SUPPLEMENTARY MATERIAL

Estimating the Natural History of Cervical Carcinogenesis Using Simulation Models: A CISNET Comparative Analysis

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METHODS

Baseline model descriptions and inputs

The Harvard model is an individual-based (i.e., microsimulation) model of cervical carcinogenesis that tracks a birth cohort of individual women through a series of monthly transitions beginning at age 9 years over their lifetimes (1). Each month, a woman may acquire or clear an HPV infection, progress or regress to/from CIN2 or CIN3 and progress to invasive cervical cancer. In contrast to the other CISNET-cervix models, CIN2 and CIN3 are modeled as non-sequential precancerous health states with distinct probabilities of progression to cancer, whereas CIN1 is interpreted as a microscopic manifestation of acute HPV infection and is therefore incorporated into the HPV-infected state. Preclinical cancer may be detected through symptoms or may progress to a more advance clinical stage. Each month, all women are subjected to all-cause mortality and hysterectomy; women with cervical cancer additionally face excess mortality from cervical cancer. Transitions can be a function of age (i.e., HPV incidence), time spent in a health state (i.e., HPV clearance, precancer progression/regression), HPV genotype (HPV16, HPV18, HPV31, HPV33, HPV45, HPV52, HPV58, pooled other high-risk types, and pooled low-risk types), and history of HPV infection (natural immunity). Initial model parameterization of HPV incidence and clearance, progression and regression from CIN2 or CIN3 involved a multi-disciplinary approach requiring analysis of primary empirical data (2, 3), and supplemented by data from published literature (4, 5) and expert opinion. Finally, for parameters with high uncertainty, we relied on a multi-parameter calibration process (1, 6) to maximize correspondence between model-projected outcomes and empirical targets (**Supplementary Table 1**). To capture uncertainty in the natural history process, all Harvard model outputs are reported as the mean, minimum and maximum across the 50 top-fitting natural history parameter sets.

The MISCAN-cervix model is a microsimulation model originally developed to evaluate screening of disease. Individuals are simulated successively and independently of each other. The model produces output on the effects of screening procedures, morbidity and mortality, which can be used to explain and predict trends in cancer incidence and mortality, and to quantify the effects of primary and secondary prevention. The model consists of three parts: 1) demography, 2) natural history, and 3) screening. In the demography module, a large population of women from the age of 9 years until age of 100 years with individual life histories is simulated based on demographic and hysterectomy data. These women can acquire a high-risk HPV infection (HPV16, HPV18, pooled HPV31, HPV33, HPV45, HPV52, HPV58, and pooled other HR) that is either transient or leads to the development of CIN in the natural history module. Transitions are based on age- and HPV genotype specific probabilities that assign women to different natural history pathways that divide cervical disease into seven sequential stages: HPV infection; three precancerous stages (i.e., CIN 1, CIN 2, and CIN 3); and four invasive cancer stages (micro-invasive, local, regional, distant). Following transition to health state, the mean dwell times for HPV, CIN1, CIN2 and CIN3 do not vary by HPV genotype or age. The assumptions of the natural history of cervical cancer are based on literature, expert opinion and SEER-data. For example, HPV dwell time (mean=1 year; Weibull shape=1), CIN1 (mean=1.5 years; Weibull shape=1), and CIN2 (mean=2 years; Weibull shape=1) are based on the literature (7-10). Similar to the other models, not all parameters can be obtained directly from data; therefore, these baseline input parameters, including HPV incidence and CIN3 dwell time and progression to cancer, were calibrated to fit the CISNET-defined empirical data from the US (**Supplementary Table 1**). To calibrate, we used a built-in optimization method, which is an adaptation of the Nelder-Mead Simplex Method to optimize these and other parameters.

Policy1-Cervix is a comprehensive model of HPV transmission, HPV vaccination, cervical precancer, cancer survival, screening, diagnosis and treatment. The platform has been used

to perform policy evaluations across a range of countries including Australia, England, New Zealand, USA and China (11-17). The model simulates HPV infection which can persist and/or progress to CIN1, CIN2, or CIN3; CIN 3 can then progress to invasive cervical cancer. Progression and regression rates depend on the underlying HPV types present (HPV16, HPV18, pooled HPV31, HPV33, HPV45, HPV52, HPV58, and pooled other high-risk types), and can also vary by age, generally being more aggressive in older women. This structure is consistent with estimates in the literature at the time of the model structure development (18-22). Unique to Policy1-Cervix, the model incorporates more aggressive post-treatment natural history to capture increased risk of cervical precancer and cancer in women previously treated for precancer. Finally, in addition to the model inputs (e.g., background mortality) and calibration targets standardized across the CISNET models, Policy1-Cervix incorporates data reflecting improved survival for women with screen-detected cervical cancer compared to clinically-detected cervical cancer (e.g., via symptoms), based on published studies (23-25). The Policy1-Cervix model has been extensively validated against data from a range of settings (11, 15, 21, 26) including rates of HPV infection, high-grade disease and cervical cancer.

The UMN-HPV CA model is a recently developed microsimulation model of the natural history of HPV infection, cervical pre-cancer, cancer, cancer survival, screening, follow up, diagnosis and treatment. Individual women cycle through the model from the age of 9 until death or age 100 years. During this time they can acquire a type-specific HPV infection (HPV16, HPV18, pooled HPV31, HPV33, HPV45, HPV52, HPV58, and pooled other high-risk types) that can either clear or progress sequentially or non-sequentially through CIN grades 1, 2, and 3 to invasive cervical cancer. Transitions are a function of age and genotype, with other types generally being more aggressive with increasing age and severity of lesion. In the absence of screening, women can have their cancer (Stages I through IV) detected through symptoms or progress to a more advanced stage. Cancer survival is age and stage-specific. The model also accounts for background mortality and benign hysterectomy. Uncertain parameters (See Appendix Table 1) including HPV type-specific incidence and clearance, as well as CIN progression and regression are calibrated to CISNET-defined empirical data using a stochastic optimization algorithm (i.e., simulated annealing) and manual fine-tuning (**Supplementary Table 1**). Transition probabilities have been validated to multiple outcomes, including prospective data from a Canadian randomized controlled trial (27).

All models applied common inputs from the U.S. population, including 2009 hysterectomy rates from the National Hospital Discharge Survey (28), all-cause mortality from the Berkeley Mortality Database (29), and conditional 5-year stage-specific cervical cancer survival from the Surveillance, Epidemiology, and End Results (SEER) program (30).

For the imperfect compliance scenario, we assumed 70% compliance with primary testing and 90% compliance with follow-up management as recommended, including diagnostic colposcopy/biopsy and treatment to remove high-grade lesions. All models reflected test sensitivity and specificity of cytology for the presence (absence) of CIN2+ (72.7% and 91.9%, respectively), which were based on 18 studies identified in a systematic review (31).

Key structural differences

A direct comparison of model input values without taking into account differences in structure, underlying mechanism and functional forms used to model cervical cancer risk is not meaningful (32). Structurally, for three of the models, dwell times are estimated as a function of various transition probabilities between different disease states, whereas in the MISCAN-Cervix model, dwell time is used as a direct input into the model. MISCAN-cervix inputs and outputs are not identical due to other competing risks (such as background mortality or background hysterectomy). In general, the models can be grouped into three

categories according to what governs dwell times: transitions probabilities (Harvard, Policy1-Cervix, UMN-HPV CA) or input dwell time (MISCAN-Cervix). For two models (Policy1-Cervix and UMN-HPV CA), transition probabilities (and therefore output dwell times) are a function of HPV genotype and age; for one model (Harvard), transition probabilities (and therefore output dwell times) are a function of HPV genotype and the duration of an infection or lesion, but not age; finally, in MISCAN-Cervix, dwell time inputs are invariant to HPV genotype, duration of infection or lesion, and age.

Another key difference is that while all models calibrate multiple 'uncertain' parameters, the specifications of probabilities can differ between models. In three of the models, the calibration affects the probability of progressing or regressing at each discrete time step, which ultimately impacts the model output dwell time. In contrast, the calibration approach in the MISCAN-Cervix model, involves varying the states that individuals can transition to by age and HPV genotype, while the dwell time inputs for HPV, CIN1 and CIN2 are fixed. Such structural and parameter decisions were made independently by each team.

Model fit to empirical data following model calibration

The natural history models were fit to match common, standardized observed U.S. data on age-specific HPV prevalence and HPV genotype distribution in high-grade precancer (i.e., cervical intraepithelial neoplasia grades 2 (CIN2) or 3 (CIN3))), and age-specific genotype distribution in invasive cervical cancer from seven U.S. population-based cancer registries. The calibration process for MISCAN-Cervix, which differs from the other three models that predominately calibrate in the absence of screening, involves model fitting in the context of current screening behavior (33) based on screening attendance in New Mexico (34); therefore, a few additional calibration targets (i.e., 2007-2009 SEER cancer incidence rates, 2007-209 SEER cancer stage distribution, CIN and cancer detection rates by age (35)) for MISCAN were agreed upon in working-group consensus meetings. The UMN-HPV CA model also used additional calibration targets for model fitting including historical cancer incidence from multiple tumor registries prior to widespread cytology-based screening, which is similar to the calibration approach described for another analysis (27).

In a validation exercise following model calibration, we compared model outputs to age-specific cancer incidence from the Connecticut Tumor Registry (36) prior to widespread cytology-based screening (1950-1969), as well as compared the cumulative proportion of detected cancers by age (**Supplementary Figures 4 and 5**). For the Harvard, MISCAN-Cervix and Policy1-Cervix models, these data were not used directly in model parameterization or calibration but used to assess predictive validity for underlying cervical cancer risk (**Supplementary Figure 4**).

ADDITIONAL RESULTS

Additional results are provided in **Supplementary Tables 2-5** and Supplementary **Figures 8 and 9**.

