	18.38	0.01	25,112

Abbreviations: Colpos: colposcopies; Cyto: cytology; HPV: human papillomavirus.

* Cervical cancer cases averted, compared to no intervention (i.e., natural history).
† Incremental values may be slightly different due to rounding.

Appendix Table 10. Efficient Cervical Cancer Screening Strategies, Varying HPV Testing Switch Age, Interval, and Screening End Age in Terms of Colposcopies per Life-Year Gained

#, Strategy	Colpos	Δ Colpos*	Life-years	Δ Life-years*	Efficiency ratio (Δcolpo/ΔLY)
Scenario A					
0, No screening	0		63921.34		
1, CYTO-3Y, 21-65	645	645	64181.89	260.56	3
1, CYTO-3Y, 21-70	689	44	64184.58	2.65	17
1, CYTO-3Y, 21-75	724	36	64185.93	1.35	26
8, CYTO-3Y, 21 / HPV-5Y (16/18), 30-70	1700	976	64194.50	8.58	114
8, CYTO-3Y, 21 / HPV-5Y (16/18), 30-75	1752	52	64194.93	0.43	123
7, CYTO-3Y, 21 / HPV-5Y (16/18), 27-75	1984	232	64196.36	1.43	163
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-75	2186	202	64196.93	0.57	353
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-75	2687	501	64197.01	0.08	5,972
Scenario B					
0, No screening	0		63921.34		
1, CYTO-3Y, 21-65	645	645	64181.89	260.56	3
1, CYTO-3Y, 21-70	689	44	64184.58	2.65	17
1, CYTO-3Y, 21-75	724	36	64185.93	1.35	26
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30-70	1508	783	64194.18	8.26	95
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30-75	1552	44	64194.63	0.45	99
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27-75	1752	200	64196.12	1.49	135
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25-75	1926	174	64196.89	0.77	225
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25-75	2340	414	64196.93	0.04	10,854
Scenario C					
0, No screening	0		63921.34		
1, CYTO-3Y, 21-65	645	645	64181.89	260.56	3
1, CYTO-3Y, 21-70	689	44	64184.58	2.65	17
1, CYTO-3Y, 21-75	724	36	64185.93	1.35	26
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30-70	1508	783	64194.18	8.26	95
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30-75	1552	44	64194.63	0.45	99
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27-75	1752	200	64196.12	1.49	135
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25-75	1926	174	64196.89	0.77	225
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-75	2687	762	64197.01	0.12	6,239
Scenario D					
0, No screening	0		63921.34		
1, CYTO-3Y, 21-65	645	645	64181.89	260.56	3
1, CYTO-3Y, 21-70	689	44	64184.58	2.65	17
1, CYTO-3Y, 21-75	724	36	64185.93	1.35	26
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30-70	1508	783	64194.18	8.26	95
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30-75	1552	44	64194.63	0.45	99
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27-75	1752	200	64196.12	1.49	135
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25-75	1926	174	64196.89	0.77	225
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-75	2687	762	64197.01	0.12	6,239

Abbreviations: Colpos: colposcopies; Cyto: cytology; HPV: human papillomavirus; LY: life-year.

* Incremental values may be slightly different due to rounding.

Appendix Table 11. Efficient Cervical Cancer Screening Strategies, Varying HPV Testing Switch Age, Interval, and Screening End Age in Terms of Tests per Life-Year Gained

#, Strategy	Screening tests	∆ Tests*	Life-years	∆ Life-years*	Efficiency ratio (∆tests/∆LY)
Scenario A					
0, No screening	0		63921.34		
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-65	11771	11771	64195.39	274.05	43
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-70	12536	766	64196.47	1.08	707
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-75	13222	685	64196.93	0.46	1,497
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-75	19018	5796	64197.01	0.08	69,064
Scenario B					
0, No screening	0		63921.34		
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25-65	12042	12042	64195.35	274.01	44
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25-70	12818	776	64196.41	1.06	731
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25-75	13512	694	64196.89	0.48	1,444
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25-75	19380	5868	64196.93	0.04	153,816
Scenario C					
0, No screening	0		63921.34		
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-65	11771	11771	64195.39	274.05	43
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-70	12536	766	64196.47	1.08	707
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-75	13222	685	64196.93	0.46	1,497
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-75	19018	5796	64197.01	0.08	69,064
Scenario D					
0, No screening	0		63921.34		
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-65	11771	11771	64195.39	274.05	43
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-70	12536	766	64196.47	1.08	707
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-75	13222	685	64196.93	0.46	1,497
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-75	19018	5796	64197.01	0.08	69,064

Abbreviations: Colpos: colposcopies; Cyto: cytology; HPV: human papillomavirus; LY: life-year.

* Incremental values may be slightly different due to rounding.

Appendix Table 12. Efficient Cervical Cancer Screening Strategies, Varying HPV Testing Switch Age, Interval, and Screening End Age in Terms of Colposcopies per Cervical Cancer Case Averted*

