MICHIGAN MEDICINE
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DETECTION OF GERMLINE MUTATIONS IN LOCALIZED AND METASTATIC PROSTATE CANCER THROUGH GUIDELINE-BASED TESTING

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Presentation Overview

- Introduction/Background
- Methods
- Results
- Conclusion

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Introduction

- There's increasing awareness that prostate cancer patients frequently harbor germline mutations.
- These mutations carry significant implications for:
  - Targeted therapies
  - Cascade testing of family members
  - Detection of hereditary cancer syndromes
- Most studies, however, were performed on metastatic patients and prospective data from clinical practice is lacking.
- We aimed to compare rates of germline mutations in men with metastatic and localized prostate cancer (PCa).

Methods

- In accordance with NCCN guidelines, men diagnosed with PCa at Michigan Medicine and Michigan Institute of Urology between 2017 - 2019 were offered multi-gene panel testing.
  - A Urologist or Medical Oncologist performed all pre-test counseling and test ordering.
  - Our patient cohort included both metastatic and localized PCa patients
- We performed a comparison of pathogenic/likely pathogenic variants and variants of uncertain significance (VUS) rates according to demographics and disease characteristics.

Methods

- Guidelines for offering genetic testing:
  1. Personal history ≥ Gleason 7 localized PCa with any of the following
     - 1+ close blood relative with ovarian cancer, pancreatic cancer, metastatic prostate cancer; or breast cancer (≤50)
     - 2+ relatives with breast or PCa (G7+)
     - Ashkenazi Jewish ancestry
  2. Metastatic PCa

Methods

- Metastatic or intraductal prostate cancer at any age[h]
- High-grade (Gleason score ≥7) prostate cancer with:
  - Ashkenazi Jewish ancestry; or
  - ≥1 close relative[e] with breast cancer at age ≤50 y or ovarian, pancreatic, or metastatic or intraductal prostate cancer at any age; or
  - ≥2 close relatives[e] with breast or prostate cancer (any grade) at any age.

Patient Disease distribution

- Overall 398 patients have undergone genetic testing.
  - 189 with localized disease
  - 209 with metastatic disease

Demographic information by disease status

Overall (n = 398)	Localized (n=189)	Metastatic (n=209)
Age, Median (IQR)	65.5 (40-83)	72.0 (48-93)
Positive Family History % (count)	91.5% (173)	56.5% (118)
Race %		
Caucasian	89.4%	89.9%
African American	8.8%	7.6%
American Indian	--	--
Asian	--	2.0%
Hispanic	1.8%	0.5%

Clinical characteristics

Overall (n = 378)	Localized (n = 181)	Metastatic (n = 197)
PSA, Median (IQR)	6.79 (4.4 – 12.6)	15.1 (5.9 – 81)
Clinical stage		
T1c	68.23%	
T2	27.1%	
T3	4.69%	

Localized disease: Gleason Score Distribution at Diagnosis

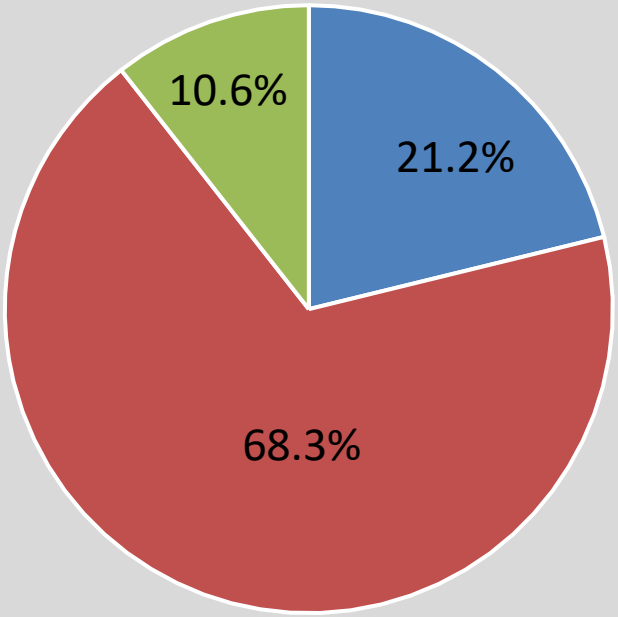
Gleason Score	Overall (count, %) (n=187)
Gleason 6	25 (13.4%)
Gleason 7 (3+4)	56 (29.9%)
Gleason 7 (4+3)	37 (19.8%)
Gleason 8	26 (13.9%)
Gleason 9	41 (21.9%)
Gleason 10	2 (1.1%)

