Society of Breast Imaging (SBI) Statement on the WISDOM Trial

The results of the Women Informed to Screen Depending on Measures of Risk (WISDOM) Trial were recently published. The goal of this trial was to determine whether risk-based breast cancer screening is an effective alternative to annual mammographic screening. Unfortunately, due to significant methodological flaws, the trials conclusions are unsupported, and it remains uncertain whether risk-based screening is feasible for population-wide application.

Specifically, the researchers sought to determine if risk-based screening resulted in noninferior diagnosis rates of stage ≥ IIB breast cancers (which would suggest that risk-based screening did not increase advanced stage cancer rates) and reduced biopsy rates (which would suggest that risk-based screening decreased unnecessary biopsies). The researchers concluded that diagnosis rates of stage ≥ IIB breast cancers were noninferior for women randomized to the risk-based screening regimen versus annual mammogram screening. They also concluded that breast biopsy rates were similar between screening arms, indicating that risk-based screening failed to reduce breast biopsies.

The SBI highlights the following concerns with this study and its conclusions:

1. 40% of women declined randomization and participated in a separate observational cohort. It is unclear why this large number of women declined randomization and why these women were given the choice to decline randomization. This methodology raises the significant possibility of selection bias with trial enrollment.
2. The study enrolled considerably fewer women than expected (28,372 women enrolled to be randomized, far fewer than the expected 65,000 women). This limits the power of the study to detect differences in cancer rates.
3. The overall number of cancers was low (21 in the risk-based screening cohort and 31 in the annual mammogram screening cohort). This outcome again suggests an underpowered study which cannot support its proposed conclusions.
4. The study only recorded stage ≥ IIB breast cancers, which are often clinically detectable. Annual screening detects cancers at earlier, non-palpable stages. Thus, the exclusion of earlier stage breast cancers fails to acknowledge the critical benefit of screening mammography. Moreover, mammogram screening downsizes breast cancers within stages, and this downsizing benefit also reduces mortality. In other

words, screening mortality benefits arise from downstaging AND downsizing, a benefit which is underestimated by this study design.

5. Contamination and noncompliance within the randomized cohorts was substantial. For the annual mammogram group, mammogram utilization was low and a fair number of these women obtained screening breast MRI outside of the study. Moreover, the use of MRI was low in the high-risk group. In the end, overall mammogram utilization was similar for the risk-based cohort and the annual mammogram cohort, precluding comparison of actual screening outcomes.
6. In the risk-based screening cohort, yearly questionnaire responses were used to reclassify risk and update screening recommendations. It is unclear how many women changed their risk category and the resultant screening recommendations.
7. Risk-based screening led to more biopsies than annual screening, though the difference was nonsignificant. Thus, risk-based screening did not reduce percutaneous needle biopsies.
8. The majority of women were already undergoing regular mammogram screening prior to initiation of the trial. Thus, women who were predisposed to develop advanced cancers may already have been screened out of this study population, meaning that the study is likely underpowered to detect advanced cancers in this remaining study cohort.
9. As currently performed, genetic-based risk assessment and testing is impractical for population-wide deployment in the United States. If risk-based screening were implemented, compliance would be challenging.
10. The study relied on self-reporting of cancers, biopsies, and imaging procedures. Patient self-reporting is an unreliable source of data.
11. Because the study population was largely college-educated white women, the results are not generalizable across the population.
12. It is unsurprising that the risk-based group had fewer advanced cancers because they underwent overall more MRI's than the control group. MRI is already widely recommended for breast cancer screening in women at elevated risk.
13. It is laudable that the risk-based screening cohort were counseled to implement risk-reducing strategies. However, even with this intervention, adherence to risk-reducing strategies was poor.

Ultimately, risk-based breast cancer screening could theoretically help to personalize screening regimens for all women and triage precious medical resources to maximize population benefit, a goal which the SBI supports in principle. However, the contaminated and underpowered WISDOM trial has not demonstrated a reliable pathway for systematic implementation and effective risk-based screening regimens. Therefore, the SBI continues

to recommend annual mammogram screening starting at age 40 for all women at average risk which confers the greatest mortality benefit. All women should undergo risk assessment, and if found to be high risk, they should supplement annual screening mammography with annual screening breast MRI. These recommendations align with those of the American College of Radiology and National Comprehensive Cancer Network.