

PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

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When to Use Somatic Tumor Testing in Prostate Cancer



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H&O Which patients with prostate cancer are eligible for somatic tumor testing?

TF To begin with, we should be clear about some definitions. Somatic tumor testing refers to testing the DNA or other genetic material of tumor tissue as opposed to patient's healthy germline tissue. When we talk about *genetic* testing, we generally refer to testing the DNA of a cell to look for genetic mutations. When we talk about *genomic* testing, however, we are looking at other genetic material (RNA, for example) inside the cell. Each of these types of testing have different uses in prostate cancer.

All patients with metastatic prostate cancer are eligible for somatic tumor genetic (DNA) testing to look for mutations in the cancer that may be targetable with therapies, and we should be doing it in all these patients. When it comes to localized disease, somatic tumor genomic testing using approved genomic panels is indicated for men who have intermediate-risk prostate cancer in order to help determine the risk for relapse.

H&O What are the goals of somatic tumor testing in these patient groups?

TF In metastatic prostate cancer, we generally order a broad genetic panel to see which genes are mutated in specific person's cancer. The goal is to find out what agents are most likely to be effective in that patient. For example, a patient with a *BRCA1*, *BRCA2*, or *ATM* mutation is eligible for treatment with a poly(ADP-ribose) polymerase (PARP) inhibitor, such as olaparib (Lynparza, AstraZeneca) or rucaparib (Rubraca, Clovis Oncology). Other mutations in the homologous recombination repair

pathway may make tumors sensitive to PARP inhibition.

A drug called ipasertib that inhibits the AKT gene, which is involved in the PTEN/PI3K/AKT pathway, is being studied to see if it can help patients with deletions of the *PTEN* gene in their tumor. When I have a patient with a *PTEN* mutation, I often consider enrolling him in a clinical trial using an AKT inhibitor or another agent that specifically targets this pathway.

Although it is possible to find *NTRK* fusions in patients with metastatic prostate cancer, this rarely occurs and not all panels will pick it up. If it occurs, however, we have the drug larotrectinib (Vitrakvi, Bayer) approved to target this mutation. This agent is part of a trend toward tumor-agnostic drugs, in which the mutation is more important than the type of cancer. When agents are not approved for the type of cancer we are treating, we can often prescribe them through an expanded access program.

If the patient's tumor is microsatellite instability–high (MSI-high) or mismatch repair–deficient (dMMR), or if it has a high tumor mutational burden (TMB)—generally defined as more than 10 mutations per megabase—it is more likely to respond to immunotherapy agents such as pembrolizumab (Keytruda, Merck) than tumors without these characteristics. Like larotrectinib, pembrolizumab is an example of an agent that is approved for patients with specific tumor characteristics such as MSI-high or high TMB, regardless of cancer type.

The presence of mutations in or deletions of the tumor suppressor genes *PTEN*, *RBI*, or *TP53* does not generally affect treatment, in the sense that there is no specific drug that restores the function of these genes, but it does point to a worse overall prognosis.

In the localized setting, somatic tumor genomic testing can be used to determine whether a man is able to safely choose active surveillance over definitive therapy such as surgery or radiation. This type of testing quantifies the amount of specific RNA transcripts inside a cell, which is also known as “expression profiling.” Somatic tumor genomic testing provides more information about risk than we can obtain from microscopic tumor analysis and prostate-specific antigen (PSA) testing alone. We know that a patient needs surgery or radiation if his cancer is very aggressive under the microscope or the PSA level is greater than 10 ng/mL, and genomic testing using these approved panels is unlikely to influence this decision. If the patient has the lowest grade of prostate cancer and the PSA level is less than 10 ng/mL, the best option is usually active surveillance. As a result, the place where tumor genomic testing really makes a difference is in men whose tumors are categorized as intermediate risk. These risk groups are well defined by the National Comprehensive Cancer Network (NCCN) and other groups.

H&O What tests are in use?

TF Multiple tests are available in the metastatic setting. The most commonly used genetic test to profile DNA mutations and other DNA aberrations is FoundationOne CDx from Foundation Medicine; other tests are available from Caris and Invitae. In addition, many major academic sites have their own platforms. Here at the University of California, San Francisco (UCSF), we have the UCSF 500 Cancer Gene Panel test (UCSF500). Memorial Sloan Kettering Cancer Center has a 468-gene oncopanel called MSK-IMPACT that is widely used, especially on the East Coast.

I generally use the UCSF500 test because it is based at my institution and therefore is the most convenient for me. The UCSF500 also has the advantage of testing for germline mutations as well as tumor mutations, which allows us to remove those germline variants from the results. Getting the germline results also allows us to refer family members for testing if an inherited mutation is found; as many as 1 in 7 patients with prostate cancer have a germline mutation. Patients with certain germline mutations may also need additional screening for other cancers besides prostate cancer.

