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Personalized mammography screening and screening adherence – A simulation and economic evaluation

Matthias Arnold, MBR MSc Dipl-Volkws. [1,2*], Anne S. Quante, MD/MPH[3,4]

[1] Munich Center of Health Sciences, Ludwig-Maximilians-Universität, Munich, Germany

[2] Institute of Health Economics and Health Care Management, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany

[3] Institute of Genetic Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany

[4] Frauenklinik, Klinikum Rechts der Isar, Technical University Munich (TUM), Munich, Germany.

* Correspondence to:

Matthias Arnold, Ludwig-Maximilians-Universität München, Institut für Gesundheitsökonomie und Management im Gesundheitswesen, Ludwigstr. 28 RG, 5. OG., 80539 Munich, Germany, Tel.: +49-(0)89-2180 3579, Fax.: +49-(0)89-2180 1475, eMail: arnold@bwl.lmu.de

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1. Introduction

Many countries worldwide have introduced systematic population-based mammography screening programs. However, it remains controversial whether the benefit of screening, in terms of reduced mortality, outweighs the harm caused by overdiagnosis, referring to cancers detected at screening that would not have been detected during the woman's lifetime, as well as unnecessary diagnostic procedures involving radiation (1-4). The Cochrane Review concluded that, for every 2,000 women invited for screening over a period of 10 years, one will be saved from cancer-related death but 10 will be treated unnecessarily, and more than 200 will suffer distress from false-positive findings (1). The Swiss Medical Board's report 2014 concluded that "no new systematic mammography screening programs be introduced and that a time limit be placed on existing programs" (5). With increasing knowledge about the development of breast cancer and its potential drivers, the identification of high-risk women has become more and more feasible and allows risk-based screening recommendations. It has been shown that better understanding about the individual risk of breast cancer strengthens informed choices and may thus motivate those with a higher risk to use screening opportunities (6) while reducing false-positive findings in individuals at lower risk. A risk-based approach would therefore allocate expensive screening resources to those who would benefit the most.

Participation in breast cancer screening programs is low, especially in European countries (average 53.5%) (7). These levels therefore do not reach the European Union benchmark of acceptable participation (>70%) for effectiveness in the reduction of mortality (8). There is scientific evidence that screening adherence is influenced by a woman's perceived risk (9-11). All of this raises the imperative to re-think current, one-size fits all mammographic screening programs. It has been suggested to guide screening decisions by patients' individual risk profiles and preference (12).

Decision analytical modeling is a very useful tool to balance the benefits and harms of personalized screening under a variety of circumstances (13-17). However, these simulation models have not so far incorporated adherence into the decision analysis. We decided to base our simulations on a validated Markov state transition model (13), which allows the integration of non-adherence. This is the first study to incorporate screening adherence into the economic evaluation of personalized mammography screening, using three different risk–adherence associations.

2. Methods

2.1. Model structure and adaptation

We use a Markov state transition model of individual women, as described by Schousboe, Kerlikowske (13). The original model is validated (13) and provides an elaborate technical report, allowing for reconstruction. The Markov model assumes that healthy women may develop invasive breast cancer, ductal carcinoma in situ (DCIS), or die from other causes. For women who develop breast cancer, the time spent in a healthy state before death from breast cancer or from other causes is determined depending on the cancer stage at diagnosis (local, regional, or distant). Women diagnosed with DCIS can progress to invasive cancer. Figure 1 shows the state transition paths via the health states. Additional descriptions are given in the supplementary material.

[insert Figure 1 here]

We use a micro-simulation approach to simulate individual women with combinations of three independent risk factors—history of previous biopsy (28.2% of women), history of breast cancer in first-degree relative (16.1% of women), and breast density (at 50 years, 39.2% of women have heterogeneously dense and 6.4% have extremely dense tissue)—and compare three different scenario-dependent adherence behaviors (positive, negative, and curvilinear). A sample size of 3,000,000 women was found to produce robust results at relatively little variability in results within strategies compared to variability across strategies (18). Simulations run from a start age of 50 years until the end of their life or 100 years.

2.2. Breast cancer incidence and mortality

Breast cancer incidence, breast cancer mortality, and overall mortality are extracted from the original model by Schousboe, Kerlikowske (13) and the Surveillance, Epidemiology, and End Results Program (SEER) (19). Schousboe, Kerlikowske (13) used the SEER register data to calculate invasive and in situ breast cancer incidence rates, breast cancer mortality, and overall mortality. As the description in Schousboe, Kerlikowske (13) does not provide the complete set of age-specific mortality rates, data were extracted directly from the SEER program using the updated relative survival rates from November 2014. The calculation follows the description in the original model (13).

Cancer incidence is stratified by the relative risk of each woman, using three risk factors: (1) breast biopsy yes/no, (2) history of breast cancer yes/no, and (3) breast density, classified by four categories 1 to 4 from the Breast Imaging Reporting and Data System (BI-RADS) (20). Consistent with Schousboe, Kerlikowske (13) and Tice,

Cummings (21), the relative risk of invasive cancer is 1.454 or 0.938 in the presence or absence of a family history and 1.495 or 0.906 in the presence or absence of a previous biopsy. The relative risk of breast density lies between 0.388 and 1.675 depending on the BI-RADS categorization of breast density levels and the age of the woman. We assumed that the relative risks are mutually independent and have a multiplicative effect. More details are given in the supplementary material.