TABLES

Supplementary Table 1. Baseline model assumptions, parameters and sources

	Microsimulation Model											
	Harvard			MISCAN-Cervix			Policy1-Cervix			UMN-HPV CA		
	Model transition assumption	Parameter Calibrated	Empirical data (ref)	Model transition assumption	Parameter Calibrated	Empirical data (ref)	Model transition assumption	Parameter Calibrated	Empirical data (ref)	Model transition assumption	Parameter Calibrated	Empirical data (ref)
Progression												
HPV incidence	Age- and genotype-specific	Yes	(3)	Age and genotype-specific	Yes	See Footnotes*	Age- and genotype-specific	Yes	(37, 38)	Age- and genotype-specific	Yes	Footnote Refs 1-7
HPV to CIN1	N/A	N/A	N/A	Age and genotype-specific (fixed duration mean 1 year)	Yes	See Footnotes*	Age- and genotype-specific	Yes	Footnotes*	Age and Genotype-specific. HPV 16 has higher progression rates by age.	Yes	Footnote Refs 1,5,8-24
HPV to CIN2	Duration and genotype-specific (increases with persistence; HPV16 has highest carcinogenicity)	Yes (only after year 5)	(2)	N/A	N/A	N/A	Age- and genotype-specific	Yes	Footnotes*	Age and Genotype-specific. HPV 16 has higher progression rates by age	Yes	
HPV to CIN3	Duration and genotype-specific (increases with persistence; HPV16 has highest carcinogenicity)	Yes; only after year 5	(2)	N/A	N/A	N/A	N/A	N/A	N/A	Age and Genotype-specific. HPV 16 has higher progression rates by age	Yes	
CIN1 to CIN2	N/A	N/A	N/A	Age and genotype-specific (fixed duration mean 1.5 years)	Yes	See Footnotes*	Age- and genotype-specific	Yes	Footnotes*	Age- and genotype-specific. HPV 16 has higher progression rates by age than other types	Yes	

	Microsimulation Model											
	Harvard			MISCAN-Cervix			Policy1-Cervix			UMN-HPV CA		
	Model transition assumption	**Parameter Calibrated**	**Empirical data (ref)**	**Model transition assumption**	**Parameter Calibrated**	**Empirical data (ref)**	**Model transition assumption**	**Parameter Calibrated**	**Empirical data (ref)**	**Model transition assumption**	**Parameter Calibrated**	**Empirical data (ref)**
CIN2 to CIN3	N/A	N/A	N/A	Age and genotype-specific (fixed duration mean 2 years)	Yes	See Footnotes*	Age- and genotype-specific	Yes	Footnotes*	Age- and genotype-specific. HPV 16 has higher progression rates by age than other types	Yes	
CIN2 to Cancer	Duration and genotype-specific (increasing with persistence; HPV16 has highest carcinogenicity)	Yes	(5)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
CIN3 to Cancer	Duration and genotype-specific (increases with persistence; HPV16 has highest carcinogenicity)	Yes	(5)	Genotype specific. Technically, progression chances are independent of duration.	Yes	See Footnotes*	Age- and genotype-specific	Yes	(5)	Age- and genotype-specific; increases with increasing age. Other high risk types have higher progression rates at older ages	Yes	
Cancer detection	Exponential, stage-specific	Yes	(39)	Age and stage-specific	Yes		Age- and stage-specific	Yes	See Footnotes*	Exponential, stage-specific	No	(39)
Cancer progression	Exponential, stage-specific	Yes	(39)	Age and stage-specific	Yes		Age- and stage-specific	Yes	See Footnotes*	Exponential, stage-specific	No	(39)
Regression												
HPV clearance	Duration- and genotype-specific (decreasing with persistence; HPV16 less likely to clear)	No	Primary data (2)	Age and genotype - specific	Yes	See Footnotes*	Age- and genotype-specific	Yes	See Footnotes*	Age- and genotype-specific; decreases with increasing age. HPV16 less likely to clear	Yes	
CIN1 to Normal	N/A		N/A	Genotype - specific	Yes	See Footnotes*	Age- and genotype-specific	Yes	See Footnotes*	Age- and genotype-specific;	Yes	

	Microsimulation Model											
	Harvard			MISCAN-Cervix			Policy1-Cervix			UMN-HPV CA		
	Model transition assumption	Parameter Calibrated	Empirical data (ref)	Model transition assumption	Parameter Calibrated	Empirical data (ref)	Model transition assumption	Parameter Calibrated	Empirical data (ref)	Model transition assumption	Parameter Calibrated	Empirical data (ref)
										decreases with increasing age. HPV16 less likely to clear.		
CIN2 to Normal	Duration- and genotype-specific (decreasing with persistence; HPV16 less likely to clear)	No	(4)	Genotype - specific	Yes	See Footnotes*	Age- and genotype-specific	Yes	See Footnotes*	Age- and genotype-specific; decreases with increasing age. HPV16 less likely to clear.	Yes	
CIN3 to Normal	Duration- and genotype-specific (decreasing with persistence; HPV16 less likely to clear)	No	(4)	Genotype - specific	Yes	See Footnotes*	N/A	N/A	N/A	Age- and genotype-specific; decreases with increasing age. HPV16 less likely to clear.	Yes	
CIN3 to CIN2	N/A	N/A	N/A	N/A	N/A	N/A	Age- and genotype-specific	Yes	See Footnotes*	Age- and genotype-specific; decreases with increasing age. HPV16 less likely to clear.	Yes	
CIN2 to CIN1	N/A	N/A	N/A	N/A	N/A	N/A	Age- and genotype-specific	Yes	See Footnotes*	Age- and genotype-specific; decreases with increasing age. HPV16 less likely to clear.	Yes	
Footnotes (MISCAN-Cervix)	*The parameters above were calibrated grouped together in a three- steps calibration approach in the context of screening (33) (see main manuscript Methods for additional calibration targets). **As in the MISCAN model, following the input dwell time in a given health state, we calibrate the progression and regression rates within the context of screening, our screening assumptions might influence the natural history of the disease. HPV dwell time (mean=1 year; Weibull shape=1), CIN1 (mean=1.5 years; Weibull shape=1), and CIN2 (mean=2 years; Weibull shape=1) are based on the literature [7-10].											

	Microsimulation Model											
	Harvard			MISCAN-Cervix			Policy1-Cervix			UMN-HPV CA		
	Model transition assumption	Parameter Calibrated	Empirical data (ref)	Model transition assumption	Parameter Calibrated	Empirical data (ref)	Model transition assumption	Parameter Calibrated	Empirical data (ref)	Model transition assumption	Parameter Calibrated	Empirical data (ref)
Footnotes (Policy1-Cervix)	Policy1-Cervix: *These parameters were all calibrated together as part of a large calibration exercise using the following targets: - Incidence of HPV 16, HPV18 and oncogenic HPV types other than HPV16/18, pre-vaccination (37) and (38) - Cervical cancer incidence by stage and age; Data obtained from ACIM (Australian Cancer Incidence and Mortality) Books (40) - Cervical cancer mortality by stage and age; Data obtained from ACIM (Australian Cancer Incidence and Mortality) Books (40) - High grade histology rate in women screened 20-69 years; Data obtained from Cervical screening in Australia 2010-2011 (41) - Low-grade cytology abnormalities detected in women 20-69 years; Data obtained from Cervical screening in Australia 2010-2011 (41) - High-grade cytology abnormalities detected in women 20-69 years; Data obtained from Cervical screening in Australia 2010-2011 (41) - Age-standardized annual progression rate from CIN3 to asymptomatic localized cancer (5)											
Footnotes (UMN-HPV CA)	1 Castle PE, Schiffman M, Herrero R, et al. A prospective study of age trends in cervical human papillomavirus acquisition and persistence in Guanacaste, Costa Rica. J Infect Dis. 2005;191(11):1808-1816. 2 Dunne EF, Unger ER, Sternberg M, et al. Prevalence of HPV infection among females in the United States. JAMA. 2007;297(8):813-819. 3 Moscicki AB, Hills N, Shiboski S, et al. Risks for incident human papillomavirus infection and low-grade squamous intraepithelial lesion development in young females. JAMA. 2001;285(23):2995-3002. 4 Myers ER, McCrory DC, Nanda K, Bastian L, Matchar DB. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. Am J Epidemiol. 2000;151(12):1158-1171. 5 Schiffman M, Kjaer SK. Chapter 2: Natural history of anogenital human papillomavirus infection and neoplasia. J Natl Cancer Inst. 2003;Monographs(31):14-19. 6 Winer RL, Feng Q, Hughes JP, O'Reilly S, Kiviat NB, Koutsky LA. Risk of female human papillomavirus acquisition associated with first male sex partner. J Infect Dis. 2008;197(2):279-282. 7 Winer RL, Lee SK, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. Am J Epidemiol. 2003;157(3):218-226. 8 Baseman JG, Koutsky LA. The epidemiology of human papillomavirus infections. J Clin Virol. 2005;32 Suppl 1:S16-24. 9 De Aloysio D, Miliffi L, Iannicelli T, Penacchioni P, Bottiglioni F. Intramuscular interferon-beta treatment of cervical intraepithelial neoplasia II associated with human papillomavirus infection. Acta Obstet Gynecol Scand. 1994;73(5):420-424. 10 Hildesheim A, Schiffman MH, Gravitt PE, et al. Persistence of type-specific human papillomavirus infection among cytologically normal women. J Infect Dis. 1994;169(2):235-240. 11 Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. N Engl J Med. 1998;338(7):423-428. 12 Holowaty P, Miller AB, Rohan T, To T. Natural history of dysplasia of the uterine cervix. J Natl Cancer Inst. 1999;91(3):252-258. 13 Kataja V, Syrjanen K, Mantyjarvi R, et al. Prospective follow-up of cervical HPV infections: life table analysis of histopathological, cytological and colposcopic data. Eur J Epidemiol. 1989;5(1):1-7. 14 Koutsky LA, Holmes KK, Critchlow CW, et al. A cohort study of the risk of cervical intraepithelial neoplasia grade 2 or 3 in relation to papillomavirus infection. N Engl J Med. 1992;327(18):1272-1278. 15 Matsumoto K, Yasugi T, Oki A, et al. IgG antibodies to HPV16, 52, 58 and 6 L1-capsids and spontaneous regression of cervical intraepithelial neoplasia. Cancer Lett. 2006;231(2):309-313. 16 McCredie MR, Sharples KJ, Paul C, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. Lancet Oncol. 2008;9(5):425-434. 17 Syrjanen K, Kataja V, Yliskoski M, Chang F, Syrjanen S, Saarikoski S. Natural history of cervical human papillomavirus lesions does not substantiate the biologic relevance of the Bethesda System. Obstet Gynecol. 1992;79(5 (Pt 1)):675-682. 18 Winer RL, Kiviat NB, Hughes JP, et al. Development and duration of human papillomavirus lesions, after initial infection. J Infect Dis. 2005;191(5):731-738. 19 Woodman CB, Collins S, Winter H, et al. Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. Lancet. 2001;357(9271):1831-1836. 20 Yokoyama M, Iwasaka T, Nagata C, et al. Prognostic factors associated with the clinical outcome of cervical intraepitheliaI neoplasia: a cohort study in Japan. Cancer Lett. 2003;192(2):171-179. 21 Clifford GM, Smith JS, Aguado T, Franceschi S. Comparison of HPV type distribution in high-grade cervical lesions and cervical cancer: a meta-analysis. Br J Cancer. 2003;89(1):101-105. 22 Clifford GM, Smith JS, Plummer M, Munoz N, Franceschi S. Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. Br J Cancer. 2003;88(1):63-73. 23 Insinga RP, Dasbach EJ, Elbasha EH. Epidemiologic natural history and clinical management of Human Papillomavirus (HPV) Disease: a critical and systematic review of the literature in the development of an HPV dynamic transmission model. BMC Infect Dis. 2009;9:119. 24 Joste NE, Ronnett BM, Hunt WC, et al. Human papillomavirus genotype-specific prevalence across the continuum of cervical neoplasia and cancer. Cancer Epidemiol Biomarkers Prev. 2015;24(1):230-240. 25 SEER Program. SEER*Stat Database: Cancer Mortality, Total U.S. (1975-2012) <Howlader Algorithm>. National Cancer Institute, DCCPS, Surveillance Research Program; 2014. 26 Centers for Disease Control and Prevention (CDC). National Hospital Discharge Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2009.											

