

TECHNICAL APPENDIX

Harvard Cervical Cancer Natural History Model
Calibration and Costing Approach for Norway

2017

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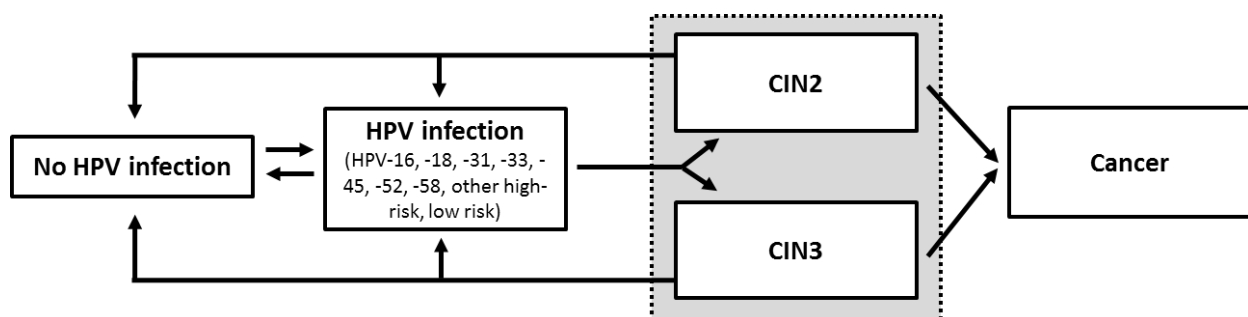
1. DECISION-ANALYTIC MODEL

We used an individual based, stochastic Monte Carlo simulation model of Human papillomavirus (HPV) and cervical cancer. The model has been previously described,(1, 2) and was recently updated(1) to reflect recent advances in the understanding of cervical carcinogenesis.

The model simulates individual women through health states until death (entering the model at age 9 in a healthy state), and allows women to transition between health states or remaining in the current health state at monthly cycles (**Appendix Figure 1**). Health states include HPV infection status (stratified by HPV types -16, -18, -31, -33, -45, -52, -58, pooled other high-risk types, and pooled low risk types) and cervical precancer (defined as either cervical intraepithelial neoplasia (CIN) grade 2 (CIN2) or grade 3 (CIN3)), and cancer (stratified by local, regional and distant). Cervical cancer can be clinically detected (i.e., through screening or symptoms) or remain undetected and progress to more advanced stages of cancer. Death can occur from non-cervical causes from any health state (based on life-tables from Norway(3)), or from cervical cancer. For each woman's simulated life course, the model tracks clinical events, including screening and treatment procedures, cancer incidence, mortality and life expectancy, and quantifies the associated resource use and expenses. We simulate a large number of women (i.e., a cohort of 1,000,000 unvaccinated women or a cohort of 4,000,000 women vaccinated against HPV infections) to estimate the expected total cost per screened woman, resource use and health benefits of each alternative screening strategy.

Transitions between health states are determined by transition probabilities, based on best available empirical data, and assumes that cervical carcinogenesis does not vary across settings. However, we adjusted baseline parameter inputs to account for country-specific epidemiology (i.e., risk factors such as sexual behavior and cervical cancer incidence). In order to achieve good fit to multiple targets from observed epidemiologic data from Norway, we used calibration to identify parameter sets of progression and regression parameters for the health state transitions.

Appendix Figure 1. Model schematic.



2. CALIBRATION TO NORWAY

2.1. Calibrating model inputs to empirical data from Norway

We used a likelihood-based calibration approach to identify sets of parameter values that would achieve good fit to 70 target outcomes based on primary epidemiologic data from Norway. The initial calibration of the simulation model to the Norwegian context has been described previously (4, 5), and was updated to reflect changes in the model structure as well as the importance of other high-risk HPV prevalence among vaccinated women (1). The parameter search process for calibration input values was based on random search using the uniform distribution. Calibration targets included age-specific prevalence of HPV-16, -18, -33, -45, -52, -58, and pooled other high-risk HPV (i.e., HPV-35, -39, -51, -56 and -59) infections, in addition to the distribution of the respective HPV-types in high-grade precancers (i.e., cervical intraepithelial lesions grade 3 (CIN3)) and cancers. HPV prevalence data are based on a random sample of Norwegian women aged 18-49 years who attended screening in St. Olavs hospital in Trondheim, Norway, in 2007 (4). HPV type-distribution in precancerous and cancerous lesions is based on a working paper from a Norwegian epidemiologic study using HPV DNA detection (4). Further details regarding target values are available from a Norwegian study using a previous version of the decision-analytic model (4). For each calibration target we calculated a point estimate from the empirical data, and estimated the 95% confidence interval of the binomial distribution using STATA/SE 14.2 to quantify the upper and lower empirical bounds. Calibration was used to identify 50 good-fitting parameter sets that were used in probabilistic sensitivity analysis of 188 transition probabilities determining underlying natural history of disease. To estimate model outcomes, we used the average value across all 50 parameter sets for the base-case values, and used the minimum and maximum value as uncertainty bounds.

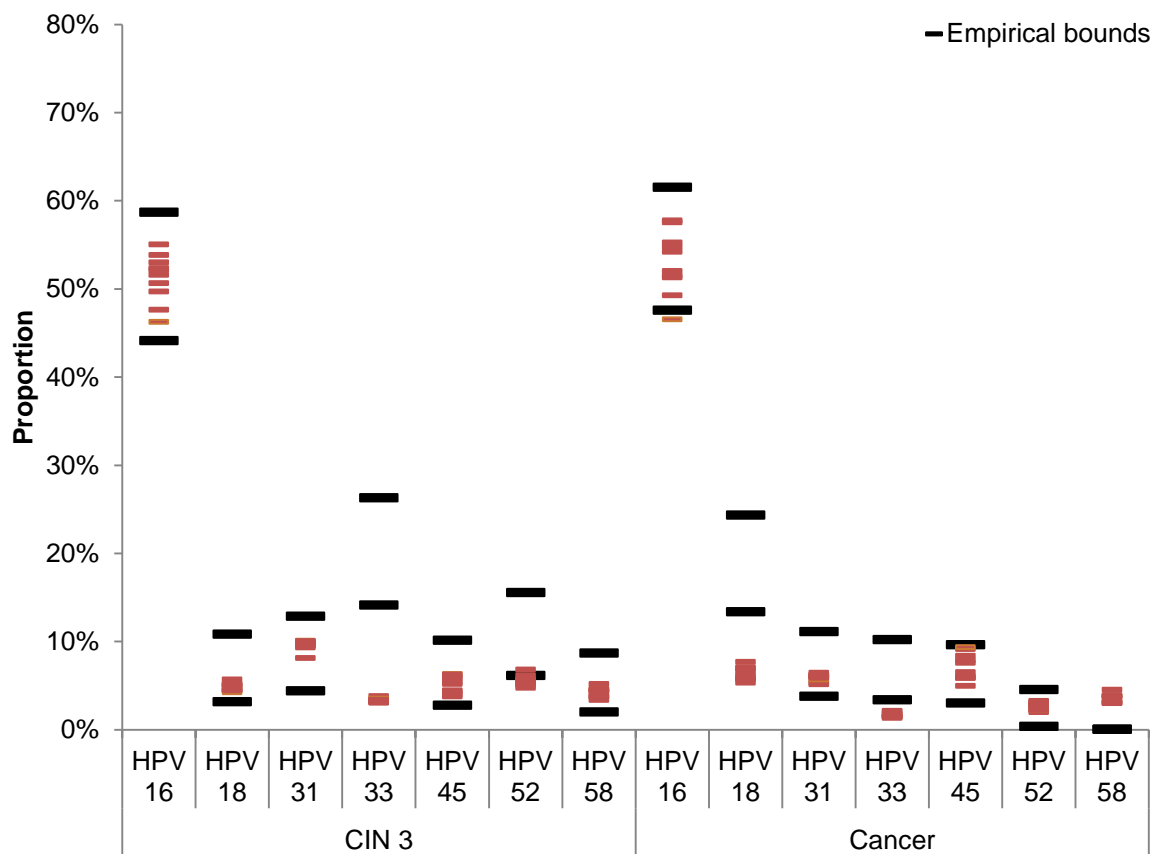
2.2. Model fit with empirical data from Norway

