Impact of Offering Cervical Cancer Screening and HPV Vaccination Against Types 16 and 18 on Cervical Cancer

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This report summarizes estimates of health impact and cost-effectiveness that were created to assess the relative value of most of the clinical preventive services recommended by the United States Preventive Services Task Force (USPSTF) and the Advisory Committee on Immunization Practices (ACIP). This ranking of clinical prevention priorities is guided by the National Commission on Prevention Priorities (NCPP).

The results presented in this report are based on earlier analysis and were inflation adjusted to 2012 US dollars to align with other services in the Prevention Priorities project. The report has been reorganized and edited. The model itself was not updated nor rerun for this update of the report.

A. USPSTF Cervical Cancer Screening Recommendation

The U.S. Preventive Services Task Force updated its recommendation on cervical cancer screening in March 2012 to strongly recommend screening for cervical cancer in women aged 21-65 years with cytology (Pap smear) every three years, or for women ages 30-65 years who want to lengthen the screening interval, screening with a combination of cytology and human papillomavirus (HPV) testing every five years.[1] This analysis assesses screening the general population of women aged 21-65 using Pap smears and does not assess the alternate screening interval with use of HPV testing.

The USPSTF found good evidence that screening for cervical cancer using Pap smears reduces mortality from and the incidence of cervical cancer.[1] The USPSTF found no direct evidence that annual or biannual screening with Pap smears is more effective than triennial screening.[1,2] The existing effectiveness literature, to which we have calibrated our simulation model, includes populations who were offered screening every two to five years. Our base-case model assumes triennial screening recommendation with Pap smear starting at the latest of age 21 or the onset of sexual activity. Within the model, a positive Pap smear is followed by a confirmatory Pap smear with HPV DNA test prior to final diagnosis and treatment.[3-8]

B. ACIP HPV Vaccine Recommendations

At the time of this analysis two HPV vaccines were licensed by the FDA. The Advisory Committee on Immunization Practices (ACIP) refers to them as bivalent (HPV 2) or quadrivalent (HPV 4), based on the number of HPV types addressed, as bivalent (HPV 2).[9] GARDASIL™, (an HPV 4 vaccine) protects against the four most common HPV types 6, 11, 16 and 18. CERVARIX™ (an HPV 2 vaccine) protects against HPV types 16 and 18. Both are administered as 3 injections over six months. HPV types 6 and 11 are known to cause approximately 90% of genital warts in females and males. HPV types 16 and 18 are known to cause approximately 75% of cervical cancer cases, approximately 70% of vaginal cancer cases, and up to 50% of vulvar cancer cases.[10-14] Thus, vaccination with GARDASIL™ has the potential to significantly lower the incidence and subsequent burden of all these diseases.

The ACIP recommended a three-dose series of either HPV 4 or HPV 2 for all females at ages 11-12 years (or for 13-26 year-olds not previously vaccinated against HPV).[9] Males ages 11-12 are recommended to receive HPV 4 in a three-dose series, with catch-up vaccinations recommended from ages 13-21 for those not previously vaccinated. In the model described below, HPV occurs exogenously rather than through an infectious disease process and males were not included in the modeling for this service.

C. HPV-Related Diseases Excluded from the Model

The current model of the cost-effectiveness of HPV vaccine is based on an existing model of cervical cancer. Consequently, estimates of clinically preventable burden and cost effectiveness are limited to

the vaccine's impact on the burden and costs directly associated with that disease. This limitation results in conservative estimates of the value of the HPV vaccine.

HPV types 6 and 11 are known to cause approximately 90% of genital warts in females and males, and there is an increasing literature regarding their impact [15-19]. HPV types 16 and 18 are known to cause approximately 70% of vaginal cancer cases and up to 50% of vulvar cancer cases; there is a growing literature regarding the associated burden of both diseases [20-26]. However, when compared with cervical cancer, which has a median age of 48 at diagnosis and accounted for 4,074 deaths and 12,042 diagnoses in 2012[27], it is reasonable to assume the impact of either vulvar cancer (median age of diagnosis =68; 900 estimated annual deaths) or vaginal cancer (median age of diagnosis=70; 770 estimated deaths) on the overall cost-effectiveness of vaccinating women under the age of 26 from HPV is small.