Each woman in the simulation has a risk profile using a random combination of these three risk factors. The choice of risk factors follows the original model (13) and is derived from prevalence and relative risks from the Breast Cancer Surveillance Consortium (22). Accordingly, 28% of all woman have a family history of breast cancer and 16% have experienced a previous biopsy. Schousboe, Kerlikowske (13) assigned breast density categories independently of each other in intervals of 10 years. However, in this model, breast density is allowed to change with age, similar to Sprague, Stout (16) and Trentham-Dietz, Kerlikowske (15). In order to reflect the natural decrease in breast density, especially at menopause, we allowed breast density to change every 10 years. With this approach, we can simulate a change in breast density and thus evaluate the complete screening strategy even when risk profile and recommendation change. We used the age-specific BI-RADS distribution from Schousboe, Kerlikowske (13) to calculate the probability of maintaining the same breast density or dropping one category every 10 years. Details can be found in the supplementary material, section *1.2 Relative risk and prevalence of breast density levels*.

2.3. Screening strategies

We assess mammography screening strategies for women aged between 50 and 74 years, for whom routine mammography screening is recommended. In our model, women have a combination of three risk factors reflecting a 10-year risk of breast cancer between 0.41% and 4.65%. Women with very high risk, such as the breast cancer (BRCA) susceptibility gene carriers, or high risk at younger ages have access to intensified screening including magnetic resonance imaging (MRI) and are excluded from this study. Three different personalized strategies are identified from the literature with stratified screening intervals based on the combination of the three risk factors, as shown in Table 1: (1) Schousboe, Kerlikowske (13), (2) Vilaprinyo, Forné (14), and (3) Trentham-Dietz, Kerlikowske (15). We use the following annotation when referring to the strategies above: SK, VF, and TDK.

[insert Table 1 here]

2.4. Adherence scenarios

From the literature, three alternative adherence scenarios were chosen. The first scenario is that women with higher perceived risk are more likely to adhere to screening. This scenario is supported by systematic reviews (23, 24) and meta-analyses (9-11). Section *1.1.1 Positive risk-dependent adherence* describes the supporting evidence.

A second cluster of studies found the opposite association between perceived risk and adherence: high perceived risk may lead to psychological distress, and any form of psychological distress causes non-adherence to mammography screening. The supporting evidence consists mainly of observational studies (25-27) and experiments (28). Section *1.1.2 Negative risk-dependent adherence* describes the supporting literature.

A third group of studies exists aiming to combine the first and second hypotheses. These studies found that moderate levels of perceived risk lead to increased compliance, but low or high levels have detrimental effects. Section *1.1.3 Curvilinear risk-dependent adherence* describes the supporting literature. The assumption is that moderate risk comes with moderate levels of worry or anxiety, which were found to be positively associated with screening adherence. However, very high levels of worry and anxiety produce a barrier, which was observed in women at high risk of breast cancer. The result is a curvilinear relationship between risk and adherence. This scenario is supported by observational studies (29, 30) and narrative reviews (31). As a simplification, we assume that assigned risk also represents perceived risk in this simulation.

2.5. Implementation of adherence

In this simulation study, we introduce an adherence variable that describes the likelihood of adhering to screening recommendations dependent on the risk level. We implemented non-adherence by randomly deciding for each woman whether she will attend the next screening appointment or not. If a woman does not attend one screening appointment, the distribution of cancer stages at diagnosis is similar to women who do not go to screening at all. The simulation continues with this distribution until the next screening invitations, in which she has a new random probability of being adherent.

The risk levels are calculated with three risk factors, breast density, family history, and breast biopsy. These risk factors can be used to calculate a risk score based on the BCSC risk calculator tool developed by Tice, Cummings (21). We assume that, at the time point for the first screening, each woman is confronted with her risk level and is assigned a probability of adhering to screening based on this risk score. We used logarithmic functions to represent the positive and negative relationships and quadratic functions to represent the curvilinear relationship. The logarithmic function for positive or negative associations was chosen to best represent the risk distribution in the

population. The quadratic function for a curvilinear association was fitted to best represent the curvilinear nature reported by Andersen, Smith (30). All functions represent an effect size of 19% between risk perception and adherence, as reported by Katapodi, Lee (10), and an average adherence rate of 72.4%, as reported by Centers for Disease Control and Prevention (32). The mathematical form can be found in the supplementary material section *1.1.4 Technical implementation*. In addition to these three risk-dependent adherence scenarios, we included two base case scenarios: the uniform or risk-independent scenario, in which all women have the same probability of 72.4% of adherence to screening, and a full adherence scenario, in which women follow every screening invitation. Table 2 shows the three adherence scenarios, the corresponding risk levels, and the expected participation rate assuming the prevalence of risk factors as in Schousboe, Kerlikowske (13).

[insert Table 2 here]

2.6. Beneficial and harmful effects of screening

The main effect of screening is to reduce mortality from breast cancer by allowing a stage shift from later cancers to early cancers at detection. With this stage shift toward earlier and more treatable cancer forms, the survival of affected women is increased. In some cases, though, mammographic screening is not sensitive enough to find all treatable cancers and, in other cases, positive results turn out to be false results. False-positive results are included using age- and breast density-dependent specificity rates, as reported by Carney et al (33). These false-positive screening results have both cost and utility consequences, in the form of unnecessary diagnostic work up and utility decrements of 0.013 quality-adjusted life years (QALY), which reflects a QALY loss of 0.156 over the duration of 2 months for 50% of the women receiving false-positive results (13). In some events, mammography screening may, however, also identify either in situ cancers, which never progress to an invasive form, or invasive cancers, which would never progress fast enough to be harmful. Once detected though, these cancers are being treated. Breast cancer screening may thus lead to overdiagnosis. Overdiagnosis is defined as the number of screening-detected cancer cases that would have never have been detected or treated if the woman had not been screened (15, 34).

2.7. Utility and cost

Utility values are based on the Swedish time-trade-off (TTO) tariff using the five-dimensional Euroqol questionnaire (EQ-5D), originally developed by Lidgren, Wilking (35) and adapted for use in an American context by Schousboe, Kerlikowske (13). The tariff uses QALY decrements over age and cancer stages. QALY losses are distinct in the first year and the following years to allow a differentiation between initial and follow-up treatment

phases of care. In order to stay as close as possible to the original model, the utility weights were used as described (13). The parameters are described in Table S2 in the supplement, section *1.3 Utility and cost input parameters*.

