EVALUATING STRUCTURAL ASSUMPTIONS IN MODELLING OF CERVICAL CANCER PREVENTION STRATEGIES IN NORWAY

-Extending the natural history model to account for multiple cancer histologies

MASTER THESIS

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ABSTRACT

Background: Model-based studies within the field of cervical cancer prevention usually simplify the structural assumptions of the natural history models to either only account for the most frequent cancer histology, squamous cell carcinoma, or pool it with other histological types without differentiating the natural history. Along with an observed increase of adenocarcinoma the past years, there are reports of cytology-based testing in cervical cancer screening being less effective at preventing this second most frequent cervical cancer form.

Objective: Our objective is to evaluate the impact of extending model-based studies to account for both cervical cancer histologies and how this influences policymaking on cervical cancer screening guidelines in Norway.

Methods: leveraging epidemiological data from Norway and findings in the literature, we were able to develop two natural history models of HPV-induced cervical cancer; Structure 1 that accounts for squamous cell carcinoma and Structure 2 that is extended to also account for adenocarcinoma. Thereafter we conducted a cost-effectiveness analysis of primary cytology-based screening versus primary HPV-based screening under both model structures to quantify the impact of different structural assumptions on the incremental cost-effectiveness ratio (ICER).

Results: Results from the base-case analysis revealed that extending the natural history model for HPV-induced cervical cancer to include adenocarcinoma in addition to squamous cell carcinoma has an impact on the ICER in favor of HPV-based screening compared to cytology-based screening. Under all scenarios, including the sensitivity analysis, HPV-based testing dominated cytology-based testing, but the magnitude of dominance was increased under Structure 2.

Conclusions: Given reports of increasing incidences of adenocarcinoma and its precursor adenocarcinoma *in situ* in the Norwegian female population, this is an issue that requires more attention and research. Future model-based studies evaluating CC prevention policies should incorporate ADC-related health states.

ACKNOWLEDGEMENT

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Victoria Fife

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ABBREVIATIONS

ADC Adenocarcinoma

AIS Adenocarcinoma in situ

AGUS Atypical glandular cells of undetermined significance

ASC-H Atypical squamous cells, cannot exclude high-grade lesion

ASC-US Atypical cells of undetermined significance

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)

CEA Cost-effectiveness analysis

DSA Deterministic sensitivity analysis

HPV Human papillomavirus

hrHPV High risk human papilloma virus

HSIL High-grade squamous intraepithelial neoplasia

ICER Incremental cost-effectiveness ratio

lrHPV Low risk human papilloma virus

LSIL Low grade squamous intraepithelial lesion

LYs Life years

NCCSP The Norwegian cervical cancer screening program

NOK Norwegian Kroner

PSA Probabilistic sensitivity analysis

QALY Quality adjusted life-years

1 INTRODUCTION

It is essential that priority-setting and resource allocation in Norway meet the simultaneous criteria of being efficient, feasible, and optimal; therefore, the use of economic evaluation has been, and will continue to be, a valuable instrument for decision-making within healthcare. Norway has the advantage of having worked systematically with priority setting within health care since the eighties and will continue to strengthen and expand the use of health technology assessment. The Norwegian secretary of state, Anne Grethe Erlandsen, made a clear point of this in her key note speech held the 21st Commonwealth Fund International Symposium in Washington in November 2018;

"As part of the decision-making processes for introducing new health technologies, all new pharmaceuticals and many other new technologies undergo health technology assessments. Now we are planning to expand the system to also include primary care. In the years to come, a bigger share of total services will be delivered locally. Our municipalities, with their large degree of autonomy, already prioritize every day, based on local needs and priorities. This is the way it has to be."[1(p7)]

The global burden of cervical cancer (CC) is high, representing 6.6% of all female cancers and being the fourth most frequent cancer in women[2]. Due to extensive screening programs in middle- and high-income countries, the burden mostly falls on low-income countries[2]. However, in Norway, 316 women were diagnosed with cervical cancer in 2017[3]. It is therefore crucial to preserve and continuously improve a comprehensive prevention approach that includes early diagnosis, vaccination, effective screening and treatment programs.

Within policy making on cervical cancer prevention in Norway, decision-analytic models are becoming more relevant in the assessment of screening strategies when it comes to identifying optimal algorithms and choice of technology. However, as models are simplifications of reality it is crucial to address and characterize the structural assumptions and simplifications of the models. While there are two main histological CC types, squamous cell carcinoma (SCC) and adenocarcinoma (ADC) the majority of model-based policy studies only account for SCC (the most frequent histology) or pool the two histologies into a single model structure. However, there is evidence to support that the natural history of these two cancer subtypes are different from each other. More importantly, studies have shown that cytology-based screening programs have had different impacts on the cervical cancer histologies, suggesting that the screening offers poorer protection against adenocarcinoma (cite). The aim of this thesis is to evaluate the

structural assumptions of natural history models for cervical cancer that do not incorporate ADC, and explore the possible implications of including these health states for cervical cancer prevention policies.

2 BACKGROUND

2.1 CERVICAL CANCER AND HUMAN PAPILLOMAVIRUS EPIDEMIOLOGY

Cervical cancer (CC) is one of the most common cancers among Norwegian females aged between 15 and 49 years.[3] In 2016, 370 new cases of CC were detected and 95 Norwegian women lost their lives.[3] Nevertheless, CC is regarded as one of the most preventable cancers[4], demonstrated with a clear decline in CC incidence and improved follow-up of cases after the implementation of screening programs in many countries. For example, a study reported that CC incidence has been reduced with 40% since the introduction of screening in the 1950s.[5] Furthermore, The identification of human papillomavirus (HPV) as a causal factor of CC has led to the development of novel technologies in the form of highly efficacious HPV-vaccines[6]. This has drastically improved the outlook of eliminating CC as a public health concern[4].

HPV-viruses are a common and highly transmittable group of DNA viruses that are known to infect the skin and mucosa of animals and humans. There are more than 200 genotypes; most are harmless, but some are considered high-risk viruses with the potential of causing cancer. HPV genotypes 16 and 18 are identified as the most carcinogenic types, cumulatively accounting for 85% of the CC incidences worldwide[7].

Transmission of HPV is most common through sexual intercourse, resulting in infection rates among the population typically starting from the age of 15 onwards. Infections are asymptomatic and are therefore rarely detected, most of the time clearing naturally after 1-2 years. Cofactors determining the persistence and progression of cervically acquired HPV infections are viral factors (such as HPV genotype), the host's immune response and behavioral factors impacting the general health state of the woman (smoking, use of contraceptives etc). These cofactors will together impact the persistence of infection and if it is sufficiently long for precancer to develop. The time from infection to cancer is usually long, therefore allowing screening programs to be effective in detecting precancerous lesions before it becomes invasive cancer.

The most common histologic type of CC is squamous cell carcinoma (SCC) which develops in the epithelial cell layer of the cervix, and accounts for approximately 80% of all CC types.[8] The

second most frequent CC-type is adenocarcinoma (ADC), which originates in the gland cells that produce mucus in the cervix. The remaining CC types are largely a combination of these two cells and are rare. The squamous cells line the uterus while the glandular cells are located slightly deeper (Figure 1).

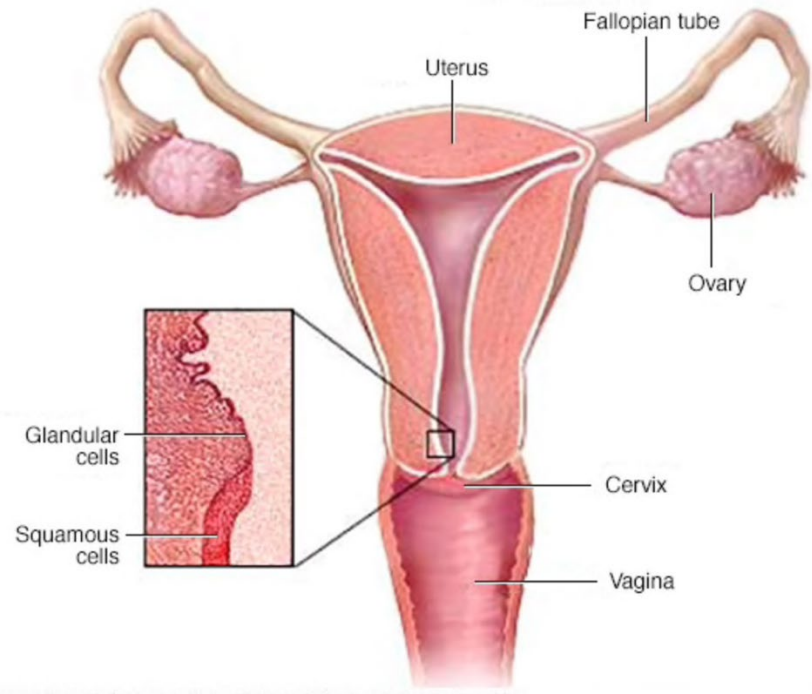

Figure 1. The uterus is divided into body *(upper two-thirds) and* cervix*. The walls of the uterus are composed of a mucosal layer, the* endometrium*, and a fibromuscular layer, the* myometrium*. The squamous cells line the inner wall of the uterus, while glandular cells are found slightly deeper within the endometrium. Illustration retrieved from Mayo Clinic*[9]

2.2 CERVICAL CANCER PREVENTION

2.2.1 VACCINATION

Primary prevention of CC involves vaccination of the population against high risk HPV-viruses (hrHPV) to avoid the infections that cause lesions and cancer. Norway is one of the many countries that introduced HPV-vaccination of adolescent girls as part of the child vaccination program (initiated in 2009). Additionally, an HPV-vaccine catch-up program was initiated in 2016 for women born in 1991 or later. From autumn 2018 boys are also offered the HPV-vaccine as part of the childhood vaccination program.

2.2.2 SCREENING: CURRENT- & NEW PROGRAM UNDER IMPLEMENTATION IN NORWAY

Screening as a secondary prevention strategy will remain an important preventive measure for the coming decades, as a large proportion of the female population did not receive the HPV vaccine in adolescence and will remain at higher risk of developing CC.

The Norwegian Cervical Cancer Screening Program (NCCSP) invites women aged 25 to 69 years to attend screening. The program is managed by the Cancer Registry of Norway, which collects and monitors data on screening and cancer data, such as cytology, HPV test and histology results, as well as CC diagnoses. One of the concerns with the program is that the screening coverage is not high enough due to lack of compliance to the guidelines. A study conducted by Pedersen, Burger & colleagues using population- based data from the Cancer Registry of Norway reported that less than half of women eligible for screening attended screening at the recommended repeated intervals[10]. The recommended changes to the program involve replacing cytology as the primary screening method with HPV DNA testing in combination with cytology. Comprehensive scientific studies show that HPV-based screening could lead to better target achievement – i.e. reducing mortality and CC with a cost-effective resource utilization both in terms of increased safety, improved quality and economic efficiency[11].

The updated screening guidelines present different screening strategies depending on the age of the women and is under Nationwide implementation. The strategy applies primary cytology-based screening for women ages 25-33 in three-year intervals (figure 2), while women ages 34-69 receive HPV-based testing every five years (figure 3). Since 2015, four counties in Norway have implemented and tested the new screening strategy and it is expected to be fully implemented on a national level from 2021[12] .

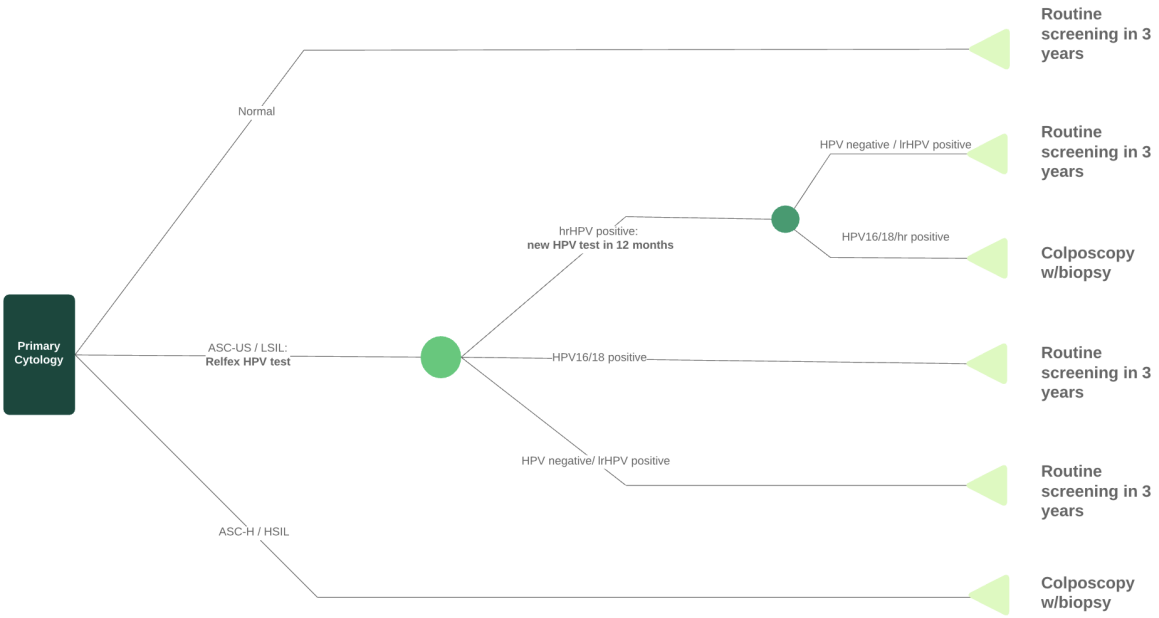

Figure 2. Flowchart of the cytology-based screening strategy, simplified and adapted from the Cancer Registry's webpage. ASC-US atypical squamous cells of undetermined significance, ASC-H atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion; LSIL Low-grade squamous intraepithelial lesion, HSIL high-grade squamous intraepithelial lesions, hrHPV high-risk human papillomavirus, lrHPV low risk human papillomavirus, HPV16/18 human papillomavirus genotype 16/18

The procedure requires that the cells of the cervix lining are examined for any abnormalities, which could indicate risk of developing cancer if it is not already present. Findings of atypical squamous cells of undetermined significance or ASC-US / LSIL result in HPV testing as protocol. Findings of ASC-H / HSIL result directly in colposcopy w/biopsy as protocol. Cervical cytological test is taken by a doctor, usually a general practitioner or a gynecologist.

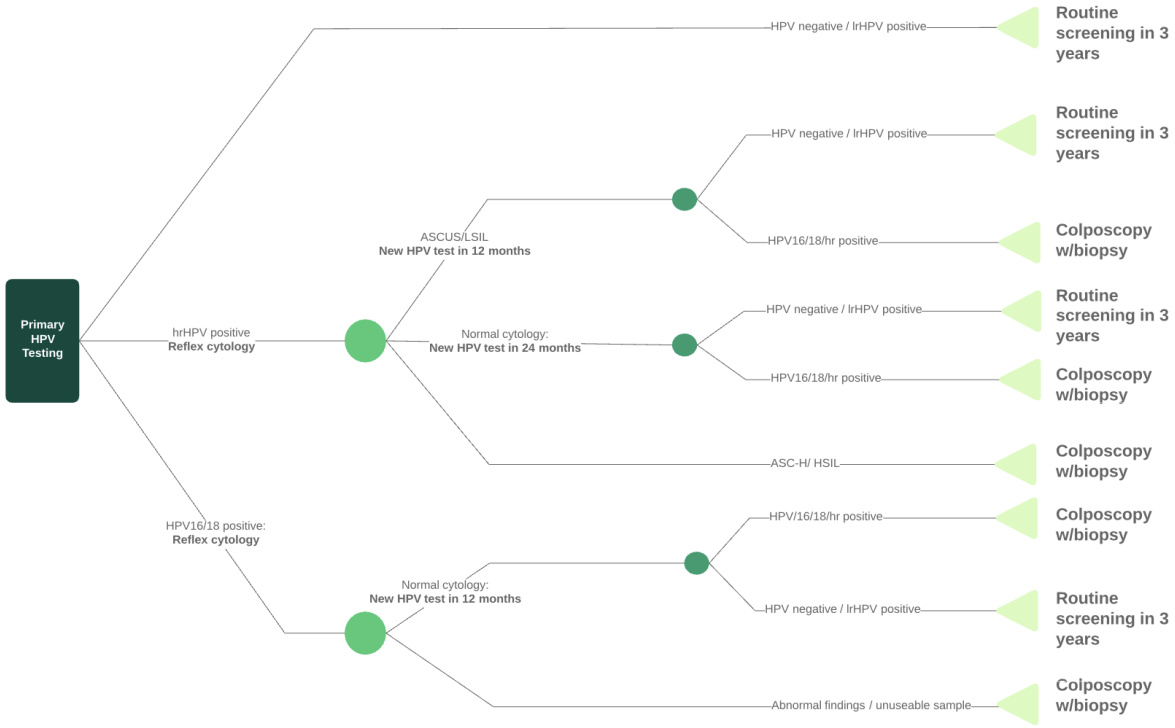

Figure 3. Flowchart of the primary HPV-based screening strategy, adapted from The Cancer Registry's webpage. ASCUS atypical squamous cells of undetermined significance, ASC-H atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion; LSIL Low-grade squamous intraepithelial lesion, HSIL high-grade squamous intraepithelial lesions, hrHPV high-risk human papillomavirus, lrHPV low risk human papillomavirus, HPV16/18 human papillomavirus genotype 16 or 18

The procedure of HPV-based testing is similar to cytology-based testing when collecting specimens but uses molecular testing of the tissue where detection of hrHPV-DNA/RNA is a marker for women at risk of developing high-grade lesions and cervical cancer. The protocol of an HPV test positive for HPV16/18/hr is examining the histology of the cell sample to subcategorize the woman at risk and determine an appropriate protocol for further follow-up.

2.3 CLASSIFICATION SYSTEMS & TEST CHARACTERISTICS

There are several types of classification systems of precancerous cells and cancer in the cervix, distinguished by the method of detection used. The methods comprise of histology, cytology and molecular testing. Terminology used for the reporting of precancer- and cancer cells is complex and there have been major changes over the last two decades. The most common approaches are the World Health Organization terminology, the cervical intraepithelial neoplasia (CIN) terminology or the 2001 Bethesda System5. Pathology laboratories in Norway use the same classification system for cytology (Bethesda) and histology (CIN)[13].

The CIN-system divides the cells into three histological grades, depending on how much they still look like normal cells (see figure 4.). For diagnosis of squamous lesions, the cervical intraepithelial neoplasia (CIN) scale is used, and distinguishes CIN1 (mild dysplasia), CIN2 (moderate dysplasia) and CIN3 (severe dysplasia and carcinoma in situ) by the fraction of epithelium replaced by undifferentiated cells. Adenocarcinoma in situ (AIS) corresponds to CIN3, but for the precancerous stage of ADC. AIS and CIN3 both refer to a precancerous lesion that has not invaded to the surrounding tissue in the cervix. It is relatively common in the population to develop lesions, and the majority regress naturally by themselves. Unfortunately, it is not a transparent matter to assess lesions and identify the ones that have malignant potency and actually progress to invasive cancer, which is why close follow-up and treatment of high-grade lesions are standard protocols to minimize such risk even though it involves overtreatment.

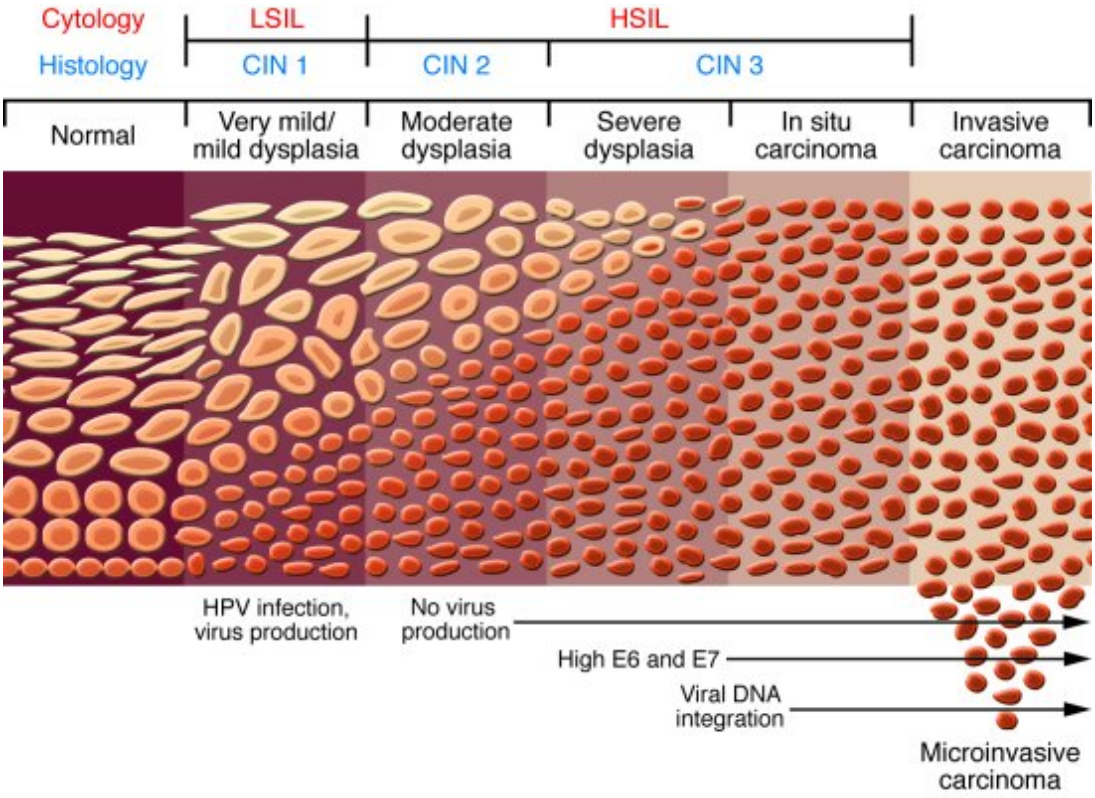

Figure 4: Progression from a benign cervical lesion to invasive CC and corresponding terminologies. Schematic retrieved from JCI.org[14] *LSIL Low-grade squamous intraepithelial lesion, HSIL high-grade squamous intraepithelial lesions, CIN1 Cervical intraepithelial neoplasia grade 1, mild changes; CIN2 Cervical intraepithelial neoplasia grade 2, indicates moderate changes; CIN3 Cervical intraepithelial neoplasia grade 3, indicates severe changes, HPV Human papillomavirus*

Cytology is the study of a cell sample using a microscope[15]. The cytology sample is done with a brush specifically designed to collect ectocervical, endocervical and transformation-zone cells with a single device[16]. In Norway, the Cervex-Brush is used for conventional cytology testing, but liquid-based cytology is increasingly being used since it offers the ability to conduct additional molecular and biomarker tests, such as for HPV testing[17]. ThinPrep®Pap Test or BD SurePath™Pap Test is recommended for cytology laboratories in the country[18].

Samples for HPV testing is collected in the same way as a cervical cytology sampler, with either a brush or a swab, which is then vigorously rinsed into a vial. For HPV testing, the Norwegian cancer registry recommends the cobas® HPV test[19] from either a Thinprep or Surepath vial. The Roche cobas® 6800 HPV test is a polymerase chain reaction (PCR) assay. It targets 14 high-risk HPV (hrHPV) genotypes and provides information on the following three infection statuses[20]:

- **HPV 16:** detected or not detected
- **HPV 18:** detected or not detected

- **hrHPV: (other high risk infections)** detected or not detected (panel result)
  Indicates presence of one or more of high-risk HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68

While cytology is a method to detect the presence or absence of cervical abnormalities (dysplasia), an HPV DNA test detects the presence or absence of HPV-DNA. Schiffman et al. argue that molecular assays might provide a better reference measurement of cancer risk, where tissue can be classified as normal when there is no detection of high-risk HPV by DNA or RNA testing[7].

