Using decision-analytic modeling to isolate interventions that are feasible, efficient and optimal: An application from the Norwegian Cervical Cancer Screening Program

Short title: Modeling cervical cancer screening strategies

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Key words: Decision Analysis; Decision Making; Economic Evaluation; Health Care Utilization

Abstract **[First-level Header]**

Objectives: Decision makers often need to simultaneously consider multiple criteria or outcomes when deciding whether to adopt new health interventions. Using decision analysis within the context of cervical cancer screening in Norway, we aimed to aid decision-makers in identifying a subset of relevant strategies that are simultaneously efficient, feasible and optimal.

Methods: We developed an age-stratified probabilistic decision tree model following a cohort of women attending primary screening through one screening round. We enumerated detected precancers (*i.e.*, CIN2+), colposcopies performed, and monetary costs associated with 10 alternative triage algorithms for women with abnormal cytology results. As efficiency metrics, we calculated incremental cost-effectiveness, and harm-benefit, ratios (ICER/IHBR), defined as the additional costs, or the additional number of colposcopies, per additional CIN2+ detected. We estimated capacity requirements and uncertainty surrounding which strategy is optimal according to the decision-rule, involving willingness-to-pay (monetary or resources consumed per added benefit).

Results: For ages 25-33, we eliminated four strategies that did not fall on either efficiency frontier, while one strategy was efficient with respect to both efficiency metrics. Compared to current practice in Norway, two strategies detected more precancers at lower monetary costs, but some required more colposcopies. Similar results were found for women ages 34-69.

Conclusions: Improving the effectiveness and efficiency of cervical cancer screening may necessitate additional resources. Although efficient and feasible, both society and individuals must specify their willingness-to-accept the additional resources and perceived harms required to increase effectiveness, before a strategy can be considered optimal.

Background [First-level Header]

The efficiency, feasibility and optimality of new health interventions are important criteria that stakeholders often need to consider simultaneously when choosing between multiple competing strategies (*e.g.*, alternative cancer screening algorithms). Because it is often not feasible for clinical trials to evaluate all possible aspects related to new health interventions, decision-analytic modeling, an approach to provide epidemiologic projections and policy guidance, is gaining acceptance [1]. This quantitative framework formally synthesizes available data and explicitly incorporates decision uncertainty [2]. Analytic modeling can enumerate multiple outcomes of interest associated with each candidate strategy, and can easily be extended to evaluate multiple epidemiologic and resource outcomes. While it is more common for decision analyses to examine the value of alternative strategies in terms of the monetary costs and quality-adjusted life-years gained, however, evaluating resource use and harms to patients has received less attention, but is often of interest to decision-makers. For example, alternative strategies often involve multiple tradeoffs such as surrogate endpoints in terms of benefits and harms to patients, as well as capacity requirements in the health service delivery, which may help predict resource use at different levels of the health system. These outcomes, however, may help inform individual-level decision-making (*i.e.*, patients), thus complementing cost-effectiveness analyses and ensuring the viability of new health care interventions.

Recently, Norwegian decision-makers, who were tasked with improving the current organized cervical cancer screening program, were interested in evaluating the impact of alternative screening strategies on precancer detection, total costs and number of colposcopy referrals. In Norway, current cervical cancer prevention strategies include triennial Pap smear (cytology)-based screening, nationally organized since 1995, and a school-based HPV vaccination program for 12-year old girls since 2009. Nonetheless, cervical cancer remains the third most common cancer among women aged 25-49 [3], contributing to motivate decision-makers to evaluate alternative screening guidelines that could improve screening program effectiveness. Following advances in cervical cancer screening technology, Norwegian decision-makers considered how to augment the current program by introducing retesting of a woman's initial cytology sample for HPV (called reflex HPV testing), in order to guide the management of

women with atypical or low-grade cytology results (ASC-US and LSIL). Multiple stakeholders aimed to maximize the detection of high-grade precancerous lesions (*i.e.*, CIN2+), while simultaneously keeping the number of required consultations, losses to follow-up, and diagnostic tests (especially colposcopies) with their associated harms and monetary costs at an acceptable level. Furthermore, of particular interest to decision-makers was what would happen within a single screening round. In July 2014 an updated algorithm for the follow-up of screen-positives utilizing reflex HPV testing was implemented by the Norwegian health authorities.

