Supplemental online content for:

Germline and Somatic Mutations in Prostate Cancer for the Clinician

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**eTable 1. Key Terms and Definitions**

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<th>Term</th>
<th>Definition</th>
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<tr>
<td>Cascade testing</td>
<td>Genetic counseling and testing in blood relatives of individuals who have been identified with specific genetic mutations; may include screening, counseling, or referral for a patient with a relative who has tested positive for a genetic mutation.</td>
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<td>CTC</td>
<td>Circulating tumor cells. Tumor cells from the circulation (blood) that can be enumerated, measured, and/or evaluated.</td>
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<td>ctDNA</td>
<td>Circulating tumor DNA. Typically measured from cell-free DNA in the plasma.</td>
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<td>DDR</td>
<td>DNA damage response pathways. Includes homologous recombination, MMR, base excision repair, and others.</td>
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<td>dMMR</td>
<td>Deficiency in mismatch repair. Refers to the inability to use a mechanism of correcting errors in DNA by detecting and replacing bases in the DNA that are paired incorrectly (mismatched bases). dMMR in the tumor may be associated with susceptibility to treatments, such as immune checkpoint inhibitors.</td>
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<td>Genetic counseling</td>
<td>The evaluation and understanding of a family’s risk for an inherited medical condition. A genetic counselor is a healthcare professional with specialized training in medical genetics and counseling.</td>
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<tr>
<td>Genetic testing</td>
<td>Laboratory methods to evaluate DNA of an individual to identify increased risks of specific conditions (eg, cancer), select treatment, or determine response to treatment.</td>
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<td>Germline DNA</td>
<td>Constitutional DNA that is inherited from mother and father, present in nucleated cells of the body, such as lymphocytes, and may be passed on to children. Some genes may be shared with siblings.</td>
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<td>HRD</td>
<td>Homologous recombination deficiency. Refers to the inability to use a common mechanism of repairing harmful breaks that occur on both strands of DNA, known as doublestrand breaks, through genetic recombination. Examples: BRCA2, BRCA1, PALB2.</td>
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<td>MSI-H</td>
<td>Microsatellite instability. MSI-high refers to microsatellite instability, a measure of dMMR. Can result from defects in genes such as MLH1, MSH2, MSH6, or PMS2.</td>
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<td>NGS</td>
<td>Next-generation sequencing. High-throughput DNA sequencing technologies. Millions or billions of DNA strands can be sequenced in parallel to yield more throughput. Practically, this allows multiple genes to be tested at the same time in gene “panels.”</td>
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<td>Pathogenic variant</td>
<td>A genetic alteration that increases an individual’s susceptibility or predisposition to a certain disease or disorder (eg, prostate cancer). Development of prostate cancer is more likely, but not certain, when such a variant (or mutation) is inherited.</td>
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<td>Somatic DNA</td>
<td>Acquired mutations and genetic changes to the germline DNA. Often refers to tumor-associated genetic changes that are not heritable.</td>
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<td>VUS</td>
<td>Variant of uncertain significance. Typically refers to a genetic change in germline DNA where there is insufficient information available to know if it causes an increased susceptibility to cancer or not.</td>
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</table>

**Abbreviations:** CTC, circulating tumor cells; ctDNA, circulating tumor DNA; dMMR, mismatch repair deficiency; HRD, homologous recombination deficiency; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability–high; NGS, next-generation sequencing; VUS, variant of uncertain significance.
### eTable 2. Obtaining a Comprehensive Family History of Cancer

**Detailed family history includes:**
- Parents
- Children
- Siblings/Half siblings
- Grandparents and great-grandparents (specify maternal or paternal)
- Nieces and nephews
- Aunts and uncles (specify maternal or paternal)
- Cousins (specify maternal or paternal)
- Ethnicity/Country of origin
- Consanguinity

**Minimal data for each cancer-affected relative:**
- Current age and age at diagnosis (if not known exactly, decades can be helpful)
- Age at and cause of death (especially if cancer-related)
- Type of cancer (note multiple primaries)
- Results of any prior genetic testing

**Resources for collecting family history:**
- Cancer.net, [https://www.cancer.net/sites/cancer.net/files/cancer_family_history_questionnaire.pdf](https://www.cancer.net/sites/cancer.net/files/cancer_family_history_questionnaire.pdf)
- NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (see algorithm page HRS-A; available online at NCCN.org).

Abbreviation: CDC, Centers for Disease Control and Prevention.
Germline DNA is inherited from both biologic parents and is present in all cells in the body. It does not change over time, therefore repeat testing will typically be of limited value.

Somatic (tumor) DNA is comprised of germline genetic material with additional acquired mutations; however, somatic testing platforms may or may not report suspected germline mutations (pathogenic variants).

Tumor testing may suggest the need for, but should never replace, dedicated germline testing.

Tumor evolution over time means repeat somatic testing may be of value.

Germline testing can identify increased risk for heritable cancers.

Germline DNA may have therapeutic implications for some patients.

Tumor sequencing can be performed to find actionable mutations that may have therapeutic implications in advanced disease.

Germline mutation testing should be offered to patients with a family history of prostate other cancers, or those with a personal history of high- and very high-risk localized prostate cancer, regional, or metastatic disease.

All patients with pathogenic germline mutations should be referred to a genetic counselor.

When there is a strong family history, genetic counseling is recommended before genetic testing whenever possible.

If germline testing is negative or inconclusive (ie, there is no known cancer associated with the identified mutation) but there is a strong family history for cancers, referral to genetic counseling is indicated.

Variants of uncertain significance (VUS; including in BRCA1/2) should not be used for medical management.

Intraductal histology has a higher association with actionable tumor and germline mutations.

Genetic counselors can be found at https://www.nsgc.org/findageneticcounselor.

Carriers of the BRCA1/2 mutation are at increased risk of prostate cancer before age 65 years, and prostate cancer in men with germline BRCA2 mutations occurs earlier and is more likely to be associated with prostate cancer mortality.

Men with germline BRCA1/2 mutations may consider beginning shared decision-making about PSA screening at age 40 years and at annual intervals, factoring in age-adjusted median PSA values. Early detection clinical trials are recommended whenever possible.