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Rethinking Germline Testing in Localized Prostate Cancer: Prevalence of Germline Variants is Independent of Gleason Score and NCCN Risk Grouping

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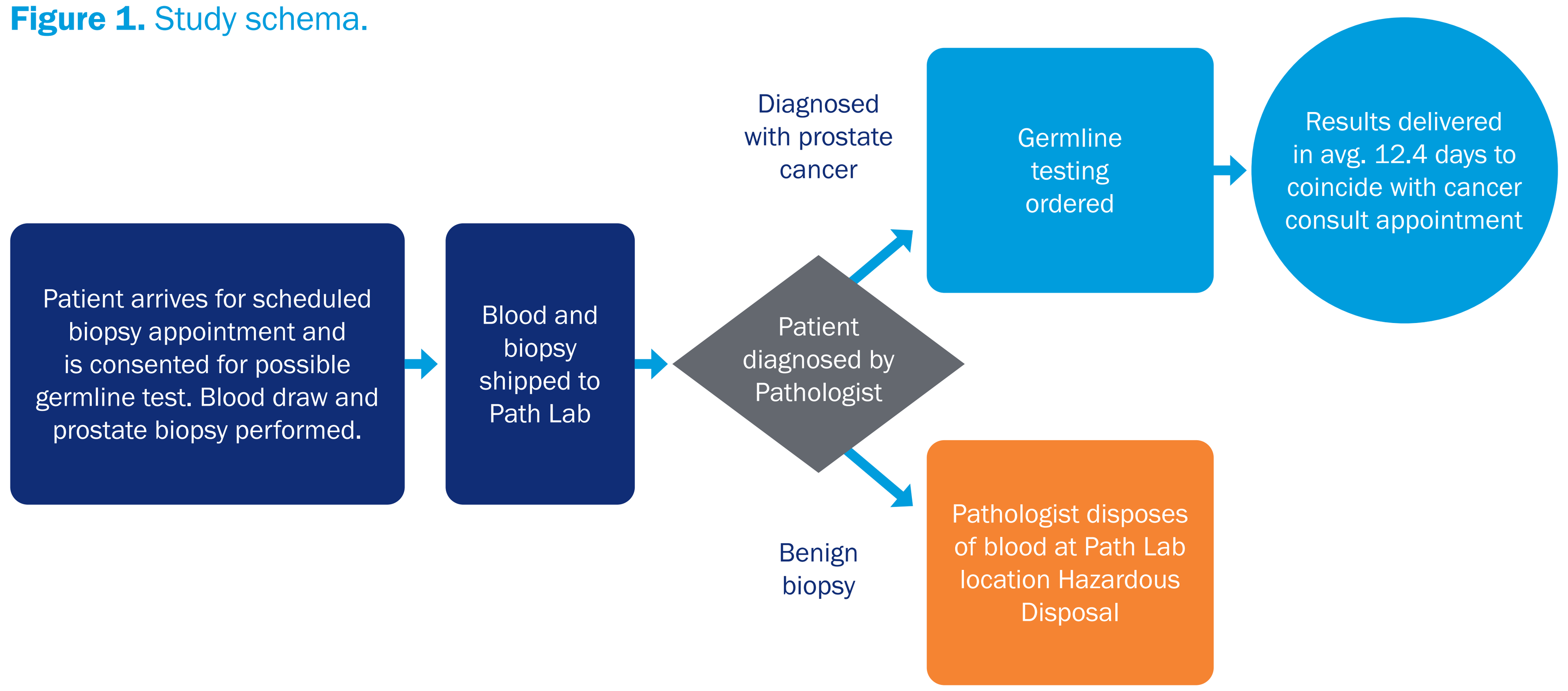
Background

- Men with prostate cancer who harbor germline pathogenic variants have increased likelihood of a more aggressive cancer and/or an increased risk for second primary cancers.
- However, current National Comprehensive Cancer Network (NCCN) guidelines limit germline genetic testing recommendations to those with higher Gleason scores or NCCN Risk Groups, metastatic disease and/or a family history of cancer.[1]
- We examined the prevalence of pathogenic variants in a multi-center (n=24 sites) real-world cohort of men with localized prostate cancer, stratified by Gleason score and NCCN Risk Group.

Methods

- Blood was drawn for germline genetic testing by Myriad Genetics at the time of prostate cancer diagnostic biopsy. For patients who had biopsy-confirmed cancer, germline testing was initiated. Samples from patients with a benign biopsy were not sent for germline testing and are not included in this analysis (**Figure 1**). Personal and family cancer history were not collected.
- A positive result was defined as a pathogenic variant in at least one of the up to 49 genes tested (**Figure 2**).
- Positive test result rates are reported with 95% exact confidence intervals.
- Relationships between a positive test result and Gleason score or NCCN Risk Group were assessed using logistic regression.

