CASE PRESENTATION

A 51-year-old man with a BRCA2+ p.Q3037* mutation presented for prostate cancer screening evaluation. He had no history of lower urinary tract symptoms, urinary tract infection, trauma, or prior urologic evaluation. He underwent a colonoscopy at age 50 that demonstrated a benign polyp. He had a skin lesion removed that was considered premalignant.

The patient’s father was diagnosed with breast cancer at age 79. His paternal grandmother was diagnosed with melanoma in her 50s and ultimately died from metastatic disease. In addition, his maternal grandmother and grandfather died from cancer, but their exact diagnoses were uncertain.

The patient’s father underwent genetic testing (GT) and was found to carry a BRCA2 mutation. The patient then underwent GT himself and was found to carry a BRCA2+ p.Q3037* mutation. He sought genetic counseling and based on the evaluation was referred for urologic evaluation.

The patient’s medical history was otherwise negative and he had no prior surgical history. He had no smoking history. He reported a baseline International Prostate Symptom Score (IPSS) of 1 and a Sexual Health Inventory for Men (SHIM) Questionnaire score of 25.

The patient’s past medical history was notable only for Parkinson’s disease, which was mild and well controlled with medication. His past surgical history included appendectomy at age 16.

EVALUATION AT NYU LANGONE HEALTH

Physical exam: On exam, the patient was found to be a normal, well-developed adult male. No inguinal, scrotal, or penal abnormalities were noted. Digital rectal examination (DRE) demonstrated a 25 cc prostate without evidence of nodules or induration. The remainder of the examination was normal.

Laboratory evaluation: Serum PSA was 0.77 ng/mL.

Radiographic evaluation: Despite a normal PSA and DRE, the patient was advised to undergo a multiparametric MRI (mpMRI) of the prostate, which demonstrated a 22.5 cc prostate and a PI-RADS 3 lesion measuring 5 mm x 4 mm in the right posteromedial midgland peripheral zone (Figure 1). No evidence of pathologic lymph nodes or osseous lesions was found.
**CASE OF THE MONTH**

**Tissue evaluation:** A transrectal ultrasound-guided prostate biopsy using MRI-US fusion biopsy was performed using the Artemis prostate biopsy device. A systematic 12-core template was combined with 4 targeted cores directed to the PI-RADS 3 lesion.

The biopsy demonstrated a single positive core from the left lateral mid sextant on systematic sampling. The targeted biopsy cores were negative for cancer.

The single core of cancer contained 1.8 mm of Gleason Grade Group (GGG) 2 prostate cancer. The percent of Gleason pattern 4 in the core was measured as 40%. No intraductal or cribriform features were noted. No perineural invasion was noted.

**Pretreatment predictors:** Based on the patient’s clinical features, his UCSF-CAPRA (Cancer of the Prostate Risk Assessment) score was 1 (low risk). His National Cancer Care Network (NCCN) risk categorization was favorable intermediate risk. Pre-prostatectomy nomograms predicted a 94% probability of organ confined disease, a 5% risk of extracapsular extension, and a 1% risk of either lymph node involvement or seminal vesicle invasion.

The consensus recommendation of our institutional tumor board was for the patient to undergo radical prostatectomy based on his young age, presence of any Gleason pattern 4 disease, and known genetic mutation.

**COMMENT**

Effective screening strategies for malignant cancer aim to reduce disease morbidity and mortality through early disease detection. Ideally, disease detection at an early stage increases the likelihood of curative treatment. Barring disease prevention strategies, such as reduction of environmental or behavioral risk factors, early detection is the best available opportunity for disease control. Depending on the organ system involved, screening methods vary considerably, ranging from routine physical examination to screening imaging and invasive procedures. Furthermore, screening protocols frequently evolve alongside advances in biochemical, radiologic, or tissue evaluation.

Prostate cancer is the second most common cancer diagnosed and the fifth leading cause of cancer-related death in men worldwide. Nevertheless, the value of a screening protocol derived from serum PSA measurement continues to undergo rigorous scrutiny. In an effort to reduce...
CASE OF THE MONTH

Overtreatment of low-risk disease, the use of active surveillance has increased. Improved disease risk stratification and adoption of active surveillance have allowed for the reinstatement of a Grade C recommendation for PSA screening by the U.S. Preventive Services Task Force (USPSTF).

Acknowledging the limitations of PSA screening, the American Urological Association (AUA) recommends shared decision-making on PSA testing for men ages 55 to 69 and individualized screening for men ages 40 to 54 at higher-than-average risk. Higher risk includes a family history of metastatic or lethal adenocarcinoma, including prostate as well as breast, ovarian, and pancreatic cancer. Consideration is also given to multiple generations of disease and to disease in multiple first-degree relatives and development of disease at younger ages.

