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Health Policy Analysis

Designing Guidelines for Those Who Do Not Follow Them: The Impact of Adherence Assumptions on Optimal Screening Guidelines

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ABSTRACT

Objectives: Model-based cost-effectiveness analyses can inform decisions about screening guidelines by quantifying consequences of alternative algorithms. Although actual screening adherence is imperfect, incorporating nonadherence into analyses that aim to determine optimal screening may affect the policy recommendations. We evaluated the impact of nonadherence assumptions on the optimal cervical cancer screening in Norway.

Methods: We used a microsimulation model of cervical carcinogenesis to project the long-term health and economic outcomes under alternative screening algorithms and adherence patterns. We compared 18 algorithms involving primary human papillomavirus testing (5-yearly) that varied follow-up management of different human papillomavirus results. We considered 12 adherence scenarios: perfect adherence, 8 high- and low-coverage "random-complier" scenarios, and 3 "systematic-complier" scenarios that reflect conditional screening behavior over a lifetime. We calculated incremental cost-effectiveness ratios and considered a strategy with the highest incremental cost-effectiveness ratio $<$ 55 000 US dollars/quality-adjusted life-year as "optimal."

Results: Under perfect adherence, the least intensive screening strategy was optimal; in contrast, assuming any nonadherence resulted in a more intensive optimal strategy. Accounting for lower adherence resulted in both lower costs and health benefits, which allowed for a more intensive strategy to be considered optimal, but more harms for women who screen according to guidelines (ie, up to 41% more colposcopies when comparing the optimal strategy in the lowest-adherence scenario with the optimal strategy under perfect adherence).

Conclusions: Assuming nonadherence in analyses designed to inform national guidelines may lead to a relatively more intensive recommendation. Designing guidelines for those who do not adhere to them may lead to over-screening of those who do.

Keywords: adherence, economic evaluation, guidelines, screening, simulation modeling.

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Introduction

Cost-effectiveness analysis (CEA) is a type of decision analysis that is widely used to inform decision making in the healthcare sector.[1] These analyses can aid priority setting in a wide range of contexts and address questions such as whether to adopt a new technology in the healthcare sector or which strategy should be used to improve adherence to a screening program. CEAs can also inform clinical guidelines by quantifying the benefits and harms of alternative courses of action.[2,3] Clinical guidelines exist across diseases and therapeutic areas. For example, in the context of cervical cancer screening, clinical guidelines result from many choices involving target population (eg, age group), primary screening test (eg, human papillomavirus [HPV] test vs cytology), screening frequency (eg, 3-yearly, or 5-yearly), and the follow-up algorithm for screen-positives and the threshold for diagnostic referral. The combination of different algorithm levers results in different trade-offs in harms and health benefits of screening, for example, the expected number of cancer cases averted weighed against the number of referrals for diagnostic colposcopy with biopsy.[3]

CEAs are often based on decision-analytic modeling (ie, simulation model), a framework to synthesize multiple sources of data and quantify the impact of using an intervention in different ways and under different analytic assumptions.[4] Outcomes in CEAs, such as costs, health benefits, and the incremental cost-effectiveness ratio (ICER), a frequently used efficiency indicator of a particular screening strategy, depend on several analytic assumptions within the simulation model. Alternative analytic assumptions can be varied in uncertainty analyses to explore the impact on key outcomes and consequently, the optimal decision. Nevertheless, the results of the

analysis under the primary set of analytic assumptions (ie, the "base case") are highlighted and therefore most impactful on stakeholders.