#, Strategy	Colpos	Δ Colpos†	Cancer cases averted	Δ Cases averted†	Efficiency ratio (Δcolpo/Δcases averted)
Scenario A					
0, No screening	0		0.00		
1, CYTO-3Y, 21-65	645	645	16.52	16.52	39
1, CYTO-3Y, 21-70	689	44	16.88	0.36	122
1, CYTO-3Y, 21-75	724	36	17.10	0.22	162
8, CYTO-3Y, 21 / HPV-5Y (16/18), 30-75	1752	1028	18.11	1.01	1,020
7, CYTO-3Y, 21 / HPV-5Y (16/18), 27-75	1984	232	18.28	0.17	1,333
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-75	2186	202	18.36	0.08	2,479
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-75	2687	501	18.38	0.02	23,138
Scenario B					
0, No screening	0		0.00		
1, CYTO-3Y, 21-65	645	645	16.52	16.52	39
1, CYTO-3Y, 21-70	689	44	16.88	0.36	122
1, CYTO-3Y, 21-75	724	36	17.10	0.22	162
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30-75	1552	827	18.08	0.98	847
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27-75	1752	200	18.26	0.19	1,081
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25-75	1926	174	18.35	0.08	2,064
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25-75	2340	414	18.37	0.02	17,110
Scenario C					
0, No screening	0		0.00		
1, CYTO-3Y, 21-65	645	645	16.52	16.52	39
1, CYTO-3Y, 21-70	689	44	16.88	0.36	122
1, CYTO-3Y, 21-75	724	36	17.10	0.22	162
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30-75	1552	827	18.08	0.98	847
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27-75	1752	200	18.26	0.19	1,081
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25-75	1926	174	18.35	0.08	2,064
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-75	2186	260	18.36	0.02	15,899
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25-75	2340	154	18.37	0.01	19,645
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-75	2687	348	18.38	0.01	25,112
Scenario D					
0, No screening	0		0.00		
1, CYTO-3Y, 21-65	645	645	16.52	16.52	39
1, CYTO-3Y, 21-70	689	44	16.88	0.36	122
1, CYTO-3Y, 21-75	724	36	17.10	0.22	162
14, CYTO-3Y, 21 / HPV-5Y (cyto), 30-75	1552	827	18.08	0.98	847
13, CYTO-3Y, 21 / HPV-5Y (cyto), 27-75	1752	200	18.26	0.19	1,081
12, CYTO-4Y, 21 / HPV-5Y (cyto), 25-75	1926	174	18.35	0.08	2,064
6, CYTO-4Y, 21 / HPV-5Y (16/18), 25-75	2186	260	18.36	0.02	15,899
9, CYTO-4Y, 21 / HPV-3Y (cyto), 25-75	2340	154	18.37	0.01	19,645
3, CYTO-4Y, 21 / HPV-3Y (16/18), 25-75	2687	348	18.38	0.01	25,112

Abbreviations: Colpos: colposcopies; Cyto: cytology; HPV: human papillomavirus.

* Cervical cancer cases averted, compared to no intervention (i.e., natural history).
† Incremental values may be slightly different due to rounding.

Appendix Table 13. Range of Outcomes for Cervical Cancer Screening Strategies Over Lifetime of Screening (Screening End Age 65) Across 50 Top-Fitting Parameter Sets

#	Strategy	Per 1,000 women									
		Cyto tests	HPV tests	Total tests*	Colpos	CIN2,3 detected	CIN3+ detected†	False positives‡	CC cases	CC deaths	Life-years
0	No screening	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	18.86 (13.05-24.07)	8.34 (5.78-10.76)	63921.34 (63844.9-64006.01)
1	CYTO-3Y, 21	13877 (13806-13939)	786 (773-797)	14662 (14579-14736)	645 (593-691)	160 (121-197)	46 (35-57)	484 (473-495)	2.34 (1.75-2.84)	0.76 (0.54-0.99)	64181.89 (64178.07-64185.61)
2	CYTO-3Y, 21 / COTEST-5Y, 30	11425 (11185-11641)	8380 (8139-8602)	19806 (19324-20243)	1630 (1393-1864)	201 (150-248)	54 (41-66)	1429 (1243-1616)	1.08 (0.8-1.34)	0.3 (0.2-0.43)	64192.97 (64191.52-64194.54)
3	CYTO-4Y, 21 / HPV-3Y (16/18), 25	1905 (1798-2020)	14807 (14432-15116)	16712 (16230-17136)	2530 (2159-2889)	218 (164-269)	57 (43-70)	2312 (1995-2620)	0.74 (0.52-0.93)	0.23 (0.13-0.34)	64195.61 (64194.38-64196.64)
4	CYTO-3Y, 21 / HPV-3Y (16/18), 27	2876 (2780-2989)	13772 (13423-14066)	16648 (16203-17056)	2278 (1942-2611)	214 (161-264)	56 (44-70)	2063 (1781-2348)	0.83 (0.6-1.02)	0.25 (0.15-0.36)	64195.08 (64193.92-64196.34)
5	CYTO-3Y, 21 / HPV-3Y (16/18), 30	3824 (3740-3929)	12428 (12124-12692)	16252 (15865-16621)	1978 (1688-2273)	205 (153-252)	54 (41-67)	1773 (1535-2021)	1.01 (0.76-1.26)	0.27 (0.18-0.38)	64193.51 (64192.11-64195.08)
6	CYTO-4Y, 21 / HPV-5Y (16/18), 25	1706 (1625-1793)	10065 (9703-10377)	11771 (11328-12170)	2068 (1743-2386)	211 (159-259)	55 (42-68)	1857 (1585-2127)	0.79 (0.54-1.02)	0.25 (0.14-0.37)	64195.39 (64194.02-64196.61)
7	CYTO-3Y, 21 / HPV-5Y (16/18), 27	2697 (2626-2785)	9290 (8947-9588)	11987 (11573-12373)	1861 (1568-2157)	207 (155-255)	55 (42-67)	1655 (1413-1902)	0.89 (0.63-1.12)	0.28 (0.16-0.41)	64194.69 (64193.29-64196.03)
8	CYTO-3Y, 21 / HPV-5Y (16/18), 30	3675 (3609-3759)	8476 (8195-8735)	12151 (11805-12495)	1635 (1382-1897)	199 (149-246)	53 (41-66)	1435 (1233-1652)	1.05 (0.77-1.31)	0.29 (0.18-0.4)	64193.38 (64191.97-64194.94)
9	CYTO-4Y, 21 / HPV-3Y (cyto), 25	2277 (2085-2415)	14790 (14425-15090)	17067 (16510-17506)	2209 (1855-2530)	217 (163-267)	56 (43-69)	1992 (1693-2263)	0.75 (0.53-0.94)	0.23 (0.13-0.33)	64195.53 (64194.5-64196.58)
10	CYTO-3Y, 21 / HPV-3Y (cyto), 27	3205 (3021-3339)	13738 (13395-14026)	16943 (16416-17364)	1992 (1673-2288)	213 (160-262)	56 (42-70)	1779 (1513-2027)	0.85 (0.62-1.06)	0.25 (0.15-0.36)	64194.82 (64193.64-64196.11)
11	CYTO-3Y, 21 / HPV-3Y (cyto), 30	4102 (3931-4226)	12397 (12097-12655)	16499 (16029-16882)	1734 (1459-1996)	203 (153-251)	54 (41-67)	1530 (1307-1746)	1.04 (0.78-1.3)	0.28 (0.18-0.39)	64193.19 (64191.76-64194.63)
12	CYTO-4Y, 21 / HPV-5Y (cyto), 25	1993 (1851-2101)	10049 (9696-10351)	12042 (11547-12452)	1826 (1515-2114)	209 (157-257)	55 (42-67)	1617 (1358-1857)	0.81 (0.56-1.04)	0.25 (0.14-0.38)	64195.35 (64194.07-64196.59)
13	CYTO-3Y, 21 / HPV-5Y (cyto), 27	2950 (2810-3055)	9273 (8938-9564)	12223 (11748-12619)	1648 (1368-1915)	205 (154-253)	54 (41-67)	1443 (1215-1663)	0.91 (0.64-1.15)	0.28 (0.16-0.41)	64194.44 (64193.09-64195.79)
14	CYTO-3Y, 21 / HPV-5Y (cyto), 30	3888 (3757-3989)	8459 (8183-8713)	12348 (11940-12701)	1452 (1211-1690)	198 (148-244)	53 (40-66)	1254 (1063-1446)	1.08 (0.79-1.35)	0.29 (0.19-0.42)	64193.07 (64191.49-64194.47)
15	CYTO-4Y, 21 / COTEST-3Y, 25	15723 (15411-15979)	14693 (14383-14950)	30416 (29794-30929)	2535 (2188-2851)	223 (167-275)	57 (43-70)	2312 (2022-2577)	0.76 (0.54-0.95)	0.23 (0.13-0.34)	64195.5 (64194.52-64196.49)
16	CYTO-3Y, 21 / COTEST-3Y, 27	15765 (15470-16009)	13723 (13432-13969)	29488 (28901-29978)	2303 (1990-2596)	218 (163-269)	57 (43-70)	2084 (1827-2327)	0.83 (0.6-1.03)	0.25 (0.15-0.36)	64194.75 (64193.45-64195.79)
17	CYTO-3Y, 21 / COTEST-3Y, 30	15456 (15192-15674)	12411 (12156-12635)	27867 (27348-28309)	2021 (1750-2280)	209 (156-257)	55 (42-68)	1812 (1595-2023)	1.03 (0.77-1.28)	0.27 (0.18-0.38)	64193.17 (64191.94-64194.73)
18	CYTO-4Y, 21 / COTEST-5Y, 25	10944 (10638-11204)	9914 (9609-10175)	20859 (20247-21380)	2029 (1723-2313)	213 (160-263)	55 (42-68)	1816 (1564-2051)	0.82 (0.58-1.06)	0.26 (0.14-0.39)	64195.26 (64194.02-64196.45)
19	CYTO-3Y, 21 / COTEST-5Y, 27	11275 (10985-11524)	9233 (8942-9485)	20508 (19927-21008)	1846 (1570-2110)	209 (156-258)	55 (42-68)	1637 (1414-1853)	0.89 (0.64-1.11)	0.27 (0.17-0.4)	64194.4 (64192.85-64195.58)