Localized Treatment Frequency

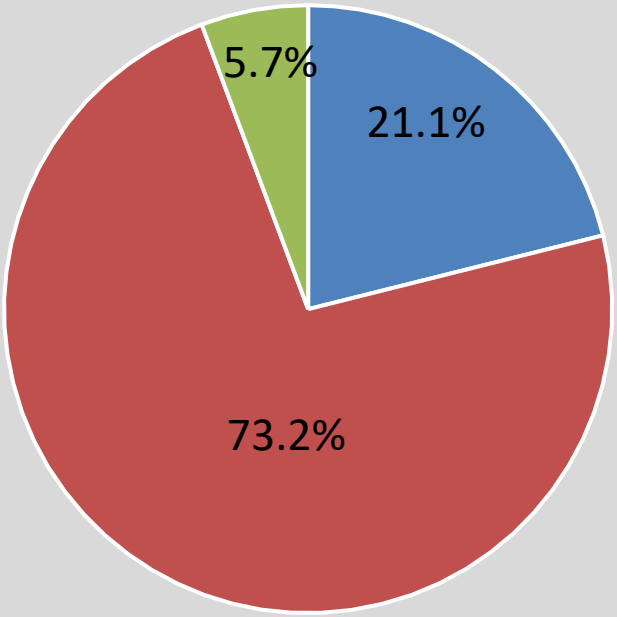
Treatment	Count	Percentage
Radical prostatectomy	115	79.9%
Radiation therapy	15	10.4%
Active Surveillance	12	8.3%
Cryotherapy	2	1.4%

Genetic Testing Results

Localized	Metastatic
N=181	N=209



Positive Negative VUS



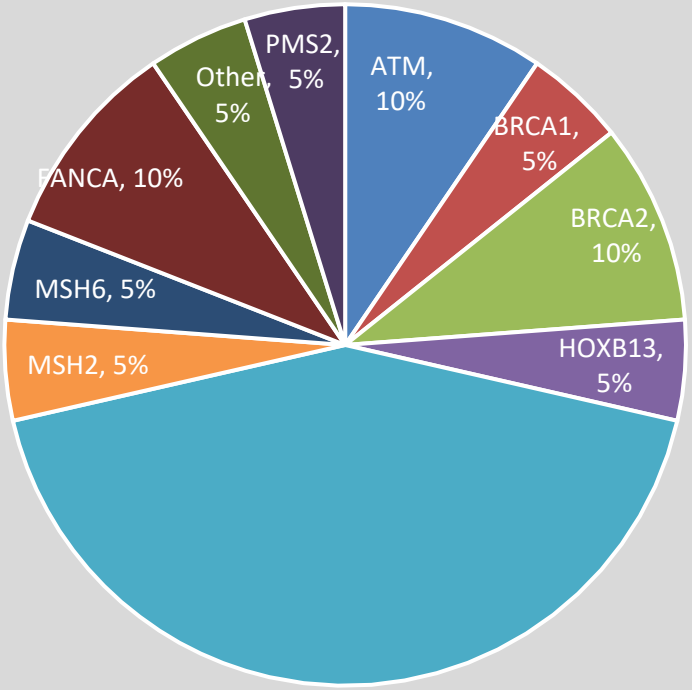
Positive Negative VUS

Most common pathogenic variants

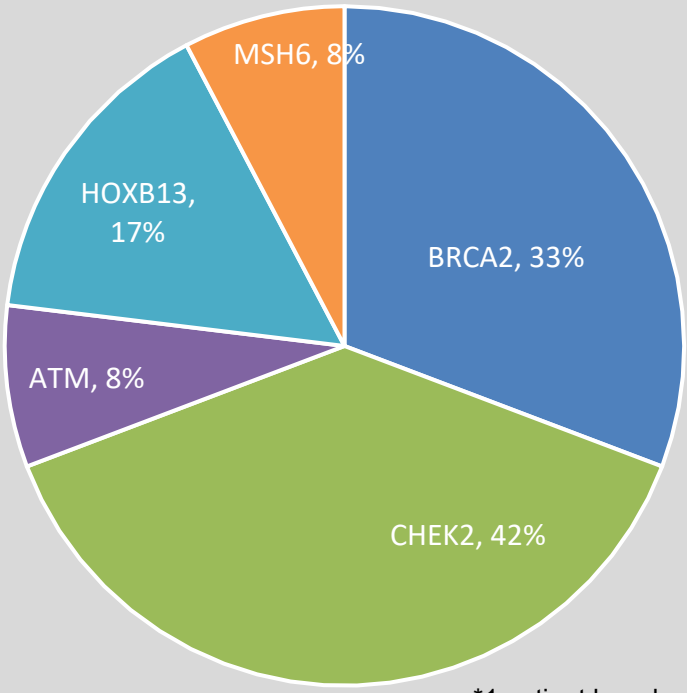
- Rates of pathogenic germline mutations:
  - Localized: 10.6%
  - Metastatic: 5.8%
- Most common mutations:
  - *CHEK2* - 43.8%
  - *BRCA2* -18.8%
  - *HOXB13* - 9.4%
  - *ATM* - 9.4%

Positive variants

Localized		Metastatic	
Total Genetic Tests	Positive	Total Genetic Tests	Positive
189	20*	209	12*



*1 patient has dual mutation:
- MSH6 and FANCA



*1 patient has dual mutation:
- BRCA2 and CHEK2

Conclusions

- A large proportion of men with prostate cancer harbor mutations in vital DNA damage repair genes.
  - This includes men with localized disease.
- Detection of germline mutations have potential implications for patient management and cascade testing.
- These data support genetic testing following the national guidelines.

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Contributing Authors

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