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Abstract OT2-08-01: Personalized breast cancer screening in a population based study: Women Informed to Screen Depending On Measures of risk (WISDOM)

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Abstract

Background: WISDOM is a 100,000 healthy women preference-tolerant, pragmatic study comparing annual to personalized risk-based breast screening. The novelty of WISDOM personalized screening is the integration of previously validated genetic and clinical risk factors (age, family history, breast biopsy results, ethnicity, mammographic density) into a single risk assessment model that directs the starting age, timing, and frequency of screening. The goal of WISDOM is to determine if personalized screening, compared to annual screening, is as safe, less morbid, enables prevention, and is preferred by women. The study is registered on ClinicalTrials.gov, NCT02620852.

Methods: Women aged 40-74 years with no history of breast cancer or DCIS, and no previous double mastectomy can join the study online at wisdomstudy.org. Participants can elect randomization or self-select a study arm, and provide electronic consent and Release for Medical Information using DocuSign. For all participants, 5-year risk of developing breast cancer is calculated according to the Breast Cancer Screening Consortium (BCSC) model. Participants in the personalized arm undergo panel-based mutation testing, and their 5-year risk is calculated using the BCSC score combined with a Polygenic Risk Score (BCSC-PRS) that includes 75 single nucleotide polymorphisms (SNPs, increase to 229) known to increase breast cancer risk. SNPs and mutations (BRCA1, BRCA2, TP53, PTEN, STK11, CDH1, ATM, PALB2, and CHEK2) are assessed by saliva-based testing through Color Genomics. 5-year risk level thresholds are used to stratify for low-, moderate- and high risk. Risk stratification determines age to start, stop, and frequency of screening.

Enrollment: As of July 2018, the WISDOM study is open to all eligible women in California, North Dakota, South Dakota, Minnesota and Iowa. To date, 23,329 eligible women have registered and 14,393 women have consented to participate in the trial. We analyzed 3,255 participants who have completed risk assessment in the personalized arm. The median age was

56 years. 82% were Caucasian, 1% African-American, and 6% Asian. 9% self-reported as Hispanic. We are partnering with health insurers and self-insured companies using coverage with evidence progression. To strengthen generalizability, we are expanding to other states. WISDOM enrollment will continue past 2019.

Feasibility: To evaluate the addition of PRS, we used paired statistical tests (McNemar) to compare the distributions of BCSC, and BCSC-PRS risk estimates around low-risk (<1.3%), and very-high risk (>6%) thresholds, the latter corresponding to 5-year risk of a BRCA mutation carrier. The median 5-year risk was 1.5% (IQR 1.0-2.1%) using the BCSC model, and 1.4% (IQR 0.8-2.5%) using the BCSC-PRS model. The BCSC-PRS model classified more women into the low (<1%) and very high (≥6%) risk categories compared to the BCSC model ($p < 0.001$).

Conclusions: Our findings demonstrate that incorporating genetic variants into a validated clinical model is feasible and impacts risk classification compared to a model without genetic risk factors. Results at 5 years will reveal if this classification improves healthcare value by reducing screen volumes and costs without jeopardizing outcomes.

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