D. Markov Model of Cervical Cancer Screening and HPV Vaccination Recommendation

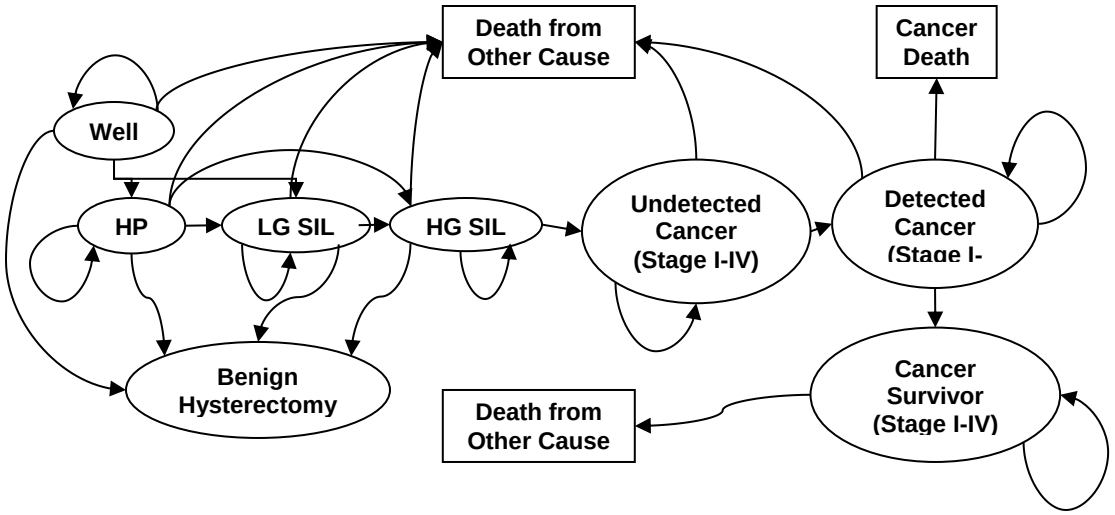
Our estimates reflect a societal perspective and are from a HealthPartners Institute for Education and Research's ModelHealth™: Cervical Cancer model, a Markov micro-simulation of a U.S. birth cohort. The estimates provided in this report focus on the impact of HPV vaccination on the burden and costs of cervical cancer. Our goal is not an examination of the comparative effectiveness of HPV 4 and HPV 2 vaccines, thus genital warts are currently excluded from the model. Estimates can more directly be viewed as the impact of vaccinating young women against HPV types 16 and 18 on the burden of cervical cancer as has been done by others.[28-31]

The model was developed in three steps. First, a Markov model was developed that simulates the natural history of cervical cancer. We found no evidence of differences in disease morphology by racial or ethnic group, so a single natural history model was used. However, differences in the incidence of HPV by racial and ethnic groups send a higher portion of some groups down the natural history model for development of cancer. Second, the model was expanded to account for the current utilization of pap smears. Here, observed differences in utilization of cervical cancer screening, follow-up and treatment were incorporated. Finally, offering HPV vaccination to young women aged 11-12 along with catch-up opportunities through age 26 was incorporated.

<u>Natural History Model</u>

We developed a 19-state, discreet-time Markov model of the natural progression of cervical cancer. In this natural history model, diagnosis and treatment occur only in response to symptomatic presentations. A Markov model tracks the progression of individuals through various disease states over time. This model borrows from previous efforts and resembles other simulation models of cervical cancer. It differs in that the model is analyzed on an individual level using micro-simulation. Figure 1 illustrates histological states and allowed transitions in the natural history model.

Figure 1: Markovian states for the natural history in ModelHealth™: Cervical cancer



The model tracks a simulated birth cohort starting at age 11, through age 85. Screening for cervical cancer with Pap smears ends at age 65 per the USPSTF recommendation; however, the model does allow women older than age 65 to receive a Pap smear as part of diagnosing a symptomatic presentation. Each person in the model is independent, and there is no disease transmission. Each individual's risk of contracting HPV is based on observed age-specific incidence rates, and these rates are constant. Thus, the model does not assess effects of overall vaccine uptake rates or "herd immunity".

