Discussion

DISCUSSION

In developed countries, most women within the 50-70 age range have been regularly screened for breast cancer in the last decades. (1, 2) However, measuring the public health impact of breast cancer screening has been challenging for several reasons. First, it is unknown how many breast cancers diagnoses and breast cancer deaths would have occurred had there been no screening. The lack of a control group of women who are not screened makes it difficult to quantify the impact of screening. Second, the simultaneous improvements in breast cancer screening and treatment make it difficult to quantify the contributions of either. These are areas where models come into play. (3, 4) Models can simulate a population of women in the presence and in the absence of various screening and treatment strategies. Further, models can extrapolate the findings from randomized controlled trials by synthesizing data on breast cancer epidemiology, demographics, screening accuracy, and treatment effectiveness to estimate the magnitude of harms and benefits associated with many different screening strategies. The predictions by the Cancer Intervention and Surveillance Modeling Network (CISNET) models have been used to support the current United States Preventive Services Task Force (USPSTF) screening guidelines. (5) Overall, there are numerous reasons why models can contribute to a better understanding of trends in breast cancer incidence and mortality. Nevertheless, breast cancer microsimulation models can also be perceived as complex and be challenging to fully understand.

Research question 1: How can model description, comparison, and validation contribute to a better understanding of model predictions?

Microsimulation model MISCAN-Fadia

One way to improve the understanding of model predictions is to provide a detailed description of the model. The tumor size-oriented MIcrosimulation SCreening ANalyses (MISCAN) model is characterized by exponential continuous tumor growth based on the tumor volume doubling time concept. The tumor FAtal DIAmeter (FADIA) concept represents distant metastasis of breast cancer. These concepts form an intuitive biological entry to modeling breast cancer natural history. One advantage is that tumor size can be observed at diagnosis and if real data on tumor progression rates becomes available in the future this can be used directly in the model. A challenge however, is that trials evaluating the performance of screening modalities often only report test sensitivity, and have to be recalibrated to tumor sizes in order to be applicable in the model. Logically, newer and more sensitive screening tests are able to detect tumors of smaller diameter sizes than less sensitive (older) screening modalities such single view film mammography. Similarly, the efficacy of breast cancer treatment found in studies (6) is translated into a tumor size that can be cured by a specific treatment.

In randomized controlled trials, randomization of participants is a key step to reduce the chance of systematic differences between study participants in the intervention and control groups. In the model this is imitated by simulating a target population twice with the exact same characteristics, except the screening strategy. In general, describing the demography, breast cancer natural history, screening and treatment part of a model and including the model inputs, should contribute to a better understanding of the model. In 2018, a special issue in Medical Decision Making was dedicated to providing a detailed description of all CISNET breast cancer models.(7)

Comparison of DCIS models

One of the most important harms of routinely screening asymptomatic women for breast cancer, that has profound implications for quality of life, is overdiagnosis and overtreatment. The magnitude of overdiagnoses has been a matter of extensive debate because the standard of care is that all tumors are treated immediately upon diagnosis. Moreover, overdiagnoses is difficult to measure as it not observable in individual women and estimates vary widely. (8) The CISNET models project that 34-72% of DCIS diagnoses are overdiagnosed in a biennial 50 to 74 screening scenario.(9) The comparison of multiple approaches to modeling DCIS (in chapter 3) showed that models assuming a stable background trend in breast cancer incidence predicted the highest rates of overdiagnoses of DCIS. The stable background trend implied that the majority of the increase in breast cancer diagnoses due to screening were overdiagnoses. Models with a relatively long pre-clinical duration of DCIS and therefore a relatively long period to detect DCIS by screening, also predicted a high percentage of DCIS overdiagnoses. Models including invasive breast cancer which can be non-progressive, predicted relatively low levels of DCIS overdiagnoses. Overall, and similar to what other studies have found, the comparative modeling outcomes showed that even though there is uncertainty about DCIS natural history, the amount of overdiagnoses among DCIS cases is substantial and greater than the amount of overdiagnoses among invasive breast cancers. (10)

Evidently, the quality of model inputs is related to the quality of model outputs. Since the information about DCIS natural history is still limited, the model projections for DCIS overdiagnoses may therefore not be sufficiently accurate yet to inform clinical practice. A key step in the improvement of our understanding of DCIS natural history and the associated value of modeling DCIS is using observed data from DCIS trials. The COMET(11), LORD, and LORIS (12) trials monitor women with DCIS with the intent of only offering treatment when needed and thereby reduce the risk of overtreatment. Future steps that modeling groups have to make are including new trial information and predictors for disease progression. Predictors for progression include cytologic grade, younger age at diagnosis, ethnicity, or DCIS tumor size. (13, 14)

