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# The value of improving failures within a cervical cancer screening program: An example from Norway

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**Failures in cervical cancer (CC) screening include nonparticipation, underscreening and loss to follow-up of abnormal results. We estimated the long-term health benefits from and maximum investments in interventions targeted to improving compliance to guidelines while remaining cost-effective. We used a mathematical model empirically calibrated to simulate the natural history of CC in Norway. A baseline scenario reflecting current practice using cytology-based screening was compared to scenarios that target different sources of noncompliance: (*i*) failure to follow-up women with abnormal results, (*ii*) screening less frequently than recommended (*i.e.*, underscreening) and (*iii*) absence of screening. A secondary analysis included human papillomavirus (HPV)-based screening as the primary test. Model outcomes included reductions in lifetime cancer risk and incremental net monetary benefit (INMB) resulting from improvements with compliance. Compared to the *status quo*, improving all sources of noncompliance leads to important health gains and produced positive INMBs across a range of developed-country willingness-to-pay (WTP) thresholds. For example, a 2% increase in compliance could reduce lifetime cancer risk by 1–3%, depending on the targeted source of noncompliance and primary screening method. Assuming a WTP threshold of $83,000 per year of life saved and cytology-based screening, interventions that increase follow-up of abnormal results yielded the highest INMB per 2% increase in coverage [$19 ($10–21)]. With HPV-based screening, recruiting nonscreeners resulted in the largest INMB [$23 ($18–32)]. Considerable funds could be allocated toward policies that improve compliance with screening under the current cytology-based program or toward adoption of primary HPV-based screening while remaining cost-effective.**

Organized cervical cancer (CC) screening programs are credited with significant reductions in cancer risk and death, but areas for improvement nonetheless exist. Surveillance of three Nordic screening programs has indicated that at least half of all CCs are diagnosed among women who are noncompliant with screening guidelines, identifying potential areas for improvement in program goals.[1–3] Specifically in Norway, roughly 65% of eligible women attend cytology-based screening every 3 years in compliance with national guidelines, but the remaining never attend (*i.e.*, nonscreeners) or attend less frequently than the recommended interval (*i.e.*, underscreeners). In addition, at least 35% of women with abnormal results fail to return within 1 year for follow-up testing as recommended.[4]

Interventions to increase screening participation and adherence to guidelines, such as mass-media campaigns, prescheduling appointments,[5] reminder letters[6,7] and telephone reminders,[6] have been explored. Surveillance of the Norwegian screening program indicates that after repeated reminder letters, screening coverage rates increased to nearly 80% within a 5-year period.[4] Conceivably, more intensive interventions aimed at improving screening compliance could yield even greater benefits. In addition, primary human papillomavirus (HPV) testing for women over age 30, not yet adopted in Norway, could improve CC prevention in a cost-effective manner.[8] Importantly, primary HPV testing may also facilitate improved coverage rates through the use of patient-collected (*i.e.*, self) sampling.[9]

Studies that assess interventions to increase participation are often limited to reporting outcomes in terms of the percent increase in coverage as longer term health gains, such as cancer reduction or life expectancy gains, are not readily observable.[10] In addition, few studies evaluate whether the gains in coverage justify the additional cost associated with programs to decrease noncompliance. Studies that can translate the surrogate endpoint of coverage into a meaningful clinical benefit and measure costs are able to assess the value of the intervention. In the absence of trials, decision-analytic

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**What's new?**
**Diagnosis of cervical cancer often occurs in women who do not participate in screening programs or visit less frequently than recommended. This Norwegian study quantifies the value of improving failures in current cervical cancer screening practices. The study demonstrates that the largest gains in health involve improvements in participation among women lost to follow-up after an abnormal test result, as well as recruiting previously unscreened women, underscoring the benefit of allocating public funds to the targeted strengthening of participation and adherence of women to existing screening programs.**

models can help estimate the downstream impact of reducing failures in the screening program and determine whether investing in interventions to increase participation is a valuable use of scarce resources. Therefore, we conducted a model-based analysis to estimate the additional health benefits associated with programs to improve compliance to CC screening, as well as the maximum amount that can be invested for these programs to remain cost-effective.

## Methods

### Analytic overview

We used a model-based approach, using an existing individual-based (*i.e.*, first-order) Monte Carlo model that simulates the natural history of CC. The model was empirically calibrated to reflect the burden of HPV and cervical disease in Norway and was previously used to evaluate HPV-based screening strategies.[8] In our analysis, we compared a baseline scenario representing *status quo* cytology-based screening and participation to scenarios that target three different failures in screening: (*i*) absence of screening, (ii) underscreening and (*iii*) loss to follow-up after an abnormal result. Model outcomes included reductions in lifetime risk of cancer, discounted life expectancy and lifetime costs under different scenarios of improved screening compliance. Cost-effectiveness results were expressed in terms of incremental net monetary benefits (INMBs), which translate the additional benefit and costs of an intervention into a single unit of monetary cost for a given willingness-to-pay (WTP) threshold. The WTP, or cost-effectiveness, threshold signifies the amount society is willing to pay for a unit of health benefit, such as a year of life saved (YLS), and can be regarded as the amount below which an intervention may be considered "good value for money." Multiplying the incremental benefit accrued from one intervention compared to another by the WTP threshold allows the monetization of the benefit, which can then be compared against the intervention's incremental cost. Interventions with a positive INMB are considered cost-effective. We used the INMB, expressed on a per-woman basis, as a proxy for the maximum cost that could be additionally incurred before the incremental cost-effectiveness ratio associated with the intervention exceeds the WTP threshold, or in other words, the maximum added cost that could be spent to improve screening. In the base case, we assumed a WTP threshold of 500,000 Norwegian Kroner (NOK) (83,000 U.S. dollars) per YLS in Norway[11]; however, we also explored a threshold range often cited in the United States (*i.e.*, \$50,000–\$100,000 per YLS) to reflect the lack of consensus around a single threshold and to facilitate international comparisons.

