Genetic Alterations: Implications for Clinical Decision-Making in Advanced Prostate Cancer
Objectives

• Gain an understanding of how genetic alterations drive oncogenesis and cancer progression
  – Inherited and acquired alterations accumulate and disrupt normal cellular pathways
  – Disrupted DNA damage repair mechanisms are both a factor in oncogenesis and a therapeutic entry point against some cancers

• Explore the significance of genetic alterations in prostate cancer
  – DNA damage repair genes are implicated in disease risk, severity, and mortality

• Consider the rationale for and potential utility of genetic testing in prostate cancer
  – Testing in advanced disease states offers an opportunity to improve clinical management
Genetic Alterations: Drivers of Oncogenesis and Disease Progression
Cancer Is Now Understood to Be a Genetically Driven Disease

• Genetic alterations can disrupt normal cellular processes (and cause genomic instability)\(^1,2\)
  
  – Can occur as mutations on specific genes; chromosome amplifications, deletions, or rearrangements; and the gain or loss of entire chromosomes\(^1\)

• In some cells, genetic alterations can promote\(^1,3,4\):
  
  – Oncogenesis
  
  – Survival, growth, and proliferation of cancer cells


Genetic Alterations Can Be Inherited or Develop Over Time

**Germline (Inherited) Cells**
The alteration is continually present and affects every cell in the body\(^1,2\)

**Germline Alteration**
- Germline alteration in PARENTAL GAMETES
- Entire Organism Carries Alteration
- Sperm or Egg

**Somatic (Acquired) Cells**
The alteration arises in certain cells and only affects tissues derived from these cells\(^1,3\)

**Somatic Alteration**
- Early
  - Sperm
  - Egg
  - Alteration Only in Affected Area
- Later
  - Sperm
  - Egg
  - Alteration in Single Cell and All Daughter Cells

Only **germline alterations** can be inherited or passed on to offspring.\(^2\)

Genetic Alterations Can Disrupt the Normal Cell Cycle

- Genomic stability normally is maintained by a tightly regulated cell cycle\(^1\)
- Genes have specific roles in cell-cycle signaling in both healthy and cancer cells\(^1\)
- Signaling pathways that are disrupted in cancer cells can drive:
  - Uncontrolled growth and proliferation\(^1\)
  - Resistance to therapy and relapse\(^2\)

Genetic Alterations Are Implicated in a Number of Cancers

- Examples include:
  - *EGFR* alterations in prostate, breast, and other cancers\(^1\)
  - *BCR-ABL* fusion gene in certain leukemias (ie, CML, AML, ALL)\(^2\)
  - *KRAS* alterations in colon and nonsmall cell lung cancers\(^3\)
  - *BRCA1/2* alterations in ovarian and breast cancers, and other solid tumors\(^4,5\)

- These alterations have been identified and leveraged\(^1,6-8\):
  - As markers or drivers of disease
  - For patient identification and stratification
  - As therapeutic targets

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Prostate Cancer Is Characterized by Diverse Genetic Alterations

Prostate cancer is among the most genetically driven cancers\textsuperscript{1,2}

\begin{itemize}
  \item 57% of variation in risk among patients is due to inherited genetic factors\textsuperscript{2}
  \item As many as 90% of mCRPC cases are believed to harbor alterations in recognized, targetable pathways\textsuperscript{3}
\end{itemize}

mCRPC, metastatic castration-resistant prostate cancer.

Genetic Alterations Have Clinical Implications in Prostate Cancer

- Specific gene alterations can\(^1-3\):
  - Provide additional insights into disease risk and clinical course
  - Supplement clinical information (eg, PSA level, Gleason score)

- Genetic testing potentially can help clinicians\(^2-4\):
  - Prevent overtreatment of indolent disease
  - Identify aggressive disease variants
  - Tailor management approaches more effectively

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nmCRPC, nonmetastatic castration-resistant prostate cancer; PSA, prostate-specific antigen.