External model validation

There is a complex interplay between multiple factors that contribute to the effects of screening and treatment on cancer incidence and mortality. These factors include, sensitivity and specificity of screening, screening frequency, attendance to screening, treatment effectiveness, treatment adherence, disease risk and natural history of the disease. Models can synthesize data from various sources to simulate the interplay between such factors and make predictions for the impact of screening and treatment. If collaborative modeling outcomes point to similar conclusions by different models, this should improve the credibility of the conclusion. To formally assess a model´s predictive ability, model predictions should be compared to observed clinical trial outcomes. This is called model validation. The comparison of model predictions to observed event data not used in model development, is called external validation and is seen as one of the strongest forms of model validation. (15)

The effectiveness of screening below age 50 is an important issue in breast cancer screening. While young women (< age 50) are at lower risk to develop breast cancer than older women, tumors grow faster and mammography performs less well due to the prevalence of dense breasts in younger women. (16) The different screening guidelines reflect the uncertainty about screening in this age group. The U.K. Age trial was specifically designed to address the question about the effectiveness of screening in women in the 40 to 49 age range. (17) In chapter 4, Five CISNET models, primarily built for making predictions of screening and treatment in the United States, made predictions for breast cancer screening in the United Kingdom. Predictions were compared to the findings of the U.K. Age trial that compared annual mammography screening of women ages 40 to 49 years with no screening in this age group. The models underestimated the effect of screening on breast cancer mortality at 10-year follow-up. On average, the modeled breast cancer mortality reduction due to screening was 15% (range across models, 13% to 17%) vs. 25% (95% CI, 3% to 42%) observed in the Age trial. (18) At 17-year follow-up, the models predicted 13% (range across models, 10% to 17%) vs. the non-significant 12% (95% CI, -4% to 26%) observed in the trial.

On closer inspection and comparison of model outcomes, we observed that models with slower tumor progression on average predicted a slight increase in breast cancer mortality reduction between 10 and 17-year follow-up. The models with faster tumor progression, and thus a shorter time to breast cancer metastases, on average showed a decline or stable trend in breast cancer mortality reduction. Given that the underestimation at 10-year follow-up was present across all models, it might be explained by a common model input not related to screening. Specifically, no treatment information has been reported in the trial. The models used a derived treatment dissemination based on U.K. surgical oncology reports that may have been different from the actual treatments received by women diagnosed with breast cancer in the trial.

It is known that if screening is first introduced there is a delay in the impact on cancer mortality. The Age trial is one example that shows that lifetime follow-up is important when measuring the impact of screening and treatment. If an extension of the U.K. screening program to women under age 50 was based on the conclusions of the trial at 10-year follow up, one could argue that based on the breast cancer mortality reduction at 17-year follow up this should be reversed. A different challenge of the Age trial was that an ongoing national screening program was in place for women aged 50 and older, and for justified ethical reasons women in both arms of the trial were invited to participate in this program. To assess the effectiveness of screening on breast cancer mortality, the trial restricted their analyses to breast cancers diagnosed during the intervention phase. With regard to screening quality in the trial, the models and the trial itself showed more breast cancer diagnoses due to symptoms (interval cancers) than from early detection by screening in the intervention group. We attributed this finding to the relatively low sensitivity of single view mammography at the time.

Overall we conclude that the models captured the observed long-term effect at 17-year follow-up of screening from age 40 to 49 years on breast cancer incidence and mortality in the UK Age trial, suggesting that the model structures, input parameters, and assumptions about breast cancer natural history are reasonable for estimating the impact of screening on mortality in this age group. It can be noted that it is quite common to have relatively wide confidence intervals in randomized trials on cancer screening. The wide confidence intervals are partly due to the limited number of women included and absolute number of breast cancer deaths. In modeling studies, the outcomes and simulations are not limited to a certain number of women, but models are ultimately informed by these observed data as well.

