

Title: The utility of enhanced screening for people with inherited risk of developing aggressive prostate cancer in the PATROL study

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Background: Germline pathogenic variants (PV) in prostate cancer risk genes are associated with aggressive disease and worse outcomes. However, the optimal PSA thresholds for biopsy and utility of MRI for screening are not well characterized. Here, we report initial PSA and MRI screening results of participants in the PATROL study (NCT04472338), a prospective multi-center early detection study for high-risk individuals with germline PVs.

Methods: The primary endpoint of PATROL is to determine the positive predictive value (PPV) of predefined age-adjusted PSA thresholds and prostate multiparametric MRI (mpMRI) imaging for biopsy. Key eligibility criteria include: males ≥ 40 yr with a PV in one or more of 13 prostate cancer risk genes. Participants undergo screening with an annual PSA and are encouraged to undergo a mpMRI at baseline and/or within one year of any biopsy. Participants are offered prostate biopsy for elevated age-adjusted PSA (>1.0 ng/mL if <50 yr, >1.5 ng/mL if 50-59 yr, >2.0 ng/mL if ≥ 60 yr) or suspicious MRI (PI-RADS ≥ 3 lesion). Clinically significant disease was defined as grade group (GG) ≥ 2 prostate cancer.

Results: To date, 264 participants have completed at least one round of screening with PSA and mpMRI. The most frequent PVs were in *BRCA2* ($n = 137$, 48%), *BRCA1* ($n = 65$, 23%), and *ATM* ($n = 22$, 8%). Of the 89 participants who underwent prostate biopsy, 60 (67%) had an elevated age-adjusted PSA, 61 (69%) had an abnormal mpMRI (PI-RADS ≥ 3), and 35 (39%) had both. Biopsy detected 21 clinically significant cancers (24%) and 13 GG1 cancers (15%). For detection of clinically significant prostate cancer, abnormal mpMRI (PI-RADS ≥ 4) demonstrated a PPV of 44% with 71% sensitivity, whereas elevated age-adjusted PSA had a PPV of 28% with 81% sensitivity. In decision curve analysis, combinatorial MRI-based screening strategies achieved superior net benefit for detecting significant cancers and reducing unnecessary biopsies compared to PSA thresholds alone. In a logistic regression model adjusting for age, gene and PSA level, PI-RADS ≥ 4 lesion on mpMRI was significantly associated with clinically significant prostate cancer (OR 9.7, $p=0.001$).

Conclusions: Screening germline PV carriers using age-adjusted PSA and mpMRI resulted in 24% of biopsies detecting clinically significant prostate cancer. Combined MRI and PSA-based screening strategies demonstrate higher biopsy PPV and net benefit compared to PSA alone. Ongoing enrollment, site expansion and longer-term follow-up will help improve early detection of significant prostate cancer among high-risk PV carriers.

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