The health benefits achieved by national screening programs, in terms of reduced morbidity and mortality [4-6], demand health care resources with an opportunity cost and involve potential harms to patients throughout the screening process (screening test, diagnostic test and treatment). Although the evidence is sparse, anxiety among both participants and non-participants may result from invitation to the screening program and subsequent diagnostic procedures as well as awaiting test results [7-9]. Furthermore, diagnostic confirmation of high-grade precursors requires a semi-invasive procedure, *i.e.*, colposcopy directed biopsy, which may induce pain, bleeding or discharge [10]. If a high-grade precursor (CIN2+) is detected, the woman is advised to undergo conization, an excisional procedure usually performed under local anesthesia, with associated adverse effects such as bleeding, discomfort, and occasionally infections. Conizations have also been associated with increased risk of late-term abortions, preterm delivery, low birth weight, and caesarean section [11, 12]. Moreover, population-based screening results in some degree of over-treatment, as the majority of those who undergo conization would never develop invasive cervical cancer [13]. It is unknown, however, both *ex ante* and *ex post*, which high-grade lesions would progress to cancer or regress spontaneously, and in the absence of more accurate progression markers, generally all CIN2+ lesions are treated among women aged 25 years and over. For women younger than 25 years with well-defined and visible precursor lesions, and during pregnancies, these lesions can be followed up without immediate treatment because of higher regression rates [14]. Screening and treatment guidelines must deal with a fundamental trade-off between the potential harms and benefits caused by the detection and removal of high-grade lesions. Furthermore, increased effectiveness may necessitate additional resources, requiring both available health care capacity, and a willingness to pay the additional resource costs, in order for the strategies to be viable and optimal.

Decision-analytic models have been previously applied to cervical cancer screening in Norway and elsewhere [15-17]; however, investigating surrogate endpoints and resource use in natural units have received less attention. While traditional cost-effectiveness analyses focus on the additional monetary cost per additional (quality-adjusted) life-year gained, our analysis offers a more comprehensive investigation of outcomes associated with candidate cervical cancer screening strategies. In particular, we projected the short term (*i.e.*, through a single screening round) monetary cost and required colposcopies per additional precancer detected associated with alternative strategies. Our objective was to provide Norwegian stakeholders with a formal consequence analysis to isolate screening strategies that were simultaneously efficient, feasible and optimal according to a set of efficiency metrics.

Materials and methods [First-level Header]

Analytical approach [Second-level Header]

In a decision-making process, initial steps involve the identification of relevant candidate strategies, outcomes and efficiency metrics. We defined strategies and outcomes in collaboration with multiple stakeholders, including clinicians, economists and representatives of management and advisory groups of the Norwegian Cervical Cancer Screening Program. We included strategies that had been outlined by the stakeholders who were tasked with improving the current screening program. In order to assist the stakeholders to determine the optimal screening algorithm, we defined efficiency metrics according to their primary concerns, namely, how these strategies would perform in terms of precancer detection, colposcopy referrals and total costs, within one screening interval. Consequently, we defined two efficiency metrics. For our primary analysis, we conducted a harm-benefit analysis by calculating incremental harm-benefit ratios (IHBRs) defined as the additional number of colposcopies required to detect an additional CIN2+ compared to the next most “harmful” strategy. In addition, we performed a cost-effectiveness analysis and investigated the incremental cost-effectiveness ratios (ICERs) in terms of additional costs per additional CIN2+ detected of a strategy compared with the next most costly strategy.

In order to detect efficient strategies, we first excluded strategies that resulted in higher harms/costs and lower benefits than others (strongly dominated), or higher harms/costs per additional benefit compared with the next most harmful/costly strategy (weakly dominated), and then calculated the IHBRs/ICERs for the non-dominated strategies. In the traditional cost-effectiveness framework, a strategy is considered "good value for money", or cost-effective, if its ICER is below the value of the decision threshold, *i.e.*, the willingness-to-pay for an additional unit of the outcome (in this case; CIN2+). In contrast to analyses where health benefits are measured in life-years or quality-adjusted life-years, there is no established threshold which constitutes a reasonable relationship between costs and health benefits when measured in natural units, such as CIN2+ [18]. Similarly, there is no established benchmark for how many additional colposcopies women are willing to accept for one additional detected CIN2+. Therefore, we explored the optimal strategy as a function of the willingness-to-pay or willingness-to-accept thresholds, depicted in harm-benefit and cost-effectiveness acceptability curves. Finally, due to capacity constraints in Norwegian pathology laboratories, we investigated the feasibility of the alternative strategies by calculating the relative resource use (*i.e.*, number of tests and colposcopies) required by each strategy compared with the baseline strategy (Strategy 1).

