MODEL PROFILE
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UNIVERSITY OF MINNESOTA

Important note: This document will remain archived as a technical appendix for publications. New versions will be added periodically as model refinements and updates are completed. The most current version is available at http://cisnet.cancer.gov/profiles. Note that unlike most PDF documents, the CISNET model profiles are not suitable for printing as they are not typically written or read in sequential fashion.

We recommend you let your interests guide you through this document, using the navigation tree as a general guide to the content available.

The intent of this document is to provide the interested reader with insight into ongoing research. Model parameters, structure, and results contained herein should be considered representative but preliminary in nature.

We encourage interested readers to contact the contributors for further information.

Go directly to the: Reader's Guide.

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READER'S GUIDE

Core Profile Documentation

These topics will provide an overview of the model without the burden of detail. Each can be read in about 5-10 minutes. Each contains links to more detailed information if required.

Model Purpose

This document describes the primary purpose of the model.

Model Overview

This document describes the primary aims and general purposes of this modeling effort.

Assumption Overview

An overview of the basic assumptions inherent in this model.

Parameter Overview

Describes the basic parameter set used to inform the model, more detailed information is available for each specific parameter.

Component Overview

A description of the basic computational building blocks (components) of the model.

Output Overview

Definitions and methodologies for the basic model outputs.

Results Overview

A guide to the results obtained from the model.

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MODEL PURPOSE

SUMMARY

This document summarizes the overall goal of the University of Minnesota Cervical Cancer model (UMN-HPV CA).

PURPOSE

The UMN-HPV Cancer (CA) Model was developed to model the natural history of human papillomavirus (HPV) infection and resulting health outcomes related to cervical cancer. UMN-HPV CA simulates different interventions to quantify the effectiveness of HPV vaccination and cervical cancer screening. Model findings are intended to inform public health policies and explain population-level trends in cervical cancer incidence and mortality.

UMN-HPV CA Model consists of two models: a dynamic transmission model and a cohort model. The dynamic transmission model is able to replicate sexual acquisition of type-specific HPV. The output from this model can be combined with the cohort model. The cohort model simulates the natural history of HPV infection, cervical pre-cancer and cancer as well as primary and secondary prevention through vaccination and screening. The UMN-HPV CA Model can be run in two ways 1.) simulation of a single birth cohort 2.) simulation of multiple cohorts reflecting the United States population.

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Model Overview

Summary

This document provides an overview of the UMN-HPV CA Model's structure and components.

Purpose

The UMN-HPV CA Model was developed to examine HPV transmission and cervical cancer natural history dynamics and impact on cost-effectiveness analyses of vaccination and screening strategies. Results from the model are intended to be disseminated broadly to decision-makers and stakeholders to provide evidence and recommendations for cancer prevention and control guidelines. Refer to Model Purpose for detail.

Background

The UMN HPV CA Model contains:

1. A natural history component that tracks progression and regression between HPV infection, precancer states, and cancer states stratified by different HPV types.
2. A vaccination component that allows for a reduction in the likelihood of HPV infections and captures herd immunity benefits;
3. A screening and treatment component that allows for the detection and removal of precancerous lesions and diagnosis of preclinical cervical cancers; and
4. A detection and survivor component for all women diagnosed with cervical cancer.

The UMN HPV CA Model specifically incorporates:

1. Population-level sexual behavior trends by age and sexual activity group.
2. Population-level trends in vaccination rates and vaccine efficacy.
3. Population-level trends in competing risks for cervical cancer, namely hysterectomy and background mortality;
4. Population-level trends in cervical cancer screening participation rates and test performance of various screening options to detect precancerous and cancerous lesions.

The primary model outcomes are HPV prevalence, cervical cancer incidence, and cervical cancer deaths. These outcomes are compared to state-level cancer registry data, incidence data from the Surveillance, Epidemiology, and End Results (SEER), and mortality data from the US Vital Statistics. Additional outcomes include number of life years and quality-adjusted life years (QALY's) gained under various screening and vaccination strategies as compared to natural history.