Abbreviations: CC: cervical cancer; CIN: cervical intraepithelial neoplasia; Colpos: colposcopies; Cyto: cytology; HPV: human papillomavirus.

*Total number of tests, irrespective of primary, triage or surveillance context

†CIN3+ includes CIN3s and cervical cancers detected through screening (excludes clinically detected cancers)

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

Appendix Table 14. Outcomes for Cervical Cancer Screening Strategies Over Lifetime of Screening (Screening End Age 65) Assuming Cytology Sensitivity of 81.5% and Specificity of 88.0%

#	Strategy	Per 1,000 women								
		Cyto tests	HPV tests	Total tests*	Colpos	CIN2,3 detected	False positives†	CC cases	CC deaths	Life-years
1	CYTO-3Y, 21	14116	1164	15280	904	173	730	1.99	0.66	64185.81
2	CYTO-3Y, 21 / COTEST-5Y, 30	11574	8537	20111	1818	208	1610	0.99	0.29	64193.80
3	CYTO-4Y, 21 / HPV-3Y (16/18), 25	1939	14829	16768	2585	221	2364	0.72	0.23	64195.66
4	CYTO-3Y, 21 / HPV-3Y (16/18), 27	2934	13821	16755	2352	218	2134	0.79	0.24	64195.35
5	CYTO-3Y, 21 / HPV-3Y (16/18), 30	3903	12504	16407	2071	210	1860	0.92	0.26	64194.18
6	CYTO-4Y, 21 / HPV-5Y (16/18), 25	1740	10088	11828	2115	213	1902	0.77	0.25	64195.45
7	CYTO-3Y, 21 / HPV-5Y (16/18), 27	2755	9342	12097	1930	211	1718	0.85	0.27	64194.97
8	CYTO-3Y, 21 / HPV-5Y (16/18), 30	3754	8540	12294	1720	205	1515	0.96	0.28	64194.05
9	CYTO-4Y, 21 / HPV-3Y (cyto), 25	2310	14812	17122	2279	220	2059	0.73	0.23	64195.57
10	CYTO-3Y, 21 / HPV-3Y (cyto), 27	3261	13790	17051	2079	217	1862	0.80	0.24	64195.29
11	CYTO-3Y, 21 / HPV-3Y (cyto), 30	4180	12475	16656	1838	209	1628	0.94	0.27	64194.00
12	CYTO-4Y, 21 / HPV-5Y (cyto), 25	2027	10072	12099	1884	212	1671	0.78	0.25	64195.42
13	CYTO-3Y, 21 / HPV-5Y (cyto), 27	3006	9326	12333	1726	210	1516	0.86	0.27	64194.93
14	CYTO-3Y, 21 / HPV-5Y (cyto), 30	3966	8523	12490	1546	204	1342	0.98	0.28	64193.86
15	CYTO-4Y, 21 / COTEST-3Y, 25	15893	14859	30752	2771	227	2544	0.73	0.23	64195.59
16	CYTO-3Y, 21 / COTEST-3Y, 27	15952	13911	29864	2548	224	2324	0.78	0.24	64195.27
17	CYTO-3Y, 21 / COTEST-3Y, 30	15650	12613	28263	2268	215	2053	0.92	0.26	64194.05
18	CYTO-4Y, 21 / COTEST-5Y, 25	11080	10046	21126	2196	217	1979	0.80	0.26	64195.34
19	CYTO-3Y, 21 / COTEST-5Y, 27	11439	9398	20837	2027	215	1812	0.84	0.27	64194.89