The model assumes the annual incidence of HPV is 15% and low-grade squamous intraepithelial lesion (LG SIL) is 1% at age 15, with incidence at other ages as shown in Table 1. There are differences in incidence of HPV by race and ethnicity that underlie the population averages shown in Table 1. These differences (taken from the same sources) are built into the model. Modeling cycle lengths are 1 year. The model assumes a disease progression similar to other Markov models of cervical cancer. The probability of an individual shifting from one state to another is age-dependent. Women infected with HPV can undergo regression, no change, or progression. Women with LG SIL can undergo regression (to "Well" or HPV infection), no change, or progression to high-grade squamous intraepithelial lesion (HG SIL). Women with HG SIL can regress, stay the same, or progress to cancer. Women with cancer either become symptomatic and are detected, remain at the same stage, or progress to a more severe cancer stage. Once a cancer becomes symptomatic and a diagnosis is made, the probability of survival is stage-specific. Rates of benign hysterectomy among women without cancer were derived from the national hospital discharge survey. Death rates for causes other than cervical cancer are from condition-adjusted death tables. Transitional probabilities between model states and their sources are listed in Table 1.

In the model, most cervical cancers develop from an initial HPV type 16 or 18 infection that typically progresses to an LG SIL, but may more rapidly develop into an HG SIL. Cervical cancer is staged clinically using the Ferderation Internationale de Gynecologie et Obstetriques (FIGO) system and the Tumor, Nodes and Metastases (TNM) stages system of the American Joint Committee on Cancer (AJCC). Our

cancer incidence and progression rates are calibrated to progression rates that are consistent with Surveillance, Epidemiology, and End Results (SEER) data.

Model of Prevention, Diagnosis and Treatment

A Markov micro-simulation tracks the disease state of individuals as they progress through model cycles. From the histological state at the beginning of a cycle (e.g. at the beginning of the year) the histological state at the end of the cycle (e.g. at the end of the year) is determined based on applicable transitional probabilities. In the model, these state transitions are conditioned on intra-cycle actions such as prevention (vaccination and/or screening), diagnosis and treatment received during the year. For example, a women's cervical cancer status at the end of any cycle (i.e. year) is partly determined by actions during that year (i.e. what treatments she received and their effectiveness). Women who successfully complete the HPV vaccination regime will not contract HPV (100% efficacy). Similarly, those who are screened have a higher likelihood of being detected, and women detected in early stages have a higher survival probability than those detected at later stages. This conceptual approach is presented in Figure 2.

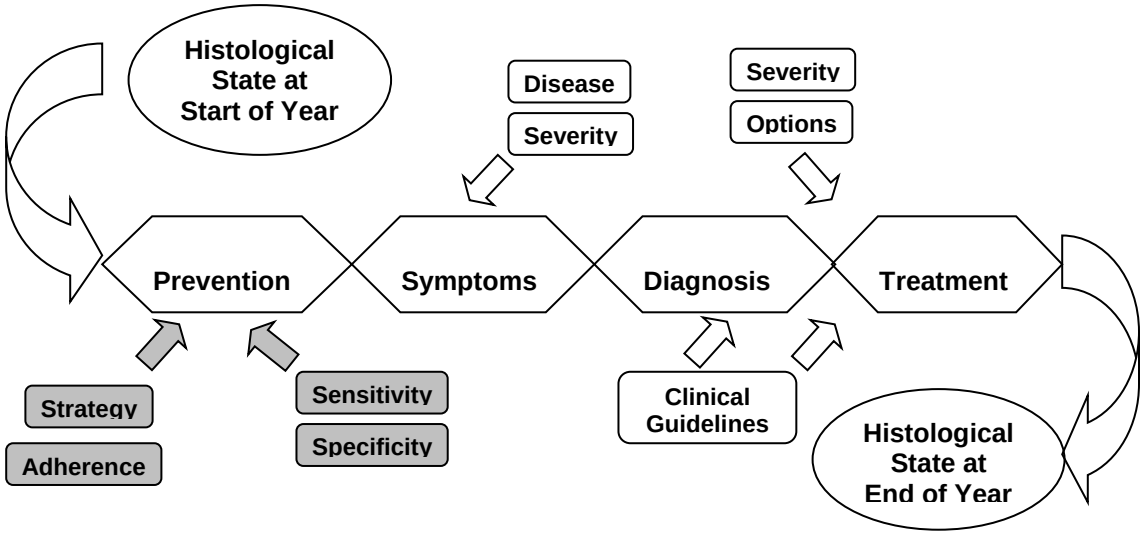


Figure 2: Within-State Modeling of cervical cancer screening recommendations: Recommendations are reflected by altering specific model parameters.

