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Commentary

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Breast Cancer Screening in the Precision Medicine Era: Risk-Based Screening in a Population-Based Trial

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Abstract

Ongoing controversy over the optimal approach to breast cancer screening has led to discordant professional society recommendations, particularly in women age 40 to 49 years. One potential solution is risk-based screening, where decisions around the starting age, stopping age, frequency, and modality of screening are based on individual risk to maximize the early detection of aggressive cancers and minimize the harms of screening through optimal resource utilization. We present a novel approach to risk-based screening that integrates clinical risk factors, breast density, a polygenic risk score representing the cumulative effects of genetic variants, and sequencing for moderate- and high-penetrance germline mutations. We demonstrate how thresholds of absolute risk estimates generated by our prediction tools can be used to stratify women into different screening strategies (biennial mammography, annual mammography, annual mammography with adjunctive magnetic resonance imaging, defer screening at this time) while informing the starting age of screening for women age 40 to 49 years. Our risk thresholds and corresponding screening strategies are based on current evidence but need to be tested in clinical trials. The Women Informed to Screen Depending On Measures of risk (WISDOM) Study, a pragmatic, preference-tolerant randomized controlled trial of annual vs personalized screening, will study our proposed approach. WISDOM will evaluate the efficacy, safety, and acceptability of risk-based screening beginning in the fall of 2016. The adaptive design of this trial allows continued refinement of our risk thresholds as the trial progresses, and we discuss areas where we anticipate emerging evidence will impact our approach.

A woman's risk of developing breast cancer is influenced by many factors, but breast cancer screening recommendations are based primarily on age. Professional society guidelines in the United States disagree over the optimal age to begin breast cancer screening, as well as the frequency of screening and the age at which to stop. Historically, yearly mammography was offered to women age 40 and older, but in 2009 the United States Preventive Services Task Force (USPSTF) became the first American professional body to solely recommend biennial screening for women age 50 to 74 years, with a shared decision-making approach to screening for women age 40 to 49 years (1). Other guidelines continue to recommend annual screening starting at age 40 years (2,3), with screening occurring annually or biennially depending on age (Table 1) (4). A national health survey found that 60% of female respondents age 40 to 49 years had a mammogram within the last two years (5). Likewise, many providers continue to recommend annual screening; in one recent survey of academic general internists,

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Table 1. Mammography guidelines in the United States

Country and organization	Start screening at age, y	Terminate screening at age, y	Frequency of assessment	Comments
United States Preventive Services Task Force (USPSTF) (7)	50	74	Every 2 y (for women at average risk of breast cancer)	Screening for women age 40–49 y is a grade C recommendation ("offer or provide this service for selected patients depending on individual circumstances")
American Cancer Society (ACS) (4)	45	As appropriate based on life expectancy	Annually then biennially at age 55 y and older	Suggest continued screening as long as good health and life expectancy exceeding 10 y
American College of Obstetricians and Gynecologists (ACOG) (3)	40	As appropriate based on life expectancy	Annually	Suggest discussing cessation of screening with physician starting at age 75 y
American College of Radiology (ACR)/Society of Breast Imaging (SBI) (2)	40	As appropriate based on life expectancy	Annually	Suggest continued screening as long as life expectancy exceeds 5–7 y

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65% recommended yearly mammography for women age 50 to 74 years (6).

A systematic review found that "trial data are too limited to directly inform the question of what the best screening strategy is for women or how clinicians can best tailor that strategy to the individual" (7). Age is an imperfect marker for risk, given that genetic susceptibility, lifestyle factors, and reproductive history can impact a woman's chance of developing breast cancer. Risk-based screening, in which individualized risk assessment is used to inform screening practices, has been proposed as an alternative to age-based screening (8,9). Simulation models have suggested that tailoring screening frequency based on individual risk factor profiles may be more cost-effective than uniform screening (8) and using genetic risk thresholds rather than age may more efficiently identify candidates for screening (10). However, there have been no prospective studies that directly evaluate the efficacy, safety, and cost-effectiveness of risk-based screening (11).