Abbreviations: CC: cervical cancer; CIN: cervical intraepithelial neoplasia; Colpos: colposcopies; Cyto: cytology; HPV: human papillomavirus.

* Total number of tests, irrespective of primary, triage or surveillance context.
†Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

Appendix Table 15. Outcomes for Cervical Cancer Screening Strategies Over Lifetime of Screening (Screening End Age 65) Assuming Cytology Sensitivity of 51.4% and Specificity of 93.6%

#	Strategy	Per 1,000 women								
		Cyto tests	HPV tests	Total tests*	Colpos	CIN2,3 detected	False positives†	CC cases	CC deaths	Life-years
1	CYTO-3Y, 21	13723	614	14336	506	128	377	3.64	1.16	64166.02
2	CYTO-3Y, 21 / COTEST-5Y, 30	11357	8327	19684	1542	185	1356	1.39	0.33	64190.18
3	CYTO-4Y, 21 / HPV-3Y (16/18), 25	1881	14805	16686	2505	213	2292	0.79	0.23	64195.32
4	CYTO-3Y, 21 / HPV-3Y (16/18), 27	2835	13757	16592	2240	204	2036	0.95	0.26	64193.95
5	CYTO-3Y, 21 / HPV-3Y (16/18), 30	3767	12400	16168	1929	191	1738	1.29	0.31	64190.86
6	CYTO-4Y, 21 / HPV-5Y (16/18), 25	1682	10063	11745	2046	205	1841	0.84	0.26	64195.11
7	CYTO-3Y, 21 / HPV-5Y (16/18), 27	2656	9275	11931	1828	197	1631	1.01	0.29	64193.55
8	CYTO-3Y, 21 / HPV-5Y (16/18), 30	3619	8458	12077	1590	185	1405	1.32	0.32	64190.74
9	CYTO-4Y, 21 / HPV-3Y (cyto), 25	2253	14792	17045	2177	209	1968	0.82	0.24	64195.01
10	CYTO-3Y, 21 / HPV-3Y (cyto), 27	3165	13726	16891	1949	201	1747	1.01	0.27	64193.42
11	CYTO-3Y, 21 / HPV-3Y (cyto), 30	4047	12371	16418	1681	188	1492	1.36	0.32	64190.10
12	CYTO-4Y, 21 / HPV-5Y (cyto), 25	1970	10051	12021	1799	201	1598	0.88	0.26	64194.82
13	CYTO-3Y, 21 / HPV-5Y (cyto), 27	2910	9262	12172	1611	194	1416	1.07	0.30	64193.02
14	CYTO-3Y, 21 / HPV-5Y (cyto), 30	3834	8445	12280	1404	183	1221	1.39	0.34	64189.96
15	CYTO-4Y, 21 / COTEST-3Y, 25	15652	14632	30284	2431	214	2216	0.83	0.24	64195.03
16	CYTO-3Y, 21 / COTEST-3Y, 27	15680	13651	29331	2192	206	1986	0.99	0.26	64193.57
17	CYTO-3Y, 21 / COTEST-3Y, 30	15361	12332	27693	1905	192	1712	1.34	0.31	64190.34
18	CYTO-4Y, 21 / COTEST-5Y, 25	10890	9870	20760	1956	204	1751	0.88	0.27	64194.80
19	CYTO-3Y, 21 / COTEST-5Y, 27	11202	9174	20376	1764	197	1567	1.05	0.29	64193.24

Abbreviations: CC: cervical cancer; CIN: cervical intraepithelial neoplasia; Colpos: colposcopies; Cyto: cytology; HPV: human papillomavirus.

* Total number of tests, irrespective of primary, triage or surveillance context.
† Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

Appendix Table 16. Outcomes for Cervical Cancer Screening Strategies Over Lifetime of Screening (Screening End Age 65) Assuming Lower HPV Sensitivity (Relative Sensitivity of 1.15)

