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

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Prepared by:
Duke Evidence-based Practice Center
2400 Pratt Street
Durham, NC 27705

Minnesota Evidence-based Practice Center
420 Delaware Street SE
Minneapolis, MN 55455

Investigators:
Shalini L. Kulasingam, PhD
Laura Havrilesky, MD, MHSc
Rahel Ghebre, MD
Evan R. Myers, MD, MPH

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This report was first published in May 2011. Since then, further analyses were conducted to evaluate the strategy of screening women for cervical cancer with cytology every 3 years before age 30 years and then co-testing every 5 years after age 30 years. The results of these additional analyses appear at the end of this report (pages 55 to 66).

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Structured Abstract

Background: Despite recommendations from the U.S. Preventive Services Task Force (USPSTF) regarding the age at which to begin and end cervical cancer screening, as well as the interval at which to conduct screening, there is limited direct evidence beyond that inferred from epidemiologic and natural history studies to support these recommendations. In addition, concerns about the poor sensitivity (approximately 50 percent) of cytology-based screening have led to the development of new tests with potentially improved sensitivity for the detection of cervical intraepithelial neoplasia (CIN) grades 2 and 3. Although there is widespread use of these tests—including the Hybrid Capture 2 high-risk human papillomavirus (HPV) deoxyribonucleic acid (DNA) test—the USPSTF has, to date, not recommended their use due to a lack of definitive evidence regarding their performance in screening. The availability of new data, including data from randomized controlled trials, suggests a need to re-evaluate the previous recommendations. Simulation modeling can provide additional guidance on the risks, benefits, and resources associated with different screening test strategies, as well as the trade-offs involved in varying the age at which to begin and end screening.

Purpose: A decision model was used to address two specific aims: 1) How many colposcopies per life-year gained are associated with each of the different ages for beginning screening for cervical cancer (varying in 1 year increments from ages 15 to 25 years)? and 2) How many colposcopies per life-year gained are associated with cervical cancer screening strategies that use HPV DNA testing in conjunction with cytology, compared to strategies based on cytology only?

In addition, as a sub-aim of Specific Aim 1, the age at which to end screening for cervical cancer in women who have previously been screened every 3 years prior to age 65 years or who have never been screened was also examined.

Methods: The model used for the analysis (the Duke Cervical Cancer model) was developed as part of a previous evidence report prepared for the Agency for Healthcare Research and Quality. The model describes the natural history of HPV infection, including progression to CIN2-3 and cancer, as well as the impact of screening and treatment on the prevention of disease progression in a cohort of unvaccinated girls who are followed until either death or age 100 years. Test characteristics for the different screening tests are primarily based on a companion evidence report prepared by the Oregon Evidence-based Practice Center. For each question, outcomes presented include (per 1,000 women): false-positive test results, colposcopies performed, cases of CIN2-3, cases of cervical cancer, and cervical cancer deaths. The main outcome is colposcopies per (undiscounted) life-year. This outcome, which is not based on cost, was chosen by the USPSTF for the primary analysis as a metric that best represents a reasonable trade-off between the burden and benefits of screening. Strategies are compared using incremental ratios. Strategies that are associated with 1) more colposcopies but less effectiveness or 2) fewer colposcopies but higher incremental colposcopies per life-year than an adjacent strategy are considered to be dominated and are eliminated from consideration for this analysis. The remaining strategies (after this elimination process) lie on an "efficiency" frontier (although efficiency in this context is measured using colposcopies per life-year instead of cost per life-year) and, as such, may represent a reasonable trade-off between the burden and benefits of screening.

Results: An analysis of the age at which to begin screening shows that screening with cytology in the teens is associated with a high number of false-positive test results and few detected cases of cancer. Analyses using the metric of colposcopies per life-year suggest that screening less frequently than annually beginning in the twenties might provide a reasonable trade-off between the burden and benefits of screening. However, since American Society for Colposcopy and Cervical Pathology guidelines recommend rescreening instead of immediate referral to colposcopy for women younger than age 21 years, colposcopies per life-year may underestimate the burden of screening in this age group. A sensitivity analysis that uses number of screening cytology tests instead of colposcopies as the metric of interest also identifies screening strategies that begin at later ages, including the USPSTF's current recommended strategy of beginning screening no later than age 21 years, and conducted at least every 3 years, as strategies that may better represent a reasonable trade-off between the burden and benefits of screening.

In terms of the age at which to end screening, among women who have never been screened prior to age 65 years, strategies associated with screening every 2 to 5 years and ending in the 70s are identified as representing a reasonable trade-off between the burden and benefits of screening. Beyond this decade, the gains in life expectancy are small compared to the number of colposcopies performed. Among women who have been screened every 3 years prior to age 65 years, the incremental colposcopies per life-year gained associated with any further screening are high for all strategies due to the smaller gains in life expectancy. These findings are robust across a range of sensitivity analyses.

Analyses comparing cytology with and without HPV testing show that identifying co-testing (cytology and HPV, with screening every 3 years assumed for women with HPV negative and cytology normal results) as an efficient strategy depends on how the burden of screening is quantified. If colposcopies per life-year is used as the outcome, co-testing strategies are identified as efficient. However, if screening and triage tests are used to quantify burden, cytology-only strategies are identified as more efficient than co-testing strategies. In sensitivity analyses, a strategy of HPV testing followed by cytology for high-risk HPV positive women, with referral to colposcopy if both tests are abnormal, is consistently identified as efficient, regardless of whether colposcopies or tests (screening and triage) are used to quantify burden.

Conclusions: This decision analysis supports current recommendations regarding the age at which to begin and end screening. A strategy of co-testing with cytology and HPV (and screening every 3 years for women with dually negative results) is identified as efficient compared to cytology if colposcopies are used to quantify burden. However, if tests are used to quantify burden, cytology-only strategies are identified as efficient compared to co-testing. A sensitivity analysis suggests that a strategy of HPV followed by cytology (for women with HPV positive test results) warrants further study.

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Background

Worldwide, carcinoma of the cervix is one of the most common malignancies in women.[1] In the United States in 2010, approximately 12,200 women were expected to be diagnosed with cervical cancer, and 4,210 women were expected to die.[2] Assuming no change in risk, approximately 0.68 percent of women born today will be diagnosed with cervical cancer at some time during their lifetime, and the risk of dying from the disease is 0.24 percent.

The incidence of cervical cancer and associated mortality have both decreased by over 40 percent since 1973.[3] These declines are largely attributable to the success of mass screening using the Papanicolaou (Pap) cytology test to diagnose premalignant or early-stage disease.[4] The decrease in invasive cervical cancer incidence and mortality since the introduction of this test has been so dramatic that it is one of the few interventions to receive an "A" recommendation from the U.S. Preventive Services Task Force (USPSTF).[5]

Despite the impact of cytology-based screening, there is still uncertainty about the details of cytology test performance, with specific concerns surrounding the poor sensitivity of cytology for detection of cervical intraepithelial neoplasia (CIN) grades 2 and 3.[6-9] Efforts to improve cytology test performance have focused on reducing the number of false-negative smears; that is, cases in which premalignant or malignant cells are not diagnosed either because of sampling error (failure to place abnormal cells on the slide) or detection error (abnormal cells are misdiagnosed as normal).

The human papillomavirus (HPV) deoxyribonucleic acid (DNA) test is currently recommended for use in cervical cancer screening.[10] Squamous cell carcinoma of the cervix and its cytologic precursors occur among women who are sexually active. Infection with high-risk types of HPV, acquired sexually, is the most important risk factor for cervical cancer. Based on sensitive HPV detection methods, 95 to 100 percent of squamous cell cervical cancer and 75 to 95 percent of CIN2-3 lesions have detectable HPV DNA.[11-12] In the United States, peak incidence and prevalence of HPV infection occur among women younger than age 25 years,[13-15] but most infections in younger women are transient. HPV infections in older women are much less prevalent, but may carry a higher risk of progression to cervical neoplasia.[16] As such, the American Cancer Society currently recommends that HPV testing be limited to women aged 30 years and older as part of a strategy of combination screening with cytology.[10] HPV DNA tests currently approved for use in the United States include the Cervista HPV HR (Hologic, Inc., Bedford, MA), the Cervista HPV 16/18 (Hologic, Inc., Bedford, MA), and the Hybrid Capture 2 (HC2) high-risk HPV DNA test (Qiagen Inc., Germantown, MD). In its previous recommendations, the USPSTF concluded that the evidence was insufficient to recommend for or against the routine use of HPV testing as a screening test for cervical cancer, although the U.S. Food and Drug Administration approved the use of HPV DNA testing for triage of atypical squamous cells of undetermined significance (ASC-US) or in conjunction with cytology for women aged 30 years or older. Quantifying the harms and benefits of HPV testing in order to inform any changes to the existing recommendations is one focus of this report. For the purposes of this report, HPV testing refers to use of the HC2 test only.

Other questions addressed in this report include the optimal ages at which to begin and end screening, as well as the interval at which screening should be conducted. Currently, the USPSTF recommends that women begin screening within 3 years of onset of sexual activity or at age 21 years (whichever comes first), and that screening be conducted at least every 3 years.[5] In terms of the age at which to end screening, the USPSTF recommendation states that screening should not be routinely recommended for women aged 65 years or older who have a history of normal Pap tests and are not otherwise at high risk for cervical cancer. Despite these recommendations, the summary states that direct evidence to estimate the optimal starting and stopping age and interval for screening is limited.[5]

This report summarizes the results from a decision analysis conducted using a previously developed and validated cervical cancer decision model.[9] The Duke Cervical Cancer model was originally developed as part of a review of new screening technologies for the Agency for Healthcare Research and Quality.[17] The model has been used to estimate the effectiveness of new screening technologies in a number of different settings and populations.[18-21] It can be updated to incorporate the best available evidence on the natural history of HPV and cervical cancer, as well as new screening tests, to project various outcomes, such as life-years gained. The model is now used to provide evidence to answer two questions posed by the USPSTF concerning the age at which to begin screening and the use of HPV DNA tests. These questions are presented in the form of specific aims and have been worded to complement the key questions and contextual questions posed by the USPSTF to the Oregon Evidence-based Practice Center (EPC). Operational decisions and model outcomes are presented in Appendix A. Appendix B provides a summary of the model, including model inputs for the natural history component of the model. Appendix C presents the criteria used to select studies for estimating the sensitivity and specificity of cytology and HPV DNA testing. Key inputs and changes to the model to address the specific aims are discussed below.

Purpose and Specific Aims

The purpose of this report is to provide data to address the following two specific aims outlined by the USPSTF.

Specific Aim 1

To estimate expected colposcopies, life-years, and colposcopies per life-year gained using cytology, with a repeat cytology test for results of ASC-US, to determine the appropriate age at which to begin screening (varying in 1-year increments from ages 15 to 25 years).

Sub-Aim 1

To estimate expected colposcopies, life-years, and colposcopies per life-year gained using cytology, with a repeat cytology test for results of ASC-US, to determine the appropriate age at which to end screening (varying in 5-year increments from ages 65 to 90 years).

Sub-Aim 2

To estimate expected colposcopies, life-years, and colposcopies per life-year gained based on screening intervals of 1, 2, 3, or 5 years, to determine the appropriate screening interval and whether it varies by age at which to begin and end screening.

Specific Aim 2

To estimate expected colposcopies, life-years, and colposcopies per life-year gained associated with screening strategies that use HPV DNA testing in conjunction with cytology, compared to strategies that use cytology only.

Sub-Aim 1

To estimate expected colposcopies, life-years, and colposcopies per life-year gained based on screening intervals of 1, 2, 3, or 5 years, to determine the appropriate screening interval.

Methods

An overview of the model, including inputs, is provided in Appendix B. The following provides a summary of the main changes made to the model to address the specific aims and sub-aims.

Natural History

Recent evidence suggests that the natural history of HPV in young women (aged <30 years) may be such that establishment of a high-grade CIN lesion occurs early in the course (within 2 years) of a high-risk HPV infection.[22-24] Studies also suggest that the burden of CIN may be higher than previously thought in young women, but that progression to cancer from high-grade CIN is low—approximately 1 percent per year.[25-26] In the original model, only a small percentage (5 percent) of infections were assumed to directly result in CIN2-3. Approximately 4 percent of women were assumed to progress from CIN to cancer each year. To address this, a revised natural history model was developed (details presented in Appendix B). This model, which was used in sensitivity analyses, incorporates estimates of HPV and CIN incidence and regression that are higher than those used in the original model, but also includes lower rates of progression between CIN states and from CIN2-3 to cancer.

CIN2 or 3 Versus CIN2-3

There is evidence to suggest that CIN2 behaves similarly to CIN1 (i.e., a high proportion regress), especially in young women.[27-28] It is also a much less reproducible histologic result than CIN3.[29-30] The current model retains CIN2-3 as a single disease state instead of two separate states based on clinical guidelines that treat these outcomes in a similar manner.[31] However, in order to address the possibility that CIN2 may be a false-positive result (that can lead to overdiagnosis and treatment), especially in young women (aged <30 years), a sensitivity analysis

is conducted in which CIN2-3 is further stratified into CIN2 and CIN3 to estimate the percentage of CIN2-3 outcomes that are CIN2 for those strategies that are identified as "efficient" in the base-case analysis. For this sensitivity analysis, the percentage of CIN2-3 that is CIN2 is approximated by age based on data from a study of women undergoing screening in Kaiser Permanente Northwest by Insinga et al.[32] These estimates are presented in Table 1. The number of CIN2-3 cases (per 1,000 women) is estimated using the model; the percentage of women younger than age 30 years whose disease is categorized as CIN2 is then calculated by multiplying the estimates of the number of CIN2-3 cases by the age-specific percentage in Table 1.

Table 1. Percentage of CIN2 Diagnoses By Age Based on Incidence of CIN2 and CIN3 per 1,000 Women Younger Than Age 30 Years[32]

Age	CIN2	CIN3	Percentage CIN2
15-19	0.8	0.3	73
20-24	3.2	1.3	71
25-29	3.8	4.1	48

Screening

Four strategies (based on discussions and agreement with the USPSTF) are examined in this report. The first three strategies, recommended in recent guidelines, are as follows:

1. *Cytology, with a repeat cytology test for results of ASC-US*. For this strategy, all women are screened with cytology. Women with a cytology result of atypical squamous cells–high grade (ASC-H), low-grade squamous intraepithelial lesion (LSIL), or high-grade squamous intraepithelial lesion (HSIL) are referred for followup and treatment based on American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines.[33] Women with an ASC-US cytology result are assumed to receive a repeat cytology test at 6 and 12 months, consistent with ASCCP guidelines.[33] Women with normal cytology results are assumed to return to routine screening conducted every 1, 2, 3, or 5 years. This strategy is used to estimate outcomes for Specific Aim 1, Sub-Aim 1, and Specific Aim 2.
2. *Cytology, with HPV DNA testing for cytology results of ASC-US*. For this strategy, all women are screened with cytology. Women with a cytology result of ASC-H, LSIL, or HSIL are referred for followup and treatment based on ASCCP guidelines.[33] Women with an ASC-US cytology result are assumed to undergo HPV testing, with triage to colposcopy if HPV positive or repeat testing at 1 year if HPV negative. Women with normal cytology results are assumed to return to routine screening conducted every 1, 2, 3, or 5 years. This strategy is used to determine outcomes for Specific Aim 2.
3. *Cytology and HPV*. This strategy is recommended for women aged 30 years and older.[34] For this strategy, women are screened with both HC2 and cytology. Women with a cytology result of ASC-H, LSIL, or higher are referred to colposcopy. Women with a cytology result of ASC-US undergo HPV DNA testing using HC2, with triage to colposcopy if HPV positive or repeat testing at 1 year if HPV negative. Women with a normal cytology result who have a positive HPV test result are assumed to undergo repeat testing with both tests 1 year later, with triage to colposcopy if the cytology result shows ASC-US or higher or if the HPV test is positive. Women with a normal cytology result who have a negative HPV test result are assumed to be screened with both HPV and cytology

every 3 years, as per ASCCP guidelines.[33] Prior to age 30 years, women are assumed to be screened with cytology only, with a repeat cytology test for ASC-US results. Women with normal cytology results are assumed to return to routine screening conducted every 1, 2, 3, or 5 years.

The fourth strategy, which is not part of current recommendations, is as follows:

4. *HPV followed by cytology if HPV positive*. This strategy is included in a sensitivity analysis for Specific Aim 2. For this strategy, women aged 30 years or older are assumed to be screened with an HPV DNA test. Women who have a positive HPV test result undergo cytology testing. Women with ASC-US or a more severe cytology result are assumed to be referred to colposcopy. Women with a normal cytology result who are HPV positive are assumed to return in 1 year for repeat testing with cytology and HPV. Women who have an HPV negative test result are assumed to return to routine screening conducted every 1, 2, 3, or 5 years. Prior to age 30 years, women are assumed to be screened with cytology only, with a repeat test for ASC-US results. Women with normal cytology results are assumed to return to routine screening conducted every 1, 2, 3, or 5 years.

For Specific Aim 1 and Sub-Aim 1, the age at which to begin screening is varied. For Specific Aim 2, the age at which to begin screening is fixed at age 21 years. Except for Sub-Aim 1 (in which age to end screening is varied), all women are assumed to be screened until age 85 years. Women are assumed to enter the model at age 12 years and to be followed until age 100 years or death.

Screening Test Characteristics

Estimates of sensitivity and specificity for the different tests (HC2 and cytology) are based on estimates provided by the Oregon EPC in a separate evidence report.[35] Details of the studies used to derive the estimates are presented in Appendix C. For the purpose of this report, we do not distinguish between liquid-based cytology (LBC) and conventional cytology (CC). We use the term "cytology" to refer to both LBC and CC; this decision is based on recent data showing no significant difference between the two tests in terms of sensitivity and specificity.[35] For Specific Aim 2, three different sets of estimates for HC2 and cytology test accuracy are used, including estimates from a large randomized controlled trial of HPV testing and cytology by Mayrand et al,[8] as well as summary estimates for sensitivity and specificity for cytology and HC2 from a meta-analysis by Koliopoulos et al.[36] The third set of estimates is based on the predicted relative increase in sensitivity and decrease in specificity based on differences in cytology and HPV test performance reported by Mayrand et al[8] and Bigras et al.[37] The differences (delta) in sensitivity and specificity (for CIN2+ compared to cytology) are also presented for the HPV test accuracy estimates.

Table 2. Sensitivity and Specificity of Cytology and HPV Testing for Primary Screening and Triage of Abnormal Cytology Results

Screening or Triage Test	Sensitivity of Test for CIN2+	Specificity of Test for <CIN2	Delta of HPV Compared to Cytology in Same Study	
			Sensitivity (CIN2+)	Specificity (CIN2+)
Cytology				
EPC-QRS[35]	0.569	0.945		
Mayrand et al[8]	0.564	0.973		
Koliopoulos et al[36]	0.727	0.919		
Range[8,37,41-43]	0.20-0.772	0.847-0.990		
Triage for ASC-US[44]	0.762	0.638		
Range[45-47]	0.45-0.956	0.475-0.756		
HPV DNA using HC2				
EPC-QRS[35]	0.964	0.906	0.395	-0.039
Mayrand et al[8]	0.974	0.943	0.41	-0.03
Koliopoulos et al[36]	0.948	0.86	0.221	-0.059
Range[8,37,41-43]	0.341-1.00	0.767-0.966		
Triage for ASC-US[44]	0.892	0.641	0.13	0.003
Range[45-47]	0.67-0.976	0.31-0.672		

Colposcopy and Biopsy Sensitivity and Specificity

Colposcopy and biopsy are assumed to be perfectly sensitive and specific in the base case, to allow for comparison with previous cost-effectiveness analyses. The impact of less than perfect sensitivity and specificity is explored in sensitivity analyses using estimates of the performance of colposcopy (with biopsy as the gold standard) from Mitchell et al.[48]

Table 3. Sensitivity and Specificity of Colposcopy and Biopsy

	Base Estimate	Sensitivity Analysis Estimate
Sensitivity (CIN1+)	1	0.96
Specificity (<CIN1)	1	0.48

Cytology-Histology Conditional Probabilities

Conditional probabilities of cytology results among women with an abnormal histology result are presented in Table 4. These results are used to determine the percentage of women with an abnormal cytology result who are categorized as ASC, LSIL, HSIL, or cancer. A study comparing cytology-histology correlations for LBC and CC found no significant differences between the two.[49] However, to account for findings reported by Ronco et al,[50] which show a higher percentage of women with ASC-US among those screened with LBC, compared to those screened with CC, a sensitivity analysis is conducted using estimates of conditional probabilities of LBC given histology from a screening study in Seattle, Washington (Akhila Balasubramanian, personal communication).[51] In the absence of data for determining the conditional probabilities of LBC for detecting cancer, a distribution similar to that of CC is assumed, and the ratio of HSIL to cancer cytology given a certain histology result is assumed to be the same as that reported for CC.

Table 4. Conditional Probabilities of Cytology Results for a Given Histology Result

Probability of Cytology Result Given Histology Result	Base	Sensitivity Analysis
Probability of cancer given cancer	0.604	0.604
HSIL given cancer	0.21	0.21
LSIL given cancer	0.071	0.071
ASC given cancer	0.116	0.116
Cancer given HSIL	0.01	0.011
HSIL given HSIL	0.586	0.6316
LSIL given HSIL	0.307	0.1711
ASC given HSIL	0.097	0.1974
Cancer given LSIL	0.0015	0.0038
HSIL given LSIL	0.078	0.1957
LSIL given LSIL	0.688	0.3696
ASC given LSIL	0.233	0.4348
Cancer given normal	0.0028	0.0023
HSIL given normal	0.088	0.0714
LSIL given normal	0.384	0.2143
ASC given normal	0.525	0.7143

Conditional probabilities for ASC-H. Among women with ASC cytology results, 14 percent of those with underlying CIN1 and 72 percent of those with underlying CIN2-3 or cancer are categorized as ASC-H.[52] In the absence of data on the percentage of ASC classified as ASC-H with underlying normal histology, we assume a similar percentage to those with underlying CIN1 (14 percent).[52]

Followup for Abnormal Screening Test Results

Followup for abnormal screening test results and abnormal histology is based on recently published ASCCP guidelines.[44] Women younger than age 21 years are treated according to guidelines for adolescent women who have abnormal screening test or histology results.