Cytology (Bethesda)	Histology (CIN)	Molecular
Normal	Normal	Normal
ASCUS AGUS ASC-H LSIL	CIN1	HPV infection
HSIL AIS	CIN2 CIN3	Precancer
Cancer	Cancer	Cancer

Figure 5: Table of nomenclature and classification systems, adapted from Schiffmann[7] with information from guidelines for gynecological oncology in Norway[21]. The table is not an accurate representation of how the different classification levels correspond to each other but approximates how different analysis results and disease severity can be compared when utilizing different methods. ASCUS atypical squamous cells of undetermined significance, AGUS atypical glandular cells of undetermined significance, ASC-H atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion; LSIL Low-grade squamous intraepithelial lesion, HSIL high-grade squamous intraepithelial lesions, AIS/ACIS adenocarcinoma in situ, 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.

2.4 INFORMING CERVICAL CANCER PREVENTION POLICY-MAKING USING DECISION-ANALYTIC MODELING

While RCTs are the gold standard for gathering clinical evidence, model-based evaluations are increasingly being used to complement trial-based evaluations[22]. The evidence derived from clinical trials will remain important for the development of model-based studies, but for informing in public funding decisions, model-based evaluations have a significant role.

Several model-based studies have been of importance when Norwegian policy makers have assessed the NCCSP. For a short-term analysis of outcomes, a decision tree model has been used to evaluate the use of reflex HPV DNA testing in triage of women with minor cervical lesions[23]. Other studies have used a microsimulation state-transition model of HPV and cervical carcinogenesis to quantify the health and economic outcomes associated with candidate screening strategies with a long-term horizon[24–26]. Despite different features of the model types, they can all be adapted and extended depending on the specific evaluation objective and share equally important roles in the decision-analytic approach taken by policy makers and researchers.

These studies have contributed to addressing important knowledge gaps in the field of CC-screening policy in Norway. There have been several important findings suggesting (a) that the use of novel biomarkers to triage young women with minor cervical cytological lesions have the potential to detect additional precancers[23], (b) de-intensification of screening for HPV-vaccinated women for the program to remain cost-effective[24], (c) that HPV-based screening should start at an earlier age and rather utilize a less intensive triage algorithm HPV positive/cytology negative women[27].

Due to limited knowledge about ADC and lack of data, most modeling studies in Norway and internationally simplify the model structure by only accounting for SCC[28], or pool SCC and ADC histologies into a single model structure that does not allow for the differential natural history pathway or cytological test characters between SCC and ADC. There is sparsity of studies that have evaluated the differences in clinical parameters associated with the two cancer types and precursors. At the same time, studies report that HPV-based testing being especially more sensitive to AIS and ADC compared to cytology[29]. Models that have simplified the natural history may be underestimated the value of transitioning to HPV-based screening, which can impact on the optimal choice of screening algorithm and technology. While SCC-incidence is declining in

many countries, ADC seems to be increasing not only relatively to SCC but also in absolute terms[30]. It is therefore becoming more critical to capture specifically ADC in the decision-models. Furthermore, with enhanced understanding of HPV epidemiology, we need continue to make improvements in the models as they should be continuously updated and extended to align with the best available evidence.

Findings in the literature suggest that cytological screening does not prevent AIS and ADC as efficiently as it does against SCC[31]. However, it is reported that cytological screening detects adenocarcinoma at an earlier stage than diagnosis in the absence of screening[30]. It is further hypothesized that a combination of HPV vaccination, HPV testing and new technologies will result in a considerable decrease in the burden of adenocarcinoma of the cervix[30]. This emphasizes why it is important to consider ADC in decision-making of CC-prevention strategies.

3 THEORETICAL FRAMEWORK

3.1 ECONOMIC EVALUATION AND THE ROLE OF MATHEMATICAL MODELLING IN HEALTH CARE POLICY

Within health care decision-making, the focus has shifted from merely assessing clinical effectiveness, to assessing both clinical effectiveness and cost-effectiveness[32]. Therefore, the need for a systematic approach to this has been met with economic evaluation, offering a framework with a wide range of techniques for the appraisal of healthcare programs:

"Economic evaluation provides a framework to make the best use of clinical evidence through an organized consideration of the effects of all the available alternatives on health, health care costs, and other effects that are regarded as valuable".[33(p1)]

A well-designed methodology should be one of the prerequisites for making good decisions for both management, clinical practitioners and decision-makers in the central health care system. The approach assesses the cost-effectiveness of candidate interventions on the basis of trade-off between resource use and health-benefit yielded. The analysis can build on information from a randomized controlled trial or be supported by mathematical simulation modelling, which can vary broadly in structure and methodology. Yet, these models have been highly relevant in designing policies across many settings, such as coronary heart disease in the United states and even within anti-tobacco education programs[34]. The models have in common that they assist decision makers in identifying the optimal allocation of resources in health systems under pressure and maximizing health benefits.

The strength to this approach compared to arranging clinical studies is that it requires far less time, people and financial investment to be conducted. Modeling allows for greater flexibility in the medical research as it doesn´t rely on direct recruitment of patients and can be applied to multiple settings. Also, RCT's are often conducted under certain circumstances that do not reflect the real-world conditions regarding effects and cost[34]. Even though decision analytic models are subject to uncertainties, decisions based on analysis and the best evidence available are preferred over informal assessments that don't attempt to quantify the outcomes of an intervention. Used correctly, economic evaluation is a powerful tool.

Drummond[32] underlines that economic evaluation has two key features. First, it deals with the resource use and outcomes of alternative courses of action, i.e. the costs and benefits expected. Second, economic evaluation entails the assessment of alternatives, i.e. a comparative feature. Therefore, the basic tasks of an economic evaluation is to identify, measure, value and compare the costs and consequences of alternatives being considered[32].

3.1.1 TYPES OF ECONOMIC EVALUATION

There are different techniques available to identify and value the outcomes of interventions in an economic evaluation. Identification and measurement of costs is done the same way across the techniques using monetary units, but the method for identifying, measuring and valuing benefits varies. The three most common techniques used for economic evaluation are cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA). CEA measures effects in natural units such as life-years gained, disability days saved or other measurements that can quantify the impact of the intervention. CUA measures the benefit in the form of quality adjusted life years (QALYs). Measuring health through QALYs has the advantage of capturing both life years gained but also the improvement in health during this time. Since health is a function of length of life and quality of life, the QALY was developed as an attempt to combine the value of these attributes into a single index number. Even though valuation of a QALY is a very complex process, the QALY calculation is intuitive. The change in utility value induced by the treatment is multiplied by the duration of the treatment effect to provide the number of QALYs gained. Total QALYs can then be compared with total medical costs to evaluate the cost-effectiveness of an intervention.

CBA measures benefit in monetary units. This enables the program to be assessed in a much broader context, not just limited to the healthcare sector. However, this requires that the outcomes of the program are exchanged into monetary units and information on the willingness-to-pay or market value of the outcome is needed. Deciding on the appropriate technique entails that value judgements must be made either way.

Once a technique is chosen the measure of benefit can be incorporated with costs to arrive at a final denominator of cost per unit of benefit. This metric can be used to compare the cost-effectiveness of any treatment. When doing a comparative analysis, as in an economic evaluation, the incremental cost effectiveness ratio (ICER) is the central metric. This is an estimate yielded by information on the additional costs one intervention imposes over another, compared with the additional effects, benefits or utilities it delivers[32], and is informative in

assessing value for money of interventions. This is done by subtracting the costs of alternative B from the costs of alternative A and dividing this number by the difference in effects of the alternative interventions, as shown below.

$$ICER = \frac{Cost_A - Cost_B}{\Delta Effect_A - \Delta Effect_B}$$

Interpreting the ICER is straightforward; if both the cost difference and effect difference is positive, the intervention of interest is more effective and more costly than the comparator (the alternative strategy we are comparing with). If the cost difference is negative and the intervention is more effective, the ICER is negative and it means that the intervention *dominates* the alternative. There are two other possible ratio interpretations of the ICER. All four are summarized in figure 6.

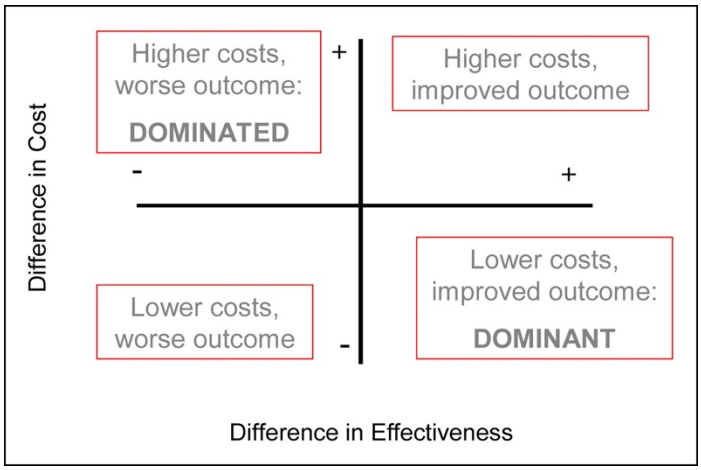

Figure 6. The cost-effectiveness plane, with differences in effects measured on the horizontal axis and difference in costs measured on the vertical axis. Schematic retrieved from NeoReviews[35]

Economic evaluations and ICERs are useful tools for both the provider side and the consumer side of health, but they are not the only criteria a decision maker should rely on. In general, ICERs need to be considered in light of affordability, budget impact, fairness in the distribution of health gains, feasibility and any other criteria of relevance in the setting. The Norwegian Committee on Priority Setting has proposed the use of three criteria, which are health benefit, health loss and resources – and suggested differentiating thresholds across the different categories of potential health loss[36].

3.1.2 THE COST-EFFECTIVENESS THRESHOLD

For a decision maker, the criteria for choosing an alternative program can be several, and economic evaluations offer some means to assist the policymakers in the process of prioritization. Many countries operate with a cost-effectiveness threshold (CE-threshold) as a cut-off to effectively assess whether or not they should invest in a new program or treatment[37]. This threshold is defined as the opportunity cost a health care system can bear when investing in a new treatment which generates a positive net health in the system. The introduction of a new treatment that imposes additional costs on a system is equivalent to a marginal reduction in the resources available for other activities[38]. If the ICER is above the CE-threshold, investment in the new treatment would lead to reallocation of resources that would result in a potential health loss. The CE-threshold differs across countries, depending on the characteristics of the health care system and the general income level the country has. It is commonly cited that Norway has a general threshold cut-off at $100'000 per QALY per gained[25]. For reference, the United Kingdom and the United States have had a threshold of $ 20'223 and $ 24'283-$ 40'112, respectively[38].

3.1.3 ANALYTIC PERSPECTIVE

A question to be addressed when designing an economic evaluation is which perspective that should be adopted. This is a matter of which costs and consequences that should be incorporated into the analysis. The perspective taken depends on the nature of the health system and who the economic evaluation is intended to inform. the two main approaches include the *healthcare perspective* and the *societal perspective*. In the health care perspective, costs included are limited to the activities within the healthcare sector and which directly impact the healthcare budget. However, the societal perspective has a much broader approach, suggesting that costs and productivity losses falling on other sectors in the society need to be acknowledged as well, also referred to as social opportunity costs. Including this information will encourage decisions that ultimately yield a greater welfare to society. This entails that not only treatment costs are accounted for, but also the costs falling on the patient, social services, productivity losses due to inability to work and more. It becomes more complex to calculate the costs associated with an intervention, and for practical reasons not all costs can be included. Norwegian guidelines for pharmacoeconomic analyses require a societal point of view where all relevant health effects and costs must be included in the analyses including their allocation amongst different groups in society[39].

3.1.4 DECISION-ANALYTIC MODELLING IN ECONOMIC EVALUATION

Being increasingly applied to inform on a wider range of decisions within healthcare, it has been indicated that economic evaluation no longer can rely a randomized trial as a single vehicle as this becomes too limiting[32]. Therefore, evidence needs to be collected and synthesized from a number of different sources, including cohort studies, clinical- and outcome data, surveys and etc. in addition to randomized trials. With the help of decision-analytic modelling the decision maker can be informed on all relevant and currently available evidence in the process of decision making.

Drummond explains that "*Decision-analytic modelling provides a framework for decision-making under conditions of uncertainty. More specifically, a decision-analytic model defines a set of mathematical relationships between entities (usually health states or pathways) characterizing the range of possible disease prognoses and the impacts of alternative interventions. These entities themselves predict the quantities we are interested in for economic evaluation: costs and health effects*".[40(p312)]

Decision analysis satisfies several important objectives for an economic evaluation. These include providing structure in the analysis, building on the best available evidence, supporting evaluation by translating relevant evidence into estimates of costs and effects of the alternative interventions, facilitates assessment of uncertainty, variability and heterogeneity relating to the evaluation, and finally it gives direction to where more research is needed in the future[32].

Key elements of decision-analytic modelling are probabilities and the expected values of the costs or outcomes. These are common among all models. The use of probabilities reflects the likelihood of events or changes in health, and the expected values of the alternative interventions are used to inform decisions. The theory is grounded in statistical decision theory and has features of expected utility theory[32].

3.1.4.1 DEVELOPING A MODEL

Once the decision problem is defined and the scope of what the model includes is determined, the next steps of developing a model is conceptualizing and implementing the

model. The former involves a series of decisions concerning the parameterization and structure of the model in terms of characterizing clinical events and deciding on which health states to include. Creating a mathematical structure of a medical course of events requires that judgements and assumptions must be made. For example, in the context of CC, conceptualizing a decision model entails that one is *systemizing* or *creating a logic* to a natural disease history with the help of health states and corresponding probabilities relating to the course of the disease. Some CC-models include a separate health state for each precancer stage[28], while others simplify and only account for single high-grade lesion CIN2/3 health state[41]. Some models also differentiate between HPV-genotypes while others pool them all together[42]. The structure can vary depending on how detailed the analysis is intended to be, how much data is available and what the research objective is.

3.1.4.2 GATHERING EVIDENCE FROM THE LITERATURE

An important component in the development of a model is gathering relevant information and evidence in the literature to determine model inputs and validate what the model projects. A literature review is a method aimed at identifying what has been written on a subject or topic. Therefore, a systematic approach to searching for published evidence is needed so that the evidence used is not selected in a potentially biased way[32]. The key steps of conducting a literature review consist of *Formulating the research questions and objectives,* searching the existing literature, screening for inclusion, assessing the quality of primary studies, extracting data, analyzing and synthesizing data[43].

3.1.4.3 IMPLEMENTING A MODEL

There are several ways of implementing a model and the literature shows that a wide range of models are used in economic evaluations. Within CC-modelling, the most common models applied are the decision-tree model, state-transition models (either markov- or individual-sampling models (ISM)), dynamic transmission models and discrete event simulation models[23,44–46] There is no consensus on which model is preferred in general, but the chosen model should be suited to reflect the decision at-hand. In brief, a decision-tree model represents the possible prognosis following an intervention by a series of pathways with corresponding probabilities, costs and outcome values expected for each pathway. Since a decision-tree model has several limitations, a state-transition model is often preferred if there is a need to reflect more complex features, allowing the patient to transition through several recursive health states over discrete time periods, called cycles. In each health state, there is an associated cost and health utility used to measure the overall resource use and effects generated at the end of the

time horizon. The drawback of a Markov model is the lack of time dependency and memoryless feature, meaning that the transition probabilities cannot depend on information from earlier on in the model, such as time spent in the health state and earlier events that have occurred. Therefore, the ISM is a great alternative to the traditional Markov model, as it incorporates memory and time dependency. Dynamic transmission models allow the health of individuals to be impacted by the health of others, enabling communicable diseases to be modelled more accurately[32]. Discrete simulation models are a less common alternative that avoids the use of states and fixed cycle lengths and instead models events at the individual level.[44]

3.1.4.4 MONTE-CARLO SIMULATION

When used in the context of state transition models with discrete cycles, the ISM is referred to as a Monte-Carlo simulation or microsimulation[32]. The concept of a Monte Carlo simulation is based on a statistical technique used to model probabilistic (stochastic) systems and establish the odds for a variety of outcomes[47]. The method is useful when one has to handle complex interaction of many variables to predict future outcomes. It is a well-established method in fields from physics to engineering and finance and is gaining momentum within health economics as well.

The model simulates individuals one at a time and tracks the process of the patients throughout the predefined time horizon of the model. They can enter several health states, like in the Markov model, but the model allows for more flexibility since the prognosis of the patient can vary depending on the history of the individual, effectively incorporating memory. The parameters related to the transition through states are randomly sampled for each individual, so that the simulation of a large cohort of individuals will ultimately produce probable outcomes that can be combined and averaged to reflect the expected costs and effects of an intervention. The element of random sampling makes the simulation stochastic.

Given the increased complexity of this type of model, more accurate empirical data and evidence is required to feed the models parameters and produce realistic simulation results. This type of simulation is also time-consuming to run, and requires skilled programming, powerful software and efficient computers.

3.1.4.5 CALIBRATION

A key component of model development is choice of parameters and input estimates. While most inputs are informed by existing knowledge or data (e.g., from previous studies or registry data), some parameters are unknown and/or cannot be informed by existing data[48], due to, for example, ethical issues. This is often the case for parameters related to the underlying natural history of disease, such as onset of disease, progression and regression rates. A commonly used approach to handling this 'gap' in data is calibration, or "model fitting". The method involves the comparison of model outputs (for example disease prevalence rates) with empirical data, leading to the identification of model parameter values that achieve a good fit so that model output replicates observed data[49]. Simply put, input estimates are adjusted until the model fits with what is observed in a specific setting, in turn increasing validation and the reliability of the model.

There are a variety of different calibration methods and they vary in complexity and computational workload. There has been little consensus on the best practice of calibrating a model, but there are seven common steps to be taken in the process, best described by Vanni et al.[49] "*The seven steps are (i) Which parameters should be varied in the calibration process? (ii) Which calibration targets should be used? (iii) What measure of goodness of fit should be used? (iv) What parameter search strategy should be used? (v) What determines acceptable goodness-of-fit parameter sets (convergence criteria)? (vi) What determines the termination of the calibration process (stopping rule)? (vii) How should the model calibration results and economic parameters be integrated?".*[49(p38)]

Figure 7. The first six steps of model calibration defined by Vanni et al.[49]

The first step is to identify which parameters need adjustment to achieve a better model fit. In a disease model, the underlying course of disease in individuals is often difficult or not possible to observe. Therefore, the parameters in HPV-related disease related to onset of disease, progression and regression need to be calibrated.

Step two is to decide on which output we want the model to project, which requires a literature review in addition to collecting epidemiological data to define the appropriate target outputs. Targets may be statistically calculated based on high quality data but access to some forms of data may also be limited. Hence, it may be appropriate to explore several values for a single target.

Third, a Goodness-of-fit (GOF) metric is needed to measure the projected output against the target values. This can be done qualitatively through visual inspection of model fit, for example by comparing model projections with observed values for age-specific incidence curves of a disease or event. Quantitative approaches include likelihood metrics that specifically quantifies the probability of achieving a good fit to the target data, depending on what the input is. An example is measuring the distance from the model output to the target with the sum of squared errors and calculating a weighted average across multiple targets.

The search algorithm refers to how one selects the parameter sets from all possible feasible parameter values to evaluate during the calibration process[50]. Here as well it is possible to choose from a variety of techniques that vary in complexity and comprehensiveness. An informal approach is trial-and-error and other more formal approaches include random search within a given parameter bound, grid search, directed search etc. The choice can depend on the number and parameters under calibration and model complexity.

The acceptance criteria determine when the parameter set provides a reasonable fit to the target data. A GOF-threshold can be met or there may be several parameters sets that can be used to characterize uncertainty in parameter values. The Bayesian calibration approach is slightly different from traditional calibration in that the goal is not to fit targets with a single parameter set, but find a parameter set that reduces the uncertainty in the inputs in a manner consistent with the data. This is particularly useful when a model is highly sensitive to the input and there is limited measured data to use for calibration[51].

Finally, the stopping rule lets the modeler determine if the calibration process is complete. The stopping rule may be based on the extent of the parameter space searched or other criteria related to the GOF metric. When the calibration process is complete, the parameters need to be integrated into the decision model.

Documenting the calibration process is important to ensure transparency and to improve knowledge on the different methods available. Unfortunately, documentation of model development and calibration is limited, resulting in model-based studies receiving criticism for being "black boxes"[50]. Lack of model transparency makes it hard for the decision makers to assess the work in terms of quality and making comparisons with other studies.

3.1.4.6 VALIDATION

It is essential that models undergo adequate validation so that decision makers and researchers can have confidence that the model's results are reliable. The methodology of model validation is widely discussed, and the literature mentions different approaches. The ISPOR—SMDM Task Force on Good Research Practices published guidelines for the development and validation of decision-analytic models used in economic evaluations[52]. The guidelines consider model structure, data and validation as criteria for model quality, with specific validation criteria distinguishing between internal, between-model, external- and predictive validation[53]. Kopec et

al. consider model validation as the process of gathering evidence, both theoretical and empirical, which is in support of the model's intended use[54]. In general, the process of **model development**, the **performance of the model** and the **quality of decisions based on the model** are all relevant in the context of validation[54].

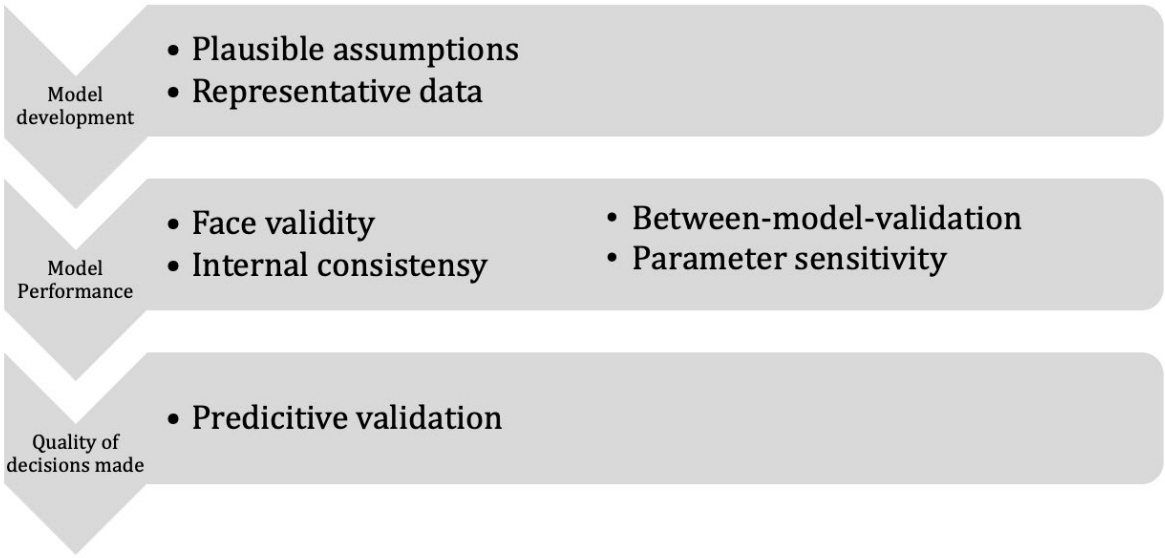

Figure 8. Kopec et al. highlight three categories of model validation[54]

Through model development, the theories and assumptions underlying the conceptual model should be correct and the model representation of the problem statement and structure, logic, mathematical and causal relationships are plausible for the intended purpose of the model[55]. Assessment of this is often qualitative and relies on the opinion of experts in the relevant fields[55]. Other elements of consideration in assessing the model development process are choice of parameters and where they are obtained from, how representative they are to the population of interest, and also how computer implementation is done[54].