Model Description

The natural history model of HPV infection and cervical is a state-transition micro-simulation model that simulates a single birth cohort of women who are at average risk (defined as not immune-compromised and not HPV vaccinated). The transitions are age dependent. The cycle length is 1 year. The cohort starts at age 9 and all girls are assumed to be normal (i.e., not HPV infected). Every year, women are at risk of becoming infected with HPV stratified by type (described later). Women who are infected can clear their infection, stay infected or progress to CIN (either CIN 1 or directly to CIN 2/3). Women with CIN 1 can progress to CIN 2 or CIN 3 and/or regress (to normal or HPV). Women with CIN 2 can remain in the same state, progress to CIN 3, or regress (to CIN 1, HPV or normal). Women with CIN 3 can remain in the same state, progress to cancer (Stage I), or regress (to either CIN or normal). Cancer is modeled as 4 stages (Stage I, Stage II, Stage III and Stage IV). The state-transition diagram of the natural history of HPV infection and cervical cancer stratified by age and HPV type is shown in Figure 1.

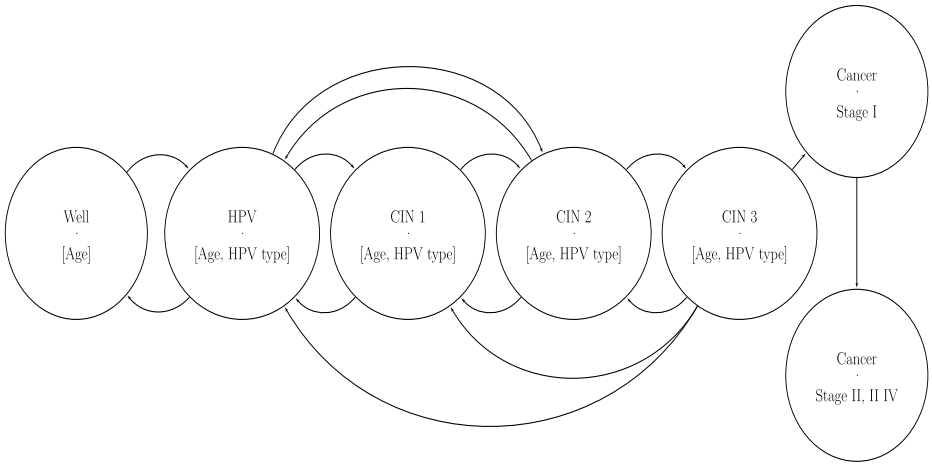

Figure 1. State-transition diagram of the natural history of HPV infection and cervical.

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ASSUMPTION OVERVIEW

SUMMARY

This section outlines the UMN-HPV CA model assumptions.

BACKGROUND

The UMN-HPV CA model relies on assumptions regarding aspects of the disease's natural history prior to diagnosis, screening effectiveness and outcomes, vaccination efficacy, and the costs and harms resulting from different prevention strategies.

ASSUMPTION LISTING

Population demographics

Both the cohort and dynamic models assume birth and mortality rates consistent with U.S. census data available in the Human Mortality Database (formerly Berkeley Lifetables). These rates are annual based on 2015 cohort life tables. The cohort model begins as a first-order microsimulation of each individual at age 9.

Sexual behavior

We used National Survey for Family Growth (NSFG) data from 2010-2011 to assign gender- and age-specific distributions of the maximum number of heterosexual partners possible in a given year. Sexual mixing is assumed to be dependent on an individual's age and maximum number of partners. We assume that concurrent partnerships are possible.

Sexual partnerships were assigned a duration according to gender- and age-specific NSFG data. Individuals that age into a new age group may be reassigned a maximum number of partners and partnership duration. Type-specific sexual transmission of HPV is possible between either gender. We assume all unvaccinated individuals in the model are susceptible to HPV infection upon sexual debut, which is age specific.