Adherence to Screening, Followup, and Treatment

Adherence to screening, followup, and treatment is assumed to be 100 percent for the base case. Age-specific estimates of screening used in sensitivity analyses are based on a study of rates of screening in a population of women at Kaiser Permanente Northwest by Schabert et al.[53] These estimates should be treated with caution, however, since they may overrepresent screening estimates by age, due to the inclusion of more than one (multiple) screening test from some women. Although this study is from a health maintenance organization population, it was used to provide information on screening adherence because it provides data based on chart review rather than self-report. A concern with self-reported screening is that studies have shown that only 65 to 70 percent of self-reports of cervical cancer screening within 3 years can be validated through subsequent chart review.[54-57] An additional sensitivity analysis for Specific Aim 1, in which age to begin screening is varied, is conducted using self-reported screening from the National Survey of Family Growth, since this survey provides information on self-reported screening in 1 year intervals and includes data on young women (aged <21 years).[58]

Table 5. Screening Adherence Estimates*

Age	Estimate
15-19	0.163
20-24	0.411
25-29	0.617
30-39	0.594
40-49	0.522
50-59	0.485
60-69	0.376
70-79	0.087
80+	0.025

*From Schabert et al.[53]

Table 6. Screening Adherence Estimates From the National Survey of Family Growth[58]*

Age	Estimate	Age	Estimate
15	0.040	30	0.768
16	0.119	31	0.727
17	0.206	32	0.690
18	0.398	33	0.691
19	0.418	34	0.687
20	0.616	35	0.632
21	0.777	36	0.704
22	0.614	37	0.606
23	0.714	38	0.643
24	0.638	39	0.653
25	0.735	40	0.711
26	0.748	41	0.529
27	0.693	42	0.753
28	0.764	43	0.630
29	0.713	44+	0.577

*Women older than age 44 years are assumed to undergo screening at the same rate as women aged 44 years. These estimates are used in a sensitivity analysis for Specific Aim 1 only.

Analytic Approach

Base-Case Analyses

Base-case analyses (using a single set of test accuracy estimates) are conducted for Specific Aim 1. The analyses for Specific Aim 2 are conducted as preliminary analyses, with three different sets of test accuracy estimates to reflect a range in the published literature as well as a lack of meta-analytic results from the accompanying EPC report.[35] For each question, outcomes presented include (per 1,000 women): expected false-positive test results (defined as a positive screening test but normal colposcopy-biopsy result), colposcopies performed, CIN2-3 lesions detected, cervical cancer cases, and cervical cancer deaths. If a result is less than 1 per 1,000, the outcome is also presented using a denominator of 100,000. The main outcome is colposcopies per (undiscounted) life-year gained. This outcome was requested by the USPSTF, which bases its recommendations on the trade-off between clinical benefits and harms. A previous decision analysis conducted for the Task Force on screening for colorectal cancer used colonoscopies per life-year gained as the primary outcome.[59] Colposcopy, the current standard for definitive diagnosis after an abnormal cervical cancer screening result, was chosen as the closest analogue to colonoscopy.

Strategies are compared using incremental ratios based on the difference in expected number of colposcopies, divided by the difference in life expectancy. Strategies that are associated with more colposcopies and less effectiveness or fewer colposcopies but a higher colposcopy per life-year ratio than an adjacent strategy are considered to be dominated. The remaining strategies (after this elimination process) lie on an "efficiency" frontier. It should be noted, however, that the use of the term "efficient" is non-traditional, since this is not a cost-effectiveness analysis. Efficiency in this case refers to a strategy that represents a potentially reasonable trade-off between the burden and benefits of screening. Strategies that fall on the steepest part of the efficiency frontier are noted, since these are considered to be the most efficient. However, it is important to note that there is no formal definition for what constitutes a "high burden" using colposcopies per life-year gained. As a result, the incremental colposcopies per life-year associated with strategies identified as efficient vary by question.

For the purpose of interpreting the results, the current USPSTF recommendations regarding ages at which to begin and end screening are used. The USPSTF recommends that women begin screening within 3 years of onset of sexual activity or at age 21 years (whichever comes first), and that screening be conducted at least every 3 years.[5] In terms of the age at which to end screening, the USPSTF recommendation states that screening should not be routinely conducted in women aged 65 years or older who have a history of normal cytology tests and are not otherwise at high risk for cervical cancer. As such, for Specific Aim 1, the strategies are also compared and contrasted with a strategy based on the current USPSTF recommendations. For Sub-Aim 1, in which it is assumed that women have been screened every 3 years since age 21 years, a baseline strategy that assumes that screening ends at age 65 years is included.

Sensitivity Analyses

For each of the specific aims, an analysis is conducted using a different model of the natural history of HPV and CIN (details provided in Appendix B). In addition, one-way sensitivity analyses are conducted in which screening adherence and the sensitivity and specificity of colposcopy and biopsy are varied. Additional analyses (for Specific Aim 1 and Sub-Aim 1) include using the lowest and highest estimates for sensitivity and specificity of the screening tests and using different conditional probabilities of CIN given an abnormal cytology result to account for potential differences due to the use of LBC. The following sensitivity analyses are also conducted.

Specific Aim 1: Age at which to begin screening.

1. A shorter time horizon, in which all women are followed to age 30 years, is included to determine whether there are patterns in outcomes affected by age at first screening that are obscured if women are followed for a longer timeframe.
2. Estimates of the percentage of CIN2-3 that is CIN2 are presented for strategies identified as efficient using colposcopies per life-year.
3. One concern with the use of colposcopies per life-year for the analysis of age at which to begin screening is that this measure may underestimate the burden of screening in this population, since ASCCP guidelines[33] now allow for adolescent women younger than age 21 years to be rescreened if they have an abnormal cytology test result. To address this, a

sensitivity analysis is conducted that estimates the number of screening cytology tests per life-year.

Specific Aim 1–Sub-Aim 1: Age at which to end screening.

4. Studies show that older women are at an increased risk of dying from cervical cancer even after adjusting for cancer stage.[60] To address this, a sensitivity analysis is conducted using age- and stage-specific hazard ratios based on data from Ries et al for women aged 50 to 69 years and 70 years and older. These analyses should be interpreted with caution, however, since the estimates were not provided in detail to determine conditional 5-year survival probabilities. As such, the same ratio is applied to each year for 5 years, and may overestimate the impact of age on stage-specific survival.

Specific Aim 2: Role of HPV DNA testing.

5. Since the strategy of HPV testing followed by cytology (described previously) is not a currently recommended strategy, this strategy is examined in a sensitivity analysis.
6. A sensitivity analysis is conducted in which screening and triage tests are used to quantify burden instead of colposcopies. This analysis is conducted to address the fact that the use of colposcopies may underestimate the burden of screening for HPV-based strategies, since women with discordant (HPV positive, normal cytology) test results undergo repeat testing instead of immediate referral to colposcopy.
7. A sensitivity analysis is conducted in which women who are screened with HPV and cytology and are dually negative are assumed to be screened every 5 years instead of every 3 years.

Results

Overview

The results are presented by specific aim. Each section refers to a table that presents the expected number of false-positives (defined as women with abnormal screening results and normal histology), colposcopies, cases of CIN2-3, cases of cancer, and cancer deaths per 1,000 women. The outcomes in these tables are presented with two significant digits so that the outcome per 100,000 women can also be determined. The base-case results for Specific Aim 1 and Sub-Aim 1 are summarized in the accompanying tables and figures. Each table presents only the strategies that are identified as efficient, in the sense that they provide a reasonable trade-off between the burden and benefits of screening. Each figure presents the same strategies using an efficiency curve; the metric used for each curve is colposcopies per (undiscounted) life-year. Three different sets of results are presented for Specific Aim 2. Key sensitivity analyses are presented as outlined previously.

Summary of Results for Specific Aim 1

Tables 7 through 9 and Figures 1 and 2 summarize the results for the base-case analyses for Specific Aim 1, regarding the age at which to begin screening. Tables 7 and 8 present estimates of expected false-positive test results, colposcopies, CIN2-3 cases, cancer cases, and cancer deaths associated with screening in 1-year age increments, beginning at age 15 years and ending

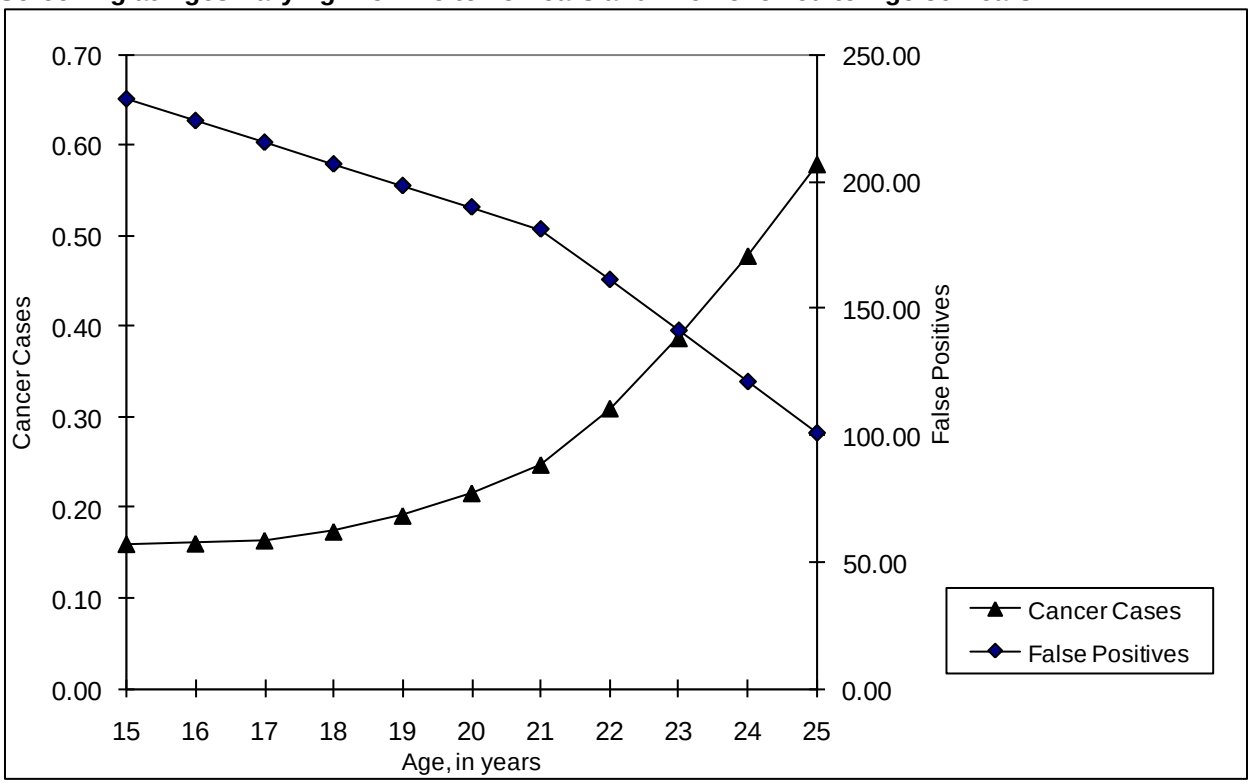
at age 25 years. The results are grouped according to screening interval (every 1 year [q1], 2 years [q2], 3 years [q3], and 5 years [q5]). Tables 7 and 8 show results over a short time horizon (cohort is followed until age 30 years) and lifetime horizon (cohort is followed until age 100 years). When comparing by age across the row, increasing age at first screening is generally associated with fewer false-positive test results, fewer colposcopies, and fewer CIN2-3 cases, but more cancer cases and cancer deaths. There are some fluctuations between successive ages due to differences based on screening interval and age at which to end screening. However, some of the fluctuation in the estimates is also due to ASCCP guidelines,[33] which allow for repeated screening in women younger than age 21 years with abnormal cytology results. If all adolescent women are assumed to attend colposcopy, the outcomes are more consistent by age (data not shown). The inclusion of this aspect of the guidelines in the decision model may also explain the shape of the curve for false-positive test results presented in Figure 1, in which the largest number of false-positive test results occurs in adolescents younger than age 21 years (range per 1,000, 190 at age 20 years to 232 at age 15 years). This age group also has the lowest number of expected cancer cases (range per 1,000, <1 [or 16 to 22 cancer cases per 100,000]). In contrast, the number of false-positive test results is lower (range per 1,000, 101 at age 25 years to 161 at age 22 years) with each successive year that screening is delayed beyond age 21 years (compared to beginning at age 21 years). However, as shown in Figure 1, the number of expected cancer cases begins to rise (range per 100,000, 31 at age 22 years to 58 at age 25 years) with each successive year that screening is delayed beyond age 21 years.

In terms of screening interval, for both time horizons the patterns are similar: the number of false-positive test results and colposcopies increase as screening frequency increases, whereas the number of CIN2-3 cases, cancer cases, and cancer deaths decrease. Of the two time horizons, the lifetime horizon shows fewer fluctuations within successive age intervals. For both horizons, a screening interval of every year is associated with the highest number of colposcopies, exceeding one per woman screened for the lifetime horizon. Compared to screening beginning at age 21 years and conducted every 3 years (which is part of the current USPSTF recommendations), screening every year beginning at age 21 years results in more (1,931 vs. 758 per 1,000) colposcopies but is also associated with a reduction (approximately 3 vs. 9 per 1,000) in cancer cases. Screening every 2 years is associated with approximately 1,084 colposcopies and 6 cancer cases per 1,000 women. Taken together, these patterns can be used to explain the base-case findings presented in Table 9 and summarized in Figure 2. If the strategies that fall on the steepest part of the efficiency curve are assumed to represent a reasonable trade-off between colposcopies and life expectancy gained, then strategies of screening every 3 to 5 years beginning in the early 20s are more attractive, compared to those strategies that are identified as efficient but are based on screening every year in the teens. A strategy of screening every 5 years beginning at age 22 years is also more effective, but is associated with more colposcopies than screening every 5 years beginning at age 20 years. This is because the ASCCP guidelines for triage to immediate colposcopy start at age 21 years.[33] Even though women aged 20 years have one more opportunity for screening (14 vs. 13, when screened through age 85 years), this additional screening occurs before age 21 years. As a result, those with abnormal results undergo repeat cytology instead of immediate referral to colposcopy; all women with abnormal test results are not referred for immediate colposcopy until age 26 years. This aspect of the guidelines may also explain why the currently recommended strategy of the USPSTF is not identified as an efficient strategy—the number of colposcopies is high, but fewer cancer cases are prevented at age 21 years compared to earlier ages.

Table 7. Sensitivity Analysis Showing Expected False-Positives, Colposcopies, CIN2-3 Cases, Cancer Cases, and Cancer Deaths Associated With Screening Beginning at Age 15 Years and Increased in 1-Year Increments to Age 25 Years, Among Women Followed to Age 30 Years*

Strategy		Age 15	Age 16	Age 17	Age 18	Age 19	Age 20	Age 21	Age 22	Age 23	Age 24	Age 25
Cytology with repeat cytology for ASC-US												
q5	False Positives	40.62	51.90	51.90	51.82	51.17	31.57	42.86	42.88	42.80	42.17	21.71
q3	False Positives	82.25	82.16	82.40	73.20	73.12	73.38	64.20	64.13	63.53	42.99	42.72
q2	False Positives	132.68	113.06	123.66	104.04	114.66	95.07	105.74	85.27	84.63	63.99	63.19
q1	False Positives	232.42	223.87	215.32	206.80	198.29	189.85	181.18	161.29	141.25	121.07	100.88
q5	Colposcopies	68.59	100.23	101.26	102.16	102.40	59.53	91.09	91.94	92.60	92.52	47.99
q3	Colposcopies	152.67	153.66	154.97	143.61	144.55	145.76	134.25	134.98	134.99	92.50	92.79
q2	Colposcopies	244.44	204.84	235.41	195.78	226.27	186.56	217.03	176.12	176.04	176.45	134.37
q1	Colposcopies	411.63	403.07	394.50	385.89	377.24	368.59	360.61	322.27	283.84	245.27	206.61
q5	CIN 2-3s	9.06	10.56	11.83	13.04	14.15	9.04	10.45	11.53	12.49	13.29	7.47
q3	CIN 2-3s	14.09	15.55	16.93	14.08	15.47	16.72	13.71	14.90	15.87	12.17	12.95
q2	CIN 2-3s	18.90	17.36	18.90	17.31	18.75	17.05	18.39	16.46	17.50	15.19	15.97
q1	CIN 2-3s	21.08	21.08	21.05	20.98	20.84	20.65	20.41	20.02	19.50	18.84	18.00
q5	Cancer Cases	0.42	0.42	0.46	0.50	0.57	0.42	0.43	0.49	0.56	0.65	0.52
q3	Cancer Cases	0.35	0.39	0.43	0.35	0.40	0.45	0.39	0.46	0.54	0.52	0.62
q2	Cancer Cases	0.31	0.29	0.31	0.30	0.33	0.33	0.37	0.40	0.48	0.53	0.64
q1	Cancer Cases	0.16	0.16	0.16	0.17	0.19	0.22	0.25	0.31	0.39	0.48	0.58
q5	Cancer Deaths	0.06	0.06	0.06	0.06	0.05	0.06	0.06	0.07	0.07	0.07	0.08
q3	Cancer Deaths	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.06	0.07	0.08	0.09
q2	Cancer Deaths	0.03	0.03	0.03	0.04	0.04	0.04	0.05	0.06	0.07	0.08	0.09
q1	Cancer Deaths	0.02	0.02	0.02	0.02	0.02	0.03	0.03	0.04	0.06	0.08	0.09

Figure 1. Expected False-Positives and Cancer Cases for Adolescent Women Who Begin Screening at Ages Varying From 15 to 25 Years and Are Followed to Age 30 Years*



*Results presented assume an annual screening interval and are calculated per 1,000 women.

Table 8. Sensitivity Analysis Showing Expected False-Positives, Colposcopies, CIN2-3 Cases, Cancer Cases, and Cancer Deaths Associated With Screening Beginning at Age 15 Years and Increased in 1-Year Increments to Age 25 Years, Among Women Followed for a Lifetime*

Strategy		Age 15	Age 16	Age 17	Age 18	Age 19	Age 20	Age 21	Age 22	Age 23	Age 24	Age 25
Cytology with repeat cytology for ASC-US												
q5	False Positives	220.74	223.01	220.20	217.50	214.84	211.69	213.97	211.17	208.49	205.85	201.86
q3	False Positives	367.97	362.65	352.67	358.93	353.61	343.65	349.92	344.62	333.82	328.80	323.33
q2	False Positives	542.21	529.73	533.19	520.72	524.19	511.74	515.26	501.94	494.23	480.77	472.93
q1	False Positives	1002.73	994.17	985.63	977.09	968.58	960.13	951.45	931.62	911.68	891.64	871.61
q5	Colposcopies	481.05	492.49	487.71	483.13	478.74	471.99	483.36	478.44	473.65	469.01	461.00
q3	Colposcopies	776.54	766.76	746.04	767.48	757.65	736.59	758.16	748.16	725.97	717.04	706.79
q2	Colposcopies	1,110.92	1,085.93	1,101.89	1,076.87	1,092.75	1,067.65	1,083.52	1,057.27	1,042.80	1,016.43	1,001.77
q1	Colposcopies	1,982.10	1,973.54	1,964.96	1,956.35	1,947.67	1,939.00	1,931.00	1,892.74	1,854.45	1,816.09	1,777.71
q5	CIN 2-3s	67.38	66.10	66.66	67.12	67.56	67.36	66.01	66.39	66.64	66.81	66.25
q3	CIN 2-3s	80.55	80.87	79.80	80.53	80.80	79.61	80.21	80.30	78.88	79.22	79.03
q2	CIN 2-3s	88.01	87.64	88.00	87.59	87.86	87.35	87.52	86.85	86.89	86.05	85.92
q1	CIN 2-3s	92.14	92.14	92.11	92.04	91.91	91.72	91.50	91.25	90.94	90.56	90.08
q5	Cancer Cases	12.70	12.67	12.65	12.66	12.73	12.70	12.69	12.69	12.74	12.85	12.89
q3	Cancer Cases	8.45	8.47	8.66	8.45	8.48	8.62	8.50	8.55	8.73	8.70	8.82
q2	Cancer Cases	5.73	5.73	5.73	5.73	5.75	5.77	5.80	5.84	5.93	6.01	6.14
q1	Cancer Cases	2.41	2.41	2.41	2.42	2.44	2.47	2.50	2.56	2.65	2.75	2.86
q5	Cancer Deaths	2.70	2.70	2.69	2.69	2.70	2.70	2.71	2.70	2.71	2.73	2.75
q3	Cancer Deaths	1.54	1.54	1.59	1.54	1.54	1.57	1.55	1.56	1.60	1.60	1.62
q2	Cancer Deaths	0.90	0.91	0.90	0.91	0.91	0.92	0.92	0.94	0.95	0.98	1.00
q1	Cancer Deaths	0.31	0.31	0.31	0.31	0.31	0.32	0.32	0.33	0.35	0.37	0.40

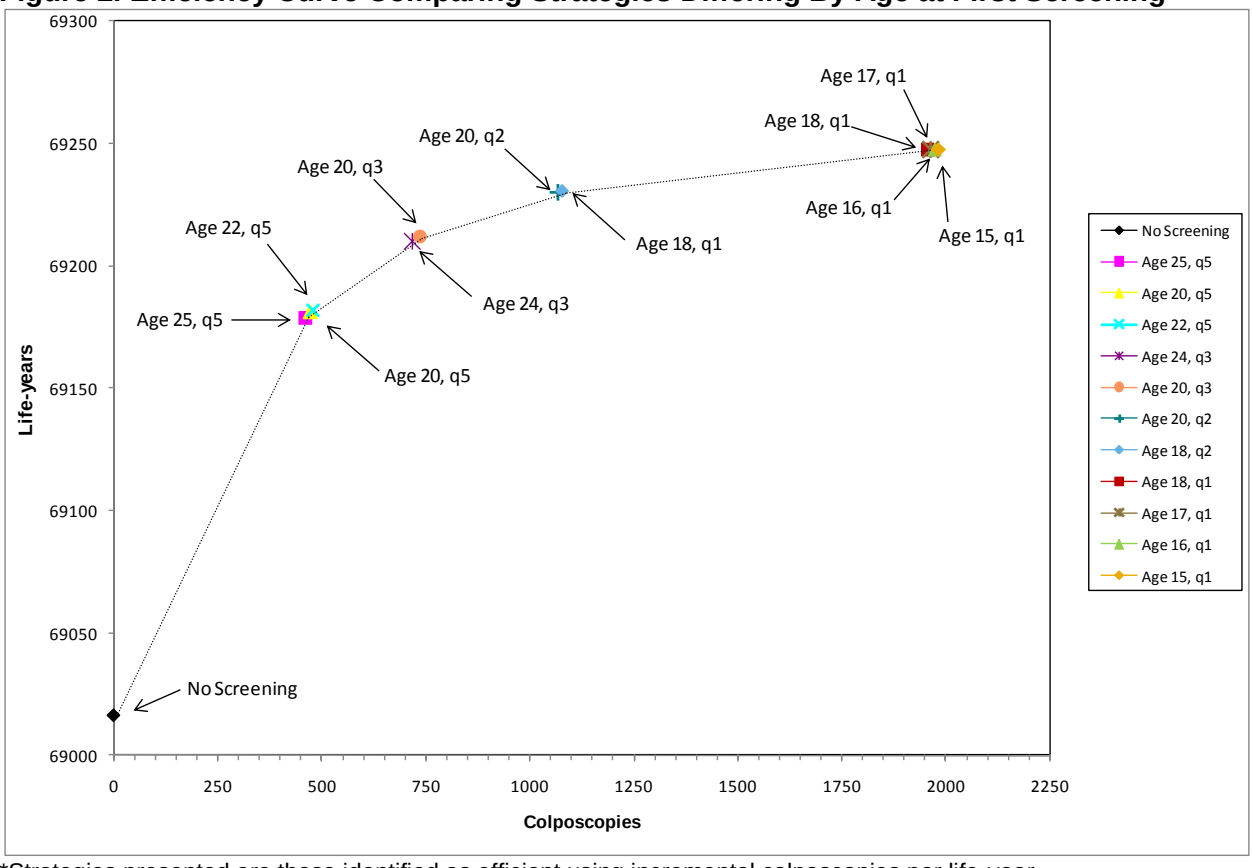
*Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared. Cases are per 1,000 women.