### Model

Individual girls enter the model at age 9 (before sexual initiation) with a healthy cervix, and at each month, face age-dependent probabilities of type-specific HPV incidence and clearance, progression and regression of precancerous lesions and progression to cancer. The model tracks and records outcomes for a cohort of women, such as the number of detected cancers and the discounted (4% per year) life expectancy and cost associated with each strategy. The model allows for complex pathways (*i.e.*, screening, treatment and expenditures) between individual women to be recorded. This accounts for a large amount of heterogeneity between individual women with respect to screening compliance and history, arguably the most important risk modifier of CC risk. As reported previously,[8] the model was calibrated, using a likelihood-based algorithm, to empirical epidemiological outcomes observed in Norway including age-specific prevalence of HPV-16, −18[8] and high-grade precancerous lesions,[12,13] type distribution of HPV-16, −18 in high-grade precancerous lesions[14] and prescreening age-specific cancer incidence rates from the Cancer Registry of Norway (1953–1969). Observational data from Northern European[15–17] and Canadian[18] cancer registries suggest that an elevated (10–60% higher) baseline risk of CC may exist among nonparticipants. Therefore, we calibrated baseline input values for two populations: (*i*) a higher risk population for the 10% of nonscreeners and (*ii*) a lower risk population for the 90% of women who either underscreen or who are lost to follow-up. The calibration process resulted in multiple parameter sets that fit well to the empirical data; we elected to use 50 "good-fitting" sets for each population in analyses to reflect uncertainty in input values (see Supporting Information Fig. 1). To estimate the population-level outcomes we calculated the weighted average of the expected costs and benefits between these two populations. Credible bounds (CBs) for the INMB represent the minimum and maximum values across the good-fitting parameter sets. To reflect decision making from a societal viewpoint, we included all direct medical and nonmedical costs (*e.g.*, transport costs) as well as patient time costs associated with screening, management and treatment (Table 1). All costs were measured in 2010 NOK and converted to U.S.

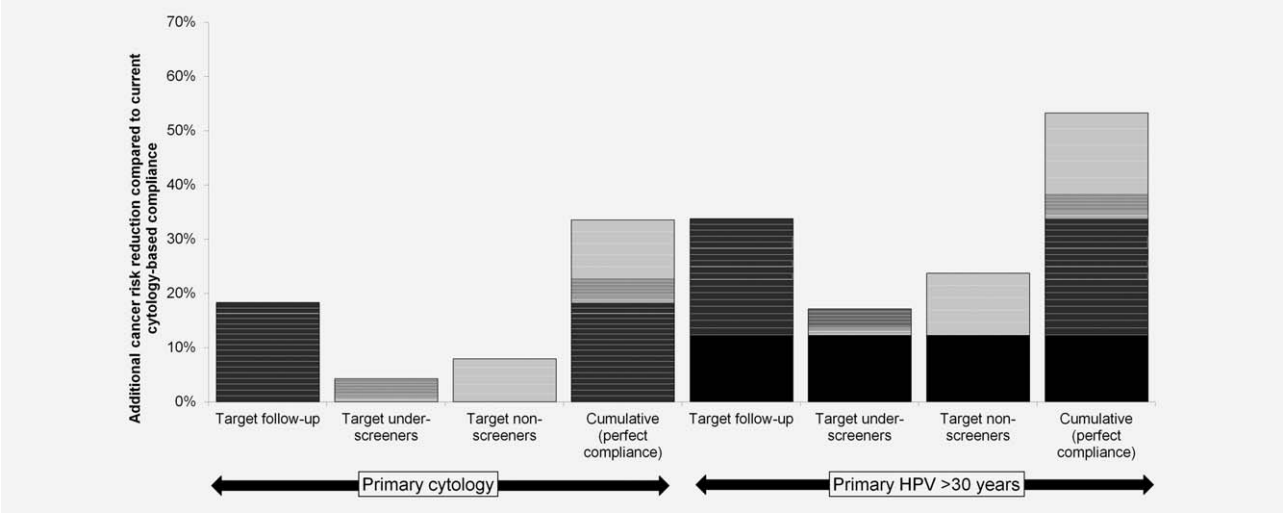


**Figure 1.** Additional cancer risk reduction and incremental net monetary benefit (INMB) associated with targeted interventions to improve compliance to screening guidelines. The height of each bar corresponds to the *y*-axis (additional cancer risk reduction compared to *status quo* screening using cytology) for increasing compliance to 100% within each scenario or for an incremental (2%) increase in screening adherence, designated by white lines. The reductions associated with human papillomavirus (HPV)-based scenario are inclusive of the benefit (designated by the darkest solid box) associated with switching current screeners to primary HPV testing for women aged 30 years or older. For the primary HPV testing strategy, we assumed that women with a positive HPV test underwent additional cytology testing. Those who were both HPV- and cytology-positive (*i.e.*, atypical cells or worse) were referred directly to colposcopy; for women HPV-positive but cytology-negative, two additional persistent HPV-positive, cytology-negative results were required (each 12 months apart) before prompting referral to colposcopy.