Which model aspects drive model predictions (MCLIR method)

A necessary step in the interpretation of collaborative model results is to understand how model structure and assumptions contribute to variations in cancer incidence and mortality predictions. However, explaining differences in model predictions is not always straightforward for reasons related to the nature of the disease. Modeling breast cancer involves the representation of unobservable processes such as tumor onset and tumor progression, upon which interventions are overlaid. To model breast cancer, models must make assumptions about the timing of tumor inception, tumor progression, and progression variability among tumors. These assumptions, in conjunction with model structure, impact 3 key determinants of screening effectiveness: 1) pre-clinical duration of breast cancer in which cancers could be detected by screening; 2) the sensitivity of the screening test; and 3) the improvement in prognosis from treatment, e.g., to what extent (earlier) treatment actually reduces (more) breast cancer mortality. The maximum clinical incidence reduction (MCLIR) method was used to isolate the effects of tumor onset,

tumor progression, screening test sensitivity, and breast cancer treatment by comparing model results before and after imposing a one-time screening intervention at age 62 under varying assumptions about screening performance and treatment effectiveness.

Even though different models may use the same data on screening sensitivity and breast cancer treatment effectiveness, the implementation of screening and treatment varies because model structures are different. The MCLIR method was designed to gain insight into how model structure and assumptions influence model predictions. The rationale behind this method is that in the absence of screening, breast cancers will only be diagnosed because of clinical symptoms; referred to as clinical incidence and defined as breast cancers diagnosed due to symptoms. Screening is assumed to detect some of these cancers before symptomatic diagnosis, thereby reducing clinical incidence, and possibly cancer mortality. Differences in 'clinical incidence reduction' reflect differences in how models portray the pre-clinical detectable phase of breast cancer (tumor onset and progression) and mechanisms of screen detection (incorporation of sensitivity). On the other hand, differences in breast cancer mortality are expected to capture model-specific assumptions about implementation of treatment as well as the impact of tumor onset and progression on breast cancer natural history.

The hypothetical 'perfect screening test' scenario showed that some models have relatively large numbers of tumors in existence at screening. On closer inspection, these models have in common a model structure that simulates tumor inception long before the start of the sojourn time (the screen-detectable phase). Moreover, the outcomes also indicated that the tumors in these models are, on average, slowly progressing with longer survival times. On the other hand, models with few cancers in existence at screening, were models with structures that simulated tumors at the start of the sojourn time and with assumptions of relatively fast tumor progression that resulted in shorter survival times on average. Overall, models may be perceived as complex, however the interplay between screening and treatment interventions with unobservable disease natural history is also complex in itself. The MCLIR method can isolate model parts and provide more insight into the factors that drive incidence and mortality predictions. Overall we conclude that in models, the timing of tumor inception and its effect on the length of the pre-clinical phase of breast cancer can have substantial impact on their predictions for breast cancer incidence and mortality reduction.

PART 2: QUANTIFYING THE HARMS AND BENEFITS OF AGE-BASED BREAST CANCER SCREENING IN THE UNITED STATES.

The evidence obtained from randomized controlled trials on the effectiveness of breast cancer screening in the past 30 years led to the widespread use of mammography screen-

ing. Despite this body of evidence, the magnitude of the harms and benefits of breast cancer screening has been debated extensively and the lack of consensus is reflected in the current screening guidelines. This debate has been fueled by the increase in harms such as false-positives and overdiagnoses. Also, the simultaneous improvements in breast cancer screening and treatment over time make it difficult to disentangle the contributions of either to the overall harms and benefits.

Research question 2: What are the benefits and harms of current age-based breast cancer screening in the United States?

Explaining the decline in U.S. breast cancer mortality

Advances in breast cancer screening and treatment have both contributed to the decline in U.S. breast cancer mortality in the last 30 years. In 2005, the CISNET models estimated that screening and treatment contributed about equally to the decline in breast cancer mortality between 1975 and 2000.(3) After the year 2000, two important developments have emerged: digital mammography screening and improvements in molecularly targeted treatments. To further reduce breast cancer mortality, it is useful to assess the relative contributions of screening and treatment to breast cancer mortality in the first decade of the 21st century. No single cancer registry in the U.S., nor any randomized trial, collected sufficient long-term information about ER/ERBB specific treatment to quantify the contributions of screening and treatment by molecular subtype at the population level.