Supplementary Table 2. Summary of the median age (years) of causal high-risk human papillomavirus (HPV) infection under assumptions of no screening (i.e., natural history), imperfect compliance to triennial cytology-based screening (HPV triage for atypical cells of undetermined significance (ASCUS)), and perfect compliance to triennial cytology-based screening.

	Microsimulation Model			
	Harvard	**MISCAN-Cervix**	**Policy1-Cervix**	**UMN HPV-CA**
Natural History	20.8	34.0	22.8	19.1
Imperfect Screening Compliance*	25.4	49.9	27.9	25.1
Perfect Screening Compliance	35.6	56.2	45.2	47.8

*Screening assumes 70% compliance triennial cytology-based testing between ages 21 and 65 years and 90% compliance to follow-up, colposcopy and treatment recommendations.

Supplementary Table 3. Mean, median and interquartile range (IQR) dwell times (years) for women that developed invasive cervical cancer across preclinical phases of cancer development, stratified by any high-risk (hr) human papillomavirus (HPV) infection, HPV16 infections, and non-HPV16 infections.*

	Microsimulation Model			
Dwell time stage	**Policy1-Cervix**	**MISCAN-Cervix**	**Harvard**	**UMN-HPV CA**
HPV/CIN1 dwell time				
Mean: Any hrHPV	5.2	2.6	9.9 (8.8-11.2)	4.7
Median: Any hrHPV	4.0	2.2	8.0 (7.2-9)	4.0
Interquartile range: Any hrHPV	2-7	1.2-3.5	5.5-13.9	2-6
Mean: HPV16	5.7	2.6	6.9 (6.3-7.9)	4.2
Median: HPV16	5.0	2.2	6.7 (6.3-7.4)	3.0
Interquartile range: HPV16	2-8	1.2-3.5	5.1-10.2	1-6
Mean: non-HPV16	4.8	2.6	13.6 (12.1-15.6)	5.4
Median: non-HPV16	4.0	2.2	11.7 (9.8-13.7)	4.0
IQR range: non-HPV16	2-6	1.2-3.5	6.4-21.5	2-7
CIN2/3 dwell time				
Mean: Any hrHPV	19.0	11.0	15.8 (14.3-16.6)	20.0
Median: Any hrHPV	16.0	8.2	13.3 (11.8-14.2)	17.0
Interquartile range: Any hrHPV	8-27	4.2-15.0	6.5-23.6	8-29
Mean: HPV16	20.9	11.0	13.9 (12.7-14.5)	21.5
Median: HPV16	18.0	8.2	11.7 (10.5-12.4)	18.0
Interquartile range: HPV16	10-30	4.2-15.0	5.91-20.8	10-30
Mean: non-HPV16	17.1	11.1	18.2 (16.4-19.4)	17.7
Median: non-HPV16	14.0	8.3	16.1 (14-17.8)	14.0
IQR range: non-HPV16	7-24	4.2-15.0	6.8-28.1	6-27
Sojourn dwell time				
Mean: Any hrHPV	4.1	6.1	3.1 (3-3.1)	3.6
Median: Any hrHPV	3.0	5.3	2.3 (2.3-2.3)	3.0
Interquartile range: Any hrHPV	2-5	3.1-8.2	1.0-4.6	2-5
Mean: HPV16	4.2	6.1	3.1 (3.0-3.1)	3.6
Median: HPV16	3.0	5.3	2.3 (2.3-2.4)	3.0
Interquartile range: HPV16	2-5	3.1-8.2	1.1-4.3	2-5
Mean: non-HPV16	4.0	6.1	3.0 (3.0-3.1)	3.5
Median: non-HPV16	3.0	5.3	2.3 (2.2-2.3)	3.0
IQR range: non-HPV16	2-5	3.1-8.3	1.0-4.3	2-5
Total dwell time				
Mean: Any hrHPV	28.3	19.8	28.8 (27.6-29.9)	28.3
Median: Any hrHPV	26.0	17.5	25.7 (24.5-26.6)	25.0
IQR range: Any hrHPV	17-37	12.2-25.0	16.7-39.6	16-38
Mean: HPV16	30.7	19.7	23.9 (23.2-24.6)	29.3
Median: HPV16	29.0	17.5	22.0 (21.3-22.8)	26.0
IQR range: HPV16	20-40	12.2-24.9	15.3-31.1	17-38
Mean: non-HPV16	25.9	19.8	34.8 (33-36.3)	26.7
Median: non-HPV16	23.0	17.6	33.7 (31.2-35.8)	24.0
IQR range: non-HPV16	16-34	12.3-25.0	19.3-47.9	14.5-37.0

*For the Harvard model, error bars reflect the min and max IQR values across the 50 good-fitting parameter sets. Cervical intraepithelial neoplasia (CIN).

Supplementary Table 4. Mean, median and interquartile range (IQR) dwell times (years) for women that developed invasive cervical cancer assuming imperfect compliance to screening guidelines stratified by any high-risk (hr) human papillomavirus (HPV) infection, HPV16 infections, and non-HPV16 infections.

	Microsimulation Model			
Dwell time stage	**Policy1-Cervix**	**MISCAN-Cervix**	**Harvard**	**UMN-HPV CA**
HPV/CIN1 dwell time				
Mean: Any hrHPV	8.4	2.5	9.2 (8.3-1)	4.5
Median: Any hrHPV	5.0	2.1	7.7 (7.1-8.6)	3.0
Interquartile range: Any hrHPV	2-9	1.2-3.4	5.4-12.1	2-7
Mean: HPV16	8.8	2.5	6.9 (6.5-7.8)	3.8
Median: HPV16	5.0	2.1	6.8 (6.4-7.5)	3.0
Interquartile range: HPV16	3-10	1.2-3.4	5.12-10.2	1-6
Mean: non-HPV16	8.0	2.5	12.7 (11.1-16.3)	5.4
Median: non-HPV16	4.0	2.1	10.0 (8.8-11.2)	4.0
Interquartile range: non-HPV16	2-8	1.2-3.3	6.3-22.5	2-7
CIN2/3 dwell time				
Mean: Any hrHPV	11.7	7.2	6.9 (6.5-7.1)	10.9
Median: Any hrHPV	8.0	5.0	5.5 (5.1-5.8)	6.0
Interquartile range: Any hrHPV	4-16	2.5-9.5	2.5-9.3	2-14
Mean: HPV16	13.2	7.1	6.8 (6.3-7.1)	13.1
Median: HPV16	9.0	5.0	5.6 (5.3-5.8)	8.0
Interquartile range: HPV16	4-18	2.5-9.5	2.8-9.3	4-18
Mean: non-HPV16	10.5	7.2	7 (6.8-7.4)	8.2
Median: non-HPV16	7.0	5.0	5.2 (4.8-5.6)	4.0
Interquartile range: non-HPV16	4-14	2.6-9.5	2.1-9.8	2-9
Sojourn dwell time				
Mean: Any hrHPV	3.0	4.1	2.1 (2.1-2.1)	2.7
Median: Any hrHPV	2.0	3.2	1.5 (1.5-1.6)	2.0
Interquartile range: Any hrHPV	1-4	1.6-5.8	0.7-3.0	1-4
Mean: HPV16	3.1	4.1	2.1 (2.1-2.1)	2.8
Median: HPV16	2.0	3.2	1.5 (1.5-1.6)	2.0
Interquartile range: HPV16	1-4	1.5-5.7	0.7-3.0	1-4
Mean: non-HPV16	2.9	4.1	2.1 (2-2.1)	2.5
Median: non-HPV16	2.0	3.2	1.5 (1.5-1.6)	2.0
Interquartile range: non-HPV16	1-4	1.6-5.8	0.7-3.0	1-4
Total dwell time				
Mean: Any hrHPV	23.0	13.8	18.2 (17.3-19.6)	18.1
Median: Any hrHPV	18.0	12.0	15.3 (14.9-15.8)	14.0
Interquartile range: Any hrHPV	12-31	7.9-17.7	12.4-22.6	8-23.5
Mean: HPV16	25.1	13.8	15.8 (15.4-16.2)	19.7
Median: HPV16	21.0	12.0	14.5 (14.3-14.9)	15.0
Interquartile range: HPV16	13-34	7.9-17.7	12.0-19.1	9-25
Mean: non-HPV16	21.4	13.8	21.8 (20.2-25.2)	16.1
Median: non-HPV16	17.0	12.0	17.6 (16.6-19.5)	12.0
Interquartile range: non-HPV16	11-28	7.9-17.8	13.0-34.3	8-20