dollars (U.S. $) using the average annual 2010 exchange rate (U.S. $1 = NOK 6.05).[19] Total lifetime costs associated with the scenarios of increased participation included the upfront screening costs as well as any downstream costs incurred (or averted) for diagnosis and/or treatment of precancer and invasive cancer. Details of the calibration process and cost estimation methods have been reported elsewhere.[8,20–22]

### Scenarios

Published screening rates in Norway[4] were used to estimate a distribution of screening frequency and compliance across the simulated cohort of women. We assumed 10% were nonscreeners, 65% complied with triennial screening and the remaining 25% were underscreeners (*i.e.*, 10, 5 and 10% of women were screened every 4, 5 and 8 years, respectively). Of those women requiring triage testing or diagnostic colposcopy, we assumed that 64% complied. We compared this baseline *status quo* scenario to three scenarios that improve different sources of noncompliance: (*i*) increasing follow-up after an abnormal result, (*ii*) increasing screening frequency among the underscreened and (*iii*) increasing recruitment of previously unscreened women to attend triennial screening (but assuming the same 64% compliance after an abnormal result). For a woman who does not comply, the model requires the individual to wait until her next primary screening month where she will have an opportunity to be rescreened (*i.e.*, the individual in not permanently lost to follow-up). We also considered a fourth scenario that improves all three issues simultaneously, essentially mimicking perfect compliance with guidelines. We assessed each scenario assuming primary cytology-based testing (current practice) but repeated all analyses assuming primary HPV testing for women over age 30. For Scenarios 1–4, we calculated the INMB of reaching full compliance and interpreted this value as an upper bound of the amount that could be spent to improve adherence for each source of noncompliance. To allow for comparison and prioritization between scenarios, we then recalculated the INMB assuming a common absolute increase (*i.e.*, 2%) in participation in each scenario. In sensitivity analysis, we explored the impact of varying input costs, screening test characteristics and lengthening (to 5 years) the primary HPV screening interval (assuming the same distribution of compliance) on results.

## Results

### Cancer risk reduction

After undergoing calibration for the two risk groups, the model estimated a 28% higher background risk of CC for the high-risk population than the low-risk population. Assuming the *status quo* screening program in Norway, the model projected a population-level lifetime CC risk of 1.0% (CB: 0.7%, 1.3%) and a risk before age 65 of 0.7% (CB: 0.5%, 0.9%). These model estimates are consistent with the empirical data from the Cancer Registry of Norway that reports a 0.9% cumulative risk of CC by age 75.[4] Following-up women who are currently noncompliant after an abnormal test (*i.e.*, Scenario 1) would reduce

Table 1. Selected model inputs

| Costs | Baseline ($) | Range ($) |
|---|---|---|
| **Screening** | | |
| Cytology | 49 | 8[1] |
| hr-HPV DNA testing[2] | 62 | 54[1] |
| Office visit[3] | 160 | 80–320 |
| Colposcopy with biopsy[3] | 340 | 170–670 |
| **Treatment**[3] | | |
| High-grade precancer | 2,200 | |
| Local | 25,800 | 12,900–51,500 |
| Regional | 51,600 | 25,800–100,200 |
| Distant | 59,600 | 29,800–119,300 |
| **Test characteristics** | **Baseline (%)** | **Range (%)** |
| **HPV DNA**[4] | | |
| Probability of HR-HPV given high-grade precancer or worse | 85 | 62–99 |
| Probability of no HR-HPV given no high-grade precancer | 89 | 85–94 |
| **Cytology**[5] | | |
| Probability of abnormal cytology given low-grade precancer | 70 | 50–70 |
| Probability of abnormal cytology given high-grade precancer or worse | 80 | 50–80 |
| Probability of normal cytology given normal histology | 95 | |

All costs are expressed in 2010 U.S. dollars (U.S. $ = NOK 6.05).
[1]Based on published reimbursement fees.
[2]Shares co-collection fee for cytology.
[3]Includes patient time and transport, rounded. Surveillance of women after treatment for high-grade precancer varies in clinical practice but was assumed to involve three negative primary screening results before returning to routine screening. The model records all costs associated with post-treatment surveillance.
[4]Probability of hr-HPV DNA positivity given hr-HPV is assumed to be 100%, but reduced to 90% in sensitivity analysis.
[5]Abnormal cytology is defined as atypical squamous cells of undetermined significance (ASCUS) or worse.
Abbreviations: hr-HPV: high-risk human papillomavirus; DNA: deoxyribonucleic acid; Local: Stage Ia–IIa; Regional: Stage IIb–IIIb; Distant: IVa–IVb.



lifetime cancer risk by 18% compared to the *status quo* (Fig. 1, left). Resolving all screening failures simultaneously (*i.e.*, Scenario 4) was projected to reduce cancer risk by 34% compared to the *status quo*. Even without improvements in screening compliance rates, switching to an HPV-based program in women over age 30 was expected to reduce cancer risk by 12% compared to current cytology-based screening (Fig. 1, right). Achieving perfect compliance to guidelines using primary HPV testing increased this reduction to nearly 51% compared to *status quo* participation using cytology. Per 2% increase in the follow-up rate, the expected cancer risk reduction was 1% under the current cytology-based screening program and nominally higher under a program that adopts HPV testing for older women. Every 2% increase in uptake by nonscreeners reduced cancer risk by 1.6% using cytology and by 2.3% using HPV testing. When screening recruitment was accompanied by perfect follow-up compliance after an abnormal result, the cancer risk reduction increased to 2.3 and 3.0%, respectively.