Validating performance can be done by examining the plausibility of the model output (face validity), internal consistency, parameter sensitivity, between-model comparisons and comparisons with external data are all recommended approaches[54]. Assessment of face validity consists of detecting if the model output seems reasonable and makes intuitive sense, requiring one to compare output with what is expected based on general knowledge and understanding of the disease area modeled[55]. Internal consistency determines whether the mathematical relationships in the model are behaving consistently with theory. A lack of consistency may imply that there is a "bug" or an error in the model or computational logic which needs to be resolved. Using historical data on cancer incidence rates is a common approach to testing external validity, which would mean that the model projects cancer incidence consistent with historical rates. Parameter sensitivity can be explored with sensitivity analysis

Predictive validation can be defined as the degree of consistency between model output and prospective data (future events). Any differences between the observed and predicted values may be explored with uncertainty analysis. However, prospective validation can be difficult to achieve, especially in models with long time horizons such as with screening interventions. Thus, the overarching purpose of decision-analytic models are to assist and improve decision-making, not predict future events[56].

3.1.5 CHARACTERIZING MODEL UNCERTAINTY

Characterizing uncertainty in a decision-analytic model is a fundamental part of an economic evaluation. This is to ensure that model results can be relied on to guide decision-makers in answering the problem entity. The extent of uncertainty in a model can also be interpreted as an indicator of how much additional information and research is needed to strengthen the credibility of a model[57], giving rise to a methodology more commonly known as *expected value of perfect information* (EVPI).

Uncertainty can be related to many aspects in the model development process but also to the model components, and the literature is not entirely consistent when interpreting and referring to uncertainty in models. ISPOR—SMDM guidelines highlights that the most important uncertainty to address relates to heterogeneity, stochastic-, parameter- and structural uncertainty[32]. Drummond et al. on the other hand, emphasize particularly parameter uncertainty and structural uncertainty.

Heterogeneity	• The variability between patients that can be attributed to personal characteristics such as gender and age. This is an observed variability which is systematic and can be explained and accounted for through different statistical techniques.
Stochastic Uncertainty	• Refers to the random variability in outcomes between identical patients in a model, which in a Monte Carlo simulation can be termed as the Monte Carlo error[31]
Parameter uncertainty	• Related to the estimates of parameter inputs in a model, which can be the variability in a cost or effect of a treatment, often quantified with a standard error of the estimate in question.
Structural uncertainty	• Related to the scientific judgements that are made when building a model and deciding on inclusion of health states and parameters. The sources of structural uncertainty fall into fours general themes; inclusion of relevant comparators, inclusion of relevant events, alternative statistical estimation methods, and finally clinical uncertainty[51]

Figure 9. The four main sources of uncertainty addressed by ISPOR—SMDM[58]

There are several alternative approaches to address and quantify uncertainty in a model. The most common and established approaches are to conduct a deterministic sensitivity analysis (DSA) or a probabilistic sensitivity analysis (PSA). The DSA requires a single value for each input of a parameter, so that when each one is varied sequentially, the change in output of the model can be reported. This provides transparent information on the quantitative relationship between changes in inputs and outputs and can be achieved through different levels of complexity with either a one-way- or multiway sensitivity analysis. Although this indicates how sensitive the model may be to changes, it does not provide information on how uncertain a decision may be if based on the model result[32]. The PSA however, attempts to reflect a larger scope of uncertainty in an ICER. This is done by assigning a distribution to each of the model parameters which account for the realistic variation in input parameters. The model is then simulated sequentially many times, each parameter being varied randomly within it is given distribution, to generate a range of possible ICERs. The output of ICERs are normally represented in a scatter plot on the cost effectiveness plane. In short, this is to give an understanding of how much uncertainty the ICER is subject to, the chances are that the ICER is cost-effective, and also what the odds are that the ICER is under the WTP-threshold. The PSA is recommended by ISPOR in several guidelines for cost-effectiveness analysis[32].

Characterizing other sources of uncertainty, specifically structural uncertainty (or structural simplifications), can be done through simulating several probabilistic scenarios, parametrizing uncertainty and elicitation from experts[32]. These methods are less established, lack formal guidelines and may be very time consuming (e.g. if it requires building two or more models). In general, the ISPOR-SMDM guidelines recommend as best practice to consider structural uncertainties if these have been identified during the development of the model, as these are at just as important as parameter uncertainty:

"VI-11 Where uncertainties in structural assumptions were identified in the process of conceptualizing and building a model, those should be tested in uncertainty analysis. Consideration should be given to opportunities to parameterize these uncertainties for ease of testing. Where it is impossible to perform structural uncertainty analysis, it is important to be aware that this uncertainty may be at least as important as parameter uncertainty" .[59(p839)]

It is further stated that structural uncertainty may be represented deterministically by reporting results under each set of structural assumptions where they can be assessed in terms of plausibility and combined for decision-making. Quantitative uncertainty analysis can support structural uncertainty analysis by reporting the results separately under each structural

assumption[58]. Thus, a deterministic analysis is one way of conveying how the model results depend on the model structure.

Bojke et al. suggest a more comprehensive method for addressing structural uncertainty. In their article "*A Framework for Addressing Structural Uncertainty in Decision Models*", they provide a step-by-step guide in how to address and handle structural uncertainty of models with selection of models and averaging of results. The method involves weighting the results of each structural alternative according to the level of credibility and adequacy. Expert elicitation is recommended for selection of which models to average among. The concept of model averaging is intuitive but requires time and comprehensiveness when averaging to capture the uncertainty in all scenarios[57]. This method goes beyond the scope of the thesis but will be acknowledged in the methods- and discussion chapters.

3.1.6 Reporting guidelines

The presentation and reporting of an economic evaluation may vary across settings and raise questions about interpretation of methods and results among the audience. Therefore, attempts at making reporting guidelines have been made to increase the transparency and quality of economic evaluations. This way, readers and in particular decision-makers can critically assess the methods and results and make comparisons with other reports.
The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement is an example of consolidating and updating previous health economic evaluation guidelines into one reporting guidance. Here, a checklist with 24 items are accompanied with corresponding recommendations on how the item should be reported/discussed[60]. See appendix for the specific checklist.

4 THESIS OBJECTIVES

Model-based studies have been, and will continue to be, essential in the evaluation of costs and benefits of strategies to prevent CC. Therefore, it is vital that the models continue to be updated and extended as scientific evidence and methods improve. The main contribution of my thesis is to explore the structural uncertainty of not including more than one histological cancer in modelling of CC prevention strategies in Norway. I intend to build two simplified natural history models based on the Harvard CC by Campos and colleagues[41], and adapted to the Norwegian setting[45]. The aim of this thesis is to extend the disease pathways in one of the models with additional health states, including ADC and its precursor ACIS, to reflect both histologic cancer types. The output of the two models will be used to conduct a cost effectiveness analysis of cervical screening strategies involving primary HPV-based with cytology triage compared to the current primary cytology-based strategy.

Research question: What is the impact on the cost-effectiveness of CC screening strategies of including ADC in a decision-analytic model?

The main objective of this thesis is thus to evaluate the importance of differentiating between both histological CC types in the CC natural history models, to inform future policy-analyses related to CC prevention. To answer the research question, the secondary objectives of this thesis are to: (1) synthesize evidence about the carcinogenic pathway of HPV-induced ADC through a review of literature; (2) demonstrate how a natural history simulation model of CC can incorporate both SCC and ADC; and (3) illustrate how extending the model to include ADC will impact the cost-effectiveness (CE) of CC screening strategies.

5 METHODS AND MATERIALS

The following chapter is divided into two main sections. Part I presents model development, including model conceptualization for two structures (Structure 1, reflecting SCC only, and Structure 2, reflecting both SCC and ADC), an overview of parameter inputs to inform the models, and calibration and validation using empirical data. Part II describes our methodological approach to quantify differences in the two model structures using a cost-effectiveness approach.

5.1 ANALYTIC APPROACH

We developed two decision-analytic models reflecting two different structures. The first model, herein referred to as "Structure 1", is restricted to reflect the natural history of HPV-induced for a single histological type, i.e., SCC. The second model, herein referred to as "Structure 2", is extended to reflect both HPV-induced SCC and ADC stratified to capture the differential natural histories and test performance of the two CC histologies. The models are individual-based (i.e., microsimulation) in order to capture age- and time-dependencies in each health state as well as disease history, which are important features in this context. Furthermore, an individual sampling model is convenient when there are many possible health-state pathways for a woman to go through over the time-horizon. Parameterization and health states of model 'Structure 1' highly based on available information on the *Harvard Cervical Cancer Natural History Model* (herein referred to as "Harvard CC") [41,61].

In order to expand the model structure to reflect both SCC and ADC histologies, we reviewed the literature to identify evidence and data to inform the structure and parameters of ADC (Structure 2). Although a systematic review was beyond the scope of this thesis, we performed MESH-driven keyword searches in several databases; findings are summarized in chapter 4.3 and appendix figure 10. When empirical data was not available, we relied on calibration to fit the model to epidemiological data from Norway or similar setting when not available. When empirical data was not available, we relied on calibration to fit the model to epidemiological data from Norway, or from a European setting when Norwegian data was not available. Finally, following calibration, we performed several validation exercises to evaluate model fit to data not used to inform calibration.

The models were developed in R programming software (version 1.1.463), with code adapted from recently published tutorials.[62,63]

5.2 MODEL CONCEPTUALIZATION

We developed two first-order (individual-based) Monte Carlo simulation models of cervical carcinogenesis, highly based on the Harvard CC. The Harvard CC is a mathematical model which was developed to reflect the natural history of HPV-induced SCC. In previous work, the Harvard CC has been adjusted to the Norwegian context using primary clinical and cost data from Norway to project the health and economic outcomes associated with different scenarios of screening, and provides outcomes including the lifetime risk of cancer, life expectancy and lifetime costs[45]. It has previously been used to inform on a wide range of screen-related issues such as primary screening method, screening intervals, switch-age of different screening strategies, triage-strategies for positive primary testing, determining screening protocols and has also accounted for HPV-vaccination in the population[24,26,45].

Structure 1 was developed and simplified based on the Harvard CC and accounts for SCC and related precancers, operating with a total of 16 mutually exclusive health states (figure 10); Healthy, acquired HPV infection (with separate health states for HPV16, HPV18, pooled low risk HPV (lrHPV) and pooled high risk HPV (hrHPV)), precancer (with separate health states reflecting CIN2 and CIN3), and SCC (stratified by local, regional and distant stages, as well as by clinically detected and undetected). Death can occur from cancer or other causes. The women can transition at monthly cycles. For specifics on simplifications we made due to technical- and time constraints, see supplementary details (Appendix 15).

Structure 2 is identical to Structure 1 but was extended to incorporate an extra precancer health state for AIS, and cancer states for local ADC, regional ADC and distant ADC, also adding states for detected and undetected cancer. In total, Structure 2 includes 26 health states (Figure 10; red outlined boxes).

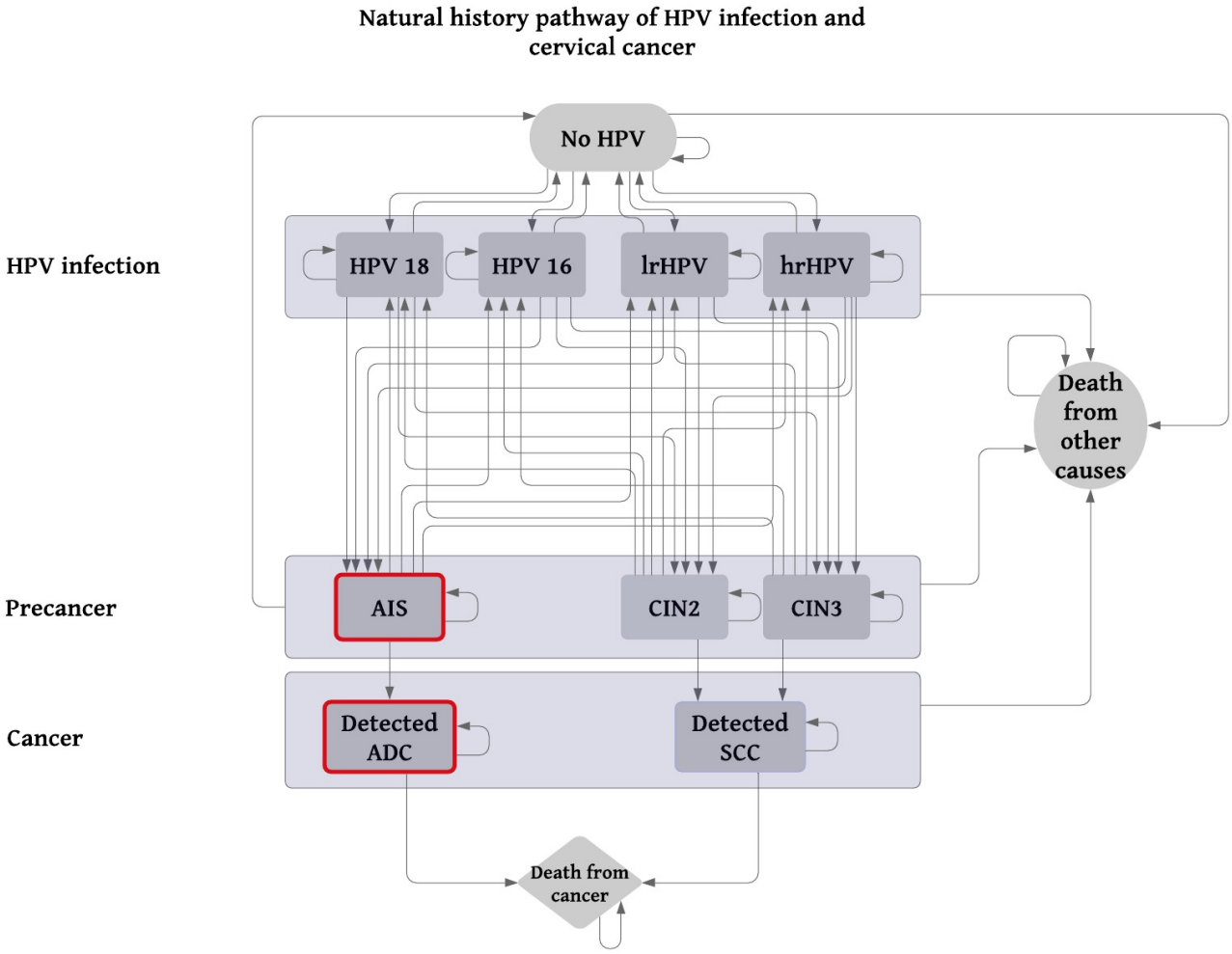

Figure 10. Schematic of the natural history model pathways, where additional health states for Structure 2, AIS and ADC, are accentuated in red. Simplifications in the figure constitute of cancer stages being pooled and the exclusion of undetected cancer states. HPV human papillomavirus, lrHPV low risk human papillomavirus, hrHPV high risk human papillomavirus, AIS adenocarcinoma in situ, CIN cervical intraepithelial lesions, ADC adenocarcinoma, SCC squamous cell carcinoma.

The code for the natural history model is presented in appendix 14. Note that the probabilities are imported in a separate script.

5.3 REVIEW OF THE LITERATURE

Literature searches were conducted to find evidence that could inform ADC-related natural history parameters for model Structure 2, either as direct model inputs or as calibration targets. To narrow down the scope of the literature search, parameters and costs associated with CIN2, CIN3 and SCC were excluded from the search as these are provided in recent literature and studies, such as the Harvard CC calibrated to a Norwegian setting[61].

Transition probabilities	Calibration targets
Progression from HPV infection to AIS	HPV genotype distribution in AIS
Regression from AIS	HPV genotype distribution in ADC
Progression from AIS to ADC	
Progression among ADC stages: local → regional → distant	
Stage-specific mortality for ADC	

Figure 11. Searches were conducted to inform the above transition probabilities and calibration targets. HPV human papillomavirus, AIS adenocarcinoma in situ, ADC adenocarcinoma.

The following databases were searched; Pubmed, Cochrane library, Medline and Embase. For exact search terms, see Appendix Table 10.The main goal was to identify studies and trials with information on differences in the natural history between ADC and SCC, preferably quantitative studies but also any qualitative studies that may inform relationships between SCC- and ADC-related natural histories. The search was designed to be quite broad at the beginning to get a general overview of how much literature there is on AIS and ADC of the cervix. Syntax varied with MESH-terms such as “adenocarcinoma in situ”, “adenocarcinoma”, “atypical glandular cells”, “in combination with organ specific terms such as “cervix uteri”, “cervical cancer”, “endocervical”, “endometrial” to see how sensitive the hits were to variations. Abstracts and titles were screened, and anything giving particular attention to ADC or ACIS was further screened in full text, looking through references as well.

Depending on the parameter being informed, searches were narrowed down with additional terms among title/abstract and even in full text such as “natural history”, “progression”, “regression”, “watchful waiting” or “conservative management” to explore results.

In addition to the results among searches conducted, additional articles were found from other sources (e.g., publications from WHO and through personal communication with Kine Pedersen & Emily Burger). In total, 86 articles from various databases and sources were reviewed in full text. Few studies were limited to AIS and ADC, and few CC-related studies stratified for histological types when presenting baseline characteristics of patients and study outcomes. CIN3 and AIS were mostly pooled among studies because the number of AIS/ADC were small. Most of the articles examined the physical characteristics of AIS lesions and ADC tumors, were focused on efficacy of cancer treatments or changes in epidemiology of the precancer and cancer types. Hence, there are no robust conclusions regarding explicit differences between the natural histories of SCC and ADC. Consequently, for estimation of parameters related to AIS and ADC we relied on calibration and plausible assumptions to identify parameter value sets that fit well to Norwegian epidemiological data on AIS and ADC.

For HPV-genotype prevalence among AIS- and ADC specimens in Norway, applicable information was found in one published study. This was a cross-sectional, multicentric, epidemiological study on HPV type distribution among ADC and AIS was, pooling data from 17 European countries including Norway[64]. The HPV positive women diagnosed with high grade precancer comprised of N = 2445 in the study, where n=17 of the women were diagnosed with AIS. The rest of the subjects were diagnosed with CIN. Due to the small sample size for AIS in the study, the data was pooled with data from a Dutch study. The Netherlands was not among the contributing countries in the European study and could offer a larger sample size of n=49 AIS specimens infected with a single HPV type[65]. For the European study, samples were collected between 2001-2008 and PCR was used to identify HPV DNA in the samples. The Dutch study used samples collected between 1996-2000 and also utilized PCR for HPV DNA identification. Given the difference in time periods of sample collection, the Dutch estimates may not be representative anymore of today's HPV type prevalence, but due to the small sample size in the European study and lack of estimates for other hrHPV types, it was necessary to supplement with additional data.

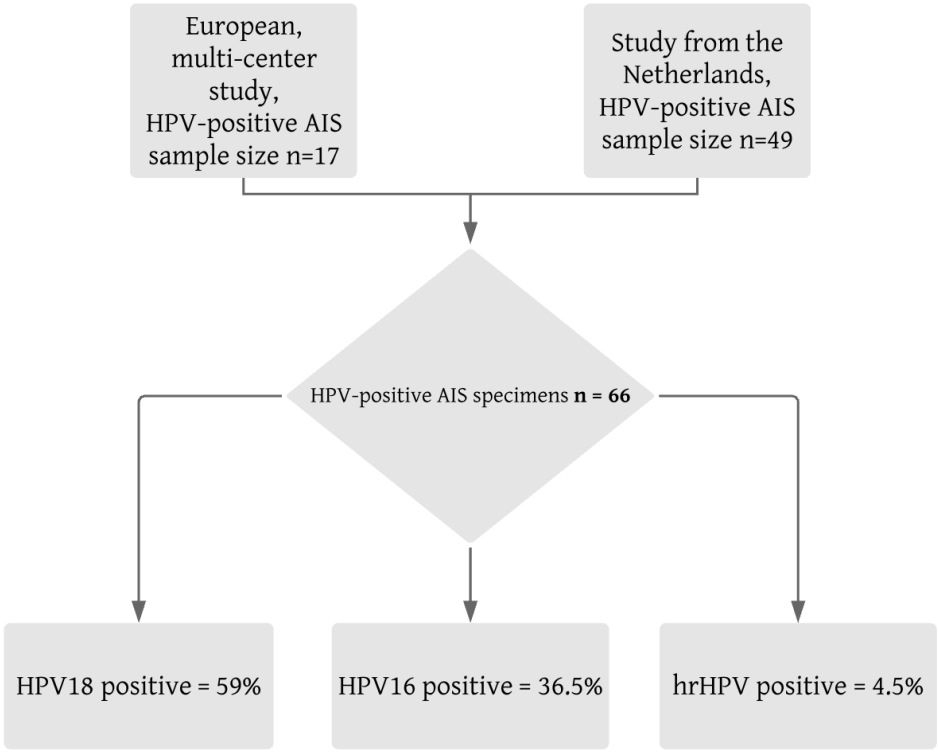

Figure 12. Flow chart of calibration target data for pooled AIS samples to derive HPV-genotype distributions. HPV human papillomavirus, hrHPV high risk human papillomavirus, AIS adenocarcinoma in situ.

The HPV prevalence results for AIS were 36.5% for HPV16, 58.9% for HPV18 and 4.5% for hrHPV (Figure 12). Two American studies also conducted for HPV genotyping in AIS specimens provide similar findings, with HPV18 accounting for 48-50%[66,67] of AIS and HPV16 accounting for 48%, while other studies have more contradicting findings where HPV18 only accounts for 26%[68] and HPV16 accounts for 25%[65]. Given the small sample sizes in all studies, estimates are quite sensitive to any variations. We decided to put weight on the studies conducted in a European setting.

For estimates on the HPV type distribution among ADC, access was offered to the Norwegian report used for the same European study[64]. The eligible HPV-positive cohort consisted of n=310 including histologically diagnosed ADC specimens of n=60, the remaining being histologically diagnosed SCC or adenosquamous carcinoma (ASC). The sample size of ADC specimens was considerably large, therefore we decided to not conduct a pooling with samples from other Nordic countries. Biopsies were collected between 2001-2008 from three large cities in Norway. The findings of HPV distribution among the women diagnosed with ADC showed that HPV16, HPV18 and HPV45 accounted for 47.3%, 45.5% and 7.3% respectively. This corresponds well

with the general findings of the pooled data from the European study, which increases the validity of the estimates.

5.4 PARAMETERIZATION AND CALIBRATION

Parameterization for Structure 1 is presented in the following section. Initial estimates for the SCC-related parameters were provided by Kine Pedersen and Emily Burger (personal communication) from their updated Harvard CC calibrated to a Norwegian setting. Further details regarding calibration for probability estimation has been described in the Norwegian technical appendix for Harvard CC[61].