*Screening involved HPV triage for atypical cells of undetermined significance (ASCUS). Imperfect compliance assumes 70% compliance to primary screening and 90% compliance to follow-up management, including colposcopy/biopsy and precancer treatment. The Harvard values reflect the mean, min and max across the 50 good-fitting natural history parameter sets. Cervical intraepithelial neoplasia (CIN)

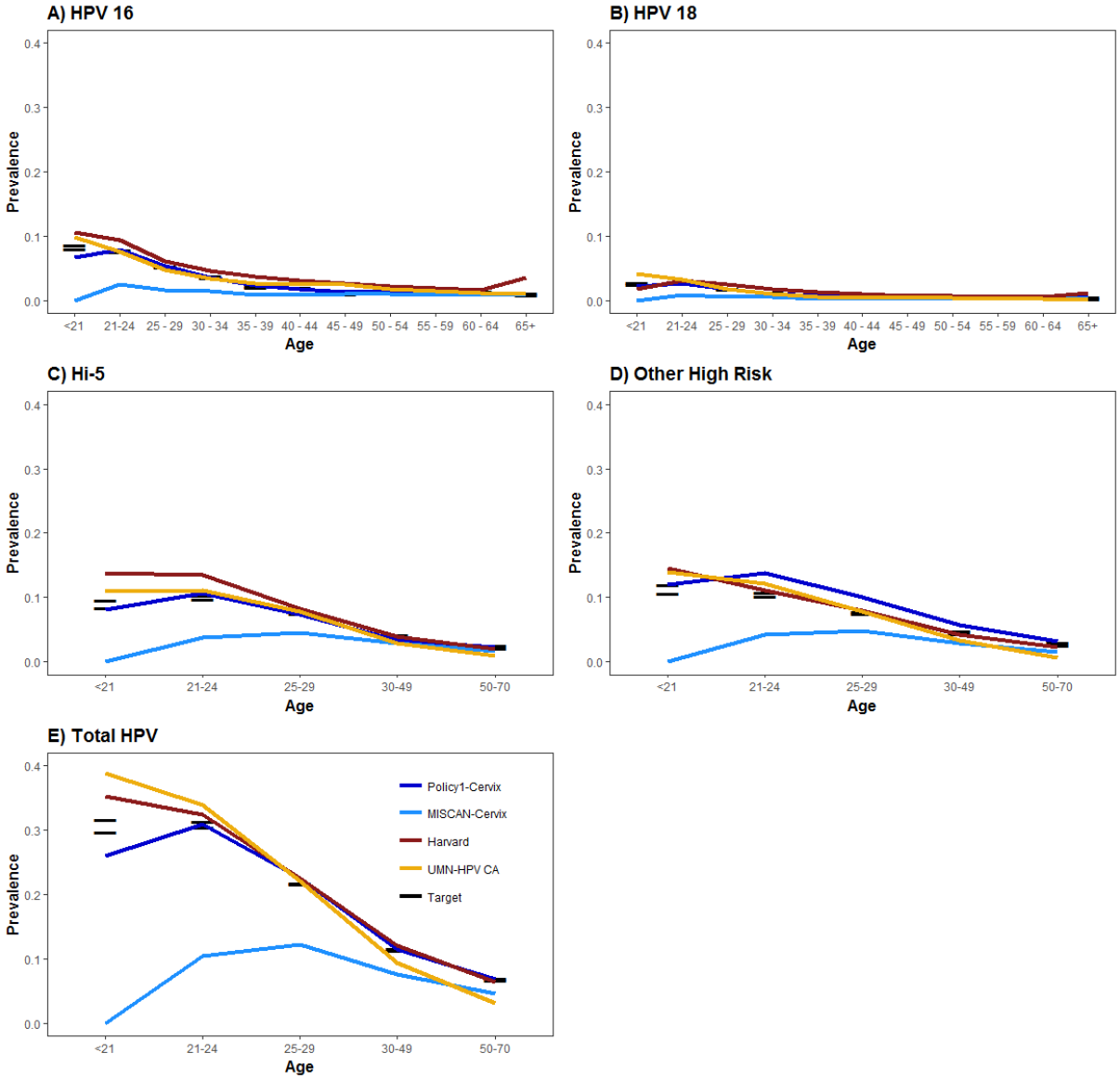
Supplementary Table 5. Mean, median and interquartile range (IQR) dwell times (years) for women that developed invasive cervical cancer assuming perfect compliance to screening guidelines.*

	Microsimulation Model			
Dwell time stage	**Policy1-Cervix**	**MISCAN-Cervix**	**Harvard**	**UMN-HPV CA**
HPV/CIN1 dwell time				
Mean: Any hrHPV	12.2	2.5	9.8 (8.2-12.1)	4.4
Median: Any hrHPV	6.0	2.1	8.0 (7.1-9.3)	3.0
Interquartile range: Any hrHPV	3-14	1.2-3.4	5.4-13.3	1-6
Mean: HPV16	13.6	2.5	6.98 (6.3-8)	3.3
Median: HPV16	7.0	2.1	7.0 (6.3-8)	2.0
Interquartile range: HPV16	3-17	1.2-3.4	5.1-10.3	1-4
Mean: non-HPV16	11.2	2.5	13.5 (11.2-17.8)	5.6
Median: non-HPV16	5.0	2.1	10.5 (8.8-13.2)	4.0
Interquartile range: non-HPV16	2-12	1.2-3.4	6.3-24.4	2-8
CIN2/3 dwell time				
Mean: Any hrHPV	5.7	7.4	5.9 (5.3-6.2)	4.3
Median: Any hrHPV	4.0	5.2	4.2 (3.6-4.7)	3.0
Interquartile range: Any hrHPV	2-8	2.4-10.2	1.5-8.3	2-6
Mean: HPV16	5.8	7.4	5.8 (5-6.3)	5.2
Median: HPV16	5.0	5.2	4.4 (3.6-5)	4.0
Interquartile range: HPV16	2-8	2.4-10.2	1.7-8.4	2-7
Mean: non-HPV16	5.7	7.4	6 (5.5-6.5)	3.3
Median: non-HPV16	4.0	5.2	3.9 (3.3-4.5)	2.0
Interquartile range: non-HPV16	2-8	2.4-10.1	1.3-8.9	1-4
Sojourn dwell time				
Mean: Any hrHPV	2.1	3.8	1.9 (1.8-2)	2.1
Median: Any hrHPV	2.0	2.6	1.3715 (1.3-1.4)	2.0
Interquartile range: Any hrHPV	1-3	1.2-5.4	0.6-2.7	1-3
Mean: HPV16	2.1	3.8	1.9 (1.8-2)	2.1
Median: HPV16	2.0	2.6	1.4 (1.3-1.5)	1.0
Interquartile range: HPV16	1-3	1.2-5.4	0.6-2.6 (0.5-2.8)	1-3
Mean: non-HPV16	2.1	3.8	1.9 (1.8-2.1)	2.1
Median: non-HPV16	2.0	2.7	1.3 (1.3-1.4)	2.0
Interquartile range: non-HPV16	1-3	1.21-5.4	0.5-2.8	1-3
Total dwell time				
Mean: Any hrHPV	20.0	13.7	17.6 (16.3-19.9)	10.8
Median: Any hrHPV	13.0	12.1	14.5 (13.9-15.3)	10.0
Interquartile range: Any hrHPV	8-24	7.4-18.2	11.5-23.8	7-14
Mean: HPV16	21.5	13.8	14.7 (14.1-15.2)	10.6
Median: HPV16	15.0	12.2	13.5 (13.2-14.0)	9.0
Interquartile range: HPV16	9.0-26.0	7.4-18.2	11.0-17.9	7.0-13.0
Mean: non-HPV16	19.0	13.6	21.4 (18.7-26.0)	10.9
Median: non-HPV16	13.0	12.1	16.9 (15.1-21.7)	10.0
Interquartile range: non-HPV16	8.0-22.0	7.4-18.1	12.1-35.8	7.0-14.0