Similar to utility parameters, cost parameters are also extracted from Schousboe, Kerlikowske (13). Prices were inflated to represent 2016 US$ using the medical care services component of the consumer price index (36). Screening costs represent median reimbursement rates for mammography (13). In addition, false-positive screenings require diagnostic work up, which were calculated by Tosteson, Stout (37) and also used by Schousboe, Kerlikowske (13). Treatment costs represent average costs for a patient in the respective treatment stage at diagnosis. Treatment is differentiated into initial, follow-up, and terminal treatment. Schousboe, Kerlikowske (13) calculated treatment costs using estimates from Yabroff, Lamont (38) and Taplin, Barlow (39) for continuing care. The cost parameter can be found in the supplementary material, section *1.3 Utility and cost input parameters*.

2.8. Validation

The model was validated using the AdViSHE guidance for model validation. The newly added parts of the model, especially the adherence module, were validated using the four steps described in the AdViSHE guidance: validation of the conceptual model, the input parameters, the computerized model, and the operational function. The model replicated real-world data or other published studies within a narrow range and with consistent findings. As the model was originally designed and validated by Schousboe, Kerlikowske (13), aspects such as age-specific incidence, incidence ratio in the breast density categories, breast cancer mortality, and mortality reduction through screening were already assessed. As we run the model with newer data, reflecting current incidence, treatment, and mortality, we also validated the model against external data and other studies. We specifically checked lifetime incidence and mortality with different starting ages, incidence ratios for breast density, and mortality reduction for biennial and annual screening using different age intervals. Details can be found in the supplementary material, section *2 Validation*.

2.9. Sensitivity analysis

We used deterministic (univariate and multivariate) and probabilistic sensitivity analyses (PSA) to check the impact of individual parameter uncertainty on the model and the combined effects on the overall model robustness. As we introduced the adherence variable and designed the scenarios in order to allow uncertainty about the true nature of the adherence and risk relationship, we also wanted to check the effects of the adherence scenarios and the extent of the adherence variation in the sensitivity analyses. For the univariate sensitivity analysis and the PSA, parameters are varied around 10% or the specified value ranges from the original model, see section *3.1 Ranges*

and distributions in the supplementary material. The complete list of variables and the sensitivity ranges used are described in the supplementary material, section *3.2 Sensitivity analysis*. For the PSA, 1,000 runs with 100,000 trials were used. Although higher trial number reduce variance from the first-order Monte Carlo simulation, 100,000 trials were found to produce manageable computation times (70 hours on a 26-core cluster using i5 processors) and reasonable variance increase. For the second-order Monte Carlo simulation, we tested several iterations with 100, 300, 1,000, and 3,000 runs. 1,000 runs were found to produce reasonably stable confidence intervals. We use cost-effectiveness acceptability curves to compare PSA results.

3. Results

Figure 2 describes the three personalized strategies (SK, VF, TDK), which differ in the recommended screening intervals (annual, biennial, or triennial) based on age group and a combination of three risk factors (breast density, previous biopsy, family history). For each stratum, the population share is given, which is based on the prevalence of risk factors reported by Schousboe, Kerlikowske (13). Table 3 presents screening performance indicators across the three personalized (SK, TDK, VF) and the biennial routine strategies. For each strategy, we show results for the full adherence, uniform (risk-independent) adherence, and the three risk-dependent adherence scenarios reflecting positive, negative, or curvilinear risk–adherence relationships. Compared to routine screening, SK reduces screening intervals for 26% of the population to every 3 years (Figure 2), which leads to a slightly reduced number of screenings (Table 3). VF reduces intervals to 3 years for 97% of the population and increases the intervals to annual screening for 3% of the population. This leads to a significant reduction in the overall number of screenings. TDK maintains biennial screening for 54% of the population, reduces intervals to 3 years for 38%, and increases intervals to every year for 8% of the population (Table 3). In total, the number of screenings is reduced, similar to SK, as seen in Table 3. At the population level, all three strategies suggest fewer total screening invitations.

[insert Figure 2 here]

3.1. Uniform (risk-independent) adherence vs full adherence

When comparing full adherence to uniform adherence, we find that non-adherence affects all performance indicators in a consistent way: a reduction of 27–28% across all strategies in almost all performance indicators in Table 3. As expected, screening rates drop by 28%, reflecting the average adherence of 72.4% in the uniform scenario. As a result of non-adherence, both cost and utility increments are consistently reduced by 28%. As expected, the incremental cost-effectiveness ratio (ICER) is not affected, as both cost and utility decrease to the

same extent. If we assume full adherence, TDK and SK both outperform VF regarding days in perfect health, but both are marginally less effective than routine screening (Table 3).

[insert Table 3 here]

3.2. Risk-dependent adherence vs uniform (risk-independent) adherence

For risk-associated adherence, the changes in cost and effects are not consistent. ICERs decrease for risk-positive adherence (5.5% for SK, 4.5% for TDK, 7.6% for VF, and 3.3% for routine screening) and increase for risk-negative adherence (4.6% for SK, 4.5% for TDK, 6.8% for VF, and 5.8% for routine screening). All personalized strategies perform better than routine screening if we assume a risk-positive adherence: this is an expected result as we offer intensified screening to women at higher risk. Further, all three personalized strategies (SK, VF, and TDK) reduce cost and increase days alive and days in perfect health significantly compared to risk-independent adherence (Table 3).

As expected, the negative risk–adherence association has exactly the opposite effect. Here, all three personalized strategies (SK, VF, and TDK) increase costs compared to risk-independent adherence, but reduce days alive and in perfect health. With curvilinear risk–adherence, costs are significantly lower for all strategies, and days in perfect health are significantly higher than with risk-independent screening. However, compared with positive risk–adherence, the differences in costs and QALY are not significant (Table 3).