Natural history parameters	**Source**
HPV prevalence	Based on a random sample of women aged 18-49 attending screening in St.Olavs hospital Trondheim in 2007[54]
HPV progression and clearance	Based on data from an earlier version of the Harvard CC by Campos et al. 2014, but previously adjusted to fit the Norwegian setting [38,54]
CIN regression	Based on data from an earlier version of the Harvard CC by Campos et al. 2014 But previously adjusted to fit the Norwegian setting[38,54]
CIN progression	Based on a combination of values from the Harvard CC by Campos et al. 2014 and a values from burger et al. 2012[45]
HPV type distribution in CIN & SCC	Based on a working paper from a Norwegian epidemiologic study using HPV DNA detection[61]
Cancer progression	Based on values from the Harvard CC by Campos et al. 2014 [62–64]
Cancer survival by stage	Based on data from an earlier version of the Harvard CC by Campos et al. 2014 [65]
Age-specific mortality rate in the Norwegian female population	2018 estimates, retrieved from Statistics Norway
Calibration targets	
HPV genotype frequency in AIS and ADC	Retrieved from an epidemiological study on HPV type distribution among ADC and AIS [56]
Data for model validation	
Cases of ADC and SCC	Data from the Cancer Registry of Norway, observation period from 1953-1969 (personal communication)

Table 1. Summary of sources used to inform model inputs and calibration targets. HPV human papillomavirus, AIS adenocarcinoma in situ, CIN cervical intraepithelial lesions, ADC adenocarcinoma, SCC squamous cell carcinoma.

5.4.1 HPV INCIDENCE, CLEARANCE AND PROGRESSION

The HPV genotypes are divided into four separate health states, comprising of HPV16, HPV18, pooled lrHPV and pooled hrHPV (Appendix Figure 2). The HPV incidence is a function of age of the women and the HPV-genotype. The projected output of the model provides information on the general age-specific HPV prevalence in the female population simulated and the distribution of HPV genotypes among lesions and cancer.

Progression and regression from an HPV-infection depends on the specific HPV-genotype infection and time since infection (Appendix Figure 3). The model assumes all lesions and cancers are caused by an HPV infection and that the DNA of the causal HPV genotype is detectable if tested.

5.4.2 REGRESSION- AND PROGRESSION PARAMETERS ASSOCIATED WITH PRECANCER

Women are allowed to progress directly to CIN2 or CIN3 from an HPV-infected state, without the possibility of transitioning between CIN2 and CIN3. CIN2 is more prevalent than CIN3 but has lower progression- and higher regression probabilities than CIN3. Regression and progression probabilities depend on HPV-genotype and duration in health state (appendix figure 5 & 6). The more associated the lesion is with an HPV-genotype, the higher the progression probability is and the lower the regression probability is. Lesions induced by lrHPV cannot progress to invasive cancer and are not regarded as malignant lesions in a screening scenario.

5.4.3 CANCER PROGRESSION AND MORTALITY

In a setting without a screening program, cancer epidemiology depends on the clinically diagnosed cases through symptom detection. This is coherent with how cancer incidence in a population is measured in real life. Once a woman is detected, she remains in the cancer stage she has been detected in. We assume the woman receives stage specific treatment and further progression of the disease is stopped. However, she can still die from cancer or other causes.

5.5 CALIBRATION OF MODEL INPUTS

Our objective with calibration was to identify parameter input values that could not be informed by the literature or clinical data. Given the complex nature of a microsimulation model, and computational limitations, we used a calibration approach that balanced computation burden and model fit. Baseline parameters for Structure 1 were based on the Harvard CC fits to Norwegian CIN and SCC data, but updated to reflect the changes in model structure used for this thesis. Baseline model inputs for Structure 2 were then subsequently used as base estimates for calibrating parameter sets for the ADC-arm that would achieve a good fit to the target outcomes. For AIS and ADC, the HPV-genotype distribution is based on the pooled data from Europe and an epidemiological study from Norway (section 5.3). Data on diagnosed lesions in Norway was not obtainable through the Cancer Registry of Norway. However, AIS is assumed to be under-detected until it reaches more advanced stages of ADC[30]. Thus, there is a lot of uncertainty regarding this estimate and we opted to not adjust the Harvard estimates provided for CIN, and simply attempt to keep AIS prevalence slightly lower than the CIN3 prevalence. We aimed for a total of 2.5-3% lifetime cancer risk in the models as reasonable estimate for a setting without screening, as this corresponds with the maximum lifetime risk derived from historical pre-screening era data from Norway. We aimed for a 20-25% proportion of ADC incidence among the total cancer incidence in Structure 2, which is the observed proportion in Norway in recent years (Cancer registry, personal communication).

5.5.1 CALIBRATION APPROACH

A quantitative manual trial-and-error calibration approach was used to adjust the input parameters to fit the empirical target data. For HPV-genotype distribution in AIS and ADC, the goal was to achieve a distribution within the 10% upper and lower bounds of the mean values. Through visual inspection of the model projection against the targets we were able to assess the goodness-of-fit of the parameters sets provided. Any systematic discrepancies were compared with what the Harvard CC projected for between-model validation. The stopping rule was when a set of parameters from a simulation of one million women simultaneously achieved a fit within the upper and lower bounds of the targets.

The calibration process was two-fold. As Structure 1 was slightly different than the Harvard CC, we began with re-calibration of the SCC-arm followed by calibration of the ADC-arm of the model. For each arm, we began with calibration of HPV-genotype distributions in the high-grade

lesions. When the targets for HPV-distributions were reached we made additional adjustments to make sure the total prevalence level of each health state was reasonable. We had the same strategy for calibration of cancer, beginning with HPV-targets followed by adjustments for total cancer incidence. Each HPV-genotype was fitted independently to be able to document the impact on the model output and to gain an understanding of how other parameters were affected. A considerable amount of time was spent on making systematic adjustments, documenting and exploring alternative scenarios to study the changes in model output and ensure that there were no technical faults in the model (i.e. "debugging"). Given the nature of a microsimulation model, multiple health states and parameters to inspect for every adjustment, the process required a considerable amount of time.

5.5.2 Recalibration of Structure 1

We started with a base-case scenario where SCC inputs were based on the original Harvard CC estimates. The base-case output was largely consistent with what the Harvard CC projects, but due to structural differences between the Harvard CC and our model, parameters related to cancer incidence required substantial fitting to reach the target level of 2.5-3% lifetime risk of cancer. To achieve a good fit, an increase in progression probabilities from precancer was combined with lower regression rates from precancer, allowing the women to stay long enough in a precancer state to eventually progress to cancer.

5.5.3 Calibration of Structure 2

The second step of the calibration involved adjustments to ADC-related parameters. In short, the AIS parameters were adjusted for HPV-genotyping and overall prevalence, followed by similar adjustments to ADC parameters. For the ADC arm, AIS-related values were initially equal to CIN3 values for progression and regression between HPV-infection and precancer. We achieved the best fit when the progression probabilities from AIS to ADC were based on CIN2 to SCC values (figure 15).

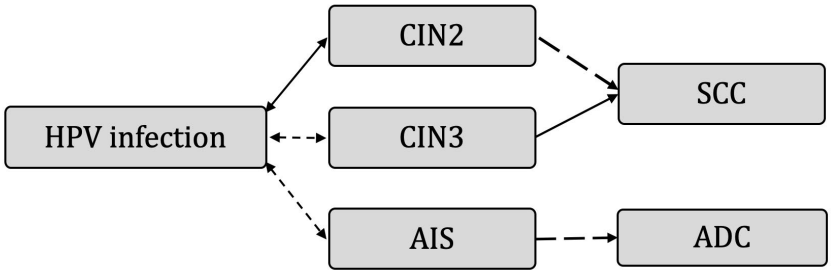

Figure 15. For calibration of AIS and ADC parameter sets, the best results were achieved when progression from AIS to ADC was based on the progression values from CIN2 to SCC (represented by the dotted lines), instead of a 25% ratio of CIN3 to SCC probabilities. HPV human papillomavirus, AIS adenocarcinoma in situ, CIN2 Cervical intraepithelial neoplasia grade 2, CIN3 Cervical intraepithelial neoplasia grade 3, SCC squamous cell carcinoma, ADC adenocarcinoma.

For progression to ADC, we explored the potential of using a value derived from the literature on progression risks from AGC to ADC[69]. The study reported and estimated total incidence rate of 138.6 ADC per 100 000 women within the first 0.5-3.5 years of having AGC. Using AGC as a proxy for AIS, this estimate was computed to a monthly progression probability and tested for a scenario. The results did not fit with our targets, hence we continued to calibrate through a trial-and-error approach until we achieved a parameter set with a fit within our targets.

5.5.4 MODEL PROJECTION OF HPV- AND LESION PREVALENCE

Both structures project the same prevalence of HPV infections. Infections peak at 50% for age 20 and decrease subsequently, with lesions peaking 5-7 years later close to 7% for Structure 1 and 9% for Structure 2 when AIS is included. A limitation with our model is that we didn't have data to validate lesion prevalence, but the results appear plausible in terms of the average time from infection to lesion[7].

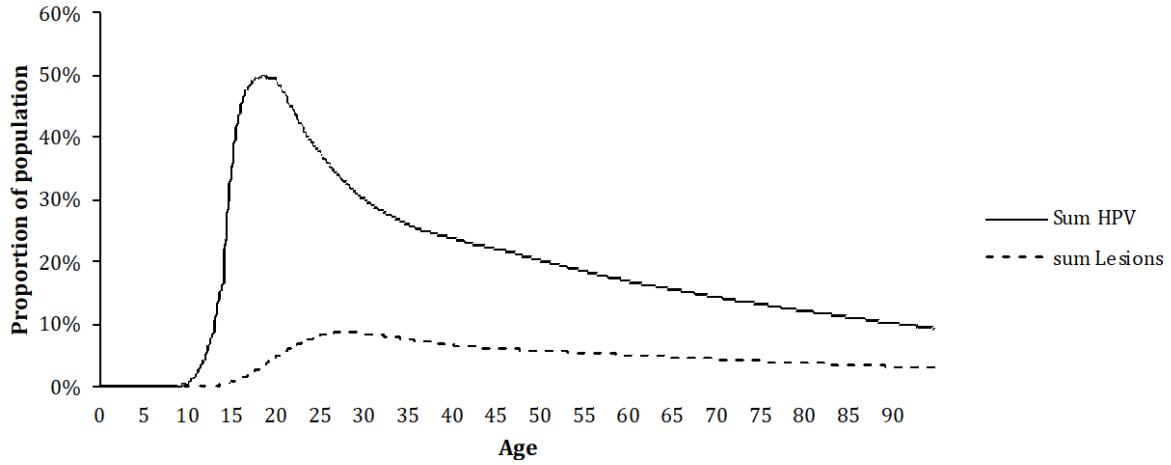

Figure 16: age-specific HPV prevalence (solid line) and lesion prevalence (dotted line) projected in the population over the lifetime horizon in Structure 2. HPV human papillomavirus.

5.5.5 MODEL FIT WITH EMPIRICAL DATA FROM NORWAY

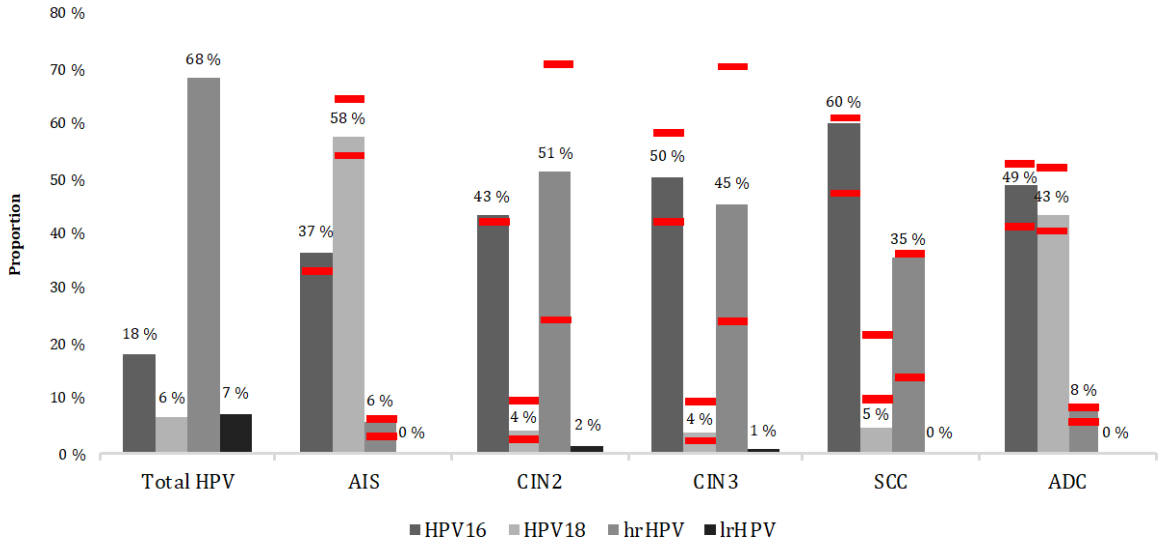

Figure 17. HPV type distribution in precancer and cervical cancer stratified by histology, with empirical bounds in red. The empirical bounds for Structure 1 (CIN2, CIN3 and SCC) are retrieved from Burger et al.[61] *while the empirical bounds for Structure 2 (AIS and ADC) were based on ±10% of the estimates yielded from the literature findings. HPV human papillomavirus, lrHPV low risk human papillomavirus, hrHPV high risk human papillomavirus, AIS adenocarcinoma in situ, CIN cervical intraepithelial lesions, ADC adenocarcinoma, SCC squamous cell carcinoma.*

The general distribution of HPV-genotype infections fit well to the empirical bounds (figure 17). The distributions for Structure 1 were not calibrated, as these have previously been fitted[61]. For AIS and ADC in Structure 2, the HPV-genotype distribution fits within all the target bounds. The total HPV-genotype prevalence's in the general population have a reasonable fit to the epidemiological data[45,61] (figure 16 & 17). When examining the age-specific prevalence, HPV-16/18 is underestimated for younger ages but calibrating the parameters to fit better with age-groups was not something we could not achieve within the time-frame.

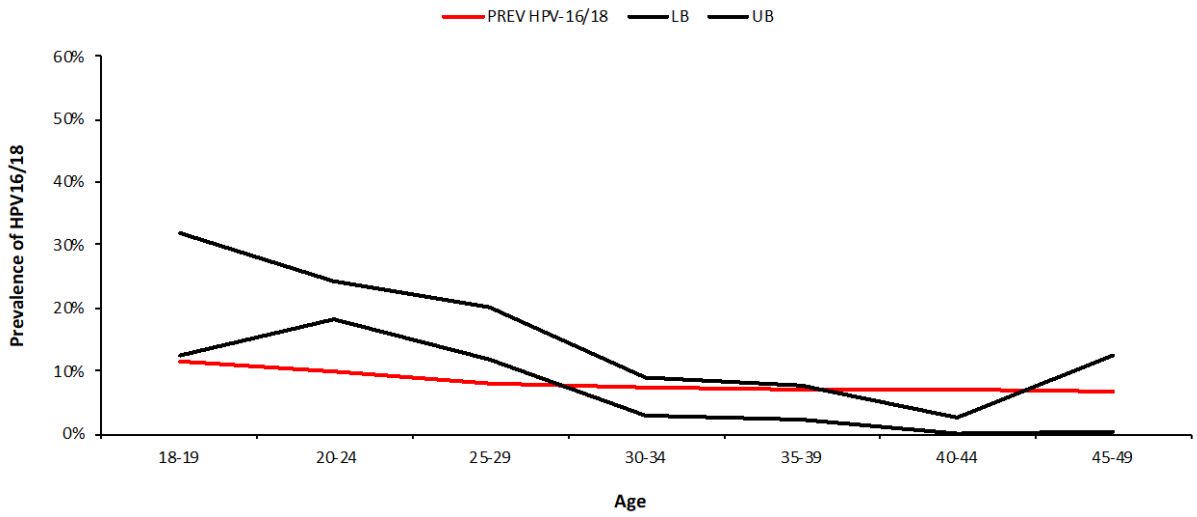

Figure 18. HPV16/18 prevalence is represented by the red line, while the lower- and upper bounds derived from epidemiological data[45] are represented by the black lines. HPV, human papillomavirus, LB lower bound, UB upper bound.

For validation of cancer cases, we obtained Norwegian registry data on the observed age-specific incidence of SCC and ADC in Norway between 1953-1969. Norway did not have any organized CC-screening during these years, and opportunistic screening was uncommon[70]. Therefore, the data from this pre-screening period is regarded as a suitable reference for what CC incidence is in a Norwegian setting without screening. Under the assumption of no screening, Structure 2 projects a lifetime cancer risk of 3%, with an SCC risk of 2.3% and ADC risk of 0.7%. The age-specific cervical cancer incidence for both histologic types are represented in Figures 19 and 20. The minimum and maximum annual incidence during 1953-1969 from the Cancer registry of Norway are represented for each cancer type.

For both cancers, the incidence is overestimated in younger age-groups compared to the historical data. The incidence rates are also higher for women over age 85 than what is observed. As it was challenging to adjust the age-distribution of cancer while maintaining the life-time risk and not affecting other parameters, it was decided to accept these discrepancies. Due to changes in risk factors over time such as sexual behavior[71], cancer incidence is assumed to be higher today than it was during the observed period before screening was implemented in the population. Historical data on ADC reported a very low incidence rate. A model assumption is that ADC comprises of 20-25% of the total cancer incidence in the population simulated. This is based on the proportion of 20% which is what has been reported in recent years[8], and when excluding other cancer histologies it increases to 25% (based on data from the Cancer Registry, obtained through personal communication). Therefore, we find it plausible that the projection of ADC in a non-screening setting today would be considerably higher than the historical rate.

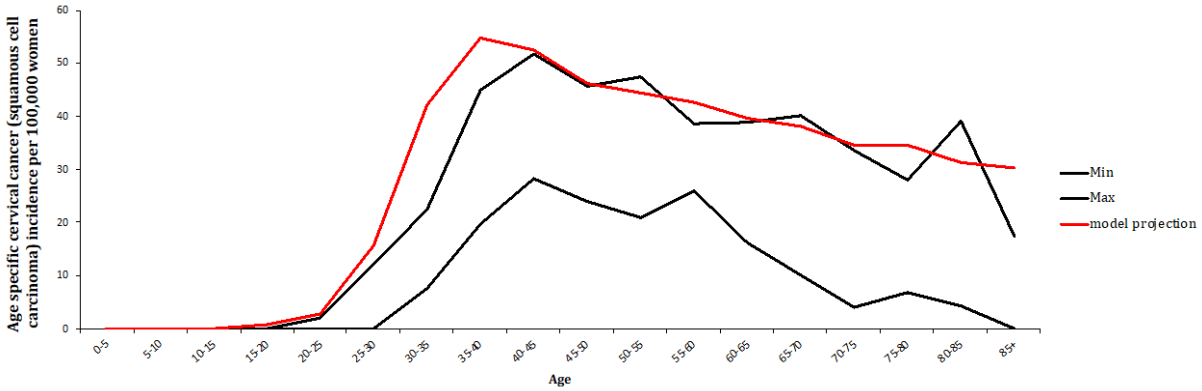

Figure 19. SCC incidence per 100 000 with historical maximum and minimum incidence bounds in black and model projection in red.

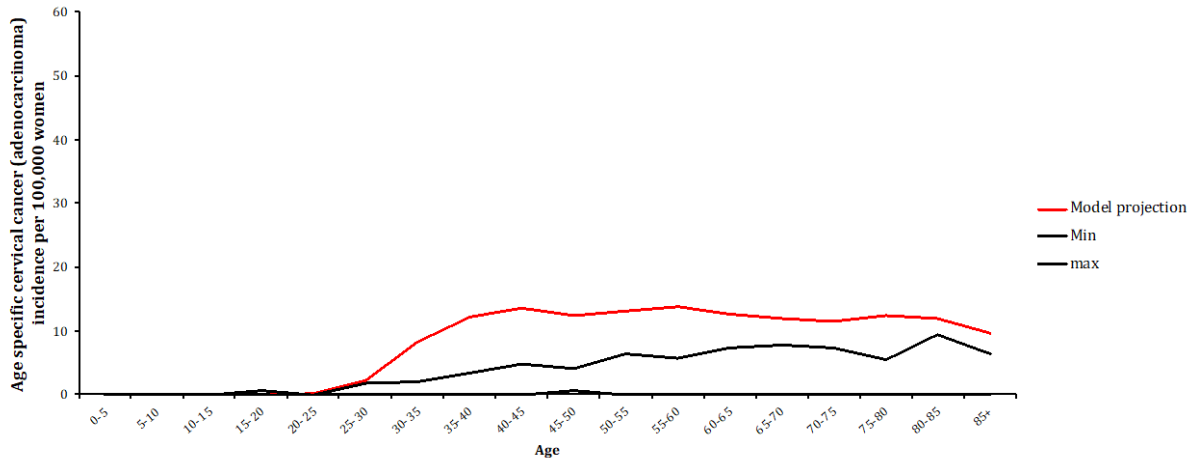

Figure 20. ADC incidence per 100 000 with historical maximum and minimum incidence bounds in black and model projection in red. The minimum bound is close to 0 for almost all age-groups.

Overall, we find that the model provides a reasonable fit with observed data.

5.6 COST-EFFECTIVENESS ANALYSIS

With two natural history models of HPV-induced CC in a Norwegian setting, we simulated two alternative screening strategies, primary HPV-based testing versus cytology-based testing and compared these strategies in terms of both their costs and consequences. The analysis was conducted under two scenarios, the primary scenario based on the Structure 1 (the un-extended natural history model) and the other based on the Structure 2 (the model extended for AIS and ADC). This will yield two ICERs that can be used to quantify the impact of including two histologically different cancer types in a comparative analysis of HPV-based testing versus cytology-based testing.

In Norway and other countries, CEA is the most commonly-used and recommended approach to economic evaluation in healthcare[72]. A CEA yields an incremental cost per unit of effect, which in this case will be QALYs.

In general, the best practice is to conduct a probabilistic sensitivity analysis, exploring the overall uncertainty in the ICER from model parameters. However, due to computational limitations, a deterministic sensitivity analysis will be conducted to explore the sensitivity of the ICER to changes in specific parameters. The strength to this approach is that we can observe and measure the direct impact on the ICER from one adjustment in the scenario.

5.6.1 STUDY POPULATION

The study population comprises of Norwegian women who have not been HPV-vaccinated and therefore still rely on a well-designed screening program to prevent CC.

5.6.2 ALTERNATIVE SCREENING STRATEGIES

The intervention is CC-screening using primary HPV DNA testing with a cytology triage. The screening algorithm is reflects the new screening guidelines being implemented in Norway for women over age 34[73]; however, simplifications have been made regarding follow-up protocols. We assumed a screening frequency of every 5 years for screen-eligible women between ages 25 and 69 years. Screening coverage for primary and secondary screening can be varied in the model. When a woman tests positive for HPV, a reflex cytology is administered to check for lesion. See figure underneath for more details of the screening protocols.