We adopted a societal perspective, and discounted costs and health benefits by 4% per year, consistent with Norwegian guidelines for economic evaluations [19]. We incorporated parameter uncertainty through probabilistic Monte Carlo simulation with 10,000 samples. In accordance with recommended modeling practice [20], we assigned beta distributions to all positivity rates (*i.e.*, the probability of having a positive test), proportions, and diagnostic test characteristics. We further assigned gamma distributions to all cost parameters, and Poisson distributions to count variables. In line with 'good modeling practice' [21], we confirmed the face validity of model inputs, *i.e.*, clinical assumptions and epidemiologic data, with Norwegian experts, to ensure model components are in accordance with current knowledge. We validated the model internally using an iterative approach involving cross-checking model equations and inputs against their sources, in addition to using TreeAge's (2013) debugging and validation tools [22].

Model overview and screening strategies **[Second-level Header]**

We developed a probabilistic decision tree model that simulated a cohort of women from the initial screening test (index test) through one screening round of follow-up (*i.e.*, three years), using the software TreeAge Pro 2014. We compared a baseline screening strategy (*i.e.*, the Norwegian screening algorithm used until July 2014 (Strategy 1)) with nine alternative HPV-based triage strategies (Strategies 2-10) that varied the follow-up of women with low-grade lesions and inadequate cytology results (Fig. 1 and Table 1). The baseline strategy (Strategy 1) involves primary Pap smear-based screening every three years. Women with an ASC-US or LSIL result are triaged with repeat cytology in combination with HPV test 6-12 months after the initial test. In contrast, all alternative strategies involve reflex HPV testing in triage of women with ASC-US or LSIL, *i.e.*, using the same specimen from the cytologic test to analyze for high-risk HPV types, followed by diagnostic work-up according to the cytology/HPV result. We also investigated the added value of applying a reflex HPV test to inadequate cytology results versus repeat cytology in three months. One of the alternative strategies, Strategy 10, represents the recently implemented strategy in Norway as of July 2014, hereafter referred to as the recent strategy (Fig. 1).

For all analyses, we maintained the 3-year screening interval and kept diagnostic work-up for women with high-grade cytology results (ASC-H/HSIL) constant. In order to account for the likely switch to primary HPV testing for women aged 34-69 following an implementation study slated to begin in the first half of 2015, we stratified our analyses for women aged 25-33 and 34-69. In order to reflect the impact of compliance with the optimal strategy, we assumed age- and referral-stratified loss-to-follow-up per procedure (*i.e.*, the risk that women with abnormal screening results drops out of screening and does not return) in line with observed Norwegian data (Table V in Supplemental Material). Primary outcomes included the number of CIN2+ detected and number of colposcopy referrals per 100,000 screened women for each strategy. In addition, we estimated the expected number of cytologic and HPV tests performed, the number of physician consultations, and costs associated with diagnostic testing and analysis, including time- and travel-costs for women to attend screening. The Cancer Registry of Norway, the University Hospital of North Norway and Norwegian fee schedules [23-25] were used to inform

Norwegian-specific epidemiologic parameters and estimate screening costs. Where Norwegian data did not exist, we supplemented the model inputs using published literature and expert opinion.

Epidemiologic data [Second-level Header]

We used data from the Cancer Registry of Norway for the positivity rate of primary cytology as well as secondary screening outcomes in our baseline strategy (Table 2). In addition, we used data on the number of observed CIN2+ in Norway to calibrate the baseline prevalence of CIN2+ at 3.3% for ages 25-33 and 0.8% for ages 34-69 (for additional information on the calibration process, see Part II in Supplemental Materials). We extracted data from cervical cancer clinical trials in Europe and the United States in situations where Norwegian data were not available (see Part I in the Supplementary Materials). As HPV testing has not yet been performed in primary screening in Norway, we used data from published literature as a proxy for expected positivity rates for primary reflex HPV testing as well as subsequent follow-up parameters (Table 2) [26-33].