A key assumption in CEAs is patient adherence to the clinical guidelines. Within cervical cancer screening, some women may adhere perfectly to guidelines, whereas others may screen more or less frequently than recommended. When using decision analysis to inform the design of guidelines, analysts can either (1) assume perfect adherence for the entire population or (2) incorporate imperfect adherence patterns, which often requires population data about screening behavior over time. Both approaches are common,[5-7] which may stem from the lack of consensus about the role of nonadherence in guideline development. Guidelines for conducting CEAs, such as those published by the National Institute for Health and Care Excellence in the United Kingdom (UK) or the Second Panel on Cost-effectiveness in Medicine in the United States, often provide reference case guidance for key assumptions, such as the types of costs to include, the analysis perspective, and whether outcomes occurring in the future should be discounted (and at what rate). Nevertheless, to the best of our knowledge, no CEA guideline provides specific recommendations for the base case adherence assumptions, particularly when informing normative clinical guidelines. For example, in the Norwegian pharmaceutical guidelines, recommendations about adherence assumptions state that "real-world data can be used to inform adherence,"[8] but adherence is not mentioned in other Norwegian public health guidelines.[9,10] In the UK, the National Institute for Health and Care Excellence guidelines state that the analysis should include the value of "the additional benefit of potential adherence improvements provided by certain process characteristics of the intervention," such as the mode of treatment delivery.[11] Furthermore, Canadian guidelines suggest that researchers should examine the impact of heterogeneity in adherence rates.[12]

The analytical choice to incorporate nonadherence into an analysis used to determine optimal screening may affect the policy recommendations and could lead to inefficient screening of women adhering to the guidelines. In our previous CEAs of cervical cancer screening,[13-17] our scenario analyses explored the impact of adherence assumptions on the optimal screening strategy and found that the preferred screening algorithm was influenced by adherence assumptions, and in some cases, the preferred strategy when including nonadherence required a more intensive follow-up algorithm than when we assumed perfect adherence.[15-17] Consequently, the proportion of women who attend less often than recommended will influence the screening recommendations for the women who plan to attend according to guidelines. Although these analyses only explored the impact of a single set of nonadherence assumptions on the cost-effectiveness, they suggest that accounting for nonadherence when designing clinical guidelines may potentially increase inefficiencies and harms to women who adhere perfectly to guidelines. Therefore, using a case example from the Norwegian cervical cancer screening program, we aim to inform discussions about the inclusion of adherence assumptions in CEAs used for clinical guidelines. By comprehensively evaluating the magnitude and approach of incorporating nonadherence assumptions, we demonstrate the impact of alternative screening adherence assumptions on the optimal (ie, cost-effective) cervical cancer screening strategy. We also explored the harm-benefit trade-offs associated with optimizing screening guidelines based on nonadherence assumptions for women who are likely to adhere to the guideline.

Methods

Analytic Overview

We used a previously developed microsimulation model of HPV and cervical carcinogenesis[15,18] to compare 18 alternative cervical cancer screening strategies under 12 screening adherence scenarios. We considered the impact of alternative adherence assumptions on 2 aspects of the decision-making process related to screening: (1) the optimal (ie, cost-effective) strategy, defined as the additional cost per additional quality-adjusted life-year (QALY) gained, and (2) the harms and benefits, defined as colposcopy referral rates and cumulative lifetime risk of cervical cancer, respectively, for women likely to adhere to the guideline.