#	Strategy	Per 1,000 women								
		Cyto tests	HPV tests	Total tests*	Colpos	CIN2,3 detected	False positives†	CC cases	CC deaths	Life-years
1	CYTO-3Y, 21	13864	785	14649	632	158	473	2.43	0.79	64180.92
2	CYTO-3Y, 21 / COTEST-5Y, 30	11128	8088	19217	1308	185	1123	1.52	0.47	64189.04
3	CYTO-4Y, 21 / HPV-3Y (16/18), 25	1907	14528	16435	2120	206	1913	0.91	0.28	64194.24
4	CYTO-3Y, 21 / HPV-3Y (16/18), 27	2876	13519	16395	1915	203	1712	1.01	0.30	64193.56
5	CYTO-3Y, 21 / HPV-3Y (16/18), 30	3820	12214	16034	1671	195	1476	1.19	0.33	64191.86
6	CYTO-4Y, 21 / HPV-5Y (16/18), 25	1705	9769	11474	1701	195	1506	1.12	0.34	64192.65
7	CYTO-3Y, 21 / HPV-5Y (16/18), 27	2695	9025	11719	1540	192	1347	1.21	0.37	64191.67
8	CYTO-3Y, 21 / HPV-5Y (16/18), 30	3670	8260	11930	1362	186	1175	1.33	0.38	64190.44
9	CYTO-4Y, 21 / HPV-3Y (cyto), 25	2280	14489	16770	1791	203	1588	0.99	0.30	64193.53
10	CYTO-3Y, 21 / HPV-3Y (cyto), 27	3204	13466	16670	1622	200	1422	1.08	0.32	64192.81
11	CYTO-3Y, 21 / HPV-3Y (cyto), 30	4098	12166	16264	1423	192	1230	1.26	0.35	64191.07
12	CYTO-4Y, 21 / HPV-5Y (cyto), 25	1990	9726	11715	1452	190	1262	1.25	0.38	64191.17
13	CYTO-3Y, 21 / HPV-5Y (cyto), 27	2943	8986	11929	1322	188	1133	1.31	0.40	64190.44
14	CYTO-3Y, 21 / HPV-5Y (cyto), 30	3880	8222	12103	1176	183	992	1.44	0.41	64189.18
15	CYTO-4Y, 21 / COTEST-3Y, 25	15371	14344	29716	2069	208	1861	1.07	0.34	64193.27
16	CYTO-3Y, 21 / COTEST-3Y, 27	15447	13409	28856	1890	205	1684	1.12	0.35	64192.70
17	CYTO-3Y, 21 / COTEST-3Y, 30	15184	12144	27328	1671	197	1474	1.30	0.38	64190.99
18	CYTO-4Y, 21 / COTEST-5Y, 25	10545	9517	20062	1595	192	1402	1.36	0.44	64190.84
19	CYTO-3Y, 21 / COTEST-5Y, 27	10920	8881	19801	1464	190	1273	1.39	0.45	64190.12

Abbreviations: CC: cervical cancer; CIN: cervical intraepithelial neoplasia; Colpos: colposcopies; Cyto: cytology; HPV: human papillomavirus.

* Total number of tests, irrespective of primary, triage or surveillance context.
† Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

Appendix Table 17. Outcomes for Cervical Cancer Screening Strategies Over Lifetime of Screening (Screening End Age 65) Assuming Imperfect Colposcopy/Biopsy Performance

#	Strategy	Per 1,000 women								
		Cyto tests	HPV tests	Total tests*	Colpos	CIN2,3 detected	False positives†	CC cases	CC deaths	Life-years
1	CYTO-3Y, 21	13912	793	14705	672	138	534	2.71	0.85	64178.64
2	CYTO-3Y, 21 / COTEST-5Y, 30	11331	8282	19613	1428	153	1275	1.19	0.31	64192.14
3	CYTO-4Y, 21 / HPV-3Y (16/18), 25	1918	14520	16438	2142	151	1991	0.77	0.23	64195.37
4	CYTO-3Y, 21 / HPV-3Y (16/18), 27	2888	13517	16405	1939	152	1787	0.89	0.25	64194.63
5	CYTO-3Y, 21 / HPV-3Y (16/18), 30	3836	12212	16048	1698	149	1548	1.13	0.28	64192.79
6	CYTO-4Y, 21 / HPV-5Y (16/18), 25	1715	9778	11493	1739	150	1589	0.82	0.26	64195.17
7	CYTO-3Y, 21 / HPV-5Y (16/18), 27	2705	9041	11747	1577	151	1426	0.95	0.29	64194.24
8	CYTO-3Y, 21 / HPV-5Y (16/18), 30	3684	8264	11949	1399	148	1251	1.16	0.30	64192.68
9	CYTO-4Y, 21 / HPV-3Y (cyto), 25	2295	14561	16856	1859	153	1705	0.79	0.23	64195.24
10	CYTO-3Y, 21 / HPV-3Y (cyto), 27	3221	13534	16755	1686	154	1533	0.92	0.26	64194.35
11	CYTO-3Y, 21 / HPV-3Y (cyto), 30	4117	12225	16343	1484	151	1333	1.15	0.29	64192.43
12	CYTO-4Y, 21 / HPV-5Y (cyto), 25	2006	9818	11824	1529	152	1377	0.84	0.26	64195.00
13	CYTO-3Y, 21 / HPV-5Y (cyto), 27	2960	9070	12031	1392	152	1240	0.97	0.28	64193.99
14	CYTO-3Y, 21 / HPV-5Y (cyto), 30	3900	8292	12193	1242	150	1092	1.19	0.30	64192.31
15	CYTO-4Y, 21 / COTEST-3Y, 25	15594	14561	30154	2192	158	2034	0.78	0.23	64195.34
16	CYTO-3Y, 21 / COTEST-3Y, 27	15651	13606	29257	2005	158	1847	0.90	0.25	64194.23
17	CYTO-3Y, 21 / COTEST-3Y, 30	15364	12315	27679	1776	155	1621	1.13	0.28	64192.33
18	CYTO-4Y, 21 / COTEST-5Y, 25	10803	9770	20573	1739	155	1583	0.85	0.27	64195.08
19	CYTO-3Y, 21 / COTEST-5Y, 27	11146	9102	20248	1595	155	1440	0.96	0.28	64193.86

Abbreviations: CC: cervical cancer; CIN: cervical intraepithelial neoplasia; Colpos: colposcopies; Cyto: cytology; HPV: human papillomavirus.