Data on the natural history of disease and the accuracy of screening diagnostics were derived from published literature [34-46]. The model does not differentiate between HPV genotypes, in addition, we did not allow for progression from 'negative for intraepithelial lesion or malignancy' or 'cervical intraepithelial neoplasia grade 1' (NILM/CIN1) to CIN2+ given the short 3-year time perspective of the analysis. To reflect the natural course of CIN2+, however, we allowed precancerous lesions to regress to CIN1 or no lesion. We also assumed that 49% of HPV-infections regressed within 12 months [39, 40, 42-44], and represented the natural history of CIN2+ by a time-dependent monthly regression rate (7% for the initial 12 months [38, 41], and 2% thereafter [36]).Finally, screening test characteristics and probability of regression of CIN2+ were based on published studies and meta-analyses (Table 2). We assumed that the sensitivity of liquid-based cytology (LBC) was 71.5% [95% CI: 62.9-78.8] [34], 90% [95% CI: 88.0-93.0] [35] for HPV testing, and 76.2% [95% CI: 73.3-79.1] for colposcopy with biopsy [37, 45, 46].

Cost data [Second-level Header]

Cost data were obtained from a recently published cost analysis of cervical cancer screening in Norway (Table 2) [47]. We identified the following cost-components in cervical cancer screening: cost of general practitioner (GP) visit and gynecologist consultation including information to patients about test result; laboratory costs of analyzing LBC, HPV test and biopsy; cost of performing colposcopy/biopsy at hospital or gynecologist; and, patient time- and travel-costs incurred by screening consultations. Quantification of consultations and procedures was determined endogenously from the model based on the enumeration of consultations diagnostic tests performed. We assumed, however, that a primary care test (cytology and/or HPV test) and diagnostic colposcopy/biopsy would require two and four hours of the patient's time, respectively. Direct medical costs were valued based on actual resource use in Norwegian pathologic laboratories in addition to national fee schedules [48-50]. Indirect costs included patient travel time in terms of opportunity cost of work absenteeism, and travel costs. To estimate the value of work absenteeism and of time we used the national wage rate data [51]. Finally, we used data on travel costs from a previous published cost analysis of breast cancer screening in Norway [52]. In line with our primary outcome of detected CIN2+, we excluded CIN2+ treatment costs from the cost calculations. All costs were expressed in 2013 Norwegian Kroner (NOK), and converted to US Dollar (USD) (1 USD$ = NOK6.35). We captured uncertainty in costs using plus-minus 20% the point estimate. More information about cost calculations is available in Part 3 in the Supplementary Materials.

Results [First-level Header]

Efficiency [Second-level Header]

For women aged 25-33, seven of the ten strategies were either strongly or weakly dominated with respect to additional costs per additional CIN2+ detected (Figure 2). Of note, dominated strategies included both the previous (Strategy 1) and the newly implemented (Strategy 10) strategies. Among the strategies on the cost-effectiveness efficiency frontier, the ICERs ranged from $1,922 to $11,550 per CIN2+ detected (Table 3). With regards to benefits and harms, only six strategies were dominated and excluded from the analysis (Fig. 2). For the remaining strategies on the harm-benefit efficiency frontier, the IHBRs ranged from 2.93 to 10.91 additional colposcopies per additional precancer detected (Table 3). When incorporating both cost-effectiveness and harm-benefit outcomes, only one strategy remained on the

frontiers for both efficiency metrics. Similar trends follow for women aged 34-69; results are presented in Part 4 in the Supplementary Materials.