Natural history of HPV infection

Natural immunity following HPV infection is assumed to provide a varying degree of protection for a variable duration of time, after which immunity wanes. Natural immunity is gender and type specific. We categorized HPV type into

four groups based on genotypes: 1.) HPV16 2.) HPV18 3.) High-5 (other pentavalent vaccine types - 31, 33, 45, 52, 58) and 4.) other high risk (all other HPV types not covered by the nonavalent vaccine - 35, 39, 51, 56, 59, 66, 68). We assumed that co-infection with multiple HPV types is possible. HPV infection can occur at any state in the model among individuals who are sexually active. Transmission is modeled as an annual probability per partnership.

Natural history of pre-cancer

HPV infection may progress to precancer, represented in the model as cervical intraepithelial neoplasia stages 1, 2, and 3, with direct progression allowed to any of the three CIN states. Limited empirical evidence exists to inform rates of progression and regression in precancer stages. Therefore, estimates of natural history regression and progression have been calibrated according to HPV prevalence and cancer incidence targets, and transitions depend on age and HPV types. Each year there is a greater probability that the disease will progress to the next proximal stage or regress to the previous stage, but progression and regression may also skip stages. Annual probabilities of total hysterectomies are based on hysterectomy rates in the US in 2009 for ages (15–99) from the National Hospital Discharge Survey (NHDS). Hysterectomy and background mortality are competing risks.

Natural history of cancer and associated mortality

UMN-HPV CA models adenocarcinoma (ADC) and squamous cell carcinoma (SCC) as combined cervical cancer. Cancer stages are modeled as Stage 1, 2, 3, and 4, according to International Federation of Gynecology and Obstetrics (FIGO) staging. For comparison to other CISNET groups, cancer stages are aggregated according to SEER staging (local, regional, distant). Women may progress from CIN3 to Stage 1 cancer. Symptomatic cancers can result in cancer-related mortality. Probability of expressing symptoms is constant across age, but dependent upon cancer stage. We assume that cancer survivors are no longer at risk of a cancer recurrence.

Screening behavior and performance

Screening algorithms are implemented in accordance with the 2012 American Society for Colposcopy and Cervical Pathology (ASCCP) Updated Consensus Guidelines for Managing Abnormal Cervical Cancer Screening Tests and Cancer Precursors. This algorithm recommends a series of primary, triage and surveillance screens according to prior test results and outcomes. These strategies include cytology, HPV genetic and genotype specific testing, and co-testing, with each test(s) absolute and relative performance modeled in the algorithm. Colposcopy and biopsy can have variable sensitivity and specificity

although the base case usually assumes 100% test accuracy. All lesions detected through screening are assumed to be treated although this assumption can be varied.

Vaccination

We assume perfect vaccine efficacy and lifetime vaccine-acquired immunity against all modeled HPV types in the base case analysis. In secondary analyses, we assume that vaccine failure is possible. Full protection is assumed for a variable duration of time (if no primary failure), after which immunity waves. Both women and men aged 11 to 26 years may be vaccinated in the model in accordance with vaccination guidelines. The vaccination series is modeled based on current guidelines but can be administered at varying intervals.

Costs and harms

Each step in screening, (pre)cancer and cancer diagnosis and treatment can have an associated disutility and cost. These are based on the literature and are detailed in elsewhere.

References:

1. University of California Berkeley. Human Mortality Database. http://www.mortality.org/hmd/USA/STATS. Accessed September 25, 2017.
2. CDC. National Survey of Family Growth. 2010-2011.
3. Wheeler C. NMHPVPR, private correspondence.
4. Han JJ, Beltran TH, Song JW, Klaric J, Choi YS. Prevalence of genital human papillomavirus infection and human papillomavirus vaccination rates among US adult men: National Health and Nutrition Examination Survey (NHANES) 2013-2014. JAMA Oncol. 2017;3(6):810-816. doi:10.1001/jamaoncol.2016.6192.
5. Saslow D, Runowicz CD, Solomon D, et al; American Cancer Society. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. CA Cancer J Clin. 2002; 52: 342-362.