Four general factors affect an individual's year-end histological state in the model: prevention, symptoms, diagnosis, and treatment. The impact of each is determined by the specifics of that factor. For example, a woman with Stage IV cervical cancer is much more likely to be symptomatic than a woman with Stage I cervical cancer. Similarly, the likelihood of being screened depends on the interval between screens, adherence rates and individual factors (age, ethnicity, and prior screening behavior). Further, the likelihood of a correct screening outcome (i.e. a true positive or true negative) depends on the sensitivity and specificity of the screening technology. The estimates underlying the model and considered ranges are contained in Table 1.

E. Clinically Preventable Burden (CPB) Estimation

CPB measures health impact. Conceptually, CPB is the burden addressed by the service multiplied by the effectiveness of the service. The Prevention Priorities project expresses this in terms of quality

adjusted life years (QALYs) saved. A year of cancer-free life is given a higher quality of life than one year with cervical cancer.

Several factors affect the estimated effectiveness of the USPSTF's recommended service regarding cervical cancer screening. Among these are screening utilization rates, adherence to follow-up treatment, the sensitivity and specificity of the screening technology, effectiveness of treatments, and assumptions made regarding a disease's impact on quality of life. Data regarding these parameters were obtained from published literature summarized Table 1. The "Base Case" column shows the best available estimate while the "Upper" and "Lower" columns show the range over which the parameters were varied in sensitivity analysis to determine how sensitive results are to variation in that parameter.

Vaccine Delivery Rates and Adherence to 3 Dose Regimen:

To estimate of the impact of systematically offering vaccination against HPV types 16 and 18, we assumed a base case vaccination uptake rate of 75% for all population groups when the vaccine is routinely offered to all patients. This is approximately equal to the percentage of children receiving the combined childhood vaccination series plus hepatitis and varicella (the 4:3:1:3:3:1 series) in 2008 (77%)[32].

Pap Smear Screening Rates and Follow-up Confirmatory Pap Smears:

There were no data on adherence by patients to offers from primary care clinicians to receive screening as recommended by the USPSTF when the service was modeled. Although imperfect, the most generalizable estimates of adherence are the uptake rates observed in countries with comprehensive screening programs. However the summary adherence estimate from national programs is lower than the BRFSS estimates of US women who are currently up to date with screening. If less than 100% of women receive offers for screening and the self-report data of the BRFSS are accurate, then estimates from the BRFSS constitute lower bounds on acceptance of offers to screen. Similar issues and similar overall adherence estimates are found in estimating adherence with other cancer screening. We used cervical cancer screening rates estimated from the Behavioral Risk Factor Surveillance Survey (BRFSS). Two sets of estimates are contained in Table 1. The first reflect the portion of women who have had a Pap smear in the last three years. However, the model allows women to have unique patterns of Pap smear utilization. Each year, or cycle within the model, women "decide" to screen or not. Thus, some women screen more frequently than every three years and some less. Our conditional probabilities of screening given time since last screen are shown below the overall screening rates in Table 1. These values were calibrated in the model to arrive at the observed screening rates.

Following an initial positive Pap smear it is recommended that women receive a confirmatory Pap smear. In the model, we assumed that an HPV DNA test would be applied at this time for women who were not previously vaccinated. This requires an additional office visit, and rates of adherence to confirmatory Pap smears were gathered from published literature regarding follow-up to an initial positive screen using a Pap smear.

As noted, we found no evidence to support different disease morphology across race/ethnicity groups; however, cervical cancer screening rates differ. The model reflects U.S. Census data regarding the relative size of race/ethnicity groups within a hypothetical U.S. birth cohort of 4,000,000. The variation of screening in Pap smear utilization and rates of confirmatory Pap smear following positive screen by race and ethnicity were included as model inputs.

