44. ARTIFICIAL INTELLIGENCE FO MANAGING THE COMPLEXITY OF BRCA1/BRCA2 ALTERATIONS IN AGGRESSIVE PROSTATE CANCER

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Introduction. BRCA1/BRCA2 alterations, particularly BRCA2, define a clinically important criteria of prostate cancer characterized by increased hereditary risk, aggressiveness, and worse outcomes. BRCA2 mutations are reported in approximately 1.2–3.2% of prostate cancer cases and increase risk by 3–8.6-fold, whilst BRCA1 mutations may confer up to a 4 times increase in risk. A major challenge remains the interpretation of rare variants, variants of uncertain significance (VUS), and homologous recombination deficiency (HRD) beyond conventional mutation testing.

Aim of study. To evaluate how artificial intelligence can improve interpretation of BRCA1/BRCA2 alterations and detection of HRD-related aggressive prostate cancer phenotypes.

Methods and materials. There was performed a narrative synthesis of studies on BRCA-associated prostate cancer and AI-based tools for variant classification, mutational signature analysis, and ctDNA-based HRD detection. Search engines like PubMed Database, Google Scholar were used and were considered the terms: BRCA, Cancer, Artificial intelligence (AI), Machine learning (ML), Prostate cancer. 15 articles were found.

Results. AI models improved BRCA variant interpretation: BRCA-ML achieved, for BRCA2, an MCC of 0.73, 97.7% sensitivity, and 85.1% specificity, while a BRCA1-specific XGBoost model trained on 3,335 reviewed variants reached 99.9% accuracy, 100% sensitivity, and 99.8% specificity, and correctly prioritized 2,115 potentially pathogenic variants among 31,058 unreviewed BRCA1 variants. On an independent set of 213 BRCA1 VUS with functional data, the same model achieved 92.0–93.4% accuracy. In prostate cancer, HRD analyses of 311 whole genomes and 498 whole exomes showed that HRD-associated signatures also occur in tumors without detectable BRCA1/2 mutations, suggesting that 5–8% of localized prostate cancers may still be candidates for PARP inhibitor therapy. In metastatic disease, DARC Sign, developed on 155 ctDNA exomes including 129 metastatic prostate cancer cases, identified BRCA2 deficiency with an AUC of 0.99.

Conclusions. In BRCA-associated prostate cancer, AI has two major clinical utilities: improving the classification of rare BRCA1/BRCA2 variants and identifying functional HRD/BRCAness beyond conventional mutation testing. This may enhance risk stratification and help identify patients more likely to benefit from targeted therapies, particularly in the setting of aggressive BRCA2-driven disease.

Keywords. Artificial intelligence, Machine Learning, BRCA 1/2, Prostate Cancer.

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