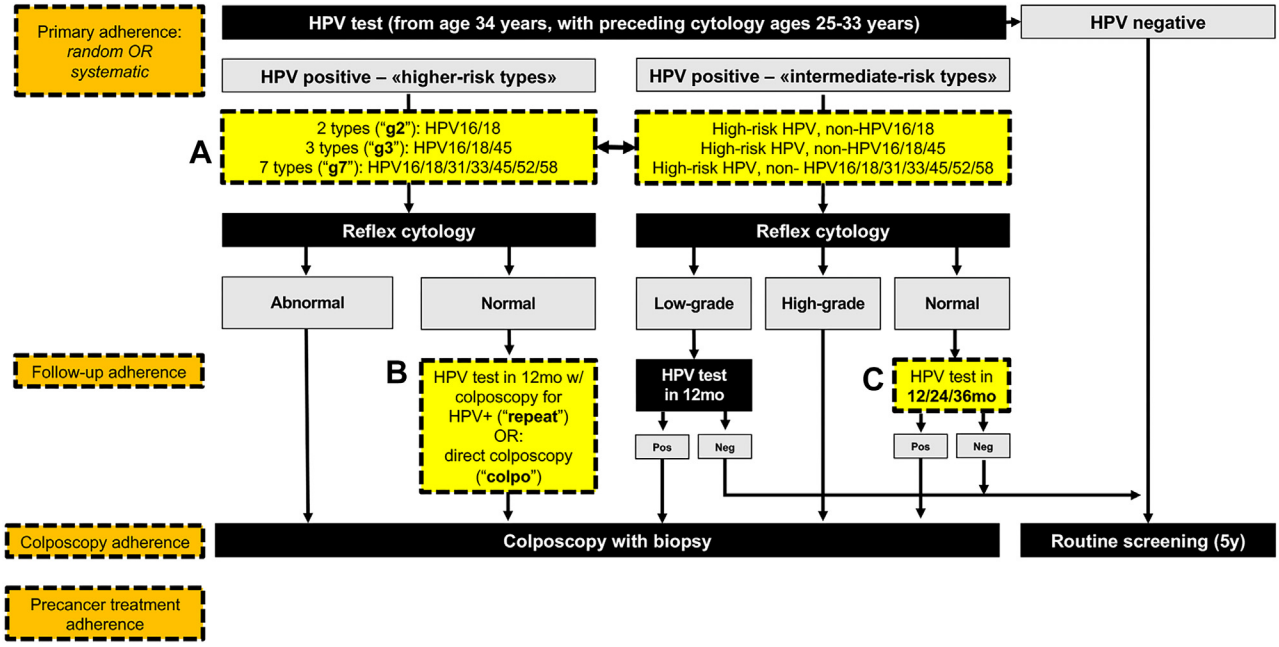
The microsimulation model has been previously described, both model development and model adaptation to reflect the epidemiologic and costing data from Norway.[15] Briefly, women enter the model at the age of 9 years and transition through health states at monthly intervals, reflecting HPV infection status (by HPV genotype), cervical precancer, cervical cancer by stage, and death. Women who are hysterectomized are removed from the model. We reflected uncertainty in the natural history of disease using 50 good-fitting parameter sets, which were previously fit using a likelihood-based calibration approach.[15,16] Model outcomes reflected the average across the 50 good-fitting natural history parameter sets.

We used 2023 as our analysis year and simulated individual women born in 1989 (age 34 years in 2023) given that these women reflect the last cohort who were neither offered catch-up vaccination in 2016 to 2018 nor received the HPV vaccine in adolescence, yet still have ~35 years left of screening eligibility and may benefit from improvements in the screening algorithm. The model reflects the birth-cohort-specific burden of HPV and cervical cancer reflecting indirect vaccine protection based on projections from a dynamic HPV transmission model, as previously described.[13,19] Model outcomes were counted from age 34 years (age of the 1989 birth cohort in 2023) over their remaining lifetime.

Comparator Screening Strategies and Adherence Assumptions

Our analysis reflects the 2022 Norwegian cervical cancer screening guidelines, which recommends that women aged 25 to 33 years screen every 3 years with cytology and women aged 34 to 69 years screen every 5 years with HPV testing. Given our analysis start age of 34 years, our screening strategies reflected 18 alternative follow-up algorithms for women aged 34 years through their screening exit at age 69 years who were HPV-positive on their primary screening test (Fig. 1). Relevant strategies to include in the analysis were identified based on previous Norwegian cost-effectiveness studies,[6,13] in addition to discussions with cervical cancer screening organizers in Norway. The strategies included 3 main variations: (1) the number of genotypes included in the "higher-risk carcinogenic types" versus the "intermediate-risk carcinogenic types" groups (ie, 2 (HPV16/18), 3 (HPV16/18/45), or 7 (HPV16/18/31/33/45/52/58) carcinogenic HPV genotypes, herein referred to as "g2," "g3," and "g7"); (2) follow-up of "higher-risk carcinogenic types" among those with normal cytology, with either repeat HPV testing in 12 months or direct colposcopy referral (herein referred to as "repeat" and "colpo"); and (3) follow-up of "intermediate-risk carcinogenic types" among those with normal cytology, with HPV testing at 12, 24, or 36 months wait time (herein referred to as "12 m," "24 m," and "36 m").