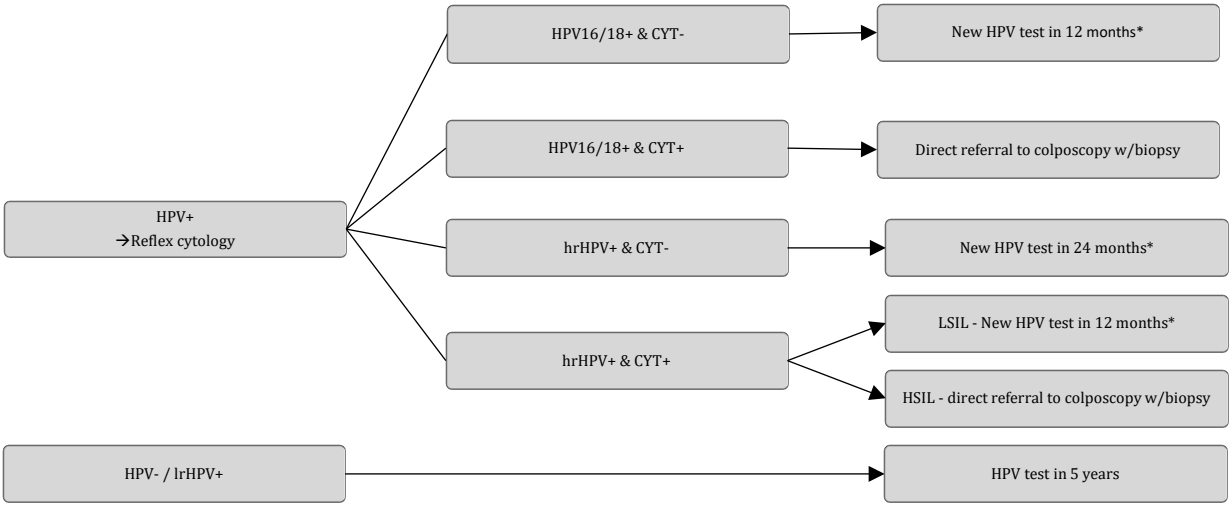

*Figure 21. Flowchart for the HPV-based screening strategy with protocols for the different risk categories. Women who test positive for lrHPV are assumed to not have an increased risk for developing CC, therefore they repeat testing at the normal 5-year interval with the women who have a negative HPV-test. *For all follow-up HPV-tests positive for HPV16/18/hr the women are referred to colposcopy w/biopsy. If negative for HPV16/18/hr the women return to the normal screening algorithm. HPV human papillomavirus, lrHPV low risk human papillomavirus, hr HPV high risk human papillomavirus, LSIL low grade intraepithelial lesions, HSIL high grade intraepithelial lesions, CYT cytology.*

For the analysis, we assume a 100% sensitivity and specificity of HPV-based testing for an HPV infection, consistent with other studies[24,26,45].

The comparator is the current screening strategy with BD SurePath™ liquid-based Pap test as primary screening strategy with HPV triage. Screening frequency is every 3 years. Women who receive a positive cytology are further categorized into HSIL or LSIL, where LSIL is followed up with a reflex HPV-test for triage. HSIL is followed up with a direct referral to colposcopy w/biopsy.

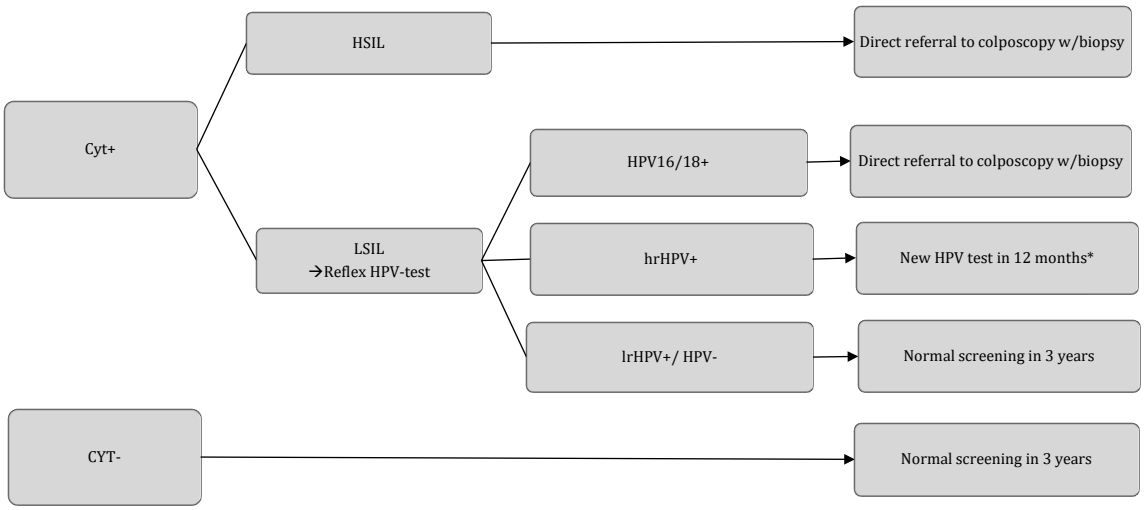

Figure 22. The current screening strategy protocols in Norway for screen-eligible women under age 34. The protocols for follow-up testing are the same as described for the primary HPV-based testing. HPV human papillomavirus, lrHPV low risk human papillomavirus, hr HPV high risk human papillomavirus, LSIL low grade intraepithelial lesions, HSIL high grade intraepithelial lesions, CYT cytology.

For the base case scenario, we assume a cytological sensitivity for AIS, ADC and CIN2+ of 44.5%, 63.5% and 73% respectively. The specificity of cytology was 91% for the analysis, based on what has been reported recently[74]. The values for AIS and ADC are based on a study conducted in Japan[75] on the primary cytological sensitivity to AIS and AIS in combination with ADC. The study did not consider sensitivity to invasive ADC, but we found it reasonable to assume a 10% lower sensitivity rate to ADC compared to SCC for our scenario. The estimate for CIN2+ is retrieved from a comprehensive systematic review on different detection methods for high grade lesions and cancer[74].

5.6.3 HORIZON

Benefits of cancer screening programs may occur long after the intervention has taken place, therefore it is appropriate to have a lifetime horizon in the analysis to capture all gains in health. The women enter the model at birth and are followed until age 95 years.

5.6.4 PERSPECTIVE

The analysis has been conducted from a societal perspective. In addition to healthcare costs, time- and travel costs associated with GP-visits for screening, screening protocols, precancer- and cancer treatment are included. The screening strategies differ in screening frequencies, and any differences in the number of cancer cases avoided and false positive tests resulting in unnecessary protocols will have a considerable impact on productivity loss. Thus, these

differences must be considered along with the differences in direct healthcare costs when doing an assessment of the screening strategies.

5.6.5 OUTCOMES

QALYs are the primary measure of effect, and are discounted at annual rate of 4% per year in alignment with guidelines for economic evaluations in Norway[76]. The utilities are retrieved from a Danish study on the age-specific HRQoL for the general female population[77]. For women with CC, the HRQoL weights are based on multiplicative dis-utilities that depend on cancer stage (appendix figure 11). The utilities are elicited through the time-trade-off method. For the analysis it is assumed that women who have survived in a cancer state for more than 5 years have the same HRQoL as the healthy population, an assumption also supported by research[78]. Due to technical constraints, the total dis-utilities for each cancer case will be accumulated to the cycle the woman enters the detected cancer state.

5.6.6 COSTS

The cost estimates are based on previously published cost-effectiveness analyses evaluating CC prevention policies[23,45,79]. All costs are based on a combination of Norwegian fee schedules and expert opinion. The medical cost categories are divided into costs associated with screening consultations, analyzing test samples at the pathology laboratory and treatment of high-grade precancer and cancer. These cost estimates are valued in 2014 Norwegian kroner (NOK) and converted to US Dollars, which at this time was 1$ = 6.30 NOK[61]. We adjusted the costs for inflation from 2014- to 2019 values with an increase 11.26% (estimate retrieved from Statistics Norway). Costs were discounted at 4% per year.

Indirect costs are based on the patient time associated with GP-visits for screening and colposcopy examinations, including traveling time to the GP-office, waiting time, the time it takes to receive care and round-trip transportation costs. For treatment of high-grade precancer the indirect costs are based on the productivity loss associated with recovering and follow-up visits. For treatment of cancer, the costs include sick leave for a given period depending on the treatment of cancer stage.

See appendix for more details on the cost categories and estimates. Specified descriptions of how each cost item is calculated is available in the Harvard CC appendix[61].

5.6.7 DETERMINISTIC SENSITIVITY ANALYSIS

For the base-case analysis, results were examined under discounting at 4% per year, outcomes measured in QALYs, and the assumption of different cytologic sensitivity to detect AIS (ie. 44.6%), ADC (ie. 63.5%) and CIN2+ (ie 73%).

Due to the complex features of the microsimulation model, it is not feasible to conduct a full PSA even though this would have been optimal. However, a deterministic sensitivity analysis was conducted to explore the potential changes in outcome with variations of key parameters.

For the deterministic sensitivity analysis we varied these assumptions and parameters, conducting CEAs for three additional scenarios:

1. Discounting outcomes and costs at 0%
2. Equal cytology sensitivity to detect both histologies (sensitivity = 73%)
3. Outcome measured in LYs

6 RESULTS

Results from the base-case analysis are presented followed by results from the sensitivity analysis. Due to negative ICERs for cytology-based testing versus HPV-based testing, the results will be focused on the explicit impact of structural assumptions on incremental costs and outcomes.

6.1 COST-EFFECTIVENESS RESULTS FROM THE BASE-CASE ANALYSIS

Primary cytology-based screening was dominated under both structures. For Structure 1, primary HPV testing was associated with 23.264 QALYs and an average cost of NOK 7,429 per woman (ICER = NOK 175,202 compared to no screening), while cytology was associated with 23.262 QALYs and an average cost of NOK 8,640, and was thus dominated compared to HPV testing (Table 2). For Structure 2, primary HPV testing had a reduced average cost of NOK 7,376 and increased QALYs of 23.265 (ICER = NOK 127,435 compared to no screening), while cytology had an increase in costs and reduced QALYs, with a cost of NOK 8,932 and 23.261 QALYs. No screening also had an increase in costs and reduced QALYs under structure 2.

	Structure 1 (SCC only)					Structure 2 (SCC + ADC)				
	Total Lifetime Costs per Woman (discounted)	Total QALYs (discounted)	Incremental Costs	Incremental QALYs	ICER	Total Lifetime Costs per Woman (discounted)	Total QALYs (discounted)	Incremental Costs	Incremental QALYs	ICER
Natural History	kr 2 438	23.235	--	--	--	kr 2 979	23.231	--	--	--
Primary HPV	kr 7 429	23.264	kr 4 991	0.028	kr 175 202	kr 7 376	23.265	kr 4 397	0.035	kr 127 435
Primary Cytology	kr 8 640	23.262	kr 1 211	-0.001	Dominated	kr 8 932	23.261	kr 1 556	-0.005	Dominated

Table 2. Base-case cost-effectiveness analysis results conducted for HPV-based testing vs. cytology-based testing under two different model structures, with "no intervention" presented for reference. Primary HPV-testing is compared to no-screening, and primary cytology-based testing is compared to HPV-testing. Structure 1 accounts for squamous cell carcinoma in the population whereas Structure 2 is extended to also account for adenocarcinoma. The cytologic sensitivity to CIN2+, AIS and ADC was 73%, 44.6% and 63.5% respectively. SCC squamous cell carcinoma, ADC adenocarcinoma, AIS adenocarcinoma in situ, LY life years, QALY quality-adjusted life year, ICER incremental cost-effectiveness ratio, HPV human papillomavirus, ADC adenocarcinoma, SCC squamous cell carcinoma.

		No. Of cancer cases per 100 000		
No intervention	Natural history SCC	2466		
	Natural history SCC & ADC	2979		
	Primary screening method		**Absolute reduction in cancer (%)**	**Difference in cancer reduction**
Base Case structure 1	HPV-based, 5-year intervals	271	89.00 %	
	Cytology-based, 3-year intervals	311	87.37 %	**1.63 %**
Base Case structre 2	HPV-based, 5-year intervals	335	88.77 %	
	Cytology-based, 3-year intervals	395	86.75 %	**2.02 %**

Table 3. The absolute cancer reduction is greater for HPV-based testing among both models, but the incremental cancer reduction increases with 24% under Structure 2, from 1.63% to 2.02%. HPV human papillomavirus, ADC adenocarcinoma, SCC squamous cell carcinoma.

Both screening strategies have a substantial impact on the cancer reduction; for example, in Structure 2, HPV testing was projected to reduce cancer incidence by 89% while cytology was projected to reduce cancer incidence by 87.37%. The difference in cancer reduction varied between the two structures, which was 88.77% for Structure 1 and 86.75% for Structure 2 (Table 3). The results show a 24% increase in the incremental cancer reduction under Structure 2.

A noteworthy observation is that primary HPV-based testing was the only strategy to less costly and more effective when incorporating ADC into the structure. For example, the incremental QALY gain of HPV testing compared with no screening was 21% higher in Structure 2 than under Structure 1 (table 4.) while incremental costs were reduced with 12% (table 5.) . In contrast, no intervention and cytology-based screening become more costly and less effective under Structure 2. The ICER for HPV-based testing was reduced with 27.3% meaning that the structural differences are in favor of HPV-based testing.

Incremental QALYs			
	Structure 1	**Structure 2**	**Ratio (%)**
No intervention	--	--	--
Primary HPV	0.0285	0.0345	121 %
Primary Cytology	-0.0014	-0.0047	337 %

Table 4. The magnitude of difference in the incremental QALYs for cytology-based screening compared to HPV-based screening increases more than three-fold under Structure 2. HPV human papillomavirus, QALYs quality adjusted life-years. Primary HPV-testing is compared to no-screening, and primary cytology-testing is compared to HPV-testing. QALY quality-adjusted life year, ICER incremental cost-effectiveness ratio, HPV human papillomavirus.

Incremental Costs			
	Structure 1	**Structure 2**	**Ratio (%)**
No intervention	--	--	--
Primary HPV	kr 4 991	kr 4 397	88 %
Primary Cytology	kr 1 211	kr 1 556	128 %

Table 5. The magnitude of incremental difference in costs for cytology-based screening compared to HPV-based screening increases under structure two with 28%. Primary HPV-testing is compared to no-screening, and primary cytology-testing is compared to HPV-testing. QALY quality-adjusted life year, ICER incremental cost-effectiveness ratio, HPV human papillomavirus.

Overall, the main findings from the base-case analysis show that the costs and effects change under Structure 2, having a potentially big impact on the ICER. The ICERs for the strategies changed considerably under structure 2, where HPV-based testing became more cost-effective with a reduction in the ICER of 27.3% and cytology became less effective and more costly, thus being more strongly dominated.

6.2 SENSITIVITY ANALYSIS

We conducted CEAs for three additional scenarios where we aimed to examine the impact of structural differences under (1) discounting at 0% instead of 4% per year, (2) the assumption of cytology testing being equally sensitive to all histologies (ie. 73%) and (3) measuring outcomes in LYs instead of QALYs.

Overall, the results from the sensitivity analysis were similar to the base-case scenario, ie. that cytology was dominated under both structures and all scenarios, while HPV-based testing became was almost always more cost-effective compared to no screening under Structure 2. However, cytology test sensitivity had the biggest impact on the incremental effects for cytology compared to HPV testing, reducing the incremental QALYs with -14% under Structure 2. Compared to the observed increase in incremental QALYs with 337% in the base-case analysis under Structure 2, we have identified that an extended model is highly sensitivity to the cytology test sensitivity chosen. The incremental costs under this scenario was were still slightly increased under Structure 2, but only with 2% instead of 28% (table 10 & 11).

6.2.1 DISCOUNTING

In a 0%-discounting scenario, primary cytology-based screening was dominated under both structures. For Structure 1, primary HPV testing was associated with 74.773 QALYs and an average cost of NOK 37, 136 per woman (ICER = NOK 65,099 compared to no screening), while cytology was associated with 74.762 QALYs and an average cost of NOK45,064, and was therefore dominated again compared to HPV testing (Table 6). For Structure 2, primary HPV testing had a reduced average cost of NOK 36,944 and increased QALYs of 74.781 (ICER = NOK 44,411 compared to no screening), while cytology had an increase in costs and reduced QALYs, with a cost of NOK 46,546 and 74.750 QALYs. The no-screening strategy again showed an increase in costs and reduced QALYs under structure 2. An observed difference was that discounting had the biggest impact on costs for HPV-based testing but impacted the QALYs mainly under cytology-based testing (table 7 & 8).

	Structure 1 (SCC only)					Structure 2 (SCC + ADC)				
	Total Lifetime Costs per Woman (undiscounted)	Total QALYs (undiscounted)	Incremental Costs	Incremental QALYs	ICER	Total Lifetime Costs per Woman (undiscounted)	Total QALYs (undiscounted)	Incremental Costs	Incremental QALYs	ICER
Natural History	kr 17 157	74.466				kr 20 575	74.412			
Primary HPV	kr 37 136	74.773	kr 19 980	0.307	kr 65 099	kr 36 944	74.781	kr 16 368	0.369	kr 44 411
Primary Cytology	kr 45 064	74.762	kr 7 928	-0.011	Dominated	kr 46 546	74.750	kr 9 602	-0.031	Dominated

Table 6. Undiscounted values for Structure 1 and 2. Primary HPV-testing is compared to no-screening, and primary cytology-testing is compared to HPV-testing. QALY quality-adjusted life year, ICER incremental cost-effectiveness ratio, HPV human papillomavirus, ADC adenocarcinoma, SCC squamous cell carcinoma.

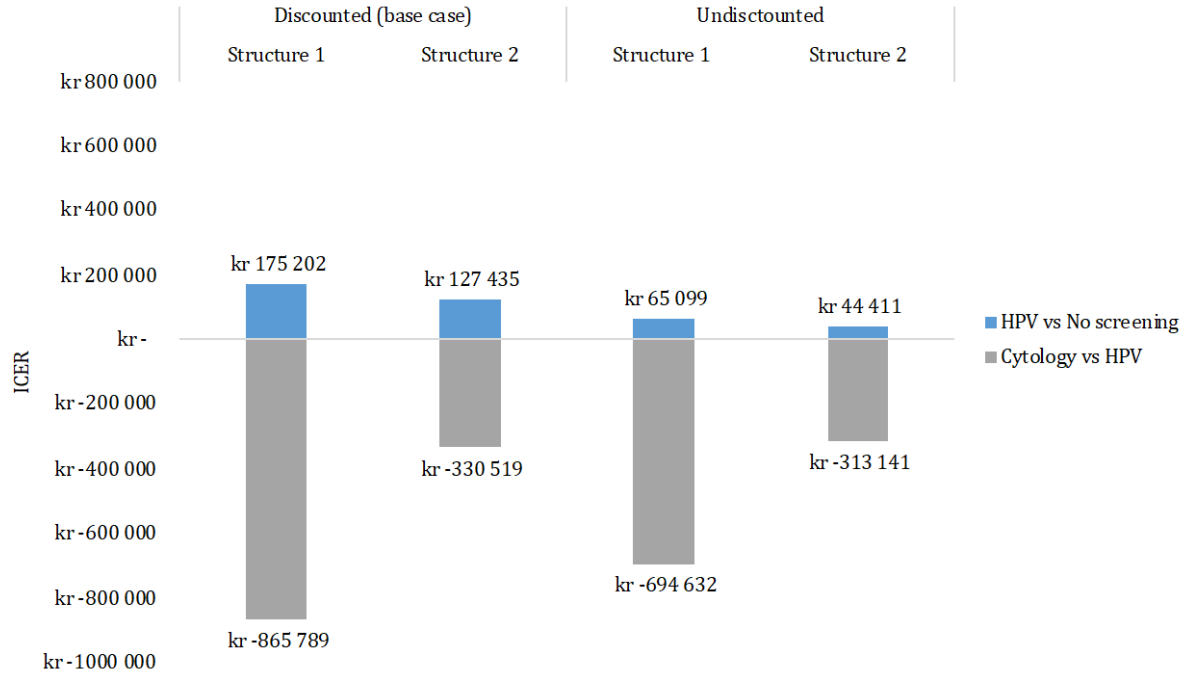

Figure 23. Visual presentation of relative impacts from discounting, for the base case (both structures) and the undiscounted results (both structures). The primary HPV-strategy is more sensitive to discounting than primary cytology, with ICERs being reduced to a greater extent under the different structures. HPV human papillomavirus, ICER incremental cost-effectiveness analyses.

Incremental Costs (undiscounted)				
	Structure 1	Structure 2	Difference (%)	Base-case
No intervention	--	--	--	--
Primary HPV	kr 19 980	kr 16 368	82 %	**88 %**
Primary Cytology	kr 7 928	kr 9 602	121 %	**128 %**

Table 7. Table presenting percentage differences in costs when discounted at 0% with reference to the base-case where costs have been discounted at 4% per year. Primary HPV-testing is compared to no-screening, and primary cytology-testing is compared to HPV-testing. HPV human papillomavirus.

	Incremental QALYs (undiscounted)			
	Structure 1	**Structure 2**	**Difference (%)**	**Base-case**
No intervention	--	--	--	--
Primary HPV	0.307	0.369	120 %	**121 %**
Primary Cytology	- 0.011	- 0.031	269 %	**337 %**

Table 8. Table presenting percentage differences in QALYs when discounted at 0% with reference to the base-case where QALYs have been discounted at 4% per year. Primary HPV-testing is compared to no-screening, and primary cytology-testing is compared to HPV-testing. HPV human papillomavirus, QALYs quality adjusted life-years.

6.2.2 CYTOLOGY SENSITIVITY

As we expected, the cytology test-sensitivity for histologies had the biggest impact on cytology-based screening, primarily for QALYs, with an increase from 23.262 QALYs to 23.264 under Structure 2 (table 11). This was the only scenario where Structure 2 had a favorable impact on cytology screening as well as HPV-based screening (table 9). This was also the only scenario where HPV-based screening became more costly under Structure 2, even though the ICER was overall improved due to an increase in QALYs (ICER = 139, 404 compared to no screening under Structure 2). As the HPV strategy incorporates cytology triage, the improved cytology test-sensitivity would increase the number of colposcopy referrals, in turn increasing the costs.

Structure 1 (SCC only)					Structure 2 (SCC + ADC)				
Total Lifetime Costs per Woman (discounted)	**Total QALYs (discounted)**	**Incremental Costs**	**Incremental QALYs**	**ICER**	**Total Lifetime Costs per Woman (discounted)**	**Total QALYs (discounted)**	**Incremental Costs**	**Incremental QALYs**	**ICER**
kr 2 438	23.235	--	--	--	kr 2 979	23.231	--	--	--
kr 7 429	23.264	kr 4 991	0.028	**kr 175 202**	kr 7 740	23.265	kr 4 761	0.034	**kr 139 404**
kr 8 640	23.262	kr 1 211	-0.001	**Dominated**	kr 8 972	23.264	kr 1 232	-0.001	**Dominated**

Table 9. Results from varying the parameter for cytological sensitivity to adenocarcinoma in situ (AIS) and adenocarcinoma (ADC) to equal the cytological sensitivity to CIN2+ of 73%. Primary HPV-testing is compared to no-screening, and primary cytology-testing is compared to HPV-testing. QALY quality-adjusted life year, ICER incremental cost-effectiveness ratio, HPV human papillomavirus, ADC adenocarcinoma, SCC squamous cell carcinoma.

