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

\[\text{PROGENITOR CELLS} \xrightarrow{\text{Genomic Alteration}} \text{PRECANCEROUS CELLS} \xrightarrow{\text{Accumulation of Alterations and Cellular Dysregulation}} \text{CANCER CELLS} \xrightarrow{\text{Tumor Growth}} \text{ADVANCED CANCER}\]


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**
  - Sperm
  - Egg

- **EMBRYO**
  - Entire Organism Carries Alteration

- **ORGANISM**
  - Half Carry Alteration

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

**SOMATIC ALTERATION**

- **Early**
  - Sperm
  - Egg
  - Somatic Alteration
  - Alteration Only in Affected Area

- **Later**
  - Sperm
  - Egg
  - Somatic Alteration
  - Alteration in Single Cell and All Daughter Cells

None Carry Alteration

None Carry Alteration

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

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia.

Prostate Cancer Is Characterized by Diverse Genetic Alterations

**Prostate cancer** is among the most **genetically driven** cancers\(^1,2\)

57% of variation in risk among patients is due to inherited genetic factors\(^2\)

As many as **90% of mCRPC cases** are believed to harbor alterations in recognized, targetable pathways\(^3\)

mCRPC, metastatic castration-resistant prostate cancer.

Genetic Alterations Have Clinical Implications in Prostate Cancer

• Specific gene alterations can\textsuperscript{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\textsuperscript{2-4}:
  – Prevent overtreatment of indolent disease
  – Identify aggressive disease variants
  – Tailor management approaches more effectively

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\(^4\)

### AR Gene Amplifications and Alterations\(^2\)

- Nonmetastatic
  - Biochemical Relapse
  - Castration Resistance
- Metastatic Hormone Naive
  - nmCRPC
  - mCRPC

60% of men with mCRPC\(^4,5\)

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\(^1\)
- A cell’s ability to accurately repair DNA damage can be lost or disrupted due to genetic alterations\(^2,3\)
- When DNA damage repair is compromised, this can\(^1\):
  - 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 stands during the cell cycle
  - Causes the formation of single- and double-strand breaks

---

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

- DNA damage occurs naturally and continuously due to¹,²:
  - 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 breaks²,³
  - Double-strand breaks are harmful to the cell because they can lead to permanent genome rearrangements²

---

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

• DNA damage can be repaired using a number of mechanisms that\(^1,2\):
  – Involve different cellular proteins
  – Vary in how accurately they repair DNA damage

• Single-strand breaks are repaired normally using base excision repair\(^3\)

• Double-strand breaks are repaired normally using homologous recombination\(^3\)

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\(^3,4\)

---

**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*.
- Alterations to these genes can disrupt or diminish the ability to accurately repair DNA.
- Higher mutation frequencies (both germline and somatic) found in mCRPC, compared to earlier disease.

Approximately 7% to 14% of patients with mCRPC have a *BRCA1/2* gene alteration.

**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**

*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:

- BRCA1 Alteration Carriers: 1.1- to 3.7-Fold Higher
- BRCA2 Alteration Carriers: 2.5- to 8.6-Fold Higher

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%, \(n=486\)); \(P=0.0007\)

![Shorter Overall Survival Times in Men With Altered Germline BRCA1/2](image)

- Noncarriers
- BRCA1 alteration carriers
- BRCA2 alteration carriers

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>0</th>
<th>2.5</th>
<th>5.0</th>
<th>7.5</th>
<th>10.0</th>
<th>12.5</th>
<th>15.0</th>
<th>17.5</th>
<th>20.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival (proportion)</td>
<td>1.0</td>
<td>0.8</td>
<td>0.6</td>
<td>0.4</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

• 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

Prevalence of $BRCA1/2$ Germline Alterations Appears to Increase 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) $P=0.32$</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) $P&lt;0.001$</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 can 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

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

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

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

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\(^1\)
  - Many have indolent or nonlethal disease\(^2,3\)
  - Some respond to curative surgery and early intervention with ADT\(^2,3\)
  - Over time, many men progress to CRPC, relapsing on multiple lines of therapy\(^4\)
  - Despite significant clinical advances, mCRPC remains a lethal disease\(^5\)

164,690 estimated new cases in 2018
78% localized disease\(^1,6\)

Radical intervention + ADT results in PSA reductions in ~90% of patients\(^2,7,8\)

Castration resistance develops in 10% to 20% of patients; >80% may be metastatic at this time\(^7\)

Progression to mCRPC in 2 to 3 years for ~30% of patients\(^2\)

29,430 estimated deaths in 2018\(^1\)

Genetic Testing Has Recognized Prognostic and Predictive Value in Prostate Cancer

• There is growing consensus that germline genetic testing should be used for patients with prostate cancer\(^1-^3\)
  – 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\(^3\)) provide details around when germline or somatic testing may be appropriate

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

Recommenations 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 Guidelines</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>ASCO</strong>&lt;sup&gt;2&lt;/sup&gt;</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, <em>BRCA1/2</em> or <em>ATM</em>)</td>
</tr>
<tr>
<td>Somatic testing can be considered in men with regional or metastatic prostate cancer</td>
<td></td>
</tr>
</tbody>
</table>

NCCN, National Comprehensive Cancer Network; ASCO, American Society of Clinical Oncology; ASTRO, American Society for Radiation Oncology; AUA, American Urological Association; SUO, Society of Urologic Oncology.

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) for Prostate Cancer V.2.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed May 9, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org.
Potential for Genetic Alterations to Proliferate Has Implications for Genetic Screening

Genetic testing done as part of screening\(^1\) or initial diagnosis\(^{1,2}\) can help assess a patient’s risk for prostate cancer and potential for aggressive disease.

- However, genetic screening programs can only identify germline and somatic alterations that are present early in the course of disease\(^3\)
  - 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

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 (eg, MSI, TMB, LOH)</td>
<td>• Minimally invasive</td>
</tr>
<tr>
<td></td>
<td>• Low cost</td>
<td></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.

Morris D et al. Genomic profiling of metastatic castration-resistant prostate cancer (mCRPC) patients for the evaluation of rucaparib: next-generation sequencing (NGS) of cell-free DNA (CFDNA) and tumor tissue Society of Urologic Oncology 19th Annual Meeting; November 28-30, 2018; Phoenix, Arizona.
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