Results of Initial Cancer Screening:
The sensitivity and specificity of a Pap smear may vary with the threshold selected to indicate a positive result – atypical squamous cell of undetermined significance (ASCUS), LG-SIL, or HG-SIL. Further, the likelihood of a certain indication (cancer, HG SIL, LG SIL, ASCUS) given a positive result depends on that individual's underlying histological state. Our base estimates assume an ASCUS threshold for determining a positive Pap smear. The parameter estimates used are provided in Table 1.

Rates of Benign Hysterectomy:
The USPSTF recommends at least triennial screening for cervical cancer using Pap smears for women who have a cervix and are either sexually active or older than 21 years. To protect against overestimates due to including women who have received a benign hysterectomy, rates of benign hysterectomy by age were included in the model based upon data obtained from the National Hospital Discharge Survey.

Cancer Deaths and Survivorship
The model assumes that if an individual eventually dies from cancer, she will become symptomatic regardless of cancer stage at detection. Once a cancer is detected, the individual will remain in that state for a period of up to five years, die from cancer, or die from other causes. If an individual survives for more than five years following a cancer diagnosis, they are assumed to be a cancer survivor. Rates of cancer death by year following a diagnosis of cancer are contained in Table 1.

F. Cost-Effectiveness Estimation
We used the same methods for producing estimates of CE across preventive services.[33-36] These methods are consistent with the 'reference case' of the Panel of Cost-Effectiveness in Health and Medicine.[37] Our methods include the use of a 3% discount rate for both cost and health benefits, the exclusion of productivity losses from disease costs, and the exclusion of medical costs that are not related to the conditions prevented by the service. All model inputs, including vaccine costs, pap smear screening costs, diagnostic and confirmatory costs, and treatment costs by histological site are expressed in 2005 dollars. Final results for this report in Section G have been inflation-adjust to 2012 dollars.

Vaccine Costs
The costs of vaccine and administering include direct medical costs of $143 per dose in 2005 $US, including wastage and indirect costs of patient time and travel as shown in Table 1.

Pap Smear Screening Costs
Direct medical costs of $191, including the costs of administering and processing Pap smears and office time associated with screening for cervical cancer, were gathered from the published literature as shown in Table 1. Direct non-medical costs of $24, including patient time and transportation costs, were added for clinic visits.

Diagnostic and Confirmatory Costs by Histological State
Following an initial positive screen and subsequent confirmatory Pap smear, additional diagnostic and confirmatory tests such as colposcopy, biopsy, laser ablation, and others are used to definitively diagnosis disease state. The model does not address specific diagnostic procedures except HPV screening follow an initial positive screen. The model assumes previously vaccinated women are not given an HPV screen. For other confirmatory tests, we constructed weighted averages of diagnostic costs by positive indication (i.e. the result of the confirmatory Pap smear) and used those estimated in

the model. The weights underlying these averages are determined by the proportion in each state of patients receiving each procedure according to published estimates. For instance, colposcopy and biopsy are common diagnostics, given an indication of LG SIL, while chest x-rays are common when cancer is indicated.

Treatment Costs by Histological State

Similar to diagnostic procedures, treatments and subsequent costs are state-dependent. Rather than attempt to model exact treatment pathways, we again constructed estimated of annual treatment costs by diagnosed histological state-based on weighted averages of procedure costs. The weights were determined by the proportion of patients receiving a given procedure according to published estimates as noted in Table 1.

G. Results

Summary results for Prevention Priorities are provided in Table 2.

CPB Estimate

A triennial screening recommendation for cervical cancer would prevent 64,424 cases of cervical cancer if screening is offered to all women older than 21 in a birth cohort of 4 million. This would result in 26,868 cervical cancer deaths prevented, providing a total CPB of 238,813 QALYs saved (Table 2). Assuming a 75% vaccination rate, offering vaccination would prevent 31,302 cases of cervical cancer. This would result in 11,807 cervical cancer deaths prevented, providing a total CPB of 126,253 QALYs saved.