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PARAMETER OVERVIEW

SUMMARY

This section describes the key parameters of the UMN-HPV CA Model.

TRANSITION PROBABILITIES

Following Kassteele et al. (2012) and C. L. Avery et al. (2016), we fit a multinomial model to describe the transition probabilities from four different health states of the natural history model of HPV infection and cervical cancer: HPV, CIN1, CIN2, CIN3. For each initial health state, we model each transition probability as a function of age and HPV type, and we take the initial health state as the reference category. The other health states are then regressed against the reference category in a multinomial regression framework.

Parameter Listing	Relevant assumptions	Data Source
Population parameters		
Population size	Variable	
Population distribution	We assume a female population for cohort model; the sex ratio at birth is used to estimate the female-to-male ratio of newborns in the population (0.51)	Human Mortality Database, formerly Berkeley Lifetables (1995). http://u.demog.berkeley.edu/~bmd/states.html
Background mortality	Annual probability of death (age, yearly, by gender)	Human Mortality Database, formerly Berkeley Lifetables (1995). http://u.demog.berkeley.edu/~bmd/states.html
Disease transmission parameters		
Birth rate	Annual birth rate (age, yearly, by gender)	Human Mortality Database, formerly Berkeley Lifetables (1995). http://u.demog.berkeley.edu/~bmd/states.html
Age distribution of population	Assumed distribution of population at model initiation by age and gender given by lifetables	Human Mortality Database, formerly Berkeley Lifetables (1995). http://u.demog.berkeley.edu/~bmd/states.html
Sexual activity	(5-year age groups based on NSFG gender-specific distributions of number of partners in the last 12 months). Partnerships may be concurrent.	CDC. National Survey of Family Growth. 2010-2011.
Partner age	Distribution of partner age	CDC. National Survey of Family Growth. 2010-2011.
Partnership duration	Maximum number of years a partnership can last	CDC. National Survey of Family Growth. 2010-2011.

Initial infection (cohort model)	(by HPV type)	Calibrated
HPV transmission	Gender-specific annual probability of contracting HPV per infected partner	Calibrated
HPV type	Distribution of HPV type (16, 18, class 1, class 2) condition on infection	Han JJ, Beltran TH, Song JW, Klaric J, Choi YS. Prevalence of genital human papillomavirus infection and human papillomavirus vaccination rates among US adult men: National Health and Nutrition Examination Survey (NHANES) 2013-2014. JAMA Oncol. 2017;3(6):810-816. doi:10.1001/jamaoncol.2016.6192.
HPV clearance	Annual probability of clearing HPV infected	Calibrated
Natural History parameters		
Competing risk of hysterectomy	New denominator at younger ages corrected for screening coverage	NHDS (2009) and US Census data (2009), (BRFSS)
Infection progression / regression for normal – CIN3 states		Calibrated
Transition probabilities for cancer states	Assumed to be constant for all types at all ages	Calibrated
Cancer symptom detection	Assumed to be constant for all types	Informed by Myers, E., McCrory, D., Nanda, K., Bastian, L., & Matchar, D. (n.d.). Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. American Journal of Epidemiology., 151(12), 1158-1171.
Cancer survival	Currently modeled as constant across ages (5-year probability at time	SEER 9, year of diagnosis = 1975+