Genetic Alterations Appear to Help Drive Progression to mCRPC

- Notable example is the AR gene
- Changes to the AR gene may
  - Promote resistance to ADT$^{1,2}$
  - Drive progression by encoding the AR signaling pathway to stimulate cell growth in the absence of androgen$^3$
- One study found AR pathway activity in nearly 90% of mCRPC tumors despite low levels of androgen$^4$

Alterations to DNA damage repair genes similarly are believed to have relevance in prostate cancer

ADT, androgen deprivation therapy; AR, androgen receptor.

Impact of Genetic Alterations on DNA Damage Repair
Gene Alterations That Impact DNA Damage Repair Can Drive Genomic Instability and Oncogenesis

- Accurate DNA damage repair is essential to ensuring the genomic integrity of healthy cells
- A cell’s ability to accurately repair DNA damage can be lost or disrupted due to genetic alterations
- When DNA damage repair is compromised, this can:
  - Promote the accumulation and permanent incorporation of genetic alterations
  - Further contribute to genomic instability and oncogenesis

DNA Damage Repair Genes Can Be Leveraged as Therapeutic Targets in Cancer Cells

• **Platinum-based chemotherapy**\(^1\)
  Damages DNA structure and causes double-strand breaks
  – Can also cause the formation of DNA crosslinks that inhibit DNA repair in cancer cells

• **Topoisomerase inhibitors**\(^1,2\)
  Disrupt the rejoining of DNA strands during the cell cycle
  – Causes the formation of single- and double-strand breaks

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DNA Damage Is Caused by a Number of Factors and Occurs Continuously

• DNA damage occurs naturally and continuously due to\textsuperscript{1,2}:
  – Disruption of chemical bonds during the normal cell cycle
  – Byproducts of normal cellular metabolism
  – Environmental factors

• Damage can be single-strand or double-strand DNA breaks
  – Unrepaired single-strand breaks can accumulate and lead to formation of double-strand breaks\textsuperscript{2,3}
  – Double-strand breaks are harmful to the cell because they can lead to permanent genome rearrangements\textsuperscript{2}

DNA Damage Repair Is Essential to Ensure the Genomic Integrity of Healthy Cells

- DNA damage can be repaired using a number of mechanisms that\textsuperscript{1,2}:
  - Involve different cellular proteins
  - Vary in how accurately they repair DNA damage

- Single-strand breaks are repaired normally using base excision repair\textsuperscript{3}

- Double-strand breaks are repaired normally using homologous recombination\textsuperscript{3}

BRCA1/2 Genes Play an Important Role in Accurate Repair of DNA Damage

• BRCA1/2 proteins normally facilitate homologous recombination repair of double-strand DNA breaks\(^1,2\)
  – Part of the DNA sequence around the break is removed\(^3\)
  – A homologous DNA sequence then is used as a template to synthesize a new DNA sequence at the break site\(^3\)

• Other genes, including ATM and CHEK2, have roles in detecting, regulating, and / or repairing double-strand breaks\(^3,4\)

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Alterations to BRCA1/2 Can Compromise Repair of Double-Strand DNA Breaks

• When BRCA1/2 is altered, the ability to repair DNA using homologous recombination is disrupted or lost\(^1,2\)

• Double-strand breaks then are repaired with less accuracy\(^1,3-5\)
  – Leads to accumulated DNA damage
  – May also promote oncogenesis in cancer-driver genes

BRCA1/2 alterations can impact course of disease and may have prognostic significance in prostate cancer

BRCA1/2 Alterations:
Implications in Advanced Prostate Cancer
Alterations to DNA Damage Repair Genes Are a Key Feature of Metastatic Prostate Cancer

- Key genes in DNA damage repair pathways include BRCA1, BRCA2, ATM, and CHEK2\textsuperscript{1-3}

- Alterations to these genes can disrupt or diminish the ability to accurately repair DNA\textsuperscript{4,5}

- Higher mutation frequencies (both germline and somatic) found in mCRPC, compared to earlier disease\textsuperscript{5,6}

Approximately 7% to 14% of patients with mCRPC have a BRCA1/2 gene alteration\textsuperscript{6-10}