Cost Effectiveness Estimates

The two rightmost rows of Table 2 present the per-person costs and the final cost-effectiveness estimate for the considered strategies relative to our base case scenario. In the absence of vaccination and cervical cancer screening among women in a hypothetical U.S. birth cohort of 4 million, there would be 79,100 cases of cervical cancer resulting in approximately 30,900 deaths. The costs for treating these cases would average $331/person, inflation-adjusted to 2012 US dollars. Offering triennial screening with varying rates of adherence and follow-up (Table 1) would significantly reduce this disease burden at a cost of $3,201 per person for a final cost effectiveness ratio of $33,146/QALY saved. Offering HPV vaccination would also significantly reduce this disease burden at an average per-person cost of $1,900 for a final cost effectiveness ratio of $34,592/QALY saved.

Sensitivity Analysis

In single variable sensitivity analysis, the CPB of cervical cancer screening is found to be most sensitive to changes in the effectiveness of screening at reducing cervical cancer deaths. Specifically, adherence to both screening and confirmatory follow-up following a positive screen had the greatest effect, with CPB decreasing 51% and increasing 149% at the extreme ranges of these parameters. Similarly, changing the sensitivity and specificity of Pap smears led to a 38% decrease and 122% increase in CPB, respectively. CPB was also sensitive to assumptions regarding disease progression from LG SIL and HG SIL to cancer and across cancer stages. Changes to each of these parameters led to changes in CPB of approximately 15%.

Following our methods, we conducted multivariate sensitivity analysis to determine the three variables that, when changed together, produce the highest and lowest estimates of CPB. Any changes to disease progression parameters (i.e. from LG SIL and HG SIL to cancer and across cancer stages) coupled with changes to adherence to either screening of confirmatory Pap smear testing had the greatest impact on

CPB. The largest impact was from the combination of Pap smear screening and progression rates from LG SIL to HG SIL and HG SIL to cervical cancer. Combined changes to these parameters resulted in a 75% decrease and a 250% increase in CBP, producing a range of 179,000 to 579,000 QALYS saved.

The CPB of offering vaccination is sensitive to rates of vaccine uptake. Under the base case assumption of 75% uptake, 25% of the population remains completely unprotected and the vaccinated 75% are still at risk of non-HPV related cancer. Multivariate sensitivity analysis indicated the three variables, when changed together, that produce the greatest change in CPB were vaccine uptake and changes to disease progression parameters (i.e. from LG SIL and HG SIL to cancer and across cancer stages). Combined changes to these parameters resulted in an 85% decrease and a 190% increase in CBP, producing a range of 179,000 to 579,000 QALYS saved.

Our estimated cost-effectiveness ratio for the cervical cancer screening is most sensitive to changes to screening adherence as well as the total costs of screening (i.e. direct medical costs as well as indirect patient costs). When varied within the ranges shown in Table 1, these variables produce CE ranges of $16,946/QALY to $41,595/QALY and $25,740/QALY to $43,592/QALY, respectively. Following our methods for sensitivity analysis, we then changed these two variables simultaneously and obtained a summary range of $16,689/QALY, to 50,132/QALY.

Our estimated cost effectiveness ratios for strategies using HPV vaccine were most sensitive to vaccine uptake and screening adherence. When varied within the ranges shown in Table 1, these produced CE ranges of $19,771/QALY to $53,278/QALY and $25,034/QALY to $47,886/QALY, respectively. Following our methods for sensitivity analysis, we then changed these two variables simultaneously and obtained a summary range of $17,460/QALY, to $58,413/QALY.

H. Limitations

To focus available resources on completion of other services, this analysis has not been updated other than to adjust results for inflation. HPV immunization was added to a model that was constructed for the purpose of estimating the value of cervical cancer screening and was therefore limited to immunization for adolescent females. A fully updated model would most impact the estimates of HPV vaccination because quadravalent and 9-valent vaccines protect against HPV types beyond 16 and 18, HPV is linked to several diseases other than cervical cancer, and ACIP recommendations now include vaccination of adolescent males.[38] The benefits of protecting against types 16 and 18 likely capture the majority of health benefits of immunization given the relative low risk of cervical cancers from other HPV types and the comparatively low risk of other cancers attributable to HPV. Yet the burden of the excluded HPV-attributable cancers is still considerable and a 50% increase in QALYs saved would increase the CPB score of HPV immunization by one point in the current Prevention Priorities ranking. In terms of cost-effectiveness, the reduction in costs from treating fewer cases of other cancers and genital warts (although a relatively small impact on quality of life), while adding vaccination of males will double the costs of intervention. A potential difference in score of one point is typical of uncertainty of estimates across services in the Prevention Priorities ranking and sensitivity analyses identified six other services that have total scores that could differ by two with different model input estimates and structures.