Figure 1. Screening strategies. Overview of the 18 alternative screening strategies considered in the analysis and adherence variables (left-side dashed boxes). Strategies varied by (A) number of genotypes to include as "higher-risk types" versus "intermediate-risk types," (B) follow-up of HPV-positive "higher-risk types" and reflex cytology normal, and (C) follow-up wait time for HPV-positive "intermediate-risk types" and reflex cytology normal. For the algorithm involving direct colposcopy in part B, the "higher-risk types" group would still receive a reflex cytology despite no formal guidance on how this information is acted upon.



HPV indicates human papillomavirus; mo, months; neg, negative; pos, positive.

To isolate the impact of different types and magnitudes of adherence assumptions on the optimal strategy, we considered a total of 12 scenarios that varied adherence for different parts of the screening pathway (ie, primary screening, follow-up testing, colposcopy referral, and precancer treatment) (Fig. 1 and Table 1). The adherence scenarios were divided into 3 main variations of adherence: (1) perfect adherence, indicating that the entire population screens according to the strategy algorithm; (2) random adherence, indicating that the entire population has a probability *p* of nonadherence to each part of the screening pathway *(ie, primary screening test, follow-up test, referral to colposcopy and treatment referral)*, independent of previous behavior; and (3)

Table 1. Adherence assumptions across adherence scenarios.

Adherence scenario	Primary screening	Follow-up testing	Colposcopy referral	Precancer treatment	Comment
Perfect adherence	100%	100%	100%	100%	
Random – high A	85%	100%	100%	100%	Adherence is independent of previous behavior. Each scenario involves incremental addition of imperfect behavior.
Random – high B	85%	85%	100%	100%	
Random – high C	85%	85%	90%	100%	
Random – high D	85%	85%	90%	95%	
Random – low A	60%	100%	100%	100%	
Random – low B	60%	60%	100%	100%	
Random – low C	60%	60%	75%	100%	
Random – low D	60%	60%	75%	80%	
Systematic – perfect	Never-screeners (10%) Under-screeners (40%), 7-y Guideline-screeners (20%), 5-y Over-screeners (30%), 3-y	100%	100%	100%	Systematic primary screening behavior with random follow-up.
Systematic – high D		85%	90%	95%	
Systematic – low D		60%	75%	80%	

Note. Percentages indicate the probability of adherence to the different parts of the screening pathway (ie, primary screening, follow-up testing, colposcopy referral, and precancer treatment), except for adherence to primary screening in the systematic adherence scenarios, where the percentages indicate the proportion of women attending screening according to each screening frequency. In the random scenarios, imperfect adherence was additive: (A) imperfect adherence to primary screening and perfect adherence to the consecutive parts of the screening algorithm; (B) imperfect adherence to primary screening and follow-up testing and perfect adherence to colposcopy referral and precancer treatment; (C) imperfect adherence to primary screening, follow-up testing, and colposcopy referral and perfect adherence to precancer treatment; and (D) imperfect adherence to all parts of the screening algorithm. In addition, for each of the A-B-C-D variations, we considered both higher (ie, 85%-95%) and lower (ie, 60%-80%) rates of adherence, referred to as the "random-high" and "random-low" scenarios. For the primary screening systematic adherence scenarios, we paired 3 different sets of adherence assumptions to nonprimary screening tests, including perfect adherence, "random-high," and "random-low" adherence rates.
y indicates yearly.

systematic adherence, indicating that the population is categorized into different adherence patterns, for example, underscreeners and overscreeners, which they follow over the lifetime. Similar to our previous analyses, we assumed that the underlying risk of developing cervical cancer was independent of screening behavior, whereas the instantaneous risk over the lifetime is affected by individual screening history and performance of a screening algorithm (eg, due to screening test characteristics).

Analysis

Analysis outcomes included discounted costs and QALYs, expected number of colposcopy referrals per 100 000 women over their lifetime, and cumulative lifetime risk of cervical cancer (adjusted for hysterectomies), projected for the 1989 cohort of unvaccinated women over their remaining lifetime.