We used 6 different CISNET models to simulate US breast cancer mortality from 2000 to 2012 for multiple birth cohorts using national data on plain-film and digital mammography patterns and performance, dissemination and efficacy of ER/ERBB2(HER2)-specific treatment, and competing mortality. In 2000, the contribution of screening to overall breast cancer mortality reduction was 44% and 56% of the reduction associated with treatment. In 2012 this changed; screening was estimated to be responsible for 37% and treatment for 63% of the total breast cancer mortality reduction in that year. Improvements in chemotherapy and hormone therapy were mainly responsible for this increase in the contribution of treatment. Molecular subtype tumors ER+/ERBB+ were mainly treated with Trastuzumab in 2012 and showed the largest relative contributions associated with treatment vs screening: 69% vs 31%. The ER-/ERBB- tumor group saw the lowest breast cancer mortality reduction (37%) and did not benefit from improvements in hormone therapy nor Trastuzumab. Overall, all models conclude there has been a shift in in the relative contributions associated with screening and treatment to U.S. breast cancer mortality. Advances in screening from film to digital mammography have contributed to the overall decline in breast cancer mortality. Even so, the dissemination of new molecularly targeted therapies and the improved delivery of standard treatment

regimens has had a stronger impact on breast cancer mortality than screening between 2000 and 2012.

Our analyses focused on explaining the decline in breast cancer mortality and did not investigate the harms associated with screening and treatment. However, in future perspective, one possible long-term implication of our findings could be that, if cancer treatments become more and more effective, more targeted, and less burdensome, early detection by screening could become less important. In such scenario, improved treatments could indirectly lead to a reduction in the number of screens and thereby a reduction in false-positives and overdiagnoses. It will be important to continuously evaluate the contributions of screening and treatment in light of new developments. In the meantime, improving the sensitivity and specificity of screening is the most direct way to reduce false positives and recall rates. The use of prognostic factors for invasive breast cancer or watchful waiting strategies in non-invasive cases could potentially reduce overdiagnoses.

Model predictions informing screening guidelines

One of the lessons learned in decades of breast cancer screening is that the harms do not always outweigh the benefits. In 2009, the United States Preventive Services Task Force used collaborative modeling outcomes to support the revision of their recommendations from annual screening beginning at age 40 years to biennial screening beginning at age 50. (19) In 2016, the CISNET models updated the model inputs to account for improvements in screening and systemic treatment. We estimated the magnitude of harms (false-positive mammograms, benign biopsies, overdiagnosis) and benefits (breast cancer mortality reduction, life-years gained, quality-adjusted life-years) of eight different screening strategies. Screening strategies varying in start age of screening (40, 45, 50) and screening interval (annual, biennial, and hybrid), where hybrid strategies consist of annual screening before age 50 followed by biennial screening, were evaluated. All models showed that, when considering the average-risk population, screening starting at age 40 led to substantially more false-positives and overdiagnoses among women in their forties than screening starting at age 50. Starting biennial screening at age 40 vs. 50 modestly lowered breast cancer mortality, and QALYs gained increased by 22% from 86 to 105 per 1.000 women screened. Overall, biennial screening strategies were efficient and preferred over annual strategies for average-risk women. Efficient strategies are strategies that result in the greatest gain in benefits per mammogram. Women at 2-to 4-fold average risk could consider annual screening at ages 40 or 50. Sensitivity analyses of screening cessation at older ages showed that comorbidity levels could be used to tailor stopping age of screening.

Overall, these results suggest that screening starting at age 40 has some benefits, but increases the harms substantially. From a public health perspective considering the ratio

between harms and benefits, extending the 50 to 74 biennial screening recommendations to include women aged 40 to 49 is not favorable for average risk women. However, from a woman's perspective the choice to start screening at age 40 may depend on the value she attaches to the potential benefits and harms of screening.

Radiation induced breast cancer

The ionizing radiation associated with repeated mammography may increase breast cancer risk and could lead to radiation induced cancer. To date, radiation induced breast cancer risk was based on exposure from routine screening only and assumed 4 views per screening. We considered radiation from routine screening for different subgroups of women, diagnostic work-up following an abnormal screening result, false-positive recalls, breast biopsies, and follow-up screening examinations. Variation in radiation dose was taken into account as some women receive more than the mean radiation dose for reasons related to breast thickness, breast augmentation, or breast movement during screening. Annual screening including diagnostic work-up among women aged 40 to 74 years induced 125 breast cancers and 16 breast cancer deaths per 100.000 women screened. Biennial screening from ages 50 to 74 resulted in 27 breast cancers and only 4 breast cancer deaths. Screening and diagnostic work-up among women with large breasts lead to 2.3 times more radiation exposure and were consequently at approximately two times greater risk of radiation induced breast cancer and breast cancer death than women with small or average-sized breasts. Overall, our estimates show that it is important to account for variation in radiation dose when quantifying the number of radiation induced breast cancer and breast cancer deaths

Previous analyses showed that the harms of annual compared to biennial screening greatly increased in terms of false-positives and overdiagnoses. We now showed that, especially when considering annual screening or screening initiation before age 50, the risk of radiation induced breast cancer and breast cancer death is substantial and should be taken into account by policy makers, healthcare providers, and ideally women themselves. Moreover, among women with large breasts who undergo more views on average for a complete screening examination, the radiation induced harms are even greater and approximately doubled. In light of the rapid adoption of digital 3-dimensional tomosynthesis in the United States and elsewhere, it is important to keep in mind that the radiation dose is similar or slightly greater than of digital mammography. It goes without saying that combining digital mammography with tomosynthesis doubles the amount of radiation exposure and risk for inducing breast cancer.

