Ambry Genetics®
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RESEARCH SUMMARY

Genetic Testing May Impact Management of Men With or At-Risk for Prostate Cancer

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Why This Matters To You

Previous studies have shown that up to 20% of prostate cancer is hereditary[1]. NCCN® guidelines recommend genetic testing for patients with a personal and/or family history of prostate cancer that is metastatic, intraductal/cribriform histology, high- or very-high-risk group, or occurs alongside other family history risk factors[2]. Recent Ambry Genetics' publications further describe the outcome of genetic testing in men with prostate cancer and continue to support the utilization of multigene panel testing (MGPT) in this patient population. Genetic testing results may impact the management of men with or at-risk for prostate cancer and can inform family members of risks.

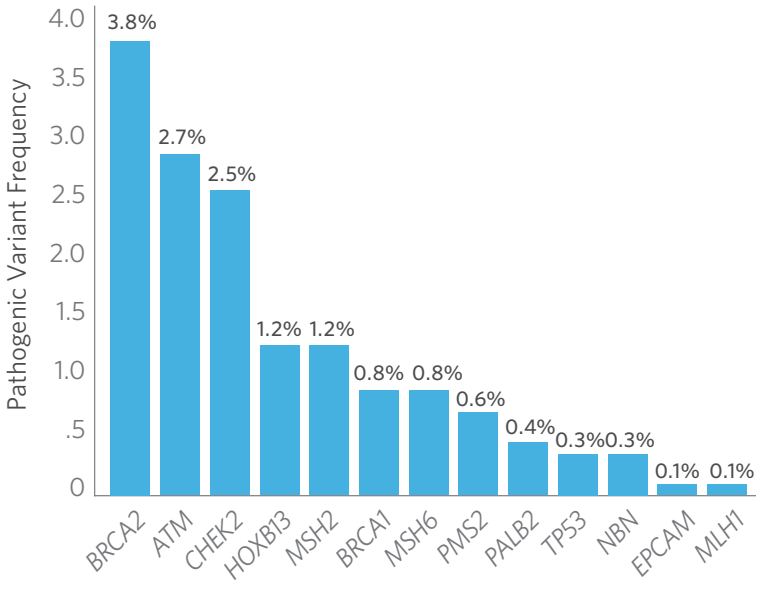
Retrospective Study of Germline Genetic Testing for Prostate Cancer

This Ambry Genetics study published in Genetics in Medicine describes the diagnostic yield, pathogenic variant spectrum, and predictors of positive results in 1,812 men with prostate cancer who underwent MGPT[3].

Key Study Findings

- Among men with no prior genetic testing, ProstateNext® resulted in a 9.4% (26/277) positive yield, while the yield of all other MGPT combined was 12.1% (168/1385).
- 47.4% (92/194) of positive patients were identified to have a pathogenic variant in a gene that may impact treatment (*i.e. BRCA1/2* for PARPi).
- Mutation frequencies were highest for *BRCA2* (3.8%), *ATM* (2.7%), and *CHEK2* (2.5%) (Fig. 1).
- Increasing Gleason score, personal history of breast or pancreatic cancer, and family history of breast, ovarian, pancreatic or Lynch-syndrome associated cancers were predictors of positive genetic test results.

FIGURE 1. PATHOGENIC VARIANT FREQUENCIES IN GENES ASSOCIATED WITH PROSTATE CANCER AMONG MEN WITH NO PRIOR GENETIC TESTING*



*Includes men with any test ordered (*i.e. BRCA1/2*, ProstateNext®, or other MGPT)

Case-Control Study Validating a Prostate Cancer Polygenic Risk Score

The Prostate published this collaboration between Ambry Genetics, Johns Hopkins University Hospital, and NorthShore University HealthSystem's Genomic Health Initiative. The retrospective study involving 1,972 prostate cancer cases and 1,919 unaffected controls examines the extent to which Ambry's 72-SNP polygenic risk score (PRS), also known as AmbryScore™, is predictive of prostate cancer in European men who tested negative for mutations in 14 prostate cancer susceptibility genes[4].

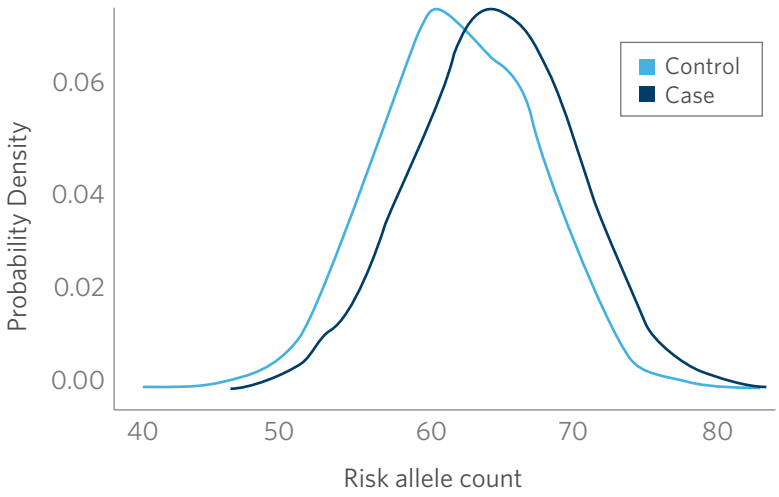
Background

In addition to germline mutations in high or moderate risk genes, common genetic variation, also known as single nucleotide polymorphisms (SNPs), can contribute to prostate cancer risk. A PRS is designed to estimate a patient's individualized cancer risk using the combined effects of SNPs that have been previously associated with cancer risk.

Key Study Findings

- The PRS was significantly higher in cases v. controls ($p<0.0001$) (Fig. 2).
- Compared with men in the 1st quartile of age-adjusted PRS, those in the 2nd, 3rd, and 4th quartile were 1.58, 2.36 and 3.98 times as likely to have prostate cancer (all $p < .0001$).
- PRS predictive performance was consistent with prior literature (area under the receiver operating curve = 0.64).

FIGURE 2. DISTRIBUTION OF THE SUM OF RISK ALLELES ACROSS 72 SNPS, FOR CASES V. CONTROLS



Points For Your Practice

- Genetic testing identifies a mutation in up to 12-20% of men with prostate cancer, and results may impact treatment and management for >47% of positive patients, supporting the use of MGPT.
- Genetic testing may be considered in patients with increasing Gleason score, personal history of breast or pancreatic cancer, and/or family history of breast, ovarian, pancreatic, or Lynch syndrome associated cancers.
- The addition of a PRS to MGPT can provide additional genetic information for men, with or without prostate cancer, who test negative, which may inform risk counseling and medical management.

REFERENCES

1. Mandelker D, *et al.*, JAMA 2017;318(9):825-835.
2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. V1.2021. All rights reserved. Accessed September 24, 2020.
3. Pritzlaff M, *et al.*,Genet. Med, 2020; 22:1517–1523.
4. Black MH, *et al,* The Prostate. 2020;80:1314–1321.

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