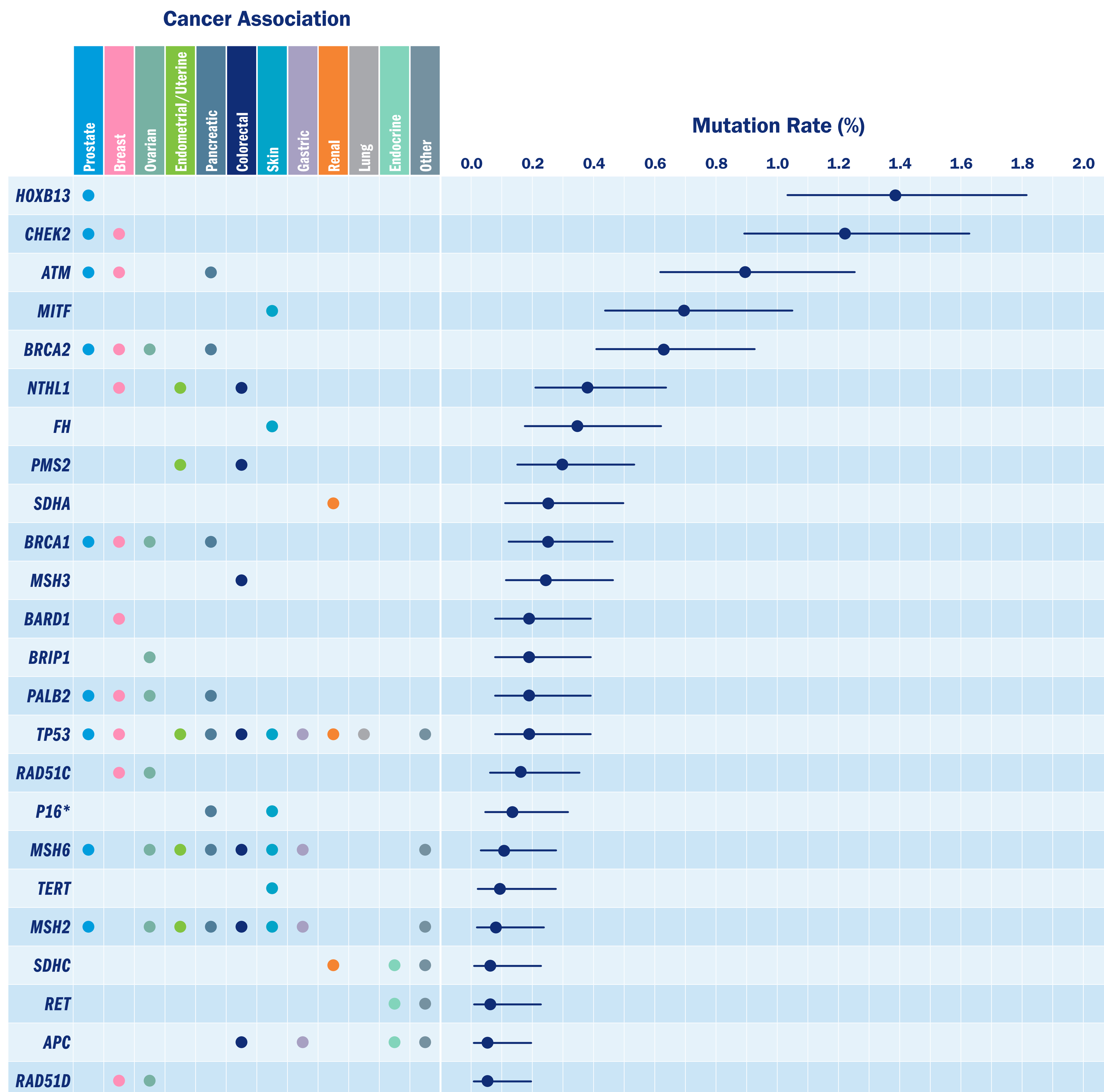
Figure 1. Study schema.



Results

- Of the 3,995 men who completed germline testing, 274 (6.9%) had a positive test result.
- The prevalence of mutations in each gene is shown in **Figure 2**. The most commonly mutated gene was *HOXB13*, with 1.38% (95% confidence interval 1.03-1.81%).
- Distributions of observed Gleason scores and NCCN Risk Groups are summarized in **Table 1**.
- Positive test rates by Gleason score ranged from 6.0% to 8.4% (**Figure 3A**).

Figure 2. Tested genes with cancer associations and observed prevalence with 95% confidence intervals.



*CDKN2A (p14ARF) & CDKN2A (p16INK4a)
Genes with 1 or fewer observed variants are not included in this figure: *SDHB, SDHD, BAP1, CTNNA1, FLCN, TSC1, VHL, MLH1, AXIN2, BMPR1A, CDH1, CDK4, EPCAM, GREM1, MYH, P14ARF, POLD1, POLE, PTEN, SMAD4, STK11, EGFR, MEN1, MET, TSC2*

- Positive test rates by NCCN Risk Group ranged from 5.6% to 8.4% (**Figure 3B**).
- There was no statistically significant difference in positive testing rates across Gleason scores (p = 0.17) or NCCN Risk Groups (p = 0.14) (**Table 2**).

Figure 3. Observed mutation prevalence by **(A)** Gleason score and **(B)** NCCN risk groups.