The inclusion of family history in screening guidelines reflects the importance of germline genetic risk factors, both known and unknown, for development of prostate cancer. As GT becomes increasingly common, referrals for prostate cancer risk consultation based on germline mutations will also increase. Screening guidelines will also subsequently evolve.

Germline Mutations Associated with Prostate Cancer

Hereditary prostate cancer is associated with several germline mutations and is involved in an estimated 5% to 10% of prostate cancer diagnoses. These germline mutations appear to significantly increase the risk of developing cancer. In addition, the cancers associated with these mutations have potential to be more aggressive.

The genetic changes associated with these germline mutations generally fall into several categories of DNA repair genes. As a result of cellular activity, DNA is frequently damaged. This damage can take many forms, including single-strand breaks, double-strand breaks, base pair mismatches, base insertions/deletions, and base alkylation. For each form of DNA damage, a dedicated repair mechanism aims to correct the damage and preserve the genomic function.

Homologous Recombination Repair Genes

One mechanism of DNA repair occurs through homologous recombination repair (HRR). HRR repair is a critical step in normal cell division (mitosis) as well as in the fixing of double-strand breaks in DNA. The HRR mechanism operates during phases S and G2 of the cell cycle and requires multiple proteins encoded by numerous genes.

Mutations in these double-strand repair mechanisms are associated with increased risk of multiple malignancies. The pathophysiology in the alteration of this repair mechanism was initially described in Fanconi anemia. Studies of this disease have identified numerous genes that cooperate to achieve successful HRR. Alterations in the HRR pathway have been implicated in the BRCA1/BRCA2 and the partner and localizer of BRCA2 (PALB2) genes. These genetic alterations are relatively rare, and the BRCA2 alteration appears to be the most common mutation in this category.

DNAMismatch Repair Genes

DNA mismatch repair (MMR) mechanisms identify and repair aberrant bases (guanine/thymine or adenine/cytosine) that develop during DNA recombination and replication. The repair process entails identifying, removing, and replacing the incorrect base.

The autosomal dominant, hereditary colon cancer syndrome known as hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome is caused by an MMR deficiency. Lynch syndrome
results in microsatellite instability (MSI), which leads to genetic errors due to difficulties in repairing strands of DNA that contain microsatellites (repeating patterns of 2 to 3 nucleotides).\textsuperscript{10}

Mutations in numerous DNA MMR genes have been implicated in Lynch syndrome. Increases in prostate cancer risk, as well as in upper tract urothelial carcinoma, have been associated with Lynch syndrome. One study demonstrated a cumulative risk of prostate cancer of 6.3\% for men with Lynch syndrome vs. 2.6\% in the general population at age 60 years and 30\% vs. 17.8\% at age 80 years.\textsuperscript{11}

**Adjusting Clinical Strategy based on Germline Mutation Status**

*Implications for Prostate Cancer Screening*

As the use of GT increases, the number of men referred to urologists for prostate cancer risk consultation based on germline mutation will also increase. Given the recognition of the disease aggressiveness associated with these mutations, screening guidelines will need to evolve as well. Toward that end, a multidisciplinary working group was convened in Philadelphia in 2017 to provide guidance on approaches to GT.\textsuperscript{12} The Philadelphia Prostate Cancer Consensus Conference updated its recommendations in 2019.\textsuperscript{13}

Guidelines on screening for men with known germline mutations have recently begun to include GT recommendations. The current NCCN guidelines for prostate cancer recommend GT for the criteria noted in Table 1.\textsuperscript{6,14-16}

<table>
<thead>
<tr>
<th>Screening Recommendations</th>
<th>Criteria</th>
<th>Age</th>
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<tr>
<td><strong>National Comprehensive Cancer Network\textsuperscript{15}</strong></td>
<td>Known <em>BRCA1/2</em> mutation or family history of hereditary breast or ovarian cancer (HBOC)</td>
<td>45</td>
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<tr>
<td><strong>American Urological Association\textsuperscript{6}</strong></td>
<td>Family history of metastatic or lethal (prostate, breast, ovarian, pancreatic) cancer</td>
<td>40 to 54</td>
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<tr>
<td><strong>European Association of Urology\textsuperscript{16}</strong></td>
<td>Known <em>BRCA2</em> mutation</td>
<td>40</td>
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**Genetic Testing (NCCN guideline)\textsuperscript{14}**