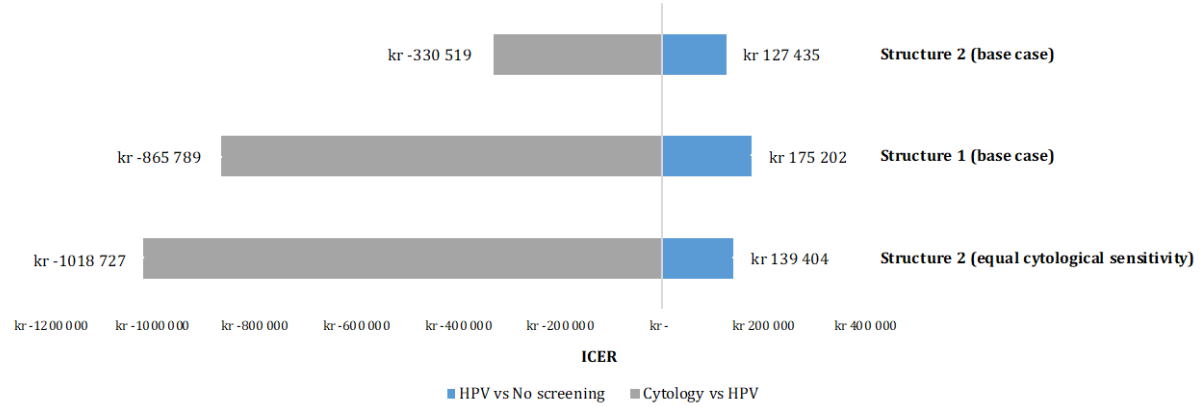

Figure 24. *Visual presentation of sensitivity to variations in cytological sensitivity. For the base-case scenario the cytological sensitivity for adenocarcinoma in situ (AIS), adenocarcinoma (ADC) and cervical intraepithelial neoplasia grade 2 or worse (CIN2+) are 44.6%, 63.5% and 73% respectively. For the sensitivity analysis the cytology is assumed to be equally sensitive 73% for all histologies. For both cytological values, HPV-based testing remains the most effective strategy, even more so under Structure 2. HPV human papillomavirus, ICER incremental cost-effectiveness analyses.*

Incremental Costs - Equal cytological sensitivity				
	Structure 1	**Structure 2**	**Ratio (%)**	**Base-case**
No intervention	--	--	--	--
Primary HPV	kr 4 991	kr 4 761	95 %	**88 %**
Primary Cytology	kr 1 211	kr 1 232	102 %	**128 %**

Table 10. Results for difference in increments for costs among the strategies, where primary HPV-testing is compared to no-screening, and primary cytology-testing is compared to HPV-testing under the assumption that cytology is equally sensitive to all histologies. HPV human papillomavirus.

Incremental QALYs- Equal cytological sensitivity				
	Structure 1	**Structure 2**	**Ratio (%)**	**Base-case**
No intervention	--	--	--	--
Primary HPV	0.028	0.034	120 %	**121 %**
Primary Cytology	- 0.001	- 0.001	86 %	**337 %**

Table 11. Results for difference in increments for QALYs among the strategies, where primary HPV-testing is compared to no-screening, and primary cytology-testing is compared to HPV-testing under the assumption that cytology is equally sensitive to all histologies. HPV human papillomavirus, QALYs quality adjusted life years.

6.2.3 LYS VERSUS QALYS

Changing the measurement of effects from QALYs to LYs had little overall effect on the results but had a minor impact in favor of HPV-based testing under Structure 2, reducing the ICER from NOK 127,435 to NOK126,955 (figure 25). Under Structure 1, HPV-based testing was however more cost-effective in the base-case scenario when using QALYs, but the difference is marginal with an increase from NOK175,202 to NOK175, 327. The incremental effects for cytology compared to HPV-testing increased from 337% to 357% when using LYs (Table 13), allowing HPV-based testing to dominate cytology even more than under the base-case scenario.

	Structure 1 (SCC only)					Structure 2 (SCC + ADC)				
	Total Lifetime Costs per Woman (discounted)	Total LYs (discounted)	Incremental Costs	Incremental LYs	ICER	Total Lifetime Costs per Woman (discounted)	Total LYs (discounted)	Incremental Costs	Incremental LYs	ICER
No intervention	kr 2 438	24.397	--	--	--	kr 2 979	24.392	--	--	--
Primary HPV	kr 7 429	24.425	kr 4 991	0.028	kr 175 327	kr 7 376	24.427	kr 4 397	0.035	kr 126 955
Primary Cytology	kr 8 640	24.424	kr 1 211	-0.001	Dominated	kr 8 932	24.422	kr 1 556	-0.005	Dominated

Table 12. Results for difference in increments when benefits are measured in life years (LYs). Primary HPV-testing is compared to no-screening, and primary cytology-testing is compared to HPV-testing. SCC squamous cell carcinoma, ADC adenocarcinoma, LYs life years, ICER incremental cost-effectiveness ratio, HPV human papillomavirus, ADC adenocarcinoma, SCC squamous cell carcinoma.

Figure 25. The impact on the ICERs from changing the outcome measurement from quality adjusted life years (QALYs) to life years (LYs). Primary cytology-based strategy was more sensitive to the change in outcome measurement than primary HPV-based testing. Overall, the results show no change in in the decision of strategy. HPV human papillomavirus, ICER incremental cost-effectiveness analyses.

	Incremental LYs			
	Structure 1	**Structure 2**	**Ratio (%)**	**Base-case**
No intervention	--	--	--	--
Primary HPV	0.028	0.035	122 %	**121 %**
Primary Cytology	- 0.001	- 0.005	357 %	**337 %**

Table 13. Results for difference in increments for LYs among the strategies, where primary HPV-testing is compared to no-screening, and primary cytology-testing is compared to HPV-testing. The base-case is measured in QALYs. HPV human papillomavirus, QALYs quality adjusted life years.

When measuring outcome in LYs for the analysis, the magnitude of difference in the increments are increased further from 337% to 357% for cytology-based testing versus HPV-based testing.

7 DISCUSSION

In thus study, we aimed to quantify the impact on the cost-effectiveness of CC screening strategies of including ADC in a decision-analytic model. Using data from existing literature, we were able to develop two natural history models of CC; Structure 1 that accounts for SCC and Structure 2 that is extended to also account for ADC. Primary HPV-based testing is already implemented in the Norwegian screening program, and recent research has proven HPV-testing to be better at detecting ADC than cytology. We therefore designed two screening strategies, primary cytology-based and primary HPV-based, to evaluate the impact of including ADC into the decision models to quantify what the effect is on the ICER in a CEA of the two strategies.

7.1 IMPACT OF STRUCTURAL ASSUMPTIONS

Results from the base-case analysis indicate that extending the natural history model for HPV-induced CC to include ADC in addition to SCC has an impact on the ICER in favor of HPV-based screening compared to cytology-based screening. With lower life-time costs and more QALYs yielded under Structure 2, the ICER for HPV-based screening compared to no screening was improved with 27.3%. Cytology-based screening became more costly and yielded fewer QALYs, shifting the ICER with 61.8% under Structure 2, which is a considerable impact from extending the model.

In the sensitivity analysis Structure 2 had an impact in favor of HPV-based testing under the scenarios for no discounting and outcomes measured in LYs. Under the assumption that cytology is **equally** sensitive to all histological types, HPV-based testing remains the cost-effective strategy but to a reduced extent under Structure 2. The incremental QALYs yielded decreased under structure two with 20%, but the incremental costs remained almost the same (an increase of 2%).

7.2 IMPLICATIONS FOR SCREENING POLICY

Prevention programs are imperative to control CC and it is essential to continue informing policy-makers on the latest evidence of what the optimal strategies are for our current and future generations.

Under all scenarios, HPV-based testing remained more efficient at preventing cancer among unvaccinated women than cytology, in addition to being cost-saving. Other model-based studies have also reported that primary cytology-based testing is dominated by primary HPV-based testing[45]. There are advantages and disadvantages of both testing methods. HPV-based testing is reported to be better at distinguishing the most progressive lesions from others compared to cytology, providing greater protection against CC-incidence and mortality.[74] However, HPV-testing yields a higher rate of false-positive tests, which are defined as positive screening tests which are not subsequently confirmed with high-grade CIN[80]. This means that more people will be followed up with unnecessary colposcopy referrals, which may inflict physical and psychological pain on the patient who has to undergo this. This is an intangible cost we have not been able to capture in the analysis. Additionally, a lower specificity results in extra costs for the health care system due to unnecessary examinations and surgery.

Results from our analysis show that the benefits of HPV-based testing outweigh the costs of extra colposcopy referrals, and under Structure 2 this is particularly enhanced. This supports the use of primary HPV-based testing and it should be considered for the future if HPV-based testing is the most beneficial for all screen-eligible ages in Norway, and not just for women above 34 years as today's screening guidelines suggest.

7.3 STRENGTHS AND WEAKNESSES

To our knowledge, this is the first analysis attempting to explore the structural uncertainty among model-based studies within CC-prevention for not stratifying between the two histological cancer types. With a deterministic approach we have been able to report results under two sets of structural assumptions, allowing us to assess and quantify the potential impact on costs and outcomes, and what they mean for decision-making. The method is aligned with recommendations from the ISPOR-SMDM for conducting structural uncertainty analysis[58]. We have searched the literature for evidence to support model development. In general, ADC and AIS receive little attention in cervical cancer research, so it was challenging to develop a model supported by findings in literature, research and epidemiologic data. Thus, we were cautious to make reasonable assumptions where needed. The natural history model has been calibrated and validated against epidemiological data. The calibration approach taken could have been more refined, using a likelihood-based approach as taken with the Harvard CC[61], but there is no consensus on what the best practice is and time and resources were scarce.[81] A weakness with our natural history model is that it overestimates cancer incidence among younger women. There is also uncertainty in the lesion prevalence, as we were not able to obtain pertinent information to inform or validate these parameters explicitly.

Additional scenarios we would have wanted to incorporate into the analysis are what the impact on costs and effects had been if ADC had a more rapid progression and higher mortality rate, as reported amongst research[6]. Treatment of AIS and ADC has also been reported to be less effective than for CIN[82]. We hypothesize that parameterizing these differences in a scenario would enhance the benefit of HPV-based screening further. However, there was no evidence suggesting that Norway faces a lower survival rate among ADC-patients (see Appendix for data from the Cancer Registry), so it was opted to not parameterize this. Nonetheless, for countries that report such challenges it would be appropriate to account for this in an analysis related to CC-prevention differentiating between histological types[6].

We attempted to variate the screening coverage as an additional sensitivity analysis scenario, adjusting the primary screening compliance down to70% and 90% for follow-up procedures aligned with what has been observed among Norwegian women's screening behavior.[83] Under Structure 1, the decision remained unchanged from the base-case, where cytology-based testing was dominated by HPV-based testing. Unfortunately, time was not sufficient to run these scenarios under Structure 2, therefore these were excluded from the analysis and are not presented. We hypothesize that Structure 2 would increase the magnitude of dominance corresponding to what the base-case demonstrated, but no conclusion can be drawn without model-based evidence to support this statement. Screening effectiveness highly depends on the

coverage of the female population; therefore, it is a limitation that we were not able to achieve complete results for this scenario.

The screening algorithms do not replicate the current screening strategy in Norway, which operates with primary cytology-based testing for women until age 34 and switches to primary HPV-based testing for women over age 34. The strategies are instead simplified by operating with one primary screening method over the whole screen-eligible age. These are consistent with the new national screening strategies for HPV- and cytology-based testing, incorporating triage of screen-positive women with management protocols[12,84]. The distribution of cancer cases remains proportionately similar to what is observed today with 60 ADC cases and 233 SCC cases diagnosed in 2017, ADC constituting of 20.5% excluding other forms of CC cancer (based on data acquired from the Cancer Registry). ADC constitutes of 17-27% of the total cancer cases across all the screening scenarios, depending on the efficiency of the screening strategy. However, the total number of cancers projected under all our scenarios are considerably lower than what is observed in Norway, mainly attributed to our assumption of perfect screening compliance. The lifetime cancer risk was 0.27-0.39% while the reported lifetime cancer risk in Norway is 1%[85]. Also, under the scenario for reduced coverage the life-time cancer risk was 0.5 for HPV-based screening and 0.52% for cytology-based screening (Appendix diagram 16). Another important reason for our low cancer incidence is that we simulated screening under the assumption that colposcopy, biopsy and treatment of precancer was 100% accurate and effective, which is not a true representation of reality[7,86]. In our model, we also assumed that all high-grade lesions and cancer had active HPV-DNA. Combined with a 100% HPV-test sensitivity to HPV-DNA, this intensifies screening effectiveness. Not all CC have present HPV-DNA, which can undermine the effectiveness of HPV-based testing. This is reported to be more common among ADC specimens[87], which is also adds uncertainty to the analysis results.

It is challenging to characterize the diagnostic accuracy of AIS and ADC with cytology. For our analysis we chose relatively extreme values supported by recent research to maximize the full potential of HPV-based testing for preventing AIS and ADC. For comparison we simulated a scenario with the assumption of cytology being equally sensitive to AIS and ADC. This is aligned with what is recommended for conducting a deterministic sensitivity analysis[59]. There is a lot of uncertainty in the estimates for cytological sensitivity to AIS and ADC, because studies conducted on this particular issue shows that the problem may lie in several steps of the procedure for diagnosing AIS. First, there is the assumption that the cytology is not sufficiently designed to collect abnormal glandular lesions in the cervix, given that glandular cells are situated deeper than the epithelial cells where squamous lesions are found[88]. Second, some

research suggest that atypical glandular cells actually may be collected as efficiently as the squamous counterpart, but the problem entity lies in the interpretation of the cells. Abnormal glandular cells are harder to interpret in comparison to CIN due to a lower level of visual differentiation, thus being overlooked[89]. A final concern is that glandular abnormalities often coexist with CIN and may be misdiagnosed as HSIL instead of AIS, meaning that women receive follow-up but under the wrong diagnosis[90]. Hence, our attribution of undetected AIS and ADC to poor test sensitivity alone is a clear limitation.

Our analysis is aimed at fitting the present setting of the female population. The model is a static in the sense that HPV-prevalence only depends on age and not sexual activity, immunity or vaccination coverage in the population. This would require more data and advanced modelling techniques, which was not feasible within the time-frame given. HPV-genotype prevalence changes over time, and combined with increasing vaccination coverage, HPV-genotype prevalence's are expected to shift significantly[91]. This entails that the analysis may lack predictive validity of what the optimal screening strategy is in a future setting.

Another future prospect to consider is that lesion prevalence's are evolving and seem to be increasing among Norwegian, unvaccinated women. Particularly AIS incidence has had a steep increase during the last 25-years, something researchers only in part can explain by changes in screening tests and the improved histological verification of cervical precancerous lesions[92]. Therefore, the cohort effects in our analysis may underestimate the future prevalence of AIS and risk of developing ADC. This development underlines the need to consider AIS- and ADC in CC-prevention studies for future policymaking.

Other noteworthy limitations are that we only accounted for ADC and SCC, even though 5-7% of cervical cancer cases comprise of other forms such as adenosquamous and small cell carcinoma. Hysterectomy is not accounted for in the model and parameters. This would also slightly alter the natural disease history.

8 CONCLUSION

Under the reasonable assumption that cytology has a lower sensitivity to ADC and AIS than HPV-based testing, this model-based analysis showcased that extending the natural history model of HPV-induced cervical cancer to include these health states had a positive impact in favor of HPV-based testing. Given reports of increasing incidences of ADC and AIS in the female population, this is an issue that requires more attention and research. Future model-based studies evaluating CC prevention policies should incorporate ADC-related health states, or acknowledge the limitation and potential impact of not reflecting these health states in the model.

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10 APPENDIX

10.1 APPENDIX FIGURE 1.

2018 mortality rates from Statbank

Age groups	mean death per 100 000	yearly mortality rate	monthly rate	monthly probability
0-4 years	45	0.00045	0.0000375	**0.0000375**
5-9 years	2	0.00002	0.0000017	**0.0000017**
10-14 years	3	0.00003	0.0000025	**0.0000025**
15-19 years	13	0.00013	0.0000108	**0.0000108**
20-24 years	6	0.00006	0.0000050	**0.0000050**
25-29 years	24	0.00024	0.0000200	**0.0000200**
30-34 years	27	0.00027	0.0000225	**0.0000225**
35-39 years	43	0.00043	0.0000358	**0.0000358**
40-44 years	68	0.00068	0.0000567	**0.0000567**
45-49 years	111	0.00111	0.0000925	**0.0000925**
50-54 years	177	0.00177	0.0001475	**0.0001475**
55-59 years	310	0.0031	0.0002583	**0.0002583**
60-64 years	495	0.00495	0.0004125	**0.0004124**
65-69 years	824	0.00824	0.0006867	**0.0006864**
70-74 years	1331	0.01331	0.0011092	**0.0011086**
75-79 years	2447	0.02447	0.0020392	**0.0020371**
80-84 years	4628	0.04628	0.0038567	**0.0038492**
85-89 years	9053	0.09053	0.0075442	**0.0075158**
90 years or older	21909	0.21909	0.0182575	**0.0180918**

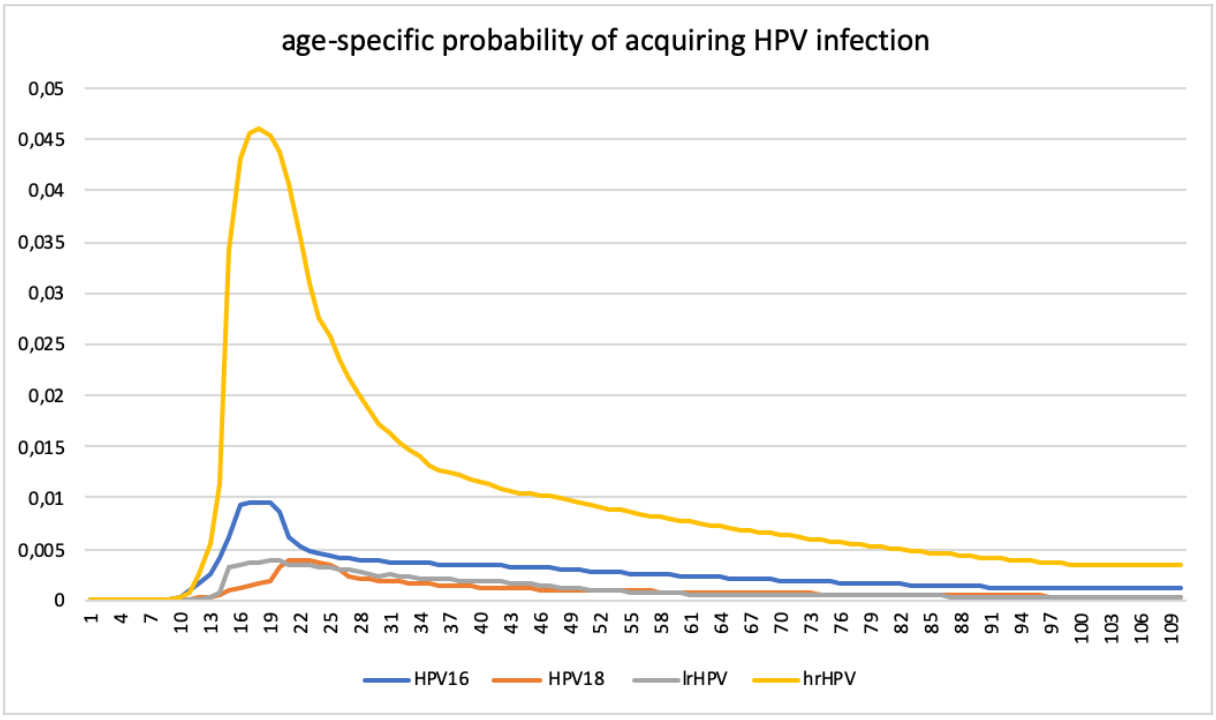
10.2 APPENDIX FIGURE 2.

Progression from Healty to acquiring one of the HPV subtypes				
Age	**HPV16**	**HPV18**	**lrHPV**	**hrHPV**
1	0.000000000	0.000000000	0.000000000	0.000000000
2	0.000000000	0.000000000	0.000000000	0.000000000
3	0.000000000	0.000000000	0.000000000	0.000000000
4	0.000000000	0.000000000	0.000000000	0.000000000
5	0.000000000	0.000000000	0.000000000	0.000000000
6	0.000000000	0.000000000	0.000000000	0.000000000
7	0.000000000	0.000000000	0.000000000	0.000000000
8	0.000000000	0.000000000	0.000000000	0.000000000
9	0.000050995	0.000019627	0.000007447	0.000141421
10	0.000254977	0.000039253	0.000014894	0.000282842
11	0.001019908	0.000117760	0.000029788	0.000673886
12	0.001529862	0.000196266	0.000148941	0.002429782
13	0.002549770	0.000274772	0.000297882	0.005375888
14	0.004079632	0.000471038	0.000744705	0.011322045
15	0.006119448	0.001020583	0.003127761	0.034156076
16	0.009281163	0.001177596	0.003455431	0.043159711
17	0.009434149	0.001452368	0.003604372	0.045663058
18	0.009485144	0.001687888	0.003722036	0.045976565
19	0.009434149	0.001923407	0.003797996	0.045473929
20	0.008718213	0.003218762	0.003842678	0.043911441
21	0.006191913	0.003859320	0.003350013	0.040602698
22	0.005151671	0.003902571	0.003362849	0.035400105
23	0.004755389	0.003885936	0.003350013	0.031015578
24	0.004473038	0.003659700	0.003273002	0.027667521
25	0.004309571	0.003327000	0.003208825	0.025766761
26	0.004185733	0.002894490	0.003080472	0.023500304
27	0.004111430	0.002262360	0.002952119	0.021640821

28	0.003992545	0.002062740	0.002798095	0.019987874
29	0.003873660	0.001996200	0.002567060	0.018631333
30	0.003863753	0.001929660	0.002387366	0.017172559
31	0.003764683	0.001863120	0.002437662	0.016264533
32	0.003665612	0.001796580	0.002313713	0.015437326
33	0.003616077	0.001730040	0.002217308	0.014728249
34	0.003591309	0.001663500	0.002134676	0.014020893
35	0.003566542	0.001596960	0.002079587	0.013165142
36	0.003541774	0.001497150	0.002038271	0.012770557
37	0.003526913	0.001430610	0.002010727	0.012445276
38	0.003517006	0.001364070	0.001969410	0.012141858
39	0.003482332	0.001297530	0.001941866	0.011829450
40	0.003393168	0.001264260	0.001886778	0.011533905
41	0.003368400	0.001230990	0.001859234	0.011247949
42	0.003343633	0.001197720	0.001804145	0.010967177
43	0.003318865	0.001164450	0.001735285	0.010672638
44	0.003269330	0.001097910	0.001680196	0.010485485
45	0.003234655	0.001084602	0.001552116	0.010409521
46	0.003170259	0.001064640	0.001459843	0.010226001
47	0.003105863	0.001041351	0.001363438	0.010104573
48	0.003046421	0.001021389	0.001267033	0.009913896
49	0.002982025	0.001001427	0.001170629	0.009708867
50	0.002922583	0.000981465	0.001101768	0.009482024
51	0.002868094	0.000961503	0.001046680	0.009295557
52	0.002808652	0.000944868	0.000991591	0.009104308
53	0.002754163	0.000924906	0.000936503	0.008924451
54	0.002699674	0.000908271	0.000881414	0.008745570
55	0.002645185	0.000888309	0.000826326	0.008575137
56	0.002595650	0.000871674	0.000771238	0.008410609
57	0.002541161	0.000855039	0.000716149	0.008238793
58	0.002491626	0.000838404	0.000674833	0.008087220
59	0.002442090	0.000821769	0.000633517	0.007926224
60	0.002392555	0.000805134	0.000619745	0.007778184