ModelHealth: Cervical Cancer was validated against 2003-2004 NHANES HPV prevalence and 2000-2007 SEER cervical cancer statistics. After this validation, updated NHANES data showed markedly higher HPV prevalence. An updated model might require recalibration and would produce different base-case estimates, but we would expect the results to be within the margins of sensitivity analysis

discussed above because age-adjusted cervical cancer incidence and mortality declined less than 5% between 1992 and 2013.[39]

Table 1: Selected Model Parameters				
Parameter	**Base Case**	**Upper**	**Lower**	**Source**
Incidence of HPV by age				40-63
15	0.15	0.15	0.05	
16-18	0.16	0.225	0.06	
19-20	0.2	0.28	0.08	
21-23	0.17	0.21	0.05	
24-29	0.06	0.09	0.03	
30-49	0.01	0.015	0.005	
50+	0.005	0.008	0.003	
Incidence of LG SIL				43,51,64-74
15	0.01	0.02	0.001	
16-20	0.005	0.0025	0.01	
21+	0.007	0.005	0.01	
Rates of Benign Hysterectomy				24,75-77
40-59	0.001	0.0015	0.0005	
60+	0.0001	0.0002	0.00005	
Progression Rates				
HPV to LG SIL	0.06	0.1	0.05	66,76,78-88
HPV to HG SIL	0.007	0.014	0.004	66,76,78,79,86,87,89
LG SIL to HG SIL				45,90-102
15-34	0.013	0.05	0.02	
35+	0.05	0.08	0.03	
HG SIL to Stage I Cancer	0.04	0.05	0.03	10,45,90-95,97,98,101-116
Stage 1 to Stage II	0.23	0.24	0.21	10,18,45,90-95,97,98,100-104,107-117
Stage II to Stage III	0.3	0.32	0.28	10,45,90,94,99,107-116
Stage III to Stage IV	0.45	0.48	0.43	10,18,45,90-98,100,102,106-116,118
Regression Rates				
HPV				80-87,89,93
15-24	0.5	0.4	0.6	
25-29	0.4	0.4	0.6	
30+	0.17	0.03	0.2	
LG SIL to HPV	0.12	0.13	0.1	45,90-95,97,98,100-104
HG SIL to LG SIL	0.08	0.09	0.05	45,90-95,97,98,100,102-104,118
Probability of Symptomatic Cancer				66,90,91,94,95,97,98,104,119-133
Stage I	0.15	0.2	0.1	

Stage II	0.23	0.5	0.2	
Stage III	0.6	0.7	0.5	
Stage IV	0.9	1	0.8	
Annual Probability of Cancer Death Following Year of Diagnosis		66,76,82,91,95,119,120,128,134-159		
Stage I				
Year 1	0.031	0.047	0.016	
Year 2	0.048	0.071	0.024	
Year 3	0.046	0.068	0.023	
Year 4	0.024	0.036	0.012	
Year 5	0.024	0.036	0.012	
Stage II				
Year 1	0.093	0.140	0.047	
Year 2	0.124	0.186	0.062	
Year 3	0.078	0.116	0.039	
Year 4	0.067	0.100	0.033	
Year 5	0.040	0.059	0.020	
Stage III				
Year 1	0.294	0.440	0.147	
Year 2	0.262	0.393	0.131	
Year 3	0.139	0.209	0.070	
Year 4	0.077	0.115	0.038	
Year 5	0.086	0.129	0.043	
Stage IV				
Year 1	0.601	0.902	0.301	
Year 2	0.502	0.753	0.251	
Year 3	0.236	0.354	0.118	
Year 4	0.135	0.202	0.067	
Year 5	0.141	0.211	0.070	
Pap Smear Characteristics				160-211
Sensitivity by Threshold				
ASCUS	0.7	1	0.2	
LG SIL	0.8	1	0.2	
HG SIL	0.95	1	0.3	
Specificity by Threshold				
ASCUS	0.86	1	0.5	
LG SIL	0.87	1	0.5	
HG SIL	0.9	1	0.5	
Positive Indication by State				
Well/HPV				
Cancer (Stages I-IV)	0.004	0.002	0.007	
HG SIL	0.088	0.176	0.044	