* Total number of tests, irrespective of primary, triage or surveillance context.
† Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

Appendix Table 18. Outcomes for Cervical Cancer Screening Strategies Over Lifetime of Screening (Screening End Age 65) Assuming CIN2/3 Treatment Effectiveness of 82%

#	Strategy	Per 1,000 women								
		Cyto tests	HPV tests	Total tests*	Colpos	CIN2,3 detected	False positives†	CC cases	CC deaths	Life-years
1	CYTO-3Y, 21	13891	791	14682	668	183	484	2.62	0.81	64179.95
2	CYTO-3Y, 21 / COTEST-5Y, 30	11458	8412	19870	1675	231	1443	1.24	0.32	64191.94
3	CYTO-4Y, 21 / HPV-3Y (16/18), 25	1906	14841	16746	2584	252	2331	0.85	0.24	64194.91
4	CYTO-3Y, 21 / HPV-3Y (16/18), 27	2877	13804	16682	2328	247	2081	0.96	0.26	64194.44
5	CYTO-3Y, 21 / HPV-3Y (16/18), 30	3827	12457	16284	2023	235	1787	1.17	0.29	64192.55
6	CYTO-4Y, 21 / HPV-5Y (16/18), 25	1707	10106	11813	2121	244	1877	0.91	0.26	64194.71
7	CYTO-3Y, 21 / HPV-5Y (16/18), 27	2699	9328	12026	1911	238	1672	1.02	0.29	64194.07
8	CYTO-3Y, 21 / HPV-5Y (16/18), 30	3679	8511	12190	1680	229	1450	1.21	0.30	64192.42
9	CYTO-4Y, 21 / HPV-3Y (cyto), 25	2276	14823	17100	2264	250	2013	0.87	0.24	64194.84
10	CYTO-3Y, 21 / HPV-3Y (cyto), 27	3205	13770	16975	2042	245	1797	0.99	0.26	64194.17
11	CYTO-3Y, 21 / HPV-3Y (cyto), 30	4105	12425	16530	1780	234	1545	1.21	0.30	64192.14
12	CYTO-4Y, 21 / HPV-5Y (cyto), 25	1994	10088	12082	1879	241	1637	0.93	0.27	64194.65
13	CYTO-3Y, 21 / HPV-5Y (cyto), 27	2950	9309	12260	1698	237	1461	1.05	0.29	64193.79
14	CYTO-3Y, 21 / HPV-5Y (cyto), 30	3892	8493	12385	1497	228	1269	1.24	0.31	64192.05
15	CYTO-4Y, 21 / COTEST-3Y, 25	15755	14724	30479	2589	257	2332	0.88	0.24	64194.91
16	CYTO-3Y, 21 / COTEST-3Y, 27	15796	13753	29549	2354	251	2102	0.97	0.26	64194.13
17	CYTO-3Y, 21 / COTEST-3Y, 30	15485	12438	27923	2066	240	1826	1.18	0.29	64192.16
18	CYTO-4Y, 21 / COTEST-5Y, 25	10982	9951	20934	2082	246	1836	0.95	0.27	64194.68
19	CYTO-3Y, 21 / COTEST-5Y, 27	11310	9267	20577	1896	241	1654	1.03	0.29	64193.76

Abbreviations: CC: cervical cancer; CIN: cervical intraepithelial neoplasia; Colpos: colposcopies; Cyto: cytology; HPV: human papillomavirus.

* Total number of tests, irrespective of primary, triage or surveillance context.
† Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

Appendix Table 19. Outcomes for Cervical Cancer Screening Strategies Over Lifetime of Screening (Screening End Age 65) Assuming Referral to Colposcopy for LSIL or Worse Result on Cytology Triage

#	Strategy	Per 1,000 women								
		Cyto tests	HPV tests	Total tests*	Colpos	CIN2,3 detected	False positives†	CC cases	CC deaths	Life-years
1	CYTO-3Y, 21	13877	786	14662	645	160	484	2.34	0.76	64181.89
2	CYTO-3Y, 21 / COTEST-5Y, 30	11425	8380	19806	1630	201	1429	1.08	0.30	64192.97
3	CYTO-4Y, 21 / HPV-3Y (16/18), 25	1905	14799	16703	2488	217	2271	0.74	0.23	64195.53
4	CYTO-3Y, 21 / HPV-3Y (16/18), 27	2876	13761	16636	2240	213	2027	0.83	0.25	64195.01
5	CYTO-3Y, 21 / HPV-3Y (16/18), 30	3824	12419	16242	1947	204	1743	1.02	0.27	64193.44
6	CYTO-4Y, 21 / HPV-5Y (16/18), 25	1705	10056	11761	2036	209	1827	0.80	0.25	64195.30
7	CYTO-3Y, 21 / HPV-5Y (16/18), 27	2697	9282	11978	1834	205	1629	0.90	0.28	64194.63
8	CYTO-3Y, 21 / HPV-5Y (16/18), 30	3675	8469	12144	1612	198	1413	1.06	0.29	64193.31
9	CYTO-4Y, 21 / HPV-3Y (cyto), 25	2275	14780	17056	2148	214	1934	0.77	0.23	64195.41
10	CYTO-3Y, 21 / HPV-3Y (cyto), 27	3204	13725	16929	1938	210	1727	0.87	0.25	64194.65
11	CYTO-3Y, 21 / HPV-3Y (cyto), 30	4101	12386	16487	1689	201	1487	1.07	0.28	64192.92
12	CYTO-4Y, 21 / HPV-5Y (cyto), 25	1992	10038	12030	1779	206	1574	0.83	0.26	64195.21
13	CYTO-3Y, 21 / HPV-5Y (cyto), 27	2948	9263	12211	1608	202	1405	0.93	0.28	64194.27
14	CYTO-3Y, 21 / HPV-5Y (cyto), 30	3888	8450	12338	1419	196	1222	1.10	0.30	64192.79
15	CYTO-4Y, 21 / COTEST-3Y, 25	15723	14693	30416	2535	223	2312	0.76	0.23	64195.50
16	CYTO-3Y, 21 / COTEST-3Y, 27	15765	13723	29488	2303	218	2084	0.83	0.25	64194.75
17	CYTO-3Y, 21 / COTEST-3Y, 30	15456	12411	27867	2021	209	1812	1.03	0.27	64193.17
18	CYTO-4Y, 21 / COTEST-5Y, 25	10944	9914	20859	2029	213	1816	0.82	0.26	64195.26
19	CYTO-3Y, 21 / COTEST-5Y, 27	11275	9233	20508	1846	209	1637	0.89	0.27	64194.40

Abbreviations: CC: cervical cancer; CIN: cervical intraepithelial neoplasia; Colpos: colposcopies; Cyto: cytology; HPV: human papillomavirus.