	of detection given years of survival)	
Targets		
HPV Prevalence	Used linear interpolation to generate yearly targets. (age, and type-specific)	Wheeler CM, Ph D, Hunt WC, et al. A Population-based Study of HPV Genotype Prevalence in the United States: Baseline Measures Prior to Mass HPV Vaccination. 2014;132(1):1-19. doi:10.1002/ijc.27608.A. Additional age ranges per personal correspondence
Cancer Incidence	These values were generated by fitting a line just above the incidence curves from IARC CI5C, 1959-1963, CTR, 1950-1954, and CTR, 1955-1959, and by applying type-specific % from Mona Saraiya, personal communications (see HPV Type Distribution in Cancer)	IARC CI5C, 1959-1963, CTR, 1950-1954, and CTR, 1955-1959 Mona Saraiya, personal communications. Data received 10/03/2016 via email
HPV Type Distribution in Cancer	Total cervical cancer (ADC +SCC), conditioned on HPV+ status	Mona Saraiya, personal communications. Data received 10/03/2016 via email
CIN Prevalence	CIN curves generated by review of recent literature and clinical trials	1. Goldie SJ, Grima D, Kohli M, Wright TC, Weinstein M, Franco E. A comprehensive natural history model of HPV infection and cervical cancer to estimate the clinical impact of a prophylactic HPV-16/18 vaccine. Int J Cancer. 2003;106(6):896-904. doi:10.1002/ijc.11334. 2. Hariri S, Johnson ML, Bennett NM, et al. Population-based trends in high-grade cervical lesions in the early human papillomavirus vaccine era in the United States. Cancer. 2015;121(16):2775-2781. doi:10.1002/cncr.29266.

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6. Ramanakumar A V, Naud P, Roteli-Martins CM, et al. Incidence and duration of type-specific human papillomavirus infection in high-risk HPV-naïve women: results from the control arm of a phase II HPV-16/18 vaccine trial. BMJ Open. 2016;6(8):e011371. doi:10.1136/bmjopen-2016-011371.

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8. Vesco KK, Whitlock EEP, Eder M, et al. Screening for Cervical Cancer: A Systematic Evidence Review for the U.S Preventive Services Task Force. Evid

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HPV Type Distribution in CIN		Joste NE, Ronnett BM, Hunt WC, Pearse A, Langsfeld E, Leete T, Jaramillo M, Stoler MH, Castle PE, and Wheeler CM. New Mexico HPV Pap Registry Steering Committee. Cancer Epidemiol Biomarkers Prev January 1 2015 (24) (1) 230-240;DOI: 10.1158/1055-9965.EPI-14-0775, NMHPVPR
Vaccination parameters		
Vaccine efficacy	Primary and secondary vaccine failure possible. Full protection assumed at 100% efficacy and lifetime duration for all HPV types in base case analysis.	
Natural immunity	Full protection assumed for some duration of time, after which natural immunity wanes. Natural immunity is assumed to be gender-specific.	

Screening parameters		
Cytology test performance	Pooled absolute sensitivity and specificity	Koliopoulos, George et al. Diagnostic accuracy of human papillomavirus testing in primary cervical screening: A systematic review and meta-analysis of non-randomized studies. Gynecologic Oncology. January 2007 (104) (1) 232-246
HPV and Cotest test performance	Relative sensitivity and specificity	Arbyn M, Ronco G, Anttila A, Meijer C, Poljak M, Ogilvie G, Koliopoulos G, Naucler P, Sankaranarayanan R and Peto J. Evidence Regarding Human Papillomavirus Testing in Secondary Prevention of Cervical Cancer. Vaccine, November 20, 2012 (30) F88-F99 ATHENA Summary of cobas HPV Test Result and Central Pathology Review Panel Diagnosis in the Primary Screening Population (>=25 years) at Baseline
Screening practice	% of women who screen at different intervals (Q1-Q5)	Cuzick J, Myers O, Hunt W C, Saslow D, Castle, PE, Kinney W, Waxman A, Robertson M, Wheeler CM. and on behalf of the New Mexico HPV Pap Registry Steering Committee (2015), Human papillomavirus testing 2007–2012: Co-testing and triage utilization and impact on subsequent clinical management. Int. J. Cancer, 136: 2854–2863. doi:10.1002/ijc.29337; NMHPVPR - sent by Curtis Hunt on 1/17/2013

COMPONENT OVERVIEW

SUMMARY

This document outlines the components that make up the UMN-HPV CA Model.