BRCA1/2 Alterations Have Clinical Significance in Prostate Cancer

- Compared with noncarriers, men with BRCA1/2 alterations appear to have:
  - Higher risk of disease
  - More aggressive disease
  - Higher rates of cancer-specific mortality
- Additionally, BRCA1/2 alteration status could aid clinical decision-making:
  - One study found significantly shorter MFS among carriers receiving RT vs RP
  - First study to suggest a predictive role for BRCA1/2 alterations when considering radical intervention in localized disease

MFS in Men Treated With RP (left) and RT With Curative Intent Following Diagnosis

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*BRCA1/2* alteration carriers are shown in blue, noncarriers in gray. Retrospective study of men with local or locally advanced prostate cancer, including 67 *BRCA1/2* alteration carriers and 1235 noncarriers.

CI, confidence interval; MFS, metastasis-free survival; RP, radical prostatectomy; RT, radiation therapy.
BRCA1/2 Alterations Appear to Be Associated With a Higher Risk for Prostate Cancer

- Compared with men without a BRCA1/2 alteration, the estimated relative risk of developing prostate cancer before age 65 is:

<table>
<thead>
<tr>
<th>BRCA1 Alteration Carriers</th>
<th>BRCA2 Alteration Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1- to 3.7-Fold Higher</td>
<td>2.5- to 8.6-Fold Higher</td>
</tr>
</tbody>
</table>

Increased Risk (fold)

Germline BRCA1/2 Alterations Are a Feature of More Aggressive Disease

• Germline BRCA1/2 alterations have been found more frequently in patients with:
  – Gleason score ≥8 (P=0.00003)
  – T3/T4 stage disease (P=0.003)
  – Nodal involvement (P=0.0005)
  – Metastases at diagnosis (P=0.005)

• Among patients with localized disease, the 5-year rate of MFS was significantly higher in men without a BRCA1/2 alteration compared with alteration carriers (93% vs 77%; P=0.0001)

MFS in Noncarriers and Men With Altered Germline BRCA1/2

- Study of 2019 men with prostate cancer, including 18 BRCA1 alteration carriers, 61 BRCA2 alteration carriers, and 1940 noncarriers
- Patients with metastatic disease: 14 (17.7%) of BRCA alteration carriers and 166 (8.6%) of noncarriers
- Treatment received: 79% of noncarriers and 72% of BRCA alteration carriers had radical treatment with surgery or radiotherapy; 36% and 37%, respectively, also received adjuvant ADT
Germline BRCA1/2 Status Is Associated With Worse Overall Survival

• Median overall survival times have been shown to be shorter in germline BRCA1/2 alteration carriers vs noncarriers (figure)$^1$
  
  • Another study found the frequency of BRCA1/2 and ATM alterations to be significantly associated with$^2$:
    – Age at death ($P=0.046$)
    – Time to death since diagnosis ($P=0.0006$)
    – Survival times ($P=0.006$)

• Combined alteration frequency was significantly higher in lethal disease (6.07%, n=313) vs low-risk localized disease (1.44%, n=486); $P=0.0007^2$

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Noncarriers</th>
<th>BRCA1 mutation carriers</th>
<th>BRCA2 mutation carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>1,940</td>
<td>18</td>
<td>61</td>
</tr>
<tr>
<td>BRCA2</td>
<td>1,394</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>ATM</td>
<td>896</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>Median</td>
<td>467</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Survival</td>
<td>186</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Risk</td>
<td>68</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Median</td>
<td>22</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Survival</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rate</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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BRCA1/2 Germline Alterations Appear to Become More Apparent as Disease Advances

Percent of Men With Germline BRCA1/2 Alterations

<table>
<thead>
<tr>
<th></th>
<th>General Population (N=53,105)</th>
<th>Localized Prostate Cancer (N=499)</th>
<th>mCRPC (N=692)</th>
<th>Relative Risk of Carrying the Alteration in Localized vs mCRPC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>0.22%</td>
<td>0.60%</td>
<td>0.87%</td>
<td>1.4 (0.5-3.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P=0.32</td>
</tr>
<tr>
<td>BRCA2</td>
<td>0.29%</td>
<td>0.20%</td>
<td>5.35%</td>
<td>26.7 (18.9-36.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Data sets (N=692) include the Exome Aggregate Consortium (general population), The Cancer Genome Atlas cohort with primary prostate cancer (localized), and 7 case series of men with metastatic disease in the US and UK (mCRPC).