* Total number of tests, irrespective of primary, triage or surveillance context.
† Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

Appendix Table 20. Outcomes for Cervical Cancer Screening Strategies Over Lifetime of Screening (Screening End Age 65) Assuming 6-Month Follow-Up for HPV-Positive, Cytology-Negative Women

#	Strategy	Per 1,000 women								
		Cyto tests	HPV tests	Total tests*	Colpos	CIN2,3 detected	False positives†	CC cases	CC deaths	Life-years
1	CYTO-3Y, 21	13877	786	14662	645	160	484	2.34	0.76	64181.89
2	CYTO-3Y, 21 / COTEST-5Y, 30	11720	8674	20394	1865	203	1661	1.04	0.29	64193.28
3	CYTO-4Y, 21 / HPV-3Y (16/18), 25	1909	15226	17135	2825	220	2604	0.72	0.23	64195.63
4	CYTO-3Y, 21 / HPV-3Y (16/18), 27	2881	14176	17057	2537	216	2321	0.79	0.24	64195.19
5	CYTO-3Y, 21 / HPV-3Y (16/18), 30	3828	12769	16596	2194	206	1988	0.98	0.26	64193.60
6	CYTO-4Y, 21 / HPV-5Y (16/18), 25	1711	10442	12153	2297	213	2083	0.75	0.24	64195.47
7	CYTO-3Y, 21 / HPV-5Y (16/18), 27	2700	9579	12279	2055	208	1847	0.86	0.27	64194.82
8	CYTO-3Y, 21 / HPV-5Y (16/18), 30	3679	8755	12434	1800	201	1599	1.01	0.28	64193.57
9	CYTO-4Y, 21 / HPV-3Y (cyto), 25	2285	15385	17670	2639	220	2419	0.73	0.23	64195.59
10	CYTO-3Y, 21 / HPV-3Y (cyto), 27	3214	14307	17521	2372	215	2156	0.80	0.24	64194.96
11	CYTO-3Y, 21 / HPV-3Y (cyto), 30	4109	12880	16989	2053	206	1847	0.99	0.26	64193.55
12	CYTO-4Y, 21 / HPV-5Y (cyto), 25	2004	10585	12589	2159	213	1946	0.76	0.24	64195.53
13	CYTO-3Y, 21 / HPV-5Y (cyto), 27	2956	9694	12650	1933	208	1725	0.87	0.27	64194.65
14	CYTO-3Y, 21 / HPV-5Y (cyto), 30	3896	8863	12759	1696	200	1495	1.02	0.27	64193.58
15	CYTO-4Y, 21 / COTEST-3Y, 25	16245	15215	31460	2959	226	2733	0.72	0.22	64195.74
16	CYTO-3Y, 21 / COTEST-3Y, 27	16212	14170	30382	2675	221	2453	0.79	0.24	64194.96
17	CYTO-3Y, 21 / COTEST-3Y, 30	15836	12790	28626	2333	211	2122	0.98	0.26	64193.52
18	CYTO-4Y, 21 / COTEST-5Y, 25	11335	10306	21641	2349	216	2132	0.78	0.25	64195.48
19	CYTO-3Y, 21 / COTEST-5Y, 27	11588	9545	21133	2122	212	1910	0.86	0.27	64194.57

Abbreviations: CC: cervical cancer; CIN: cervical intraepithelial neoplasia; Colpos: colposcopies; Cyto: cytology; HPV: human papillomavirus.

* Total number of tests, irrespective of primary, triage or surveillance context.
† Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

Appendix Table 21. Outcomes for Cervical Cancer Screening Strategies Over Lifetime of Screening (Screening End Age 65) Assuming 24-Month Follow-Up for HPV-Positive, Cytology-Negative Women

#	Strategy	Per 1,000 women								
		Cyto tests	HPV tests	Total tests*	Colpos	CIN2,3 detected	False positives†	CC cases	CC deaths	Life-years
1	CYTO-3Y, 21	13878	786	14663	646	161	484	2.35	0.76	64181.83
2	CYTO-3Y, 21 / COTEST-5Y, 30	11098	8052	19151	1343	196	1146	1.14	0.30	64192.47
3	CYTO-4Y, 21 / HPV-3Y (16/18), 25	1894	14199	16094	2176	214	1962	0.77	0.24	64195.40
4	CYTO-3Y, 21 / HPV-3Y (16/18), 27	2870	13319	16189	1975	211	1764	0.85	0.25	64194.93
5	CYTO-3Y, 21 / HPV-3Y (16/18), 30	3820	12050	15870	1721	203	1518	1.03	0.27	64193.46
6	CYTO-4Y, 21 / HPV-5Y (16/18), 25	1700	9675	11375	1797	207	1590	0.82	0.26	64195.21
7	CYTO-3Y, 21 / HPV-5Y (16/18), 27	2693	8939	11632	1627	203	1424	0.92	0.28	64194.53
8	CYTO-3Y, 21 / HPV-5Y (16/18), 30	3672	8199	11872	1441	197	1244	1.07	0.29	64193.30
9	CYTO-4Y, 21 / HPV-3Y (cyto), 25	2255	13905	16160	1686	209	1477	0.84	0.24	64195.16
10	CYTO-3Y, 21 / HPV-3Y (cyto), 27	3192	13060	16252	1536	206	1330	0.90	0.26	64194.24
11	CYTO-3Y, 21 / HPV-3Y (cyto), 30	4093	11834	15927	1353	199	1153	1.09	0.28	64192.81
12	CYTO-4Y, 21 / HPV-5Y (cyto), 25	1982	9469	11451	1424	201	1223	0.89	0.26	64194.97
13	CYTO-3Y, 21 / HPV-5Y (cyto), 27	2940	8753	11693	1299	198	1100	0.98	0.29	64193.87
14	CYTO-3Y, 21 / HPV-5Y (cyto), 30	3883	8041	11924	1160	193	967	1.14	0.30	64192.60
15	CYTO-4Y, 21 / COTEST-3Y, 25	14994	13964	28958	2018	215	1803	0.82	0.24	64195.09
16	CYTO-3Y, 21 / COTEST-3Y, 27	15153	13111	28264	1848	212	1636	0.89	0.25	64194.24
17	CYTO-3Y, 21 / COTEST-3Y, 30	14947	11902	26849	1640	204	1436	1.08	0.28	64192.63
18	CYTO-4Y, 21 / COTEST-5Y, 25	10486	9457	19943	1636	205	1430	0.88	0.27	64194.76
19	CYTO-3Y, 21 / COTEST-5Y, 27	10849	8806	19655	1501	203	1298	0.97	0.29	64193.82

Abbreviations: CC: cervical cancer; CIN: cervical intraepithelial neoplasia; Colpos: colposcopies; Cyto: cytology; HPV: human papillomavirus.

