Considerations of multigene test findings among men with prostate cancer – knowns and unknowns

Saud H. AlDubayan, MD[1,2]

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts, USA

[2]Division of Genetics, Brigham and Women's Hospital, Boston, Massachusetts, USA

ALDUBAYAN SH. Considerations of multigene test findings among men with prostate cancer – knowns and unknowns. *Can J Urol* 2019;26(Suppl 2):14-16.

Germline genetic testing has become an increasingly informative tool in the management of cancer patients. Over the past few years, the landscape of germline testing of prostate cancer patients has evolved significantly with the introduction of several multi-gene panel tests. Here, we dissect the clinically available prostate cancer-specific multi-gene panels and explore their performance on clinical series of prostate cancer patients from different ethnic groups.

Key Words: cancer predisposition, clinical germline genetic testing, hereditary prostate cancer

Introduction

Clinical germline testing has become an increasingly useful tool guiding the clinical management of prostate cancer patients.[1] Alterations in several genes, such as *BRCA1*, *BRCA2*, and the DNA mismatch repair (MMR) genes, have been associated with a large or moderate increase in the risk of developing prostate cancer where preventive measures could be implemented.[2] Furthermore, pathogenic germline alterations in *BRCA2* and other DNA repair genes have predictive utility for disease progression as well as patient's response to targeted therapeutics such as poly (ADP-ribose) polymerase inhibitors (PARPi) and immune checkpoint blockades.[3,4] As such, prostate cancer-specific clinical germline multi-gene panels (MGPs) have evolved substantially over the past few years. Here, we explore the current landscape of clinical MGP testing for hereditary prostate cancer and examine the prevalence of germline cancer gene alterations in prostate cancer patients who underwent clinical testing.

Address correspondence to Dr. Saud H. AlDubayan, Dana-Farber Cancer Institute, 41 Avenue Louis Pasteur, Suite 303-01, Boston, MA, 02115 USA

Materials and methods

Clinical germline MGP tests that are specifically designed for PC patients and reported in the Genetic Testing Registry (https://www.ncbi.nlm.nih.gov/gtr/) were systematically evaluated. We also conducted a literature review to assess the prevalence of pathogenic germline variants in clinical cohorts reported between January 2017 and August 2019.

Results and discussion

The number of clinical prostate cancer-specific MGPs grew from 3 in 2017[2] to at least 10 panels that can be currently ordered in the United States. The median number of genes in these panels is 12 (range: 4-16). All panels appropriately included *BRCA1* and *BRCA2*. However, while all panels included *NBN*, *CHEK2*, and *TP53*, which either only had emerging or insufficient evidence as prostate cancer risk genes, 20% of these MGPs did not test the DNA MMR genes or *HOXB13* which are established prostate cancer susceptibility genes,[2] Figure 1. Notably, DNA repair genes (DRGs) (such as *PALB2* and *RAD51D*), where germline pathogenic variants can influence treatment decisions, were only tested in 50% of the panels, highlighting an area for potential further improvement.

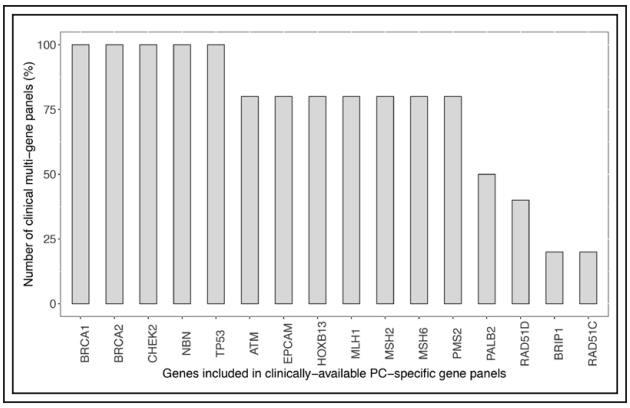

Figure 1. Genes tested in 10 clinically available multiple gene panels specifically designed for hereditary prostate cancer.

In a cohort of 3,607 prostate cancer patients, who underwent clinical testing using a 14-gene panel (62%, n = 2,250) or a custom clinician-selected MGP (38%, n = 1,357), 17.2% (95% CI:16.0-18.4) had pathogenic cancer predisposition variants.[5,6] However, only 8.2% (95% CI:7.3-9.1) of all tested patients had pathogenic variants in prostate cancer predisposition genes with high- or moderate-grade evidence (*BRCA1*, *BRCA2*, *HOXB13*, and the MMR genes) while another 2.1% (95% CI:1.6-2.5) had pathogenic variants in genes with emerging evidence for prostate cancer susceptibility (*ATM* and *NBN*) totaling to 10.3% (95% CI: 9.3-11.2) of prostate cancer patients with informative results for prostate cancer risk management, Table 1. Additionally, 3.4% (95% CI:2.8-3.9) patients had pathogenic variants in *CHEK2*, *PALB2*, *RAD51C*, or *RAD51D* which have prognostic and/or therapeutic predictive utility in prostate cancer, highlighting a nontrivial subset of prostate cancer patients who may not have an identifiable prostate cancer predisposition variant but can potentially benefit markedly from clinical germline sequencing.