- Incidence of germline mutations in mCRPC
  - Does not appear to differ significantly based on age at diagnosis or family history of prostate cancer
  - May be associated with Gleason score 8-10 vs ≤7
**BRCA1/2 Somatic Alterations Can Arise Throughout the Course of Disease**

- Somatic mutations to *BRCA1/2* are more prevalent in mCRPC
  - Also appear in locoregional and biochemically recurrent disease states
- Matched biopsies taken from the same patient have shown higher alteration counts in metastatic vs localized tumors

The greater number of *BRCA1/2* alterations in mCRPC has implications for genetic testing strategies.

Prevalence of Somatic *BRCA1/2* Alterations Across Prostate Cancer Disease States

<table>
<thead>
<tr>
<th></th>
<th>BRCA2</th>
<th>BRCA1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locoregional</td>
<td><img src="locoregional.png" alt="Graph" /></td>
<td><img src="locoregional.png" alt="Graph" /></td>
</tr>
<tr>
<td>Metastatic Noncastrate</td>
<td><img src="met_noncastrate.png" alt="Graph" /></td>
<td><img src="met_noncastrate.png" alt="Graph" /></td>
</tr>
<tr>
<td>mCRPC</td>
<td><img src="mcrpc.png" alt="Graph" /></td>
<td><img src="mcrpc.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

Data from the Memorial Sloan Kettering IMPACT data set, a target sequencing assay involving 504 tumors from 451 patients with prostate cancer.

Genetic Testing: Issues and Approaches in Prostate Cancer
Prostate Cancer Is Characterized by Distinct Clinical States and Variable Outcomes

• About 11% of men in the United States will be diagnosed with prostate cancer at some point during their lives
  – Many have indolent or nonlethal disease
  – Some respond to curative surgery and early intervention with ADT
  – Over time, many men progress to CRPC, relapsing on multiple lines of therapy
  – Despite significant clinical advances, mCRPC remains a lethal disease

Genetic Testing Has Recognized Prognostic and Predictive Value in Prostate Cancer

- There is growing consensus that germline genetic testing should be used for certain patients with prostate cancer\textsuperscript{1-3}
  - A family history of hereditary breast, ovarian, or prostate cancer
  - A family history of Lynch syndrome
  - High-risk, very high-risk, regional, or metastatic prostate cancer

- The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines\textsuperscript{®})\textsuperscript{3} provide details around when germline or somatic testing may be appropriate

- Genetic testing can be used to help\textsuperscript{1,4-6}:
  - Determine a cancer’s aggressiveness (prognostication)
  - Guide management approaches in individual patient management (prediction)

# Recommendations Address Identifying BRCA1/2 Alteration Status in Patients With Prostate Cancer

<table>
<thead>
<tr>
<th>Advanced Disease</th>
<th>Localized Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NCCN Guidelines⁰¹</strong></td>
<td><strong>ASCO²</strong></td>
</tr>
<tr>
<td>Germline genetic testing is recommended for all men with high-risk, very high-risk, regional, or metastatic prostate cancer, regardless of family history</td>
<td>In patients with mCRPC, next-generation sequencing should be conducted for DNA repair gene alterations (eg, BRCA1/2 or ATM)</td>
</tr>
<tr>
<td>Germline genetic testing is recommended for men with prostate cancer and a suspicious family history or the presence of intraductal/cribriform histology</td>
<td></td>
</tr>
<tr>
<td>Somatic testing is recommended for men with metastatic prostate cancer</td>
<td></td>
</tr>
<tr>
<td>Somatic testing can be considered in men with regional prostate cancer</td>
<td></td>
</tr>
<tr>
<td>Somatic testing may require repetition when prostate cancer progresses after treatment</td>
<td></td>
</tr>
</tbody>
</table>
Potential for Genetic Alterations to Proliferate Has Implications for Genetic Screening