Feasibility **[Second-level Header]**

We evaluated the feasibility of each strategy on the efficiency frontiers by estimating the relative resources required, in terms of additional costs and colposcopies, compared to the baseline strategy (Strategy 1). The relative effectiveness, cost, and colposcopy use for each strategy on the efficiency frontiers, compared to the baseline strategy, are presented in Table 3. The strategy (Strategy 5) that was identified as efficient by both cost-effectiveness and harm-benefit efficiency metrics, provided more benefits (36% increase in CIN2+ detection) for similar use of monetary costs, but required more colposcopies (66%) compared to the baseline strategy. Strategies 7 and 3 projected a 1% and 32% increase in the number of CIN2+ detected, while simultaneously reducing costs by 4% and 1%, respectively. For the four strategies that were efficient with respect to colposcopy use (Strategies 6, 8, 4 and 5), one strategy (Strategy 8) detected 2% more CIN2+ while simultaneously requiring 6% fewer colposcopies. For strategies 4 and 5, 28% and 36% more precancers could be detected at a cost of 47% and 66% more colposcopies, compared to current guidelines, respectively. Consequently, while Strategy 8 provides an opportunity for a resource-saving intervention, implementing Strategies 4 and 5 would require additional colposcopy resources, in order to be feasible. Moreover, the potential increase in CIN2+ detection afforded by the efficient strategies require that health care resources for the treatment of detected CIN2+ are available, in order to be deemed viable.

Optimality and uncertainty **[Second-level Header]**

The ICERs and IHBRs presented in Table 3 represent the threshold value of a decision rule required for a strategy to be deemed optimal, in terms of the willingness-to-pay financially, and the willingness-to-accept additional colposcopies per additional detected precursor, respectively. Parameter uncertainty surrounding which strategy is optimal for given values of the decision rule is presented in the cost-effectiveness and harm-benefit acceptability curves (Fig. 3). As the willingness-to-pay and willingness-to-

accept values increase, the more effective strategies become increasingly 'cost-effective' in the majority of iterations. For example, the two most effective strategies in terms of CIN2+ detection, Strategy 4 and 5, were cost-effective in the majority of iterations given a willingness-to-accept 6 and 12 additional colposcopies, per additional CIN2+ detected, respectively. Furthermore, Strategy 5 was cost-effective in the majority of iterations given a willingness-to-pay $12,000 per additional CIN2+ detected.

Discussion [First-level Header]

The results of our case example indicate that that there is a potential for improving the baseline screening algorithm by implementing reflex HPV testing for women with inadequate or low-grade cytology results, both for women aged 25-33 and 34-69. Four strategies were dominated with respect to either cost-effectiveness or harm-benefit outcomes, and were excluded from consideration and further analyses. Among the efficient strategies, the incremental cost-effectiveness and harm-benefit ratios were closely related as colposcopy referrals could also be interpreted as a proxy for monetary costs. Our analysis highlights the important, but not so often discussed, trade-offs in cervical cancer screening, and further explores how multiple outcomes can be assessed independently in a single analysis. We provide decision-makers with a set of strategies that are efficient with respect to total costs and number of colposcopies, respectively. Moreover, we report the required capacity for these strategies to be feasible. Finally, we inform decision-makers about the willingness to pay and accept additional costs and harms needed in order for these strategies to be optimal. For example, the most effective strategy was projected to detect 36% more precancer compared to what is currently the case in Norway (baseline strategy), but, despite similar cost levels, required 66% more colposcopies. In order for these strategies to be optimal, capacity requirements must be met by the health sector, and decision-makers as well as individual women must be willing to accept additional costs and colposcopies.

We found that harm-benefit acceptability curves represent a useful method for expressing harm-benefit trade-offs explicitly, while simultaneously incorporating uncertainty in the estimates. The model can be used to assess the potential impact of various screening strategies in terms of CIN2+ detection and the accompanying resource requirements. For decision-makers worldwide concerned with health

care interventions, our analysis illustrates how the cost-effectiveness framework can be used to quantify and assess multiple trade-offs independently in a single analysis, while also considering capacity constraints. Moreover, decision-makers in other cervical cancer screening settings with similar screening algorithms, diagnostic accuracy and underlying risk of CIN2+, may use the results of our study in their evaluation of potential screening algorithms and the associated tradeoffs between benefits and harms. In turn, the model can serve as a tool for screen-eligible women to balance the screening trade-offs according to their preferences for harms contingent to the benefits. Ultimately, by allowing women to decide which strategy is optimal according to their willingness to accept additional harms for additional benefits, the harm-benefit acceptability curves introduce a potential framework for shared decision-making in screening follow-up. For instance, for the younger ages, we projected that the guidelines in Norway until 1st July 2014 (*i.e.*, baseline strategy) entailed 2.6 colposcopies per CIN2+ detected. This harm-benefit ratio may represent a good benchmark for how many colposcopies women are currently willing to accept in order to achieve the current benefits of screening. If this is the case, only the resource-saving strategies (*i.e.*, Strategy 6 and 8) would be considered optimal. With higher thresholds for willingness-to-accept harms and costs, more alternative strategies become available, with the baseline strategy as well as the recently implemented strategy in Norway ranking among the most conservative, and therefore least effective in terms of CIN2+ detection.