Table 9. Base-Case Analysis*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69016.30		
Age 25, q5	461	461	69178.79	162.49	3
Age 20, q5	472	11	69181.23	2.44	5
Age 22, q5	478	6	69182.04	0.81	7
Age 24, q3	717	239	69210.25	28.21	8
Age 20, q3	737	20	69212.16	1.91	10
Age 20, q2	1068	331	69230.20	18.04	18
Age 18, q2	1077	9	69230.60	0.40	23
Age 18, q1	1956	879	69247.39	16.79	52
Age 17, q1	1965	9	69247.48	0.09	100
Age 16, q1	1974	9	69247.51	0.03	300
Age 15, q1	1982	8	69247.51	<0.01	1990

*Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) associated with screening beginning at different ages (varying in 1-year increments from age 15 to 25 years). Screening intervals of 1 (q1), 2 (q2), 3 (q3), and 5 years (q5) are compared.

Figure 2. Efficiency Curve Comparing Strategies Differing By Age at First Screening*



*Strategies presented are those identified as efficient using incremental colposcopies per life-year.

CIN2 as a Percentage of CIN2-3

Table 10 uses different outcomes than other tables included in this report. Table 10 presents the total number of cases of CIN2-3 (per 1,000 women) over the shorter time horizon (until age 30 years), and the percentage of CIN2-3 cases estimated to actually be CIN2.

Table 10. Percentage of CIN2-3 Cases Estimated to Be CIN2*

Strategy	Total CIN2-3 (per 1,000)	% CIN2
Age 25, q5	7.47	48
Age 20, q5	9.04	71
Age 22, q5	11.53	71
Age 24, q3	12.17	71
Age 20, q3	16.72	71
Age 20, q2	17.05	71
Age 18, q2	17.31	73
Age 18, q1	20.98	73
Age 17, q1	21.05	73
Age 16, q1	21.08	73
Age 15, q1	21.08	73

*Strategies listed are those identified as efficient in the base-case analysis.

Key Sensitivity Analyses

Tables 11 through 16 present the results of the sensitivity analyses. The range of sensitivity analyses confirm the base-case findings, namely that screening frequently in the teens is associated with a large number of colposcopies, but relatively small gains in life expectancy. Results were similar to the base case when the sensitivity and specificity of colposcopy and biopsy were varied or different conditional probabilities of cytology results given underlying histology were used (data not shown). As shown in Table 10, approximately 70 percent of high-grade disease detected in this younger age group may be CIN2 rather than CIN3. This suggests that disease detected in these early years may be very likely to regress and that overdiagnosis and treatment of these lesions are potential concerns. The sensitivity analysis that uses screening cytology tests per life-year also shows that screening in the teens is associated with a high number of cytology tests per life-year gained. Finally, results from the revised natural history model, in which higher disease regression and lower progression is modeled, suggests that, if correct, screening could potentially be delayed past the early 20s.

1. Natural History

Table 11. Sensitivity Analysis Varying Multiple Natural History Parameters*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69074.37		
Age 25, q5	598	598	69191.45	117.08	5
Age 25, q3	874	276	69216.05	24.60	11
Age 24, q3	885	11	69216.57	0.52	21
Age 25, q2	1187	302	69230.39	13.82	22
Age 24, q2	1202	15	69230.97	0.58	26
Age 20, q2	1256	54	69232.06	1.09	50
Age 18, q2	1266	10	69232.27	0.21	48
Age 25, q1	1983	717	69244.98	12.71	56
Age 24, q1	2023	40	69245.52	0.54	74
Age 23, q1	2063	40	69246.00	0.48	83
Age 18, q1	2169	106	69247.20	1.20	88
Age 17, q1	2177	8	69247.25	0.05	160
Age 16, q1	2186	9	69247.27	0.02	450
Age 15, q1	2195	9	69247.28	0.01	900

*Refer to Appendix B for details.

2. Screening Cytology Tests per Life-Year (Undiscounted)

Table 12. Sensitivity Analysis Showing Expected Screening Cytology Tests, Incremental Cytology Tests, Life-Years, Incremental Life-Years, and Incremental Cytology Tests per Life-Year Associated With Screening Beginning at Different Ages*

Strategy	Screening Cytology tests	Incremental Screening Cytology test	Life Years (LYs)	Incremental LYs	Incremental Cytology tests per LY
No intervention	0		69016.30		
Age 25, q5	9834	9834	69178.79	162.49	61
Age 23, q5	10139	305	69181.25	2.46	124
Age 22, q5	10266	127	69182.04	0.79	161
Age 24, q3	15998	5732	69210.25	28.21	203
Age 22, q3	16747	749	69212.10	1.85	405
Age 21,q3	16999	252	69212.69	0.59	427
Age 24, q2	23406	6407	69227.31	14.62	438
Age 22, q2	24406	1000	69229.32	2.01	498
Age 20, q2	25402	996	69230.20	0.88	1132
Age 22, q1	45386	19984	69245.87	15.67	1275
Age 21, q1	46333	947	69246.58	0.71	1334
Age 20, q1	47277	944	69246.92	0.34	2776
Age 19, q1	48219	942	69247.21	0.29	3248
Age 18, q1	49162	943	69247.39	0.18	5239
Age 17, q1	50105	943	69247.48	0.09	10478
Age 16, q1	51049	944	69247.51	0.03	31467
Age 15, q1	51993	944	69247.51	<.01	219524

*Per 1,000 women. Screening varies in 1-year increments from age 15 to 25 years. Screening intervals of 1 (q1), 2 (q2), 3 (q3), and 5 years (q5) are compared.

3. Adherence to Screening <100%[61]

Table 13. Sensitivity Analysis Varying Adherence to Screening*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69016.30		
Age 25, q5	207	207	69120.83	104.53	2
Age 20, q5	212	5	69122.39	1.56	3
Age 25, q3	331	119	69156.84	34.45	3
Age 24, q2	473	142	69183.18	26.34	5
Age 20, q2	494	21	69185.65	2.47	9
Age 25, q1	851	357	69217.93	32.28	11
Age 24, q1	867	16	69218.92	0.99	16
Age 23, q1	884	17	69219.86	0.94	18
Age 19, q1	924	40	69222.01	2.15	19
Age 18, q1	928	4	69222.19	0.18	22
Age 17, q1	931	3	69222.28	0.09	33
Age 16, q1	935	4	69222.32	0.04	100
Age 15, q1	939	4	69222.32	<0.01	627

*Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years , incremental life-years, and incremental colposcopies per life-year (ICLY) associated with screening beginning at different ages (varying in 1-year increments from age 15 to 25 years). Screening intervals of 1 (q1), 2 (q2), 3 (q3), and 5 years (q5) are compared.

4. Adherence to Screening <100%: NSFG Survey[58]

Table 14. Sensitivity Analysis Varying Adherence to Screening Using Estimates From the National Survey of Family Growth[8]*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69016.30		
Age 25, q5	301	301	69140.21	123.91	2
Age 20, q5	308	7	69142.23	2.02	3
Age 24, q3	470	162	69176.70	34.47	5
Age 24, q2	669	199	69201.39	24.69	8
Age 20, q2	701	32	69204.15	2.76	12
Age 18, q2	705	4	69204.40	0.25	16
Age 25, q1	1167	462	69228.78	24.38	19
Age 24, q1	1192	25	69230.03	1.25	20
Age 23, q1	1220	28	69231.27	1.24	23
Age 18, q1	1287	67	69233.65	2.38	28
Age 17, q1	1289	2	69233.69	0.04	50
Age 16, q1	1290	1	69233.70	0.01	100
Age 15, q1	1291	1	69233.70	<.01	603

* Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) associated with screening beginning at different ages (varying in 1-year increments from age 15 to 25 years). Screening intervals of 1 (q1), 2 (q2), 3 (q3), and 5 years (q5) are compared.

5. Highest Estimates of Sensitivity and Lowest Estimates of Specificity

Table 15. Sensitivity Analysis in Which the Highest Estimates of Sensitivity and Lowest Estimates of Specificity Are Assumed*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69016.30		
Age 25, q5	1299	1299	69211.02	194.72	7
Age 20, q5	1333	34	69213.66	2.64	13
Age 20, q3	2120	787	69235.38	21.72	36
Age 19, q3	2179	59	69236.15	0.77	77
Age 18, q2	3139	960	69246.04	9.89	97
Age 17, q1	5369	2230	69253.35	7.31	305
Age 16, q1	5391	22	69253.37	0.02	1100
Age 15, q1	5413	22	69253.38	0.01	2200

*Sensitivity for CIN2+ is 0.772 instead of 0.569; specificity for CIN2+ is 0.847 instead of 0.945; sensitivity for ASCUS is 0.956 instead of 0.762; specificity for ASCUS is 0.475 instead of 0.638. Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) associated with screening beginning at different ages (varying in 1-year increments from age 15 to 25 years). Screening intervals of 1 (q1), 2 (q2), 3 (q3), and 5 years (q5) are compared.

6. Lowest Estimates of Sensitivity and Highest Estimates of Specificity

Table 16. Sensitivity Analysis in Which the Lowest Estimates of Sensitivity and Highest Estimates of Specificity Are Assumed*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69016.30		
Age 22, q5	106	106	69096.58	80.28	1
Age 24, q3	158	52	69126.49	29.92	2
Age 25, q1	375	217	69194.77	68.28	3
Age 23, q1	390	15	69197.66	2.88	5
Age 19, q1	407	17	69200.16	2.50	7
Age 18, q1	409	2	69200.33	0.17	12
Age 17, q1	410	1	69200.42	0.09	11
Age 16, q1	412	2	69200.46	0.04	50
Age 15, q1	414	2	69200.46	<.01	354

*Sensitivity for CIN2+ is 0.200 instead of 0.569; specificity for CIN2+ is 0.990 instead of 0.945; sensitivity for ASCUS is 0.450 instead of 0.762; specificity for ASCUS is 0.756 instead of 0.638. Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) associated with screening beginning at different ages (varying in 1-year increments from age 15 to 25 years). Screening intervals of 1 (q1), 2 (q2), 3 (q3), and 5 years (q5) are compared.

Summary of Results for Specific Aim 1–Sub-Aim 1

Tables 17 through 19 and Figures 3 and 4 summarize the results for the base-case analyses for Sub-Aim 1, regarding the age at which to end screening. Outcomes for women, grouped by screening interval and whether they have never been screened or have been screened annually prior to age 65 years, are presented in Table 17. Among women who have never been screened, varying the age at which to end screening has a relatively small impact on cancer cases and cancer deaths, but a large impact on the number of colposcopies and false-positive test results. For instance, cancer deaths range from approximately 9 per 1,000 women (860 per 100,000) if screening is conducted every 5 years and ends at age 70 years, to approximately 8 per 1,000 women (789 per 100,000) if screening ends at age 90 years. For the same comparison, colposcopies range from 36.95 to 135.78 per 1,000 women. A similar pattern is seen with increasing the frequency of screening—small reductions in cancer cases and deaths, but large increases in false-positives and colposcopies. Although a similar pattern is also seen among women who have been screened every 3 years prior to age 65 years (i.e., many more colposcopies and false-positive test results associated with small decreases in cancer cases and deaths), compared to those who have never been screened, there is a large increase in colposcopies. For example, among women who have never been screened prior to age 65 years, screening every 5 years and ending at age 70 years is associated with approximately 37 colposcopies per 1,000 women, compared to 621 if screening is conducted every 3 years. Although deaths are increased, as expected, if age-specific survival ratios are used instead of pooled estimates of survival, the patterns observed above are similar. As a result, among those who have never been screened, strategies associated with infrequent screening (every 2 through 5 years) and ending at age 70 years fall on the steep part of the efficiency curve (Table 18 and Figure 3).

In contrast, there are much smaller differences between the strategies identified as efficient for women who have been screened frequently prior to age 65 years (Table 19 and Figure 4). The strategies cluster very closely together based on life expectancy, with an approximate 1-year gain

in life expectancy per 1,000 women at most, which represents less than 1 day's gain in life expectancy per woman. These results are robust across a range of sensitivity analyses (Tables 20-29), including the analyses which assume less than perfect compliance with screening and low estimates for sensitivity. Results are also robust when the sensitivity and specificity of colposcopy and biopsy are varied or different conditional probabilities of cytology results given underlying histology are used (data not shown).

Table 17. Sensitivity Analysis Showing Expected False-Positives, Colposcopies, CIN2-3 Cases, Cancer Cases, and Cancer Deaths Associated With Different Ages at Which to End Screening, Varying in 5-Year Increments From Age 65 to 90 Years*†‡

		Age 70	Age 75	Age 80	Age 85	Age 90
No screening (until age 65)						
q5	False Positives	13.72	36.82	46.08	52.60	56.07
q5	Colposcopies	36.95	91.70	112.94	127.84	135.78
q5	CIN 2-3s	8.16	16.49	19.31	21.26	22.28
q5	Cancer Cases	28.76	27.30	27.02	26.91	26.88
q5	Cancer Deaths	8.60	8.04	7.95	7.91	7.89
q5‡	Cancer Deaths	10.52	9.58	9.42	9.35	9.34
No screening (until age 65)						
q3	False Positives	26.24	49.63	68.71	76.60	85.78
q3	Colposcopies	66.49	118.54	160.44	177.64	197.81
q3	CIN 2-3s	12.55	18.32	22.61	24.29	26.36
q3	Cancer Cases	27.84	26.80	26.26	26.12	26.00
q3	Cancer Deaths	8.24	7.88	7.71	7.67	7.64
q3‡	Cancer Deaths	9.88	9.24	8.94	8.87	8.81
No screening (until age 65)						
q2	False Positives	38.65	72.77	92.51	114.36	122.99
q2	Colposcopies	93.45	166.42	208.35	254.84	273.17
q2	CIN 2-3s	15.02	20.94	24.14	27.75	29.15
q2	Cancer Cases	27.29	26.20	25.76	25.43	25.34
q2	Cancer Deaths	8.04	7.70	7.58	7.49	7.47
q2‡	Cancer Deaths	9.51	8.88	8.64	8.48	8.44
No screening (until age 65)						
q1	False Positives	72.43	125.82	170.98	205.32	225.27
q1	Colposcopies	162.55	272.12	364.75	435.21	476.15
q1	CIN 2-3s	18.07	23.08	27.26	30.45	32.31
q1	Cancer Cases	26.51	25.51	24.88	24.55	24.40
q1	Cancer Deaths	7.80	7.53	7.38	7.30	7.27
q1‡	Cancer Deaths	9.02	8.48	8.17	8.02	7.96
Screening q3 (until age 65)						
q5	False Positives	287.69	300.56	311.67	320.51	326.20
q5	Colposcopies	621.45	650.61	676.05	696.34	709.44
q5	CIN 2-3s	66.05	69.74	73.12	75.85	77.62
q5	Cancer Cases	10.66	9.95	9.46	9.21	9.12
q5	Cancer Deaths	2.25	2.00	1.83	1.75	1.71
q5‡	Cancer Deaths	3.62	3.18	2.89	2.75	2.70
Screening q3 (until age 65)						
q3	False Positives	300.14	323.48	334.08	349.92	358.25
q3	Colposcopies	648.96	700.23	723.36	758.16	776.44
q3	CIN 2-3s	69.02	74.33	76.62	80.21	82.09
q3	Cancer Cases	10.03	9.10	8.80	8.50	8.40
q3	Cancer Deaths	2.03	1.74	1.65	1.55	1.52
q3‡	Cancer Deaths	3.23	2.69	2.52	2.36	2.31

*Women are assumed to either never have been screened or screened every 3 years prior to age 65 years. Thereafter, they are screened until age 70, 75, 80, 85, or 90 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared for those who have never been screened, and intervals of every 3 (q3) or 5 (q5) years are compared for those who have. All women are assumed to be followed until age 100 years or death.

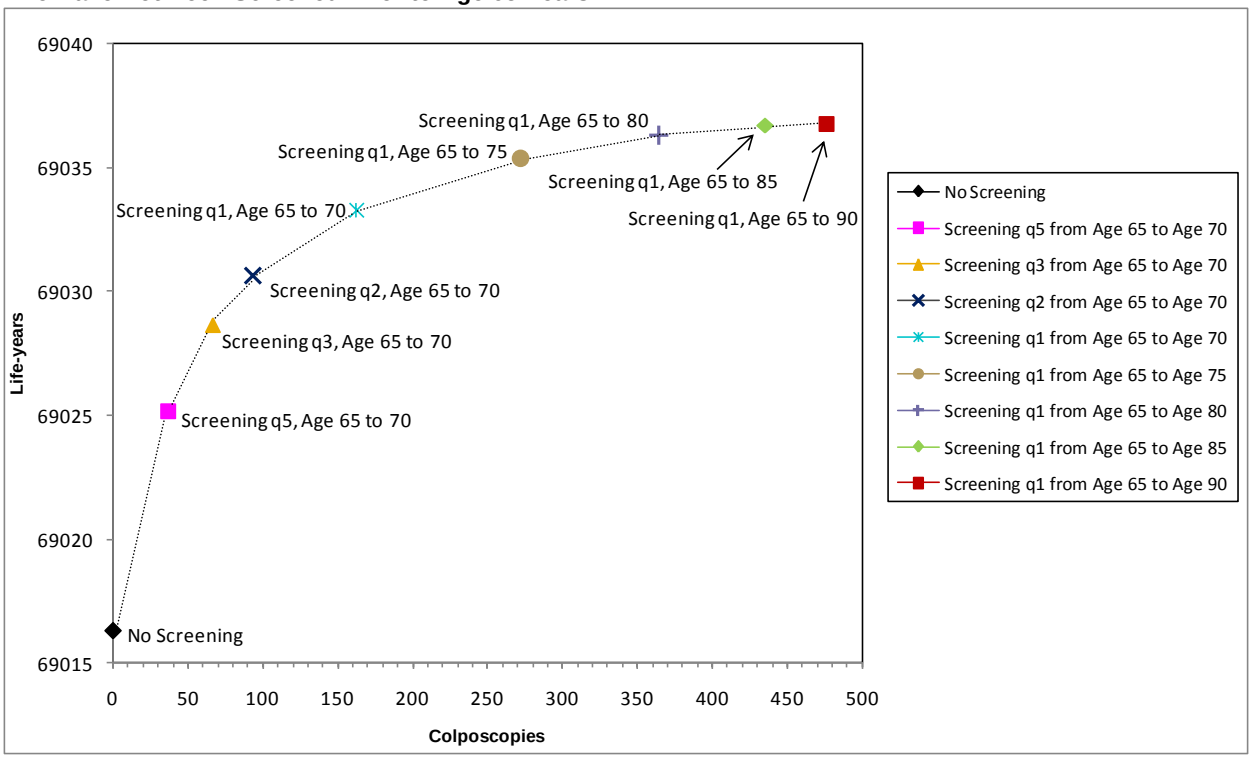
†Among women who are screened every 3 years until age 65 years, the number of false-positives, colposcopies, CIN2-3 cases, cancer cases, and cancer deaths are 273.44, 590.30, 63, 11, and 2.5, respectively.
‡Sensitivity analysis estimates are based on age-specific survival. Cancer deaths are calculated using pooled and age-specific survival.

Table 18. Base-Case Analysis for Strategies Identified as Efficient Among Women Who Have Never Been Screened Prior to Age 65 Years*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69016.30		
Screening q5 from Age 65 to Age 70	37	37	69025.14	8.84	4
Screening q3 from Age 65 to Age 70	66	30	69028.63	3.49	8
Screening q2 from Age 65 to Age 70	93	27	69030.63	2.00	13
Screening q1 from Age 65 to Age 70	163	70	69033.27	2.64	27
Screening q1 from Age 65 to Age 75	272	109	69035.38	2.11	52
Screening q1 from Age 65 to Age 80	365	93	69036.33	0.95	98
Screening q1 from Age 65 to Age 85	435	70	69036.68	0.35	200
Screening q1 from Age 65 to Age 90	476	41	69036.77	0.09	456

*Women are assumed to never have been screened prior to age 65 years. Thereafter, they are screened until age 70, 75, 80, 85, or 90 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared. Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY).

Figure 3. Efficiency Curve Comparing Strategies Differing By Age at Which to End Screening, Among Women Who Have Not Been Screened Prior to Age 65 Years*



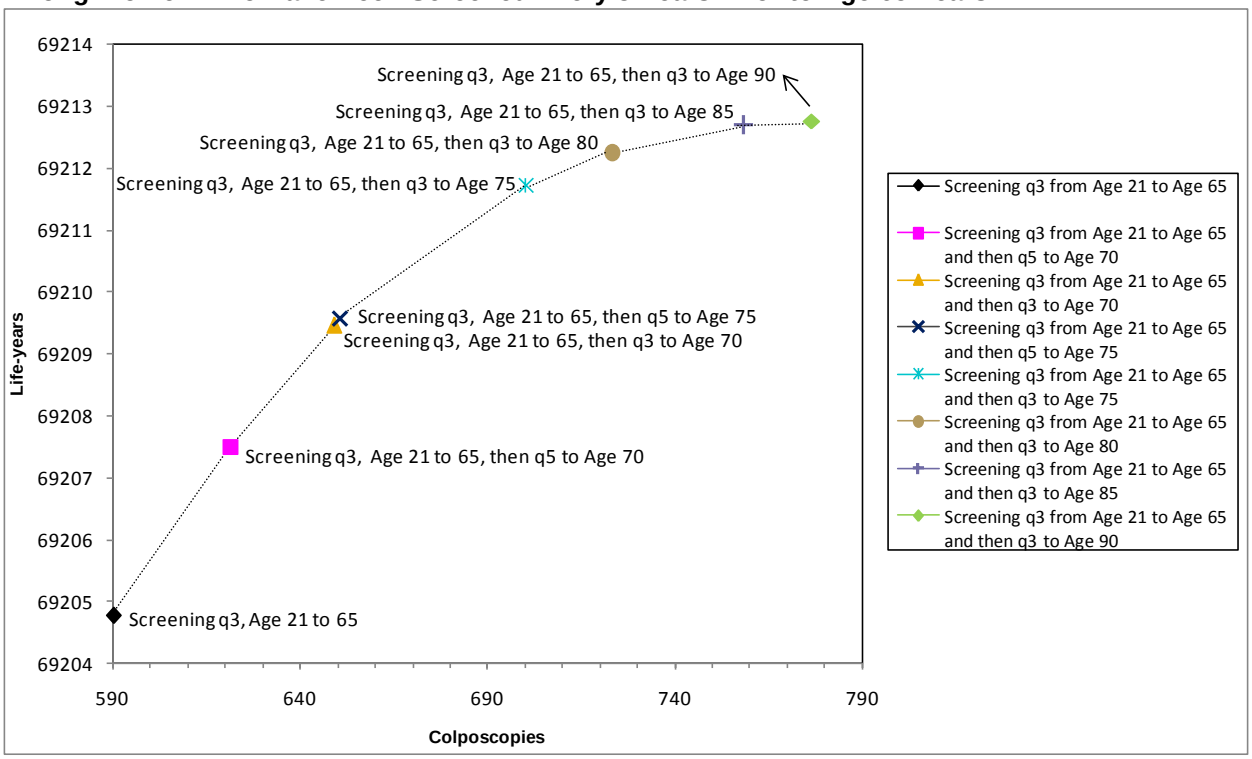
*Strategies presented are those identified as efficient using incremental colposcopies per life-year.