The Patient Centered Outcomes Research Institute (PCORI) recently funded the Women Informed to Screen Depending On Measures of risk (WISDOM) study, a pragmatic, preference-tolerant randomized controlled trial of a risk-based algorithm for screening vs standard care that includes recommendation for yearly mammography for all women (Clinical Trials identifier NCT02620852). This trial will test the hypothesis that risk-based screening will decrease mammography usage without an increase in diagnosis of late-stage breast cancers. In this commentary, we describe our approach to risk-based screening for breast cancer and provide the evidence base for the thresholds that were chosen. We integrate several methods of risk assessment that have been used independently: clinical risk prediction models, polygenic risk scores representing the effects of multiple single-nucleotide polymorphisms (SNPs), and genetic testing for high- and moderate-penetrance breast cancer gene mutations. The corresponding absolute risk estimates will be used to assign screening strategies—starting age, stopping age, frequency, and imaging modality—according to predetermined thresholds. We intend to prospectively test these thresholds in WISDOM.

Risk Assessment Method

Risk Prediction Models

Risk prediction models that estimate a woman's risk of developing breast cancer have been developed and validated. Examples include the Breast Cancer Risk Assessment Tool (including several modified versions) (12–15) and the models put forth by the Women's Health Initiative (16), Tyrer-Cuzick (17,18), Rosner-Colditz (19,20), and the Breast Cancer Surveillance Consortium (BCSC) (21,22). Variables typically include demographics (age, race/ethnicity), reproductive history, menopausal status, family history, breast biopsies, and mammographic density (23).

Risk models have an established, though limited, role in current guidelines. The USPSTF guidelines on chemoprevention suggest the use of validated clinical risk models to identify women at elevated risk (24). Similarly, the American Cancer Society (ACS) suggests using hereditary risk models that estimate one's risk of carrying a *BRCA1* or *BRCA2* mutation (25) to identify women who may benefit from supplemental screening with annual MRI (26). We believe that prospectively studying the use of clinical risk models across the entire population is essential to understanding their clinical utility.

For our risk-based screening approach, we selected the BCSC model for several reasons. Firstly, it was developed and validated in a multiracial and multiethnic population of over 1000 000 women undergoing mammographic screening in the United States (21). It was shown to be well calibrated across multiple study populations, and its c-statistic of 0.67 lies in the upper range of published values for breast cancer risk models, which range from 0.53 to 0.64 (18,21–23,27,28). Lastly, risk assessment using the BCSC model could be easily implemented as the inputs are limited and commonly collected in the clinical setting. We recognize that other models may be better suited to other settings.

Single-Nucleotide Polymorphisms

Risk estimates based on common genetic variants have been incorporated into clinical risk models. Published genome-wide association studies have identified over 90 single-nucleotide polymorphisms (SNPs) thought to explain 15% to 20% of the inherited variance in breast cancer risk, with more discovery studies forthcoming (29,30). While the risk associated with individual SNPs is low, with per-allele odds ratios ranging from 0.8 to 1.3, combining many SNPs into a polygenic risk score is powerful (31–33). The polygenic risk score can be calculated by multiplying the odds ratios associated with each genotype and standardizing to the expected mean of the odds ratios in the

population based on genotype frequencies (34). Alternatively, it can be calculated using a Bayesian approach (35).