- Ashkenazi Jewish ancestry
- Family history of high-risk germline mutations (e.g., HBOC, *BRCA1/2*, Lynch syndrome)
- Family history
  - Brother or father or multiple family members >GGG 1 prostate cancer diagnosed before age 60 or who died from metastatic prostate cancer
  - 3 or more cancers on the same side of the family with diagnoses before age 50 (e.g., bile duct, breast, colorectal, endometrial, gastric, kidney, melanoma, ovarian, pancreatic, prostate (>GGG 1), small bowel, or urothelial)
- Intraductal/cribriform histology

The NCCN recommends that men with a known *BRCA1/2* mutation or a family history of hereditary breast or ovarian cancer undergo screening starting at age 45. A biopsy is recommended for PSA above 3 ng/mL.\textsuperscript{15} The European Association of Urology’s most recent screening recommendations are for PSA screening for men with *BRCA2* mutations beginning at age 40.\textsuperscript{16}
IMPACT study initial results: Based on 3 years of biopsy data (study biopsy threshold: PSA of 3 ng/mL), the IMPACT Study—Identification of Men with a Genetic Predisposition to Prostate Cancer: Targeted Screening in BRCA1/2 Carriers and Controls (ClinicalTrials.gov NCT00261456) has demonstrated a higher rate of cancer detection, an earlier age of detection, and a higher likelihood of significant disease in BRCA2 mutation carriers vs. controls (77% vs. 40%, p=.01). To date, this study has not found similar differences for BRCA1 mutation carriers.

These results underscore the need for further refinement of screening strategies for men with germline mutations, especially BRCA2. The role of mpMRI in assisting in screening this population is under investigation (ClinicalTrials.gov NCT01990521, NCT03805919).

Implications for Prostate Cancer Treatment

Several studies report increased aggressiveness of prostate cancer associated with germline mutations. This appears to be most significant for BRCA2 mutation carriers. As a result, these considerations may limit the role of active surveillance in this population.

A novel treatment approach for men with BRCA mutations exploits the deficiencies in HRR associated with these mutations. The poly[adenosine diphosphate-ribose] polymerase-1 (PARP1) inhibitors prevent DNA damage from proceeding to the deficient HRR mechanism by inhibiting single-strand repair mechanisms such as base excision repair. This allows other mechanisms of DNA repair to identify and ameliorate the damaged DNA before allowing the deficient HRR pathway to take effect. This strategy has been shown to induce cell death via “synthetic lethality” and has shown promise, along with platinum-based chemotherapy, for men with metastatic BRCA disease. One PARP1 inhibitor, olaparib, has been approved for use in men with metastatic castrate-resistant prostate cancer and a BRCA mutation based on the demonstration of an 88% response rate for men with BRCA mutations vs. 6% for men without BRCA mutations. Similarly, platinum-based chemotherapy appears to improve outcomes for BRCA mutation carriers, possibly owing to the increase in DNA damage associated with these chemotherapy regimens.

For tumors with MMR deficiencies, PD-1 inhibitors may offer an additional novel treatment option. Somatic tumor testing of MMR can be assessed through DNA evaluation for MSI or through immunohistochemistry of MMR proteins in the tumor. The FDA has approved the use of pembrolizumab for tumors demonstrating MMR deficiency, and a few case series have demonstrated evidence of durable response for men with metastatic castrate-resistant prostate cancer and MSI-high features.

CONCLUSION

Referral of men for prostate cancer risk evaluation based on the results of GT poses a clinical scenario that challenges existing guidelines on prostate cancer screening. Given the severity of disease associated with germline mutations such as BRCA2, screening for prostate cancer in this population is recommended. The role of mpMRI in screening men with genetic mutations, normal PSA levels and benign DRE remains controversial. In addition, identification of DNA repair mutations in men with prostate cancer may affect treatment choices such as active surveillance as well as treatment options for metastatic disease. It is critical that urologists become engaged in identifying men in need of GT as well as in the evolving management of those referred with positive GT results.
REFERENCES


CASE OF THE MONTH

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James S. Wysock, MD, is assistant professor of urology at NYU Grossman School of Medicine and has a clinical practice focused on urologic oncology. In addition, he is chief of Urology at NYC Health + Hospitals/ Bellevue. He obtained his medical degree from Northwestern University Feinberg School of Medicine and completed his residency training at New York-Presbyterian/Weill Cornell Medical Center. Dr. Wysock's clinical and research efforts center on providing advanced diagnostic and treatment strategies across the breadth of urologic malignancies. He has extensive experience in image-guided prostate cancer management (MRI/US fusion prostate biopsy, transperineal prostate biopsy, and prostate ablation) as well as in robotic surgical techniques and management of multidisciplinary oncology practice teams.
Department of Urology

Our renowned urologic specialists have pioneered numerous advances in the surgical and pharmacological treatment of urologic disease.

_For questions and/or patient referrals, please contact us by phone or by e-mail._

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