Table 19. Base-Case Analysis for Strategies Identified as Efficient Among Women Who Have Been Screened Every 3 Years Prior to Age 65 Years*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
Screening q3 from Age 21 to Age 65	590		69204.77		
Screening q3 from Age 21 to Age 65 and then q5 to Age 70	621	31	69207.50	2.73	11
Screening q3 from Age 21 to Age 65 and then q3 to Age 70	649	28	69209.47	1.97	14
Screening q3 from Age 21 to Age 65 and then q5 to Age 75	651	2	69209.57	0.10	20
Screening q3 from Age 21 to Age 65 and then q3 to Age 75	700	49	69211.72	2.15	23
Screening q3 from Age 21 to Age 65 and then q3 to Age 80	723	23	69212.26	0.54	43
Screening q3 from Age 21 to Age 65 and then q3 to Age 85	758	35	69212.69	0.43	81
Screening q3 from Age 21 to Age 65 and then q3 to Age 90	776	18	69212.76	0.07	257

*Thereafter, women are screened to age 70, 75, 80, 85, or 90 years. Screening intervals of every 3 (q3) and 5 (q5) years are compared.

Figure 4. Efficiency Curve Comparing Strategies Differing By Age at Which to End Screening, Among Women Who Have Been Screened Every 3 Years Prior to Age 65 Years*



*Screening is assumed to begin at age 21 years. After age 65 years, screening is then varied by interval (q3 and q5) and age at which to end screening (70, 75, 80, 85, and 90 years). Strategies presented are those identified as efficient using colposcopies per (undiscounted) life-year.

Key Sensitivity Analyses

1. Age-Specific Survival Ratios

Table 20. Sensitivity Analysis Varying Age-Specific Survival Ratios*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		68984.74		
Screening q5 from Age 65 to Age 70	37	37	69002.67	17.93	2
Screening q3 from Age 65 to Age 70	66	29	69008.82	6.15	5
Screening q2 from Age 65 to Age 70	93	27	69012.66	3.84	7
Screening q1 from Age 65 to Age 70	163	70	69018.11	5.45	13
Screening q1 from Age 65 to Age 75	272	109	69022.33	4.22	26
Screening q1 from Age 65 to Age 80	365	93	69024.26	1.93	48
Screening q1 from Age 65 to Age 85	435	70	69024.98	0.72	97
Screening q1 from Age 65 to Age 90	476	41	69025.15	0.17	241

*Refer to Appendix B for details.

Table 21. Sensitivity Analysis Varying Age-Specific Survival Ratios*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
Screening q3 from Age 21 to Age 65	590		69186.98		
Screening q3 from Age 21 to Age 65 and then q5 to Age 70	621	31	69192.31	5.33	6
Screening q3 from Age 21 to Age 65 and then q3 to Age 70	649	28	69195.86	3.55	8
Screening q3 from Age 21 to Age 65 and then q3 to Age 75	700	51	69199.87	4.01	13
Screening q3 from Age 21 to Age 65 and then q3 to Age 80	723	23	69200.80	0.93	25
Screening q3 from Age 21 to Age 65 and then q3 to Age 85	758	35	69201.53	0.73	48
Screening q3 from Age 21 to Age 65 and then q3 to Age 90	776	18	69201.61	0.08	225

*Refer to Appendix B for details.

2. Natural History

Table 22. Sensitivity Analysis Varying Multiple Natural History Parameters*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69074.37		
Screening q5 from Age 65 to Age 70	67	67	69085.38	11.01	6
Screening q3 from Age 65 to Age 70	111	44	69089.63	4.25	10
Screening q2 from Age 65 to Age 70	146	35	69092.01	2.38	15
Screening q1 from Age 65 to Age 70	222	76	69095.03	3.02	25
Screening q1 from Age 65 to Age 75	346	124	69097.14	2.11	59
Screening q1 from Age 65 to Age 80	449	103	69097.98	0.84	123
Screening q1 from Age 65 to Age 85	526	77	69098.27	0.29	266
Screening q1 from Age 65 to Age 90	571	45	69098.34	0.07	643

*Refer to Appendix B for details.

Table 23. Sensitivity Analysis Varying Multiple Natural History Parameters*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
Screening q3 from Age 21 to Age 65	723		69210.27		
Screening q3 from Age 21 to Age 65 and then q5 to Age 70	761	38	69212.80	2.53	15
Screening q3 from Age 21 to Age 65 and then q3 to Age 70	795	34	69214.58	1.78	19
Screening q3 from Age 21 to Age 65 and then q3 to Age 75	857	62	69216.55	1.97	32
Screening q3 from Age 21 to Age 65 and then q3 to Age 80	885	28	69217.01	0.46	61
Screening q3 from Age 21 to Age 65 and then q3 to Age 85	928	43	69217.37	0.36	119
Screening q3 from Age 21 to Age 65 and then q3 to Age 90	950	22	69217.43	0.06	367

*Refer to Appendix B for details.

3. Adherence to Screening <100%[61]

Table 24. Sensitivity Analysis Varying Adherence to Screening Among Women Who Have Never Been Screened Prior to Age 65 Years*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69016.30		
Screening q5 from Age 65 to Age 70	14	14	69019.62	3.32	4
Screening q3 from Age 65 to Age 70	26	12	69021.61	1.99	6
Screening q2 from Age 65 to Age 70	38	12	69023.28	1.67	7
Screening q1 from Age 65 to Age 70	62	24	69026.28	3.00	8
Screening q1 from Age 65 to Age 75	74	12	69027.00	0.72	17
Screening q1 from Age 65 to Age 80	83	9	69027.34	0.34	26
Screening q1 from Age 65 to Age 85	86	3	69027.37	0.03	100
Screening q1 from Age 65 to Age 90	88	2	69027.38	0.01	200

*Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are screened to age 70, 75, 80, 85, or 90 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

Table 25. Sensitivity Analysis Varying Adherence to Screening Among Women Who Have Been Screened Every 3 Years Prior to Age 65 Years*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
Screening q3 from Age 21 to Age 65	319		69155.90		
Screening q3 from Age 21 to Age 65 and then q5 to Age 70	332	13	69157.63	1.73	8
Screening q3 from Age 21 to Age 65 and then q3 to Age 70	343	11	69158.90	1.27	9
Screening q3 from Age 21 to Age 65 and then q3 to Age 75	349	6	69159.25	0.35	17
Screening q3 from Age 21 to Age 65 and then q3 to Age 80	352	3	69159.34	0.09	33
Screening q3 from Age 21 to Age 65 and then q3 to Age 85	353	1	69159.36	0.02	50
Screening q3 from Age 21 to Age 65 and then q3 to Age 90	354	1	69159.36	<0.01	650

*Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are screened to age 70, 75, 80, 85, or 90 years. Screening intervals of every 3 (q3) and 5 (q5) years are compared.

4. Highest Estimates of Sensitivity and Lowest Estimates of Specificity

Table 26. Sensitivity Analysis Using the Highest Estimates of Sensitivity and Lowest Estimates of Specificity Among Women Who Have Never Been Screened Prior to Age 65 Years*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69016.30		
Screening q5 from Age 65 to Age 70	98	98	69028.58	12.28	8
Screening q3 from Age 65 to Age 70	179	81	69031.98	3.40	24
Screening q2 from Age 65 to Age 70	255	76	69033.49	1.51	50
Screening q3 from Age 65 to Age 75	327	72	69034.72	1.23	59
Screening q2 from Age 65 to Age 75	467	140	69035.96	1.24	113
Screening q2 from Age 65 to Age 80	590	123	69036.67	0.71	173
Screening q1 from Age 65 to Age 80	982	392	69037.90	1.23	319
Screening q1 from Age 65 to Age 85	1175	193	69038.18	0.28	689
Screening q1 from Age 65 to Age 90	1286	111	69038.25	0.07	1586

*Sensitivity for CIN2+ is 0.772 instead of 0.569; specificity for CIN2+ is 0.847 instead of 0.945; sensitivity for ASCUS is 0.956 instead of 0.762; specificity for ASCUS is 0.475 instead of 0.638. Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are screened to age 70, 75, 80, 85, or 90 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

Table 27. Sensitivity Analysis Using the Highest Estimates of Sensitivity and Lowest Estimates of Specificity Among Women Who Have Been Screened Every 3 Years Prior to Age 65 Years*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
Screening q3 from Age 21 until Age 65	1703		69228.04		
Screening q3 from Age 21 to Age 65 and then q5 to Age 70	1793	90	69230.71	2.67	34
Screening q3 from Age 21 to Age 65 and then q5 to Age 75	1876	83	69232.92	2.21	38
Screening q3 from Age 21 to Age 65 and then q5 to Age 80	1948	72	69234.06	1.14	63
Screening q3 from Age 21 to Age 65 and then q3 to Age 75	2018	70	69234.79	0.73	96
Screening q3 from Age 21 to Age 65 and then q3 to Age 80	2086	68	69235.32	0.53	128
Screening q3 from Age 21 to Age 65 and then q3 to Age 85	2185	99	69235.75	0.43	230
Screening q3 from Age 21 to Age 65 and then q3 to Age 90	2238	53	69235.83	0.08	663

*Sensitivity for CIN2+ is 0.772 instead of 0.569; specificity for CIN2+ is 0.847 instead of 0.945; sensitivity for ASCUS is 0.956 instead of 0.762; specificity for ASCUS is 0.475 instead of 0.638. Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are screened to age 70, 75, 80, 85, or 90 years. Screening intervals of every 3 (q3) and 5 (q5) years are compared.

Table 28. Sensitivity Analysis Using the Lowest Estimates of Sensitivity and Highest Estimates of Specificity Among Women Who Have Never Been Screened Prior to Age 65 Years*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69016.30		
Screening q5 from Age 65 to Age 70	9	9	69019.43	3.13	3
Screening q2 from Age 65 to Age 70	22	13	69022.76	3.33	4
Screening q1 from Age 65 to Age 70	39	17	69026.11	3.35	5
Screening q1 from Age 65 to Age 75	62	23	69028.22	2.11	11
Screening q1 from Age 65 to Age 80	82	20	69029.03	0.81	25
Screening q1 from Age 65 to Age 85	96	14	69029.29	0.26	54
Screening q1 from Age 65 to Age 90	105	9	69029.33	0.04	225

*Sensitivity for CIN2+ is 0.200 instead of 0.569; specificity for CIN2+ is 0.990 instead of 0.945; sensitivity for ASCUS is 0.450 instead of 0.762; specificity for ASCUS is 0.756 instead of 0.638. Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are screened to age 70, 75, 80, 85, or 90 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

Table 29. Sensitivity Analysis Using the Lowest Estimates of Sensitivity and Highest Estimates of Specificity Among Women Who Have Been Screened Every 3 Years Prior to Age 65 Years*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
Screening q3 from Age 21 until Age 65	128		69124.03		
Screening q3 from Age 21 to Age 65 and then q5 to Age 70	135	7	69125.75	1.72	4
Screening q3 from Age 21 to Age 65 and then q3 to Age 70	141	6	69126.95	1.20	5
Screening q3 from Age 21 to Age 65 and then q3 to Age 75	153	12	69128.22	1.27	9
Screening q3 from Age 21 to Age 65 and then q3 to Age 80	158	5	69128.48	0.26	19
Screening q3 from Age 21 to Age 65 and then q3 to Age 85	165	7	69128.62	0.14	50

*Sensitivity for CIN2+ is 0.200 instead of 0.569; specificity for CIN2+ is 0.990 instead of 0.945; sensitivity for ASCUS is 0.450 instead of 0.762; specificity for ASCUS is 0.756 instead of 0.638. Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are screened to age 70, 75, 80, 85, or 90 years. Screening intervals of every 3 (q3) and 5 (q5) years are compared.

Summary of Results for Specific Aim 2

Tables 30a–c and 31a–c and Figures 5 through 7 summarize the results for Specific Aim 2, which compares strategies that include HPV DNA testing to cytology only using three different sets of test accuracy estimates. As shown in Tables 30a–c, the results are similar regardless of estimates used; there are fewer colposcopies but more cancer cases and cancer deaths associated with screening using cytology tests conducted at intervals of every 2, 3, and 5 years, compared to screening with cytology only prior to age 30 years, and then with cytology and HPV beginning at age 30 years. At an annual screening interval, the cytology-only strategy is associated with more colposcopies but fewer cases of cancer and cancer deaths, compared to the cytology and HPV strategy. The reason for this switch is that at less frequent intervals, a sufficient amount of disease is detected by adding the HPV test, which offsets any loss in disease detection due to women with dually negative test results being screened once every 3 years (beginning at age 30 years) for the cytology and HPV strategy. However, at the most frequent screening interval, the impact of women with dually negative results being screened every 3 years becomes evident,

with fewer colposcopies and false-positives, but more cases of disease for the HPV and cytology strategy compared to the cytology-only strategy.

As a result, HPV and cytology is identified as a strategy that may provide a reasonable trade-off between the burden and benefits of screening, especially when conducted every 3 or 5 years (Tables 31a–c and Figures 5–7). The base-case findings are generally similar across a range of sensitivity analyses (Tables 32-37a–c), including varying the sensitivity and specificity of colposcopy and biopsy as well as the conditional probability of cytology given underlying histology (data not shown). If women with normal cytology results who are HPV negative are assumed to be screened every 5 years instead of every 3 (Tables 33a–c), and the difference in test accuracy between cytology and HPV is large (Tables 33a and 33b), cytology conducted every 3 years beginning at age 21 years is dominated (more colposcopies and fewer gains in life expectancy) by the cytology and HPV strategy. Exceptions to the findings for the base case (for the three sets of estimates) are when screening and triage tests are used to reflect the burden of screening instead of colposcopies (Tables 32a–c) and when a strategy of HPV followed by cytology for HPV positive women is modeled (Tables 36a–c and 37a–c). When screening and triage tests are used instead of colposcopies to quantify burden, cytology-only strategies are primarily identified as efficient. While the currently recommended strategy of cytology and HPV conducted every 3 years for women with dually negative results also falls on the efficiency curve, there is a large number of additional tests per life-year gained (approximately 1,000 to 1,200). A sensitivity analysis of HPV followed by cytology for HPV positive women shows that this is a potentially efficient strategy whether tests or colposcopies are used to quantify the burden of screening. This strategy, although not currently recommended, is more efficient than either the cytology-only or cytology and HPV strategies. This is because only those women with positive results on both tests are referred to colposcopy (compared to cytology-only strategies), reducing the burden of colposcopies due to false-positive results. Those women with discordant results (HPV positive, normal cytology) are assumed to undergo repeat screening 1 year later, with referral to colposcopy only if repeat testing is abnormal; thus, this strategy detects more disease than cytology only. Although the cytology and HPV strategy is associated with greater gains in life expectancy compared to HPV followed by cytology, it is associated with more colposcopies at the less frequent screening intervals (every 3 and 5 years). At the more frequent screening intervals (every 1 and 2 years), HPV followed by cytology is associated with greater gains in life expectancy because only a small proportion of women undergo routine screening at these intervals; the majority (with negative HPV and normal cytology results) are screened every 3 years. Use of tests instead of colposcopies produces similar results except when estimates of test accuracy from Koliopoulos et al[36] are used. In this instance, cytology-based screening strategies are identified as efficient, which suggests that the magnitude of the difference in test accuracy between HPV and cytology, as well as the metric used to quantify burden of screening, influences the degree to which this strategy is considered efficient.

Table 30a. Vesco et al[35]: Sensitivity Analysis Showing Expected False-Positives, Colposcopies, CIN2-3 Cases, Cancer Cases, and Cancer Deaths Associated With Cytology and HPV Test-Based Strategies Either Alone or in Combination*

Strategy	Interval	False-Positives	Colposcopies	CIN2-3 Cases	Cancer Cases	Cancer Deaths
Cytology and HPV	q5	280.88	625.91	84.78	7.07	1.29
Cytology	q5	213.97	483.36	66.01	12.69	2.71
Cytology and HPV	q3	381.33	824.74	93.10	4.73	0.74
Cytology	q3	349.92	758.16	80.21	8.50	1.55
Cytology and HPV	q2	539.64	1129.39	94.39	3.64	0.52
Cytology	q2	515.26	1083.52	87.52	5.80	0.92
Cytology and HPV	q1	727.22	1488.19	95.19	2.57	0.35
Cytology	q1	951.45	1931.00	91.50	2.50	0.32

*Per 1,000 women. Time horizon is a lifetime. Age at which to begin screening is fixed at age 21 years. For the combined cytology and HPV strategies, cytology-based screening only is assumed prior to age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing begins at age 30 years. Women with normal cytology results and HPV negative results are assumed to be screened every 3 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

Table 30b. Mayrand et al[8]: Sensitivity Analysis Showing Expected False-Positives, Colposcopies, CIN2-3 Cases, Cancer Cases, and Cancer Deaths Associated With Cytology and HPV Test-Based Strategies Either Alone or in Combination*

Strategy	Interval	False-Positives	Colposcopies	CIN2-3 Cases	Cancer Cases	Cancer Deaths
Cytology and HPV	q5	129.70	347.79	86.98	7.39	1.35
Cytology	q5	100.94	274.01	66.93	13.15	2.81
Cytology and HPV	q3	175.67	446.38	96.53	5.02	0.79
Cytology	q3	165.52	416.44	82.61	8.97	1.65
Cytology and HPV	q2	252.91	600.90	99.35	3.94	0.57
Cytology	q2	244.38	580.58	91.71	6.24	0.99
Cytology and HPV	q1	348.59	790.56	101.93	2.82	0.38
Cytology	q1	464.75	1024.42	99.89	2.79	0.36

*Time horizon is a lifetime. Age at which to begin screening is fixed at age 21 years. For the combined cytology and HPV strategies, cytology-based screening only is assumed prior to age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing begins at age 30 years. Women with normal cytology results and HPV negative results are assumed to be screened every 3 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

Table 30c. Koliopoulos et al[36]: Sensitivity Analysis Showing Expected False-Positives, Colposcopies, CIN2-3 Cases, Cancer Cases, and Cancer Deaths Associated With Cytology and HPV Test-Based Strategies Either Alone or in Combination*

Strategy	Interval	False-Positives	Colposcopies	CIN2-3 Cases	Cancer Cases	Cancer Deaths
Cytology and HPV	q5	441.29	907.30	85.28	6.23	1.01
Cytology	q5	328.93	693.97	74.85	9.76	1.86
Cytology and HPV	q3	600.89	1209.54	92.36	3.94	0.53
Cytology	q3	535.05	1090.56	86.16	5.98	0.95
Cytology and HPV	q2	834.47	1646.02	92.33	2.86	0.36
Cytology	q2	784.70	1563.96	90.13	3.79	0.51
Cytology and HPV	q1	1101.24	2141.58	91.41	1.92	0.23
Cytology	q1	1409.78	2744.25	88.30	1.37	0.16

*Time horizon is a lifetime. Age at which to begin screening is fixed at age 21 years. For the combined cytology and HPV strategies, cytology-based screening only is assumed prior to age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing begins at age 30 years. Women with normal cytology results

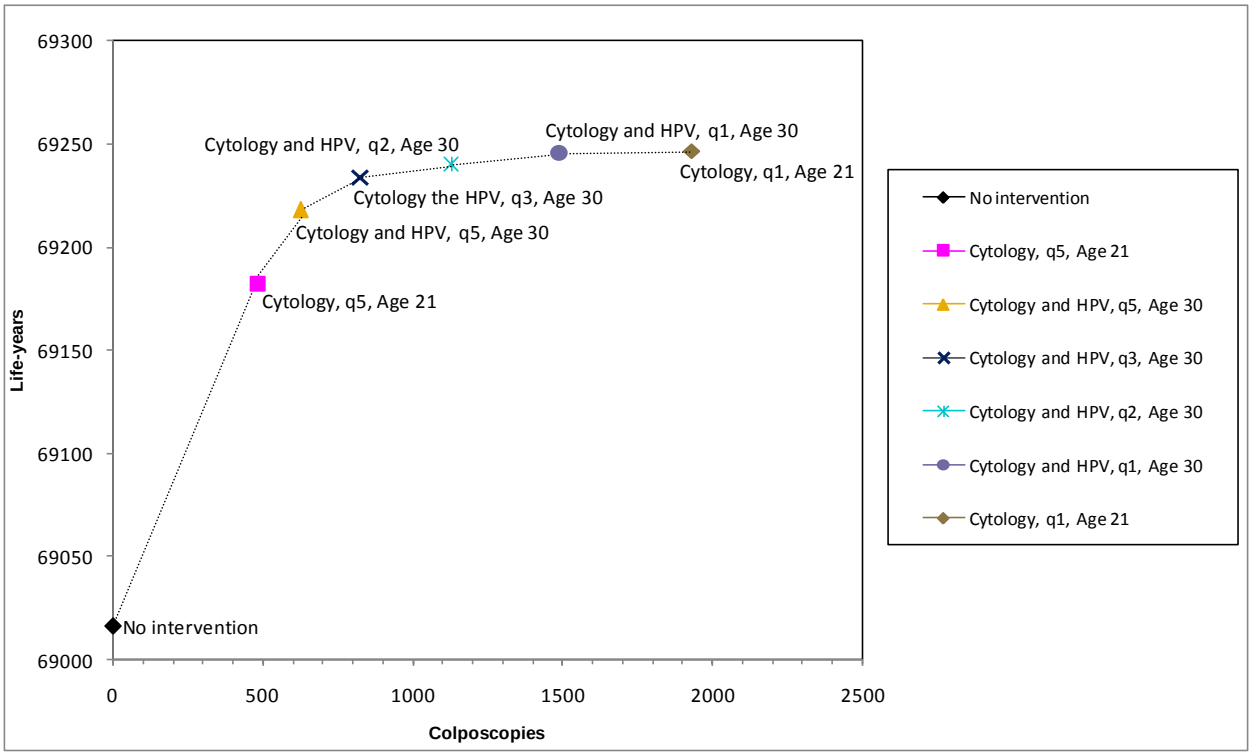
and HPV negative results are assumed to be screened every 3 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

Table 31a. Vesco et al[35]: Sensitivity Analysis Showing Expected Colposcopies, Incremental Colposcopies, Life-Years, Incremental Life-Years, and Incremental Colposcopies per Life-Year for Strategies Identified as Efficient*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69016.30		
Cytology, q5, Age 21	483	483	69182.25	165.95	3
Cytology and HPV, q5, Age 30	626	143	69218.11	35.86	4
Cytology and HPV, q3, Age 30	825	199	69233.80	15.69	13
Cytology and HPV, q2, Age 30	1129	304	69240.06	6.26	49
Cytology and HPV, q1, Age 30	1488	359	69245.94	5.88	61
Cytology, q1, Age 21	1931	443	69246.58	0.64	692

*Per 1,000 women. Women are assumed to begin screening at age 21 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

Figure 5. Efficiency Curve Comparing Strategies Based on Cytology Either Alone or in Combination With HPV*



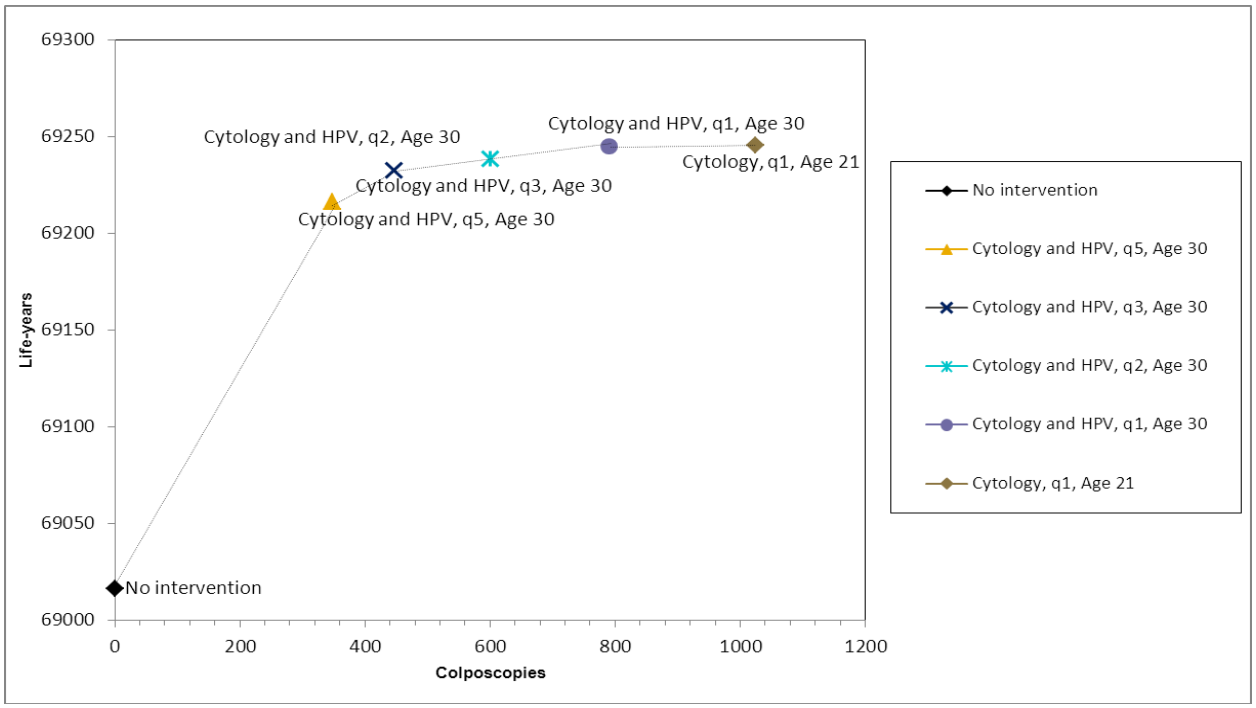
*For cytology and HPV combined strategies, women are assumed to be screened with cytology only (with a repeat cytology test for ASC-US results) before age 30 years. Strategies presented are those identified as efficient using incremental colposcopies per life-year.