Genetic testing done as part of screening or initial diagnosis can help assess a patient’s risk for prostate cancer and potential for aggressive disease.¹

• However, genetic screening programs can only identify germline and somatic alterations that are present early in the course of disease²
  – Germline alterations may be detected more often in advanced disease
  – May miss somatic alterations that arise throughout the course of disease

To Accurately Characterize Disease, Multiple Genetic Tests May Be Necessary

Somatic genetic testing in later stages of disease can help inform clinical decision-making.¹

- Biopsy of metastatic lesions can detect alterations that emerge in advanced disease or confirm the presence of germline mutations²-⁴
  - Important driver mutations appear to be widely present in the individual patient, so sampling multiple sites generally is not necessary⁵
- ctDNA purified from blood samples may be able to reliably detect both germline and somatic gene alterations⁶

ctDNA, circulating tumor DNA.

# Technologies Are Available to Facilitate Routine Testing for Germline and Somatic Alterations in Clinical Practice

<table>
<thead>
<tr>
<th></th>
<th>Saliva / Blood</th>
<th>Tissue</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Collected from patient</strong></td>
<td>Buccal swab / whole blood</td>
<td>Contemporaneous or archival tumor tissue</td>
<td>Whole blood</td>
</tr>
<tr>
<td><strong>Components analyzed</strong></td>
<td>Tissue cells / leukocytes</td>
<td>FFPE tumor tissue</td>
<td>Cell-free (CF) DNA</td>
</tr>
<tr>
<td><strong>Alteration types detected</strong></td>
<td>• Germline</td>
<td>• Germline</td>
<td>• Germline</td>
</tr>
<tr>
<td></td>
<td>• Somatic</td>
<td>• Somatic</td>
<td>• Somatic</td>
</tr>
<tr>
<td><strong>Number of genes typically assessed</strong></td>
<td>≈2–45</td>
<td>≈150–400</td>
<td>≈50–100</td>
</tr>
<tr>
<td><strong>Genes typically included</strong></td>
<td>• Cancer-related genes</td>
<td>• Cancer-related genes</td>
<td>• Cancer-related genes</td>
</tr>
<tr>
<td></td>
<td>• <em>BRCA1, BRCA2</em></td>
<td>• <em>BRCA1, BRCA2</em></td>
<td>• <em>BRCA1, BRCA2</em></td>
</tr>
<tr>
<td></td>
<td>• 5–10 other DDR genes</td>
<td>• 10–30 other DDR genes</td>
<td>• 2–10 other DDR genes</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>• Minimally invasive</td>
<td>• More comprehensive</td>
<td>• Minimally invasive</td>
</tr>
<tr>
<td></td>
<td>• Low cost</td>
<td>(eg, MSI, TMB, LOH)</td>
<td>• Queries DNA from multiple tumor lesions</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>• Limited to inherited mutations</td>
<td>• Challenging to collect metastatic tissue</td>
<td>• Technical challenges to detect certain alteration types</td>
</tr>
<tr>
<td></td>
<td>• Fewer genes</td>
<td>• High assay-failure rate</td>
<td></td>
</tr>
</tbody>
</table>

DDR, DNA damage repair; FFPE, formalin fixed, paraffin embedded; LOH, loss of heterozygosity; MSI, microsatellite instability; TMB, tumor mutational burden.

Summary

• Prostate cancer is characterized by diverse genetic alterations
  – Alterations occur in both germline and somatic cells
  – Screening and testing protocols are key to effectively identifying and stratifying patients based on genetic status

• Alterations to DNA damage repair genes, particularly BRCA1/2, are a driving factor of the disease
  – BRCA1/2 alterations are associated with higher risk for prostate cancer, and higher disease aggressiveness and mortality

• BRCA1/2 alterations in prostate cancer are emerging as:
  – A screening tool for prostate cancer risk
  – An important prognostic tool
  – A potential target for therapeutic intervention