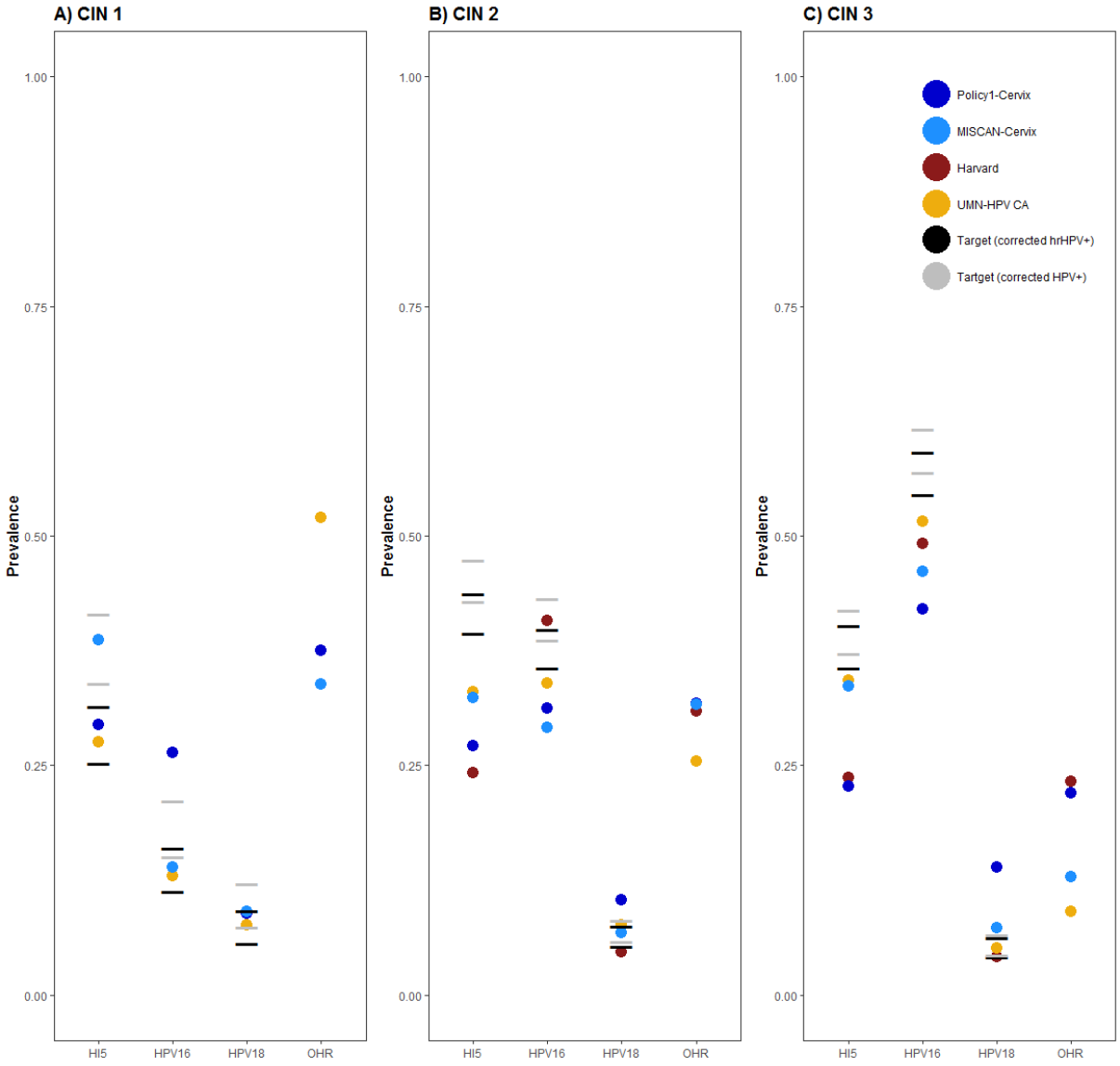
* Screening involved HPV triage for atypical cells of undetermined significance (ASCUS). The Harvard values reflect the mean, min and max across the 50 good-fitting natural history parameter sets. Cervical intraepithelial neoplasia (CIN).

FIGURES

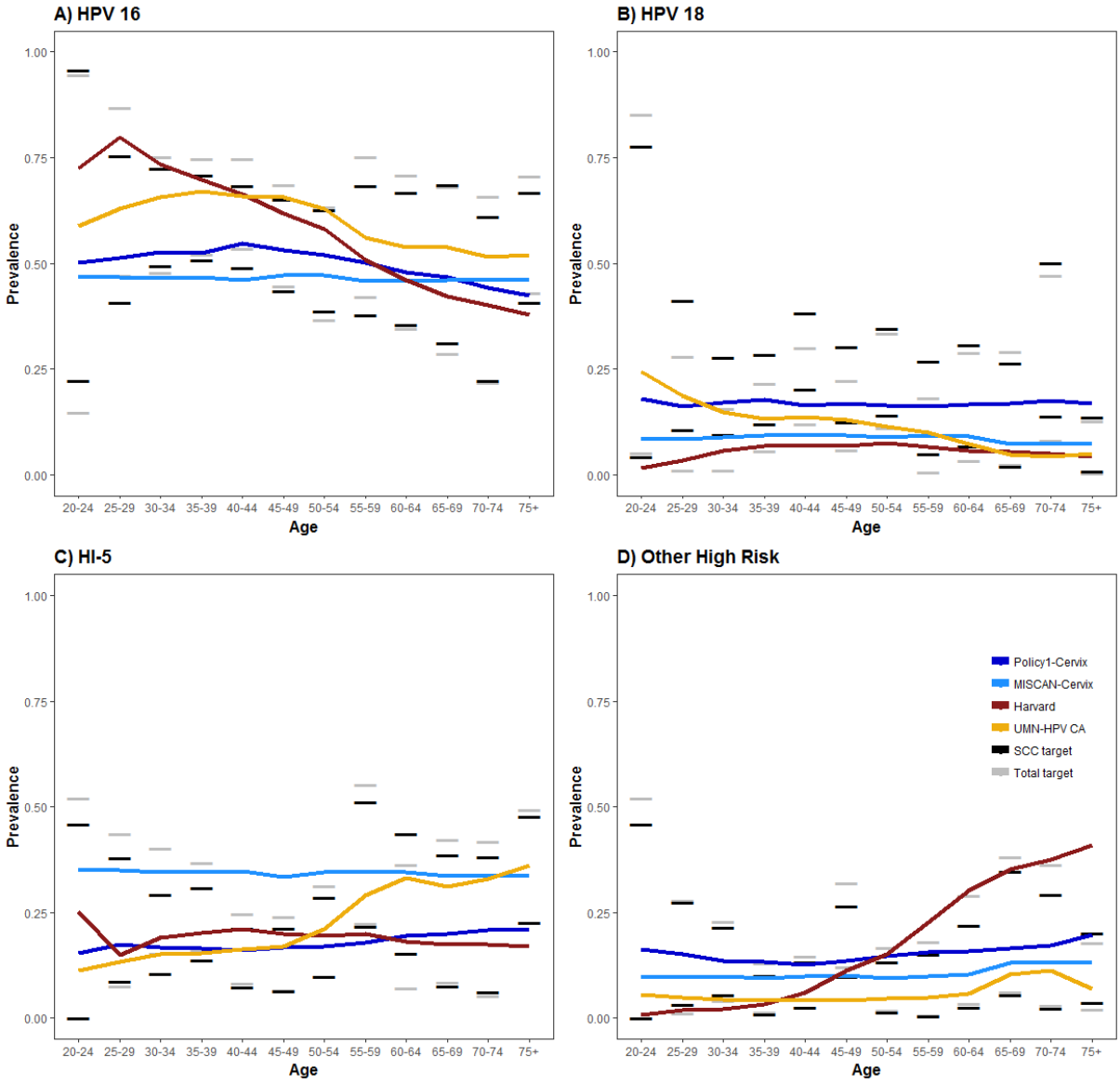
Supplementary Figure 1. Age- and genotype-specific human papillomavirus (HPV) prevalence. Empirical calibration targets (black lines), derived from the New Mexico HPV Pap Registry (42) (updated via personal communication), and model fit to empirical data from each CISNET model cite (colored lines). Note that in MISCAN-Cervix HPV prevalence represents the prevalence of progressive HPV lesions that will lead to cancer, which reflect only a proportion of the total HPV prevalence in the population.



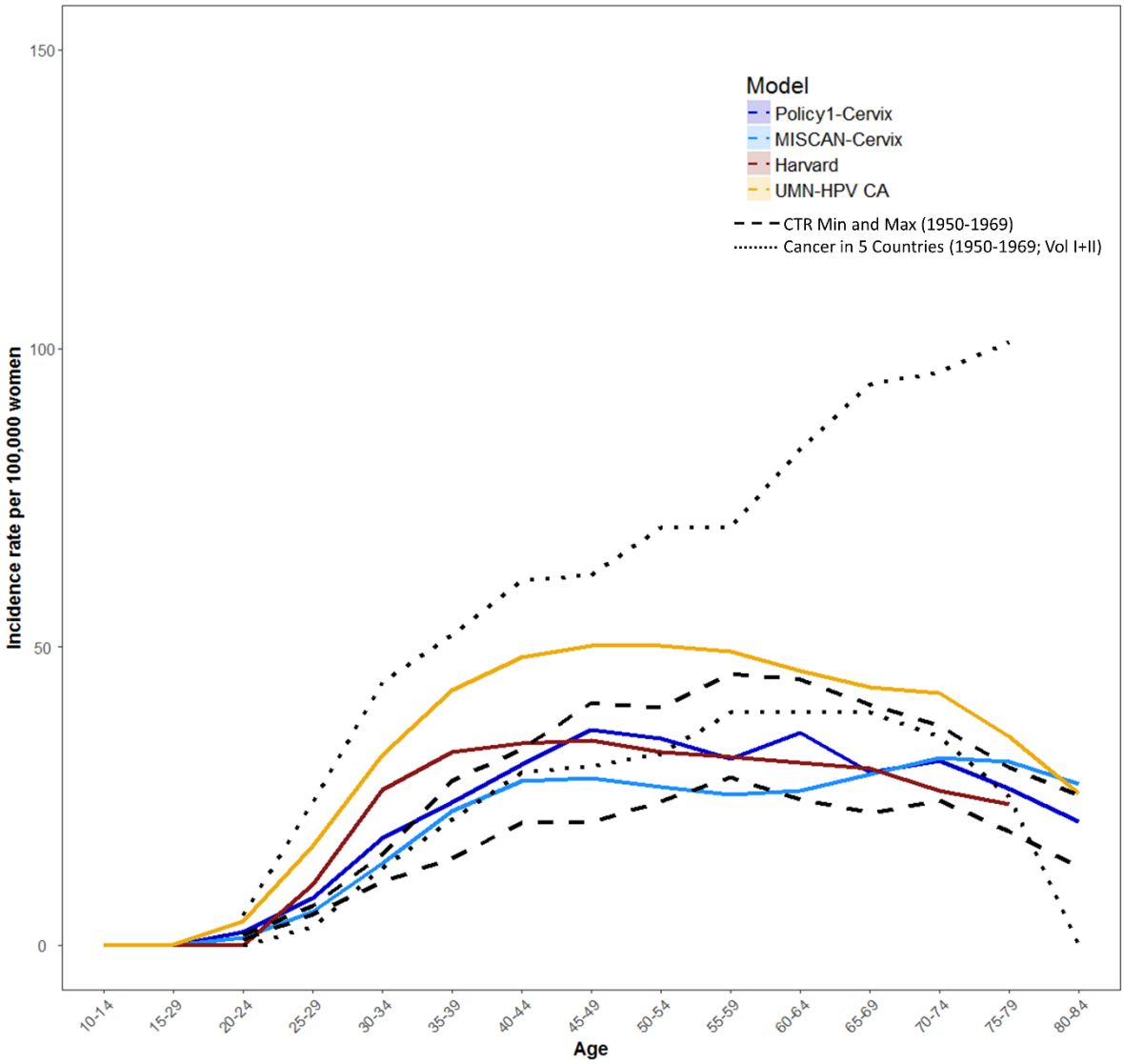
Supplementary Figure 2. Genotype-specific frequency among human papillomavirus (HPV)-positive cervical intraepithelial neoplasia (CIN) grades 1, 2 and 3. Empirical calibration targets (black and grey bars), derived from (43), and model fit to empirical data for each CISNET model (colored dots). Models that include low-risk HPV types (i.e., Harvard) fit to target data corrected for any HPV+ (i.e., removal of HPV-negatives), while models that include only high-risk HPV fit to target data corrected for hrHPV+ (i.e., removal of HPV-negatives and low-risk HPVs).



