Need for re-evaluation of current guidelines based on results from germline genetic testing in prostate cancer.

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Background

Prostate cancer (PCa) is the third leading cause of cancer-related death in men in the United States, preceded by lung and colorectal cancer. One in seven men will be diagnosed, and although serious, most of these diagnoses are not terminal. Because inherited risk for PCa is potentially associated with more aggressive disease and poorer outcomes, there is a critical need for increased genetic screening where the identification of disease-causing variants can pinpoint individuals at increased risk for metastatic castration-resistant PCa and guide treatment beyond "watchful waiting." Current practice guidelines recognize PCa with a Gleason score of ≥7 as an indication for BRCA1/2 testing. However, recent data indicate that abnormalities in DNA repair genes may be much more common than previously appreciated. We investigated the efficacy of a targeted PCa gene panel and evaluated clinical factors in relationship to current genetic screening guidelines that inform patient identification, screening, and management.

Methods

- **Patient cohort:** Under an IRB-approved protocol, results and de-identified records were reviewed for 1158 individuals with a personal history of PCa who underwent germline genetic testing between 2013 and 2016. Corresponding family histories were available for 90% of these individuals.
- **Panel composition:** The following genes were included in the PCa-specific panel analysis:

ATM	***BRCA1***	***BRCA2***	***CHEK2***	***EPCAM***
HOXB13	***MLH1***	***MSH2***	***MSH6***	***NBN***
PMS2	***TP53***	***PALB2****	***RAD51D****	

*Add-on preliminary evidence genes.

Other included genes were ordered from larger hereditary cancer panels.

- **Invitae sequencing methodology:** Sample types for this cohort included blood and saliva. Once extracted, DNA was processed using standard techniques and subjected to paired-end sequencing on an Illumina next-generation sequencing platform. All pathogenic (P), likely pathogenic (LP), and risk allele (RA) variants were confirmed with an orthogonal technology in accordance with our laboratory standard operating practices.
- **Variant Interpretation:** Variants were subjected to clinical interpretation using a classification system of refined ACMG criteria known as Sherloc (PMID: 28492532).
- **Genetic testing guideline criteria:** We assessed the personal and family histories of patients with a positive variant to determine whether they met any current guidelines for genetic testing (NCCN Genetic/Familial High Risk Breast, Ovarian, Colorectal).

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Results

Positive variants identified in patients with a personal history of PCa: Of the 1158 patients who underwent germline genetic testing, 199 were positive for at least one variant classified as P, LP, or RA based on the Invitae Sherloc criteria.

- P/LP/RA variants were identified in 199/1158 (17.2%) patients.
- 65.5% of P/LP/RA variants occurred in genes other than BRCA1/BRCA2.
  - 9.4% of P/LP/RA variants occurred in MMR genes associated with Lynch syndrome.
- 12 had P/LP/RA variants in more than 1 gene.

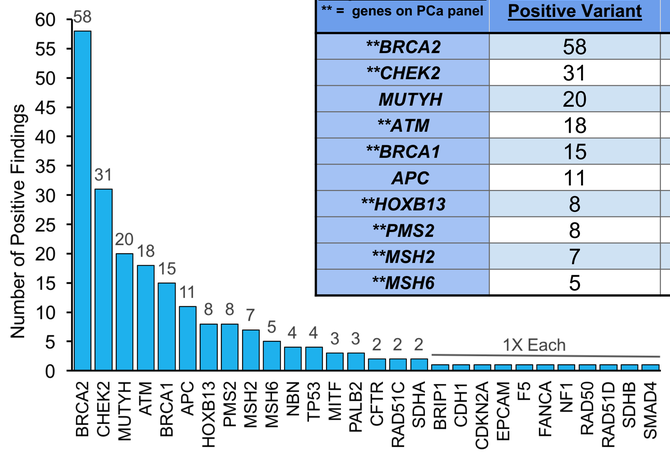
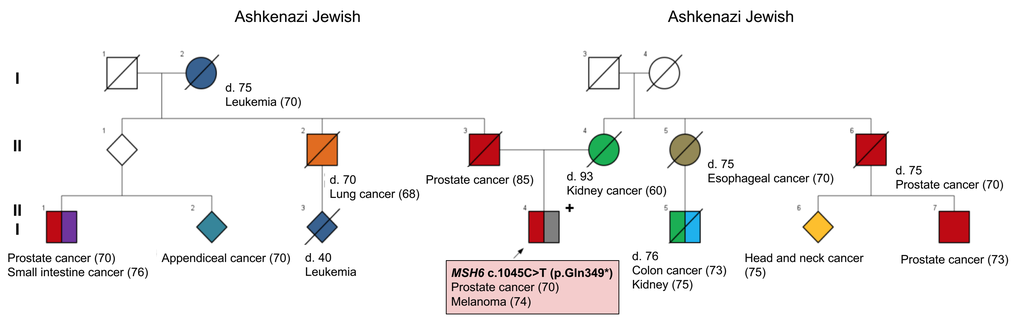