In a univariate sensitivity analysis (Figure 3), changing the screening adherence (in steps of 100%, 90%, 80%, 72.4%, and 60%) affects effectiveness and costs. TDK and SK produce very similar results, with only non-significant differences. Routine biennial screening produces the highest effect at highest cost, and VF produces significantly less effect at lowest cost. When comparing the personalized strategies, SK and TDK, to routine screening, it is important to consider the adherence level and the risk–adherence relationship. For adherence levels above 90%, SK is almost certain to produce fewer QALYs than routine screening (Section *4.1. Significance tests*, Table S12, supplementary material). For lower adherence levels and especially positive or curvilinear relationships, the differences between SK and routine are statistically non-significant (P-values > 0.1). Similarly, TDK is only statistically significantly less effective than routine screening if adherence levels are above 72% (Table S12, supplementary material, Section *4.1. Significance tests*). For lower adherence and especially positive or curvilinear adherence, the differences between TDK and routine screening are statistically non-significant (P-values > 0.1). Thus, our results show that the evaluation of personalized screening strategies compared to routine screening is dependent on the nature of the adherence level and the adherence rate.

[insert Figure 3 here]

3.3. Probabilistic sensitivity analysis

In the PSA, we test how important the risk–adherence relationship is when overall parameter uncertainty is allowed. Figure 4 presents the cost-effectiveness acceptability curves (CEAC) for all adherence scenarios, and Table S16 in the supplementary material (section *4.3. Full incremental analysis*) shows the ICER variation for all possible strategy combinations. The CEACs show the probability of a strategy being acceptable given a specific willingness-to-pay (WTP) threshold based on the net health benefit of the strategies.

[insert Figure 4 here]

If WTP is over approximately US $5,000, VF is always more acceptable than no screening (Figure 4). From the full incremental analysis (Supplementary material, Table S16, section *4.3. Full incremental analysis*), we know that the WTP varies between US $5,300 (positive adherence) and US $6,500 (full adherence). This demonstrates that, even if WTP is very low, screening, at least at very low frequencies, is more acceptable than doing nothing. VF remains the most acceptable strategy until WTP reaches almost US $50,000 (between US 49,500 for positive and US $52,500 for negative adherence). For WTP between US $50,000 and US $60,000 (US $58,500 to US $60,000), SK is more acceptable than routine screening. Routine screening becomes the strategy with the highest probability of being acceptable if WTP is above US $60,000. Last, Figure 4 shows that, for WTP up to US $60,000, there are personalized strategies with higher likelihood of being acceptable than routine screening. We also see that, although the WTP thresholds between the strategies change slightly, they do not change substantially. The actual character of the risk–adherence relationship is thus not as important in decision-making.

4. Discussion

We used decision analytical modeling to economically evaluate personalized breast cancer screening strategies in comparison with routine mammography screening. This is the first study to incorporate the effects of non-adherence into the evaluation using three potential scenarios of risk–adherence relationship (positive, negative, or curvilinear) (13-15). Two of the evaluated personalized strategies, SK and TDK, show similar performance (in terms of additional lifetime and quality of life) compared to routine screening, but at lower cost. The third strategy, VF, reduces screening intervals (3-year interval) substantially for the majority of the population, which translates to overall reduced effectiveness at substantially lower cost compared to routine screening.

Our results show that the effect differences between SK and TDK are not statistically significant and are very close to routine screening. These results were expected, as TDK recommends annual screening for 8% of the population and triennial screening for 38% of women, whereas SK recommends triennial screening for 26%. Hence, the overall number of screenings is similar. To decide which strategy is best, we evaluated how robust the strategies are in comparison to routine screening. We showed that SK is as effective as routine screening if adherence is 80% or lower. TDK is as effective as routine screening if adherence is 60% or lower.

By definition, non-adherence reduces the number of screenings, which affects screening outcomes. Our results show that the incorporation of non-adherence into the simulation model affected the performance of the strategies. Under certain adherence conditions, personalized screening strategies may perform similarly well to routine screening, but save cost. As all three personalized strategies were designed as cheaper alternatives to routine screening, it is not surprising that they are only economically efficient alternatives for WTP thresholds below US $60,000. However, the threshold of WTP below which the VF or SK is the more effective choice compared to routine screening is dependent on the rate of adherence and also on the risk–adherence relationship. Our results show that risk-stratified screening strategies are more attractive if high-risk groups are more likely to adhere (positive adherence).

Overall, our estimations reproduce similar results to the original models in terms of beneficial and harmful screening effects, given the full adherence scenario. However, we find some differences. Vilaprinyo, Forné (14) report a 20% reduction in false-positive results and overdiagnosis when comparing personalized with routine biennial screening. Our model estimates a 32% reduction in false-positive results and 28% reduction in overdiagnosis. The differences can be explained, as the personalization strategy suggested by Vilaprinyo, Forné (14) starts screening for high risk women at the age of 40 years and screening for the high to medium risk group at 50 years. In our study, we decided to focus on the age group above 50 years, for which we have the best evidence regarding adherence. Trentham-Dietz, Kerlikowske (15) report QALY gains from triennial screening over no screening of 32 in 1,000. In a similar subgroup analysis, as reported in the supplementary material, section *4.2 Subgroup analysis*, our simulation estimates QALY gains of 34 for the same comparison in a similar risk group. They also find 20–23% reduced false-positive screenings and 8–20% reduced rates of overdiagnosis from triennial screening in average risk women, a subgroup for which our simulation produces 30% reduced false-positive results and 34% reduced overdiagnosis under the assumption of full adherence. Notably, the overall overdiagnosis rate in our simulation lies between 0.3% and 0.6% of all invasive cancers, which is at the lower end of the estimation by Feig (40) of 0–5%. Feig (40) concluded that overdiagnosis is clinically not significant, which could be confirmed

in this simulation. However, the extent of overdiagnosis is controversially discussed with estimates ranging from less than 1% to over 30% (41).