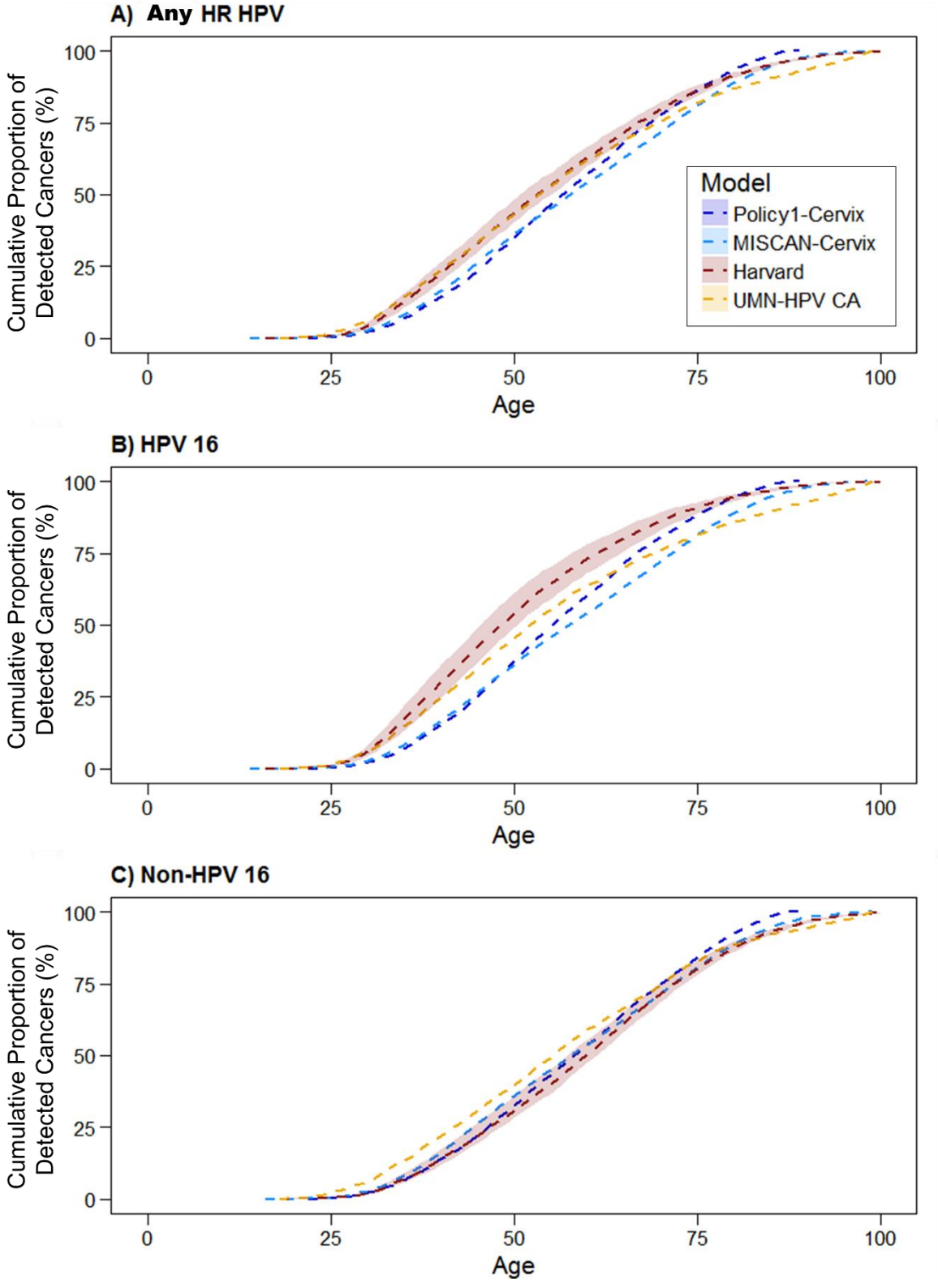
Supplementary Figure 3. Age- and genotype-specific frequency among human papillomavirus (HPV)-positive cervical cancers. Empirical calibration targets (black or grey bars), derived from (44), and model fit to empirical data for each CISNET model (colored lines). Models that reflect squamous cell carcinoma (SCC) (i.e., Harvard) fit to the 'SCC target' data (black), while models that reflect all cervical cancer histologies fit to the 'Total target' data (grey).



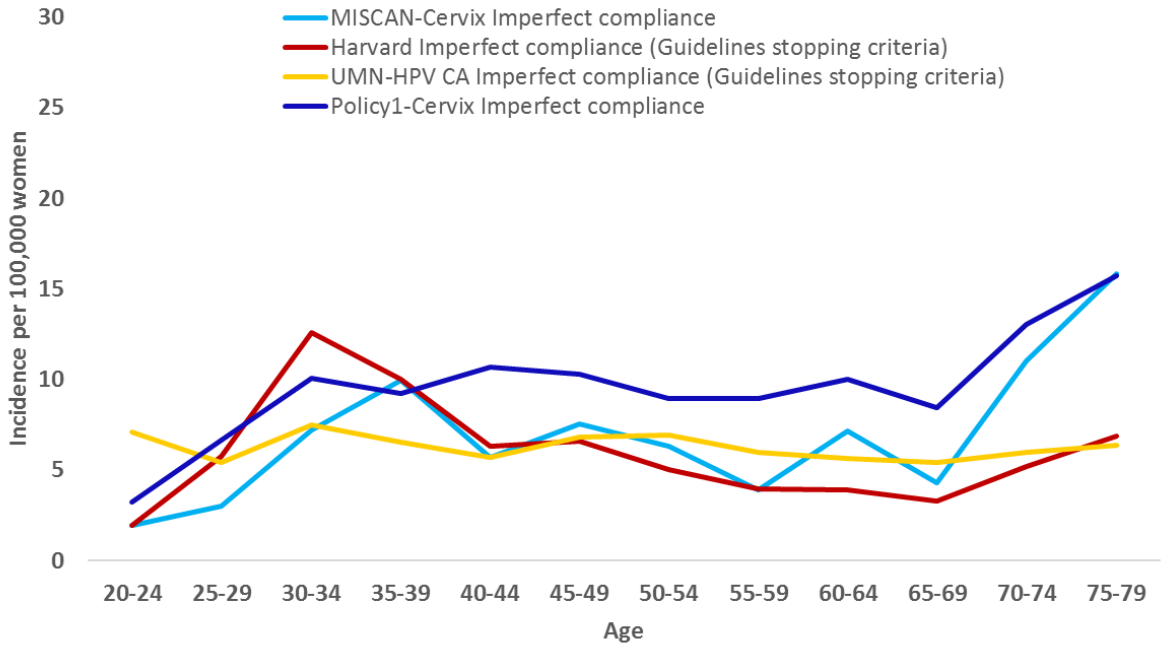
Supplementary Figure 4. Model validation to age-specific cervical cancer incidence prior to cytology-based screening, derived from the Connecticut Tumor Registry (CTR) 1950-1969 (black lines) (36), and model fit (colored lines). Model outputs adjust for hysterectomy rates projected for a 2009 birth cohort, which may be lower than historical rates. Note that UMN-HPV CA used cancer incidence from Cancer in 5 Countries (45, 46) as a formal calibration target.



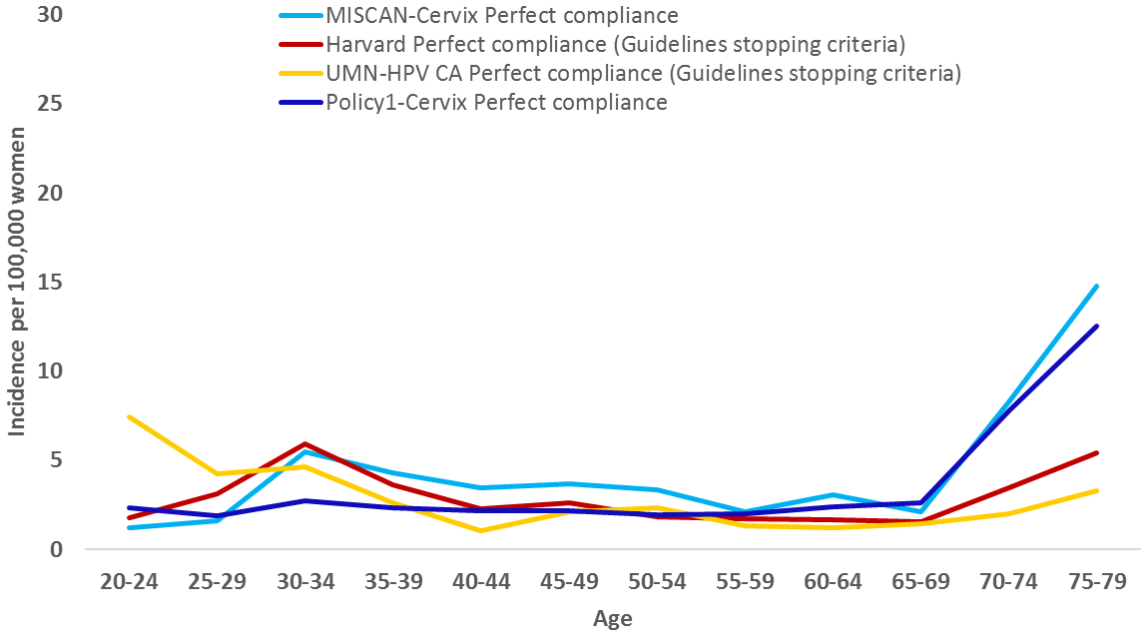
Supplementary Figure 5. Cumulative proportion of detected (i.e., clinical) cancers by age (years) in the absence of screening or human papillomavirus (HPV) vaccination (i.e., natural history) policies.