Even though modeling provides a useful tool for quantifying outcomes of multiple intervention strategies, a model is only as good as its inputs and structure, and our model has several limitations. Most importantly, the model predicts cancer precursors and not invasive cancer. The aim of cervical cancer screening is not to detect the most precursors, but to prevent the most cancers, thus the optimal strategy will depend on the extent to which cancer precursors progress to cancer or regress. We acknowledge the limitation that our model does not utilize cancer as an endpoint, but rather utilizes the surrogate endpoint of CIN2+. As CIN2+ is the treatment threshold, however, it is an important endpoint that was specifically requested by Norwegian decision-makers. Although screening harms are a composite of anxiety and pain, as well as time and travel costs, associated with physician consultations and screening procedures, we chose number of colposcopies as our primary outcome to represent the harms of screening. We find that the number of colposcopies is a meaningful outcome in the analysis, as

decision-makers aim to keep the referral rates at an acceptable level, both because of its cost-driving nature and due to the harms caused to women. In the model, we accounted for loss-to-follow-up, though it may be argued that noncompliance should not influence which strategy is optimal and that dropout rates should only be included in secondary analyses. Loss-to-follow-up, however, is a serious concern in screening policy, and the effect of screening is likely reduced due to inadequate follow-up of abnormal screening results. Additionally, imperfect screening coverage is also of concern and limits the population effects of screening [53]. More than half of new cases of cervical cancer occur in women who have not had a Pap smear exam the last 3.5 years before diagnosis [54]. Consequently, we found it important to take into account the impact of compliance on screening outcomes, and thus we employed up-to-date, age- and referral-stratified dropout rates in Norway. Another aspect of our inputs relates to the modeling of positivity rates rather than specificity. Modeling screening requires that one or the other is determined endogenously, and both alternatives introduce potential limitations. We chose to model positivity rates rather than the specificity of a diagnostic test, as we felt more confident in the observed positivity rates, having observed that the specificity for CIN2+ tends to vary with the prevalence [32, 55]. Positivity rates, however, may be dependent upon the context of retrieval (*e.g.*, characteristics of the study population), and the generalizability from international studies to the Norwegian context may be limited. Yet, modeling requires the use of best available, *existing* data, and can be updated as knew knowledge occur.

Nevertheless, more research is needed in deciding the optimal combination of benefits, harms and resource use in cervical cancer screening. In essence, enhanced knowledge of the progression and regression of cancer precursors given individual screening record, may contribute to achieve tailored individual optimizations in terms of avoiding unnecessary procedures for women with lesions likely to regress, and seamless diagnostic work-up of women with lesions likely to progress. Moreover, there is a need to acquire increased knowledge of women's preferences regarding the trade-off between reduced risk of cervical cancer and the screening side-effects, involving both short-term responses such as anxiety and pain associated with screening procedures, as well as long-term consequences of treatment in terms of childbirth complications. Knowing these preferences is crucial to underpin the decision rule of how much society is willing to pay for detecting an additional precancerous lesion, in terms of both monetary

costs and colposcopies performed, and in turn, deciding the optimal combination of benefits, harms and resource use.

Conclusion [First-level Header]

Screening for cervical cancer implies multiple trade-offs between benefits (preventing invasive cancer), harms (unnecessary procedures) and resource use (*e.g.*, monetary costs and physician consultations). In Norway, it would be possible to detect more cancer precursors at lower costs in terms of harms and resource use. In general, however, more effective strategies also require more colposcopies and monetary costs. Ideally, the choice of strategy should be based on defined efficiency measures, thorough feasibility calculations, and finally, which strategy is optimal should be based on society's willingness to pay costs and women's willingness to accept harms.

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