Through the Prostate Cancer Looking Glass: characterizing cancer-associated germline mutations by way of prostate cancer family study, registry and prostate cancer genetics clinic

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Background: Recent studies sequencing metastatic prostate cancer patients have revealed ~10% prevalence of inherited germline mutations in 16 genes involved in DNA repair[1,2]. Many of these genes have been associated with high penetrance inherited risk of cancer, especially of the breast and ovary. However, from the perspectives of prostate cancer risk, cancer biology and therapeutic consequences, the majority of these genes are incompletely characterized and pose challenges and opportunities for patient care and research[3,4].

Methods: The Prostate Cancer Family Study enrolls men with prostate cancer <60years at diagnosis with high-risk disease (Gleason sum ≥8 or metastatic) AND/OR who have a family cancer history including any of the following: ≥3 cancers of any type on one side of the family, breast cancer in a first degree relative diagnosed ≤50y, or a first degree relative with ovarian cancer or pancreatic cancer. Patients and their kin are individually contacted and consented by a certified genetic counselor for collection of cancer-specific data and blood for germline analysis, including a CLIA-certified, targeted NGS panel of >50 cancer predisposition genes (BROCA). Clinically meaningful results are returned to participants with appropriate genetic counseling. For novel findings, variant segregation within families, additional molecular studies, e.g. splicing analysis, may be performed. In addition, we have launched a Prostate Cancer Genetics Clinic to offer risk assessment, genetic counseling and testing, as well enrollment to the Prostate Cancer Family Study, Prostate Cancer Genetics Registry and clinical trials, if relevant.

Results: Over 20 families and over 100 individuals have been enrolled in the family study and registry, respectively. We are actively enrolling men with germline mutations in cancer predisposition genes, OR who have strong family histories of cancer but are not found to have a clear pathogenic gene mutations (unsolved families). Among currently enrolled families, we have begun to characterize potential new prostate cancer risk genes, to classify novel variants, and to potentially identify new mechanisms of germline disruption in genes such as *MRE11A, ATM, CHEK2* and *PALB2.*

Conclusions: The Prostate Cancer Family Study, Prostate Cancer Genetics Clinic and Prostate Cancer Genetics Registry will be complementary and valuable resources for further study of germline alterations in DNA repair genes--particularly as they influence prostate cancer risk, affect prostate cancer biology, and serve as potential predictive biomarkers for cancer treatment.

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