Table 31b. Mayrand et al[8]: Sensitivity Analysis Showing Expected Colposcopies, Incremental Colposcopies, Life-Years, Incremental Life-Years, and Incremental Colposcopies per Life-Year for Strategies Identified as Efficient*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69016.30		
Cytology and HPV, q5, Age 30	348	348	69216.41	200.11	2
Cytology and HPV, q3, Age 30	446	98	69232.50	16.09	6
Cytology and HPV, q2, Age 30	601	155	69238.85	6.35	24
Cytology and HPV, q1, Age 30	791	190	69245.03	6.18	31
Cytology, q1, Age 21	1024	233	69245.57	0.54	431

*Per 1,000 women. Women are assumed to begin screening at age 21 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

Figure 6. Efficiency Curve Comparing Strategies Based on Cytology Either Alone or in Combination With HPV*



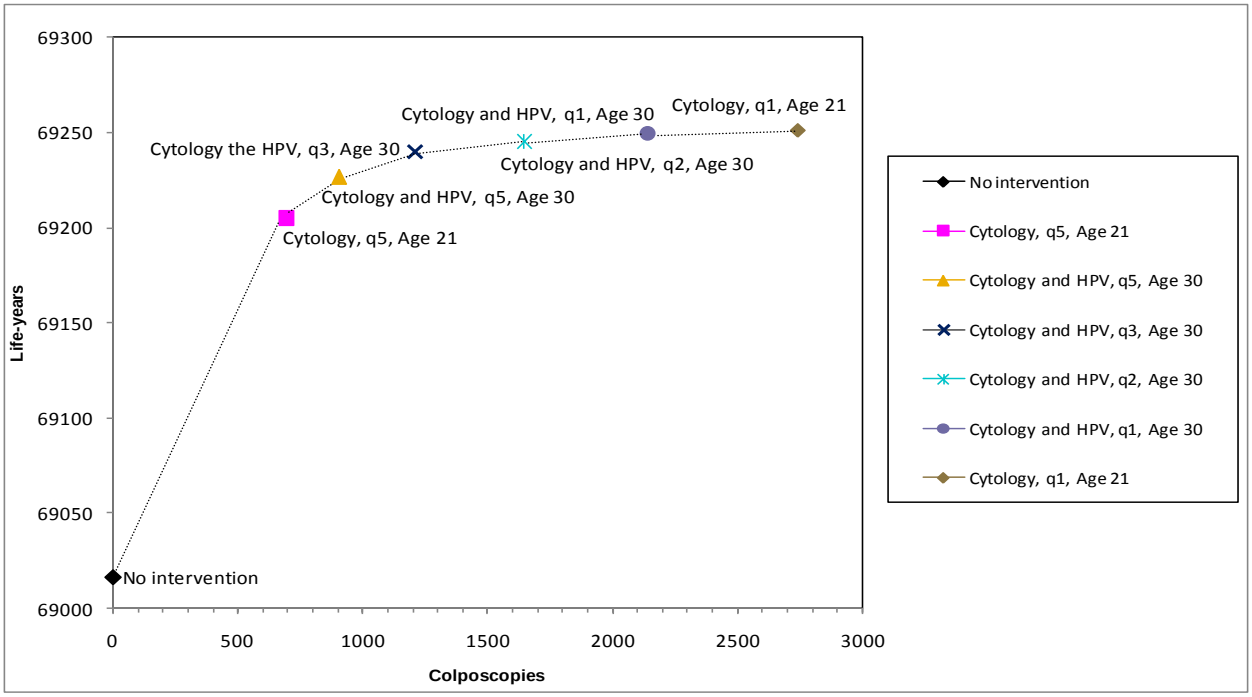
*For cytology and HPV combined strategies, women are assumed to be screened with cytology only (with a repeat cytology test for ASC-US results) before age 30 years. Strategies presented are those identified as efficient using incremental colposcopies per life-year.

Table 31c. Koliopoulos et al[36]: Sensitivity Analysis Showing Expected Colposcopies, Incremental Colposcopies, Life-Years, Incremental Life-Years, and Incremental Colposcopies per Life-Year for Strategies Identified as Efficient*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69016.30		
Cytology, q5, Age 21	694	694	69205.11	188.81	4
Cytology and HPV, q5, Age 30	907	213	69226.66	21.55	10
Cytology and HPV, q3, Age 30	1210	303	69240.14	13.48	22
Cytology and HPV, q2, Age 30	1646	436	69245.20	5.06	86
Cytology and HPV, q1, Age 30	2142	496	69249.40	4.20	118
Cytology, q1, Age 21	2744	602	69251.10	1.70	354

*Per 1,000 women. Women are assumed to begin screening at age 21 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

Figure 7. Efficiency Curve Comparing Strategies Based on Cytology Either Alone or in Combination With HPV*



*For cytology and HPV combined strategies, women are assumed to be screened with cytology only (with a repeat cytology test for ASC-US results) before age 30 years. Strategies presented are those identified as efficient using incremental colposcopies per life-year.

Key Sensitivity Analyses

1. Screening and Triage Tests per Life-Year

Table 32a. Vesco et al[35]: Sensitivity Analysis Showing Expected Tests (Screening and Triage), Incremental Tests, Life-Years, Incremental Life-Years, and Incremental Tests per Life-Year for Strategies Identified as Efficient*

Strategy	Tests	Incremental Tests	Life Years (LYs)	Incremental LYs	ITLY
No intervention	0		69016.30		
Cytology, q5, Age 21	11190	11190	69182.25	165.95	67
Cytology, q3, Age 21	18295	7105	69212.70	30.45	233
Cytology, q2, Age 21	26955	8660	69229.79	17.09	507
Cytology and HPV, q3, Age 30	31924	4969	69233.80	4.01	1239
Cytology, q1, Age 21	49887	17963	69246.58	12.78	1406

*Per 1,000 women. Age at which to begin screening is fixed at age 21 years. For the combined cytology and HPV strategies, cytology-based screening only is assumed prior to age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing begins at age 30 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

Table 32b. Mayrand et al[8]: Sensitivity Analysis Showing Expected Tests (Screening and Triage), Incremental Tests, Life-Years, Incremental Life-Years, and Incremental Tests per Life-Year for Strategies Identified as Efficient*

Strategy	Tests	Incremental Tests	Life Years (LYs)	Incremental LYs	ITLY
No intervention	0		69016.30		
Cytology, q5, Age 21	10754	10754	69179.46	163.16	66
Cytology, q3, Age 21	17593	6839	69210.24	30.78	222
Cytology, q2, Age 21	25944	8351	69227.79	17.55	476
Cytology and HPV, q3, Age 30	30797	4853	69232.50	4.71	1030
Cytology, q1, Age 21	49315	18518	69245.57	13.07	1417

*Per 1,000 women. Age at which to begin screening is fixed at age 21 years. For the combined cytology and HPV strategies, cytology-based screening only is assumed prior to age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing begins at age 30 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

Table 32c. Koliopoulos et al[36]: Sensitivity Analysis Showing Expected Tests (Screening and Triage), Incremental Tests, Life-Years, Incremental Life-Years, and Incremental Tests per Life-Year for Strategies Identified as Efficient*

Strategy	Tests	Incremental Tests	Life Years (LYs)	Incremental LYs	ITLY
No intervention	0		69016.30		
Cytology, q5, Age 21	11658	11658	69205.11	188.81	62
Cytology, q3, Age 21	18997	7339	69229.37	24.26	303
Cytology, q2, Age 21	27929	8932	69241.12	11.75	760
Cytology, q1, Age 21	50416	22487	69251.10	9.98	2253

*Per 1,000 women. Age at which to begin screening is fixed at age 21 years. For the combined cytology and HPV strategies, cytology-based screening only is assumed prior to age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing begins at age 30 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

2. Screening Every 5 Years for Women With Normal Cytology and HPV Negative Results

Table 33a. Vesco et al[35]: Sensitivity Analysis Showing Expected Colposcopies, Incremental Colposcopies, Life-Years, Incremental Life-Years, and Incremental Colposcopies per Life-Year for Strategies Identified as Efficient*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69016.30		
Cytology and HPV, q5, Age 30	535	535	69214.72	198.42	3
Cytology and HPV, q3, Age 30	825	290	69233.80	19.08	15
Cytology and HPV, q2, Age 30	1129	304	69240.06	6.26	49
Cytology and HPV, q1, Age 30	1488	359	69245.94	5.88	61
Cytology, q1, Age 21	1931	443	69246.58	0.64	692

*Per 1,000 women. Age at which to begin screening is fixed at age 21 years. For the combined cytology and HPV strategies, cytology-based screening only is assumed prior to age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing begins at age 30 years. Women with HPV negative, cytology normal test results are assumed to be screened every 3 or 5 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

Table 33b. Mayrand et al[8]: Sensitivity Analysis Showing Expected Colposcopies, Incremental Colposcopies, Life-Years, Incremental Life-Years, and Incremental Colposcopies per Life-Year for Strategies Identified as Efficient*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69016.30		
Cytology and HPV, q5, Age 30	303	303	69213.14	196.84	2
Cytology and HPV, q3, Age 30	446	143	69232.50	19.36	7
Cytology and HPV, q2, Age 30	601	155	69238.85	6.35	24
Cytology and HPV, q1, Age 30	791	190	69245.03	6.18	31
Cytology, q1, Age 21	1024	233	69245.57	0.54	431

*Per 1,000 women. Age at which to begin screening is fixed at age 21 years. For the combined cytology and HPV strategies, cytology-based screening only is assumed prior to age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing begins at age 30 years. Women with HPV negative, cytology normal test results are assumed to be screened every 3 or 5 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

Table 33c. Koliopoulos et al[36]: Sensitivity Analysis Showing Expected Colposcopies, Incremental Colposcopies, Life-Years, Incremental Life-Years, and Incremental Colposcopies per Life-Year for Strategies Identified as Efficient*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69016.30		
Cytology and HPV, q5, Age 30	773	773	69223.52	207.22	4
Cytology and HPV, q3, Age 30	1210	437	69240.14	16.62	26
Cytology and HPV, q2, Age 30	1646	436	69245.20	5.06	86
Cytology and HPV, q1, Age 30	2142	496	69249.40	4.20	118
Cytology, q1, Age 21	2744	602	69251.10	1.70	354

*Per 1,000 women. Age at which to begin screening is fixed at age 21 years. For the combined cytology and HPV strategies, cytology-based screening only is assumed prior to age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing begins at age 30 years. Women with HPV negative, cytology normal test results are assumed to be screened every 3 or 5 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

3. Natural History

Table 34a. Vesco et al[35]: Sensitivity Analysis Varying Multiple Natural History Parameters*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69074.37		
Cytology, q5, Age 21	622	622	69193.09	118.72	5
Cytology and HPV, q5, Age 30	808	186	69223.26	30.17	6
Cytology and HPV, q3, Age 30	1028	220	69235.69	12.43	18
Cytology and HPV, q2, Age 30	1342	314	69241.13	5.44	58
Cytology and HPV, q1, Age 30	1714	372	69246.53	5.40	69
Cytology, q1, Age 21	2142	428	69246.75	0.22	1945

*Refer to Appendix B for details. Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are assumed to begin screening at age 21 years. For the combined cytology and HPV strategies, cytology-based screening only is assumed prior to age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing begins at age 30 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

Table 34b. Mayrand et al[8]: Sensitivity Analysis Varying Multiple Natural History Parameters*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69074.37		
Cytology and HPV, q5, Age 30	527	527	69222.37	148.00	4
Cytology and HPV, q3, Age 30	646	119	69234.99	12.62	9
Cytology and HPV, q2, Age 30	810	164	69240.51	5.52	30
Cytology and HPV, q1, Age 30	1012	202	69246.11	5.60	36
Cytology, q1, Age 21	1239	227	69246.30	0.19	1195

*Refer to Appendix B for details. Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are assumed to begin screening at age 21 years. For the combined cytology and HPV strategies, cytology-based screening only is assumed prior to age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing begins at age 30 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

Table 34c. Koliopoulos et al[36]: Sensitivity Analysis Varying Multiple Natural History Parameters*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69074.37		
Cytology, q5, Age 21	856	856	69210.83	136.46	6
Cytology and HPV, q5, Age 30	1100	244	69229.38	18.55	13
Cytology and HPV, q3, Age 30	1426	327	69240.81	11.44	29
Cytology and HPV, q2, Age 30	1874	448	69245.51	4.70	95
Cytology and HPV, q1, Age 30	2385	511	69249.75	4.24	121
Cytology, q1, Age 21	2969	584	69251.13	1.38	423

*Refer to Appendix B for details. Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are assumed to begin screening at age 21 years. For the combined cytology and HPV strategies, cytology-based screening only is assumed prior to age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing begins at age 30 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

4. Adherence to Screening <100%[61]

Table 35a. Vesco et al[35]: Sensitivity Analysis Varying Estimates of Screening Adherence*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69016.30		
Cytology and HPV, q5, Age 30	254	254	69152.04	135.74	2
Cytology and HPV, q3, Age 30	367	112	69183.39	31.34	4
Cytology and HPV, q2, Age 30	526	160	69203.85	20.47	8
Cytology and HPV, q1, Age 30	770	243	69225.94	22.09	11

*Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Age at which to begin screening is fixed at age 21 years. For the combined cytology and HPV strategies, cytology-based screening only is assumed prior to age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing begins at age 30 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

Table 35b. Mayrand et al[8]: Sensitivity Analysis Varying Estimates of Screening Adherence*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69016.30		
Cytology and HPV, q5, Age 30	148	148	69150.17	133.87	1
Cytology and HPV, q3, Age 30	208	60	69181.46	31.29	2
Cytology and HPV, q2, Age 30	292	84	69201.93	20.47	4
Cytology and HPV, q1, Age 30	417	125	69224.30	22.37	6

*Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Age at

which to begin screening is fixed at age 21 years. For the combined cytology and HPV strategies, cytology-based screening only is assumed prior to age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing begins at age 30 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

Table 35c. Koliopoulos et al[36]: Sensitivity Analysis Varying Estimates of Screening Adherence*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69016.30		
Cytology, q5, Age 21	303	303	69140.40	124.10	2
Cytology and HPV, q5, Age 30	363	60	69160.64	20.24	3
Cytology and HPV, q3, Age 30	528	165	69191.65	31.01	5
Cytology and HPV, q2, Age 30	760	232	69211.64	19.99	12
Cytology and HPV, q1, Age 30	1114	354	69231.74	20.10	18

*Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Age at which to begin screening is fixed at age 21 years. For the combined cytology and HPV strategies, cytology-based screening only is assumed prior to age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing begins at age 30 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

5. HPV Followed By Cytology

Table 36a. Vesco et al[35]: Sensitivity Analysis Including a Strategy of HPV Followed By Cytology if HPV Positive*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69016.30		
HPV, followed by Cytology, q5, Age 30	234	234	69211.89	195.59	1
HPV, followed by Cytology, q3, Age 30	301	66	69231.50	19.61	3
HPV, followed by Cytology, q2, Age 30	423	122	69239.62	8.12	15
HPV, followed by Cytology, q1, Age 30	643	220	69247.71	8.09	27

*Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are assumed to begin screening at age 21 years. Women aged 30 years or older receive HPV testing first, followed by cytology if HPV positive. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

Table 36b. Mayrand et al[8]: Sensitivity Analysis Including a Strategy of HPV Followed By Cytology if HPV Positive*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69016.30		
HPV followed by Cytology, q5, Age 30	154	154	69211.41	195.11	1
HPV followed by Cytology, q3, Age 30	190	36	69231.08	19.67	2
HPV followed by Cytology, q2, Age 30	246	56	69239.32	8.24	7
HPV followed by Cytology, q1, Age 30	351	105	69247.51	8.19	13

*Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are assumed to begin screening at age 21 years. Women aged 30 years or older receive HPV testing first, followed by cytology if HPV positive. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

Table 36c. Koliopoulos et al[36]: Sensitivity Analysis Including a Strategy of HPV Followed By Cytology if HPV Positive*

Strategy	Colposcopies	Incremental Colposcopies	Life Years (LYs)	Incremental LYs	ICLY
No intervention	0		69016.30		
HPV followed by Cytology, q5, Age 30	334	334	69219.18	202.88	2
HPV followed by Cytology, q3, Age 30	436	102	69237.06	17.88	6
HPV followed by Cytology, q2, Age 30	632	196	69244.12	7.06	28
HPV followed by Cytology, q1, Age 30	975	343	69250.53	6.41	54
Cytology, q1, Age 21	2744	1769	69251.10	0.57	3104

*Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are assumed to begin screening at age 21 years. Women aged 30 years or older receive HPV testing first, followed by cytology if HPV positive. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

6. HPV Followed By Cytology: Tests

Table 37a. Vesco et al[35]: Sensitivity Analysis Showing Expected Tests (Screening and Triage), Incremental Tests, Life-Years, Incremental Life-Years, and Incremental Tests per Life-Year for Strategies Identified as Efficient*

Strategy	Tests	Incremental Tests	Life Years (LYs)	Incremental LYs	ITLY
No intervention	0		69016.30		
Cytology, q5, Age 21	11190	11190	69182.25	165.95	67
HPV followed by Cytology, q5, Age 30	13223	2033	69211.89	29.64	69
HPV followed by Cytology, q3, Age 30	20842	7619	69231.50	19.61	389
HPV followed by Cytology, q2, Age 30	29748	8906	69239.62	8.12	1097
HPV followed by Cytology, q1, Age 30	53079	23331	69247.71	8.09	2884

*Per 1,000 women. Women are assumed to begin screening at age 21 years. Women aged 30 years or older receive HPV testing first, followed by cytology if HPV positive. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

Table 37b. Mayrand et al[8]: Sensitivity Analysis Showing Expected Tests (Screening and Triage), Incremental Tests, Life-Years, Incremental Life-Years, and Incremental Tests per Life-Year for Strategies Identified as Efficient*

Strategy	Tests	Incremental Tests	Life Years (LYs)	Incremental LYs	ITLY
No intervention	0		69016.30		
HPV followed by Cytology, q5, Age 30	12168	12168	69211.41	195.11	62
HPV followed by Cytology, q3, Age 30	19348	7180	69231.08	19.67	365
HPV followed by Cytology, q2, Age 30	27947	8599	69239.32	8.24	1044
HPV followed by Cytology, q1, Age 30	51455	23508	69247.51	8.19	2870

*Per 1,000 women. Women are assumed to begin screening at age 21 years. Women aged 30 years or older receive HPV testing first, followed by cytology if HPV positive. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

Table 37c. Koliopoulos et al[36]: Sensitivity Analysis Showing Expected Tests (Screening and Triage), Incremental Tests, Life-Years, Incremental Life-Years, and Incremental Tests per Life-Year for Strategies Identified as Efficient*

Strategy	Tests	Incremental Tests	Life Years (LYs)	Incremental LYs	ITLY
No intervention	0		69016.30		
Cytology, q5, Age 21	11658	11658	69205.11	188.81	62
HPV followed by Cytology, q5, Age 30	14467	2809	69219.18	14.07	200
Cytology, q3, Age 21	18997	4530	69229.37	10.19	445
HPV followed by Cytology, q3, Age 30	22634	3637	69237.06	7.69	473
HPV followed by Cytology, q2, Age 30	31826	9192	69244.12	7.06	1302
Cytology, q1, Age 21	50416	18590	69251.10	6.98	2663

*Per 1,000 women. Women are assumed to begin screening at age 21 years. Women aged 30 years or older receive HPV testing first, followed by cytology if HPV positive. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.

Discussion

We conducted a decision analysis to determine the number of colposcopies per life-year associated with cervical cancer screening strategies that differed based on the age at which to start and end screening, the screening interval, and the screening test (cytology alone or in combination with HPV).