LG SIL	0.384	0.768	0.192	
ASCUS	0.525	1	0.263	
LG SIL/HG SIL				
Cancer (Stages I-IV)	0.002	0.003	0.001	
HG SIL	0.080	0.160	0.040	
LG SIL	0.683	1	0.342	
ASCUS	0.235	0.470	0.118	
Cancer (Stages I-IV)				
Cancer (Stages I-IV)	0.600	1	0.300	
HG SIL	0.206	0.412	0.103	
LG SIL	0.072	0.144	0.036	
ASCUS	0.122	0.244	0.061	
Pap Smear Utilization				4,7,70,123,155,212-238
Variation by race/ethnicity	0.75 to 0.86	1	0.5	
Probability of Screen given Prior Screen				Assumed
Screened Prior Year	.2	0	.4	
Screened 2 Years Prior	.2	0	.5	
Due for Screening (3 yrs Prior)	.5	.3	.7	
1 Year Past Due (4 yrs Prior)	.35	.15	.55	
2 Years Past Due (5 yrs Prior)	.3	.15	.45	
3+ Years Past Due (6+ yrs Prior)	.25	.1	.4	
Rates of Confirmatory Pap Smear follow Positive Screen				
Variation by race/ethnicity	0.85 to 0.96	1	0.64 - 0.72	
Costs of Pap Smear*				28,30,31,202,203,239
Pap Smear Test	$75.75	$113.63	$37.88	
Office Visit	$115.00	$172.50	$57.50	
Patient Time/Transport	$24.00	$190.00	$12.00	
HPV DNA Test				214,240-245
Sensitivity	0.83	1	0.42	
Specificity				
LG SIL	0.93	1	0.47	
HG SIL	0.93	1	0.47	
Diagnostic/Confirmatory Follow-up Costs* by Positive Indication				28,30,31,201-203,207,246-260
LG SIL	$381.02	$571.53	$190.51	
HG SIL	$646.81	$970.22	$323.41	
Stage I	$983.81	$1,475.71	$491.90	

Stage II	$1,567.51	$2,351.26	$783.75	
Stage III	$1,536.38	$2,304.58	$768.19	
Stage IV	$1,731.57	$2,597.36	$865.79	
HPV Vaccine Rates by age 25				14,32,261
White	0.75	1	0.3	
Southeast Asian	0.75	1	0.3	
Hispanic	0.75	1	0.3	
Black	0.75	1	0.3	
HPV Vaccine Cost* per Dose				255,256,262-264
Vaccine and Wastage	$134.00	$300.00	$100.00	
Supplies and Administration	$9.00	$27.004	$4.50	
Patient Time and Transport	$25.00	$70.00	$13.00	
Annual Treatment Costs*				28,30,31,51,77,203,252,257-260,265-277
LG SIL	$1,999	$2,999	$999	
HG SIL	$3,553	$5,330	$1,776	
Stage I	$15,882	$21,824	$9,941	
Stage II	$19,625	$22,746	$16,504	
Stage III	$32,849	$26,386	$29,311	
Stage IV	$42,201	$29,226	$53,176	
Terminal Costs	$58,439	$68,819	$48,060	
Quality of Life Weights				30,159,202,249,254,255,278,279
LGSIL	0.97	1	0.95	
HGSIL	0.97	1	0.95	
Stage I	0.79	0.85	0.65	
Stage II	0.62	0.75	0.50	
Stage III	0.56	0.65	0.45	
Stage IV	0.48	0.60	0.35	
Cancer Survivor	0.90	1	0.75	
Discount Rate**	0.03	0.01	0.05	280

Table 2: Results of Markov Model of Cervical Cancer Screening (2012 $US)					
	Cervical Cancer Cases Prevented	Deaths Prevented	CPB (QALYs Saved)	Per-Person Lifetime Costs	CE Ratio
Cervical cancer screening	64,424	26,868	238,813	$3,201	$33,146
Vaccine Only	31,302	11,807	126,253	$1,900	$34,592

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