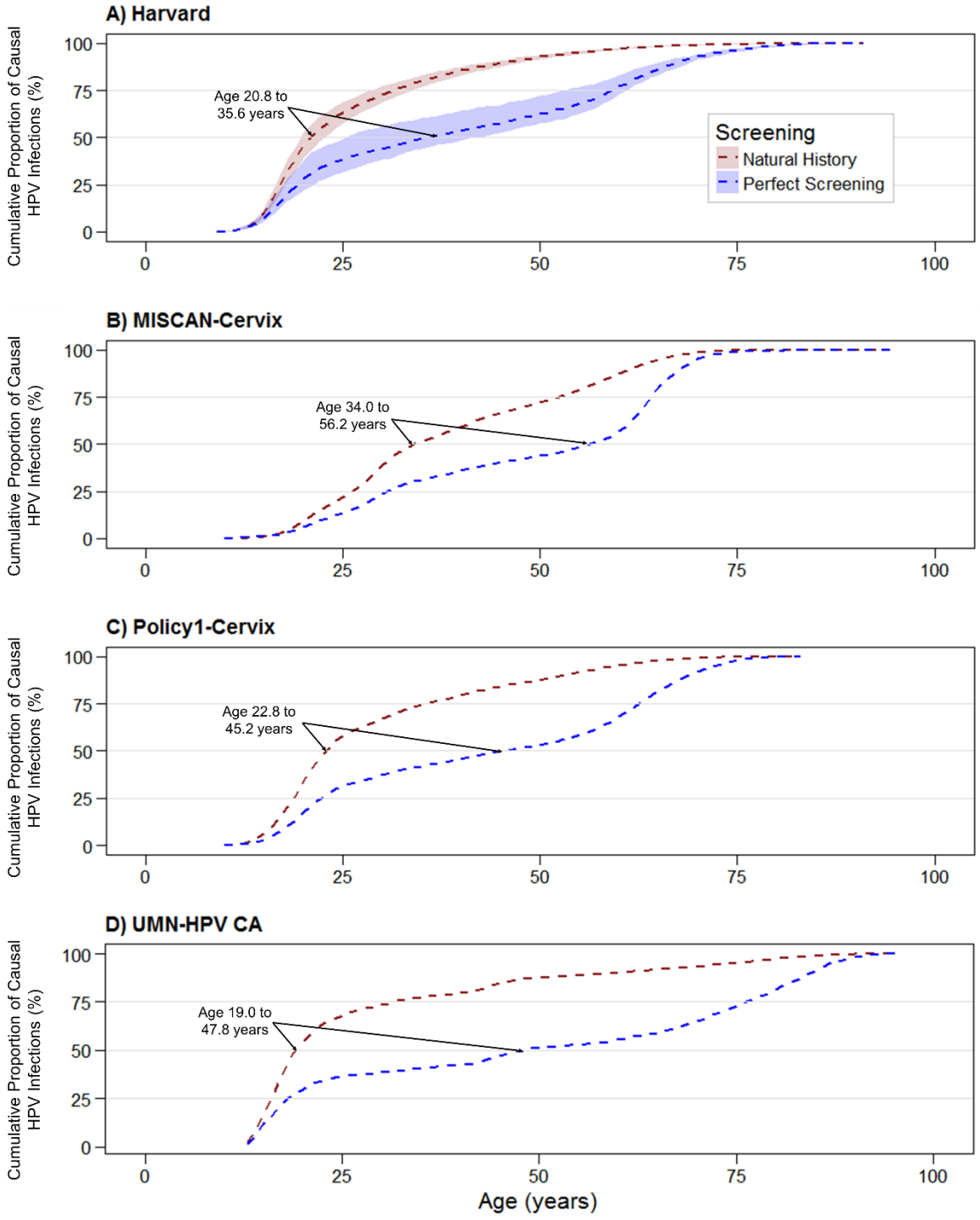
Supplementary Figure 6. Age-specific cervical cancer incidence in the context of triennial cytology-based screening assuming imperfect compliance to screening guidelines (screening compliance assumes 70% compliance to primary screening and 90% compliance to follow-up, colposcopy and treatment recommendations). Model output (colored lines).



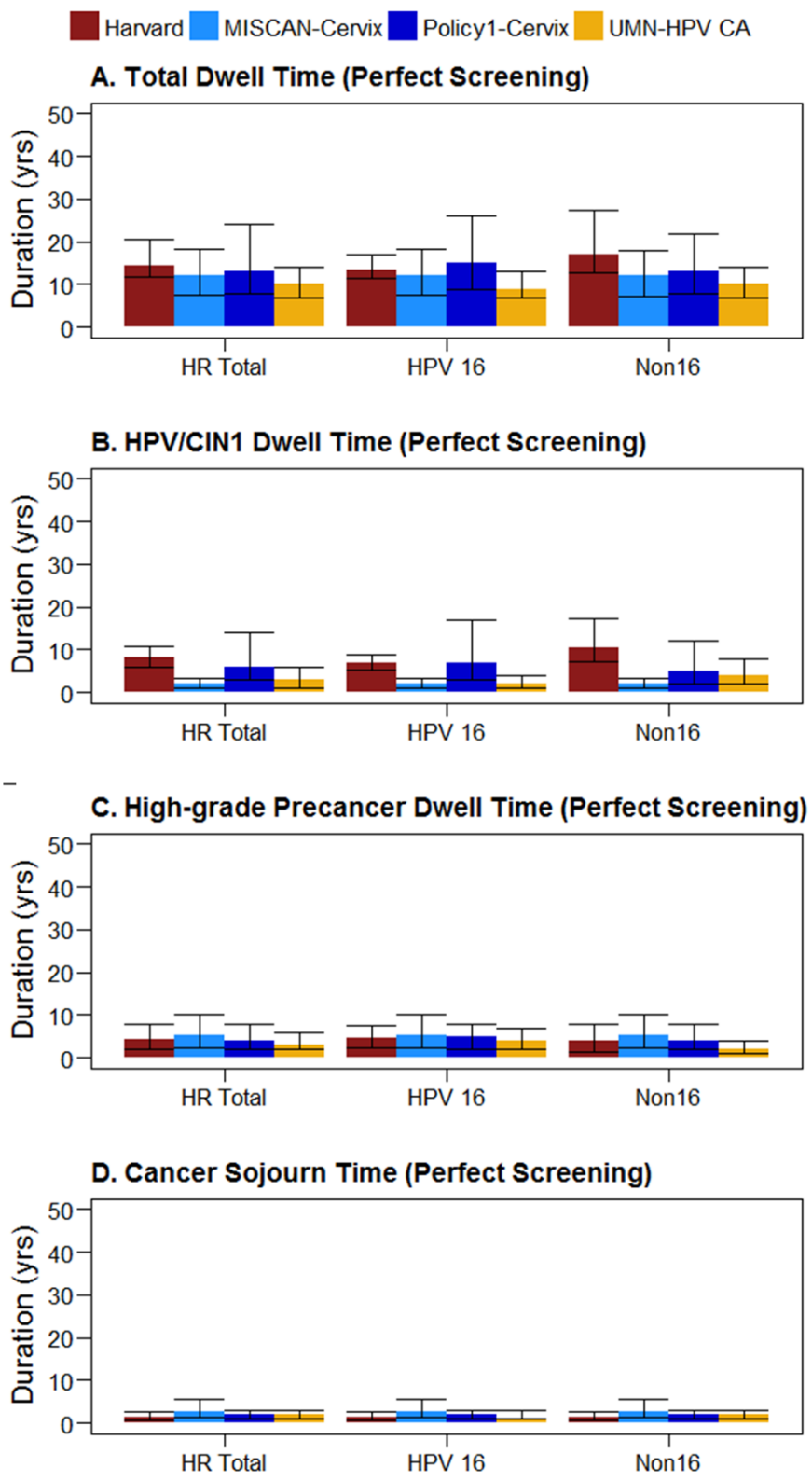
Supplementary Figure 7. Age-specific cervical cancer incidence in the context of triennial cytology-based screening assuming perfect compliance to screening. Model output (colored lines).



Supplementary Figure 8. Cumulative proportion of the causal high-risk human papillomavirus (HPV) infection by age for the natural history and in the context of triennial cytology-based screening (HPV triage for atypical-cells of undetermined significance (ASCUS)) assuming perfect screening compliance to guidelines.



Supplementary Figure 9. Median dwell times (years) for women that developed invasive cervical cancer in the context of triennial cytology-based screening (human papillomavirus (HPV) triage for atypical-cells of undetermined significance (ASCUS)) assuming perfect screening compliance to guidelines.