In terms of the age at which to begin screening, screening in the teens is associated with a high number of colposcopies but small gains in life expectancy. In addition, a large percentage of high-grade lesions are estimated to be CIN2, which is more likely to regress in younger women. As such, detection of CIN2-3 in this population may result in overdiagnosis and treatment. This is important because studies of cone or loop electrosurgical excision procedure treatments for CIN in reproductive-aged women have been associated with an increased risk of adverse pregnancy outcomes.[62-63] If the age at first screening is delayed past age 21 years, there is an increasing risk of cancer for each year that screening is delayed. Although these findings are relatively robust, it should be noted that the measure of colposcopies per life-year gained may be misleading in terms of the burden of screening, as well as resource use, when applied to adolescents, since the latest ASCCP guidelines recommend repeated screening prior to referral for colposcopy in women younger than age 21 years.[64] If a measure of screening cytology tests per life-year is used, screening beginning at age 21 years and conducted at least every 3 years, as currently recommended by the USPSTF, is also identified as a strategy that provides a reasonable trade-off between the burden and benefits of screening.

In terms of the age at which to end screening, these results support the current recommendation that women who have been screened frequently until age 65 years should no longer be screened. In this group, there are small gains in life expectancy associated with a large number of colposcopies. For women who have never been screened prior to age 65 years, these analyses suggest that a few additional screenings for these women, ending in the mid-70s, result in increased life expectancy; after this, there are diminishing gains in life expectancy, with large increases in the number of colposcopies.

Our results for HPV testing in conjunction with cytology demonstrate that the choice of strategy (cytology only or cytology and HPV [co-testing]) is sensitive to the metric chosen to quantify the burden of testing. Although cytology and HPV (co-testing) is identified as an efficient strategy using colposcopies per life-year, cytology-only strategies are identified as efficient if tests are used to quantify burden of screening. The analysis in which HPV testing is followed by cytology for women who are HPV positive suggests that this strategy warrants further study.

A limitation of this analysis is the use of colposcopies per life-year gained. This metric was chosen by the USPSTF as a measure that better captures the clinical burden and benefits of screening than cost per life-year. However, depending on the strategy modeled, not all women with abnormal test results are triaged to immediate colposcopy; some undergo repeat testing. As a result, our findings for some of the analyses, especially those that include HPV in addition to cytology, are sensitive to whether tests or colposcopies are used to quantify screening burden. It

is also unclear to what extent colposcopies represent a burden to women who undergo cervical cancer screening and what threshold of colposcopies per life-year gained should be used to define "high burden." A related issue is the definition of efficient in this analysis; while we highlighted strategies that fall on the steepest part of the curve, the incremental colposcopies per life-year associated with these strategies vary from one question to the next. Another issue is that the choice of strategies using this metric may not be consistent with those using the more traditional metrics of cost per life-year or cost per quality-adjusted life year (QALY). This is of particular concern, since there are known differences in costs, such as the costs of the tests examined in this report, that are not captured in these analyses. As such, the results of these analyses should be interpreted with caution and should not be directly compared with the results of other analyses that report different metrics. The extent to which "optimal" strategies identified by using a metric such as colposcopies/life-year or colonoscopies/life-year correlate with those identified by cost/life-year or cost/QALY is an important topic for further methodologic development.

Other potential limitations are the presentation of results per 1,000 women, and the small differences in disease outcomes which may well be within the margin of error associated with the different parameters used in the model. The USPSTF requested that the results be presented per 1,000 women for consistency with a previous decision analysis for colorectal cancer,[65] so that comparisons could be made. As noted, however, many of the differences in disease outcomes between the strategies, particularly cancer cases and deaths, are small and differ only when a denominator of 100,000 is used. These small differences translate into very small differences in life expectancy between strategies and underscore the fact that the greatest gains from screening will always be from screening unscreened or underscreened women.

Conclusions

In conclusion, this decision analysis supports current recommendations regarding the age at which to begin and end screening. In terms of the screening interval, strategies conducted every 3 to 5 years consistently fall on the steepest part of the efficiency frontier, suggesting that these intervals may provide a reasonable balance between the burden and benefits of screening. Strategies that include HPV in addition to cytology (co-testing) are sensitive to the use of either tests or colposcopies to quantify the burden of screening. Co-testing strategies are identified as efficient across a range of analyses and test accuracy estimates if colposcopies are used to quantify burden. However, cytology-only strategies are identified as efficient if tests are used to quantify burden. Finally, our analyses suggest that a strategy of HPV followed by cytology for HPV positive women may provide a reasonable trade-off between the burden and benefits of screening and warrants further study.

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Appendix A. Operational Decisions Made in Conjunction With the U.S. Preventive Services Task Force

The following decisions were made in conjunction with the U.S. Preventive Services Task Force.

1. **Vaccination to prevent infection with HPV.** The analysis is restricted to screening strategies only and does not include a strategy of vaccination to prevent infection with HPV.

2. **Adherence to screening, followup, and treatment.** Adherence to screening, followup, and treatment is 100 percent for the base case.

3. **HPV DNA testing.** HPV DNA testing refers to the Hybrid Capture 2 (HC2) high-risk HPV DNA test (Qiagen, Inc., Germantown, MD).

4. **Performance of colposcopy and biopsy.** Colposcopy and biopsy are assumed to be 100 percent sensitive and specific.

5. **Strategies for the analysis of age at which to begin and end screening.** This analysis is restricted to cytology-based strategies.

Appendix B. Model Description

An extensive description of the structure of the model, including the natural history and screening components, is published elsewhere.[9,17] A summary of the model is provided here, and key inputs to the model are summarized in Appendix B Tables 1 and 2.

Structure of the Model

The model has two components. The first component is a 20-state Markov model[66] that simulates the natural history of cervical cancer in the absence of screening. The second component is an intervention model that represents possible screening strategies. The model was originally developed using DATA 3.0 software (TreeAge Software, Inc., Boston, MA); updates were made using TreeAge Pro 2010, HealthCare Version (TreeAge Software, Inc., Boston, MA).

Natural History

The model follows a cohort of women from age 12 to 100 years and assumes that, at the beginning of the simulation, no one is infected with HPV or CIN1, CIN2-3, or cancer. Cycle lengths are 1 year long. Each year women can be infected with HPV. Women infected with HPV can undergo regression, no change, or progression to CIN. Although most progress from HPV to CIN1, a proportion progresses directly to CIN2-3. Women with CIN1 can undergo regression (to either "well" or the HPV-infected state), no change, or progression to CIN2-3. Women with CIN2-3 can regress, stay in the same state, or progress to Stage I cancer. Women with cancer either become symptomatic or progress through Stages II-IV. Once a cancer diagnosis is made, the probability of survival is stage-specific. Women without cancer are at risk for hysterectomy for other causes, and all women are at risk for death from other causes. The states and allowed transitions of the natural history model are summarized in Appendix B Figure 1.

Interventions

Screening Strategies

Details and assumptions for the different screening strategies modeled are presented in the Methods section.

Diagnostic Strategies for Abnormal Pap and HPV Test Results

Strategies for the followup of abnormal HPV and cytology test results are based on the 2006 American Society for Colposcopy and Cervical Pathology consensus guidelines for the management of abnormal screening tests and CIN.[33]

Measures of Effectiveness

The model is used to estimate the number of false-positives, colposcopies performed, CIN2-3 cases detected, cancer cases detected, and cancer deaths. The main outcome is colposcopies per life-year. In addition, average lifetime costs, life expectancy, and quality-adjusted life expectancy are estimated. Incremental ratios of the difference in colposcopies divided by the

difference in life expectancy were calculated in order to determine which strategies should be considered for the recommendation update.

Assumptions

Population

The model follows a cohort of U.S. women from age 12 to 100 years.

Histological Subtypes of Invasive Cervical Cancer

Squamous cancer of the cervix accounts for approximately 80 to 85 percent of invasive cervical cancer cases. Adenocarcinoma, which accounts for another 10 to 15 percent, may be increasing in incidence.[67] Cervical cytology may also be less sensitive for adenocarcinoma. However, we did not distinguish between histologic subtypes in any of the estimates for screening or treatment. This is consistent with the approach taken in the original model and also consistent with other models.

Patient and Provider Behavior

Consistent with other models, this model assumes that all women in the cohort (100 percent) receive the screening test at the appropriate interval and that all patients receive appropriate diagnostic and therapeutic interventions based on the results of the screening tests for the base-case analysis. The implications of less than perfect adherence to screening are explored in sensitivity analyses.

Parameter Estimates From Available Data

Hysterectomy for benign disease. Age-specific hysterectomy rates are based on estimates from Keshavarez et al.[68]

Incidence of HPV infection. Since estimates of test performance for HPV DNA testing are conditioned on underlying histology rather than HPV type, no distinction is made between different types of HPV. The incidence, progression, and regression estimates are averages for all viral types. The age-specific estimates for HPV incidence in the model were back-calculated in order to produce an HPV prevalence curve that is consistent with the reported literature (Appendix B Table 1 and Appendix B Figure 2).[13-15,69] In particular, the prevalence curve shows a peak in prevalence and magnitude that is similar to that reported in U.S. population-based studies by Dunne et al[13] and Kulasingam et al.[14]

Regression, persistence, and progression of HPV infection. These estimates are averaged for all types and are primarily based on the older model but confirmed with more recent studies. The one significant change is the estimate of progression from CIN2-3 to cancer. In the older model, this was estimated to be approximately 4 percent per year. In this model, we have revised the estimate for younger women (aged 30 years and younger) to reflect recent analyses that show that progression from CIN3 to cancer is approximately 1 percent per year.[25-26]

Appendix B. Model Description

Revised natural history model to account for different progression and regression rates of CIN. Estimates for progression and regression between low-grade and high-grade neoplasia are from the original model as well as an updated review of the literature. Historically, CIN has been viewed as a continuum, with progression from HPV infection to CIN1, CIN2, and CIN 3 assumed to take place over a period of decades, representing a slow progression of disease. The original model was developed to represent this view of CIN. Recently, however, studies suggest that CIN1 and CIN2-3 may be established separately, and that young women can develop a CIN2-3 lesion within a short period of time (2 years).[23,70-72] Based on these studies as well as others, Baseman and Koutsky have proposed a revised view of CIN, with an early establishment of high-grade lesions, but the majority regressing, with only a minority progressing.[24] However, since it is unclear whether this view of the natural history is applicable to all women, we developed a model that reflects a higher burden of disease in young women in particular, but with most of the disease regressing, and only a small proportion progressing per year. Details of the estimates used are presented in Appendix B Table 2. The model was calibrated to produce an HPV prevalence curve and cancer incidence and mortality curve similar to those observed in large screening studies and SEER data (Appendix B Figures 3-7). Assuming that most women undergo screening at least every 3 years, the model predicts a lifetime risk of developing cancer of 0.63 and a lifetime risk of dying from cancer of 0.17, compared to the SEER estimates of 0.672 and 0.23, respectively.[58]

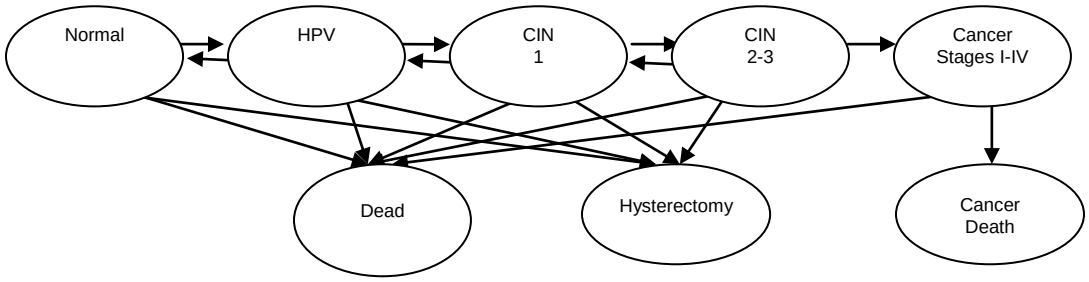
Natural history of invasive cancer. Estimates of the progression rate and the likelihood of symptoms (since cases would only be detected upon presentation with symptoms) by stage are from the original model and presented in Appendix B Table 3. These estimates were used for both natural history models.

Stage-specific survival. Survival probabilities at 1, 2, 3, 4, and 5 years post-diagnosis for each stage are from SEER data.[60] Five-year survival rates based on these data are: Stage I (local), 91.3 percent; Stages II-III (regional), 54 percent; and Stage IV (distant), 15.8 percent. An assumption is made that there is no cancer-related mortality after 5 years. This assumption is consistent with the original version of the model and also allows for comparison with other models. In a sensitivity analysis, ratios of relative survival for women aged 50 to 69 years and 70 years and older compared to ratios of overall survival were calculated to address the issue of decreased survival in these older age groups. These ratios were 0.97 (for women aged 50 to 69 years) and 0.93 (for women aged 70 years and older) for Stage I; 1.03 and 0.78, respectively, for Stage II-III; and 0.81 and 0.65, respectively, for Stage IV.

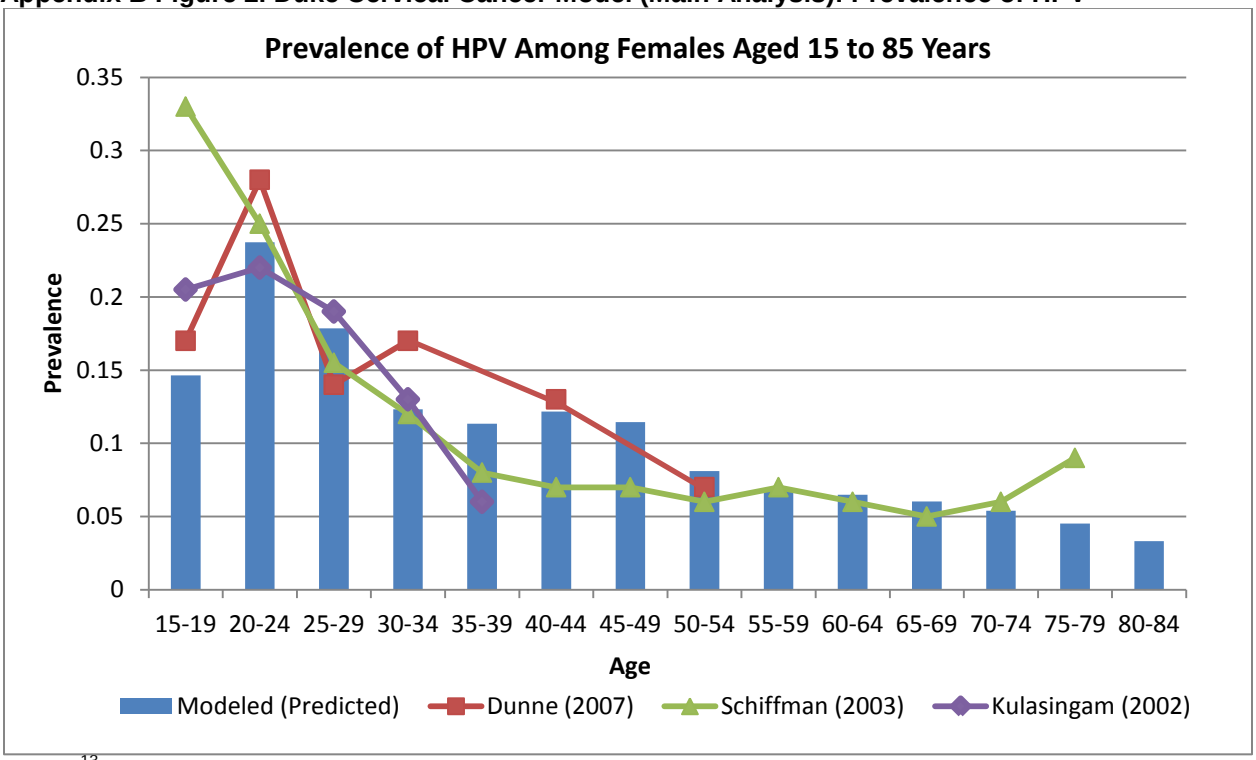
Non-cervical cancer mortality. Mortality from causes other than cervical cancer is estimated by subtracting age-specific cervical cancer mortality rates from age-specific all-cause mortality rates using U.S. life tables for women.[78]

Appendix B. Model Description

Appendix B Figure 1. Disease States and Allowed Transitions for the Natural History Component of the Cervical Cancer Markov Model



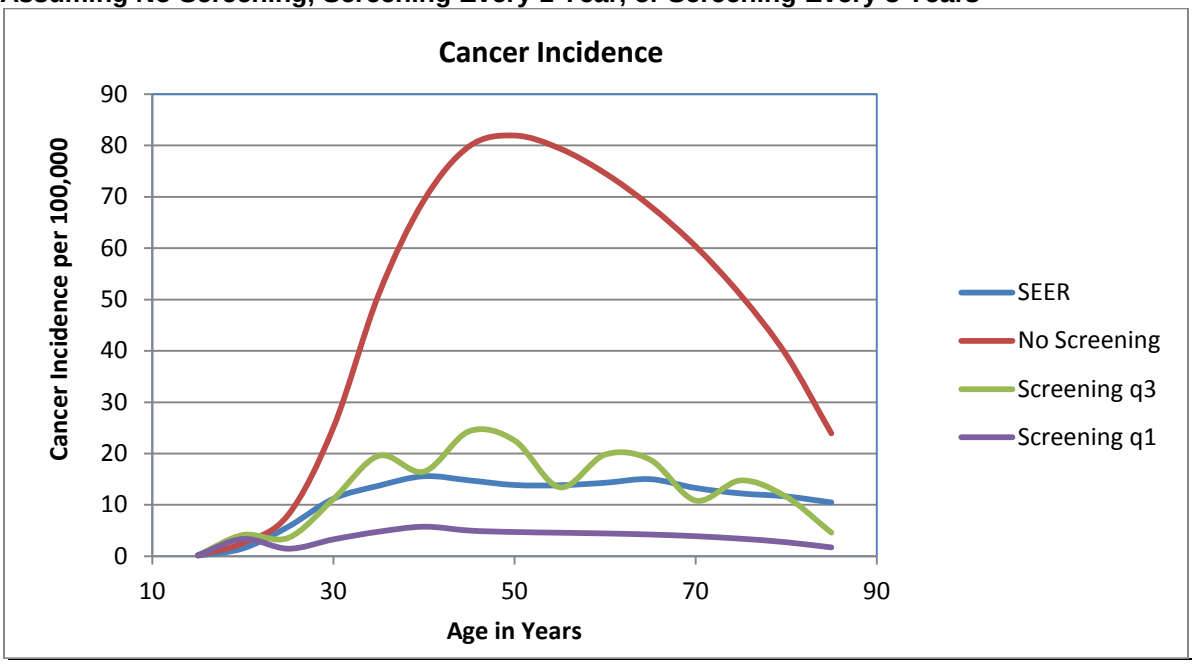
Appendix B Figure 2. Duke Cervical Cancer Model (Main Analysis): Prevalence of HPV*



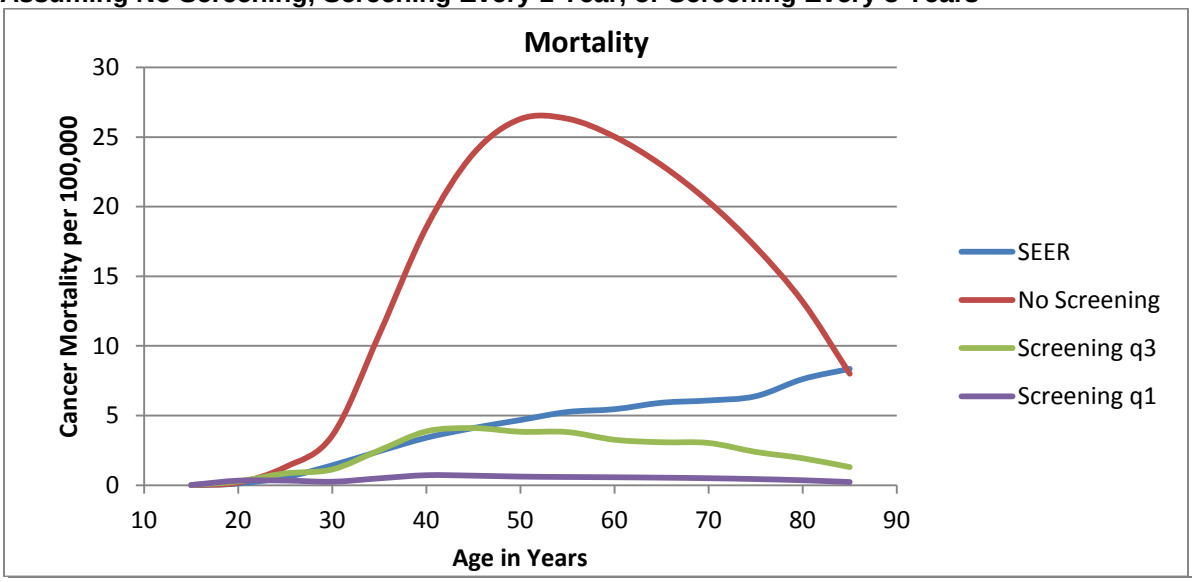
*Dunne[13] prevalence estimates are measured in 10-year increments beginning at age 30 years (30-39, 40-49, and 50-59). Kulasingam[14] estimates are measured in 5-year increments up to age 34 years, with the final estimate (0.06) measuring prevalence for ages 35 years and older.