In line with Norwegian guidelines for conducting CEA,[8] we adopted a restricted societal analytic perspective, which includes costs associated with screening and treatment procedures, as well as patient time and travel cost associated with attending these procedures. Unit costs were identified, quantified, and valued for previous analyses[13,15] and updated for this analysis to reflect 2020 values. All costs were valued in Norwegian kroner and converted to US dollars (USD) using the average annual 2020 exchange rate (USD1 = 9.4004 Norwegian kroner).[20] We adopted a lifetime time horizon and discounted costs and benefits by 4% per year, per Norwegian guidelines.[8]

In line with Norwegian guidelines for economic evaluation,[8] we applied health state utility values for the general population from a recent Norwegian study based on an EQ-5D-3L survey of a representative sample of the Norwegian general population.[21] The scoring of the EQ-5D index is based on the population-based UK tariff.[22] We assumed quality-of-life decrements for local, regional, and distant cervical cancer stages according to a previous study.[23]

For each adherence scenario, we calculated ICERs, defined as the additional cost per additional QALY gained, and identified all strategies on the cost-efficiency frontier. We further identified the cost-effective (or "optimal") strategy as the strategy with the highest ICER below $55 000/QALY, in accordance with Norwegian severity-adjusted benchmarks for cost-effectiveness and in line with our previous analyses exploring cervical cancer prevention policies.[13] We used the perfect adherence scenario as a benchmark and compared how the optimal strategy would change under alternative adherence assumptions. To evaluate the impact of adherence assumptions on the benefits and harms of screening, we compared the cumulative lifetime risk of cervical cancer and colposcopy referrals per 100 000 women, for a woman who would perfectly adhere to guidelines, for each of the strategies identified as optimal across the different adherence scenarios.

Results

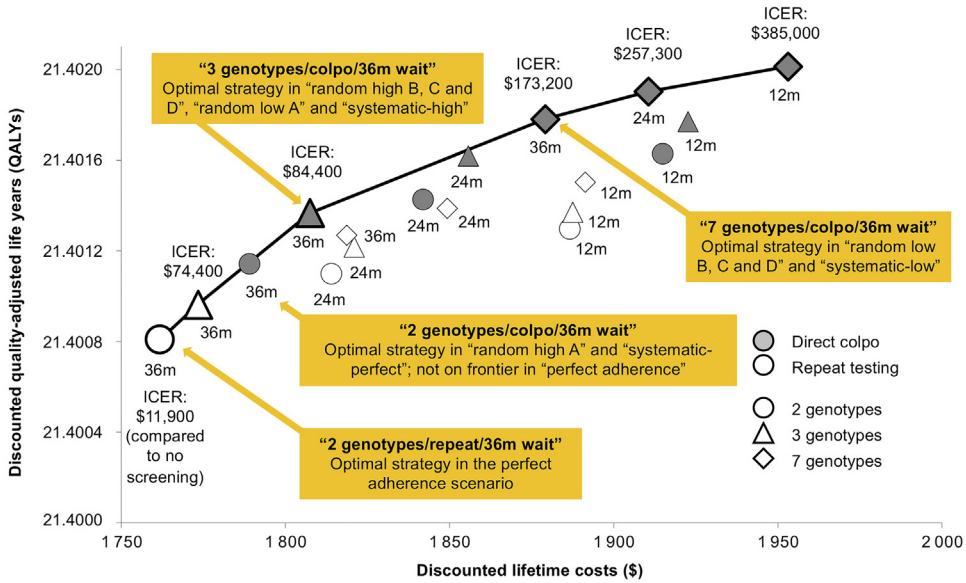
Among the 18 screening strategies, 4 different strategies were identified as optimal (cost-effective) depending on the adherence scenario (Table 2 and Fig. 2). For example, when we assumed perfect screening adherence, the least intensive strategy was identified as cost-effective, which involved the fewest HPV genotypes included in the "higher-risk carcinogenic types" group and the longest wait time between repeat testing, compared with the other strategies (ICER: $11 900 per QALY gained compared with no screening). In contrast, assuming any nonadherence

Table 2. Cost-effectiveness results across 12 screening adherence scenarios.