### INMB with maximized compliance

Given a WTP threshold of $83,000 per YLS, all but one scenario produced positive INMBs compared to the *status quo*. That is, the incremental value of increasing participation exceeded the added lifetime costs in each scenario (Fig. 2). For example, we interpreted the INMB for perfect follow-up of abnormal results of $335 (CB: $179, $372) as the maximum amount that could be spent on average per woman over her lifetime before an intervention to improve follow-up is no longer cost-effective. For a birth cohort of ~30,000 Norwegian females eligible for screening, this equates to nearly $10 million that could be allocated to achieve perfect follow-up over their lifetime. By comparison, the INMBs of improving screening frequency for underscreeners and recruiting previously unscreened women to screening were far lower (Figs. 2*b* and 2*c*). Simultaneously improving all screening failures (*i.e.*, perfect compliance) yielded an INMB of $453 (CB: $227, $545) per woman (Fig. 2*d*). Under this best-case scenario, nearly $14 million could be allocated across a birth cohort of 30,000 screen-eligible women and still remain cost-effective. The INMB and uncertainties around these values as a function of different WTP threshold values are shown for each of the four scenarios in Figure 2.

Simply switching to HPV testing without improvements in compliance resulted in an INMB of $147 (CB: $69, $234) compared to current cytology-based screening and participation under the base-case WTP threshold of $83,000 per YLS.

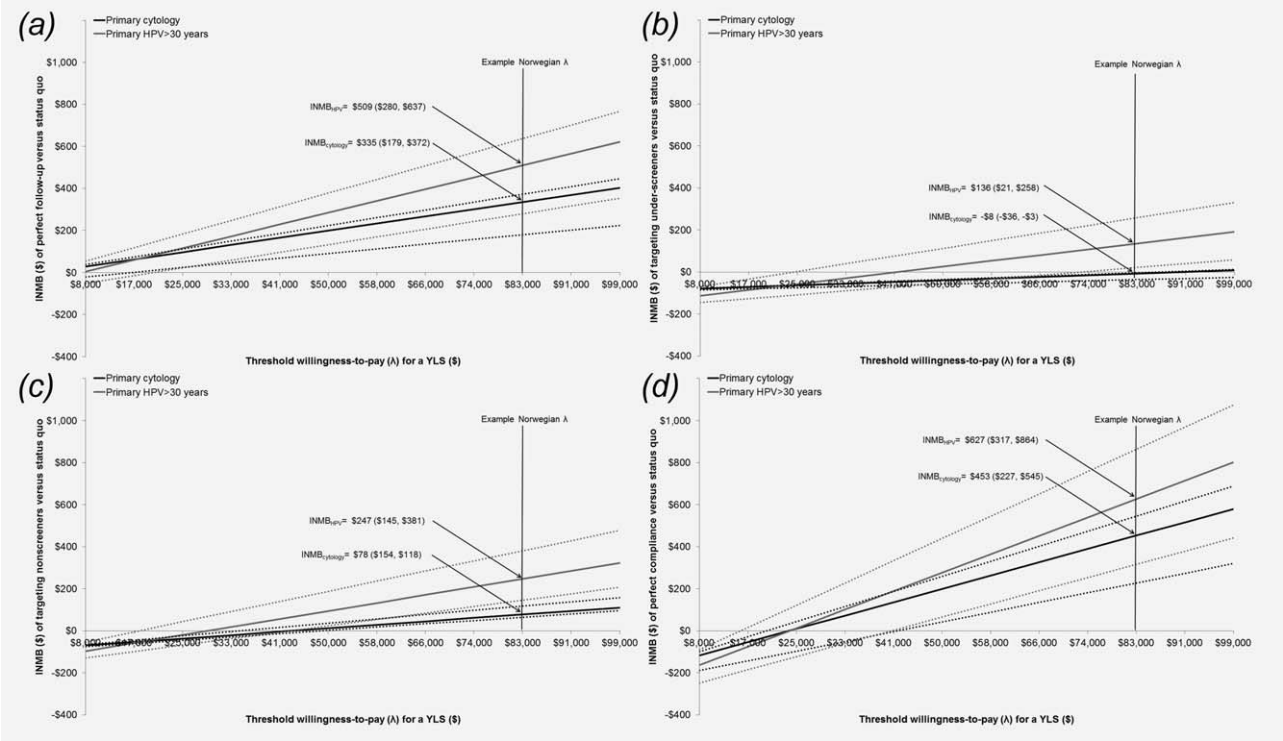


**Figure 2.** Incremental net monetary benefit (INMB) of (*a*) targeting follow-up, (*b*) targeting underscreeners, (*c*) targeting nonscreeners and (*d*) perfect compliance. Average (solid line) and credible bounds (dotted lines) for the INMB for each scenario compared to *status quo* participation using cytology and are shown as a function of the willingness-to-pay (WTP) threshold ($\lambda$) per year of life saved (YLS). Credible bounds reflect uncertainty in input values across the good-fitting parameter sets.

Switching test method as well as maximizing compliance for follow-up, underscreeners and nonscreeners resulted in INMBs of $509, $136 and $247 per woman, respectively. If, however, we assumed an organized screening program was operating in a situation where primary HPV testing for women over age 30 was already the current standard (and therefore the baseline comparator), targeting underscreeners would not provide any additional value (*i.e.*, INMB $< 0$), while eliminating loss to follow-up would have a INMB of $362 (CB: $211, $403) per woman. The INMB would be maximized at $627 (CB: $317, $864) under the best-case scenario of adopting HPV testing and perfect compliance across all failures in screening (Fig. 2*d*).