Table 1: Ten Most Frequently Detected Variants in 1158 Patients with PCa

Requisitioned Gene ** = genes on PCa panel	Samples with a Positive Variant	% of Total Positive Variants (N = 212)	% of Total Samples (N = 1158)
***BRCA2**	58	27.4	5.0
***CHEK2**	31	14.6	2.7
***MUTYH**	20	9.4	1.7
***ATM**	18	8.5	1.6
***BRCA1**	15	7.1	1.3
***APC**	11	5.2	1.0
***HOXB13**	8	3.8	0.7
***PMS2**	8	3.8	0.7
***MSH2**	7	3.3	0.6
***MSH6**	5	2.4	0.4

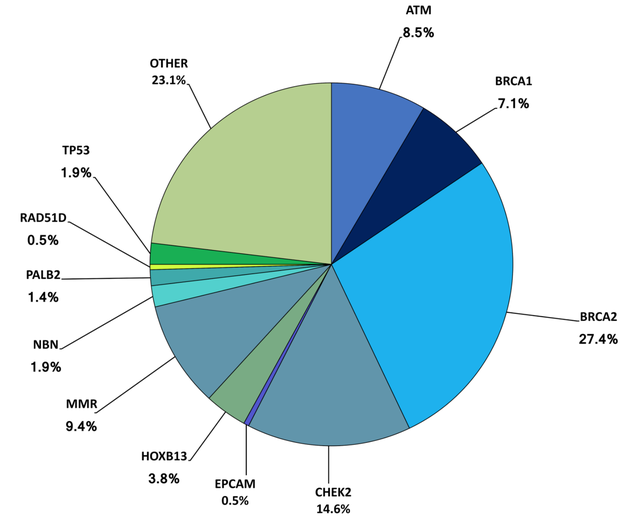
Current testing guidelines exclude a large proportion of individuals and families that would benefit from germline genetic testing: 126 (63%) patients with positive results were eligible for genetic testing based on all currently available testing guidelines, whereas 73 (37%) did not qualify.

- P/LP/RA variants were identified in 15.4% of patients with a Gleason score ≥7
  - 12.4% of pts with Gleason scores of ≤6 had P/LP/RA variants.



Sample pedigree of a family that would not qualify for genetic testing based on any available testing guidelines.

Results (continued)



Curated PCa Specific Gene Panel Improves Rate of Positive Variants Returned Beyond BRCA Testing:

- 77% of P/LP/RA variants detected were in genes offered on an expertly curated PCa panel.
  - 42.5% of P/LP/RA variants in genes on the PCa panel were not in BRCA1/2.

Conclusions

- The number of genes represented with P/LP/RA variants may indicate a role for broad multigene testing in patients with PCa.
- Curated disease-specific gene panels may increase the rate of relevant findings compared to current recommendations of testing BRCA1/2 only.
- Current NCCN guidelines and Gleason scores do not accurately predict patients that will test positive for a P/LP/RA variant.
  - Revisiting current guidelines will better serve this patient population and their families by providing greater access to germline genetic testing and therapeutic options.
- Most positive results identified in this study have important management implications.
  - Gene/variant based clinical trials, therapeutic implications (i.e. PARP-inhibitors)
  - Screening, chemoprevention, and surgical prevention of subsequent primary cancers
  - Identification of at risk relatives that can benefit from screening and prevention