Polygenic risk scores are statistically independent from established clinical risk factors (36,37) and provide risk stratification beyond family history and breast density. A 76-SNP polygenic risk score improved the discrimination of the BCSC model by increasing the c-statistic from 0.66 to 0.69 and provided a net reclassification of 11% (95% confidence interval [CI] = 7% to 15%) of cases (33). The combined model was well calibrated in the validation set (33). Likewise, a 77-SNP polygenic risk score increased the c-statistic of several familial breast cancer models by 0.03 to 0.06, a relative improvement of at least 20% (31). In the WISDOM study, we selected SNPs based on a report of genome-wide significance ($P = 5 \times 10^{-8}$) for association with overall, estrogen receptor (ER)–positive, or ER-negative breast cancer in at least one racial or ethnic group (specifically Caucasians, East Asians, Hispanic/Latinos, African Americans). Our polygenic risk score currently includes 96 SNPs and will be used to modify the BCSC risk model estimate in a Bayesian manner (38).

One important consideration is the performance of polygenic risk scores in non-Caucasian groups. The 76-SNP polygenic risk score (32) will likely perform well in East Asians and Latinas because most SNPs discovered in Caucasians have similar effects in Asian (39) and Hispanic (40) populations. Polygenic risk scores incorporating Caucasian odds ratios have been tested in Hispanic populations (41) and in a subanalysis on Asians (38), and in both cases showed similar discrimination as in Caucasian populations. Thus, we propose to initially use the odds ratios for Caucasian women in polygenic risk scores for American Hispanics and East Asians. Whether these risk SNPs would be as informative in African American women remains an area of research. Approximately 70% of SNPs discovered in Caucasians have the same directional effect in African Americans, and a polygenic risk model constructed from these SNPs is predictive (42). We are collaborating with other investigators to refine the PRS in this population.

High and Intermediate Penetrance Susceptibility Genes

Currently, genetic testing for breast cancer susceptibility is focused on detecting pathogenic mutations within high- and moderate-risk genes. As part of the trial, we will be conducting population-based testing for mutations in nine genes that have been consistently associated with breast cancer risk: *BRCA1*, *BRCA2*, *TP53*, *STK11*, *PTEN*, *CDH1*, *ATM*, *PALB2*, and *CHEK2* (43). Pathogenic germline mutations in the *BRCA1* and *BRCA2* genes dramatically increase the relative risk of breast cancer, particularly among premenopausal women. Cumulative lifetime risks of breast cancer can reach approximately 65% for *BRCA1* and 45% for *BRCA2* (44). Women with *BRCA1* mutations are more likely to develop triple-negative tumors, which are associated with poor prognosis (45). Management guidelines have been developed for *BRCA1/2* mutation carriers (46) to reduce the risk of being diagnosed with advanced stage breast cancer; options include surveillance with breast MRI and mammography, pharmacologic risk reduction with tamoxifen or aromatase inhibitors, or procedures such as prophylactic mastectomies. Testing for *BRCA1/2* has become increasingly available to women who meet USPSTF, National Comprehensive Cancer Network (NCCN), or commercial insurers' criteria for testing.

Several rare cancer predisposition syndromes also increase one's risk of breast cancer (47). Overall, pathogenic mutations in the *TP53* (Li-Fraumeni Syndrome), *STK11* (Peutz-Jeghers Syndrome), *PTEN* (Cowden Syndrome), and *CDH1* (Familial Gastric Cancer) genes are rare, but high-risk surveillance and/or risk-reducing interventions are indicated for carriers of these gene mutations. Specific recommendations often depend on family cancer burden (46).

Finally, mutations in moderate-risk genes such as *ATM*, *CHEK2*, and *PALB2* can increase breast cancer risk two- to threefold. Genetic testing for these mutations has become more widely accessible because of panel-based testing (43), and our understanding of their effects on risk continues to evolve. The degree of risk elevation conferred by *CHEK2* and *PALB2* mutations is likely modified by an individual's family history (48,49). The cumulative risk by age 80 years associated with the *CHEK2* mutation 1100delC is 22%, lower than that of a *BRCA1/2* carrier, although this risk varies by family history (50). For most women with mutations in any of these three genes, current guidelines recommend a personalized approach that takes into account family history, age, and other factors (51).