### INMB per 2% increase in participation

Although perfect compliance provides an upper-bound INMB, nominal improvements in follow-up and screening are more likely. To portray more realistic increases in compliance and to facilitate head-to-head comparison across scenarios, we expressed the INMB per 2% improvement in each scenario (Table 2). Under a WTP threshold of $83,000 per YLS, increasing follow-up by 2% yielded an INMB of $19 (CB: $10, $21) for cytology and comparable values for the primary HPV testing strategies. For primary cytology, the INMB increased by ~$3 assuming a WTP of $100,000 per YLS and decreased to $11 (CB: $5, $12) at a WTP of $50,000 per YLS. When the underscreeners were disaggregated by screening interval, we found that it was generally not cost-effective to increase participation among those women who attend screening every 4 or 5 years, though more attractive for women who seldom attend screening (*i.e.*, every 8 years), particularly at higher WTP thresholds. Under a WTP threshold of $83,000 per YLS, improving follow-up of women with abnormal results (*i.e.*, Scenario 1) yielded the highest INMB under primary cytology-based screening, while recruiting previously unscreened women assuming imperfect follow-up (*i.e.*, Scenario 3) resulted in the highest INMB with primary HPV-based testing. Moreover, recruiting nonscreeners accompanied by complete follow-up of abnormal results yielded higher INMB than any of the failures considered separately, except when WTP was low ($50,000 per YLS).

### Sensitivity analysis

For all scenarios, the INMBs decreased (strategies became less attractive) when office visit costs doubled compared to *status quo* participation using cytology (Fig. 3). Altering cytology test characteristics also had considerable impact on results. For instance, with a lower sensitivity, the INMB of any cytology-based scenario decreased, and the INMB of any HPV-based strategy became correspondingly more attractive. Under a situation of lower HPV test sensitivity, less money could be invested for improvements in all scenarios. For

**Table 2.** Average change in incremental net monetary benefit (INMB) per 2% increase among different subgroups of noncompliant women (credible bounds)

| | Cytology[1] | | | HPV > 30 years[1] | | |
|---|---|---|---|---|---|---|
| **INMB[2] per 2% increase in:** | $\lambda$ = \$50,000 | $\lambda$ = \$83,000 | $\lambda$ = \$100,000[3] | $\lambda$ = \$50,000 | $\lambda$ = \$83,000 | $\lambda$ = \$100,000[3] |
| Scenario 1 (imperfect follow-up) | \$11 (5,12) | \$19 (10,21) | \$22 (12,25) | \$12 (6,13) | \$20 (12,22) | \$24 (14,27) |
| Scenario 2 (underscreeners) | | | | | | |
| Attend every fourth or fifth year | −\$3 (−5,−2) | −\$1 (−4,0) | \$0 (−3,2) | −\$3 (−4,−1) | −\$1 (−3,1) | \$0 (−2,2) |
| Attend every eighth year[4] | −\$4 (−6,−4) | \$0 (−3,0) | \$2 (−1,2) | −\$5 (−8,−2) | \$0 (−5,2) | \$2 (−4,7) |
| Scenario 3 (nonscreeners) | \$2 (0,7) | \$16 (12,22) | \$22 (18,30) | \$5 (1,11) | \$23 (18,32) | \$32 (26,42) |
| Nonscreeners with perfect follow-up[5] | \$8 (3,13) | \$25 (18,34) | \$34 (26,44) | \$12 (4,19) | \$34 (23,45) | \$45 (32,58) |

[1]Estimates are the average difference across 2% increments in uptake, and rounded to nearest dollar. Credible bounds are based on average change in minimum and maximum of the 50 good-fitting parameter sets.
[2]INMB = $\lambda$*$\Delta$effect − $\Delta$cost.
[3]Rounded from \$99,000.
[4]No published coverage rates exist for 8-yearly screening; however, we selected this interval to represent the group of women who attend screening but very infrequently.
[5]Involves improvements in the higher risk group of nonscreeners (Scenario 3), but assumes compliance after an abnormal result is perfect.
Abbreviations: HPV: human papillomavirus; INMB: incremental net monetary benefit; $\lambda$: willingness-to-pay per year of life saved.