Appendix B. Model Description

Appendix B Figure 3. Duke Cervical Cancer Model: SEER Age-Specific Cancer Incidence Assuming No Screening, Screening Every 1 Year, or Screening Every 3 Years

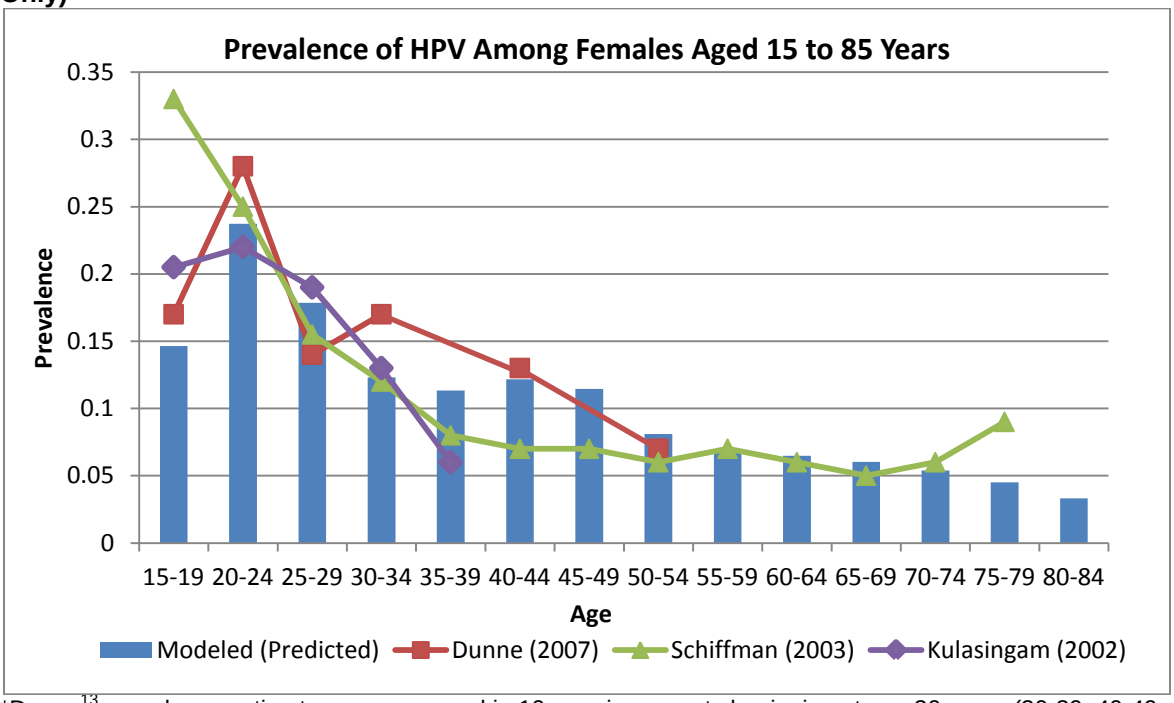


Appendix B Figure 4. Duke Cervical Cancer Model: SEER Age-Specific Cancer Mortality Assuming No Screening, Screening Every 1 Year, or Screening Every 3 Years



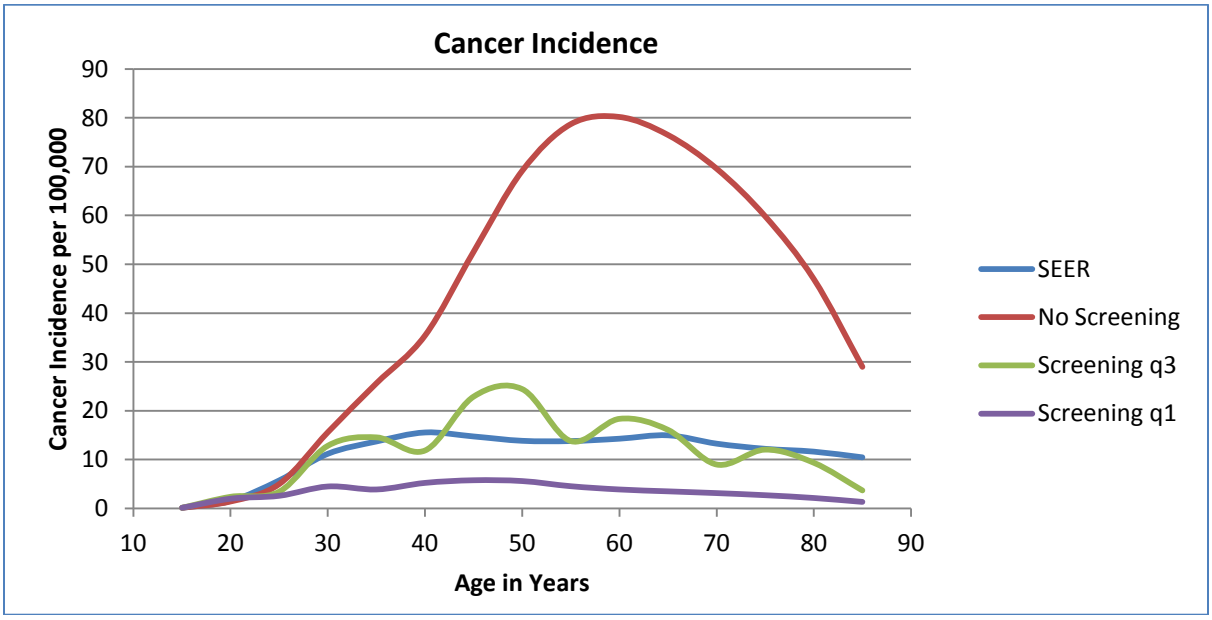
Appendix B. Model Description

Appendix B Figure 5. Prevalence of HPV-Revised Natural History Model (Sensitivity Analysis Only)[13-15]



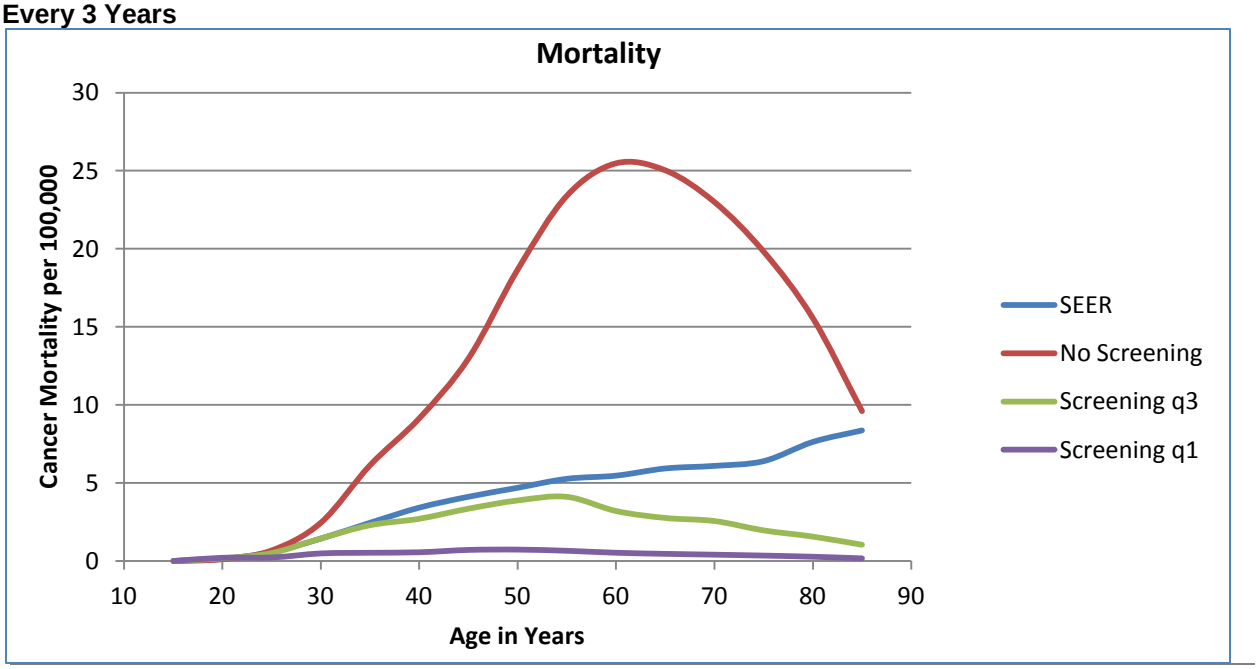
*Dunne[13] prevalence estimates are measured in 10-year increments beginning at age 30 years (30-39, 40-49, and 50-59). Kulasingam[14] estimates are measured in 5-year increments up to age 34 years, with the final estimate (0.06) measuring prevalence for ages 35 years and older.

Appendix B Figure 6. Revised Natural History Model (Sensitivity Analysis Only): SEER Age-Specific Cancer Incidence Assuming No Screening, Screening Every 1 Year, or Screening Every 3 Years



Appendix B. Model Description

Appendix B Figure 7. Revised Natural History Model (Sensitivity Analysis Only): SEER Age-Specific Cancer Mortality Assuming No Screening, Screening Every 1 Year, or Screening Every 3 Years



Appendix B Table 1. Estimates of Incidence, Progression, and Regression Applied to HPV and CIN States in Markov Model

Parameters	Age	Value
Uninfected to cervical HPV infection (age-specific incidence)	12	0
	13	0.01
	14	0.05
	15	0.1
	16	0.1
	17	0.12
	18	0.15
	19	0.17
	20	0.15
	21	0.12
	22	0.1
	23	0.1
	24-29	0.05
	30-49	0.01
	50	0.005
HPV to well	15-24	0.7
	25-29	0.5
	30-39	0.25
	40-49	0.15
	50+	0.05
HPV to CIN1 (0.9) or CIN2-3 (0.1)	--	0.06
CIN1 to HPV (0.1) or well (0.9)	15-34	0.10
	35+	0.06
Progression rate of CIN1 to CIN2-3	15-34	0.02
	35+	0.06
Regression rate of CIN2-3 to CIN1 (0.5) or well (0.5)	--	0.06
Progression rate of CIN2-3 to cancer	12-29	0.01
	30+	0.04

Appendix B. Model Description

Appendix B Table 2. Estimates of Incidence, Progression, and Regression Applied to HPV and CIN States in Markov Model

Parameters	Age	Value
Uninfected to cervical HPV infection (age-specific incidence)[16,23,71]	10	0
	13	0.01
	14	0.05
	15	0.1
	16	0.1
	17	0.12
	18	0.15
	19	0.17
	20	0.15
	24	0.1
	30	0.05
	50	0.03
HPV to well	15-24	0.37
	25-34	0.37
	35+	0.23
HPV to CIN1 (0.9 to 0.5) or CIN2-3 (0.1 to 0.5)	--	0.095
Proportion of HPV to CIN1	12	0.9
	25	0.5
Proportion of HPV to CIN2-3	12	0.1
	25	0.5
CIN1 to HPV (0.1) or well (0.9)	12-24	0.31
	25-29	0.12
	30+	0.06
Progression rate of CIN1 to CIN2-3[73-74]	15-19	0.01
	20-34	0.02
	35+	0.06
Regression rate of CIN2-3 to CIN1 (0.5) or well (0.5)[75-77]	12	0.22
	30	0.12
	40	0.01
Progression rate of CIN2-3 to cancer[25-26]	12-29	0.01
	30+	0.04

Appendix B. Model Description

Appendix B Table 3. Estimates of Symptoms, Progression, and Survival Used for Invasive Cervical Cancer States in Markov Model

State	Probability	Time Period
Stage I		
Progression	0.9	4 years
Probability of symptoms	0.15	1 year
Stage II		
Progression	0.9	3 years
Probability of symptoms	0.225	1 year
Stage III		
Progression	0.9	2 years
Probability of symptoms	0.6	1 year
Stage IV		
Probability of symptoms	0.9	1 year
Stage I		
Year 1	0.986	1 year
Year 2	0.958	1 year
Year 3	0.938	1 year
Year 4	0.929	1 year
Year 5	0.913	1 year
Stage II-III		
Year 1	0.862	1 year
Year 2	0.708	1 year
Year 3	0.621	1 year
Year 4	0.562	1 year
Year 5	0.536	1 year
Stage IV		
Year 1	0.516	1 year
Year 2	0.302	1 year
Year 3	0.220	1 year
Year 4	0.166	1 year
Year 5	0.158	1 year

Appendix C. Selection Criteria for Studies Used to Estimate Sensitivity and Specificity of Cytology and HPV DNA Testing

The inclusion criteria for selecting studies identified by the Oregon EPC[35] and used in the calculation of sensitivity and specificity are described below. The final estimates were chosen based on discussions with the AHRQ Medical Officer and Program Officer and reviewed by the Oregon EPC to confirm that they reflected the evidence report.

In the absence of the availability of summary estimates from a meta-analysis, we used the following criteria to identify estimates for use in the model.

1. **Was the study conducted in a population similar in risk to the U.S. general population?** To determine applicability to the United States, we used the Oregon EPC rating of studies as poor, fair, or good applicability. Studies rated as poor, because they were conducted in countries such as India or South Africa, were eliminated from consideration for use in the model, since estimates of test performance from these populations may not reflect performance in a low risk population, taking into account disease prevalence and familiarity with using the test.
2. **Was the study graded as good quality by the Oregon EPC?** We chose studies for the base-case analysis that were graded as good quality and provided estimates of absolute sensitivity and specificity from among the studies that were identified as having fair to good applicability to a U.S. population.

3) **Cytology and HPV DNA test with HC2 test performance characteristics.** Since there were only a few studies that fit these criteria (Kulasingam et al and Coste et al), we used a weighted average of the two to determine the base estimates of sensitivity and specificity for cytology.[14,40] However, since two additional studies showed a consistent difference between cytology and HPV DNA test accuracy (Mayrand et al and Bigras et al), we used a weighted average of these two studies to determine the incremental gain in sensitivity and decrease in specificity compared to cytology only.[8,37] These estimates are presented in Table 2 in the body of the report. Since the study by Mayrand et al had the largest difference in test accuracy performance for HPV and cytology, we used these estimates as well as the Koliopoulos et al estimates (detailed below) for the HPV analyses.[8,36] In total, three sets of test accuracy estimates were used for the HPV analyses. We used ranges from these studies, as well as those rated as fair quality to estimate the ranges of test sensitivity and specificity for the sensitivity analyses for Specific Aim 1 (age at which to begin screening) and Sub-Aim 1 (age at which to end screening).

   a. Estimates from Koliopoulos et al were also used in the HPV analyses, since these were from a meta-analysis of a wide variety of studies comparing HPV and cytology.[36]

   b. Base estimates and ranges for HC2 and cytology test performance among women with ASCUS were based on studies identified by the Oregon EPC. The suggested estimates for use in the base case were those from a single study (Manos et al) that compared both technologies that were rated as good applicability and graded as a good quality study.[44] The ranges for sensitivity and specificity are from other studies that provided relevant estimates for at least one of the technologies (cytology or HC2).

Addendum

Summary of New Analyses

The model analyses presented here were performed after the publication of the original report. These new analyses are based on a strategy of screening with cytology every 3 years (q3) before age 30 years and then after age 30 years, co-testing every 5 years (q5) in women with HPV negative/cytology normal results (referred to as "Cytology, q3, age 21; Cytology and HPV, q5, age 30").

As shown in the outcomes tables, this strategy only dominates cytology conducted every 3 years (based on a comparison of expected colposcopies and cancer), using estimates from Mayrand et al (8) and Vesco et al (35).

Sensitivity analyses show that whether co-testing strategies conducted at different intervals are identified as "efficient" depends on the metric used to quantify burden (HPV testing or expected colposcopies). The results are also sensitive to whether a strategy of HPV testing followed by cytology in women who test HPV positive is modeled. This strategy dominates co-testing regardless of whether HPV testing or expected colposcopies is used to quantify burden.

Modeling Strategies

HPV and Cytology (Co-testing)

For this strategy, women younger than age 30 years are assumed to be screened with cytology only, with repeat cytology for ASC-US results or referral to immediate colposcopy for results of ASC-H or LSIL+. The interval for screening before age 30 years varied from 1 to 3 years. Women ages 30 years and older are assumed to receive HPV testing and cytology. Women with LSIL+ cytology results or ASC-US cytology results with a positive HPV test result are assumed to be referred to colposcopy. Women with an ASC-US cytology result who have a negative HPV test result are assumed to undergo repeat testing in 1 year. Women with a normal cytology test result but a positive HPV test result are assumed to undergo repeat testing with both tests in 1 year, and if either is abnormal they are referred to colposcopy. Women with normal cytology and negative HPV test results are assumed to return to routine screening conducted every 3 or 5 years. It should be noted that for this strategy, "routine screening" means a combination of intervals; that is, screening every 1, 2, or 3 years before age 30 in women with normal cytology results, and then every 3 or 5 years in women with normal cytology and HPV test results after age 30. Women are assumed to begin screening at age 21 years and to continue screening to age 85 years.

HPV Followed by Cytology

For this strategy, women younger than age 30 years are assumed to be screened with cytology only, with repeat cytology for ASC-US results or referral to immediate colposcopy for results of ASC-H or LSIL+. All women ages 30 years and older are assumed to have an initial HPV test. Women who are HPV positive are assumed to receive cytology testing. If their cytology test result is ASC-US+, they are assumed to undergo colposcopy; if their cytology test result is normal, they are assumed to undergo repeat testing in 1 year, with referral to colposcopy if they have a subsequent abnormality. Women with negative HPV results are assumed to return to

routine HPV-based screening conducted every 1, 2, 3, or 5 years. Women are assumed to begin screening at age 21 years and to continue screening to age 85 years.

Table 1. Sensitivity and Specificity of Cytology and HPV Testing for Primary Screening and Triage of Abnormal Cytology Results

Screening or Triage Test	Sensitivity for CIN2+	Specificity for <CIN2	Delta of HPV Compared to Cytology in Same Study	
			Sensitivity (CIN2+)	Specificity (CIN2+)
Cytology				
EPC-QRS (2011)[35]	0.569	0.945		
Mayrand et al (2007)[8]	0.564	0.973		
Koliopoulos et al (2007)[36]	0.727	0.919		
Range[8,37,41-43]	0.20–0.772	0.847–0.990		
Triage for ASC-US[44]	0.762	0.638		
Range[45-47]	0.45–0.956	0.475–0.756		
HPV DNA (HC2)				
EPC-QRS (2011)[35]	0.964	0.906	0.395	-0.039
Mayrand et al (2007)[8]	0.974	0.943	0.41	-0.03
Koliopoulos et al (2007)[36]	0.948	0.86	0.221	-0.059
Range[8,37,41-43]	0.341–1.00	0.767–0.966		
Triage for ASC-US[44]	0.892	0.641	0.13	0.003
Range[45-47]	0.67–0.976	0.31–0.672		

Outcomes Tables

Table 2. Vesco et al[35]: Expected False Positives, Colposcopies, CIN2-3 Cases, Cancer Cases, and Cancer Deaths Associated With Cytology and HPV Test-Based Strategies, Either Alone or in Combination*

Strategy	False Positives	Colposcopies	CIN2-3 Cases	Cancer Cases	Cancer Deaths
Cytology, q3, age 21; Cytology and HPV, q5, age 30	255.35	575.46	84.39	7.44	1.35
Cytology, q5, age 21	213.97	483.36	66.01	12.69	2.71
Cytology, q3, age 21; Cytology and HPV, q3, age 30	381.33	824.74	93.10	4.73	0.74
Cytology, q3, age 21	349.92	758.16	80.21	8.50	1.55
Cytology, q2, age 21; Cytology and HPV, q3, age 30	539.64	1129.39	94.39	3.64	0.52
Cytology, q2, age 21	515.26	1083.52	87.52	5.80	0.92
Cytology, q1, age 21; Cytology and HPV, q3, age 30	727.22	1488.19	95.19	2.57	0.35
Cytology, q1, age 21	951.45	1931.00	91.50	2.50	0.32

* Per 1,000 women. Time horizon is a lifetime. Age at which to begin screening is fixed at 21 years. For the combined cytology and HPV testing strategies, cytology-based screening is assumed before age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing begins at age 30 years. Women with normal cytology results and HPV negative results are assumed to be screened every 3 or 5 years.

Addendum

Table 3. Mayrand et al[8]: Expected False Positives, Colposcopies, CIN2-3 Cases, Cancer Cases, and Cancer Deaths Associated With Cytology and HPV Test-Based Strategies, Either Alone or in Combination*

Strategy	False Positives	Colposcopies	CIN2-3 Cases	Cancer Cases	Cancer Deaths
Cytology, q3, age 21; Cytology and HPV, q5, age 30	117.70	323.00	86.36	7.74	1.42
Cytology, q5, age 21	100.94	274.01	66.93	13.15	2.81
Cytology, q3; age 21; Cytology and HPV, q3, age 30	175.67	446.38	96.53	5.02	0.79
Cytology, q3, age 21	165.52	416.44	82.61	8.97	1.65
Cytology, q2, age 21; Cytology and HPV, q3, age 30	252.91	600.90	99.35	3.94	0.57
Cytology, q2, age 21	244.38	580.58	91.71	6.24	0.99
Cytology, q1, age 21; Cytology and HPV, q3, age 30	348.59	790.56	101.93	2.82	0.38
Cytology, q1, age 21	464.75	1024.42	99.89	2.79	0.36

* Per 1,000 women. Time horizon is a lifetime. Age at which to begin screening is fixed at 21 years. For the combined cytology and HPV testing strategies, cytology-based screening is assumed before age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing begins at age 30 years. Women with normal cytology results and HPV negative results are assumed to be screened every 3 or 5 years.

Table 4. Koliopoulos et al[36]: Expected False Positives, Colposcopies, CIN2-3 Cases, Cancer Cases, and Cancer Deaths Associated With Cytology and HPV Test-Based Strategies, Either Alone or in Combination*

Strategy	False Positives	Colposcopies	CIN2-3 Cases	Cancer Cases	Cancer Deaths
Cytology, q3, age 21; Cytology and HPV, q5, age 30	401.90	832.28	85.13	6.62	1.08
Cytology, q5, age 21	328.93	693.97	74.85	9.76	1.86
Cytology, q3; age 21; Cytology and HPV, q3, age 30	600.89	1209.54	92.36	3.94	0.53
Cytology, q3, age 21	535.05	1090.56	86.16	5.98	0.95
Cytology, q2, age 21; Cytology and HPV, q3, age 30	834.47	1646.02	92.33	2.86	0.36
Cytology, q2, age 21	784.70	1563.96	90.13	3.79	0.51
Cytology, q1, age 21; Cytology and HPV, q3, age 30	1101.24	2141.58	91.41	1.92	0.23
Cytology, q1, age 21	1409.78	2744.25	88.30	1.37	0.16

* Per 1,000 women. Time horizon is a lifetime. Age at which to begin screening is fixed at 21 years. For the combined cytology and HPV testing strategies, cytology-based screening is assumed before age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing begins at age 30 years. Women with normal cytology results and HPV negative results are assumed to be screened every 3 or 5 years.

Addendum

Table 5. Vesco et al[35]: Expected Colposcopies, Incremental Colposcopies, Life-Years, Incremental Life-Years, and Incremental Colposcopies per Life-Year (ICLY) for Strategies Identified as Efficient*

Strategy	Colposcopies	Incremental Colposcopies	Life-Years	Incremental Life-Years	ICLY
No intervention	0		69016.30		
Cytology, q3, age 21; Cytology and HPV, q5, age 30	575	575	69217.77	201.47	3
Cytology, q3, age 21; Cytology and HPV, q3, age 30	825	249	69233.80	16.03	16
Cytology, q2, age 21; Cytology and HPV, q3, age 30	1129	305	69240.06	6.27	49
Cytology, q1, Age 21; Cytology and HPV, q3, age 30	1488	359	69245.94	5.88	61
Cytology, q1, age 21	1931	443	69246.58	0.64	690

*Per 1,000 women. Women are assumed to begin screening at age 21 years.

Table 6. Mayrand et al[8]: Expected Colposcopies, Incremental Colposcopies, Life-Years, Incremental Life-Years, and Incremental Colposcopies per Life-Year (ICLY) for Strategies Identified as Efficient*

Strategy	Colposcopies	Incremental Colposcopies	Life-Years	Incremental Life-Years	ICLY
No intervention	0		69016.30		
Cytology, q3, age 21; Cytology and HPV, q5, age 30	323	323	69216.10	199.80	2
Cytology, q3, age 21; Cytology and HPV, q3, age 30	446	123	69232.50	16.40	8
Cytology, q2, age 21; Cytology and HPV, q3, age 30	601	155	69238.85	6.35	24
Cytology, q1, age 21; Cytology and HPV, q3, age 30	791	190	69245.03	6.19	31
Cytology, q1, age 21	1024	234	69245.57	0.54	433

*Per 1,000 women. Women are assumed to begin screening at age 21 years.

Table 7. Koliopoulos et al[36]: Expected Colposcopies, Incremental Colposcopies, Life-Years, Incremental Life-Years, and Incremental Colposcopies per Life-Year (ICLY) for Strategies Identified as Efficient*

Strategy	Colposcopies	Incremental Colposcopies	Life-Years	Incremental Life-Years	ICLY
No intervention	0		69016.30		
Cytology, q5, age 21	694	694	69205.11	188.81	4
Cytology, q3, age 21; Cytology and HPV, q5, age 30	832	138	69226.18	21.07	7
Cytology, q3, age 21; Cytology and HPV, q3, age 30	1210	377	69240.14	13.96	27
Cytology, q2, age 21; Cytology and HPV, q3, age 30	1646	436	69245.20	5.06	86
Cytology, q1, age 21; Cytology and HPV, q3, age 30	2142	496	69249.40	4.21	118
Cytology, q1, age 21	2744	603	69251.10	1.70	355

*Per 1,000 women. Women are assumed to begin screening at age 21 years.