Collectively, around 13.6% (95% CI:12.5-14.7) of prostate cancer patients in this clinical cohort received an informative result for prostate cancer risk or treatment, which is similar to the reported prevalence of germline alterations in metastatic prostate cancer patients.[3] Importantly, caution should be exercised when interpreting these results given the high-risk nature of this cohort and the significant heterogeneity of the clinical features and ancestral background of the tested patients. For example, only 8.4% of African American and 5.1% of Hispanic prostate cancer

TABLE 1. **Prevalence of germline pathogenic variants in the established prostate cancer-risk gene set (*BRCA1*, *BRCA2*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *HOXB13*), genes with emerging evidence supporting their contribution to prostate cancer susceptibility (*ATM* and *NBN*), and genes with predicative utility in prostate cancer (*CHEK2*, *PALB2*, *RAD51C*,** and ***RAD51D*) across ancestral groups studied by Nicolosi et al.**

	Established PC Risk genes		**Genes with emerging evidence for PC predisposition**		**Genes with prognostic and/or therapeutic predictive utility**		**All PC relevant genes**	
Ancestral groups	Pathogenic variants (n)	(%)	Pathogenic variants (n)	(%)	Pathogenic variants (n)	(%)	Pathogenic variants (n)	(%)
White (n = 2594)	212	8.2	58	2.2	94	3.6	364	14.0
Ashkenazi Jewish (n = 234)	25	10.7	7	3.0	9	3.8	41	17.5
Black/African American (n = 227)	13	5.7	2	0.9	4	1.8	19	8.4
Hispanic (n = 78)	4	5.1	0	0.0	0	0.0	4	5.1
Asian (n = 73)	7	9.6	2	2.7	1	1.4	10	13.7
Other (n = 401)	34	8.5	6	1.5	13	3.2	53	13.2
All examined patients	295	8.2	75	2.1	121	3.4	491	13.6

patients had a positive test, Table 1, significantly lower than European and Ashkenazi Jewish prostate cancer patients (14.0% and 17.5% respectively). Similar results were also seen in another case series where none of 89 African American patients with localized prostate cancer had pathogenic variants in *BRCA1*, *BRCA2*, or *ATM* compared with 1.7% (7/352) of European patients.[7] Conversely, a relatively high diagnostic yield was seen in Asian prostate cancer patients where 13.7% had a positive result, Table 1. Similarly, 18.18% of Asian patients with lethal prostate cancer were found by Na et al to carry pathogenic variants in *BRCA1*, *BRCA2*, or *ATM*. Such variability in test performance highlights the current gaps in our understanding of the major prostate cancer risk drivers in non-European populations and the great need to study such underrepresented groups.

Conclusion

In summary, clinical germline testing of prostate cancer patients, using MGPs, has become widely available. While most MGPs include the established prostate cancer risk genes, more emphasis should be made to include genes where mutations have prognostic or therapeutic utility, Table 1. Test performance across ancestry groups should be taken into consideration when ordering MGPs on non-European prostate cancer patients. Finally, several patients had pathogenic variants in genes of unknown clinical relevance to prostate cancer, representing a significant challenge for counseling but also an opportunity to prioritize these genes in future case-control association studies.

Disclosures

Dr. Saud H. AlDubayan has no disclosures. □

References

1. AlDubayan SH. Leveraging clinical tumor-profiling programs to achieve comprehensive germline-inclusive precision cancer medicine. *JCO Precis Oncol* 2019 [cited 2019 Aug 7];no. 3 (August): 1-3.
2. Giri VN, Knudsen KE, Kelly WK et al. Role of genetic testing for inherited prostate cancer risk: Philadelphia Prostate Cancer Consensus Conference 2017. *J Clin Oncol* 2018;36(4):414-424.
3. Pritchard CC, Mateo J, Walsh MF et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med* 2016;375(5):443-453.
4. Mateo J, Carreira S, Sandhu S et al. DNA-repair defects and olaparib in metastatic prostate Cancer. *N Engl J Med* 2015;373(18): 1697-1708.
5. Giri VN, Hegarty SE, Hyatt C et al. Germline genetic testing for inherited prostate cancer in practice: Implications for genetic testing, precision therapy, and cascade testing. *Prostate* 2019;79(4):333-339.
6. Nicolosi P, Ledet E, Yang S et al. Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. *JAMA Oncol* 2019;5(4):523-528.
7. Na R, Zheng SL, Han M et al. Germline mutations in ATM and BRCA1/2 distinguish risk for lethal and indolent prostate cancer and are associated with early age at death. *Eur Urol* 2017; 71(5):740-747.