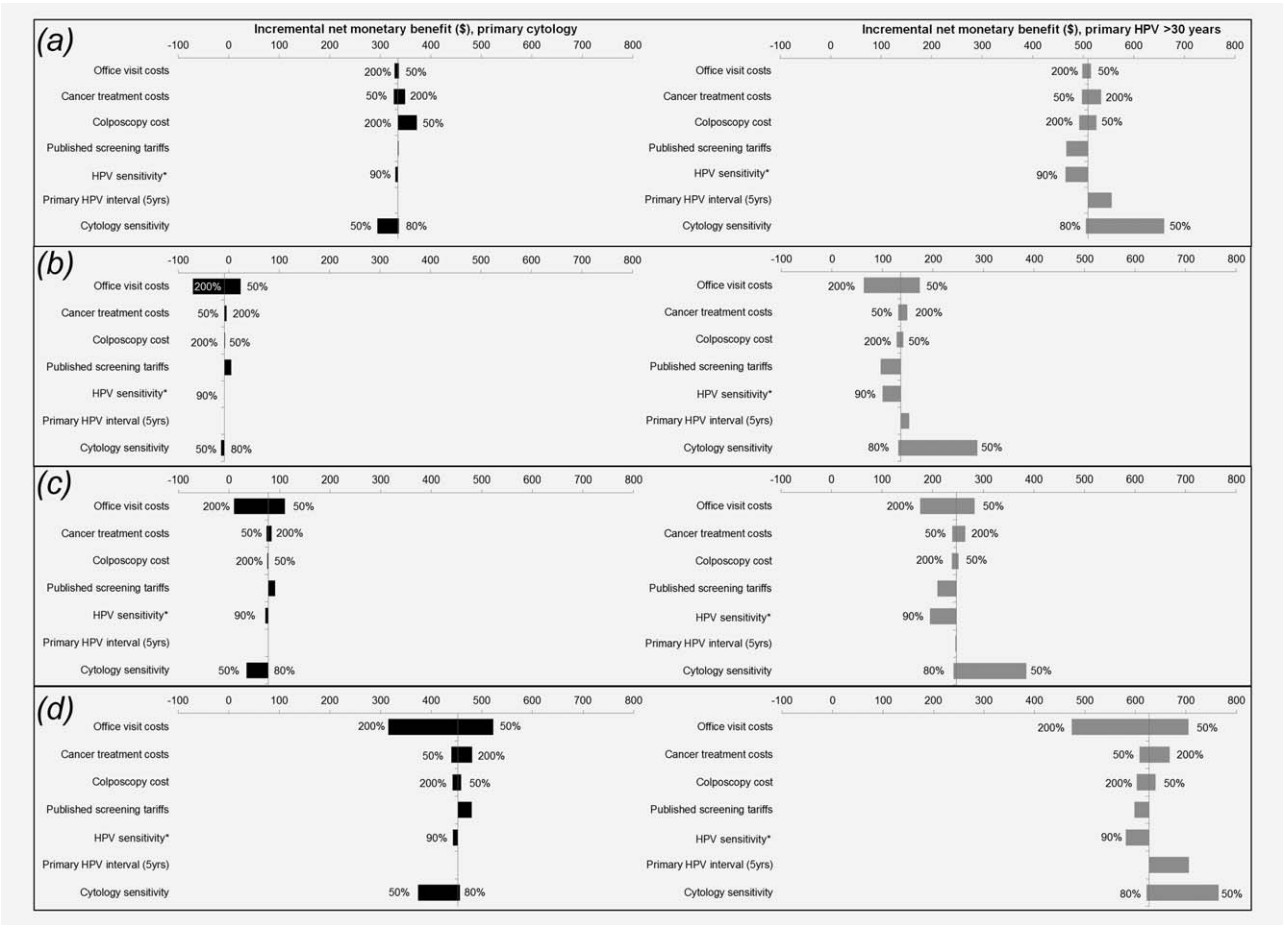


**Figure 3.** Tornado plot of influential parameters on the incremental net monetary benefit (INMB) of increasing screening among different subgroups of noncompliant women for primary cytology (black bars) and primary human papillomavirus (HPV) testing for women older than 30 (gray bars). (*a*) Targeting follow-up, (*b*) targeting underscreeners, (*c*) targeting nonscreeners and (*d*) perfect compliance. *HPV sensitivity defined as the probability of high-risk HPV DNA positivity given high-risk HPV.

example, \$0–\$10 less could be invested in the cytology-based scenarios that use HPV testing in triage, whereas \$36–\$50 less could be invested in the scenarios that use primary HPV screening. Extending the primary HPV screening interval to 5 years primarily affected those women already participating in screening. For example, 5-yearly HPV-based screening

under *status quo* participation yielded an expected reduction in lifetime cancer risk of 1.3% compared to *status quo* participation under 3-yearly cytology. We also found that health authorities could generally spend more to increase compliance among women who are lost to follow-up or underscreened, while lengthening the primary interval had a nominal impact on the amount that could be invested in interventions that target nonscreeners. Varying cancer treatment costs, colposcopy costs and screening costs had a smaller impact on INMB.

## Discussion

Our results suggest that improving common failures in CC screening can lead to important health gains. Furthermore, our analysis indicates that a substantial amount of money could be invested in improving compliance to guidelines while remaining cost-effective across a broad range of WTP threshold values. Moreover, as we did not specify the type of intervention, the information that we provide can be applied to a wide range of interventions.

Assuming 100% compliance, while overly optimistic, gives an upper bound of the expected health benefit and amount that could be spent to improve compliance; any investment beyond this is unlikely to be a good use of resources. We estimated the average INMB for a 2% increase in participation to allow for direct comparisons between the scenarios and to allow consideration of different rates of improvement in follow-up and uptake. Realistically, the hardest to reach individuals will likely require the most investment (*e.g.*, increasing follow-up from 98 to 100% may require more resources than increasing it from 64 to 66%); however, by reporting the average maximum amount that could be spent allows this quantity to be divided (not necessarily equally) among relatively easier- or harder-to-reach groups. Interestingly, the primary screening test impacted which improvements to prioritize. With cytology testing, reducing imperfect follow-up (Scenario 1) yielded the highest INMB per 2% increase in coverage, whereas with HPV testing, recruiting nonscreeners (Scenario 3) generally resulted in the highest INMB. Because of the lower sensitivity but higher specificity of a cytology test, the disease severity among the women identified and in-need of follow-up testing is greater than those identified by the more sensitive but less specific HPV test. Greater health benefits per dollar spent are achieved by ensuring the group of women identified by cytology complies with follow-up recommendations as opposed to targeting nonscreeners. Conversely, with a more sensitive HPV test, greater value is achieved through targeting nonscreeners than increasing follow-up rates.

