Risk-adapted screening with multiparametric MRI for individuals at high risk of prostate cancer in the PROGRESS study

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Background: The risk of early-onset and clinically aggressive prostate cancer is elevated among individuals with 1) rare germline pathogenic variants, 2) strong family history, and 3) Black/African ancestry. The utility of augmenting traditional PSA-based screening measures with multiparametric MRI imaging in these populations is not yet known. The Prostate Cancer Genetic Risk Evaluation and Screening Study (PROGRESS) is evaluating MRI-based screening in comparison to traditional PSA-based screening among individuals at elevated genetic risk for prostate cancer.
Methods: Individuals at high genetic risk are defined as: Cohort A) germline carriers of pathogenic/likely-pathogenic variants in any of 19 prostate cancer risk genes; B) individuals with strong family history of prostate, breast, ovarian, and/or pancreatic cancer and negative germline genetic testing; C) self-identified Black American or Black Caribbean race. Individuals between the ages of 35-75 with no prior diagnosis of prostate cancer are recruited to participate in screening with annual PSA, DRE and triennial multiparametric MRI. Individuals with abnormal DRE, elevated age-adjusted PSA (>1.5 ng/mL for 35-49 yr, >2.0 ng/mL for 50-54 yr, >3.0 ng/mL for 55-74 yr), or suspicious mpMRI (PI-RADS ≥3 lesion) are offered prostate biopsy. Alternative screening strategies were compared by decision curve analysis, using endpoints of any and clinically significant prostate cancer as detected by prostate biopsy.
Results: PROGRESS is an ongoing prospective early detection study for individuals at high risk of prostate cancer. To date, 173 men have completed the first round of screening (cohort A: 142, cohort B: 31). The greatest proportion of participants are carriers of pathogenic variants in *BRCA2* (n = 68), *BRCA1* (n= 41), and *ATM* (n = 10). In Cohort A, 28 participants have undergone biopsy, detecting 12 cancers (10 clinically significant). For detection of clinically significant prostate cancer, abnormal MRI (PI-RADS ≥3) demonstrated 90% sensitivity with a PPV of 43%, whereas PSA-based screening alone had 50% sensitivity with a PPV of 38%. Of six screening strategies evaluated in decision curve analysis, MRI-based screening alone achieved superior net benefit at all threshold probabilities compared to PSA screening. Further risk stratification incorporating prostate cancer polygenic risk scores is being evaluated.
Conclusions: Disease prevalence is high among carriers of prostate cancer-associated pathogenic germline variants. Early results suggest MRI-based screening enhances early detection of clinically significant disease beyond PSA screening alone in this high-risk population.

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