
Germline testing for prostate cancer prognosis: implications for active surveillance

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Based upon an evidence-based review of recently published manuscripts including our own studies, we first review germline variants that are significantly associated with prostate cancer aggressiveness and progression. We then discuss the clinical implication of germline variants

in predicting grade reclassification of prostate cancer patients undergoing active surveillance. Finally, based on currently available evidence, we propose a working recommendation of germline testing and corresponding clinical management for localized prostate cancer patients, including those undergoing active surveillance.

Key Words: high penetrance genes, prostate cancer, germline

Introduction

Prostate cancer is recognized as one of the most heritable cancers.¹ While family history is traditionally used as an indirect measurement of inherited risk, common prostate cancer risk-associated single nucleotide polymorphisms (SNPs) and rare pathogenic mutations in a number of genes make it feasible to directly measure genetic risk.^{2,3} Despite this progress, several major challenges exist in implementing germline testing. The first is a lack of understanding among many clinicians on the utility of germline testing for guiding prostate cancer screening, diagnosis and treatment. The second relates to an inability to distinguish three purposes of germline testing: predicting prostate cancer risk among unaffected men, predicting prognosis at time of prostate cancer diagnosis, and predicting treatment response of hormonal and targeted therapy. The third is lack of consensus on what genetic variants (common SNPs and rare mutations) are suitable for these different purposes. These challenges are exacerbated in the

multigene panel-test era where 14 genes (*ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *EPCAM*, *HOXB13*, *MLH1*, *MSH2*, *MSH6*, *NBN*, *PALB2*, *PMS2*, *RAD51D*, and *TP53*) are typically included in commercially available panels. This article will specifically focus on the second purpose of germline testing for predicting prostate cancer prognosis and its implication for active surveillance.

Genetic variants for prostate cancer prognosis

More than 160 prostate cancer risk-associated SNPs have been discovered.² Together these SNPs have a strong cumulative effect, which can be measured by polygenic risk score (PRS). PRS has been consistently demonstrated as a powerful tool for predicting prostate cancer risk among unaffected men.² However, its utility in predicting aggressiveness and prognosis is unclear at this stage.

In contrast to common SNPs, rare pathogenic mutations in several genes, especially DNA damage repair genes, have been reported to be associated with prostate cancer risk, aggressiveness/progression, and response to hormonal and targeted therapy.³⁻⁵ Although pathogenic mutations in many of these genes have been reported in advanced prostate cancer patients, it is important to note that observation of

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these mutations in prostate cancer patients with clinically significant disease alone is not sufficient to implicate them as prognostic markers. Statistical evidence is required; especially in well-designed studies where phenotypes are well characterized, and sequencing/annotation methodologies as well as racial and ethnic background are comparable between groups of prostate cancer patients.

To date, significantly different frequencies of pathogenic mutations within *BRCA2* and *ATM* have been consistently reported among men diagnosed with high-grade tumors and those who progressed to metastatic and lethal disease.^{3,6} Evidence for pathogenic mutations of *BRCA1* as a prognostic marker is weaker. A meta-analysis estimated that the risk of pathogenic mutations of *BRCA1* for prostate cancer-specific death was 1.06, $p = 0.90$ (in comparison, the same meta-analysis estimated that the risk for *BRCA2* was 2.63).⁷ Evidence remains controversial for *CHEK2* (all pathogenic mutations and the founder mutation, 1100delC).⁸

In our recent study comparing pathogenic mutations among 1,694 prostate cancer patients who underwent radical prostatectomy at Johns Hopkins Hospital, including 706 patients with high-grade [Gleason grade (GG) 4 and 5] and 988 patients with low-grade disease (GG1), we documented that the frequency of germline pathogenic mutations in the above mentioned 14 genes was significantly higher in high-grade patients (8.64%) than low-grade patients (3.54%, $p = 9.98 \times 10^{-6}$). However, at the individual gene level, significant differences were found for only three genes: *ATM* (2.12% and 0.20%, respectively, $p = 9.35 \times 10^{-5}$), *BRCA2* (2.55% and 0.20%, respectively, $p = 8.99 \times 10^{-6}$), and *MSH2* (0.57% and 0%, respectively, $p = 0.03$). Higher but not statistically significant mutation frequencies in high-grade versus low-grade were found for *BRCA1* (0.28% and 0.10%, respectively, $p = 0.65$) and *CHEK2* (1.27% and 1.01%, respectively, $p = 0.65$). The estimated carrier rate was the same (0.71%) for *HOXB13* G84E between the two groups. Our study highlights the challenge to obtain statistical evidence for rare pathogenic mutations.

Recent data on germline mutations for predicting active surveillance outcomes

Based on the above data, we tested the hypothesis that mutation carriers of men undergoing active surveillance have worse outcomes in two active surveillance cohorts at NorthShore University HealthSystem and Johns Hopkins.⁹ Of these 1,211 prostate cancer patients, mutation carriers in a three-gene panel (*BRCA2*, *ATM*, and *BRCA1*) were more likely to experience grade

reclassification (11 of 26 carriers, 42.31%) than non-mutation carriers (278 of 1,185 non-carriers, 23.45%, $p = 0.04$). The results were strongest for *BRCA2*. It is recognized that the results should be validated since the number of pathogenic mutation carriers was relatively low.

Recommendation of germline testing for localized prostate cancer patients

To reduce confusion, we propose that germline testing be offered for predicting prognosis to all prostate cancer patients at the time of diagnosis, including low-grade patients considering active surveillance. Furthermore, since most mutation carriers do not report a FH, we propose that germline testing be offered regardless of FH. Based upon available evidence of individual genes at this stage, pathogenic mutations may be classified in four prognostic groups: 'actionable' for *BRCA2* and *ATM*, 'uncertain' for *BRCA1*, *CHEK2* and *MSH2*, 'not actionable' for *HOXB13*, and 'lack of sufficient data' for the remaining genes.

Disclosures

Dr. Brian T. Helfand is a speaker for Ambry Genetics. Dr. Jianfeng Xu has no disclosures. □

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