Addendum

Sensitivity Analyses

Table 8. Vesco et al[35]: Expected Tests (Screening and Triage), Incremental Tests, Life-Years, Incremental Life-Years, and Incremental Tests per Life-Year (ITLY) for Strategies Identified as Efficient*

Strategy	Tests	Incremental Tests	Life-Years	Incremental Life-Years	ITLY
No intervention	0		69016.30		
Cytology, q5, age 21	11190	11190	69182.25	165.95	67
Cytology, q3, age 21	18295	7105	69212.70	30.45	233
Cytology, q3, age 21; Cytology and HPV, q5, age 30	20341	2046	69217.77	5.07	404
Cytology, q2, age 21	26955	6614	69229.79	12.02	550
Cytology, q3, age 21; Cytology and HPV, q3, age 30	31924	4969	69233.80	4.01	1239
Cytology, q1, age 21	49887	17963	69246.58	12.78	1406

* Per 1,000 women. Age at which to begin screening is fixed at 21 years. For the combined cytology and HPV testing strategies, cytology-based screening is assumed before age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing is assumed to begin at age 30 years.

Table 9. Mayrand et al[8]: Expected Tests (Screening and Triage), Incremental Tests, Life-Years, Incremental Life-Years, and Incremental Tests per Life-Year (ITLY) for Strategies Identified as Efficient*

Strategy	Tests	Incremental Tests	Life-Years	Incremental Life-Years	ITLY
No intervention	0		69016.30		
Cytology, q5, age 21	10754	10754	69179.46	163.16	66
Cytology, q3, age 21	17593	6839	69210.24	30.78	222
Cytology, q3, age 21; Cytology and HPV, q5, age 30	19619	2026	69216.10	5.86	346
Cytology, q2, age 21	25944	6325	69227.79	11.69	541
Cytology, q3, age 21; Cytology and HPV, q3, age 30	30797	4853	69232.50	4.71	1030
Cytology, q1, age 21	49315	18518	69245.57	13.07	1417

* Per 1,000 women. Age at which to begin screening is fixed at 21 years. For the combined cytology and HPV testing strategies, cytology-based screening is assumed before age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing is assumed to begin at age 30 years.

Table 10. Koliopoulos et al[36]: Expected Tests (Screening and Triage), Incremental Tests, Life-Years, Incremental Life-Years, and Incremental Tests per Life-Year (ITLY) for Strategies Identified as Efficient*

Strategy	Tests	Incremental Tests	Life-Years	Incremental Life-Years	ITLY
No intervention	0		69016.30		
Cytology, q5, age 21	11658	11658	69205.11	188.81	62
Cytology, q3, age 21	18997	7339	69229.37	24.26	303
Cytology, q2, age 21	27929	8932	69241.12	11.75	760
Cytology, q1, age 21	50416	22487	69251.10	9.98	2253

* Per 1,000 women. Age at which to begin screening is fixed at 21 years. For the combined cytology and HPV testing strategies, cytology-based screening is assumed before age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing is assumed to begin at age 30 years.

Addendum

Table 11. Vesco et al[35]: Expected Colposcopies, Incremental Colposcopies, Life-Years, Incremental Life-Years, and Incremental Colposcopies per Life-Year (ICLY) for Strategies Identified as Efficient*

Strategy	Colposcopies	Incremental Colposcopies	Life-Years	Incremental Life-Years	ICLY
No intervention	0		69016.30		
Cytology, q5, age 21; Cytology and HPV, q5, age 30	535	535	69214.72	198.42	3
Cytology, q3, age 21; Cytology and HPV, q5, age 30	575	40	69217.77	3.05	13
Cytology, q3, age 21; Cytology and HPV, q3, age 30	825	250	69233.80	16.03	16
Cytology, q2, age 21; Cytology and HPV, q3, age 30	1129	304	69240.06	6.26	49
Cytology, q1, age 21; Cytology and HPV, q3, age 30	1488	359	69245.94	5.88	61
Cytology, q1, age 21	1931	443	69246.58	0.64	692

* Per 1,000 women. Age at which to begin screening is fixed at 21 years. For the combined cytology and HPV testing strategies, cytology-based screening is assumed before age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing is assumed to begin at age 30 years.

Table 12. Mayrand et al[8]: Expected Colposcopies, Incremental Colposcopies, Life-Years, Incremental Life-Years, and Incremental Colposcopies per Life-Year (ICLY) for Strategies Identified as Efficient*

Strategy	Colposcopies	Incremental Colposcopies	Life-Years	Incremental Life-Years	ICLY
No intervention	0		69016.30		
Cytology, q5, age 21; Cytology and HPV, q5, age 30	303	303	69213.14	196.84	2
Cytology, q3, age 21; Cytology and HPV, q5, age 30	323	20	69216.10	2.96	7
Cytology, q3, age 21; Cytology and HPV, q3, age 30	446	123	69232.50	16.40	8
Cytology, q2, age 21; Cytology and HPV, q3, age 30	601	155	69238.85	6.35	24
Cytology, q1, age 21; Cytology and HPV, q3, age 30	791	190	69245.03	6.18	31
Cytology, q1, age 21	1024	233	69245.57	0.54	431

* Per 1,000 women. Age at which to begin screening is fixed at 21 years. For the combined cytology and HPV testing strategies, cytology-based screening is assumed before age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing is assumed to begin at age 30 years.

Addendum

Table 13. Koliopoulos et al[36]: Expected Colposcopies, Incremental Colposcopies, Life-Years, Incremental Life-Years, and Incremental Colposcopies per Life-Year (ICLY) for Strategies Identified as Efficient*

Strategy	Colposcopies	Incremental Colposcopies	Life-Years	Incremental Life-Years	ICLY
No intervention	0		69016.30		
Cytology, q5, Age 21; Cytology and HPV, q5, Age 30	773	773	69223.52	207.22	4
Cytology, q3, Age 21; Cytology and HPV, q5, Age 30	832	59	69226.18	2.66	22
Cytology, q3, Age 21; Cytology and HPV, q3, Age 30	1210	378	69240.14	13.96	27
Cytology, q2, Age 21; Cytology and HPV, q3, Age 30	1646	436	69245.20	5.06	86
Cytology, q1, Age 21; Cytology and HPV, q3, Age 30	2142	496	69249.40	4.20	118
Cytology, q1, Age 21	2744	602	69251.10	1.70	354

* Per 1,000 women. Age at which to begin screening is fixed at 21 years. For the combined cytology and HPV testing strategies, cytology-based screening is assumed before age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing is assumed to begin at age 30 years.

Table 14. Vesco et al[35]: Sensitivity Analysis Varying Multiple Natural History Parameters*

Strategy	Colposcopies	Incremental Colposcopies	Life-Years	Incremental Life-Years	ICLY
No intervention	0		69074.37		
Cytology, q3, age 21; Cytology and HPV, q5, age 30	758	758	69222.11	147.74	5
Cytology, q3, age 21; Cytology and HPV, q3, age 30	1028	270	69235.69	13.58	20
Cytology, q2, age 21; Cytology and HPV, q3, age 30	1342	314	69241.13	5.44	58
Cytology, q1, age 21; Cytology and HPV, q3, age 30	1714	372	69246.53	5.40	69
Cytology, q1, age 21	2142	428	69246.75	0.22	1945

* Refer to Appendix B for details. Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are assumed to begin screening at age 21 years. For the combined cytology and HPV strategies, cytology-based screening is assumed before age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing is assumed to begin at age 30 years.

Table 15. Mayrand et al[8]: Sensitivity Analysis Varying Multiple Natural History Parameters*

Strategy	Colposcopies	Incremental Colposcopies	Life-Years	Incremental Life-Years	ICLY
No intervention	0		69074.37		
Cytology, q3, age 21; Cytology and HPV, q5, age 30	502	502	69221.28	146.91	3
Cytology, q3, age 21; Cytology and HPV, q3, age 30	646	144	69234.99	13.71	11
Cytology, q2, age 21; Cytology and HPV, q3, age 30	810	164	69240.51	5.52	30
Cytology, q1, age 21; Cytology and HPV, q3, age 30	1012	202	69246.11	5.60	36
Cytology, q1, age 21	1239	227	69246.30	0.19	1195

* Refer to Appendix B for details. Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are assumed to begin screening at age 21 years. For the combined cytology and HPV strategies, cytology-based screening is assumed before age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing is assumed to begin at age 30 years.

Addendum

Table 16. Koliopoulos et al[36]: Sensitivity Analysis Varying Multiple Natural History Parameters*

Strategy	Colposcopies	Incremental Colposcopies	Life-Years	Incremental Life-Years	ICLY
No intervention	0		69074.37		
Cytology, q5, age 21	856	856	69210.82	136.45	6
Cytology, q3, age 21; Cytology and HPV, q5, age 30	1027	171	69228.57	17.75	10
Cytology, q3, age 21; Cytology and HPV, q3, age 30	1426	399	69240.81	12.24	33
Cytology, q2, age 21; Cytology and HPV, q3, age 30	1874	448	69245.51	4.70	95
Cytology, q1, age 21; Cytology and HPV, q3, age 30	2385	511	69249.75	4.24	121
Cytology, q1, age 21	2969	584	69251.13	1.38	423

* Refer to Appendix B for details. Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are assumed to begin screening at age 21 years. For the combined cytology and HPV strategies, cytology-based screening is assumed before age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing is assumed to begin at age 30 years.

Table 17. Vesco et al[35]: Sensitivity Analysis Varying Estimates of Screening Adherence*

Strategy	Colposcopies	Incremental Colposcopies	Life-Years	Incremental Life-Years	ICLY
No intervention	0		69016.30		
Cytology, q3, age 21; Cytology and HPV, q5, age 30	262	262	69155.13	138.83	2
Cytology, q3, age 21; Cytology and HPV, q3, age 30	367	105	69183.39	28.26	4
Cytology, q2, age 21; Cytology and HPV, q3, age 30	526	159	69203.85	20.46	8
Cytology, q1, age 21; Cytology and HPV, q3, age 30	770	244	69225.94	22.09	11

* Adherence to screening is assumed to be <100%. Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are assumed to begin screening at age 21 years. For the combined cytology and HPV strategies, cytology-based screening is assumed before age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing is assumed to begin at age 30 years.

Table 18. Mayrand et al[8]: Sensitivity Analysis Varying Estimates of Screening Adherence*

Strategy	Colposcopies	Incremental Colposcopies	Life-Years	Incremental Life-Years	ICLY
No intervention	0		69016.30		
Cytology, q3, age 21; Cytology and HPV, q5, age 30	153	153	69153.21	136.91	1
Cytology, q3, age 21; Cytology and HPV, q3, age 30	208	55	69181.46	28.25	2
Cytology, q2, age 21; Cytology and HPV, q3, age 30	292	84	69201.93	20.47	4
Cytology, q1, age 21; Cytology and HPV, q3, age 30	417	125	69224.30	22.37	6

* Adherence to screening is assumed to be <100%. Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are assumed to begin screening at age 21 years. For the combined cytology and HPV strategies, cytology-based screening is assumed before age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing is assumed to begin at age 30 years.

Addendum

Table 19. Koliopoulos et al[36]: Sensitivity Analysis Varying Estimates of Screening Adherence*

Strategy	Colposcopies	Incremental Colposcopies	Life-Years	Incremental Life-Years	ICLY
No intervention	0		69016.30		
Cytology, q5, age 21	303	303	69140.40	124.10	2
Cytology, q3, age 21; Cytology and HPV, q5, age 30	374	71	69164.08	23.68	3
Cytology, q3, age 21; Cytology and HPV, q3, age 30	528	154	69191.65	27.57	6
Cytology, q2, age 21; Cytology and HPV, q3, age 30	760	232	69211.64	19.99	12
Cytology, q1, age 21; Cytology and HPV, q3, age 30	1114	354	69231.74	20.10	18

* Adherence to screening is assumed to be <100%. Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are assumed to begin screening at age 21 years. For the combined cytology and HPV strategies, cytology-based screening is assumed before age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing is assumed to begin at age 30 years.

Table 20. Vesco et al[35]: Sensitivity Analysis Including a Strategy of HPV Testing Followed by Cytology if HPV Positive*

Strategy	Colposcopies	Incremental Colposcopies	Life-Years	Incremental Life-Years	ICLY
No intervention	0		69016.30		
HPV followed by cytology, q5, age 30	234	234	69211.89	195.59	1
HPV followed by cytology, q3, age 30	301	66	69231.50	19.61	3
HPV followed by cytology, q2, age 30	423	122	69239.62	8.12	15
HPV followed by cytology, q1, age 30	643	220	69247.71	8.09	27

*Assumes a strategy of HPV testing first, followed by cytology if HPV positive, for women ages 30 years and older. Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are assumed to begin screening at age 21 years.

Table 21. Mayrand et al[8]: Sensitivity Analysis Including a Strategy of HPV Testing Followed by Cytology if HPV Positive*

Strategy	Colposcopies	Incremental Colposcopies	Life-Years	Incremental Life-Years	ICLY
No intervention	0		69016.30		
HPV followed by cytology, q5, age 30	154	154	69211.41	195.11	1
HPV followed by cytology, q3, age 30	190	36	69231.08	19.67	2
HPV followed by cytology, q2, age 30	246	56	69239.32	8.24	7
HPV followed by cytology, q1, age 30	351	105	69247.51	8.19	13

*Assumes a strategy of HPV testing first, followed by cytology if HPV positive, for women ages 30 years and older. Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are assumed to begin screening at age 21 years.

Table 22. Koliopoulos et al[36]: Sensitivity Analysis of a Strategy of HPV Testing Followed by Cytology if HPV Positive*

Strategy	Colposcopies	Incremental Colposcopies	Life-Years	Incremental Life-Years	ICLY
No intervention	0		69016.30		
HPV followed by cytology, q5, age 30	334	334	69219.18	202.88	2
HPV followed by cytology, q3, age 30	436	102	69237.06	17.88	6
HPV followed by cytology, q2, age 30	632	196	69244.12	7.06	28
HPV followed by cytology, q1, age 30	975	343	69250.53	6.41	54
Cytology, q1, age 21	2744	1769	69251.10	0.57	3104

*Assumes a strategy of HPV testing first, followed by cytology if HPV positive, for women ages 30 years and older. Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are assumed to begin screening at age 21 years.

Addendum

Table 23. Vesco et al[35]: Sensitivity Analysis Showing Expected Tests (Screening and Triage), Incremental Tests, Life-Years, Incremental Life-Years, and Incremental Tests per Life-Year (ITLY) for Strategies Identified as Efficient*

Strategy	Tests	Incremental Tests	Life-Years	Incremental Life-Years	ITLY
No intervention	0		69016.30		
Cytology, q5, age 21	11190	11190	69182.25	165.95	67
HPV followed by cytology, q5, age 30	13223	2033	69211.89	29.64	69
HPV followed by cytology, q3, age 30	20842	7619	69231.50	19.61	389
HPV followed by cytology, q2, age 30	29748	8906	69239.62	8.12	1097
HPV followed by cytology, q1, age 30	53079	23331	69247.71	8.09	2884

* Per 1,000 women. Assumes a strategy of HPV testing first, followed by cytology if HPV positive, for women ages 30 years and older. Women are assumed to begin screening at age 21 years.

Table 24. Mayrand et al[8]: Sensitivity Analysis Showing Expected Tests (Screening and Triage), Incremental Tests, Life-Years, Incremental Life-Years, and Incremental Tests per Life-Year (ITLY) for Strategies Identified as Efficient*

Strategy	Tests	Incremental Tests	Life-Years	Incremental Life-Years	ITLY
No intervention	0		69016.30		
HPV followed by cytology, q5, age 30	12168	12168	69211.41	195.11	62
HPV followed by cytology, q3, age 30	19348	7180	69231.08	19.67	365
HPV followed by cytology, q2, age 30	27947	8599	69239.32	8.24	1044
HPV followed by cytology, q1, age 30	51455	23508	69247.51	8.19	2870

* Per 1,000 women. Assumes a strategy of HPV testing first, followed by cytology if HPV positive, for women ages 30 years and older. Women are assumed to begin screening at age 21 years.

Table 25. Koliopoulos et al[36]: Sensitivity Analysis Showing Expected Tests (Screening and Triage), Incremental Tests, Life-Years, Incremental Life-Years, and Incremental Tests per Life-Year (ITLY) for Strategies Identified as Efficient*

Strategy	Tests	Incremental Tests	Life-Years	Incremental Life-Years	ITLY
No intervention	0		69016.30		
Cytology, q5, age 21	11658	11658	69205.11	188.81	62
HPV followed by cytology, q5, age 30	14467	2809	69219.18	14.07	200
Cytology, q3, age 21	18997	4530	69229.37	10.19	445
HPV followed by cytology, q3, age 30	22634	3637	69237.06	7.69	473
HPV followed by cytology, q2, age 30	31826	9192	69244.12	7.06	1302
Cytology, q1, age 21	50416	18590	69251.10	6.98	2663

* Per 1,000 women. Assumes a strategy of HPV testing first, followed by cytology if HPV positive, for women ages 30 years and older. Women are assumed to begin screening at age 21 years.

Table 26. Vesco et al[35]:Sensitivity Analysis of a Strategy in Which Screening Ends at Age 65 Years*

Strategy	Colposcopies	Incremental Colposcopies	Life-Years	Incremental Life-Years	ICLY
No intervention	0		69016.30		
Cytology, q3, age 21; Cytology and HPV, q5, age 30	455	455	69208.97	192.67	2
Cytology, q3, age 21; Cytology and HPV, q3, age 30	640	185	69225.54	16.57	11
Cytology, q2, age 21; Cytology and HPV, q3, age 30	896	256	69233.35	7.81	33
Cytology, q1, age 21; Cytology and HPV, q3, age 30	1200	304	69238.94	5.59	54
Cytology, q1, age 21	1525	325	69239.18	0.24	1343

* Screening is assumed to end at age 65 years instead of age 85 years. Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are assumed to begin screening at age 21 years.

Addendum

Table 27. Mayrand et al[8]: Sensitivity Analysis of a Strategy in Which Screening Ends at Age 65 Years*

Strategy	Colposcopies	Incremental Colposcopies	Life-Years	Incremental Life-Years	ICLY
No intervention	0		69016.30		
Cytology, q3, age 21; Cytology and HPV, q5, age 30	255	255	69207.20	190.90	1
Cytology, q3, age 21; Cytology and HPV, q3, age 30	347	92	69224.06	16.86	5
Cytology, q2, age 21; Cytology and HPV, q3, age 30	477	130	69231.97	7.91	16
Cytology, q1, age 21; Cytology and HPV, q3, age 30	638	161	69237.81	5.84	28

* Screening is assumed to end at age 65 years instead of age 85 years. Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are assumed to begin screening at age 21 years.

Table 28. Koliopoulos et al[36]: Sensitivity Analysis of a Strategy in Which Screening Ends at Age 65 Years*

Strategy	Colposcopies	Incremental Colposcopies	Life-Years	Incremental Life-Years	ICLY
No intervention	0		69016.30		
Cytology, q5, age 21	540	540	69196.51	180.206	3
Cytology, q3, age 21; Cytology and HPV, q5, age 30	658	118	69217.09	20.59	6
Cytology, q3, age 21; Cytology and HPV, q3, age 30	937	279	69231.80	14.70	19
Cytology, q2, age 21; Cytology and HPV, q3, age 30	1305	368	69238.47	6.67	55
Cytology, q1, age 21; Cytology and HPV, q3, age 30	1726	421	69242.47	4.00	105
Cytology, q1, age 21	2167	441	69244.00	1.53	288

* Screening is assumed to end at age 65 years instead of age 85 years. Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are assumed to begin screening at age 21 years.

Table 29. Sensitivity Analysis Using the Highest Estimates of Test Sensitivity and Lowest Estimates of Specificity*†‡

Strategy	Colposcopies	Incremental Colposcopies	Life-Years	Incremental Life-Years	ICLY
No intervention	0		69016.30		
Cytology, q5, age 21	1369	1369	69214.69	198.39	7
Cytology, q3, age 21; Cytology and HPV, q5, age 30	1824	455	69232.89	18.20	25
Cytology, q3, age 21; Cytology and HPV, q3, age 30	2720	896	69244.40	11.51	78
Cytology, q2, age 21; Cytology and HPV, q3, age 30	3638	918	69248.36	3.95	232
Cytology, q1, age 21; Cytology and HPV, q3, age 30	4571	933	69251.42	3.06	305
Cytology, q1, age 21	5283	712	69252.51	1.09	651

* Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are assumed to begin screening at age 21 years. Screening intervals of every 1 (q1), 2 (q2), 3 (q3), and 5 (q5) years are compared.
† Sensitivity for CIN2+ is 0.772 instead of 0.569; specificity for CIN2+ is 0.847 instead of 0.945; sensitivity for ASC-US is 0.956 instead of 0.762; specificity for ASC-US is 0.475 instead of 0.638.
‡ HC2 sensitivity for CIN2+ is 1.000 instead of 0.860; HC2 specificity for CIN2+ is 0.767 instead of 0.844; HC2 sensitivity for ASC-US is 0.976 instead of 0.892; HC2 specificity for ASC-US is 0.310 instead of 0.641.

Addendum

Table 30. Sensitivity Analysis Using the Lowest Estimates of Test Sensitivity and Highest Estimates of Specificity*†‡

Strategy	Colposcopies	Incremental Colposcopies	Life-Years	Incremental Life-Years	ICLY
No intervention	0		69016.30		
Cytology, q3, age 21; Cytology and HPV, q5, age 30	132	132	69123.68	107.38	1
Cytology, q3, age 21; Cytology and HPV, q3, age 30	187	55	69153.38	29.70	2
Cytology, q2, age 21; Cytology and HPV, q3, age 30	250	63	69172.50	19.12	3
Cytology, q1, age 21; Cytology and HPV, q3, age 30	327	77	69191.32	18.82	4
Cytology, q1, age 21	404	77	69199.49	8.17	9

* Results are presented as expected colposcopies per 1,000 women, incremental colposcopies, life-years, incremental life-years, and incremental colposcopies per life-year (ICLY) for strategies identified as efficient. Women are assumed to begin screening at age 21 years. For the combined cytology and HPV strategies, cytology-based screening is assumed before age 30 years, with a repeat cytology test for ASC-US results. The strategy of cytology and HPV testing is assumed to begin at age 30 years.
† Sensitivity for CIN2+ is 0.200 instead of 0.569; specificity for CIN2+ is 0.990 instead of 0.945; sensitivity for ASC-US is 0.450 instead of 0.762; specificity for ASC-US is 0.756 instead of 0.638.
‡ HC2 sensitivity for CIN2+ is 0.341 instead of 0.860; HC2 specificity for CIN2+ is 0.966 instead of 0.844; HC2 sensitivity for ASC-US is 0.670 instead of 0.892; HC2 specificity for ASC-US is 0.672 instead of 0.641.