* Total number of tests, irrespective of primary, triage or surveillance context.
† Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

Appendix Table 22. Outcomes for Cervical Cancer Screening Strategies Over Lifetime of Screening (Screening End Age 65) Assuming Colposcopy Referral for All HPV-Positive Women

#	Strategy	Per 1,000 women								
		Cyto tests	HPV tests	Total tests*	Colpos	CIN2,3 detected	False positives†	CC cases	CC deaths	Life-years
1	CYTO-3Y, 21	13876	786	14662	645	160	484	2.34	0.76	64181.93
2	CYTO-3Y, 21 / COTEST-5Y, 30*	11424	8379	19803	1629	201	1428	1.08	0.30	64192.98
20	CYTO-3Y, 21 / HPV-3Y (colposcopy), 25	1145	15029	16175	3261	220	3041	0.74	0.23	64195.59
21	CYTO-3Y, 21 / HPV-3Y (colposcopy), 27	2258	14041	16299	2923	216	2706	0.81	0.24	64195.10
22	CYTO-3Y, 21 / HPV-3Y (colposcopy), 30	3364	12652	16016	2515	207	2308	0.98	0.27	64193.61
23	CYTO-3Y, 21 / HPV-5Y (colposcopy), 25	1145	10353	11499	2632	214	2417	0.78	0.25	64195.43
24	CYTO-3Y, 21 / HPV-5Y (colposcopy), 27	2258	9514	11772	2341	209	2132	0.87	0.28	64194.72
25	CYTO-3Y, 21 / HPV-5Y (colposcopy), 30	3364	8687	12051	2037	201	1835	1.02	0.28	64193.50

Abbreviations: CC: cervical cancer; CIN: cervical intraepithelial neoplasia; Colpos: colposcopies; Cyto: cytology; HPV: human papillomavirus.

* Total number of tests, irrespective of primary, triage or surveillance context.
† Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.

Appendix Table 23. Outcomes for Cervical Cancer Screening Strategies Over Lifetime of Screening (Screening End Age 65) in Women Vaccinated Against HPV-16/18*

#	Strategy	Per 1,000 women								
		Cyto tests	HPV tests	Total tests†	Colpos	CIN2,3 detected	False positives‡	CC cases	CC deaths	Life-years
1	CYTO-3Y, 21	13742	763	14504	539	87	452	0.89	0.28	64193.31
2	CYTO-3Y, 21 / COTEST-5Y, 30	10909	7922	18831	1221	110	1111	0.34	0.07	64197.65
3	CYTO-4Y, 21 / HPV-3Y (16/18), 25	1911	14012	15923	1549	116	1433	0.24	0.06	64198.41
4	CYTO-3Y, 21 / HPV-3Y (16/18), 27	2852	13013	15866	1396	114	1282	0.27	0.07	64198.18
5	CYTO-3Y, 21 / HPV-3Y (16/18), 30	3775	11783	15558	1217	109	1108	0.33	0.07	64197.74
6	CYTO-4Y, 21 / HPV-5Y (16/18), 25	1699	9341	11041	1300	111	1188	0.25	0.06	64198.38
7	CYTO-3Y, 21 / HPV-5Y (16/18), 27	2663	8601	11263	1173	109	1063	0.29	0.08	64198.08
8	CYTO-3Y, 21 / HPV-5Y (16/18), 30	3620	7950	11571	1040	106	934	0.34	0.07	64197.75
9	CYTO-4Y, 21 / HPV-3Y (cyto), 25	1910	14012	15923	1549	115	1434	0.24	0.06	64198.39
10	CYTO-3Y, 21 / HPV-3Y (cyto), 27	2853	13015	15868	1398	113	1284	0.27	0.07	64198.19
11	CYTO-3Y, 21 / HPV-3Y (cyto), 30	3775	11783	15558	1217	109	1108	0.33	0.07	64197.74
12	CYTO-4Y, 21 / HPV-5Y (cyto), 25	1700	9342	11041	1300	111	1188	0.25	0.06	64198.36
13	CYTO-3Y, 21 / HPV-5Y (cyto), 27	2663	8601	11264	1173	109	1063	0.29	0.08	64198.08
14	CYTO-3Y, 21 / HPV-5Y (cyto), 30	3621	7952	11572	1041	106	935	0.34	0.07	64197.75
15	CYTO-4Y, 21 / COTEST-3Y, 25	15019	14014	29033	1881	123	1759	0.24	0.06	64198.42
16	CYTO-3Y, 21 / COTEST-3Y, 27	15097	13097	28194	1711	120	1591	0.27	0.06	64198.19
17	CYTO-3Y, 21 / COTEST-3Y, 30	14868	11881	26749	1506	114	1392	0.32	0.07	64197.74
18	CYTO-4Y, 21 / COTEST-5Y, 25	10282	9276	19558	1508	116	1391	0.26	0.07	64198.30
19	CYTO-3Y, 21 / COTEST-5Y, 27	10634	8635	19269	1370	114	1256	0.29	0.07	64198.10

Abbreviations: CC: cervical cancer; CIN: cervical intraepithelial neoplasia; Colpos: colposcopies; Cyto: cytology; HPV: human papillomavirus.

* HPV-16/18 vaccination is assumed to provide 100% protection against 16/18 infections over the lifetime.
† Total number of tests, irrespective of primary, triage or surveillance context.
‡ Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection.