
# Resource use and economic impact of gradual implementation of primary human papillomavirus (HPV) screening in Norway: Model-based projections

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## ABSTRACT

**Background:** In cervical cancer screening, despite noticeable reduction of cervical cancer using cytology screening the more sensitive human papillomavirus (HPV) test may further reduce the burden of cervical cancer. As many other countries, Norway are implementing primary HPV-based screening among older women (i.e. aged 34-69 years). As screening with primary HPV-test are being gradually implemented, our objective was to inform expected resource use and economic impact associated with women screening with primary HPV-test over a 10-year period (2020-2029).

**Methods:** We developed a population-based multi-cohort screening model that reflects the 2018-algorithm. The model followed cohorts of women attending primary screening through multiple rounds of screening. We used a multi-model approach requiring a three step-wise analysis: 1) Cohort Markov Model; 2) Demographic Model; and 3) Multi-Cohort Model to capture ongoing screening scaled to the Norwegian population level. This multidisciplinary approach involved analysis of epidemiological primary data, literature reviews and expert opinion, and an adaptive county-specific demographic process capturing county-specific capacity- and eligibility constraints for women to be screened with a baseline (at least one) primary HPV-screen. Primary yearly outcomes were non-monetary resource use (i.e. number of positive tests, colposcopy procedures, and detected cases of CIN2/3), and monetary outcomes (indirect and total costs). We estimated expected number of colposcopies per 1 000 women using simulated colposcopy outcomes for the first screening round. We also explored a hypothetical scenario of immediate scale-up (100% switch) in 2020 in all of Norway on expected colposcopy procedures.

**Results:** We projected an increase in number of positive tests, colposcopy procedures, and detected cases of CIN2/3 for the 34 year-olds, whereas for women aged 35-69 years and for all ages (i.e. 34-69 years), we projected magnitude of volumes to fluctuate over time. We estimated two “peaks” in 2023 and 2028, with number of positive tests of 30 734 in 2023 and 33 195 in 2028, colposcopy procedures of 9 209 in 2023 and 9 818 in 2028, and detected CIN2/3 cases of 2 764 in 2023 and 1 877 in 2028, in 2023 and 2028. Associated total costs were $147 million and $112 million in 2023 and 2028, respectively. We expected a decrease in CIN2/3 detection in subsequent screening rounds, while for the number of positive tests and colposcopy procedures we anticipated increases in subsequent rounds, primarily due to population growth. For expected number of colposcopies of the first screening round, we found triage testing at 24 months contributed the most across all ages. In the hypothetical immediate scale-up, we predicted higher number of colposcopy procedures as well greater fluctuations over time compared to a gradual implementation.

**Conclusions:** National fluctuations in volumes of tests and procedures within HPV-based screening program are expected over a 10-year period, prompting an effort in resource planning; however, less variability are expected for subsequent screening rounds. In facilitating a safe, timely gradual primary HPV-implementation, model-based projections of the new triage algorithm may be helpful for preparing the health system.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AGUS | Atypical glandular cells of undetermined significance |
| ASC-H | Atypical squamous cells, cannot exclude high-grade lesion |
| ASC-US | Atypical cells of undetermined significance |
| Ca | Cancer (all types of cancer) |
| CB | Credible Bounds (Lower and Upper Bounds) |
| CRN | Cancer Registry of Norway |
| CC | Cervical cancer |
| CIN | Cervical intraepithelial neoplasia |
| CIN1 | Cervical intraepithelial neoplasia grade 1 (mild changes) |
| CIN2 | Cervical intraepithelial neoplasia grade 2 (indicates moderate changes) |
| CIN3 | Cervical intraepithelial neoplasia grade 3 (indicates severe changes) |
| <CIN2+ | CIN grade 1 or normal (no detected dysplasia) |
| CIN2+ | CIN grade 2, 3 or cancer |
| HPV | Human papillomavirus |
| HPV16/18 | Genotype HPV16 and/or HPV18 |
| hrHPV | High risk human papillomavirus |
| other hrHPV | High-risk human papillomavirus (not HPV16/HPV18) |
| HSIL | High-grade squamous intraepithelial neoplasia |
| LBC | Liquid-based cytology |
| LSIL | Low grade squamous intraepithelial lesion |
| NILM | Negative for intraepithelial lesion or malignancy |
| NCCSP | The Norwegian cervical cancer screening program |
| NOK | Norwegian Kroner |
| PSA | Probabilistic sensitivity analysis |

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# 1 INTRODUCTION

A persistent human papillomavirus (HPV) infection leads to the majority of cervical cancer cases world wide. Among the 13 high-risk HPV (hrHPV) genotypes, HPV16 and HPV18 are attributed to 70% of cases (Schiffman et. al., 2007). Cervical cancer screening, which began in Norway in the 1970`s, aims to prevent cervical cancer development (through detection of precancerous lesion) or improve diagnosis by detecting the disease at an early stage. Cytology-based, i.e., Pap-smear, screening has been estimated to contribute to reducing cervical cancer cases in Norway by 70% (Lønnberg et. al., 2015). However, there are opportunities to implement a more sensitive test, which may further reduce the burden of cervical cancer (Arbyn et. al., 2012). A recently published meta-analysis of four European randomized controlled trials found a reduction of 60-70% in invasive cervical cancers in women screened with primary HPV-based test compared to women who had primary cytology-based screening (Ronco et. al., 2014).

Norway is one of several countries implementing primary HPV-based screening to replace primary cytology-based screening for women older than age 34 years. Following a 3-year pilot HPV-based screening implementation project in 2015, the Norwegian Cervical Cancer Screening Program (NCCSP), started to, gradually inviting all women in Norway aged 34-69 years to 5-yearly primary HPV testing, while women aged 25-33 years will continue to screen every 3 years using primary cervical cytology (Cancer Registry of Norway, 2020). Due to the higher sensitivity and lower specificity of a primary HPV-based test (Arbyn et. al., 2012), the switch from 3-yearly cytology-based screening to primary HPV-based screening in older women may induce considerable changes in resource utilization over time, but these are currently unknown in Norway.

The 2018 primary HPV-based testing algorithm was initiated by the Ministry of Health and Care Service informed by evidence from the Norwegian pilot program in 2015 (Cancer Registry of Norway, 2018). Evaluations of the pilot implementing program, conducted in four Norwegian counties: Rogaland, Hordaland, Sør-Trøndelag, and Nord-Trøndelag indicated

higher referral rates to colposcopy. These findings prompted adjustments to the current screening algorithm in order to adapt to capacity constraints at gynecologist and pathology-laboratories. Modifications to the algorithm generally reflected a risk-based triage algorithm and involved geno-type specific primary HPV-based testing in order to adjust high colposcopy referrals (Birgit Engesæter, personal communication; and Cancer Registry of Norway 2019).

In the long run, a well-established HPV-based cervical screening program with longer primary screening intervals is expected to have considerable health benefits at lower costs compared to cervical cytology screening (Ronco et. al., 2014; Burger et. al., 2012). However, an immediate implementation of primary HPV testing may result in an immediate increased pressure at gynecology- and pathology-services, while a gradual scale-up may help alleviate strains to health services by spreading resource burden over a longer period. Regardless, the first transition rounds of screening with primary HPV-based test is expected to yield the highest colposcopy rates and yield a higher precancer detection rate compared with cytology-based screening (Ronco et. al., 2014). For example, evaluations from the Australian implementation of primary HPV program found that during the first 6 months after switching from cytology- to primary HPV-based screening colposcopy- rates increased; however, these referral-rates were expected to decline in subsequent rounds of screening (Machalek et. al., 2019). Therefore, expected fluctuations in resource use during the first screening rounds prompts a need for resource planning and preparing workforce in provided health care services. As for Norway, during the planned enrollment of gradual implementation of primary HPV testing, model-projections quantifying national and regional resource use are required in an effort to prepare the health system to anticipate changes.

In this study, we combined a descriptive primary data analysis using empirical data from the Cancer Registry of Norway (CRN) to inform 10-years model-based projections of the impact of the gradual national-wide implementation of primary HPV-based screening for women aged 34-69 years on resource use and costs in Norway. Specifically, we evaluated resource use and costs from the counties included in the pilot implementation program and applied these changes to other regions of Norway to inform national expected resource use of women screening with primary HPV-testing between 2020 and 2029.

# 2 MATERIALS AND METHODS

## 2.1 Analytic overview

We used a multi-model approach involving a combination of three step-wise analysis: 1) Cohort Markov Model; 2) Demographic Model; and 3) Multi-Cohort Model (**Figure 1**). Our estimations from the Cohort Markov Model and Demographic Model were used as inputs used in the Multi-Cohort Model in order to capture multiple rounds of primary HPV-based screening scaled to the population level. This multidisciplinary approach involved analysis of epidemiological primary data, literature reviews and expert opinion, and an adaptive county-specific demographic process in order to project resource utilization and costs associated with gradually implementing primary HPV testing for women aged 34-69 years between 2020 and 2029. We stratified our analysis for three distinct age-groups of women: aged 34 years, aged 35-69 years, and all ages 34-69 years, as these groups of 34 year-olds and 35-69 year-olds are expected to vary in underlying factors such as HPV-positivity (due to sexual behavior), but also to capture the guidelines of the perpetual switch of women at age 34 years.

Our base-case analysis was conducted in the context of the planned gradual scale-up of primary HPV-screening in Norway, beginning in 2015 and concluding in 2023 with 2025 being, the year in which all women aged 35-69 years would have the opportunity for at least one baseline round of primary HPV-based screening. In scenario analysis, we explored the impacts of a hypothetical immediate scale-up (100% switch) to primary HPV-based screening by 2020 in all of Norway.

We reported outcomes of non-monetary resource use and CIN2/3 detection, and monetary outcomes in each year by age-groups (women aged 34 years, women aged 35-69 years, and all ages of 34-69 years) in 2020-2029. Non-monetary resource were defined in terms of included number of positive tests, colposcopy procedures and detection of cervical intraepithelial neoplasia grades 2 (CIN2) and grades 3 (CIN2/3). We reported the composite outcome of CIN2/3 detection according to current threshold of CIN2 treatment in Norway, accounting for the treatment cost of assuming all women with detected CIN2 or CIN3 received treatment. We further assessed expected number of colposcopies per 1 000 women stratified by immediate colposcopy, 12- or 24 month triage test for the first round of screening during the gradual scale-

up. Monetary outcomes included annually direct and total costs (direct and indirect costs), expressed in 2019 USD (US $1 = NOK 8.80), discounted by 4% per year, as recommended in Norway (Norwegian Directorate of Health, 2012).

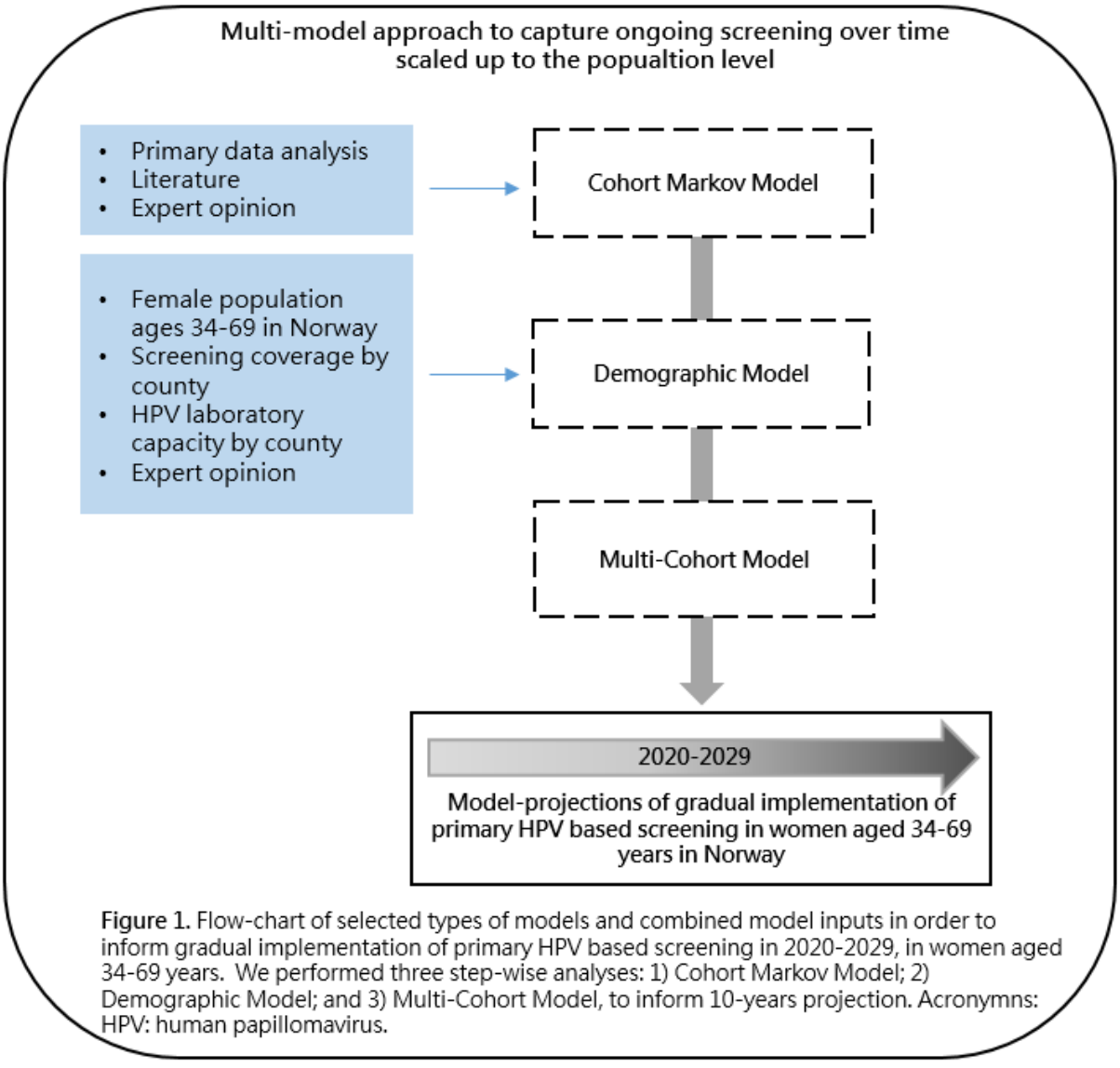



**Figure 1.** Flow-chart of selected types of models and combined model inputs in order to inform gradual implementation of primary HPV based screening in 2020-2029, in women aged 34-69 years. We performed three step-wise analyses: 1) Cohort Markov Model; 2) Demographic Model; and 3) Multi-Cohort Model, to inform 10-years projection. Acronymns: HPV: human papillomavirus.

## 2.2 Model structure

Our Cohort Markov Model reflects the cervical screening algorithm implemented by the CRN on July 1st 2018 (Cancer Registry of Norway, 2020). The model simulates cohorts of unvaccinated women through multiple rounds of screening; thus, the model did not explicitly account for vaccinated women (**Appendix Section 1**). For the prevalent screening round (i.e., "Round 1), we assumed disease detection was differential than in subsequent screening

rounds (i.e., “Round 2”) as this first round of screening would detect both prevalent and incident CIN2/3 and cervical cancer cases, while predominantly incident cases would be detected in subsequent rounds (Ronco et. al., 2014). All primary screening rounds were structurally equivalent, reflecting the CRN primary screening algorithm. In screening of women testing positive for high-risk HPV genotypes, a woman’s sample was tested for cytological abnormalities using liquid-based cytology (LBC) to inform triage management. Triage management was additionally informed by partial genotyping results (HPV16- or HPV18-positive, and “other hrHPV”-positive (not HPV16 or HPV18)) and severity of cytology result. Women were managed subsequently according to the risk-factor of abnormal cervical results associated with the screening test (Cancer Registry of Norway, 2020).

We allocated screened women to an initial screening pathway based on their primary HPV test-result and cytology reflex test (if primary test was hrHPV-positive): (1) immediate colposcopy; (2) triage-test at 12 months; (3) delayed triage-test at 24 months; and (4) return to routine screening in 5 years. Women testing positive for HPV16 or HPV18 followed by any abnormal cytology, or other hrHPV-positive with a high-grade cytology reflex test were referred to immediate colposcopy and biopsy. Women that were positive for HPV16 or HPV18 followed by a normal cytology reflex test, or hrHPV-positive followed by low-grade reflex cytology result were recommended a repeat HPV test 12-months later, while women testing positive for other hrHPV and a normal cytology reflex test were recommended a new HPV test 24 months later. If women were HPV-negative, they were recommended for a new primary HPV screening test in 5 years.

Management of women with a 12- or 24 month triage test reflected the 2018-algorithm as women who were positive for any hrHPV at the 12- or 24-month triage visit were referred to colposcopy, whereas hrHPV-negative women returned to the 5-yearly routine screening interval. We accounted for the underlying natural history of disease by allowing low-grade precancerous lesions of cervical intraepithelial neoplasia grade 1 (CIN1) to regress to negative for intraepithelial lesion or malignancy (NILM) or progress to cervical intraepithelial neoplasia grade 2 or more severe (CIN2+) during the triage period. The model did not allow for diagnosis of cancer outside the screening interval (i.e., cancer interval) to occur. We accounted for non-compliance at each step of the screening process: primary, triage,

colposcopy and treatment. The model followed compliant women, while non-compliant women were censored and were assumed to not re-enter into the model. Screening adherence at primary screen, follow-up procedures (i.e. immediate colposcopy, triage test at 12- or 24 months), and treatment were assumed to be similar between the screening rounds. To capture parameter uncertainty, we applied beta-distribution to vary probabilistically selected key parameters in Round 1 (**Table 1**). We calculated the base-case health and economic outcomes in each cycle-year as the mean value across 1 000 probabilistic simulations and used the minimum and maximum values to reflect uncertainty bounds (lower and upper bounds); herein referred to as CB (credible bounds). Our Markov Cohort Model was built in the open-source modeling framework of AMUA version 0.2.9.

Our Demographic Model reflects the expected number of women screening with primary HPV-based test in each county from the start of the pilot HPV-based screening implementation in 2015 to the end of our analytical period in 2029. We stratified women according to their type of primary screening (i.e. primary cytology-based screening or primary HPV-based screening) in line with the expected starting year of the primary HPV-implementation and anticipated scale-up of HPV-capacity. We also stratified by age-groups of women aged 34 years and women aged 35-69 years in order to capture the guidelines for the perpetual switch of women at age 34 years. Finally, our Multi-Cohort model, which reflects multiple rounds of primary HPV-based screening scaled to the Norwegian population level, was developed by applying outputs from the Markov Cohort Model linked with age- and county-specific details informed by the Demographic Model.

## 2.3 Model validation

We validated the performance by examining the plausibility of parameter sensitivity by vary probabilistically selected key parameters in line with the ISPOR – SMDM Task Force published guidelines for good modelling practice (Eddy et. al., 2012). Face validity *i.e.*, that the model components and outcomes seems reasonable given current knowledge, were assessed in accordance with Norwegian experts on cervical cancer screening and disease. Further, we excessively verified the model through detailed inspection of model inputs and calculations, as well as software debugging to ensure interval validation.

## 2.3 Baseline Model Parameterization

Parameterization of the population-based cohort-screening model involved selecting model input parameters of epidemiological, demographical and economic data to inform the initial model. Model parameterization of epidemiological data required combining analysis of primary data from the CRN and published literature when empirical data were unavailable. Projections of demographic data involved combining county-specific population data for the age groups and associated primary screening attendance reported by the CRN.

### *2.3.1 Epidemiological data*

Compliance to a primary screening test varied by Norwegian county and was informed by estimates from the CRN (Cancer Registry of Norway, 2020). For women attending screening Round 1, we derived annual from primary data along with a recently published study from the CRN (Hashim et. al., 2020) and a seminal study by Schiffman and colleagues (Schiffman, 2007) (**Table 1**).

For screening Round 2, no primary data were available; therefore, we estimated the expected changes in relative risks (RRs) of selected parameters between screening rounds using a multidisciplinary approach combining primary data analysis, demographic data, and randomized control (RCT) trial (**Appendix Section 2 Table 1**). Specifically, we applied RRs on parameters of immediate referral for colposcopy and triage screening, and following detections of CIN2+ lesion obtained from the Canadian HPV FOCAL randomized control trial (Ogilvie et. al., 2018) as these real-world data were based on similar screening age-structure as in the NCCSP. We applied the same RRs for both age-groups, assuming there was no age-specific difference in risks. In addition, we accounted for structural changes (women entering and exiting) among the 35-69 year-olds by applying RRs on screening attendance and number of positive tests for these older women in Round 2 (**Appendix Section 2 Table 1**).

Table 1 | Selected model inputs by age-cohort for Round 1. Values are reported as numbers (percentages), unless stated otherwise

| Variable | Ages 34-39 Cases | Total | (%) | Ages 34-69 Cases | Total | (%) | Distribution for PSA[4] | Source |
|---|---|---|---|---|---|---|---|---|
| **Primary Screening** | | | | | | | | |
| Compliance with primary HPV-screening[1] | | | [0.58-0.67] | | | [0.64-0.72] | | CRN Årsrapport[5] |
| Positive screening test requiring follow-up procedures | 466 | 4016 | 11.6 | 1484 | 20044 | 7.4 | Beta | Primary Analysis |
| **Among women with a positive screening test** | | | | | | | | |
| Immediate referral for colposcopy | 145 | 466 | 31.1 | 409 | 1484 | 27.6 | Beta | Primary Analysis |
| Compliance with immediate colposcopy | 130 | 144 | 90.3 | 194 | 198 | 98.0 | | Primary Analysis |
| CIN2 or worse detection | 101 | 130 | 77.7 | 254 | 362 | 70.2 | Beta | Primary Analysis |
| CIN2/3 detection among CIN2+ cases[2] | 92 | 101 | 91.1 | 215 | 254 | 84.6 | Beta | Primary Analysis |
| CIN1 cases among <CIN2+ cases[2] | 13 | 29 | 44.8 | 46 | 108 | 42.6 | Beta | Primary Analysis |
| **Distribution of overall triage test at 12 or 24 months** | | | | | | | | |
| Triage test at 12 months | 135 | 321 | 42.1 | 444 | 1075 | 41.3 | | Primary Analysis |
| **Triage Screening at 12 or 24 months** | | | | | | | | |
| Compliance with triage screening test | 9 | 21 | 42.9 | 46 | 99 | 46.5 | | Primary Analysis |
| Positive HPV screening test at 12 months | 6 | 9 | 66.7 | 33 | 46 | 71.7 | Beta | Primary Analysis |
| Positive HPV screening test at 24 months | | | 7.0 | | | 10.0 | | Schiffman et.al., 2007 |
| Compliance with colposcopy after positive triage test | 4 | 6 | 66.7 | 17 | 33 | 51.5 | | Primary Analysis |
| CIN2 or worse detection in triage test at 12 months[3] | | | 38.0 | | | 22.2 | Beta | Hashim et.al., 2020 |
| CIN2 or worse detection in triage test at 24 months[3] | | | 16.1 | | | 9.4 | Beta | Hashim et al., 2020 |
| CIN1 cases among <CIN2+ cases | 0.25 | 4 | 6.3 | 4 | 19 | 21.1 | Beta | Primary Analysis |
| **Follow-up colposcopy of immediate CIN1-detection** | | | | | | | | |
| Compliance with follow-up colposcopy | 5 | 7 | 71.4 | 14 | 23 | 60.9 | | Primary Analysis |
| Normal or CIN1-detection | 3 | 5 | 60.0 | 10 | 14 | 71.4 | Beta | Primary Analysis |
| **Treatment of precancerous lesion (CIN2/3)** | | | | | | | | |
| Treatment of CIN2/3 | 68 | 92 | 73.9 | 159 | 215 | 74.0 | Beta | Primary Analysis |

[1]Compliance with primary HPV screening are reported as a range among all counties. [2]Distribution of CIN2/3 and CIN1 cases are assumed similar in immediate referral for colposcopy and triage screening. [3]Relative differences in CIN2 or worse detection between age-groups at triage test at 12 and 24 months are derived from relative differences of CIN3+ detection in age groups from the study by Hashim et. al., 2020. [4]Probabilistic Sensitivity Analysis. The alpha & beta inputs for beta distribution: alpha = cases, beta = total - cases. [5]CRN *Årsrapport 2017-2018*. Acronymns: HPV: human papillomavirus. CIN: cervical intraepithelial neoplasia.

For our primary data analysis, we included women aged 34 – 69 years in four Norwegian counties (Rogaland, Hordaland, Sør-Trøndelag and Nord-Trøndelag) screened with primary HPV test from July 1st 2018 to capture outcomes among women screening under the recent changes to the primary HPV triage algorithm (**Appendix Section 2 Figure 1**). Primary data analysis were conducted separately for women aged 34-39 years and women aged 34-69 years, accounting for age-specific variations in HPV-positivity-rate. We excluded women with a screening result before July 1st 2018 and women that were cytology-screened after July 1st 2018. Additionally, exclusions were applied to women with insufficient test, missing HPV-genotyping, or no confirming cytology reflex test as well as women with only morphology-confirmation at primary screening (as for one case). Finally, among women with "complete" primary HPV screening we excluded women that were HPV-negative in order to inform HPV-positive analysis (**Appendix Section 2 Figure 1**).

We followed cohorts of primary HPV-positive women, starting at the date of the primary HPV-screen and continued until the highest histologically confirmation was reported. We joined cytology results of ASC-US and LSIL into one low-grade category, and ASC-H, HSIL, AGUS, ACIS, Ca into one high-grade category. Any results of low- or high-grade cytology categories were considered abnormal.

Morphological characteristics were allocated into categories of low-grade precancerous lesions of cervical intraepithelial neoplasia less than grade 2 (<CIN2+) and high-grade precancerous lesions of CIN2 or more severe (CIN2+). Two mutually exclusive groups were defined based on highest morphology reported: 1) "CIN2+", which included any cancer type, CIN3, CIN2, and unspecified dysplasia; and 2) "<CIN2+", which included irregular cylindrical epithelium and any type of normal test characteristics. We assumed distribution of both CIN2+ cases and <CIN2+ cases in triage-screeners at 12 and 24 months were proportionally equivalent as distribution in immediate colposcopy. Accounting for the natural history, we allowed for regression or progression of women detected with CIN1 within 12 months follow-up time.

For Round 1 follow-up procedures, we specified compliance-windows based on primary data analysis combined with the CRN protocols for delayed testing. We determined compliance-windows in order to identify compliers and non-compliers among screeners with complete observation period. We used a maximum-acceptable window of 12 months in complying with immediate colposcopy, colposcopy if HPV-positive triage test at 12 months, and re-colposcopy if CIN grade 1 (CIN1) was detected in the previous year. For compliance to a 12-months triage test, our window-criteria was set to 15 months. Exclusions were applied to women in need of follow-up procedures with insufficient observation time due to late testing at the end of the enrollment period. For triage testing at 24 months, no primary data were available; therefore, we assumed the 12-month compliance probability of attending triage testing and colposcopy to inform screening compliance among HPV-positive triage screeners at 24 months. All statistical analysis were performed in R Statistical Software version 3.4.4 and RStudio version 3.4.4.

### *2.3.2 Demographic data*

To calculate the number of women eligible for a baseline (at least one) primary HPV-based screening test in each year, we linked county- and age-specific population demographic data from Statistics Norway (Statistics Norway, 2020) with projections of county-level HPV laboratory capacity. These expected capacity-levels in each county were informed by the CRN (**Appendix Section 2 Table 3**), and adapted to reflect 3-yearly fluctuations in availability for women to be at least once primary HPV-screened. To inform primary screening attendance we used the 2018 screening coverage by county reported in the CRN latest annual report (Cancer Registry of Norway, 2020). Over the projection-period, we accounted for a yearly population growth among the 34 years-old, while assuming a stable population among the 35-69 years-old using 2018-population-cohort data (Statistics Norway, 2020). Details of the number of eligible women for a primary HPV-based screening test in each county are included in the Supplementary **Appendix Section 4 Figure 2 and 3.**

We expected that during the gradual scale-up, before 100% HPV-laboratory capacity is reached, a proportion of women in all age-groups (i.e. ages 34 years and 35-69 years) would still be screened with primary cytology-test due to capacity constraints, although these women were eligible for a primary HPV-screen after finishing 3-yearly cytology-based screening intervals. Further, these number of women cytology-screened will decrease as HPV-capacity is scaled-up, and eventually, all women aged 35-69 years would be screened with baseline (at least one) primary HPV-based test in the associated year they finish 3-yearly cytology-screening interval. Following the gradual national implementation, we estimated that all women would have the opportunity to be screened with a baseline primary HPV-based screening by 2025 in all of Norway. As for ongoing women aged 34 years, we assumed all would be eligible primary HPV screeners after full capacity is reached.

For example, in Oslo women are expected to start screening with primary HPV-based at screening in 2021 over a 2-year capacity scale-up. Although full capacity (100% switch) is expected reached by 2023, it will take consecutively 2 years before all of Oslo would have the opportunity to have at least one primary HPV-based screen due to those cytology-screened women during capacity scale-up.

### *2.3.3 Economic data*

Monetary costs of primary HPV-based screening were estimated using a combination of Norwegian fee schedules and a previous Norwegian cost study of the cervical cancer screening program (Pedersen et. al., 2015). We updated all economic model inputs to reflect 2019 estimates following changes in the reimbursement system and related fees (see **Appendix Section 3 Table 4**). All costs were measured in 2019 Norwegian Kroner (NOK) and converted to US dollars using the average annual 2019 exchange rate (US $1 = NOK 8.80) (Federal Reserve, 2019). Direct medical costs for screening, follow-up procedures, and treatment of precancerous lesions (CIN2/3) and cancer were based on Norwegian Diagnosis Related Groups (DRGs) (Norwegian Directorate of Health, 2019) and the Fee Schedules for General Practitioners and Specialists (Norwegian Medical Association, 2019).

Indirect costs were valued to account for production loss in terms of work absenteeism and travel time and transportation cost associated screening consultations and treatment. In order to estimate travel time including waiting, receiving care and transport we applied the 2019 average monthly income among Norwegian women obtained from Statistics Norway attached 40%, accounting for social benefits paid by employers (Statistics Norway, 2020). Transportation costs associated with screening procedures and precancer and cancer treatment were based obtained from a previous study (Pedersen et. al., 2015). Productivity costs in terms of sick leave after precancer and cancer treatment were not included.

## 2.4 Ethics approval

Access and use of the primary data were approved by the Data Protection Officer at the University of Oslo (project number 588428) in accordance with the General Data Protection Regulations (GDPR). The study has used data from the CRN. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the CRN is intended nor should be inferred.

# 3 RESULTS

## 3.1 Non-monetary resource use and CIN2/3 detection

Following the gradual transition from primary cytology-based screening to primary HPV-based screening in 2020-2029, we projected a steady increase in the number of HPV-positive tests, colposcopy procedures and detected cases of CIN2/3 among the 34 year-olds over time as the capacity for primary HPV screening increased and the number of 34 year-olds increased (**Figure 2; left panels**). As Norway is expected to reach full capacity of primary HPV-testing in 2025, the number of CIN2/3 detected within HPV-based screening program could continue to increase from 559 (CB: 380 - 786) to 771 (CB: 507 – 1 112) (38%) by 2029.

In contrast, for women aged 35-69 years, the numbers of positive tests, colposcopy procedures and CIN2/3 detection were predicted to fluctuate over time. For example, the number of HPV-positive tests with an initial peak in 2023 at 27 051 (CB: 25 492 – 58 518) followed by a second peak in 2028 at 26 273 (CB: 24 870 – 27 595) (Figure 2; middle panels). When simulating cohorts of women, we found decreases in cohort volumes of HPV-positivity rate, colposcopy procedures and CIN2/3 detection for Round 1 compared with Round 2 of screening (**Appendix Section 2 Table 2**); however, after adjusting for population-demographics we would expect absolute increases as the Norwegian female population size increases over time.

Across all ages of women screening with primary HPV-based testing, the total number of positive tests, colposcopy procedures and detected cases of CIN2/3, were primarily driven by the women aged 35-69 years (**Figure 2; right panels**). Over the 10-year period, we predicted two “peaks” in magnitude of total number of positive tests, colposcopy procedures, and detection of CIN2/3 cases among women screened with primary HPV-testing.

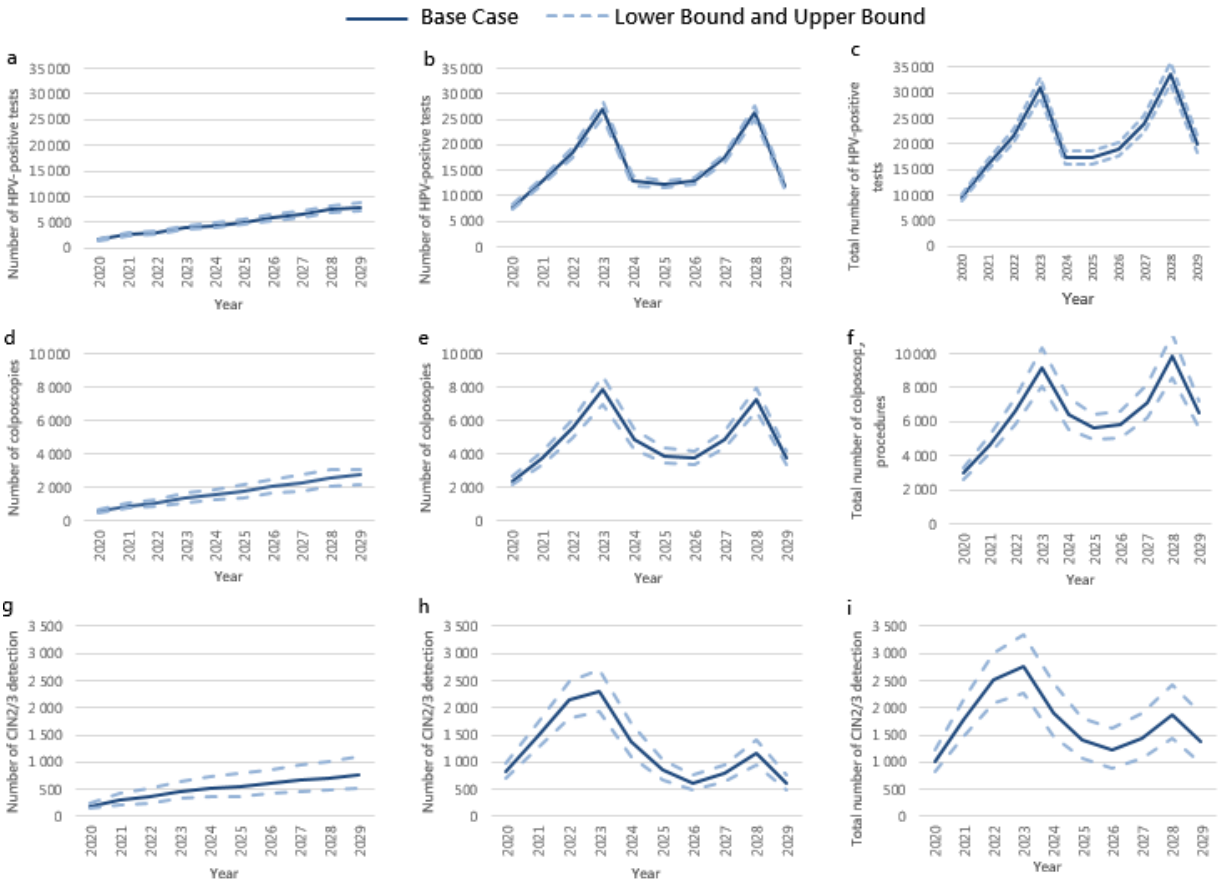



**Fig. 2** Estimated number of positive HPV-tests (top-panels) in women ages 34 (a), ages 35-69 ( b); and ages 34-69 (e), colposcopy procedures (mid-panels) in women ages 34 (d), ages 35-69 (e); and ages 35-69 (f), and CIN2/3 detection (bottom panels) in women ages 34 (g), ages 35-69 (h); and ages 34-69 (i), associated with gradual implemenetation of primary HPV based screening test under the 2018-algorithm. Values are reported in absolute numbers and scaled to the Norwegian population (see methods). Lower and upper bounds were estimated probabilistically and reflect minimum and maximum values. Acronymns: HPV: human papillomavirus. HPV-positive tests: women testing positive for HPV16, HPV18, or otherHPV (not HPV16/HPV18). CIN2/3 detection: cervical intraepithelial neoplasia grade 2 or grade 3.

For example, we estimated total number of positive tests of 30 734 (CB: 29 060 – 32 885) in 2023 and 33 195 (CB: 31 628 – 25 820)in 2028. Similarly, we projected the number of colposcopy procedures among women screened with primary HPV-based screening (Figure 2f) to be highest in years 2023 and 2028, with 9 209 (CB: 8 129 – 10 313) and 9 818 (CB: 8 616 – 11 100) number of total colposcopies, respectively. For precancerous lesions in women aged 34-69 years (Figure 2i), we projected highest CIN2/3-detection in the same years of 2023 and 2028; however, we expected a substantial decrease in CIN2/3 detections in subsequent years as a greater number of precancerous lesion were detected in Round 1 of screening. In 2023, we estimated a total CIN2/3 detection of 2 764 (CB: 2 265 – 3 347). In comparison, we estimated a total CIN2/3 detection of 1 877 (CB: 1 434 -2 430) in 2028, yielding reduction of CIN2/3 detection by 47.25% over a five-year period.

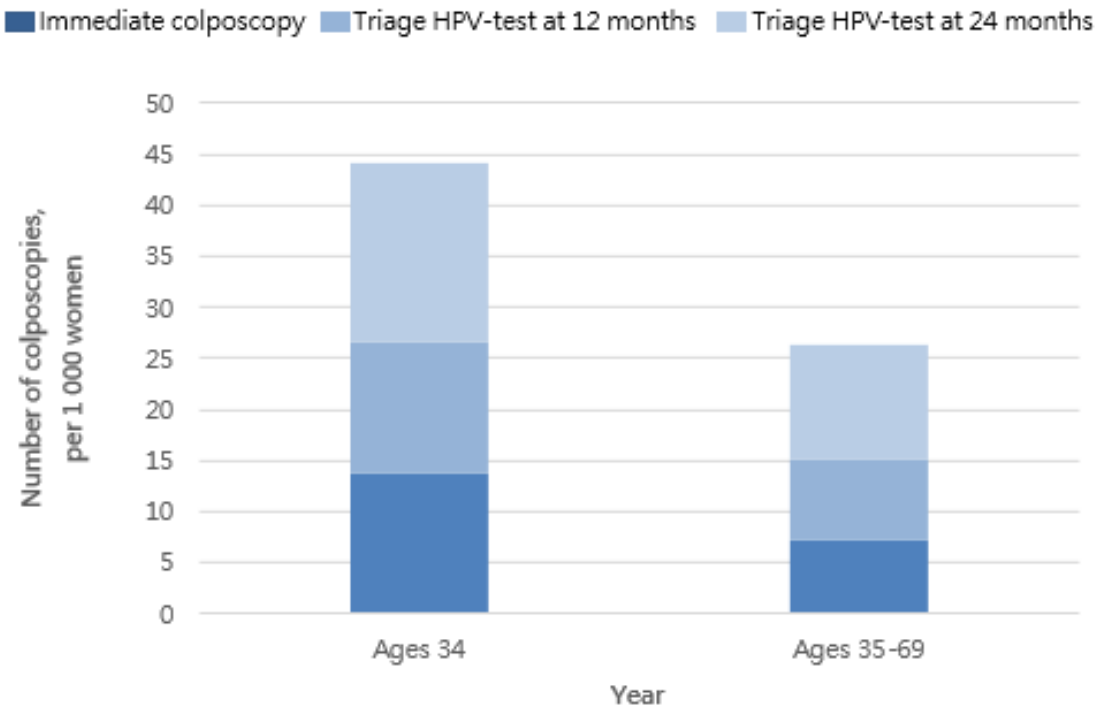



**Fig 3. Contribution of age-specific colposcopy procedures associated with primary screening and triage testing at 12 or 24 months in Round 1.** We combined three age-groups of women: 1) Ages 34, 2) Ages 35-69; and 3) the total age-groups of all women aged 34-69 years, to inform contribution of colposcopy in Round 1.

When we evaluated the expected number of colposcopy procedures per 1 000 women by age-groups in the 2018-algorithm, we found younger women face a higher colposcopy rate compared to women aged 35-69 years (Figure 3). We also found that immediate colposcopies contributed to 31% of expected colposcopies in the first 5 years of women aged 34 years, triage testing at 12 months contributed to 29% of expected colposcopies, and triage testing at 24 months contributed by 40% of expected colposcopies. We found similar patterns when we evaluated expected number of colposcopies among the 35-69 years-old; however, we expected a slightly decrease in contribution of immediate colposcopies compared to the younger group of women. For example, in the first five years, we identified contributions of immediate colposcopies by 28%, triage test at 12 months by 30%, and triage test at 24 months by 42% of expected colposcopies of women aged 35-69 years.

## 3.2 Monetary outcomes

Our estimations of the monetary costs over time (i.e., direct and indirect costs associated with screening, follow-up procedures and treatment of precancerous lesion and cancer) followed similar trends as positivity-rate, colposcopy procedures, and CIN2/3 detection (**Table 2**). For example, we projected highest annual direct and total (direct and indirect costs) in the year 2023 of $92 million (CB: $84 million - $92 million) and $147 million (CB: $147 million - $139 million), respectively. Following completion of the implementation process by 2025, we projected ongoing direct costs associated primary HPV-based testing to range between $39 million and $67 million, while total direct and indirect costs could range from $60 million and $112 million (years 2026-2029). Over the 10-year period associated with the gradual implementation of women screened with primary HPV-based test, we projected cumulative direct costs of $537 million (CB: $484 million – $531 million) and cumulative total (direct and indirect) costs of $854 million (CB: $824 million – $931 million).

Table 2. Monetary costs of primary HPV based screening. Direct and indirect costs associated with screening, follow-up procedures and treatment of CIN2/3 and cancer, according to year

| Year | Direct costs ($) | | | Indirect costs ($) | | |
|---|---|---|---|---|---|---|
| | Base-Case | Lower Bound | Upper Bound | Base-Case | Lower Bound | Upper Bound |
| 2020 | 31 404 416 | 28 129 198 | 31 375 966 | 49 450 996 | 46 191 458 | 54 809 738 |
| 2021 | 52 936 610 | 47 960 639 | 52 907 484 | 83 451 343 | 78 431 488 | 91 332 975 |
| 2022 | 73 679 599 | 66 704 657 | 73 677 357 | 115 840 221 | 108 382 843 | 126 930 071 |
| 2023 | 91 765 702 | 84 102 094 | 91 765 702 | 146 848 514 | 139 163 734 | 159 246 084 |
| 2024 | 50 441 114 | 42 746 413 | 48 488 007 | 75 763 935 | 71 349 517 | 85 478 284 |
| 2025 | 38 744 135 | 34 674 673 | 38 544 286 | 61 759 510 | 60 249 234 | 68 526 751 |
| 2026 | 39 415 727 | 36 244 397 | 39 275 016 | 64 773 794 | 64 710 766 | 70 191 760 |
| 2027 | 50 309 376 | 46 867 397 | 50 271 442 | 83 298 267 | 83 049 211 | 89 280 978 |
| 2028 | 67 584 680 | 63 345 113 | 67 576 558 | 112 118 754 | 111 024 730 | 119 415 918 |
| 2029 | 40 414 605 | 33 660 884 | 36 856 187 | 60 345 003 | 61 082 625 | 66 119 836 |
| Total | 536 695 964 | 484 435 465 | 530 738 005 | 853 650 337 | 823 635 606 | 931 332 395 |

All costs were valued in 2019-Norwegian Kroner and converted to 2019-US Dollars (US $1 = NOK 8.8001). Direct medical costs include physician office visits, laboratory cost, and cost of treatment of precancerous (CIN2/3) lesions and cancer. Indirect costs include patient time and transportation costs associated screening,follow-up procedures and treatment precancerous (CIN2/3) lesions and cancer.
Acronymns: HPV: human papillomavirus. CIN2/3: cervical intraepithelial neoplasia grade 2 or grade 3.

## 3.3 Scenario analysis

In our scenario analysis, when we hypothetically assumed an immediate nation-wide transition to primary HPV based screening with 100% capacity in 2020, we found substantially higher peaks in the number of women in need of colposcopy and greater fluctuations in resource use over time. For example, we estimated expected total volume of colposcopies of 6 208 (CB: 5 587 – 6 867) in 2020, 7 807 (CB: 6 860 – 8 761) in 2021, and 8 223 (CB: 7 212 – 9 251) in 2022. Moreover, predictions revealed greater fluctuations in colposcopy resource use in each year as all women are screened within the same 5-yearly screening interval in comparison to a gradual change; however, similar as in the gradual implementation of primary HPV-based screening, these fluctuations are expected to decrease in magnitude in each screening round.

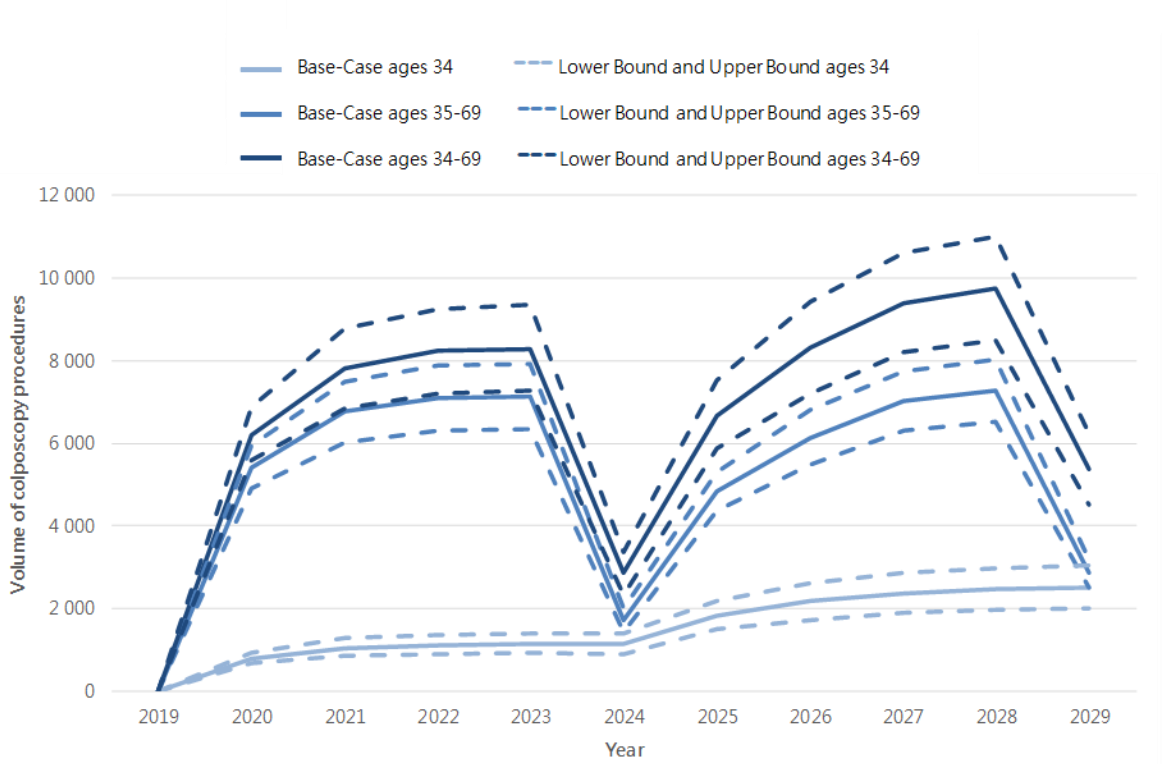



**Figure 4** Volume of age-specific colposcopy projections of primary HPV based screening test by year in a scenario analysis, 2019-2029. We combined three age-groups of women all invited for a primary HPV based screening test from 2020: 1) "Ages 34", which included new 34 years-old entering the screening program, 2) "Ages 35-69", which included women eligible for primary HPV-test over a 3-yearly switching period from the current cytology-screening; and 3) "Ages 34-69", which included the total age-groups of all women aged 34-69 years. Lower and upper bounds were estimated probabilistically and reflect minimum and maximum values. Acronyms: HPV: human papillomavirus

# 4 DISCUSSION

Our multi-cohort modelling analysis, were able to use primary data from the Cancer Registry of Norway to inform inform 10-years projections of the expected resource use and costs attributable to women screened with primary HPV-screening following the gradual implementation of primary HPV-based screening for women aged 34-69 years in Norway.

Our findings indicated that over a 10 year-period (2020-2029), as all of Norway will gradually switch from 3-yearly primary cytology-based screening interval to a 5-yearly primary HPV-based screening interval, fluctuations are expected in the number of screened women, positive tests and follow-up procedures in each year, yielding highest magnitude of volumes in 2023 and 2028. However, compared with a hypothetical immediate scale-up, fluctuations in resource use were more stable. Model-based projections may be helpful to prepare resource planning such as healthcare workforce faced with restricted capacity and resource constraints.

We expected a steady increase in number positive tests, colposcopy procedures and CIN2/3 detection among ongoing screened 34 year-olds, primary driven by continual switch to primary HPV-testing and the projected population growth. While for women aged 35-69 years, we expected a greater variability as well as fluctuations. During the gradual scale-up of screening HPV-capacity, volumes were expected to fluctuate as a consequence of mixed cohorts of women screened with 3-yearly cytology-based screening intervals became eligible for a primary HPV-based testing as well as continued 5-yearly primary HPV-based screening intervals. Over time, these fluctuations in resource use are expected to decrease consequently of complete gradual implementation to primary HPV-based screening (100% capacity) and first round of screening in Norway. Towards the end of our analytic period (2026-2029), we begin to reach a potential period of steady state. The first predictions of a steady-state period are still expected to fluctuate, primarily driven by the 5-yearly screening intervals, but of less variability in magnitude of volume than previous years due to the gradual implementation.

We additionally found that while age-specific expected numbers of colposcopy-rate in the first five years were highest in younger women compared to women ages 35-69 years,

similarly among both age-groups, delayed triage testing at 24 months contributed the most to expected number of colposcopy procedures by ranging between 40-42%. Given that we found a higher number of positive tests requiring follow-up procedures for the 34 year-olds, compared to the women aged 35-69 years, we expected these younger women would also face a higher colposcopy-rate in the first five years imposing challenges on colposcopy capacity constraints. However, these findings in the new 2018-algorithm, compared to the pilot implementation algorithm, suggests a greater proportion of transient infections are allowed to regress spontaneously, modifying the potentially immediate increased pressure at gynecologist- and pathology capacity at a small cost of precancer detection loss (Hashim et. al., 2020).

To our knowledge, this is the first analysis to investigate the short-term implications and to provide year-by-year estimates on expected resource use and costs of women screened with primary HPV-based test in the 2018-screening algorithm during the nation-wide scale-up. A recent published study that evaluated early findings of the major changes in the Australian National Cervical Cancer Screening Program (Machalek et. al., 2019) found considerably higher colposcopy referral-rates of primary HPV-based screening compared to primary cytology-based screening. However, these primary HPV-driven colposcopy-rates were expected to decrease in subsequent screening rounds, as consistent to our analysis.

## 4.1 Limitations

Our analysis has several limitations. First, in reflecting the 2018-screening algorithm, primary data for estimations of model input parameters were limited, particularly when we stratified outcomes by age or the availability of observations beyond two years. For example, we chose to use a 5-year age-grouping (i.e. ages 34-39 years) to inform parameters for the youngest group of women aged 34 years due to restricted primary data; therefore, our estimations of HPV-positivity-rate could potentially be lower compared to the 34 years-olds alone.

We informed selected parameters for 5-yearly screening-intervals of Round 1 and 2, derived from previously studies based on the 2015 pilot screening algorithm that involved a shorter time between screening tests (Hashim et. al., 2020, Ogilvie et. al., 2018). We applied these

estimations for our model input parameters, facing the risk that detection of precancer and cancer could be higher due to a longer interval; however, these potential increases could partly be balanced as potentially more HPV-positive women would also be allowed to spontaneously regress in a longer interval.

In sensitivity analysis, we tried to simulate the uncertainty restricted primary data estimations may have on HPV-positivity rate, colposcopy procedures and detected cases of CIN2/3. We found that estimations of detected CIN2/3 cases were most uncertain (widest CB) when compared to HPV positivity-rate and colposcopy procedures, which could primarily be due to the small number of women in the primary data contributing to inform CIN2/3 detection. In contrast, due to the greater number of women informing HPV-positivity rate in the primary data uncertainty surrounding number of positive tests were reduced (narrow CB). We assigned probabilistic distributions to selected parameters for screening Round 1 and used the same parameter inputs to inform uncertainty for subsequent screening rounds; however, we acknowledged that if we allowed for distribution on the RRs, we could more realistically capture uncertainties for Round 2. Furthermore, there is uncertainty in applying randomized trial data from settings other than Norway.

We also applied a more strict screening adherence assumptions than is observed in practice and assumed primary screening coverage would remain constant during the 10-years projections (Pedersen et. al.,2017). Consequently, these assumptions of screening behavior may influence estimated fluctuations in resource use and costs. By assuming a strict adherence to 3- (pre HPV implementation) or 5-year intervals (post HPV implementation), when in practice there is more variability in screening not reflected in our model, could potentially lead to a "smoothing" of fluctuations ("peaks") over time. In a Norwegian longitudinal cervical screening study using population-based registry-data, Pedersen and colleagues (Pedersen et. al., 2017) found that only 46% of eligible women were consistently screened at least once every 3.5 years with a majority of over-screeners. Further, since we did not allow for non-compliant women in any step of the screening process: primary, triage, colposcopy and treatment to re-enter into our model, we were not able to inform these potentially increases associated primary HPV-based screening, as we would might expect some women to return for delayed primary HPV-screening or follow-up procedures.

Finally, our expected resource use and economic impacts over a 10-year period are estimated among women aged 34-69 years with primary HPV-based test, and we do not consider overall resource use and economic impact of the proportion of women continuing to screening with cytology during the programmatic scale-up. Our analysis are based on anticipated starting year and scale-up of implementation of primary HPV-based screening by county, but as models never are to replace real-world observations, our model can be revised. Due to the restricted age-group included in our analysis, comparisons to data from the CRN were difficult. This would require more comprehensive data analysis and extended modelling structures, which was not feasible within the given time-frame.

In accordance with previous studies (Ronco et. al., 2014; Ogilvie et. al., 2018), a smaller number of detected precancerous lesions among women with cytology-based screening compared to HPV-based test during the first round of screening could also be expected for our analysis. Consequently, due to potentially later detections, more precancer and severe stages of cervical cancer diagnosis could be expected in subsequent rounds of screening; however, these are currently unknown in the specific context of Norway. Nevertheless, more research is needed in evaluating the impact of switching from cytology-based screening program to primary HPV-based screening program on resource economic impact. One future prospect to consider is the explicit caption of a separate cytology strategy in order to compare potential expected increases associated these two strategies.

## 4.2 Policy implications

While our projections may indicate a potential period of steady-state in resource use towards the period 2026-2029, as vaccinated cohorts enter primary HPV-screening greater fluctuations are expected. As vaccinated cohorts will enter primary HPV-based screening (when aged 34 years), these could contribute to counteract the expected increases in colposcopies and precancer treatment associated with primary HPV-screening as a result of population growth. We did not explicitly account for variability in resource use for a mixed population of unvaccinated and vaccinated screening population facing different risk-management, as this first vaccinated cohort in pre-adolescence will initiate primary HPV-screening in 2031. Moreover, a recently study evaluating several screening candidates among vaccinated women

against HPV-infections estimated that a less intensive cervical cancer (HPV-based) screening strategy, compared to those currently proposed for unvaccinated women, were required among women vaccinated in pre-adolescence in order for screening to remain cost-effective (Pedersen et. al., 2018). In turn, our projections may call for enhanced attention of cervical self-sampling, which early findings suggests could be a cost-effective intervention to improve participation (Burger et.al., 2017). Moreover, there may also be potential for targeted self-sampling to help alleviate strains to healthcare service over time, by reducing resource future burden on gynecologist-services.

Despite the many advantages of primary HPV-based screening such as high sensitivity, there is concern regarding the lower specificity of the HPV-test compared to cytology-based screening, which could potentially lead to unnecessary colposcopy referrals (Arbyn et. al., 2012). Evaluations from our analysis of expected colposcopy procedures per 1 000 women in Round 1, demonstrated that the highest contributions would be of those "watchful waiters" (i.e. referrals after triage testing at 24 months), supporting the use of primary HPV-based testing under the new 2018-algorithm. Furthermore, continued monitoring of screening performance are important to reach the full potential of implementing primary HPV-based screening.

# 5 CONCLUSION

During the gradual implementation of primary HPV-based screening among women aged 34-69 years in Norway. We project two "peaks" in 2023 and 2028 in magnitude of total number of positive tests, colposcopy procedures, and detection of CIN2/3 cases among women screened with primary HPV-testing. National fluctuations in volumes of tests and procedures within HPV-based screening program are expected during the first round of screening, requiring resource planning and effort in preparing healthcare workforce. At subsequent screening rounds, we expect these fluctuations to be of less variability. In preparing resource planning and healthcare workforce during a gradual HPV-capacity scale-up, model-based projections may help to inform implications for resource use and economic impact of the new triage algorithm in gradual implementation pilot of primary HPV screening.

# 6 REFERENCES


Arbyn M., Ronco G., Anttila A., Meijer C.J.L.M., Poljak M., Ogilvie G., Koliopoulos G., Naucler P., Sankaranarayanan R., Peto J. (2012) Evidence Regarding Human Papillomavirus Testing in Secondary Prevention of Cervical Cancer. *Vaccine* **30 (**Supplement 5)*:* F88- F99.

Burger E.A., Orthendal J.D., Kristiansen I.S., Kim J.J., (2012) Cost-effectiveness of cervical cancer screening with primary human papillomavirus testing in Norway. *Br J Cancer* **106:** 1571–1578.

Burger E.A., Sy S., Nygård M., Kim J.J. (2017) The Cost-Effectiveness of Cervical Self-Sampling to Improve Routine Cervical Cancer Screening: The Importance of Respondent Screening History and Compliance. *Cancer Epidemiol Biomarkers Prev*, **26(1):** 95-103.

Cancer Registry of Norway (2018) *Evaluation of pilot implementation of primary HPV-screening in three laboratories.* Oslo. Available from: https://www.kreftregisteret.no/globalassets/livmorhals/erfaringsdokument-hus-sus-st.olavshospital-hpv-primarscreening-juni-2018v2.pdf (Accessed at: February 15, 2020).

Cancer Registry of Norway (2019) *HPV in primary screening.* Oslo. Available from: https://www.kreftregisteret.no/screening/livmorhalsprogrammet/Helsepersonell/screeningstrategi-og-nasjonale-retningslinjer/HPV-i-primarscreening/ (Accessed at: February 15, 2020).

Cancer Registry of Norway (2020) *National Cervical Cancer Screening Program: screening guidelines and strategies.* Oslo. Available from: https://www.kreftregisteret.no/screening/livmorhalsprogrammet/Helsepersonell/screeningstrategi-og-nasjonale-retningslinjer/HPV-i-primarscreening/ (Accessed at: February 12, 2020).

Cancer Registry of Norway (2020) *Annual Report of the Norwegian Cervical Cancer Screening Program, 2017-2018.* Oslo: Cancer Registry of Norway. Available from: https://www.kreftregisteret.no/globalassets/publikasjoner-og-rapporter/livmorhalskreft/arsrapport/livmorhals-2017-18.pdf (Accessed at: June 10, 2020).

Eddy D.M., Hollingworth W., Caro J.J., Tsevat J., McDonald K.M., Wong J.B. (2012). Model transparency and validation: A report of the ISPOR-SMDM modelling good research practices task-force-7. *Med Decis Mak.* **15(6):** 843-850.

Federal Reserve (2011) *Average rates of exchange*. Available from: https://www.federalreserve.gov/releases/g5a/current/ (Accessed at: February 18, 2020)

Grolemund G. & Wickham H. (2017) *R for Data Science.* USA: O`Reilly. Available from: https://r4ds.had.co.nz/ (Accessed at: March 23, 2020).

Hashim D., Engesæter B., Skare G.B., Castle P.E., Bjørge T., Tropé A., Nygård M. Real-world data on cervical cancer risk stratification by cytology and HPV genotype to inform the management of HPV-positive women in routine cervical screening. *British Journal of Cancer* **122:** 1715–1723.

Lønnberg S., Hansen B.T., Haldorsen T., Campbell S., Schee K., Nygård M. (2015) Cervical cancer prevented by screening: Long-term incidence trends by morphology in Norway. *Int J Cancer* **137**: 1758-1764.

Machalek D.A., Robert J.M., Garland S.M., Thurloe J., Richards A., Chambers I., Sivertsen T., Farnsworth A. (2019) Routine cervical screening by primary HPV testing: early findings in the renewed National Cervical Screening Program. *Med J Aust* **211 (3):** 113-119.

Norwegian Directorate of Health (2012) *Økonomisk evaluering av helsetiltak – en veileder.* IS-1985. Oslo: Norwegian Directorate of Health. Available from: https://www.helsedirektoratet.no/veiledere/okonomisk-evaluering-av-helsetiltak/Økonomisk%20evaluering%20av%20helsetiltak%20–%20Veileder.pdf/_/attachment/inline/a4c0d8f4-6420-47a5-a052-344a5f2d0e76:637c45a5f29eda29afb9625968759e6fa4c4af61/Økonomisk%20evaluering%20av%20helsetiltak%20–%20Veileder.pdf (Accessed at May 25, 2020).

Norwegian Directorate of Health (2020) *Innsatsstyrt finansiering (ISF) – regelverk.* Available from: https://www.helsedirektoratet.no/tema/finansiering/innsatsstyrt-finansiering-og-drg-systemet/innsatsstyrt-finansiering-isfNormaltariffen (Accessed at February 28, 2020).

Norwegian Medical Association (2019) *Normaltariffen 2019-2020 for fastleger.* Available from: https://normaltariffen.legeforeningen.no/book/Fastlegetariffen-2019-XML-c/m-02 (Accessed at February 25, 2020).

Norwegian Medical Association (2019) *Normaltariffen 2019-2020 for avtalespesialister.* Available from: *https://normaltariffen.legeforeningen.no/book/Spesialisttariffen-2019-XML-a (*Accessed at February 26, 2020).

Ogilvie G., Niekerk D.V., Krajden M., Smith L.W., Cook D., Ceballos K., Quinlan D., Lee M., Martin R.E., Gentile L., Peacock S., Stuart G.C.E., Franco E.L., Coldman A.J. (2018). Effect of Screening With Primary Cervical HPV Testing vs Cytology Testing on High-grade Cervical Intraepithelial Neoplasia at 48 Months: The HPV FOCAL Randomized Clinical Trial. *JAMA* **320(1)**: 35-37.

Paradis E. (2005). *R for Beginners.* The Comprehensive R Archive Network (CRAN). Available from: https://cran.r-project.org/doc/contrib/Paradis-rdebuts_en.pdf (Accessed at: March 16, 2020).

Pedersen K., Lønnberg S., Skare G.B., Sørbye S.W., Burger E.A., Kristiansen I.S. (2015). Kostnader ved masseundersøkelsen mot livmorhalskreft. *Sykepleien Forskning* **10:**62-71.

Pedersen K., Burger E.A., Campbell S., 3, Nygård M., Aas E., Lønnberg S. (2017). Advancing the evaluation of cervical cancer screening: development and application of a longitudinal adherence metric. *The European Journal of Public Health* **27(6)**: 1089–1094.

Pedersen K., Burger E.A., Nygård M., Kristiansen I.S., Kim J.J. (2018). Adapting cervical cancer screening for women vaccinated against human papillomavirus infections: The value of stratifying guidelines. *European Journal of Cancer* **91:** 68-75

Ronco G., Dillner J., Elfström M.K, Tunesi S., Snijders P.J.F., Arbyn M., Kitchener H., Segnan N., Gilham C., Giorgi-Rossi P., Berkhof J., Peto J., Meijer C.J.L.M., and the International HPV screening working group (2014). Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet* **383:** 524–532.

Schiffman M., Castle P.E., Jeronimo J., Rodriguez A.C., Wacholder S. (2007) Human Papillomavirus and Cervical Cancer. *Lancet* **370(9590):** 890-907

Statistics Norway (2020) *Average monthly income for women and men 2019.* Available from: https://www.ssb.no/arbeid-og-lonn/statistikker/lonnansatt (Accessed at: March 2, 2020).

Statistics Norway (2020) *Population, by sex and one-year age groups 1986 – 2020*. Available from: https://www.ssb.no/statbank/table/07459/ (Accessed at: May 20, 2020).

Ward Z.J. (2019) Amua: An open source modeling framework. Available from: https://github.com/zward/Amua (Accessed at: April 22, 2020).

# 7 APPENDIX

## 7.1 Section 1: Decision-analytic modelling Theory

In conceptualizing the decision problem as a first step in decision analysis, there exits multiple model types with different characteristics and properties, such as decision-tree models, state-transition models, and dynamic transmission and/or disease models (Drummond et. al., 2015). These models types differ involving trade-offs between simplicity and transparency, and in lack of current consensus on the generally preferred model, ultimately, the chosen model should reflect the decision problem at-hand.

Briefly, decision tree-models involves mutually exclusive and collectively exhaustive pathways following an intervention, meaning that the individual can only follow one pathway and once entered a pathway they cannot move to different pathways. Due to the many limitations of a decision tree model, a state-transition model may be preferred if the decision problem is characterized by recurring events and explicit timing of events would be of importance. One type of state-transition models are Markov models, which explicitly follow cohorts across health states over time. One major drawback with these models is the lack of time dependency; therefore, use of tunnel states or microsimulation models may be necessary. In addition dynamic transition models would be preferred if the conceptualization of the decision problem requires interactions between individuals to occur, as for reflecting communicable diseases, particularly if the intervention, *e.g*. vaccine, is expected to influence the burden of the communication disease/infection between individuals.

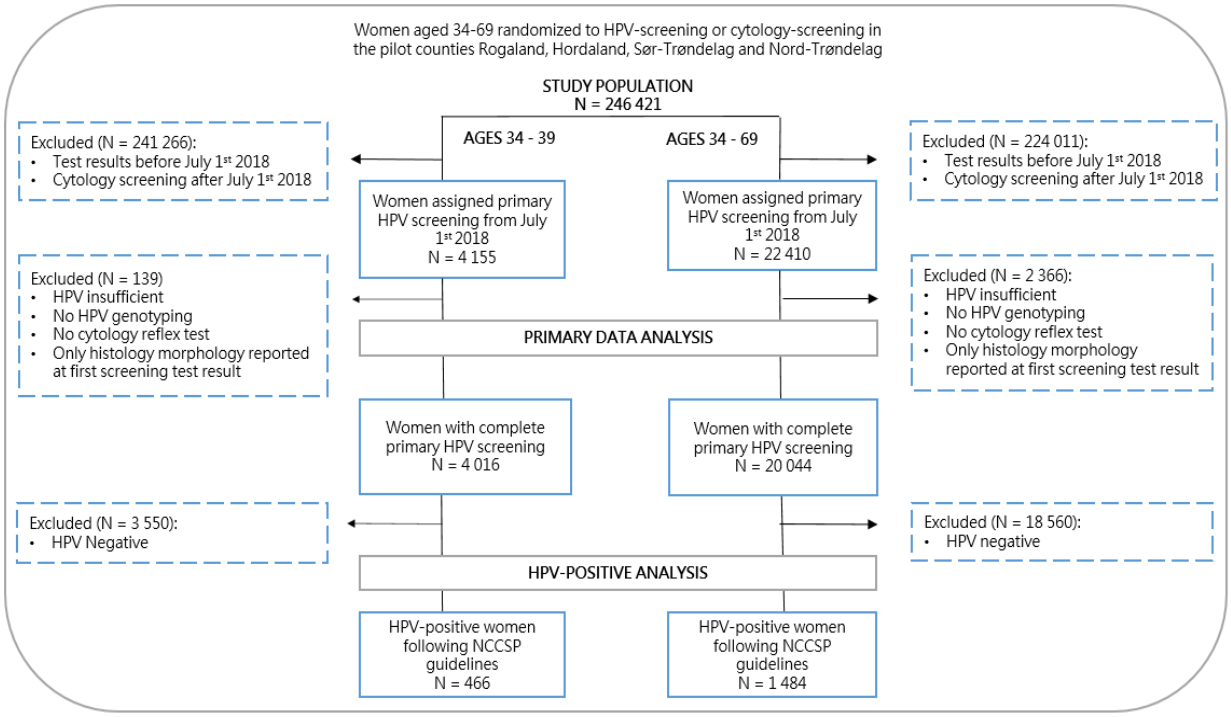
## 7.2 Section 2: Baseline Model Parameterization

**Appendix Table 1. Input parameters for screening Round 2. Values are reported as numbers (percentages) unless otherwise stated**

| | Baseline Screen | | Subsequent Screen | | | |
|---|---|---|---|---|---|---|
| Variable | Cases (%) | Total | Cases (%) | Total | RR[2] | Source |
| **Primary Screening** | | | | | | |
| Probability of screening Round 2 ages 35-69[1] | | | | | 0.9 | Statistics Norway |
| Probability test positive ages 35-69 | 1484 (7.4) | 20 044 | 1030 (5.7) | 18 009 | 0.8 | Primary Analysis |
| Immediate referral for colposcopy | 297 (38.93) | 763 | 143 (35.75) | 400 | 0.9 | Ogilvie et al., 2018 |
| CIN2 or worse detection | 98 (33) | 297 | 15.16 (10.6) | 143 | 0.3 | Ogilvie et al., 2018 |
| **Triage Screening** | | | | | | |
| CIN2 or worse detection | 49 (21.78) | 225 | 29.15 (10.6) | 275 | 0.5 | Ogilvie et al., 2018 |

[1]Excluded thus proportion who age out of screening [2] Relative Risks (RR) are calculated as the probability of an event in subsequent screening round divided by the probability of an event in baseline screening round. Acronymns: CIN: cervical intraepithelial neoplasia. HPV: human papillomavirus.

**Appendix Figure 1.** Flow diagram of inclusion and exclusion criteria of participants screened with primary HPV or cytology in the pilot implementation program in four Norwegian counties in the Norwegian Cervical Cancer Screening Program, 2015 to 2019. We constructed two sub-samples: 1) the "Primary Data Analysis Ages 34-39", which included women aged 34-39 with a registered screening test result between 2018 and 2019, and 2) the "Primary Data Analysis Age 34-69"**,** which included women aged 34-69 with a registered screening test results between 2018 and 2019. The exclusion criteria's applied (see Appendix Figure 1) are assumed similar among the sub-samples (see next page for Figure 1).




**Appendix Table 2. Selected model outcomes per 1 000 women, aged 34-69 years.** We reported HPV positivity-rate as cases of high-riskHPV-positive tests of HPV16, HPV18, and otherHPV (not 16/18). All costs were expressed in 2019 USD ($1 = NOK 8.80). Direct costs were associated screening, follow-up procedures and precancer and cancer treatment. Total costs included direct and indirect costs (time and transportation costs). Acronymns: HPV: human papillomavirus. CIN2/3 detection: cervical intraepithelial neoplasia grade 2 or grade 3 (Table 3 continued on next page).

| Variable | HPV positivity-rate | | |
|---|---|---|---|
| Cycle | Base-Case | Lower Bound | Upper Bound |
| 0 | 73.898 | 70.231 | 77.390 |
| 1 | 7.499 | 5.969 | 8.882 |
| 2 | 1.434 | 1.354 | 1.514 |
| 3 | 0.000 | 0.000 | 0.000 |
| 4 | 0.000 | 0.000 | 0.000 |
| 5 | 67.583 | 64.487 | 70.513 |
| 6 | 7.308 | 5.955 | 8.544 |
| 7 | 10.251 | 9.682 | 10.819 |
| 8 | 0.939 | 0.738 | 1.118 |
| 9 | 0.179 | 0.166 | 0.193 |

| Variable | Colposcopy procedures | | |
|---|---|---|---|
| Cycle | Base-Case | Lower Bound | Upper Bound |
| 0 | 19.9793 | 18.1435 | 21.9289 |
| 1 | 4.9532 | 4.0571 | 5.722 |
| 2 | 1.2866 | 1.113 | 1.4793 |
| 3 | 0.122 | 0.0947 | 0.1526 |
| 4 | 0 | 0 | 0 |
| 5 | 16.4448 | 14.9644 | 17.9965 |
| 6 | 6.0813 | 5.1521 | 6.9493 |
| 7 | 3.3949 | 3.1747 | 3.6261 |
| 8 | 0.9113 | 0.7666 | 1.0517 |
| 9 | 0.1607 | 0.1378 | 0.1863 |

| Variable | Detected cases of CIN2/3 | | |
|---|---|---|---|
| Cycle | Base-Case | Lower Bound | Upper Bound |
| 0 | 10.344 | 8.970 | 11.838 |
| 1 | 0.865 | 0.597 | 1.180 |
| 2 | 0.168 | 0.086 | 0.294 |
| 3 | 0.026 | 0.008 | 0.052 |
| 4 | 0.000 | 0.000 | 0.000 |
| 5 | 2.554 | 2.219 | 2.914 |
| 6 | 1.113 | 0.708 | 1.675 |
| 7 | 0.498 | 0.403 | 0.629 |
| 8 | 0.170 | 0.101 | 0.268 |
| 9 | 0.021 | 0.011 | 0.037 |

| Variable | Direct costs ($) | | |
|---|---|---|---|
| Cycle | Base-Case | Lower Bound | Upper Bound |
| 0 | 317 797 | 289 014 | 350 663 |
| 1 | 13 605 | 9 875 | 18 449 |
| 2 | 7 101 | 3 857 | 11 497 |
| 3 | 371 | 133 | 687 |
| 4 | 0 | 0 | 0 |
| 5 | 201 730 | 194 630 | 209 815 |
| 6 | 17 530 | 11 761 | 24 857 |
| 7 | 10 780 | 9 023 | 12 771 |
| 8 | 2 591 | 1 612 | 3 851 |
| 9 | 502 | 357 | 710 |

| Variable | Total costs ($) | | |
|---|---|---|---|
| Cycle | Base-Case | Lower Bound | Upper Bound |
| 0 | 495 554 | 454 025 | 538 741 |
| 1 | 17 760 | 12 617 | 24 658 |
| 2 | 9 594 | 5 517 | 15 722 |
| 3 | 469 | 180 | 902 |
| 4 | 0 | 0 | 0 |
| 5 | 339 670 | 329 516 | 350 513 |
| 6 | 22 936 | 15 736 | 32 678 |
| 7 | 15 280 | 13 088 | 18 258 |
| 8 | 3 346 | 2 135 | 5 074 |
| 9 | 712 | 533 | 1 006 |

**Appendix Table 3. Estimated starting date and planned gradual implementation following the CRN and expected capacity scale-up in each county in Norway**

| County 2020 | County divsion before 2020 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 | 2024 | 2025 | 2026 | 2027 | 2028 | 2029 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Trøndelag | Trøndelag | 0.5 | 0.5 | 0.5 | 0.75 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Rogaland | Rogaland | 0.5 | 0.5 | 0.5 | 0.75 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Vestlandet | Hordaland | 0.5 | 0.5 | 0.5 | 0.75 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Sogn og Fjordane | 0 | 0 | 0 | 0 | 0.5 | 0.75 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Møre og Romsdal | Møre og Romsdal | 0 | 0 | 0 | 0 | 0.5 | 0.67 | 0.83 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Nordland | Nordland | 0 | 0 | 0 | 0 | 0.5 | 0.67 | 0.83 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Troms og Finnmark | Troms | 0 | 0 | 0 | 0 | 0.5 | 0.67 | 0.83 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Finnmark | 0 | 0 | 0 | 0 | 0.5 | 0.67 | 0.83 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Viken | Østfold[1] | 0 | 0 | 0 | 0 | 0.5 | 0.75 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Akershus[1] | 0 | 0 | 0 | 0 | 0 | 0 | 0.5 | 0.75 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Buskerud[1] | 0 | 0 | 0 | 0 | 0 | 0 | 0.25 | 0.625 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Oslo | Oslo[1] | 0 | 0 | 0 | 0 | 0 | 0 | 0.5 | 0.75 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Innlandet | Hedmark[1] | 0 | 0 | 0 | 0 | 0 | 0 | 0.5 | 0.75 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Oppland[1] | 0 | 0 | 0 | 0 | 0 | 0 | 0.5 | 0.75 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Vestfold og Telemark | Vestfold[1] | 0 | 0 | 0 | 0 | 0 | 0.5 | 0.75 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Telemark[1] | 0 | 0 | 0 | 0 | 0 | 0.5 | 0.75 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Agder | Aust-Agder[1] | 0 | 0 | 0 | 0 | 0 | 0 | 0.5 | 0.75 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Vest-Agder[1] | 0 | 0 | 0 | 0 | 0 | 0 | 0.5 | 0.75 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

[1]Estimated starting year

## 7.3 Section 3: Cost assumptions

**Appendix Table 4. Selected economic model inputs**

| Cost | Value ($) |
|---|---|
| **Screening** | |
| Cost of general practitioner visit[1] | 68 |
| Analysis of liquid-based cytology | 9 |
| Analysis of HPV DNA testing | 35 |
| **Colposcopy procedure** | |
| Cost of colposcopy procedure[2] | 286 |
| Analysis of colposcopy with biopsy | 7 |
| **Treatment** | |
| CIN2/3[2] | 334 |
| Cancer[3] | 35 563 |
| **Time and transportation** | |
| Screening, colposcopy/biopsy, and CIN2/3-treatment | 70 |
| Cancer treatment | 9 821 |

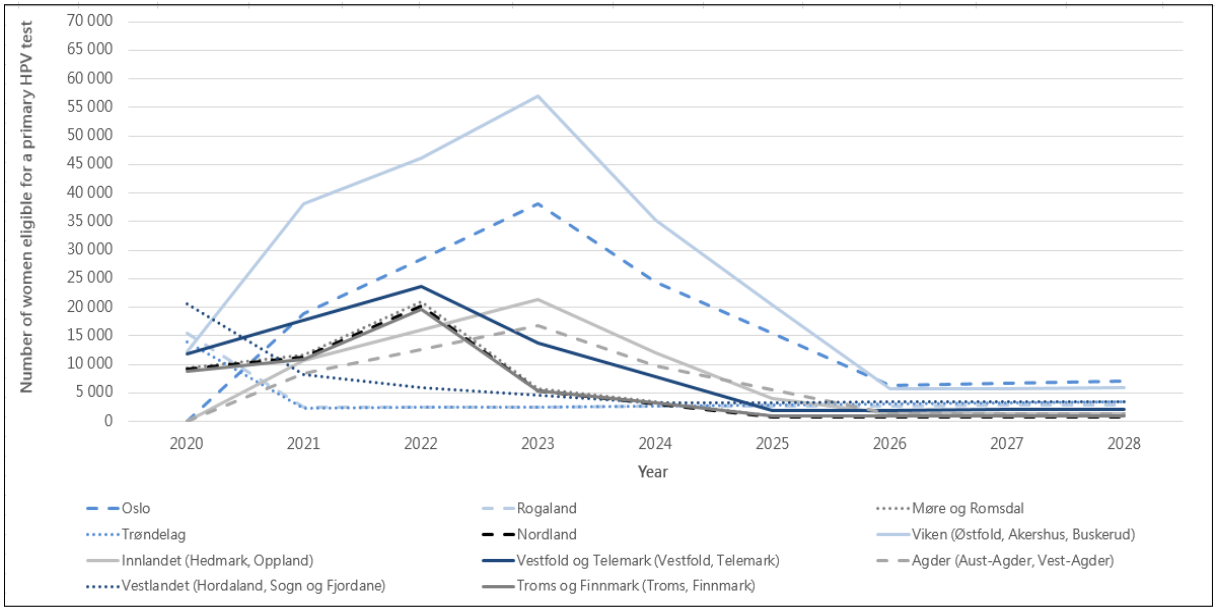
2019-Norwegian Kroner ($1 = 8.8001 NOK).

[1]We assumed a weighted average of visits of 80% at general practioner; 20% at gynecologist. [2]We assumed a weigthed average of colposcopy with biopsy and treatment of precancerours (CIN2/3) lesion of 70% are performed at the hospital; 30% are performed by gynecologist.

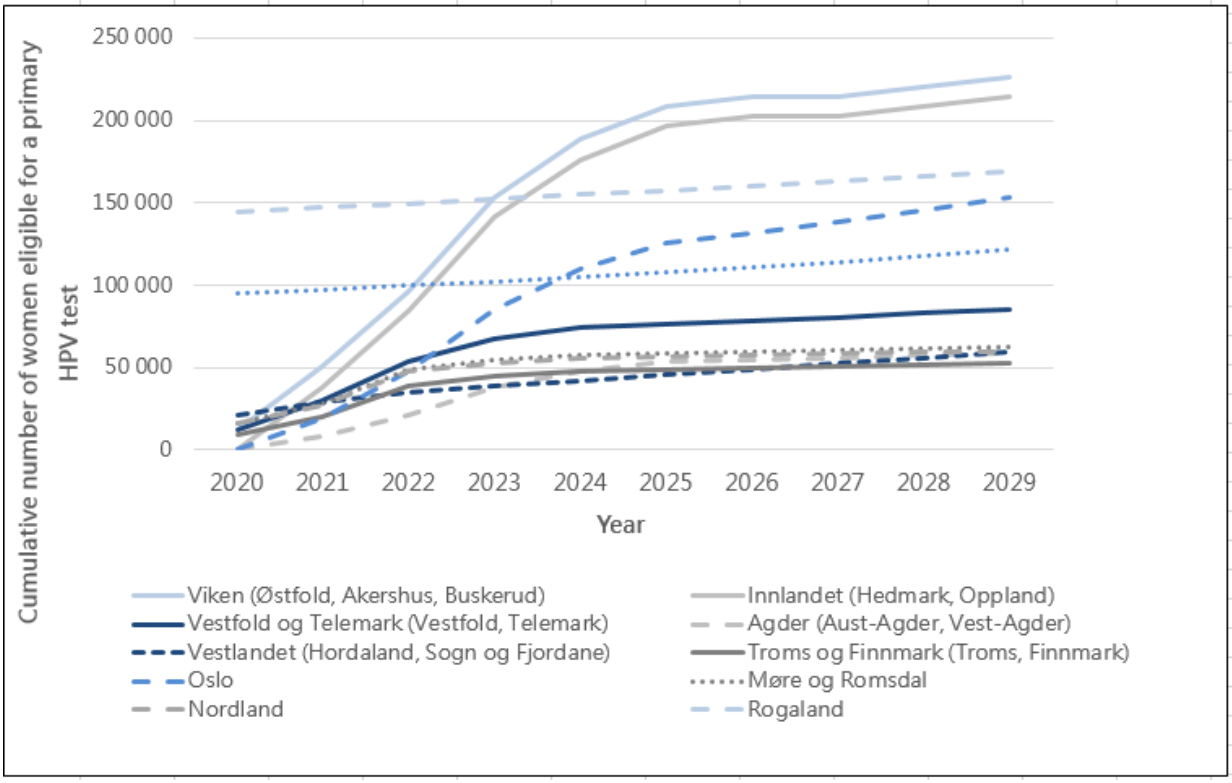
Acronymns: HPV: human papillomavirus. CIN2/3cervical intraepithelial neoplasia grade 2 or grade 3.

## 7.4 Section 4: Additional results

**Appendix Figure 2.** County-specific gradual implementation of primary screening HPV based testing among women aged 34-69 years in Norway by year, 2020-2029. Values are reported in absolute numbers and scaled to the Norwegian county-level population. We combined two age-groups: 1) "Ages 34", which included new 34 years-old entering the screening program invited for a primary screening HPV based test; and 2) "Ages 35-69", which included women invited for a primary screening HPV based test in the associated year they are eligible to switch from cytology-screening as capacity are scaled-up. Acronymns: HPV: human papillomavirus



**Appendix Figure 3.** Cumulative number of county-specific gradual implementation of primary screening HPV based testing among women aged 34-69 years in Norway by year, 2020-2029. Values are reported in absolute numbers and scaled to the Norwegian county-level population. We combined two age-groups: 1) "Age 34", which included new 34 years-old entering the screening program invited for a primary screening HPV based test; and 2) "Ages 35-69", which included women invited for a primary screening HPV based test in the associated year they are eligible to switch from cytology-screening as capacity are scaled-up. Acronymns: HPV: human papillomavirus



## 7.5 Section 5: References


Cancer Registry of Norway (2018) *Evaluation of pilot implementation of primary HPV-screening in three laboratories.* Oslo. Available from: https://www.kreftregisteret.no/globalassets/livmorhals/erfaringsdokument-hus-sus-st.olavshospital-hpv-primarscreening-juni-2018v2.pdf (Accessed at: February 15, 2020).

Cancer Registry of Norway (2019) *HPV in primary screening.* Oslo. Available from: https://www.kreftregisteret.no/screening/livmorhalsprogrammet/Helsepersonell/screeningstrategi-og-nasjonale-retningslinjer/HPV-i-primarscreening/ (Accessed at: February 15, 2020).

Cancer Registry of Norway (2020) *National Cervical Cancer Screening Program: screening guidelines and strategies.* Oslo. Available from: https://www.kreftregisteret.no/screening/livmorhalsprogrammet/Helsepersonell/screeningstrategi-og-nasjonale-retningslinjer/HPV-i-primarscreening/ (Accessed at: February 12, 2020).

Drummond M.F., Claxton K., Stoddart G.L., Torrance G.W. (2015). *Methods for the economic evaluation of health care programmes*. 4th edition. Oxford University Press.

Federal Reserve (2011) *Average rates of exchange*. Available from: https://www.federalreserve.gov/releases/g5a/current/ (Accessed at: February 18, 2020)

Grolemund G. & Wickham H. (2017) *R for Data Science.* USA: O`Reilly. Available from: https://r4ds.had.co.nz/ (Accessed at: March 23, 2020).

Norwegian Directorate of Health (2012) *Økonomisk evaluering av helsetiltak – en veileder*. IS-1985. Oslo: Norwegian Directorate of Health. Available from: https://www.helsedirektoratet.no/veiledere/okonomisk-evaluering-av-helsetiltak/Økonomisk%20evaluering%20av%20helsetiltak%20–%20Veileder.pdf/_/attachment/inline/a4c0d8f4-6420-47a5-a052-344a5f2d0e76:637c45a5f29eda29afb9625968759e6fa4c4af61/Økonomisk%20evaluering%20av%20helsetiltak%20–%20Veileder.pdf (Accessed at May 25, 2020).

Norwegian Directorate of Health (2020) *Innsatsstyrt finansiering (ISF) – regelverk.* Available from: https://www.helsedirektoratet.no/tema/finansiering/innsatsstyrt-finansiering-og-drg-systemet/innsatsstyrt-finansiering-isfNormaltariffen (Accessed at February 28, 2020).

Norwegian Medical Association (2019) *Normaltariffen 2019-2020 for fastleger.* Available from: https://normaltariffen.legeforeningen.no/book/Fastlegetariffen-2019-XML-c/m-02 (Accessed at February 25, 2020).

Norwegian Medical Association (2019) *Normaltariffen 2019-2020 for avtalespesialister.* Available from: *https://normaltariffen.legeforeningen.no/book/Spesialisttariffen-2019-XML-a (*Accessed at February 26, 2020).

Ogilvie G., Niekerk D.V., Krajden M., Smith L.W., Cook D., Ceballos K., Quinlan D., Lee M., Martin R.E., Gentile L., Peacock S., Stuart G.C.E., Franco E.L., Coldman A.J. (2018). Effect of Screening With Primary Cervical HPV Testing vs Cytology Testing on High-grade Cervical Intraepithelial Neoplasia at 48 Months: The HPV FOCAL Randomized Clinical Trial. *JAMA* **320(1)**: 35-37.

Paradis E. (2005). *R for Beginners.* The Comprehensive R Archive Network (CRAN). Available from: https://cran.r-project.org/doc/contrib/Paradis-rdebuts_en.pdf (Accessed at: March 16, 2020).

Pedersen K., Lønnberg S., Skare G.B., Sørbye S.W., Burger E.A., Kristiansen I.S. (2015). Kostnader ved masseundersøkelsen mot livmorhalskreft. *Sykepleien Forskning* **10:**62-71.

Statistics Norway (2020) *Average monthly income for women and men 2019.* Available from: https://www.ssb.no/arbeid-og-lonn/statistikker/lonnansatt (Accessed at: March 2, 2020).

Statistics Norway (2020) *Population, by sex and one-year age groups 1986 – 2020*. Available from: https://www.ssb.no/statbank/table/07459/ (Accessed at: May 20, 2020).

Ward Z.J. (2019) Amua: An open source modeling framework. Available from: https://github.com/zward/Amua (Accessed at: April 22, 2020).