61	0.002347973	0.000788499	0.000605972	0.007628009
62	0.002298438	0.000771864	0.000599086	0.007479969
63	0.002253856	0.000758556	0.000592200	0.007342176
64	0.002209274	0.000741921	0.000578428	0.007202972
65	0.002164693	0.000728613	0.000564656	0.007055756
66	0.002125064	0.000711978	0.000537112	0.006927372
67	0.002080483	0.000698670	0.000526094	0.006789580
68	0.002040854	0.000685362	0.000512322	0.006660623
69	0.002001226	0.000672054	0.000506813	0.006531666
70	0.001961598	0.000658746	0.000502682	0.006401161
71	0.001921970	0.000645438	0.000499927	0.006272205
72	0.001882341	0.000632130	0.000497173	0.006143248
73	0.001847667	0.000618822	0.000499927	0.006025111
74	0.001808038	0.000608841	0.000493041	0.005896018
75	0.001773364	0.000595533	0.000483401	0.005786192
76	0.001738689	0.000585552	0.000473760	0.005660177
77	0.001704014	0.000572244	0.000464120	0.005531202
78	0.001669340	0.000562263	0.000455857	0.005405187
79	0.001639618	0.000548955	0.000446216	0.005313924
80	0.001604944	0.000538974	0.000437953	0.005197198
81	0.001575223	0.000528993	0.000428312	0.005094390
82	0.001540548	0.000519012	0.000420049	0.004992169
83	0.001510827	0.000509031	0.000411786	0.004876974
84	0.001481105	0.000499050	0.000403523	0.004774735
85	0.001451384	0.000489069	0.000395259	0.004668830
86	0.001421663	0.000479088	0.000395259	0.004577429
87	0.001396895	0.000469107	0.000388373	0.004483892
88	0.001367174	0.000459126	0.000380110	0.004395588
89	0.001342407	0.000449145	0.000373224	0.004318105
90	0.001312685	0.000442491	0.000364961	0.004218256
91	0.001287918	0.000432510	0.000358075	0.004140772
92	0.001263150	0.000422529	0.000351189	0.004063288
93	0.001238383	0.000415875	0.000344303	0.003974259

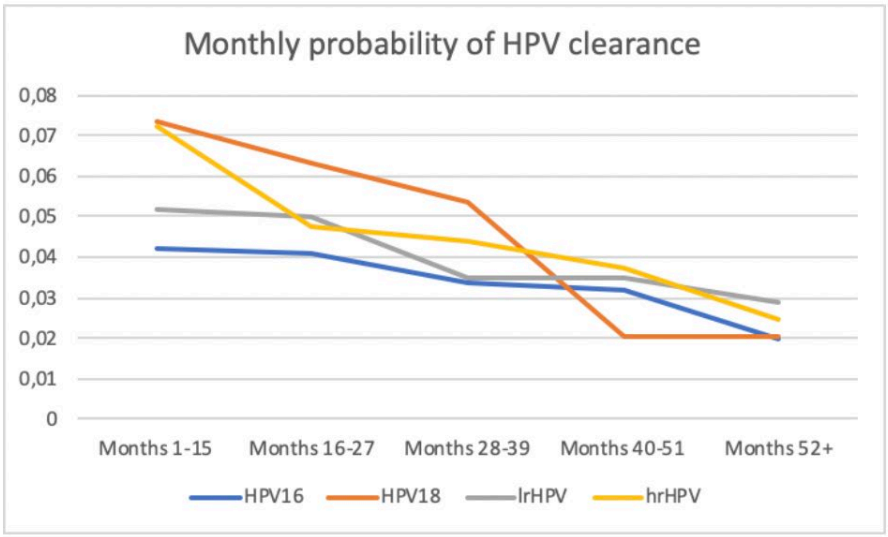
94	0.001213615	0.000405894	0.000337416	0.003896775
95	0.001188847	0.000399240	0.000330530	0.003822251



10.3 APPENDIX FIGURE 3.

Regression rates from HPV-infected health state

time interval	HPV16	HPV18	lrHPV	hrHPV
Months 1-15	0.041886394	0.07334222	0.05188752	0.07245874
Months 16-27	0.040753832	0.06323544	0.05000550	0.04780399
Months 28-39	0.033904540	0.05360469	0.03464920	0.04399987
Months 40-51	0.031887888	0.02061577	0.03464920	0.03699821
Months 52+	0.019845747	0.02061577	0.02860836	0.02435515

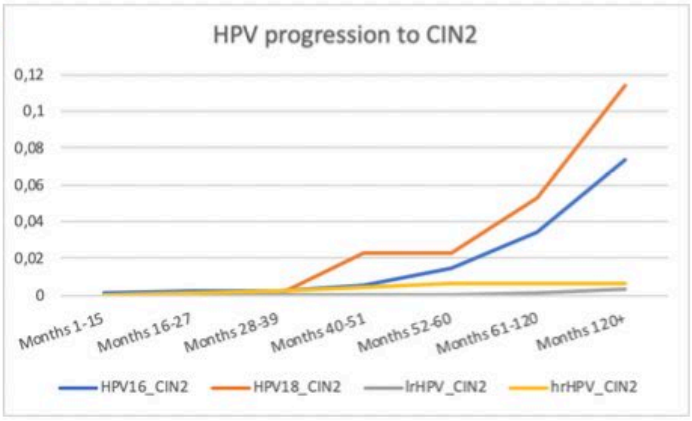


10.4 APPENDIX FIGURE 4.

Transition probabilities related to transition from HPV to Precancer

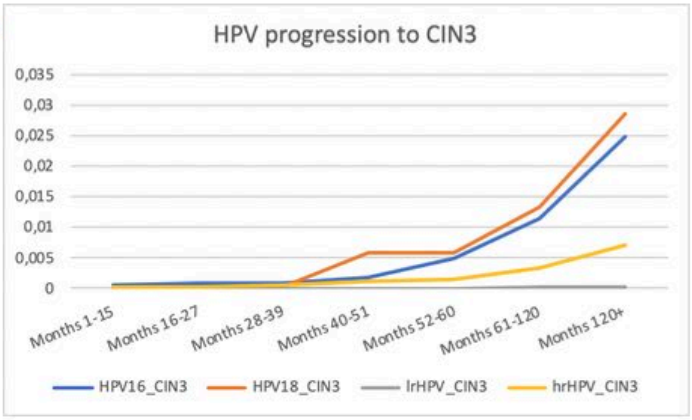
HPV progression to CIN2

time in health state	HPV16_CIN2	HPV18_CIN2	lrHPV_CIN2	hrHPV_CIN2
Months 1-15	0.00171	0.00013	0.00021	0.00043
Months 16-27	0.00242	0.00057	0.00029	0.00134
Months 28-39	0.00258	0.00057	0.00031	0.00273
Months 40-51	0.00552	0.02320	0.00066	0.00429
Months 52-60	0.01500	0.02320	0.00066	0.00585
Months 61-120	0.03414	0.05281	0.00151	0.00585
Months 120+	0.07377	0.11411	0.00326	0.00585



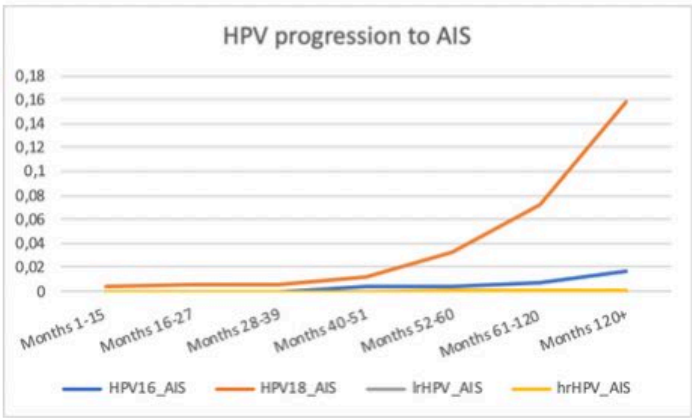
HPV progression to CIN3

time in health state	HPV16_CIN3	HPV18_CIN3	lrHPV_CIN3	hrHPV_CIN3
Months 1-15	0.00057	0.00003	0.00002	0.00011
Months 16-27	0.00081	0.00014	0.00003	0.00033
Months 28-39	0.00086	0.00014	0.00003	0.00068
Months 40-51	0.00184	0.00582	0.00007	0.00108
Months 52-60	0.00502	0.00582	0.00007	0.00147
Months 61-120	0.01144	0.01324	0.00017	0.00334
Months 120+	0.02471	0.02861	0.00036	0.00721



HPV progression to AIS

time in health state	HPV16_AIS	HPV18_AIS	lrHPV_AIS	hrHPV_AIS
Months 1-15	0.00002	0.00363	-	0.00001
Months 16-27	0.00008	0.00515	-	0.00003
Months 28-39	0.00008	0.00548	-	0.00007
Months 40-51	0.00349	0.01175	-	0.00011
Months 52-60	0.00349	0.03203	-	0.00015
Months 61-120	0.00795	0.07291	-	0.00015
Months 120+	0.01717	0.15754	-	0.00015

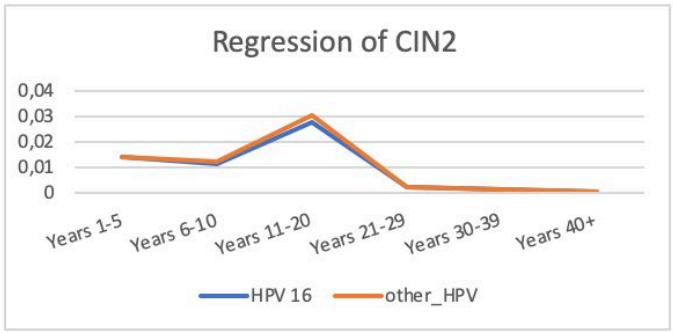


10.5 APPENDIX FIGURE 5.

Regression rates for precancer*

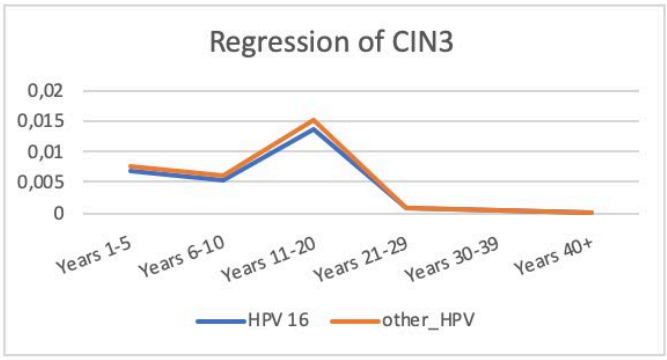
Regression of CIN2

	HPV 16	other_HPV
Years 1-5	0.0135	0.0135
Years 6-10	0.0108	0.012
Years 11-20	0.027	0.03
Years 21-29	0.0018	0.002
Years 30-39	0.0009	0.001
Years 40+	0.00045	0.0005



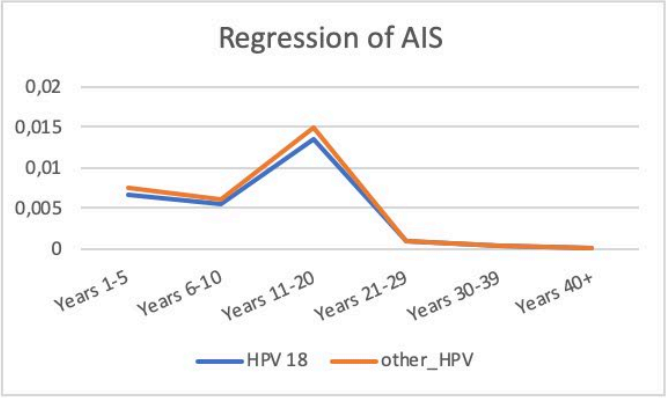
Regression of CIN3

	HPV 16	other_HPV
Years 1-5	0.00675	0.0075
Years 6-10	0.0054	0.006
Years 11-20	0.0135	0.015
Years 21-29	0.0009	0.001
Years 30-39	0.00045	0.0005
Years 40+	0.000225	0.00025



Regression of AIS

	HPV 18	other_HPV
Years 1-5	0.00675	0.0075
Years 6-10	0.0054	0.006
Years 11-20	0.0135	0.015
Years 21-29	0.0009	0.001
Years 30-39	0.00045	0.0005
Years 40+	0.000225	0.00025



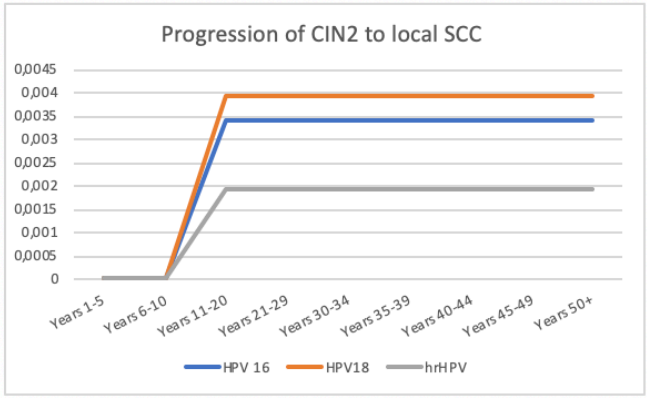
* Of those who regress, 50% go back to Healthy state and 50% return back to previous HPV-infection

10.6 APPENDIX FIGURE 6.

Progression of precancer to invasive carcinoma

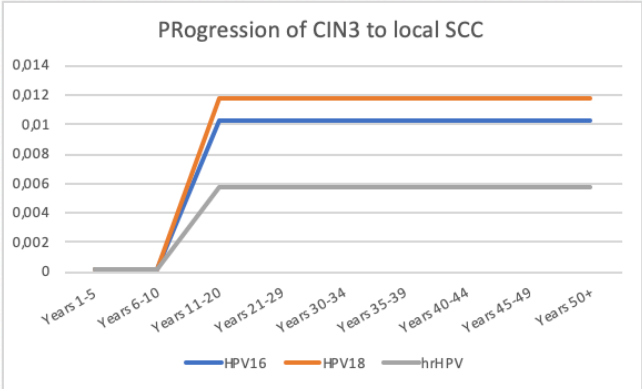
Progression of CIN2 to loSCC

	HPV 16	HPV18	hrHPV
Years 1-5	0.000042	0.000034	0.000021
Years 6-10	0.000046	0.000037	0.000023
Years 11-20	0.003430	0.003933	0.001916
Years 21-29	0.003430	0.003933	0.001916
Years 30-34	0.003430	0.003933	0.001916
Years 35-39	0.003430	0.003933	0.001916
Years 40-44	0.003430	0.003933	0.001916
Years 45-49	0.003430	0.003933	0.001916
Years 50+	0.003430	0.003933	0.001916



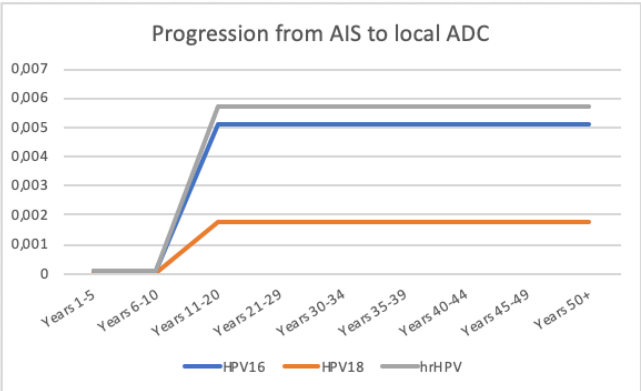
Progression of CIN3 to loSCC

	HPV16	HPV18	hrHPV
Years 1-5	0.000192	0.000178	0.000107
Years 6-10	0.000208	0.000192	0.000116
Years 11-20	0.010289	0.011799	0.005748
Years 21-29	0.010289	0.011799	0.005748
Years 30-34	0.010289	0.011799	0.005748
Years 35-39	0.010289	0.011799	0.005748
Years 40-44	0.010289	0.011799	0.005748
Years 45-49	0.010289	0.011799	0.005748
Years 50+	0.010289	0.011799	0.005748



Progression of AIS to loADC

	HPV16	HPV18	hrHPV
Years 1-5	0.000063	0.000015	0.000063
Years 6-10	0.000068	0.000017	0.000068
Years 11-20	0.005145	0.001770	0.005748
Years 21-29	0.005145	0.001770	0.005748
Years 30-34	0.005145	0.001770	0.005748
Years 35-39	0.005145	0.001770	0.005748
Years 40-44	0.005145	0.001770	0.005748
Years 45-49	0.005145	0.001770	0.005748
Years 50+	0.005145	0.001770	0.005748



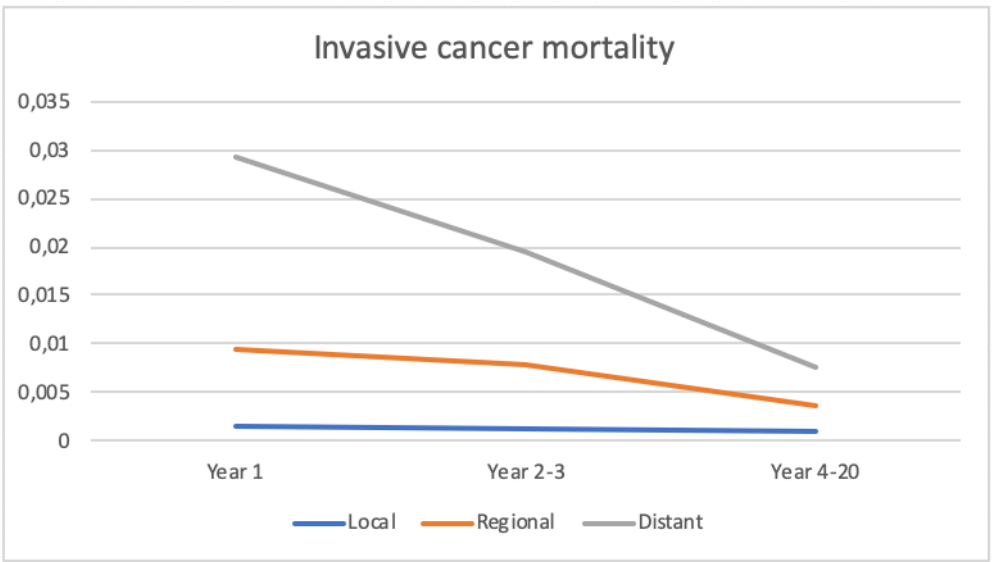
10.7 APPENDIX FIGURE 7.

Transition probabilities for invasive cancer

Progression of invasive cancer	
Local to regional	0.02
Regional to distant	0.025

Invasive cancer mortality

Time in health state	**Local**	**Regional**	**Distant**
Year 1	0.00159	0.00946	0.02934
Year 2-3	0.00141	0.00781	0.01947
Year 4-20	0.00094	0.00362	0.0076



10.8 APPENDIX FIGURE 8.

Survival cervical cancer (ICD10: C53)

5-year relative survival divided by stage, observations between 2013-2017

Method: Pohar Perme with period adjustment

Type	Stage	Number at risk*	Survival	Lower 95% CI	Upper 95% CI
Adenocarcinoma	I	258	91.5	86.4	94.7
Adenocarcinoma	II	22	81.8	61.9	92.0
Adenocarcinoma	III	28	36.1	16.8	55.9
Adenocarcinoma	IV	34	42.2	19.6	63.3
Adenocarcinoma	**Total**	**358**	**82.6**	**77.6**	**86.6**
Squamous cell carcinoma	I	790	94.2	91.8	95.9
Squamous cell carcinoma	II	150	77.7	69.9	83.7
Squamous cell carcinoma	III	112	70.4	57.0	80.3
Squamous cell carcinoma	IV	132	39.2	28.9	49.2
Squamous cell carcinoma	**Total**	**1244**	**83.3**	**80.6**	**85.7**

*number at the start of the period

10.9 APPENDIX FIGURE 9.

HPV genotype	**AIS**	Bounds	**ADC**	Bounds
HPV16	**37 %**	33% - 41%	**47 %**	42% - 52%
HPV18	**59 %**	53% - 65%	**46 %**	41% - 51%
hrHPV	**5 %**	4% - 6%	**7 %**	6% - 8%

10.10 APPENDIX FIGURE 10.

Database:	Cochrance
Search Name:	Adenocarcinoma - general findings
Date Run:	25.02.2019

ID	Search terms	Items found
#1	adenocarcinoma OR "adenocarcinoma in situ" OR "endocervical glandular lesions" in Cochrane Reviews, Trials, Clinical Answers	6997
#2	cervical carcinoma OR "cancer of the cervix uteri" in Cochrane Reviews, Trials, Clinical Answers	392
#4	#1 AND #2	59

Database:	Cochrane
Search Name:	Natural history of Adenocarcinoma
Date Run:	06.02.2019

ID	Search terms	Items found
#1	adenocarcinoma OR "adenocarcinoma in situ" OR ais OR acis OR adc	8602
#2	cervix uteri OR cervix OR endocervical OR "cervical cancer"	7099
#3	progression to invasive	35
#5	#1 AND #2 AND #4	62

Database:	Cochrane
Search Name:	progression from precancer to ADC
Date Run:	27.05.2019

ID	Search terms	Items found
#1	conservative management OR "watchful waiting"	2061
#2	atypical glandular cells	13
#3	rate of progression OR "risk of progression"	1557
#4	Adenocarcinoma	9987
#5	cervix uteri	1165
#6	#3 and #4 and #5	1
#7	#1 and #4 and #5	0
#8	#4 and #5	25

Data Base:	Cochrane
Search Name:	HPV induced ADC and AIS
Date Run:	06.02.2016

ID	Search	Hits
#1	adenocarcinoma OR "adenocarcinoma in situ" OR ais OR acis OR adc	8602
#2	cervix uteri OR cervix OR endocervical OR "cervical cancer"	7099
#3	#1 AND #2	263
#4	HPV OR "human papilloma virus"	1891
#5	#3 and #4	39

Database:	Medline	
Search Name:	Progression from HPV infection to AIS/ADC	
Date Run:	07.02.2019	
	Search terms	Items found
1	(HPV or "human papilloma virus").mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	39708
2	(progression or persistence).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	611378
3	1 and 2	4081
4	((adenocarcinoma and "adenocarcinoma in situ") or ais or adc).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	21797
5	3 and 4	31

Database:	**Pubmed**	
Search Name:	Various searches relates to adenocarcinoma in situ, adenocarcinoma, epidemiology in Norway, studies related to AIS/ADC	
Date Run:	20.01.2019 - 12.02.2019	
	Search terms	Items found
	Search (((((cervix[Title/Abstract] OR cervical[Title/Abstract])) AND (uterus[Title/Abstract] OR uteri[Title/Abstract])) AND (cancer*[Title/Abstract] OR neoplasm*[Title/Abstract] OR adenocarcinoma*[Title/Abstract]))) OR "Uterine Cervical Neoplasms"[Mesh] AND incidence AND (norway[ti] OR nordic[ti] OR norwegian[ti] OR scandinavia[ti] OR scandinavian[ti])	74
	(HPV[Title/Abstract] AND "genotype distribution"[Title/Abstract] AND adenocarcinoma[Title/Abstract] AND cervix[Title/Abstract])	4
	(((((cervix[Title/Abstract] OR cervical[Title/Abstract])) AND (uterus[Title/Abstract] OR uteri[Title/Abstract])) AND (adenocarcinoma*[Title/Abstract]))) AND incidence AND (norway[ti] OR nordic[ti] OR norwegian[ti] OR scandinavia[ti] OR scandinavian[ti])	1
	(((((cervix[Title/Abstract] OR cervical[Title/Abstract])) AND (uterus[Title/Abstract] OR uteri[Title/Abstract])) AND (cancer*[Title/Abstract] OR neoplasm*[Title/Abstract] OR adenocarcinoma*[Title/Abstract]))) OR "Uterine Cervical	15 (filter: review)
	((premalignant OR malignant AND "endocervical glandular lesions" OR "cervical cancer"[MeSH Terms])) AND (adenocarcinoma[Title/Abstract] OR "adenocarcinoma in situ"[Title/Abstract] OR ais[Title/Abstract] OR	3 (filter: review)
	Search ((("prospective study" OR "retrospective study" OR "longitudinal study"))) AND ((((((("cervix uteri" OR "cervical carcinoma" OR "PREMALIGNANT ENDOCERVICAL GLANDULAR LESIONS"[MeSH Terms]))) AND ((adenocarcinoma OR "adenocarcinoma in situ" OR "glandular dysplasia"[MeSH Terms]))))) AND ((Progression[Title/Abstract] OR regression[Title/Abstract])))	9