Irrespective of test method, the INMB values associated with improving the frequency of underscreeners were primarily driven by targeting the women who screen least frequently (at >5-year intervals). Conversely, increasing compliance among women who attend screening more frequently was unattractive except at higher WTP threshold values (Table 2). When we considered lengthening the primary screening interval to 5 years for HPV testing in sensitivity analysis, the values of improvements in compliance were greater for women lost to follow-up or underscreened. This finding underscores that compliance is relatively more important with less intensive screening intervals. On the other hand, the value of targeting nonscreeners to comply with 5-yearly screening remained comparable to encouraging them to comply with 3-yearly testing.

To our knowledge, this analysis represents the most comprehensive attempt to enumerate the benefits and value of targeting different screening shortcomings in terms of meaningful health benefits (YLS, as opposed to simply increased coverage). In 1990, Koopmanschap *et al.*[23] conducted a model-based analysis to demonstrate that resources may be better spent increasing coverage rates compared to increasing the screening intensity among a well-screened population; a similar finding was reiterated in Denmark.[24] However, these studies neither applied a distribution of screening compliance nor evaluated improvements beyond uptake of the primary screening visit. Beyond modeling analyses, few clinical studies have assessed the effectiveness of interventions using health outcomes,[10] but were unable to report on long-term endpoints such as life expectancy, given the considerable time lag between detection and cancer-related death. A recent Swedish randomized controlled trial registered upfront costs of a telephone-based intervention and reported resource use in terms of total cost per additional detected case of high-grade precancer.[25] By applying a "rule of thumb" for the ratio of treated high-grade lesions to averted CC case, the authors concluded that the telephone-based intervention would likely be cost-saving. Although such empirical studies are needed, only a relatively short time horizon and a limited number of scenarios are feasible.

### Limitations

Our study has important limitations. After decades of screening for CC, it is difficult to directly observe the comparative baseline risk between participants and nonparticipants. Universal health coverage in Norway coupled with an organized screening program may mitigate some extreme socioeconomic disparities, often used as a proxy for high-risk individuals, reported in other settings. A Norwegian analysis of nonattendance (women with no cytology exam within 4 years) did not find lower education, number of lifetime sexual partners or age of sexual debut to be significant predictors of nonattendance in a multivariable model.[26] Yet, as shown in a recent article by Dugue *et al.*[27] for a neighboring Nordic country, differences in noncervical mortality between those who participate in the national screening program and those who do not may still exist. After calibrating input parameters for two risk populations, our model predicted that the odds of CC among those who never attend were 2.9 times higher than those who attended and followed-up according to guidelines. It would be expected that this relative odds is higher than estimates published in a recent audit

of the Swedish screening program that found a relative odds among those women who had not been screened in the last 6 years of 2.5.[3] Therefore, our assumptions of differential background risk may be reasonable, at least in settings similar to Norway and Sweden, but may be less generalizable to settings without universal health coverage. In settings in which noncompliance may have a greater correlation with higher background CC risk and nonattendance, our results may be a conservative estimate of the value of increasing compliance. We also did not consider whether a higher background risk among nonscreeners would also translate into greater excess mortality. These factors are likely correlated,[27] and may result in less attractive INMBs as those women who avoid CC death would face a higher mortality from other causes compared to women who face lower mortality from other causes. Alternatively, if improvements in screening behavior impacted utilization of other health services, greater screening participation may have positive effects on other areas of health. However, such analyses were considered to be outside the scope of our article.

Simplifying assumptions were inherently necessary owing to model constraints. We assumed that increasing participation occurs instantaneously, which may have overestimated the benefit and subsequently the INMB of each scenario. However, owing to the long interval between detected abnormalities and malignant behavior, a brief lag time should have little impact on findings. Norwegian authorities have yet to decide on a screening interval for primary HPV testing; therefore, in the base case, we elected to compare the frequency of cytology and HPV screening head-to-head. However, in sensitivity analysis, we assessed the impact of extending primary screening intervals. Analyses surrounding improvements in participation should be revisited as primary screening interval decisions are finalized and actual compliance to the new recommendations is observed. We did not consider overutilization of screening, as it is not specifically reported in Norway; identification of overscreening may help to reduce total screening costs without compromising on health outcomes. Norwegian-specific CC utility values have not been elicited. Accounting for utility decrements would likely yield more attractive INMBs and, therefore, we expect our results (expressed in unadjusted life-years) to be a more conservative estimate. Lastly, the introduction of the HPV vaccination would be expected to reduce the risk of developing CC. Consequently, the value of increasing compliance to screening (assuming no changes to guidelines) would decrease. This scenario was not explicitly explored because it is not known how screening behavior and vaccination status may be correlated. In addition, national guidelines may well recommend different screening strategies for vaccinated women. These are important questions for future analyses, as studies addressing compliance with guidelines that reflect cost-effective interventions will continue to be of value.

## Conclusion

Improving compliance to CC screening guidelines increases health benefits in terms of cancer reduction and life expectancy compared to current practice. In addition, a considerable investment could be allocated toward programs to improve compliance to screening while still remaining cost-effective under the current cytology-based program or toward adoption of primary HPV-based screening.