Family risk surveys are traditionally used to determine which patients are offered genetic testing. However, these surveys are cumbersome to implement on a population-wide level and imperfect (52). Up to 50% of *BRCA1* and *BRCA2* mutation carriers may not have a suggestive family history (53). The recent United States Supreme Court ruling that prohibited patenting the human genome (54) enabled the proliferation of multigene testing providers, and market competition has resulted in greater availability of panel-based tests for genetic mutations (43). This provides the opportunity to prospectively evaluate whether the identification of individuals with genetic contribution to risk can improve outcomes. Such testing will also be useful for women who are adopted, do not know their family history of cancer, or have small or male-dominant families.

The other seven genes combined explain a similar proportion of familial risk as the *BRCA1/2* genes. The combined effects of the common genetic variants in the polygenic risk score likely explain a similar proportion of familial risk as the combined effects of moderate and high-penetrance gene mutations (55).

Risk Thresholds

Our risk thresholds (Table 2) translate the results of the risk assessment described above into screening recommendations. The thresholds were developed using evidence review, simulation modeling, and expert opinion. A multidisciplinary working group representing breast surgery, cancer genetics, cancer risk counseling, epidemiology, and general internal medicine developed the thresholds.

Our screening approach is guided by the principles in Box 1. We adopted the minimum standard of digital mammography every two years starting at age 50 years to ensure that recommendations are within established guidelines (7). For women age 40 to 49 years, screening is recommended when their five-year risk equals or exceeds that of the average woman age 50 years. Women in this age group will be screened every two years, except women with extremely dense breasts, who will be offered annual screening (56). Our screening recommendations are principally based on five-year risk estimates generated from the BCSC model modified by the polygenic risk score. We based our thresholds on five-year risk given that screening and prevention are most impactful in those at immediate risk of cancer, and five-year risk thresholds are standardly used to guide chemoprevention (57).

Table 2. Risk thresholds

	Age 40–49 y	Age 50–74 y
No screening at this time	5-y absolute risk < 1.3%	—
Biennial mammogram*	5-y absolute risk ≥ 1.3%†	All women
Annual mammogram‡	Extremely dense breasts (BIRADS d) on prior mammogram	Carriers of *ATM*, *PALB2*, or *CHEK2* mutations without a positive family history of breast cancer§
	Carriers of *ATM*, *PALB2*, or *CHEK2* mutations without a positive family history of breast cancer§	
Annual mammogram + adjunctive MRI	Carriers of *BRCA1/2*, *TP53*, *PTEN*, *STK11*, or *CDH1* mutations	
	Carriers of *ATM*, *PALB2*, or *CHEK2* mutations with a positive family history of breast cancer§	
	History of therapeutic chest irradiation between age 10–30 y	
	5-y absolute risk ≥ 6%	

*If individual does not meet criteria for annual mammogram or annual mammogram + MRI. MRI = magnetic resonance imaging.
†Except for individuals with extremely dense breasts (BIRADS d) on prior mammogram.
‡If individual does not meet criteria for annual mammogram + MRI.
§Family history is defined as a first-degree relative with breast cancer, two second-degree relatives with breast cancer, or one second-degree relative diagnosed with breast cancer prior to age 45 years.

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Box 1. Principles of risk-based screening

- No woman will be screened less aggressively than existing recommendations from major professional societies
- Minimize false positives
- Minimize interval cancers
- Minimize incidence of stage IIB and higher disease
- Women with known deleterious mutations in hereditary breast cancer genes will be screened according to National Comprehensive Cancer Network guidelines
- Screening recommendations will be practical and scalable

Carriers of genetic mutations will receive screening recommendations guided by their mutation type and family history. Women found to have high-penetrance gene mutations (and prior recipients of chest irradiation) will receive adjunctive MRI. In women with moderate-penetrance gene mutations, recommendations will be guided by age and family history. We define family history as 1) a first-degree relative with breast cancer or 2) either two second-degree relatives with breast cancer or one second-degree relative diagnosed prior to age 45 years.

Biennial Mammography

We adopted the USPSTF guideline as our baseline approach for low- to average-risk women age 50 years (7). These recommendations are based on systematic reviews (58–60) and simulation modeling (61) that have found that, relative to annual screening, biennial screening is associated with comparable benefit, with a lower frequency of false positives and unnecessary biopsies.

Given the heterogeneity of risk within women of the same age, some women age 40 to 49 years have an equivalent risk to that of a woman age 50 years. According to data from the Surveillance, Epidemiology, and End Results (SEER) registry (62), the five-year risk of an average Caucasian woman age 50 years is 1.3%. Thus, a five-year risk of 1.3% or higher represents a conservative threshold above which biennial mammography can be offered to women based on the combined BCSC model-polygenic risk score estimate. In women age 40 to 49 years without a baseline mammogram, their risk will be imputed using extremely dense breasts (Breast Imaging Reporting and Data System [BIRADS] Category d) in order to generate the conservative upper-bound risk estimate.

Annual Mammography

Compared with biennial mammography, annual mammography prevents one to two more deaths from breast cancer per 1000 women but leads to more false-positive findings (1421 more per 1000 women) and unnecessary biopsies (125 per 1000 women) over a lifetime, assuming screening begins at age 40 years (58,59). In the BCSC, only women age 40 to 49 years with extremely dense breasts (BIRADS d) had an increased risk of American Joint Committee on Cancer (AJCC) stage IIB or higher cancers when screened biennially compared with annually (56). The odds ratio of stage IIB cancers in the biennial group relative to the annual group was 1.89 (95% CI = 1.06 to 3.39). This finding, along with an increased risk (odds ratio [OR] = 2.39, 95% CI = 1.37 to 4.18) of tumor size greater than 2 cm on presentation in women age 40 to 49 years screened biennially rather than annually (56), suggests that annual screening for women with extremely dense breasts in this age group will decrease breast cancer mortality.

Most carriers of moderate penetrance mutations such as *ATM*, *PALB2*, and *CHEK2* will also receive a recommendation for annual screening. These women likely have five-year and lifetime risks that fall between those of average-risk women and carriers of high-penetrance mutations. For example, the 22% risk of developing breast cancer by age 80 years in CHEK2*1100delC carriers is within the range of the 20% to 25% lifetime risk above which the NCCN recommends adjunctive MRI. However, evidence suggests that additional risk factors

such as family history may increase the risk associated with moderate penetrance genes and some carriers will be considered candidates for adjunctive MRI.

Annual Mammography and Annual MRI

Intensive screening with annual mammography and adjunctive MRI is recommended for several high-risk groups according to guidelines by the NCCN (46) and ACS (26). The mammogram and MRI can be performed at the same time each year or alternated six months apart (26). The guidelines are supported by studies reporting increased sensitivity of MRI in high-risk groups such as genetic mutation carriers or women previously treated with radiation for childhood cancers (63–65). According to NCCN guidelines, carriers of *BRCA1* and *BRCA2* mutations are recommended to undergo this screening strategy, as are women who have unknown or negative mutation status but a lifetime risk above 20% to 25%, according to a family history–based risk model (46).

Automated testing for high-penetrance germline mutations can identify additional women who may benefit from adjunctive MRI. Women who test positive for high-penetrance mutations in *BRCA1/2*, *TP53*, *PTEN*, *STK11*, and *CDH1* will be recommended annual mammography with adjunctive MRI per NCCN guidelines (46). Those who do not test positive but have a five-year risk equivalent to that of a *BRCA1/2* carrier (6% or greater) (44) will also receive a recommendation for annual mammography with adjunctive MRI. Carriers of *ATM*, *PALB2*, and *CHEK2* with a positive family likely have an equivalent level of risk and may also be recommended this screening strategy. NCCN guidelines similarly recommend adjunctive MRI in addition to annual mammography for carriers of *CHEK2*, *ATM*, and *PALB2* mutations with additional risk factors such as positive family history (46). Age is an important consideration in this decision given that the risk for *CHEK2* and *ATM* carriers decreases with older attained age (66).

Lastly, women who received chest irradiation for treatment of Hodgkin's lymphoma (HL) have cumulative risks of breast cancer that equal or exceed those of *BRCA1/2* carriers (67,68). A systematic review of more than 7000 women who received chest irradiation for HL prior to the age of 30 years found a cumulative incidence of breast cancer of 13% to 20% by the age of 45 years (67). The magnitude of risk was higher in women treated earlier in life given the longer duration of follow-up. A subsequent study of women who received chest irradiation prior to the age of 21 years showed a cumulative incidence of 35% by the age of 50 years (68). Consistent with guidelines from several professional bodies (69–71), we will recommend yearly mammography with adjunctive MRI for survivors of childhood cancers who received therapeutic chest irradiation between the ages of 10 and 30 years. We have adapted the NCCN guidelines, which state that screening should not start before age 25 years, to define 30 years as the earliest starting age for screening (46).

Deferring Screening

For women age 40 to 49 years with a five-year risk lower than 1.3%, screening may be deferred to begin at age 50 years or the age at which their estimated risk is projected to equal or exceed a 50-year-old's risk according to the BCSC model as modified by the polygenic risk score. Screening may also be deferred based on the competing risk of death. Screening is generally not recommended for patients with life expectancy of less than 10 years (72). Geriatric prognostic indices have been developed that estimate an individual's risk of death based on comorbid medical conditions and functional status. Online decision tools such as ePrognosis (73) have been developed to estimate the benefits and harms of screening for breast cancers. We intend to prospectively evaluate the ability of ePrognosis to guide decisions to stop screening in the subset of frail or elderly trial participants.

Proportion of Women Receiving Each Screening Recommendation

Simulation modeling was used to estimate the proportion of women that would fall into each screening category if we applied our risk-based approach to an existing screening population (Table 3). The BCSC Data Resource (http://breastscreening.cancer.gov/) is a de-identified, publicly accessible data set that contains risk factors for over 6 million women who underwent mammography screening at BCSC sites in the United States between 2000 and 2009. The BCSC risk score was calculated for each woman based on her individual risk factor profile. A genetic susceptibility profile was randomly assigned to each woman using published population allele frequencies and odds ratios for each SNP, assuming independence between risk factors and SNPs. The prevalence of genetic mutations in the population was also modeled according to published data (74–76). The BCSC risk score was updated for each woman using likelihood ratios based on the simulated genetic information (SNPs and mutations in high-penetrance genes).

Based on our proposed algorithm, the vast majority of women age 50 to 74 years would receive biennial mammography, consistent with USPSTF guidelines (Table 3). Among women age 40 to 49 years, approximately 75% would be recommended to defer screening, whereas 11% would receive biennial mammography and 13% would receive annual mammography. We estimate that 1% of women in the 40–49 years and 50–74 years age groups would receive annual mammography with adjunctive MRI. Approximately 5% of women age 50 to 74 years would not be recommended to undergo any screening based on competing risks.

The WISDOM Study and Future Directions

We acknowledge the uncertainty about the efficacy of risk-based screening, which is why we are testing it prospectively in a randomized trial. Rigorous evaluation of risk-based screening is essential to optimize patient outcomes and health care costs. The WISDOM Study (77) is a randomized controlled trial using a preference-tolerant design to encourage women to participate. Women can elect to be randomly assigned or request to be assigned to the risk-based or annual screening groups. The recruitment goal is 100 000 women for adequate power to

Table 3. Estimated distribution of women in each screening strategy category

Strategy category	Age 40–49 y, %	Age 50–74 y, %
No screening at this time	75	5
Biennial mammogram	11	91
Annual mammogram	13	3
Annual mammogram + adjunctive MRI	1	1

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compare individual risk-based screening to annual screening. The risk-based arm will undergo risk stratification using the BCSC model, a polygenic risk score, and genetic testing with a nine-gene panel, and the participants randomly assigned to this arm will be screened based on the thresholds described above. Based on projections from survey and pilot data, we expect that the majority of women will select random assignment. While primary analysis will be on the randomized cohort, data from the observational cohort of self-assigned women will also be available.

Importantly, all participants in WISDOM will receive screening recommendations that fall within the bounds of current guidelines. Although some women age 40 to 49 years will not be screened, USPSTF guidelines recommend an individualized approach in this age group (7). Likewise, the ACS does not recommend routine screening until age 45 years (4). Screening frequency will be consistent with guidelines issued by the USPSTF (7), ACS (4), ACOG (3), and ACR/SBI (2) (Table 1). The ACS (26) and NCCN guidelines (46) for the adjunctive use of MRI in high-risk women were intended to inform the screening of women from high-risk families with negative (or unknown) genetic testing results. In WISDOM, population-based screening for genetic mutations allows us to more specifically identify high-risk women who could benefit from intensive screening.

WISDOM is adaptive, meaning the study design can be modified to integrate newly discovered clinical risk factors, SNPs, and mutations into the risk assessment process. For example, the performance of the polygenic risk score will likely improve as we incorporate additional data from large genome-wide association studies in Asian, Hispanic, and African American populations. The adaptive design accommodates learning over time and avoids the downsides of waiting for new results to emerge or excluding various racial or ethnic groups where further research on genetics is urgently needed (78).

Prediction of breast cancer subtype–specific risk is another evolving area that may eventually be integrated into the risk-based screening model. ER-negative cancers tend to be aggressive and present as interval cancers (79). One question is whether or not women at especially elevated risk of ER-negative cancers benefit from more frequent screening. Current work is aimed at developing versions of the BCSC model and polygenic risk score that are specifically predictive for ER-negative cancers.

Prevention is an important part of the WISDOM trial, and interventions to reduce risk will be discussed with participants at especially elevated risk. The USPSTF recommends offering endocrine risk reduction based on risk estimates from clinical models, but does not specify which model to use (57). Our approach using a risk model and polygenic risk score may refine existing risk stratification for endocrine risk reduction and identify subgroups of women who may benefit based on elevated overall, or ER-positive, breast cancer risk. Women identified as being at high risk for ER-positive cancers may be more motivated to pursue pharmacological endocrine risk reduction (57).

We have planned our study to optimize the scalability of our approach to other practice settings. We are employing commercially available tests for germline mutation testing and SNP genotyping. Such tests represent a modest, one-time expense approximately equivalent to the cost of a mammogram. Genetic counseling will be provided by a team of breast health specialists to the small proportion of participants who screen positive for mutations or are at high polygenic risk. Primary care providers, breast health specialists, and patients will have access to online tools that explain the implications of risk estimates. The trial runs on a novel platform that synthesizes demographic, clinical, and genetic data to generate risk estimates; links them to screening recommendations; and interfaces with the electronic medical record to generate the necessary alerts and communications. If successful, it can potentially be disseminated as a model for a continuous learning platform.

Conclusion

The ongoing controversy about the optimal approach to screening women for breast cancer has created an urgent need to develop a testable alternative to age-based screening. All women do not have the same risk of breast cancer. We suggest moving past debates over guidelines to focus on developing and evaluating a rational approach to screening. Individualized, risk-based screening is feasible and scalable because of the emergence of easily implemented risk prediction models, comprehensive SNP panels, and population-based germline genetic testing. We have provided the evidence base underlying our proposed risk assessment process and the risk thresholds used to inform individualized screening recommendations. This model is being tested prospectively in the WISDOM study, which will start enrolling in the fall of 2016. This framework provides a platform to evaluate the effectiveness of risk-based screening and enables continued improvement while learning about the populations most likely to benefit from screening.

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