For a decision-maker solely concerned with maximizing screening performance, the risk–adherence relationship does not affect which strategy should be chosen. If mortality reduction was the only decision-making criterion, biennial routine screening performs best, followed by SK and TDK, which reach the same number of days alive and outperform VF independently of the adherence assumptions. If avoiding false-positive results and overdiagnosis are the most important criteria, the VF strategy performs best to minimize these harmful effects. If maximizing overall quality of life (incremental days in perfect health) is the most important aim, biennial routine performs best when full adherence is assumed. In the other adherence scenario, SK and routine screening do not show substantial differences. TDK is a non-inferior alternative to routine screening only if adherence levels are lower than 80% (with a slightly higher percentage if risk is negatively associated with adherence). However, if decision-makers consider cost-effectiveness, the assumptions regarding adherence are very important for the decision between TDK, SK, VF, and routine screening.

The nature of the risk–adherence relationship has public health implications. From a public health perspective, a positive risk–adherence relationship is what decision-makers and practitioners hope for, but it might not necessarily reflect reality. From the established research, we know that there are obstacles to screening which hinder high-risk women from attending. A positive risk–adherence relationship thus might not reflect all facets of reality. From the public health and societal perspective, we clearly want those individuals with the greatest risk of disease to have the best access and the highest usage of preventive services. However, if research establishes that the relationship is rather curvilinear or even more negative than positive, then risk-stratified screening needs to be discussed under a new paradigm. Under these circumstances, risk-stratified screening as a tool to improve overall public health can only succeed if it includes interventions to increase screening adherence in women who would benefit the most. A sole focus on identifying cost-effective screening intervals would necessarily translate to reduce screening for high-risk women, which is not included in any recently discussed suggestion and also has very problematic implications from a public health perspective.

As with every model, some simplifying assumptions were used. Some of these assumptions limit the generalizability of our results. First, our model is based on screening performance as observed with analog film-screen mammography. We used this screening technology because the literature used to establish the risk–adherence relationships are based on film-screen mammography. This technology is still widely used, but is being replaced by full-field digital mammography. Digital mammography has the advantage of being more accurate in

terms of specificity and sensitivity, and thus may improve screening performance (42), especially in women with dense breast tissue (43). However, the performance increase in women over 50 years is small (44), and there is no evidence that screening adherence differs between film-screen or digital screening.

Second, in the modeling of the risk–adherence relationship, we assume that the perception of risk goes hand in hand with the actual risk. However, we do know that women with a family history have a higher perceived risk (45), and thus the link between risk and perceived risk exists. However, the perception of risk is influenced by many factors, such as health literacy (46) or the method of invitation (47), which we do not incorporate into our model.

Third, we assume that the risk stratification process works perfectly in assigning women to risk clusters. We know that risk prediction has improved in recent years, but is still not perfect especially when breast density is considered (21). We do not integrate these imperfections, which is a clear limitation of our simulation. In a simulation aiming to identify the best stratified strategy, we strongly suggest including imperfect assignments. In analyzing whether non-adherence is important in the economic evaluation of stratified screening, we do however think that imperfect risk assignments do not have a significant effect on our analysis.

Fourth, our modeling of the risk–adherence relationship has not been validated against external data. We abstracted the three risk–adherence relationships from the literature, but we have not yet validated the functional forms against external data. In the absence of hard evidence, we used an educated guess to make the risk–adherence relationship operational. To reflect this uncertainty, we used the three different forms for this relationship (positive, negative, or curvilinear) in our analysis.

5. Conclusion

We evaluated three personalized mammography screening strategies. One strategy, VF, produced less utility at lower cost. Two personalized strategies, SK and TDK, have been shown to provide similar performance at reduced cost compared to biennial routine screening. However, which strategy is the best depends on the level of adherence in different risk groups. We demonstrated that even small changes in adherence levels affect the performance of the screening strategy, and thus personalized screening may be an alternative to routine screening.

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Figure 1: State transition model