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## References

1. Nygard JF, Nygard M, Skare GB, et al. Screening histories of women with CIN 2/3 compared with women diagnosed with invasive cervical cancer: a retrospective analysis of the Norwegian Coordinated Cervical Cancer Screening Program. *Cancer Causes Control* 2005;4:463–74.
2. Ibfelt E, Kjaer SK, Johansen C, et al. Socioeconomic position and stage of cervical cancer in Danish women diagnosed 2005 to 2009. *Cancer Epidemiol Biomarkers Prev* 2012;5: 835–42.
3. Andrae B, Kemetli L, Sparen P, et al. Screening-preventable cervical cancer risks: evidence from a nationwide audit in Sweden. *J Natl Cancer Inst* 2008;100:622–9.
4. Cancer Registry of Norway. 2008 Annual report population-based screening against cervical cancer. Oslo: Cancer Registry of Norway, 2009.
5. Segnan N, Senore C, Giordano L, et al. Promoting participation in a population screening program for breast and cervical cancer: a randomized trial of different invitation strategies. *Tumori* 1998;3:348–53.
6. Eaker S, Adami HO, Granath F, et al. A large population-based randomized controlled trial to increase attendance at screening for cervical cancer. *Cancer Epidemiol Biomarkers Prev* 2004;3: 346–54.
7. Morrell S, Taylor R, Zeckendorf S, et al. How much does a reminder letter increase cervical screening among under-screened women in NSW? *Aust N Z J Public Health* 2005;1:78–84.
8. Burger EA, Ortendahl JD, Sy S, et al. Cost-effectiveness of cervical cancer screening with primary human papillomavirus testing in Norway. *Br J Cancer* 2012;9:1571–8.
9. Snijders PJ, Verhoef VM, Arbyn M, et al. High-risk HPV testing on self-sampled versus clinician-collected specimens: a review on the clinical accuracy and impact on population attendance in cervical cancer screening. *Int J Cancer* 2012;10:2223–36.
10. Everett T, Bryant A, Griffin MF, et al. Interventions targeted at women to encourage the uptake of cervical screening. *Cochrane Database Syst Rev* 2011;5:CD002834.
11. Norwegian Directorate of Health. Health effects of socio-economic analyses. Oslo: Norwegian Directorate of Health, 2007.
12. Molden T, Kraus I, Karlsen F, et al. Comparison of human papillomavirus messenger RNA and DNA detection: a cross-sectional study of 4,136 women >30 years of age with a 2-year follow-up of high-grade squamous intraepithelial lesion. *Cancer Epidemiol Biomarkers Prev* 2005;2: 367–72.
13. Molden T, Kraus I, Karlsen F, et al. Human papillomavirus E6/E7 mRNA expression in women younger than 30 years of age. *Gynecol Oncol* 2006;1:95–100.
14. Tjalma WA, Fiander A, Reich O, et al. Differences in human papillomavirus type distribution in high-grade cervical intraepithelial neoplasia and

invasive cervical cancer in Europe. *Int J Cancer* 2013;4:854–67.
15. Magnus K, Langmark F, Andersen A. Mass-screening for cervical-cancer in Ostfold County of Norway 1959-77. *Int J Cancer* 1987;39:311–16.
16. Hakama M, Rasanenvirtanen U. Effect of a mass screening-program on risk of cervical-cancer. *Am J Epidemiol* 1976;103:512–17.
17. Lonnberg S, Nieminen P, Luostarinen T, et al. Mortality audit of the Finnish cervical cancer screening program. *Int J Cancer* 2013;132:2134–40.
18. Fidler H, Boyes D, Worth A. Cervical cancer detection in British Columbia. *J Obstet Gynaecol Br Cwlth* 1968;75:392–404.
19. .Federal Reserve. Historical rates for the Norwegian Krone, 2011. Available at: http://www.federalreserve.gov/RELEASES/H10/Hist/dat00_no.htm. (Accessed June 13, 2011).
20. Goldhaber-Fiebert JD, Stout NK, Salomon JA, et al. Cost-effectiveness of cervical cancer screening with human papillomavirus DNA testing and HPV-16,18 vaccination. *J Natl Cancer Inst* 2008; 5:308–20.
21. Kim JJ, Goldie SJ. Health and economic implications of HPV vaccination in the United States. *N Engl J Med* 2008;8:821–32.
22. Kim JJ, Kuntz KM, Stout NK, et al. Multiparameter calibration of a natural history model of cervical cancer. *Am J Epidemiol* 2007;2: 137–50.
23. Koopmanschap MA, van Oortmarssen GJ, van Agt HM, et al. Cervical-cancer screening: attendance and cost-effectiveness. *Int J Cancer* 1990;3: 410–15.
24. Gyrd-Hansen D, Holund B, Andersen P. A cost-effectiveness analysis of cervical cancer screening: health policy implications. *Health Policy* 1995;1: 35–51.
25. Broberg G, Jonasson JM, Ellis J, et al. Increasing participation in cervical cancer screening: telephone contact with long-term non-attendees in Sweden. Results from RACOMIP, a randomized controlled trial. *Int J Cancer* 2012;1:164–71.
26. Hansen BT, Hukkelberg SS, Haldorsen T, et al. Factors associated with non-attendance, opportunistic attendance and reminded attendance to cervical screening in an organized screening program: a cross-sectional study of 12,058 Norwegian women. *BMC Public Health* 2011; 11:264.
27. Dugue PA, Lynge E, Rebolj M. Mortality of non-participants in cervical screening: registry-based cohort study. *Int J Cancer* 2013. Epub ahead of print. doi: 10.1002/ijc.28586.