REFERENCES

1. Campos NG, Burger EA, Sy S, Sharma M, Schiffman M, Rodriguez AC, et al. An updated natural history model of cervical cancer: derivation of model parameters. American journal of epidemiology. 2014;180(5):545-55.
2. Herrero R, Hildesheim A, Rodriguez AC, Wacholder S, Bratti C, Solomon D, et al. Rationale and design of a community-based double-blind randomized clinical trial of an HPV 16 and 18 vaccine in Guanacaste, Costa Rica. Vaccine. 2008;26(37):4795-808.
3. Munoz N, Mendez F, Posso H, Molano M, van den Brule AJ, Ronderos M, et al. Incidence, duration, and determinants of cervical human papillomavirus infection in a cohort of Colombian women with normal cytological results. The Journal of infectious diseases. 2004;190(12):2077-87.
4. Keefe KA, Schell MJ, Brewer C, McHale M, Brewster W, Chapman JA, et al. A randomized, double blind, Phase III trial using oral beta-carotene supplementation for women with high-grade cervical intraepithelial neoplasia. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2001;10(10):1029-35.
5. McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. The Lancet Oncology. 2008;9(5):425-34.
6. Kim JJ, Kuntz KM, Stout NK, Mahmud S, Villa LL, Franco EL, et al. Multiparameter calibration of a natural history model of cervical cancer. American journal of epidemiology. 2007;166(2):137-50.
7. Berkhof J, de Bruijne MC, Zielinski GD, Meijer CJ. Natural history and screening model for high-risk human papillomavirus infection, neoplasia and cervical cancer in the Netherlands. International journal of cancer. 2005;115(2):268-75.
8. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. Lancet (London, England). 2007;370(9590):890-907.
9. Moscicki AB, Ma Y, Wibbelsman C, Darragh TM, Powers A, Farhat S, et al. Rate of and risks for regression of cervical intraepithelial neoplasia 2 in adolescents and young women. Obstetrics and gynecology. 2010;116(6):1373-80.
10. Moscicki AB, Shiboski S, Hills NK, Powell KJ, Jay N, Hanson EN, et al. Regression of low-grade squamous intra-epithelial lesions in young women. Lancet (London, England). 2004;364(9446):1678-83.
11. Lew JB, Simms K, Smith M, Lewis H, Neal H, Canfell K. Effectiveness Modelling and Economic Evaluation of Primary HPV Screening for Cervical Cancer Prevention in New Zealand. PloS one. 2016;11(5):e0151619.
12. Lew JB, Simms KT, Smith MA, Hall M, Kang YJ, Xu XM, et al. Primary HPV testing versus cytology-based cervical screening in women in Australia vaccinated for HPV and unvaccinated: effectiveness and economic assessment for the National Cervical Screening Program. The Lancet Public health. 2017;2(2):e96-e107.
13. Simms KT, Laprise JF, Smith MA, Lew JB, Caruana M, Brisson M, et al. Cost-effectiveness of the next generation nonavalent human papillomavirus vaccine in the context of primary human papillomavirus screening in Australia: a comparative modelling analysis. The Lancet Public health. 2016;1(2):e66-e75.
14. Simms KT, Smith MA, Lew JB, Kitchener HC, Castle PE, Canfell K. Will cervical screening remain cost-effective in women offered the next generation nonavalent HPV vaccine? Results for four developed countries. International journal of cancer. 2016;139(12):2771-80.
15. Kitchner H, Canfell K, Gilham C, Sargent A, Roberts C, Desai M, et al. The clinical effectiveness and cost-effectiveness of primary human papillomavirus cervical screening in England: extended follow-up of the ARTISTIC randomised trial cohort through three screening rounds. Health Technology Assessment No 1823. 2014.

16. Canfell K, Shi JF, Lew JB, Walker R, Zhao FH, Simonella L, et al. Prevention of cervical cancer in rural China: evaluation of HPV vaccination and primary HPV screening strategies. Vaccine. 2011;29(13):2487-94.
17. Smith MA, Lew JB, Walker RJ, Brotherton JM, Nickson C, Canfell K. The predicted impact of HPV vaccination on male infections and male HPV-related cancers in Australia. Vaccine. 2011;29(48):9112-22.
18. Hildesheim A, Schiffman MH, Gravitt PE, Glass AG, Greer CE, Zhang T, et al. Persistence of type-specific human papillomavirus infection among cytologically normal women. J InfectDis. 1994;169(2):235-40.
19. Kjaer S, Hogdall E, Frederiksen K, Munk C, Van den Brule A, Svare E, et al. The absolute risk of cervical abnormalities in high-risk human papillomavirus-positive, cytologically normal women over a 10-year period. Cancer Research. 2006;66(21):10630-6.
20. Molano M, Van den Brule A, Plummer M, Weiderpass E, Posso H, Arslan A, et al. Determinants of clearance of human papillomavirus infections in Colombian women with normal cytology: a population-based, 5-year follow-up study. AmJ Epidemiol. 2003;158(5):486-94.
21. Canfell K, Barnabas R, Patnick J, Beral V. The predicted effect of changes in cervical screening practice in the UK: results from a modelling study. Br J Cancer. 2004;91(3):530-6.
22. Bulkmans NW, Berkhof J, Bulk S, Bleeker MC, van Kemenade FJ, Rozendaal L, et al. High-risk HPV type-specific clearance rates in cervical screening. Br J Cancer. 2007;96(9):1419-24.
23. Andrae B, Andersson TM, Lambert PC, Kemetli L, Silfverdal L, Strander B, et al. Screening and cervical cancer cure: population based cohort study. BMJ (Clinical research ed). 2012;344:e900.
24. van der Aa MA, Schutter EM, Looijen-Salamon M, Martens JE, Siesling S. Differences in screening history, tumour characteristics and survival between women with screen-detected versus not screen-detected cervical cancer in the east of The Netherlands, 1992-2001. European journal of obstetrics, gynecology, and reproductive biology. 2008;139(2):204-9.
25. Zucchetto A, Ronco G, Giorgi Rossi P, Zappa M, Ferretti S, Franzo A, et al. Screening patterns within organized programs and survival of Italian women with invasive cervical cancer. Preventive medicine. 2013;57(3):220-6.
26. Lew JB, Simms K, Smith MA, Kang YK, Xu XM, Caruana M, et al. National Cervical Screening Program Renewal: Effectiveness modelling and economic evaluation in the Australian setting (Assessment Report). MSAC application number 1276. Canberra: Department of Health 2014.
27. Sawaya GF, Sanstead E, Alarid-Escudero F, Smith-McCune K, Gregorich SE, Silverberg MJ, et al. Estimated Quality of Life and Economic Outcomes Associated With 12 Cervical Cancer Screening Strategies: A Cost-effectiveness Analysis. JAMA internal medicine. 2019.
28. Center for Disease Control and Prevention. National Center for Health Statistics: 2009 National Hospital Discharge Survey. Available at https://www.cdc.gov/nchs/nhds/nhds_questionnaires.htm Accessed August, 7, 2017.
29. Berkeley Mortality Database. 1995 Birth Cohort Data for the United States. Available at: http://www.demog.berkeley.edu/~bmd/states.html. Accessed August 2, 2016.
30. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Survival- Aggregated With State, Total U.S. (1969-2015) <Katrina/Rita Population Adjustment>, National Cancer Institute, DCCPS, Surveillance Research Program, released December 2017. Underlying mortality data provided by NCHS (www.cdc.gov/nchs).
31. Koliopoulos G, Arbyn M, Martin-Hirsch P, Kyrgiou M, Prendiville W, Paraskevaidis E. Diagnostic accuracy of human papillomavirus testing in primary cervical screening: a systematic review and meta-analysis of non-randomized studies. Gynecologic oncology. 2007;104(1):232-46.

32. van Ballegooijen M, Rutter CM, Knudsen AB, Zauber AG, Savarino JE, Lansdorp-Vogelaar I, et al. Clarifying differences in natural history between models of screening: the case of colorectal cancer. Medical decision making : an international journal of the Society for Medical Decision Making. 2011;31(4):540-9.
33. Naber SK, de Kok IM, Matthijsse SM, van Ballegooijen M. The potential harms of primary human papillomavirus screening in over-screened women: a microsimulation study. Cancer Causes Control. 2016;27(4):569-81.
34. Cuzick J, Myers O, Hunt WC, Saslow D, Castle PE, Kinney W, et al. Human papillomavirus testing 2007-2012: co-testing and triage utilization and impact on subsequent clinical management. International journal of cancer. 2015;136(12):2854-63.
35. Kinney W, Hunt WC, Dinkelspiel H, Robertson M, Cuzick J, Wheeler CM. Cervical excisional treatment of young women: a population-based study. Gynecologic oncology. 2014;132(3):628-35.
36. Connecticut Tumor Registry, Connecticut Department of Public Health. Cervical Cancer Incidence 1950-1969. https://portal.ct.gov/DPH/Tumor-Registry/CTR-Home [
37. Garland, S., Brotherton, J., Stevens, M. P., Condon, J., McIntyre, P. B., Smith, D. and Tabrizi, S. (2010). WHINURS HPV genotype prevalence in Australian women pre-vaccination: What differences might there be for Indigenous women?
38. Kitchener HC, Almonte M, Wheeler P, Desai M, Gilham C, Bailey A, et al. HPV testing in routine cervical screening: cross sectional data from the ARTISTIC trial. Br J Cancer. 2006;95(1):56-61.
39. Myers ER, McCrory DC, Nanda K, Bastian L, Matchar DB. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. Am J Epidemiol. 2000;151(12):1158-71.
40. Australian Cancer Incidence and Mortality (AIHW) (2012) "ACIM (Australian Cancer Incidence and Mortality) Books." Available at: http://www.aihw.gov.au/aihw-national-mortality-database/.
41. Australian Cancer Incidence and Mortality (AIHW) (2013). Cervical screening in Australia 2010-2011. Cancer series 76. Cat no. CAN 72. Cancer series. Canberra, AIHW.
42. Joste NE, Ronnett BM, Hunt WC, Pearse A, Langsfeld E, Leete T, et al. Human papillomavirus genotype-specific prevalence across the continuum of cervical neoplasia and cancer. Cancer Epidemiology and Prevention Biomarkers. 2014:cebp. 0775.2014.
43. Joste NE, Ronnett BM, Hunt WC, Pearse A, Langsfeld E, Leete T, et al. Human papillomavirus genotype-specific prevalence across the continuum of cervical neoplasia and cancer. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2015;24(1):230-40.
44. Saraiya M, Unger ER, Thompson TD, Lynch CF, Hernandez BY, Lyu CW, et al. US Assessment of HPV Types in Cancers: Implications for Current and 9-Valent HPV Vaccines. Journal of the National Cancer Institute. 2015;107(6):djv086.
45. Doll R, Muir CS, Waterhouse JAH, eds. Cancer Incidence in Five Continents, Vol. II Union Internationale Contre le Cancer, Geneva. 1970.
46. Doll R, Payne P, Waterhouse JAH, eds. Cancer Incidence in Five Continents, Vol. I. Union Internationale Contre le Cancer, Geneva. 1966.