Model output from the 10 best fitting parameter sets (out of the total 50 good-fitting parameter sets) and accordance with the upper and lower empirical bounds are shown in **Appendix Figures 2 and 3**. Calibration targets do not include cervical cancer incidence in Norway, however, in **Appendix Figure 4**, we have presented model fit with empirical data from the Cancer Registry of Norway on observed cervical cancer incidence in Norway in the period 1953-1969, i.e., prior to the introduction of opportunistic screening in Norway. Model projections follow the upper empirical bound. Similar to other studies, we assume that changes in cervical cancer incidence over time may be attributable to changes in risk factors (e.g., sexual behavior) (6). Consequently, in the absence of screening, we expect a higher cancer incidence today than during the period 1953-1969.

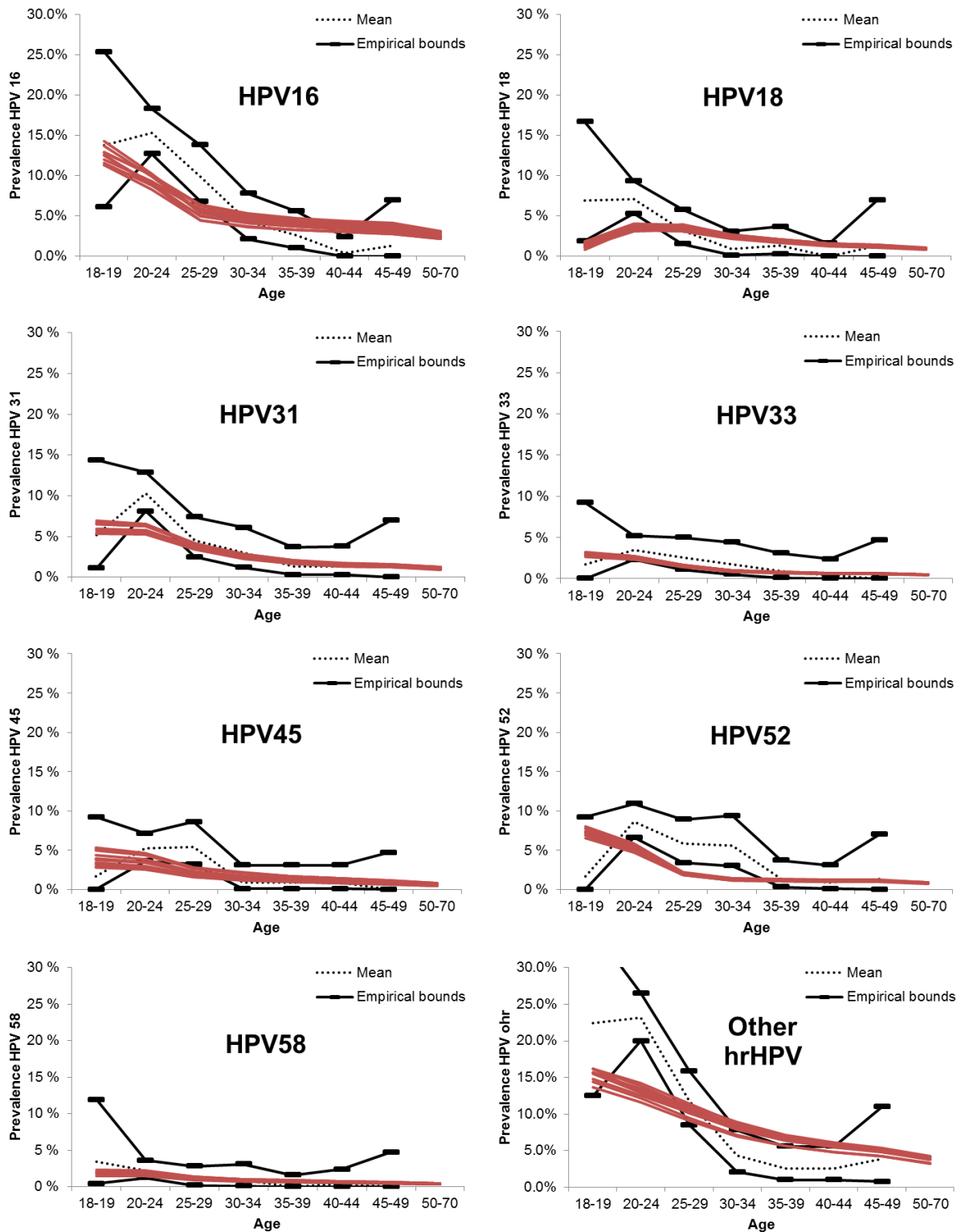
External validation of the microsimulation model against U.S.-based cervical cancer clinical trials and registry data has been described previously (7). In order to allow for external validation to Norwegian epidemiologic data, we simulated current screening practice in Norway (i.e., screening guidelines from 2005-2014 using observed screening compliance in Norway), and compared model output to primary epidemiologic data using the annual number of cervical cancer (i.e., squamous cell carcinoma) cases and age-specific incidence in Norway during 2010-2014 (8). To mirror compliance with screening guidelines in Norway, we used primary data from the Cancer Registry of Norway to estimate long-term screening frequency (i.e., every 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 15-, and 20-years, and non-compliers) (9), as well as data on observed compliance to follow-up procedures following an abnormal screening result (10). We find that the model provides a reasonable fit with observed data

(Appendix Figure 5); for example, for an average birth cohort of women in Norway (i.e., ~30,000 women), our model projects an annual number of squamous cervical cancer incidence of 227 cases, while the average annual observed cases during 2010-2014 in Norway were 223 (8). The model overestimates cervical cancer incidence for ages 30-34 and underestimates incidence for ages 45-49 when using the average value across the 50 parameter sets; however, for these age-groups, uncertainty bounds (i.e., the minimum and maximum value across the 50 parameter sets) overlap with the empirical bounds. When validating a cohort model to age-specific cross-sectional data, there are inherent limitations to using a model that does not allow screening behavior to vary by age. For example, opportunistic screening prior to age 25 years (i.e., the screening start age in Norway), may explain the deviation from the empirical data in the younger women. For the older women, the deviation from the empirical data may be explained by a decreasing screening coverage as women get older (10), which we cannot currently capture in the model.

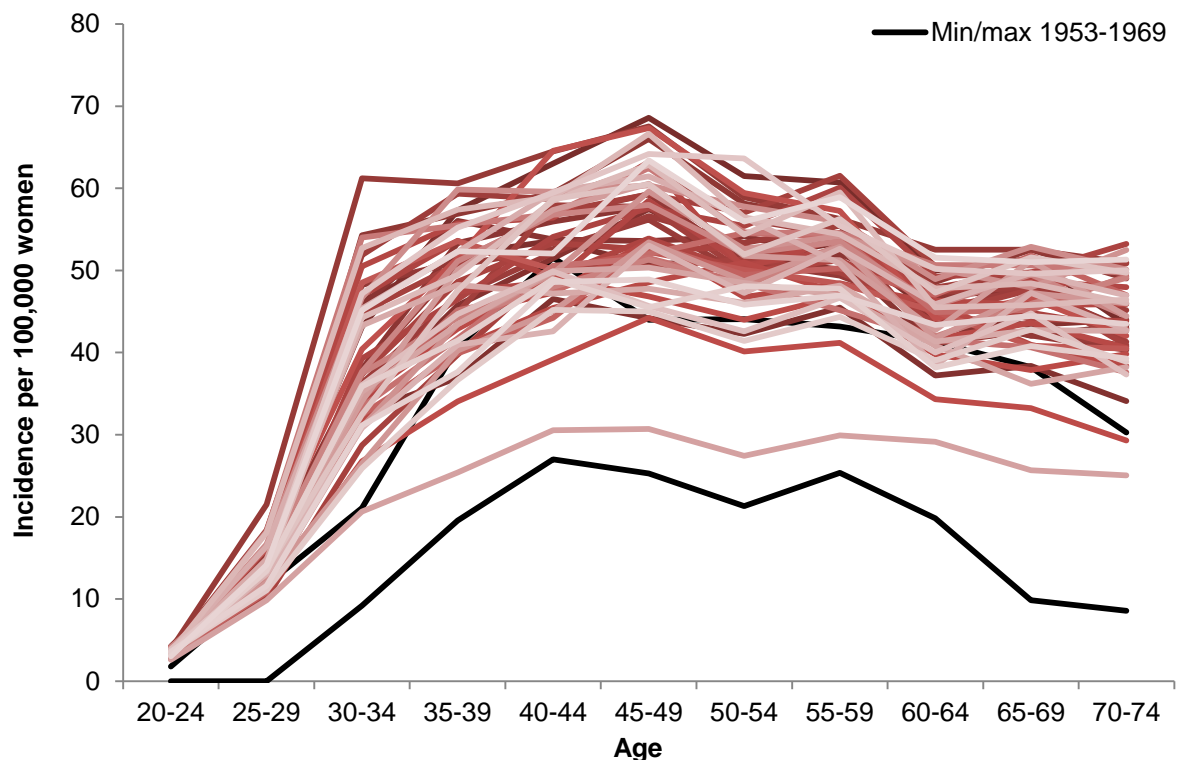
Appendix Figure 2. HPV type distribution in cervical intraepithelial neoplasia grade 3 (CIN3) and cervical cancer: Model output from the 10 best-fitting sets (red lines) and the upper and lower bound (black bold lines) estimated from the empirical data.



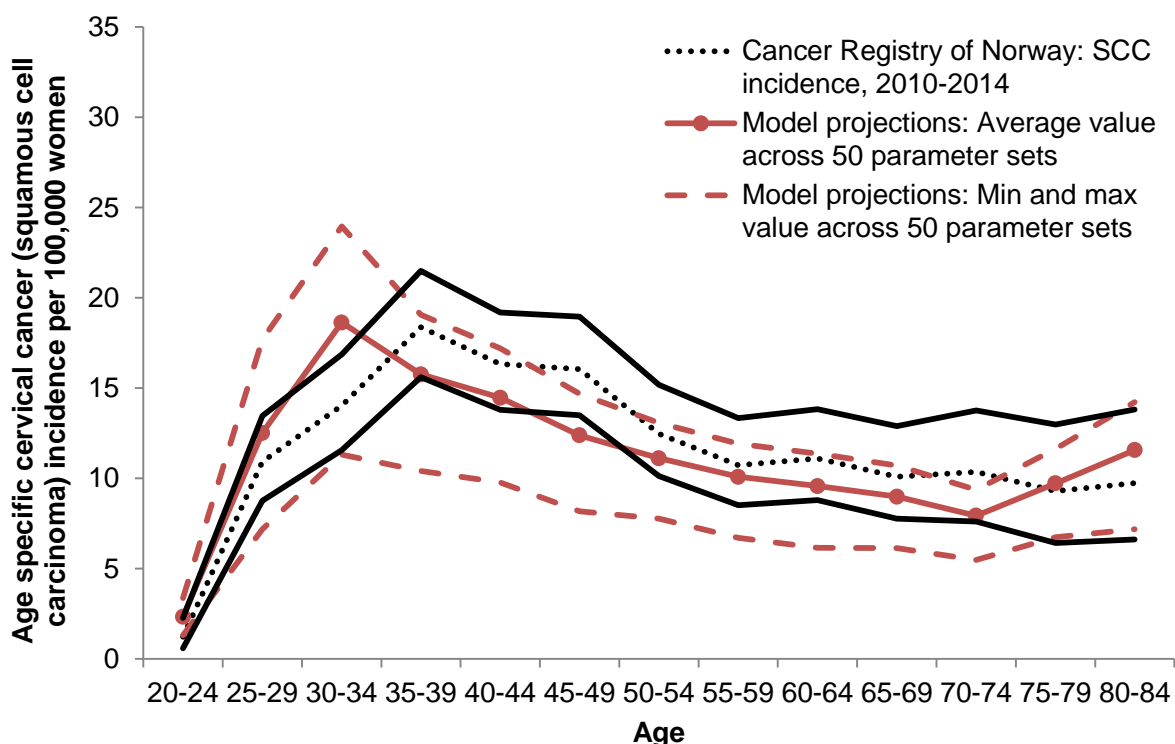
Appendix Figure 3. HPV prevalence by HPV genotype: Model output from the 10 best-fitting sets (red lines) and the upper and lower bound (black bold lines) estimated from the empirical data.



Appendix Figure 4. Age-specific cervical cancer incidence in Norway: Minimum and maximum annual incidence during 1953-1969 from the Cancer Registry of Norway (black lines) and model output from the 50 good-fitting sets (colored lines).



Appendix Figure 5. Age-specific cervical cancer incidence in Norway during 2005-2014 from the Cancer Registry of Norway (black line) and model output from the 50 good-fitting sets (blue lines), with mean (solid lines) and minimum and maximum (dashed lines) values when assuming imperfect adherence to screening guidelines.



3. COSTING ASSUMPTIONS

Direct medical and non-medical costs associated with screening and treatment procedures were initially estimated for previous Norwegian analyses based on a combination of Norwegian fee schedules and expert opinion (4, 11, 12). We updated all costs to reflect 2014-values following changes in the reimbursement system and associated fees (**Appendix Table 1**). All costs were valued in 2014 Norwegian kroner, and converted to US Dollars (USD (\$)) (\$1 = NOK6.30)(13). The identification and valuation of costs followed Norwegian guidelines for economic evaluation.(14)

3.1. Medical costs

Direct medical costs include physician office visits, laboratory cost of analyzing test sample, and the hospital costs of treatment procedures. Laboratory costs are estimated based on actual resource use in Norwegian pathology laboratories and unit costs for the cost components, including the number of physicians, bioengineers/secretaries, disposables per test and required office space, initially compiled for a cost study of the Norwegian Cervical Cancer Screening Program,(12) and another Norwegian cost-effectiveness analysis.(11) Cost estimates includes the cost of lighting, heating, cleaning, laboratory personnel, administrative overhead, clothing, disposables, IT and software service, service of laboratory equipment and capital costs.

3.2. Non-medical costs

Direct non-medical costs include patient time and transportation costs associated with screening and procedures. We assumed it would take the patient 1.5 hours to attend a screening consultation (i.e., including cytology and/or HPV test), 2 hours to attend a colposcopy examination, and 2.25 hours to receive precancer treatment. We valued patient time cost based on productivity loss using the 2014 annual wage rate for women aged 25 and older in Norway, assuming 1870 annual hours and adding 40% to account for payroll tax and other expenses covered by the employer (i.e., \$59 per hours).(15) Round-trip transportation costs were valued based on estimates from a Norwegian cost study of mammography screening from 2012 and adjusted for inflation (i.e., \$32)(16).

Appendix Table 1. Cost estimates (2014 USD, 1\$=NOK6.30).

Category	Description	Base-case (\$)	Including productivity losses due to sick leave (\$)	Source
Screening consultations				
General practitioner office visit	Cost of office visit for taking liquid-based cytology and/or HPV test. Includes the cost of staff, facilities, equipment, sending the sample to the laboratory and informing patient about test result. We assume 70% of all visits are at a general practitioner (reimbursement codes: 2ad, 103b, 10a, 701a) and 30% are at a gynecologist (reimbursement codes: 3ad, 10a, 701a), and use the weighted mean for our cost estimate.	122		(17)
Patient time associated with general practitioner office visit	Cost of patient time to travel (60 minutes round-trip), wait (15 minutes) and receive care (15 minutes) at a primary care clinic, including round-trip transportation costs.	120		(15, 16)
Colposcopy examination	Cost of office visit for colposcopy examination. Includes the cost of staff, facilities, equipment, sending the sample to the laboratory and informing patient about test result. We assume 70% of all visits are at the hospital (reimbursement codes: 201b and DRG 813S) and 30% are at a gynecologist (reimbursement codes: 3ad, 10a, 10c, 4b1, 4e, 208, 100, 701a), and use the weighted mean for our cost estimate.	258		(17-19)
Patient time associated with colposcopy examination	Cost of patient time to travel (60 minutes round-trip), wait (30 minutes) and receive care (30 minutes) at a primary care clinic, as well as round-trip transportation costs.	150		(15, 16)
Analyzing test sample at pathology laboratory				
Liquid-based cytology	Cost of collection materials, disposables, facilities and staff.	45		(11, 12)
HPV DNA test	Cost of collection materials, disposables, facilities and staff.	39		(11, 12)
Cervical biopsy	Cost of collection materials, disposables, facilities and staff.	124		(11, 12)
Treatment of high-grade precancer and cancer				
Treatment of cervical intraepithelial neoplasia grade 2 and 3	Cost of treating a precancerous lesion (defined as CIN2 and CIN3), using a weighted average of conization (98.7%), simple hysterectomy (1%) and other treatments (0.3%) (based on the Norwegian Diagnostic Related Groups system). Includes round-trip transportation costs to the hospital as well as time spent receiving and recovering from the treatment (1 day). Indirect costs include the cost of productivity loss associated with recovering and follow-up visits (1 week).	1,682	4,773	(10, 17-19)
Treatment of local cervical cancer	Includes costs associated with diagnosis, conizations (19%), simple hysterectomy (19%), radical hysterectomy (41%), radiotherapy and/or adjuvant chemotherapy (19%), fertility preserving treatment (2%), complications (10%), relapse/recurrence treatment (20%), and recommended follow-up for 5 years conditioned on survival, as well as transportation costs and productivity loss associated with treatment and follow-up. Indirect costs include 5 weeks sick leave.	26,941	39,856	(4)
Treatment of regional cervical cancer	Includes costs associated with diagnosis, radical hysterectomy (6%), brachytherapy, external radiotherapy and adjuvant chemotherapy (92%), simplified external radiotherapy (2%), complications (10%), relapse/recurrence treatment (20%), and recommended follow-up for 5 years conditioned on survival, as well as transportation costs and productivity loss associated with treatment and follow-up. Indirect costs include 1 year sick leave.	56,601	161,730	(4)
Treatment of distant cervical cancer	Includes costs associated with diagnosis, radiotherapy with boost and adjuvant chemotherapy (50%), 6 rounds chemotherapy (15%), radiotherapy with adjuvant chemotherapy (28%), simplified radiotherapy (8%), complications (10%), relapse/recurrence treatment (20%), and recommended follow-up for 5 years conditioned on survival, as well as transportation costs and productivity loss associated with treatment and follow-up. Indirect costs include 1 year sick leave.	41,367	146,571	(4)

4. 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. 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.
3. Statistics Norway, 2015. URL: <http://ssb.no/befolkning/statistikker/dode/aar/2015-03-26?fane=tabell&sort=nummer&tabell=220943> (Accessed: October 16, 2015).
4. Burger EA, Ortendahl JD, Sy S, Kristiansen IS, Kim JJ. Cost-effectiveness of cervical cancer screening with primary human papillomavirus testing in Norway. *British journal of cancer*. 2012;106(9):1571-8.
5. Pedersen K, Burger EA, Sy S, Kristiansen IS, Kim JJ. Cost-effective management of women with minor cervical lesions: Revisiting the application of HPV DNA testing. *Gynecologic oncology*. 2016.
6. Vaccarella S, Franceschi S, Engholm G, Lonnberg S, Khan S, Bray F. 50 years of screening in the Nordic countries: quantifying the effects on cervical cancer incidence. *British journal of cancer*. 2014;111(5):965-9.
7. Goldhaber-Fiebert JD, Stout NK, Ortendahl J, Kuntz KM, Goldie SJ, Salomon JA. Modeling human papillomavirus and cervical cancer in the United States for analyses of screening and vaccination. *Population health metrics*. 2007;5:11.
8. Cancer Registry of Norway. The Norwegian Cervical Cancer Screening Program. 2016: Oslo, Norway.
9. Pedersen K, Burger EA, Campbell S, Nygard M, Lonnberg S. Risk of Cervical Cancer by Screening Intensity: A Registry-based Analysis. *International Papillomavirus Conference*, September 17-21, Lisbon, Portugal. 2015.
10. Cancer Registry of Norway. Annual Report of the Norwegian Cervical Cancer Screening Program, 2013-14 Accessed at https://www.kreftregisteret.no/globalassets/publikasjoner-og-rapporter/livmorhalskreft/arsrapport/livmorhals_2015pdf on October 16, 2015 Oslo: Cancer Registry of Norway, 2015.
11. Pedersen K, Sørbye SW, Kristiansen IS, Burger EA. Using novel biomarkers to triage young adult women with minor cervical lesions: A cost-effectiveness analysis. *BJOG: An International Journal of Obstetrics and Gynaecology*. 2016; Accepted March 24, 2016.
12. Pedersen K, Lonnberg S, Skare GB, Sorbye SW, Burger EA, Kristiansen IS. Kostnader ved Masseundersøkelsen mot livmorhalskreft. *Sykepleien Forskning*. 2015;nb. 1, 2015(10):62-71.
13. Federal Reserve. Average rates of exchange 2014. Available at: <http://www.federalreserve.gov/releases/G5A/current/> (Accessed: November 22, 2015). . 2015.
14. Norwegian Directorate of Health (2012). Økonomisk evaluering av helsetiltak - en veileder. URL: <http://helsedirektoratet.no/publikasjoner/okonomisk-evaluering-av-helsetiltak--en-veileder/Publikasjoner/IS-1985.pdf> (Accessed: 15.09.2014). 2012.
15. Statistics Norway, 2014. URL: <http://www.ssb.no/english>. (Accessed: 22.04.2015).
16. Moger TA, Kristiansen IS. Direct and indirect costs of the Norwegian Breast Cancer Screening Program. *HERO Working Paper 2012(2012:3)*.
17. Norwegian Medical Association. Normal tariff for private general practice 2014–2015. Available at: http://normaltariffen.legeforeningen.no/pdf/Fastlegetariff_2014.pdf (Accessed: 22.04.2015). 2012.
18. Lovdata. Forskrift om godtgjørelse av utgifter til helsehjelp som utføres poliklinisk ved statlige helseinstitusjoner og ved helseinstitusjoner som mottar driftstilskudd fra regionale helseforetak. Available at: <http://lovdata.no/dokument/SF/forskrift/2007-12-19-1761> (Accessed: October 15, 2015).
19. Norwegian Directorate of Health (2014). Activity-based funding 2014. Available at: <https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/87/Innsatsstyrt-finansiering-2014-regelverk-IS-2162.pdf> [Access date: October 4, 2015].