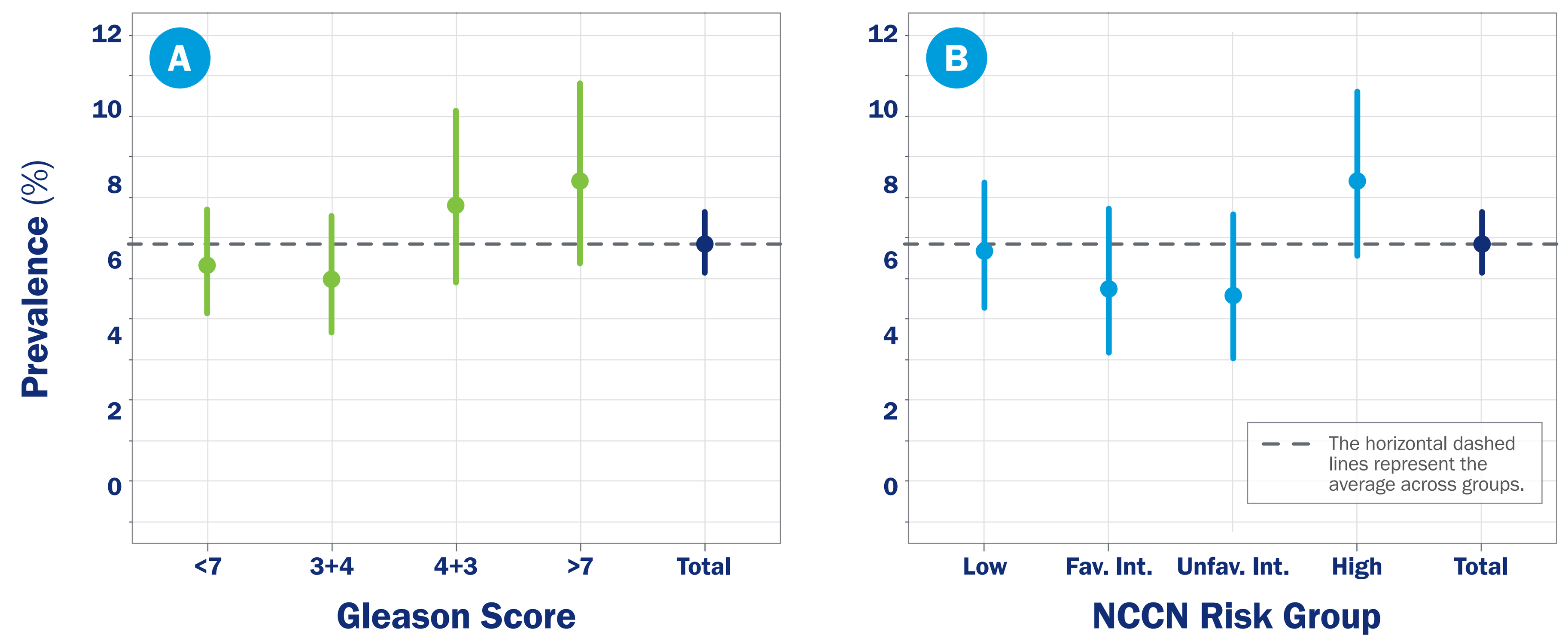


Table 1. Distribution of Gleason Score and NCCN Risk Group (N=3,995).

Gleason Score	N (%)	NCCN Risk Group	N (%)
3+3	1454 (36.4)	Low	1031 (25.8)
3+4	1056 (26.4)	Favorable Intermediate	679 (17.0)
4+3	640 (16.0)	Unfavorable Intermediate	663 (16.6)
>7 (8, 9, 10)	620 (15.5)	High	726 (18.2)
Unknown	225 (5.6)	Unknown	896 (22.4)

Table 2. Results of logistic regression models.

Gleason Score predicting positive test result			NCCN Risk Group predicting positive test result		
Gleason Score	OR (95% confidence interval)	p-value	NCCN Risk Group	OR (95% confidence interval)	p-value
<7	Reference	0.17	Low	Reference	0.14
3+4	0.94 (0.67-1.30)		Favorable intermediate	0.85 (0.56-1.27)	
4+3	1.25 (0.87-1.79)		Unfavorable intermediate	0.82 (0.54-1.24)	
>7	1.36 (0.95-1.92)		High	1.28 (0.89-1.83)	

Conclusions

- A substantial proportion of men with localized prostate cancer harbor pathogenic germline variants.
- Positive germline test results rates were not significantly different across Gleason scores or NCCN Risk Groups.
- Limiting germline testing to those with higher Gleason scores or NCCN Risk may miss a significant number of patients who harbor a pathogenic variant.
- These data support universal germline genetic testing at prostate cancer diagnosis, independent of Gleason score or NCCN Risk Group.

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic and Prostate V.2.2026. © National Comprehensive Cancer Network, Inc. 2026. All rights reserved. Accessed February 5th, 2026. To view the most recent and complete version of the guideline, go online to NCCN.org.

Email questions or comments to rfinch@myriad.com