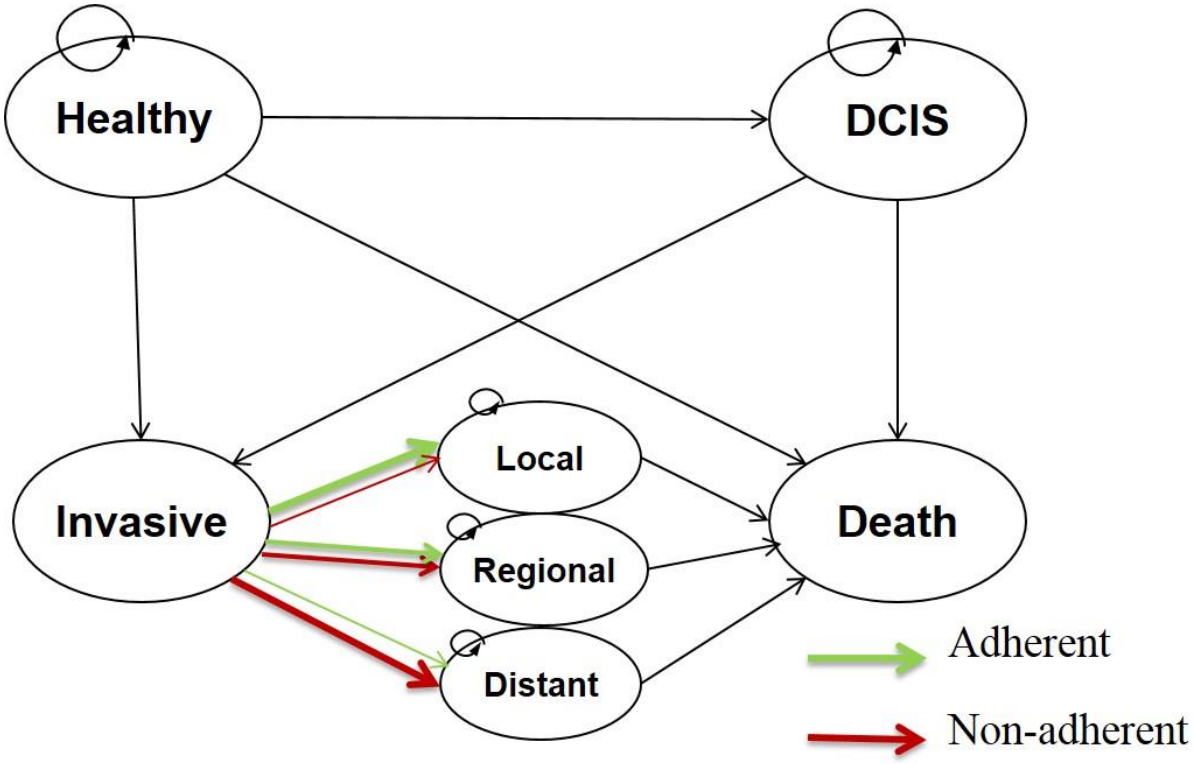

Figure 2: Personalized strategies, intervals and population shares

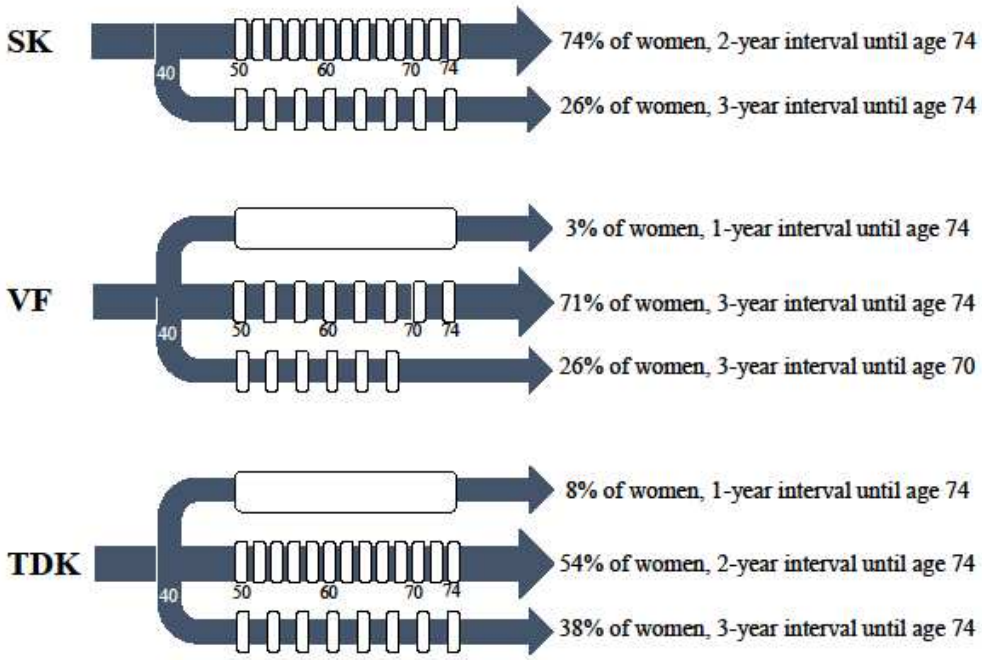

Figure 3: Cost-effectiveness plane, adherence variations (60%, 72.4%, 80%, 90%, and 100%) and adherence scenarios