Strategy label (variation A/B/C)	Perfect	Random "high A"	Random "high B"	Random "high C"	Random "high D"	Random "low A"	Random "low B"	Random "low C"	Random "low D"	Systematic perfect	Systematic high	Systematic low
G2/repeat/36 m												
G2/repeat/24 m												
G2/repeat/12 m												
G3/repeat/36 m												
G3/repeat/24 m												
G3/repeat/12 m												
G7/repeat/36 m												
G7/repeat/24 m												
G7/repeat/12 m												
G2/colpo/36 m												
G2/colpo/24 m												
G2/colpo/12 m												
G3/colpo/36 m												
G3/colpo/24 m												
G3/colpo/12 m												
G7/colpo/36 m												
G7/colpo/24 m												
G7/colpo/12 m												

Note. Strategies with an incremental cost-effectiveness ratio just below $55 000 are denoted by green-shaded cell, whereas strategies on the cost-efficiency frontier are denoted by blue-shaded cell. Strategy labels: G2/G3/G7 indicate the number of genotypes included in the "higher-risk carcinogenic types" versus the "intermediate-risk carcinogenic types" groups (ie, 2 [HPV16/18], 3 [HPV16/18/45], or 7 [HPV16/18/31/33/45/52/58] high-risk HPV genotypes), repeat/colpo indicate follow-up of "higher-risk types" with normal cytology, with either repeat HPV testing in 12 months or direct colposcopy referral, and 12 m/24 m/36 m indicate wait time before repeat testing in follow-up of "intermediate-risk types" with normal cytology. Assumptions for each adherence scenario are presented in Table 1.
HPV indicates human papillomavirus; m, months.

Figure 2. Cost-effectiveness results for the perfect adherence scenario. Cost-effective strategies across adherence scenarios are indicated in the boxes. Assumptions for each adherence scenario are presented in Table 1. Costs are expressed in 2020 USD.



ICER indicates incremental cost-effectiveness ratio; m, months; USD, US dollars.

resulted in a more intensive optimal strategy, that is, the strategy involved direct referrals for additional HPV genotypes (Table 2). Moreover, the lower the adherence-rate assumptions, the more intensive the optimal strategy became. For example, when we assumed random adherence to both primary and follow-up testing was 60% (in 3 of the random-low scenarios), the optimal strategy involved the most HPV genotypes included in the "higher-risk carcinogenic types" group and direct colposcopy referral rather than repeat testing. For women who perfectly adhere to screening, this strategy was associated with an ICER of $173 200 per QALY, which is well above the willingness-to-pay benchmark. Even at a higher willingness-to-pay threshold (ie, $90 000 per QALY), the optimal strategy varied according to the adherence scenario.

When we isolated the implications of implementing national guidelines based on an analysis assuming nonadherence, we found that the 4 strategies identified as optimal across the adherence scenarios provided different trade-offs in harms and benefits of screening if recommended for the women who perfectly adhere (Fig. 3). For example, although the lifetime risk of cervical cancer decreased by 6% from the least intensive optimal strategy to the most intensive strategy (from 0.300% to 0.281%), the number of colposcopies expected over a lifetime increased by 41% (from 61 400 per 100 000 women to 86 800 per 100 000 women). Importantly, the average ratio of harms-to-benefits for the women who would adhere to guidelines increased by 36% (ie, from 119 colposcopies per cancer prevented to 161 colposcopies per cancer prevented).