PART 3: PROJECTING THE HARMS AND BENEFITS OF RISK-BASED BREAST CANCER SCREENING IN THE UNITED STATES.

In developed countries, the majority of women adhere to breast cancer screening guidelines. Whilst all guidelines recommend women to be screened regularly, there are differences in the start and stop age of screening as well as in screening interval. (19-21) The guidelines have in common the age-based approach to recommend screening. The logic behind this approach is that age is the strongest risk-factor for most women and ethically all women should have the same rights to potential benefits of screening. However, there is also a downside to an age-based approach to screening. For instance, a screening guideline of biennial screening from ages 50 to 74 essentially treats all women between ages 50 and 74 as being at equal risk for developing breast cancer. It is known that breast cancer risk varies among women of the same age.

Research question 3: To what extent can risk-based breast cancer screening improve the harm-benefit ratio of current age-based screening guidelines?

Risk-stratified screening implies that women are screened in a way that is based on their risk level. A prerequisite is that ahead of screening some sort of risk-assessment has to be made. This could for instance be assessed by asking about their personal or family history of breast cancer, measuring their breast density, or testing for genetic risk factors such as SNPs or rare variants.

Tailoring breast cancer screening intervals by breast density and risk

Despite the consensus about screening women aged 50 and older that is reflected in the various age-based guidelines, it remains challenging to incorporate information on breast cancer risk into screening routines beyond age. Breast density is a risk factor for breast cancer, may change as women age, and affects mammography performance. (22, 23) We estimated the outcomes for screening strategies in the U.S. varying interval of screening (annual, biennial, and triennial) tailored to women aged 50 years or older with various combinations of breast density and relative risk. Four density levels, in line with the American College of Radiology's Breast Imaging reporting were considered: 1) almost entirely fat, 2) scattered fibroglandular density, 3) heterogeneously dense, and 4) extremely dense. Additionally, increased risk levels 1.3, 2.0, and 4.0 that represent for example post-menopausal obesity, history of a benign breast biopsy, or personal history of breast cancer were included. The results showed that screening, regardless of interval and age group, yielded more breast cancer deaths averted, life-years gained, and quality adjusted life-years among women with dense breast and among women at increased relative risk within each density group. In other words, higher breast cancer risk was

associated with more benefits of screening. The number of false-positives and benign biopsies decreased with increasing risk and density, while overdiagnoses increased by risk. When considering a cost-effectiveness threshold of $100,000 per QALY, triennial screening was the only effective strategy for women with low breast density at average risk. Biennial screening was cost-effective among women at increased risk regardless of density, and annual screening was only cost-effective across subgroups at the highest (4.0) risk level and breast density categories 3 and 4 (extremely dense).

Overall, we conclude that breast density and risk level can be used to guide screening intervals. Across women with varying levels of risk and breast density, those with dense breasts at increased risk are most likely to benefit from the current USPSTF guidelines of biennial screening from ages 50 to 74. From a policy maker perspective, the results suggest that only women with extremely dense breasts at the highest risk levels should consider annual screening. Otherwise, annual screening is not cost-effective. Triennial screening was cost-effective for a relatively large group of women with low breast density and average risk. In international perspective, triennial screening is standard practice in the U.K. while in the U.S. this interval is not considered in any guidelines. The modeling results show that triennial screening has a similar balance between harms and benefits compared to biennial screening. In absolute numbers, the benefits, but also the harms are greater for biennial screening, but if relative measures or harm-benefit ratios are leading, triennial screening could be considered for low density, average-risk women. It remains difficult to extend this analysis to younger (<50) women as breast density is unknown until the first mammogram. Incorporating changes in breast cancer risk over time or by age could potentially increase the benefits and reduce the harms of risk-stratified screening.