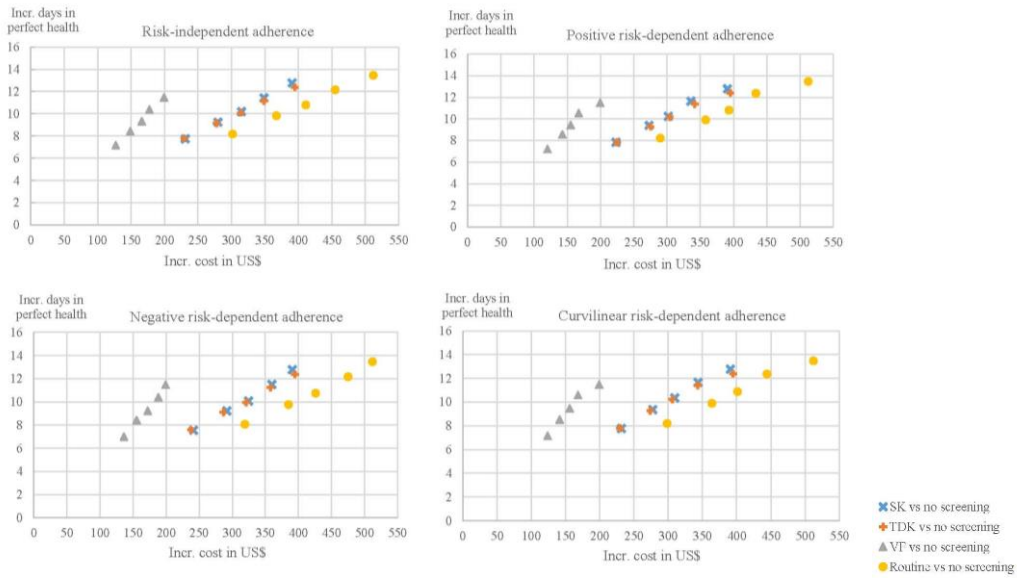

Figure 4: Cost-effectiveness acceptability curves

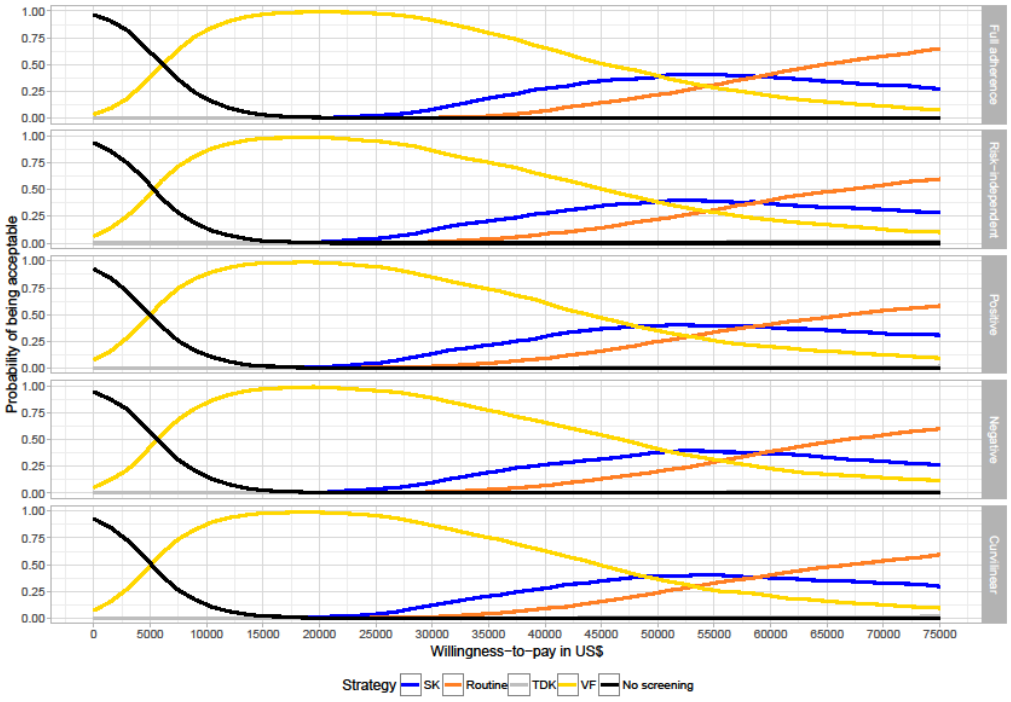

Table 1: Personalized mammography screening strategies, interval length in years

Strategy	Age	BI-RADS 1				BI-RADS 2				BI-RADS 3				BI-RADS 4			
		0	FH	Bio	both	0	FH	Bio	both	0	FH	Bio	both	0	FH	Bio	both
SK (13)	50-59	3	3	3	3	3	2	2	2	2	2	2	2	2	2	2	2
	60-69	3	3	3	3	3	2	2	2	2	2	2	2	2	2	2	2
	70-74	3	3	3	3	3	2	2	2	2	2	2	2	2	2	2	2
VF (14)	50-59	3	3	3	3	3	3	3	3	3	3	3	1	3	3	3	1
	60-69	3	3	3	3	3	3	3	3	3	3	3	1	3	3	3	1
	70-74						3	3	3	3	3	3	1	3	3	3	1
TDK (15)	50-59	3	3	3	3	3	3	3	2	2	2	2	1	2	1	1	1
	60-69	3	3	3	3	3	3	3	2	2	2	2	1	2	1	1	1
	70-74	3	3	3	3	3	3	3	2	2	2	2	1	2	1	1	1

BI-RADS: breast density categorization according to the Breast Imaging Reporting and Data System (20)
0: No additional risk factors
FH: family history in first-degree relative
Bio: history of previous biopsy
Both: both risk factors

Table 2: Adherence probability and risk score

Breast Density (BI-RADS*)	Family history (y/n)	Previous biopsy (y/n)	Proportion of population	10-year risk of invasive breast cancer (in %) (21)	Adherence probability		
					Positive association	Negative association	Curvilinear association
1	0	0	2.65%	0.41	62.91%	81.87%	65.00%
1	0	1	1.04%	0.62	66.14%	78.65%	67.44%
1	1	0	0.51%	0.78	67.94%	76.86%	69.10%
2	0	0	21.26%	0.85	68.61%	76.19%	69.77%
1	1	1	0.20%	1.17	71.11%	73.70%	72.43%
2	0	1	8.35%	1.28	71.81%	72.99%	73.18%
3	0	0	28.19%	1.37	72.34%	72.46%	73.74%
2	1	0	4.08%	1.60	73.56%	71.25%	74.92%
4	0	0	8.13%	1.67	73.89%	70.92%	75.21%
3	0	1	11.07%	2.05	75.49%	69.32%	76.22%
2	1	1	1.60%	2.39	76.69%	68.12%	76.30%
4	0	1	3.19%	2.50	77.05%	67.77%	76.16%
3	1	0	5.41%	2.57	77.26%	67.56%	76.03%
4	1	0	1.56%	3.13	78.80%	66.02%	73.82%
3	1	1	2.12%	3.83	80.38%	64.45%	68.12%
4	1	1	0.61%	4.65	81.90%	62.93%	57.29%
Expected participation rate					72.50%	72.30%	72.99%

*Breast Imaging Reporting and Data System (BI-RADS)