Database:	Medline	
Search Name:	Natural history of adenocarcinoma and adenocarcinoma in situ	
Date Run:	05.02.2019	
	Search terms	items found
1	(adenocarcinoma* and "cervix uteri" and HPV).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	153
2	(AIS and Adenocarcinoma and "cervix uteri").mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	76

Database:	Medline	
Search Name:	HPV-induced AIS and ADC	
Date Run:	05.02.2019	
	Search terms	items found
1	(HPV or "human papilloma virus").mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	39708
2	(progression or persistence).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	611378
3	1 and 2	4081
4	((adenocarcinoma and "adenocarcinoma in situ") or ais or adc).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	21797
5	3 and 4	31

Database:	Embase	
Search Name:	Natural history of adenocarcinoma	
Date Run:	04.05.2019	
		items found
	Search terms	
1	(((adenocarcinoma* and "adenocarcinoma in situ") or ais or adc) and "cervix uteri").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	48
2	(progression or "time to invasive cancer" or "time to progression").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	727516
3	limit 2 to full text	335544
4	1 and 2	4

Database:	Pubmed	
Search Name:	Cytology performance for detection of AIS	
Date Run:	24.05.19	
Search	Search terms	Items found
#3	Search Cytology[Title/Abstract] AND sensitivity[Title/Abstract] AND adenocarcinoma[Title/Abstract] AND cervix[Title/Abstract] Sort by: Best Match	16
#2	Search cytology AND sensitivity AND (adenocarcinoma OR "adenocarcinoma in situ") AND MeSH Terms Sort by: Best Match	2
#1	Search (((cervix OR "cervical cancer"[MeSH Terms]))) AND (((((sensitivity[Text Word]) AND "adenocarcinoma"[Title/Abstract]) AND cytology[MeSH Terms])) AND diagnostic accuracy[Text Word]) Sort by: Best Match	5

10.11 APPENDIX FIGURE 11.

Age group	HRQoL	Health state	HRQoL adjustment
<20	1	No cancer	1
20-29	0.9203	Local cancer	0.76
30-39	0.9118	Regional cancer	0.67
40-49	0.8763	Distant cancer	0.48
50-59	0.8499	Dead	0
60-69	0.8552		

70-79	0.8320		
80+	0.6919		

10.12 APPENDIX FIGURE 12.

Cost item	unadjusted values from Norwegian Harvard model appendix		reconverted to NOK		Base case (inflation-adjusted)
Screening consultations					
General Practitioner (GP) office visit	$	122.00	kr 769	kr	855
Productivity loss for patient associated with GP visit	$	120.00	kr 756	kr	841
Colposcopy examination	$	258.00	kr 1 625	kr	1 808
Productivity loss for patient associated with colposcopy examination	$	150.00	kr 945	kr	1 051
Analyzing test sample at pathology laboratory					
Liquid based cytology	$	45.00	kr 284	kr	315
HPV DNA test	$	39.00	kr 246	kr	273
Cervical biopsy	$	124.00	kr 781	kr	869
Treatment of high-grade precancer and cancer					
Treatment of high-grade precancer	$	1 682.00	kr 10 597	kr	11 790
Treatment of local cancer	$	26 941.00	kr 169 728	kr	188 838
Treatment of regional cancer	$	56 601.00	kr 356 586	kr	396 734
Treatment of distant cancer	$	41 367.00	kr 260 612	kr	289 954
Productivity loss associated with treatment of high-grade precancer	$	4 773.00	kr 30 070	kr	33 455
Productivity loss associated with treatment of local cancer	$	39 856.00	kr 251 093	kr	279 363
Productivity loss associated with treatment of regional cancer	$	161 730.00	kr 1 018 899	kr	1 133 617
Productivity loss associated with treatment of distant cancer	$	146 571.00	kr 923 397	kr	1 027 363

10.13 APPENDIX FIGURE 13.

CHEERS checklist—Items to include when reporting economic evaluations of health interventions		
Section/item	Item No	Recommendation
Title and abstract		
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.
Introduction		
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.
Methods		
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.
Results		
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.
Discussion		
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.
Other		
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.

10.14 APPENDIX FIGURE 14.

```
set.seed(hyper_seed)

### set model features ###
extended_model <- hyper_extended_model  ## 1 = SCC & ADC  0 = only SCC



### Model input  ###
nr_individuals   <- hyper_nr_individuals # number of simulated individuals
nr_months  <- hyper_nr_months #time horizon in months, from age 0-95 = 1140 months

age <- (nr_months)/12
Health_states   <- c("H","HPV16","HPV18","lrHPV","hrHPV",
                     "CIN2","CIN3", "AIS", "loSCC", "reSCC",
                     "diSCC", "dSCC","det_loSCC", "det_reSCC", "det_diSCC","loADC", "reADC",
                     "diADC", "dADC", "det_loADC", "det_reADC", "det_diADC", "D")      # the model states: healthy, acquired HPV infection (stratified by genotypes 16, 18, pooled low risk and pooled high risk), precancerous states (CIN1 & CIN2), cancer stages (local, regional, distant), death from cancer (dSCC) and death from other causes (D)

nr_health_states   <- length(Health_states)          # the number of health states
first_health_state <- rep("H", times = nr_individuals)




# CREATE RESULT MATRICES
# m.M: health state for each patient at each cycle
# 1 - current state, 2 - time at current state, 3 - Treatment Type, 4- Treatment Outcome
Model_array = array(NA, c(nr_individuals, nr_months + 1, 5));

rownames(Model_array) = paste("ind",   1:nr_individuals, sep = " ")
colnames(Model_array) = paste("cycle", 0:nr_months, sep = " ")

# START SIMULATION
p <- Sys.time()

# individuals 1 thru nr_individuals
for (i in 1:nr_individuals) { # open individuals loop

  Model_array[i, 1, 1] <- first_health_state[i]      # initial health state for individual i
  Model_array[i, 1, 2] <- 1              # initial time at state
```

```
# cycles 1 thru nr_months
for (t in 1:nr_months) { # open time loop

 # D -> D absorbing health states for death from cancer and other causes
 if(Model_array[i, t,   1] %in% c("D", "dSCC", "dADC"))       Model_array[i, t+1, 1] = Model_array[i, t, 1]

 else {

  # Any health state -> Dead (D) (background mortality rate)
  Model_array[i, t+1, 1] = sample(x = c(NA, "D"), prob = c(1-1*p.D[t]  , 1*p.D[t]), size = 1)



  # H -> HPV (HPV incidence)
  if(Model_array[i, t, 1] %in% c("H")& !(Model_array[i, t+1, 1] %in% c("D")))
   Model_array[i, t+1, 1] = sample(x = c("H", "HPV16","HPV18","lrHPV","hrHPV"), prob = c(1-sum(p.H_HPV[t,]), p.H_HPV[t,]), size = 1)



  if(extended_model == 1) {


   # HPV -> HPV, H, CIN2, CIN3 or AIS      (Transition from HPV to clearance or progression to lesion if the model is extended)
   if(Model_array[i, t, 1] %in% c("HPV16","HPV18","lrHPV","hrHPV") & !(Model_array[i, t+1, 1] %in% c("D")))
    Model_array[i, t+1, 1] = sample(x = c(Model_array[i, t, 1],"H", "CIN2", "CIN3", "AIS"), prob = c(1-p.HPV_H[ as.numeric(Model_array[i, t, 2]),
Model_array[i, t, 1]]-p.HPV_CIN2[as.numeric(Model_array[i, t, 2]), Model_array[i, t, 1]]-p.HPV_CIN3[as.numeric(Model_array[i, t, 2]),
Model_array[i, t, 1]]-p.HPV_AIS[as.numeric(Model_array[i, t, 2]), Model_array[i, t, 1]],
                                                    p.HPV_H[   as.numeric(Model_array[i, t, 2]), Model_array[i, t, 1]],
                                                    p.HPV_CIN2[as.numeric(Model_array[i, t, 2]), Model_array[i, t, 1]],
                                                    p.HPV_CIN3[as.numeric(Model_array[i, t, 2]), Model_array[i, t, 1]],
                                                    p.HPV_AIS[as.numeric(Model_array[i, t, 2]), Model_array[i, t, 1]]), size = 1)


  }else{
   # HPV -> HPV, H, CIN2, CIN3       (Transition from HPV to clearance or progression to lesion if the model is NOT extended)
   if(Model_array[i, t, 1] %in% c("HPV16","HPV18","lrHPV","hrHPV") & !(Model_array[i, t+1, 1] %in% c("D")))
    Model_array[i, t+1, 1] = sample(x = c(Model_array[i, t, 1],"H", "CIN2", "CIN3"), prob = c(1-p.HPV_H[ as.numeric(Model_array[i, t, 2]),
Model_array[i, t, 1]]-p.HPV_CIN2[as.numeric(Model_array[i, t, 2]), Model_array[i, t, 1]]-p.HPV_CIN3[as.numeric(Model_array[i, t, 2]),
Model_array[i, t, 1]],
                                                  p.HPV_H[   as.numeric(Model_array[i, t, 2]), Model_array[i, t, 1]],
                                                  p.HPV_CIN2[as.numeric(Model_array[i, t, 2]), Model_array[i, t, 1]],
                                                  p.HPV_CIN3[as.numeric(Model_array[i, t, 2]), Model_array[i, t, 1]]), size = 1)


  }
```

```
    # CIN2 -> HPV, H, loSCC (transition from CIN2 to clearance -either back to healthy or previous HPV infection, or progression to invasive cancer))

    if(Model_array[i, t, 1] %in% c("CIN2") & !(Model_array[i, t+1, 1] %in% c("D")))
      Model_array[i, t+1, 1] = sample(x = c("CIN2", Model_array[i, t - as.numeric(Model_array[i, t, 2]), 1], "H", "loSCC"), prob = c(1-p.CIN2_HPV[as.numeric(Model_array[i, t, 2]), Model_array[i, t - as.numeric(Model_array[i, t, 2]), 1]]-p.CIN2_loSCC[as.numeric(Model_array[i, t, 2]), Model_array[i, t - as.numeric(Model_array[i, t, 2]), 1]],
                                                                    p.CIN2_HPV[as.numeric(Model_array[i, t, 2]), Model_array[i, t - as.numeric(Model_array[i, t, 2]), 1]]/2,
                                                                    p.CIN2_HPV[as.numeric(Model_array[i, t, 2]), Model_array[i, t - as.numeric(Model_array[i, t, 2]), 1]]/2,
                                                                    p.CIN2_loSCC[as.numeric(Model_array[i, t, 2]), Model_array[i, t - as.numeric(Model_array[i, t, 2]), 1]]), size = 1)


    # CIN3 -> HPV, H, loSCC  (transition from CIN3 to clearance -either back to healthy or previous HPV infection, or progression to invasive cancer))

    if(Model_array[i, t, 1] %in% c("CIN3") & !(Model_array[i, t+1, 1] %in% c("D")))
      Model_array[i, t+1, 1] = sample(x = c("CIN3", Model_array[i, t - as.numeric(Model_array[i, t, 2]), 1], "H","loSCC"), prob = c(1-p.CIN3_HPV[as.numeric(Model_array[i, t, 2]), Model_array[i, t - as.numeric(Model_array[i, t, 2]), 1]]-p.CIN3_loSCC[as.numeric(Model_array[i, t, 2]), Model_array[i, t - as.numeric(Model_array[i, t, 2]), 1]],
                                                                    p.CIN3_HPV[as.numeric(Model_array[i, t, 2]), Model_array[i, t - as.numeric(Model_array[i, t, 2]), 1]]/2,
                                                                    p.CIN3_HPV[as.numeric(Model_array[i, t, 2]), Model_array[i, t - as.numeric(Model_array[i, t, 2]), 1]]/2,
                                                                    p.CIN3_loSCC[as.numeric(Model_array[i, t, 2]), Model_array[i, t - as.numeric(Model_array[i, t, 2]), 1]]), size = 1)


    if(extended_model == 1) {
      # AIS -> HPV, H , loADC (If extended model: transition from AIS to clearance -either back to healthy or previous HPV infection, or progression to invasive cancer))

      if(Model_array[i, t, 1] %in% c("AIS") & !(Model_array[i, t+1, 1] %in% c("D")))
        Model_array[i, t+1, 1] = sample(x = c("AIS", Model_array[i, t - as.numeric(Model_array[i, t, 2]), 1], "H", "loADC"), prob = c(1-p.AIS_HPV[as.numeric(Model_array[i, t, 2]), Model_array[i, t - as.numeric(Model_array[i, t, 2]), 1]]-p.AIS_loADC[as.numeric(Model_array[i, t, 2]), Model_array[i, t - as.numeric(Model_array[i, t, 2]), 1]],
                                                                    p.AIS_HPV[as.numeric(Model_array[i, t, 2]), Model_array[i, t - as.numeric(Model_array[i, t, 2]), 1]]/2,
                                                                    p.AIS_HPV[as.numeric(Model_array[i, t, 2]), Model_array[i, t - as.numeric(Model_array[i, t, 2]), 1]]/2,
                                                                    p.AIS_loADC[as.numeric(Model_array[i, t, 2]), Model_array[i, t - as.numeric(Model_array[i, t, 2]), 1]]), size = 1)


    }



    ###Transitions from invasive cancer stages



    # loADC -> reADC or dADC (transition from local adenocarcinoma to regional, or death from local cancer)

    if(Model_array[i, t, 1] %in% c("loADC") & !(Model_array[i, t+1, 1] %in% c("D")))
      Model_array[i, t+1, 1] = sample(x = c("loADC","reADC", "dADC", "det_loADC"), prob = c(1-p.loADC_reADC-p.loADC_dADC[as.numeric(Model_array[i, t, 2])]-p.symptom_det_loADC,
                                                                    p.loADC_reADC,
                                                                    p.loADC_dADC[as.numeric(Model_array[i, t, 2])],
```

```
                                                    p.symptom_det_loADC), size = 1)


    # loSCC -> reSCC or dSCC (transition from local squamous cell carcinoma to regional, or death from local cancer)

    if(Model_array[i, t, 1] %in% c("loSCC") & !(Model_array[i, t+1, 1] %in% c("D")))
      Model_array[i, t+1, 1] = sample(x = c("loSCC", "reSCC", "dSCC", "det_loSCC"), prob = c(1-p.loSCC_reSCC-
p.loSCC_dSCC[as.numeric(Model_array[i, t, 2])]-p.symptom_det_loSCC,
                                                    p.loSCC_reSCC,
                                                    p.loSCC_dSCC[as.numeric(Model_array[i, t, 2])],
                                                    p.symptom_det_loSCC), size = 1)




    # reADC -> diADC or dADC (transition from regional adenocarcinoma to distant carcinoma, or death from regional cancer)

    if(Model_array[i, t, 1] %in% c("reADC") & !(Model_array[i, t+1, 1] %in% c("D")))
      Model_array[i, t+1, 1] = sample(x = c("reADC", "diADC", "dADC", "det_reADC"), prob = c(1-p.reADC_diADC-
p.reADC_dADC[as.numeric(Model_array[i, t, 2])]-p.symptom_det_reADC,
                                                    p.reADC_diADC,
                                                    p.reADC_dADC[as.numeric(Model_array[i, t, 2])],
                                                    p.symptom_det_reADC), size = 1)



    # reSCC -> diSCC or dSCC  (transition from regional squamous cell carcinoma to distant carcinoma, or death from regional cancer)

    if(Model_array[i, t, 1] %in% c("reSCC") & !(Model_array[i, t+1, 1] %in% c("D")))
      Model_array[i, t+1, 1] = sample(x = c("reSCC","diSCC","dSCC", "det_reSCC"), prob = c(1-p.reSCC_diSCC-
p.reSCC_dSCC[as.numeric(Model_array[i, t, 2])]-p.symptom_det_reSCC,
                                                    p.reSCC_diSCC,
                                                    p.reSCC_dSCC[as.numeric(Model_array[i, t, 2])],
                                                    p.symptom_det_reSCC), size = 1)



    #diADC -> dADC (probability of dying from distand adenocarcinoma)

    if(Model_array[i, t, 1] %in% c("diADC") & !(Model_array[i, t+1, 1] %in% c("D")))
      Model_array[i, t+1, 1] = sample(x = c("diADC", "dADC","det_diADC"), prob = c(1-p.diADC_dADC[as.numeric(Model_array[i, t, 2])]-
p.symptom_det_diADC,
                                                    p.diADC_dADC[as.numeric(Model_array[i, t, 2])],
                                                    p.symptom_det_diADC), size = 1)



    #diSCC -> dSCC  (probability of dying from distand squamous cell carcinoma)

    if(Model_array[i, t, 1] %in% c("diSCC") & !(Model_array[i, t+1, 1] %in% c("D")))
      Model_array[i, t+1, 1] = sample(x = c("diSCC","dSCC", "det_diSCC"), prob = c(1-p.diSCC_dSCC[as.numeric(Model_array[i, t, 2])]-
p.symptom_det_diSCC,
                                                    p.diSCC_dSCC[as.numeric(Model_array[i, t, 2])],
```

```
                                        p.symptom_det_diSCC), size = 1)

##Transition probabilities for detected cancer stages, because if detected, the women cannot progress further


# det_loADC -> dADC   (probabilitiy of dying from detected local adenocarcinoma)
if(Model_array[i, t, 1] %in% c("det_loADC") & !(Model_array[i, t+1, 1] %in% c("D")))
  Model_array[i, t+1, 1] = sample(x = c("det_loADC", "dADC"), prob = c(1-p.loADC_dADC[as.numeric(Model_array[i, t, 2])],
                                        p.loADC_dADC[as.numeric(Model_array[i, t, 2])] ), size = 1)

# det_loSCC -> dSCC  (probabilitiy of dying from detected local squamous cell carcinoma)
if(Model_array[i, t, 1] %in% c("det_loSCC") & !(Model_array[i, t+1, 1] %in% c("D")))
  Model_array[i, t+1, 1] = sample(x = c("det_loSCC", "dSCC"), prob = c(1- p.loSCC_dSCC[as.numeric(Model_array[i, t, 2])],
                                        p.loSCC_dSCC[as.numeric(Model_array[i, t, 2])]), size = 1)



# det_reADC -> dADC (probabilitiy of dying from detected regional adenocarcinoma)
if(Model_array[i, t, 1] %in% c("det_reADC") & !(Model_array[i, t+1, 1] %in% c("D")))
  Model_array[i, t+1, 1] = sample(x = c("det_reADC", "dADC"), prob = c(1-p.reADC_dADC[as.numeric(Model_array[i, t, 2])],
                                        p.reADC_dADC[as.numeric(Model_array[i, t, 2])]), size = 1)


# det_reSCC -> dSCC (probabilitiy of dying from detected regional squamous cell carcinoma)
if(Model_array[i, t, 1] %in% c("det_reSCC") & !(Model_array[i, t+1, 1] %in% c("D")))
  Model_array[i, t+1, 1] = sample(x = c("det_reSCC","dSCC"), prob = c(1-p.reSCC_dSCC[as.numeric(Model_array[i, t, 2])],
                                       p.reSCC_dSCC[as.numeric(Model_array[i, t, 2])]), size = 1)



#det_diADC -> dADC (probabilitiy of dying from detected distant adenocarcinoma)
if(Model_array[i, t, 1] %in% c("det_diADC") & !(Model_array[i, t+1, 1] %in% c("D")))
  Model_array[i, t+1, 1] = sample(x = c("det_diADC", "dADC"), prob = c(1-p.diADC_dADC[as.numeric(Model_array[i, t, 2])],
                                        p.diADC_dADC[as.numeric(Model_array[i, t, 2])]), size = 1)



#det_diSCC -> dSCC (probabilitiy of dying from detected distant squamous cell carcinoma)
```

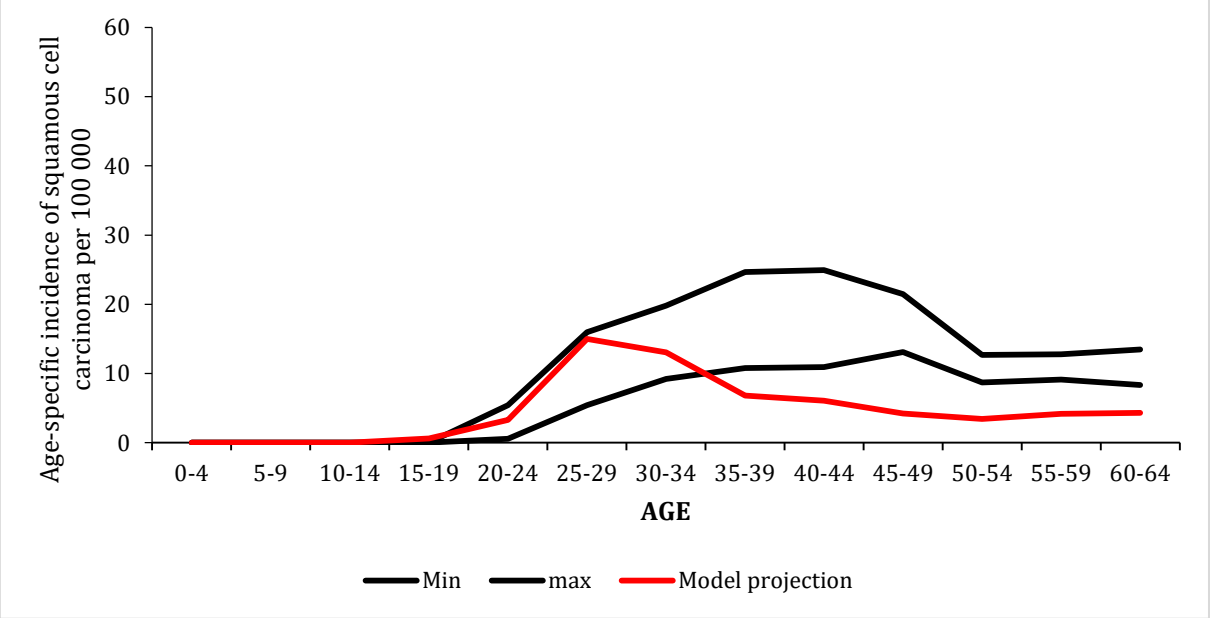
```
    if(Model_array[i, t, 1] %in% c("det_diSCC") & !(Model_array[i, t+1, 1] %in% c("D")))
      Model_array[i, t+1, 1] = sample(x = c("det_diSCC","dSCC"), prob = c(1-p.diSCC_dSCC[as.numeric(Model_array[i, t, 2])],
                                                                          p.diSCC_dSCC[as.numeric(Model_array[i, t, 2])]), size = 1)




    # if a woman has not transitioned to a new state, keep the previous one
    if(is.na(Model_array[i, t+1, 1])) Model_array[i, t+1, 1] = Model_array[i, t, 1]




    # save time at current state
    Model_array[i, t+1, 2] = ifelse(Model_array[i, t+1, 1] == Model_array[i, t, 1], as.numeric(Model_array[i, t, 2]) + 1, 1)
   }

  } # close time loop
} # close individuals loop
comp.time = Sys.time() - p
comp.time
```

10.15 APPENDIX FIGURE 15.

Due to technical and time- constraints, the following features not incorporated into our model:

1. Hysterectomy
2. HPV-Vaccination
3. The ability to be exposed to and acquire multiple HPV infections at the same time, each of which can progress to precancer and invasive cancer

10.16 APPENDIX FIGURE 16



Age-specific cancer incidence projected by the model under reduced screening coverage for cytology-based screening. Upper- and lower bounds are derived from the Cancer Registry of Norway (personal communication), from years 2013-2017.

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