Personalizing breast cancer screening based on polygenic risk and family history

A first-degree family member diagnosed with breast cancer is a risk factor to develop breast cancer and relatively easy to assess. Polygenic risk can be assessed by a SNP test using blood or saliva and polygenic risk is presumed to remain unchanged during life. These characteristics are the rationale behind our study assessing risk-stratified screening approaches using first-degree family history (FH) and polygenic risk scores (PRS). The models established risk groups based on first-degree family history and risk groups based on a 77-and 167 SNP polygenic risk score. Annual, hybrid, biennial, and triennial digital mammography screening strategies starting at ages 30, 35, 40, 45, and 50 were evaluated for each risk group. Women at high risk due to a first degree family history of breast cancer and/or high polygenic risk could initiate screening before age 50. Women with below-average polygenic risk could consider triennial screening. We projected greater benefits (breast cancer deaths averted, life years gained) when targeted screening was based on polygenic risk scores rather than family history. The screening

approach combining risk from polygenic risk and family history resulted in the maximum improvement in benefits compared to current age-based screening guidelines.

Sensitivity analyses including additional, more recently identified SNP only modestly improved the benefits and harms. If the discriminatory performance of polygenic risk scores improves in the future, different screening scenarios may be optimal from a public health perspective. From an individual perspective, the attitude towards the harms and benefits of polygenic risk-based screening may result in a different preferred screening strategy. We noticed that quite some screening strategies were associated with more intense screening than the current biennial 50-74 screening guidelines. To remove this aspect and quantify the benefit from just the risk-stratification, we redistributed the guideline-concordant number of screens across all women. The outcomes showed that life-years gained and breast cancer deaths averted still increased modestly. Conversely, this showed that a considerable part of the projected increase in benefits was explained by the increase in cancer detection following from more screening examinations.

Increasing number of guidelines advise women to discuss individual breast cancer risk with their healthcare providers. Ongoing trials such as the WISDOM trial (24) and My-PEBS just started to investigate screening approaches based on genetic markers. Until results become available, the model estimates provide specific screening strategies based on genetic risk factors that could be considered in practice. Combining multiple risk factors such as polygenic risk, breast density, and reproductive, lifestyle, and hormonal factors is likely to improve risk prediction and the harm-benefit ratio for stratified screening. In all scenarios, obtaining genetic information should be done with utmost care and ethical approval. Other ethical aspects of genetic testing such as patient autonomy, accessibility to polygenic risk testing, and differential effects across ancestries should be considered before the implementation or recommendation of polygenic risk-based screening.

DIRECTIONS FOR FUTURE RESEARCH BY BREAST CANCER SIMULATION MODELS

Microsimulation models are commonly used to evaluate and quantify the benefits and harms, i.e. cost and effects of health care policies and interventions. Several applications and topics for future research related to breast cancer screening modalities, breast cancer detection, risk-based screening, and treatment are listed here.

Breast cancer screening modalities

- Estimate the potential impact of screening strategies combining multiple modalities such as mammography, tomosynthesis, magnetic resonance imaging, and/or liquid biopsies.

- Estimate the impact of breast self-examination strategies in developing countries.
- Evaluate active surveillance screening strategies using liquid biopsies to monitor disease activity and possible treatment response.

Breast cancer detection

- Estimate the harms and benefits of currently available blood-based liquid biopsies in detecting circulating tumor DNA and confirming healthy tissue.
- Estimate the required test performance for liquid biopsies to be cost effective.
- Estimate the current and future potential of computer aided detection reducing the harms of screening including false positives, overdiagnoses, and false reassurances.

Risk-based screening

- Estimate the cost and effects of screening targeted to individual, age-specific, breast cancer risk based on a combination of risk factors including polygenic risk (SNPs), breast density, rare variants, and lifestyle factors.
- Find the optimal screening strategies for mutation carriers who are at increased risk to develop breast cancer with distinct natural history.
- Estimate the potential of combining breast cancer risk (e.g. subtype-specific risk) with assumptions about tumor progression rates to inform screening strategies.

Breast cancer treatment

- Assess the impact of a new treatment or vaccine discovery that can prevent or treat metastatic breast cancer.
- Estimate 'watchful waiting' strategies for the treatment of DCIS.

Model development / methodology

- Develop models for the interaction between breast cancer risk and tumor progression.
- Develop models to predict local, regional, and distant breast cancer recurrence.
- Extend the current DCIS models by including prognostic factors for DCIS.
- Further develop the Maximum Clinical Incidence Reduction method to explore the effects of model structure and assumptions on predictions about the harms of screening.

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