OVERVIEW

The model is made up of the following components:

HPV transmission

Transmission of HPV infections in males and females is modeled in the dynamic individual-based model, with individual partnerships characterized by sex, age, and sexual activity. Females and males form heterosexual partnerships as they age, and transmission of type-specific HPV can occur as a function of sexual behavior patterns in the population, prevalence of HPV in the population, and female-to-male or male-to-female transmission probabilities of HPV per susceptible-infected partnership. Following clearance of HPV, individuals develop natural immunity, reducing future risk of that same type of infection. Women with high-risk infection can develop precancerous lesions (i.e., cervical intraepithelial neoplasia (CIN1, CIN2 or CIN 3), which may regress naturally, and those with CIN 3 may develop invasive cancer. Death can occur from age- and sex-specific background mortality or excess mortality in women with invasive cervical cancer.

Cervical carcinogenesis

Both the dynamic and cohort models include health states that reflect cervical carcinogenesis associated with HPV-16, 18 and other HPV types. In these models, women transition between health states, which reflect the cohort's underlying true health and include HPV infection status, grade of CIN (CIN 1, CIN 2 and CIN 3), and stage of invasive cancer (I through IV). In the cohort model, women enter the model before sexual debut and transition between health states according to probabilities that depend on age, HPV type, type-specific natural immunity, CIN status, and treatment history. Death can occur each year from non-cervical cancer causes from all health states, or from cervical cancer after its onset. Hysterectomy is modeled as a competing risk.

Vaccination

The dynamic model is used to project the effects of HPV vaccination in reducing HPV-16, HPV-18 and other high-risk type infections over time, capturing both

direct and indirect benefits. The dynamic model can also account for the impact of these effects on CIN and cancer by combining impact on HPV incidence with the cohort model. The immunity conferred by vaccination has a specified duration of full protection and a waning period. The model can account for vaccine inefficacy.

Screening, diagnosis and treatment of CIN

The cohort model can accommodate detailed features of screening strategies, including algorithms that are based on a single test or multiple tests (either in parallel or serial). The models reflect screening, follow-up and treatment recommendations based on American Cancer Society (ACS), US Preventive Services Task Force (USPSTF) and American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines, but assumptions can be modified flexibly. The models both incorporate a detailed post-treatment surveillance component. (3)

Cancer treatment and survival

The models include cancer states by stage (I through IV) and conditional probabilities of survival based on stage of detection. The models also include a separate state for survivors and cancer-related deaths based on data from the Surveillance, Epidemiology, and End Results (SEER) Program.

Calibration and validation

The cohort model was calibrated by varying HPV incidence, CIN progression and regression rates, and probability of symptoms by cancer stage. The parameter set that achieved best fit to historic data (in the absence of screening) using goodness of fit estimation is used for the base case. The face validity of the models is assessed by comparing model-projected estimates of age-specific HPV prevalence and age-specific cervical cancer incidence, as well as the lifetime risk of cervical cancer to empirically observed values from SEER and state level cancer registries.

OUTPUT OVERVIEW

SUMMARY

This is a general overview of the outputs generated by the UMN-HPV CA model.

OVERVIEW

Base Case Outputs

Base Case outputs assume that no screening is performed and when the model is calibrated to yearly HPV prevalence, cancer incidence, and CIN1, CIN2, and CIN3 targets. The following outputs are generated and aggregated in five-year age groups for comparison to other CISNET models:

1. HPV prevalence by age and HPV genotype
2. HPV type distribution in cancer by age
3. Prevalent preclinical (undetected) cancer by age, cancer stage and HPV genotype
4. Prevalent clinical (detected) cancer by age and cancer stage
5. Clinical cancer stage distribution (proportion) by age
6. Clinical cancer incidence per 100,000 by stage and age or overall clinical cancer incidence
7. HPV-type distribution in CIN1, 2, and 3
8. CIN 1, 2, and 3 prevalence
9. Cancer mortality per 100,000

Initial Cervical Cancer Screening Outputs

An initial comparison of screening outputs after overlaying screening on natural history estimates. The first round of screening comparisons was composed of five strategies: cytology once every 1, 2, 3, 4, or 5 years. The following outputs were generated and aggregated in five-year age groups for comparison to other CISNET models:

1. Average Screening tests per woman by age groups
2. Average Pre-cancer treatments per woman by age groups
3. Average colposcopies per woman by age groups

4. Life years gained through screening

OUTPUT LISTING

Cohort Model Base Case Outputs Note: these outputs also produced when initial screening carried out	
Total population alive: Hysterectomized women included and excluded	Counts by age, year, and hysterectomy status
HPV Prevalence:	Counts by age, year, and HPV type (four groups: HPV16, HPV18, High 5 HPV types, all other HPV)
Prevalent (undetected) Cancer Cases	Counts by age, year, and cancer stage
Prevalent Clinical Cancer Cases	Counts by age, year and cancer stage
Incident Clinical Cancer Cases by type	Counts by age, year and HPV type
Incident Clinical Cancer Cases by stage	Counts by age, year and cancer stage
Total Cancer Rate per 100,000 women	Counts by age and year
Clinically Detected Cancer Deaths	Counts by age and year
Cancer Death per 100,000 women	Counts by age and year
Prevalent Counts of CIN 1	Counts by age, year, and HPV type
Prevalent Counts of CIN 2	Counts by age, year, and HPV type
Prevalent Counts of CIN 3	Counts by age, year, and HPV type
Initial Screening Outputs	
Average Screening tests per woman by age groups	Counts by age, year and screening strategy (no screening, Q1-Q5)
Average Pre-cancer treatments per woman by age groups	Counts by age, year and screening strategy (no screening, Q1-Q5)
Average colposcopies per woman by age groups	Counts by age, year and screening strategy (no screening, Q1-Q5)
Life years gained through screening	Total life years per strategy (no screening, Q1-Q5)

Quality adjusted life years	Total quality-adjusted life years per strategy (no screening, Q1-Q5)
Outcomes for cervical cancer screening strategies over the lifetime of screening (screening end age 65)	
Number of Cytology tests performed	Total number of cytology tests administered in a cohort from ages 20-100, irrespective of primary, triage, or surveillance context
Number of HPV tests performed	Total number of HPV genetic tests administered in a cohort from ages 20-100, irrespective of primary, triage, or surveillance context
Number of Total tests performed	Total number of tests administered in a cohort from ages 20-100, irrespective of primary, triage, or surveillance context
Total number of Colposcopies performed	
Total number of CIN2, CIN3 lesions detected through screening	
Total number of CIN3 lesions and cervical cancers detected through screening	Excludes symptomatic cancers diagnosed clinically
False positive colposcopies	Total number of colposcopies that did not result in CIN2, CIN3 or cancer detection
Total number of cervical cancer cases per 100,000	
Total number of deaths due to cervical cancer per 100,000	

RESULTS OVERVIEW

RESULTS LIST

Expanding upon US Preventive Services Task Force Decision Analysis Screening Outputs

CISNET teams carried out the full screening algorithm to expand upon Harvard's analysis of the U.S. Preventive Services Task Force Decision Analysis of primary HPV testing by 1) adding costs, 2) including screening adherence, 3) reflecting obstetric harms from pre-cancer excisional treatment. UMN-HPV CA provides comparative results for this analysis carried out by the Harvard CISNET group. This analysis was composed of 19 screening strategies including cytology, HPV primary testing, cotesting and combinations of these tests in accordance with the algorithm. Outcomes were calculated from age 20 to 100 years. A series of sensitivity analyses will be carried out by varying the HPV testing switch age, interval, and screening end age (65, 70, 75). The following results were compared per 1,000 women:

1. Number of cytology tests
2. Number of HPV tests
3. Total number of tests, irrespective of primary, triage or surveillance context
4. Number of colposcopies
5. Number of CIN2 and CIN3 lesions detected
6. Number of CIN3 lesions or higher detected (not including those detected by clinical symptoms)
7. Number of false positives, defined as the total colposcopies that did not result in CIN2, CIN3 or cancer detection
8. Number of cervical cancer cases
9. Number of deaths due to cervical cancer
10. Number of life-years