Table 3: Screening performance per adherence scenario

Suggested strategy vs no screening		Units per woman [95% Confidence Intervals]									
		Incr. total cost in US$	Incr. cost screening + diagnostic work up in US$	Incr. cost treatment DCIS + local in US$	Incr. cost treatment regional + distant in US$	Incr. days alive	Incr. days in perfect health	Proportion of overdiagnosed cancers of invasive cancers	Number of screenings	Number of false positive results	Rejected screening invitations
SK (13)	Full adh.	371.13 (362.22,380.04)	1240.7	414.12	-1283.51	25.95 (24.98,26.93)	13.16 (12.92,13.4)	0.6 (0.58,0.63)	10.25 (10.25,10.25)	0.76 (0.76,0.76)	0
	Uniform adh .	266.69 (259.1,274.27)	898.28	300.02	-931.48	18.51 (17.68,19.34)	9.49 (9.29,9.7)	0.43 (0.41,0.45)	7.42 (7.42,7.42)	0.55 (0.55,0.55)	2.83 (2.83,2.83)
	Positive adh.	256.41 (248.79,264.03)	896.15	301.9	-941.52	18.81 (17.98,19.63)	9.63 (9.42,9.83)	0.43 (0.41,0.45)	7.39 (7.38,7.39)	0.55 (0.55,0.55)	2.87 (2.86,2.87)
	Negative adh.	277.67 (270.11,285.23)	904.16	299.8	-926.16	18.47 (17.64,19.3)	9.42 (9.22,9.63)	0.43 (0.41,0.45)	7.49 (7.48,7.49)	0.55 (0.55,0.55)	2.76 (2.76,2.77)
	Curvi. adh.	263.13 (255.5,270.75)	903.15	302.82	-942.72	18.81 (17.98,19.63)	9.63 (9.43,9.84)	0.43 (0.41,0.45)	7.45 (7.44,7.45)	0.56 (0.56,0.56)	2.8 (2.8,2.81)
VF (14)	Full adh.	181.88 (173.59,190.18)	929.38	347.47	-1094.82	22.47 (21.59,23.35)	11.64 (11.41,11.86)	0.47 (0.45,0.49)	7.64 (7.64,7.64)	0.57 (0.57,0.57)	0
	Uniform adh .	133.34 (126.3,140.38)	672.94	250.81	-790.3	16.29 (15.55,17.04)	8.46 (8.26,8.65)	0.34 (0.32,0.36)	5.53 (5.53,5.53)	0.42 (0.42,0.42)	2.11 (2.11,2.11)
	Positive adh.	125.05 (117.96,132.13)	671.66	252.73	-799.24	16.44 (15.69,17.19)	8.54 (8.35,8.74)	0.34 (0.32,0.36)	5.51 (5.51,5.52)	0.42 (0.42,0.42)	2.13 (2.13,2.13)
	Negative adh.	141.76 (134.75,148.77)	676.71	250.12	-784.96	16.21 (15.46,16.95)	8.38 (8.19,8.57)	0.34 (0.32,0.36)	5.57 (5.57,5.57)	0.42 (0.42,0.42)	2.07 (2.07,2.07)
	Curvi. adh.	127.59 (120.53,134.66)	672.17	252.58	-797.06	16.37 (15.63,17.12)	8.54 (8.35,8.73)	0.34 (0.32,0.36)	5.52 (5.52,5.53)	0.42 (0.42,0.42)	2.12 (2.11,2.12)
TDK (15)	Full adh.	371.86 (362.97,380.75)	1208.66	407.44	-1244.06	24.78 (23.82,25.75)	12.61 (12.37,12.85)	0.6 (0.58,0.63)	9.96 (9.95,9.96)	0.75 (0.75,0.75)	0
	Uniform adh .	269.27 (261.72,276.82)	875.08	294.53	-900.22	17.67 (16.85,18.49)	9.09 (8.89,9.29)	0.43 (0.41,0.45)	7.21 (7.2,7.21)	0.54 (0.54,0.54)	2.75 (2.75,2.75)
	Positive adh.	261.55 (253.95,269.15)	875.95	296.69	-910.98	18 (17.18,18.82)	9.23 (9.03,9.44)	0.43 (0.41,0.46)	7.19 (7.19,7.2)	0.55 (0.55,0.55)	2.76 (2.76,2.76)
	Negative adh.	278.1 (270.58,285.63)	877.95	294	-893.74	17.55 (16.72,18.37)	9.01 (8.8,9.21)	0.43 (0.41,0.45)	7.25 (7.25,7.25)	0.54 (0.54,0.54)	2.7 (2.7,2.71)
	Curvi. adh.	265.12 (257.53,272.71)	877.98	296.94	-909.69	17.91 (17.08,18.73)	9.23 (9.03,9.44)	0.43 (0.41,0.45)	7.22 (7.21,7.22)	0.55 (0.55,0.55)	2.74 (2.74,2.74)
Biennial routine screening	Full adh.	485.08 (476.03,494.13)	1412.23	433.39	-1360.34	28.01 (27.01,29.02)	13.81 (13.57,14.06)	0.66 (0.64,0.69)	11.69 (11.69,11.69)	0.85 (0.85,0.85)	0
	Uniform adh .	349.5 (341.79,357.2)	1022.4	314.09	-986.87	20.17 (19.31,21.02)	9.99 (9.78,10.2)	0.47 (0.45,0.49)	8.46 (8.46,8.47)	0.61 (0.61,0.61)	3.23 (3.23,3.23)
	Positive adh.	333.77 (326.03,341.5)	1012.41	315.29	-993.79	20.35 (19.49,21.21)	10.11 (9.9,10.32)	0.47 (0.45,0.5)	8.36 (8.36,8.36)	0.61 (0.61,0.61)	3.33 (3.33,3.33)
	Negative adh.	365.2 (357.51,372.Fr9)	1036.2	314.58	-985.44	20.21 (19.35,21.07)	9.95 (9.74,10.15)	0.47 (0.45,0.5)	8.6 (8.59,8.6)	0.62 (0.62,0.62)	3.09 (3.09,3.1)
	Curvi. adh.	341.98 (334.23,349.72)	1021.6	316.43	-995.92	20.37 (19.51,21.23)	10.11 (9.9,10.32)	0.48 (0.45,0.5)	8.44 (8.44,8.44)	0.62 (0.61,0.62)	3.25 (3.25,3.25)