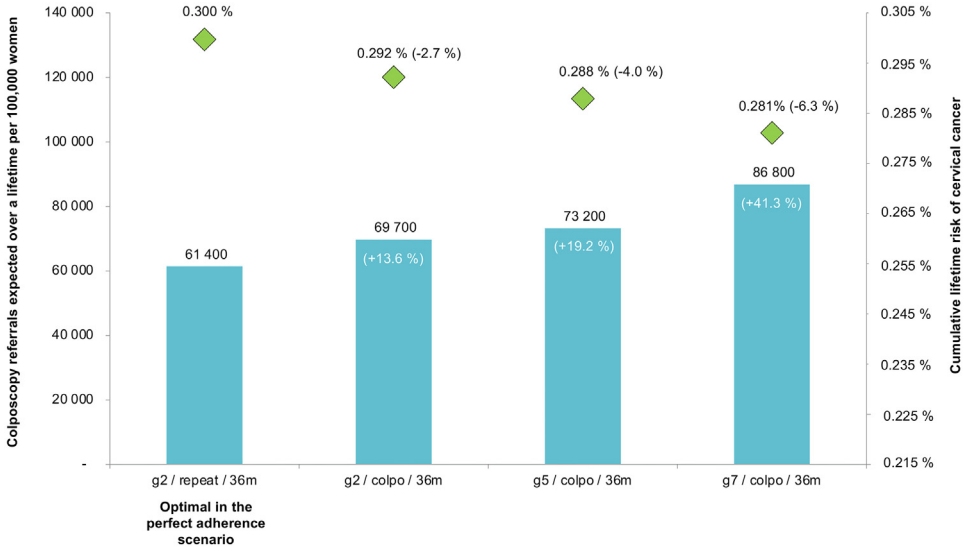
Discussion

In our analysis, we showed that alternative adherence assumptions included in a model-based CEA can lead to different optimal screening strategies, potentially influencing national guidelines. Across the 12 adherence scenarios, we identified 4 different optimal strategies. In particular, all our scenarios that assumed nonadherence favored a screening algorithm that was more intensive than the optimal strategy under perfect adherence assumptions. Additionally, we found that the lower the adherence-rate assumption, the more intensive the optimal strategy became. Moreover, if national guidelines are based on low adherence assumptions, there would be additional harms for women who would plan to adhere to guidelines compared with the optimal guidelines when assuming perfect adherence. For example, for women who adhere to screening according to the optimal strategy when assuming the lowest nonadherence rates, their colposcopy rate could be up to 41% greater and their harm-to-benefit ratio 36% greater than national guidelines informed by assumptions of perfect compliance.

Our findings that a more intensive optimal strategy is required as adherence declines can in part be explained by an average decrease in costs and an increase in the cervical cancer burden as adherence rates decrease. Consequently, more intensive strategies are favored because they involve more direct pathways to diagnostic colposcopy rather than strategies that require repeat testing with additional opportunities for loss-to-follow-up. Due to the multistep screening pathway that leads to precancer treatment, we found follow-up adherence to be more impactful than primary screening adherence. This is illustrated by the 3 systematic-complier scenarios with consistent primary screening behavior over individuals' lifetimes and random follow-up adherence, which resulted in 3 different optimal strategies. It should be noted that the design of the screening algorithm can influence adherence itself; for example, the adherence-rate for a more intensive strategy may be lower than a less-intensive strategy.

Designing national screening guidelines based on nonadherence could be equated to recommending paracetamol more frequently (eg, every 4 hours) instead of every 8 hours, to account for individuals who would forget—following this logic would result in very real harms to patients who follow these recommendations. Instead, paracetamol recommendations are based on optimizing the harm-benefit ratio. Similarly, clinical guideline evaluations should follow the same suite. Importantly, organized

Figure 3. Health benefit and resource trade-offs. Bars indicate the number of colposcopy referrals and diamonds indicate the cumulative lifetime risk of cervical cancer, for women perfectly adhering to screening guidelines for 4 selected screening strategies. The 4 selected strategies represent the strategies identified as optimal across the 12 adherence scenarios. Strategy labels are explained in Table 2. Numbers in parenthesis indicate the percentage change compared with the strategy identified as optimal in the perfect adherence scenario.



screening programs can set up checks and balances (eg, reminder letters, call-recalls) to help remind women to attend a program according to the recommendations. Programs could redirect money from costly, intensive screening programs to targeted interventions to improve adherence among nonattenders. For example, the difference in average total cost per woman between the most and least intensive optimal strategy identified across scenarios was $117, which could be spent on cost-effective interventions to improve adherence.

To the best of our knowledge, no previous study has explored the impact of alternative adherence assumptions on the cost-effectiveness of cancer screening strategies as the primary research objective. Nevertheless, policy evaluations often include nonadherence either as the base case or as a scenario analysis. We identified one older study (published in 2001) reviewing the impact of nonadherence on the cost-effectiveness of pharmaceuticals.[24] The study found that nonadherence always resulted in reduced effectiveness, whereas the impact on costs varied considerably across analyses. The authors concluded that failure to account for patient adherence may lead to selection of suboptimal treatment strategies. Nevertheless, there may likely be different preferred approaches to incorporating nonadherence in evaluations of pharmaceuticals compared with prevention efforts if, for example, nonadherence is due to drug toxicity. Even so, for individual patient-level decisions, understanding the maximum potential benefits and harms (ie, excluding nonadherence) should be provided to patients given that average adherence is not relevant for the individual patient.

We acknowledge that we investigate the impact of nonadherence within a limited application area. In particular, we consider the context in which decision makers are designing cervical cancer screening guidelines and need to choose among multiple alternative screening algorithms. Although our application example showcases that different adherence assumptions lead to different optimal strategies, this may not necessarily be the case for different applications. Thus, there is a need to evaluate the impact of adherence assumptions on a broader set of therapeutic and medical areas. We also emphasize that there is a distinction between our application on designing guidelines and analyses aiming to project the population impact of an intervention, in which case applying real-world adherence rates is of critical importance and should not be ignored. Furthermore, we did not explore age-period-cohort trends in adherence rates, which should also be addressed in future analyses to understand the population-level impact of such time trends.

The question of which set of adherence assumptions should be incorporated in the base case analysis and which should be considered in scenario analysis may depend on the stakeholders' objectives and value judgments. Particularly, the most cost-effective strategy may not necessarily lead to the optimal harm-benefit balance. In our application example, the perfect adherence scenario resulted in the least intensive strategy being optimal, thus reflecting the most conservative scenario in terms of cost-effectiveness and harm-benefit balance for women invited to screening. At the same time, we know with certainty that the entire population will not perfectly adhere to guidelines, and as such, a more intensive strategy could achieve greater health benefits while remaining cost-effective per willingness-to-pay benchmarks.

Although nonadherence may be more reflective of a real-world setting, an argument in favor of assuming perfect adherence in guidelines development is that there are several challenges with estimating real-world adherence. There are multiple approaches to estimating adherence. A common approach, which is also a key performance indicator of cervical cancer screening programs,[25] is to estimate cross-sectional adherence rates for the past screening interval, for example, 5 years. Nevertheless, given that the benefit of cancer screening relies on attendance to consecutive screening rounds, adherence should ideally be estimated over a longer period. For example, in our previous study,[14] we developed a longitudinal screening adherence metric and estimated adherence over multiple screening rounds, which enabled us to categorize women into different adherence profiles (ie, never-screeners, underscreeners, guidelines-based screeners, and over-screeners).

For this study, we used the entire screening database from the Cancer Registry of Norway, responsible for administering and monitoring the Norwegian screening program, consisting of > 20 years of screening for nearly 1.3 million individuals. Even with the availability of such comprehensive data, it requires additional analysis time. It also requires a complex model structure to enable simulated individuals to follow a certain pattern over their lifetime, rather than random adherence to each procedure. Moreover, even if one adequately estimates observed adherence rates, these represent historic rates of the previous target population offered the previous set of guidelines. In contrast, the future guidelines will be offered to a (slightly) different target population, given that some individuals age out of screening and some individuals enter screening age, and these individuals may have different preferences for screening approach. In sum, we recommend that identification of optimal screening recommendations should be based on evaluation of candidate strategies with the assumption of perfect adherence, while exploring the impact of imperfect behavior in secondary analyses.

Conclusion

Alternative nonadherence assumptions may lead to more intensive optimal screening strategies than assuming perfect adherence and, therefore, more intensive clinical guidelines. Furthermore, designing guidelines for those who do not follow them may lead to over-screening of those who do. To standardize cost-effectiveness evaluations, there is a need to make recommendations for how to incorporate patient behavior in CEA and which set of assumptions should be applied in the most impactful base case scenario. When choosing adherence assumptions for the base case analysis, we believe that there needs to be strong arguments to support choosing any other assumption than perfect adherence. We further suggest that recommendations for conducting CEAs should be informed by multiple studies that evaluate the impact of alternative adherence assumptions across several therapeutic and medical areas.

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