Several proprietary tests are available for somatic tumor genomic testing in localized prostate cancer: Decipher Biopsy from GenomeDx, Prolaris Biopsy from Myriad Genetics, Oncotype DX from Genomic Health, and ProMark from Metamark. We are working on an additional test at UCSF called GEMCaP.

H&O How often is somatic tumor testing used?

TF Somatic tumor genomic testing is used very frequently in the localized setting for men with intermediate-risk prostate cancer, as recommended in the NCCN guidelines.

I always discuss somatic tumor genetic testing in my initial visit with patients who have metastatic disease, even though the benefits of somatic tumor genetic testing are less immediately clear in the metastatic setting than the benefits of using the approved genomic panels to determine risk in a man with localized, intermediate-risk disease confined to the prostate. Because the standard treatment for men with metastatic prostate cancer is androgen deprivation therapy (ADT) and we have no evidence to suggest that early genetic testing will affect the decision to use ADT, tumor genetic testing is unlikely to change first-line treatment of these men. Tumor genetic testing can be useful for prognosis in these patients, however—for example, a change in *PTEN*, *RBI*, or *TP53* augurs a worse prognosis. It can also offer information that can help us to plan and start lining up which treatment to use after ADT stops working. One shortcoming of this approach is that after ADT stops working and the cancer starts growing again, it may pick up new mutations. So if we test before beginning ADT in 2022 but need to start second-line treatment in 2027, the genetic testing we did earlier may no longer tell the full story. Should we rely on 5-year-old genetic findings, or should we biopsy a growing metastasis to get a more accurate and up-to-date genetic picture?

In addition, the number of genes that these panels can sequence has been growing. Early gene panel tests sequenced 60 genes, later ones sequenced 300 genes, and the UCSF500 test sequences the full coding region of more than 500 cancer genes. In 5, 10, or 20 years, we may be able to reliably sequence and interpret the whole genome. It may therefore be reasonable to wait until we need the information; it would also be reasonable to test more than once as the cancer evolves over time.

The ASCO Provisional Clinical Opinion from the American Society of Clinical Oncology says that oncologists should strongly consider genetic testing of nearly all our patients with metastatic prostate cancer. Many oncologists are already doing this, and I think that the Clinical Opinion will encourage even more oncologists to follow suit. As the science evolves, ASCO will be able to provide more granularity regarding such issues as the use of tissue vs circulating tumor DNA (ctDNA), how frequently to conduct testing, and how the answers to these questions vary depending on tumor type.

H&O What treatment options are available for patients who have tumor mutations that do not have targeted therapies available?

TF It is a tough situation when the genetic report shows mutations in multiple genes but none of them are targetable. Even if we had an agent that targeted a specific mutation, it might simply be a passenger mutation and not a driver of the cancer. There is no easy way to distinguish between passenger and driver mutations in the metastatic setting, so practitioners are often left to guess.

One approach we use at UCSF is to present the case at our Genetic Molecular Tumor Board, which consists of oncologists, geneticists, pathologists, and other medical staff with expertise in genetic analysis. If one oncologist is unclear about how to treat a specific patient based on the result of genetic testing, other practitioners on the Board can make their recommendations. We always follow up afterwards to see how the patient is doing based on the recommended treatment approach.

H&O What tissue is best for somatic tumor testing in prostate cancer?

TF The gold standard is to obtain tissue from the actual prostate tumor, either from the original surgery or from a needle biopsy of a metastatic lesion. The downside of this approach is that getting biopsies of metastatic disease is not easy—it is painful and costly, and carries a risk of bleeding, infection, and damage to nearby organs. In one-third of cases, men with metastatic prostate cancer have metastases to the bone only, and sampling bone from the vertebrae or pelvis is even more difficult than sampling it from the liver, lung, or lymph nodes. In addition, metastases can trigger scarring of the bone to the point that the tumor contains very little cancer DNA for analysis.

These disadvantages of tissue testing in prostate cancer make liquid biopsy an especially attractive option. Conducting the genetic profiling using intact cancer cells from circulating blood comes with its own problems, however. One disadvantage is that circulating tumor cells (CTCs) are rare and can represent a very small fraction of all the circulating cells. As a result, we may only get 1000 or 1500 cells to analyze, which is a very low number to use when performing comprehensive genetic testing. In addition, testing of CTCs produces a high rate of false-positive and false-negative results.

That said, an important study by Antonarakis and colleagues showed that analysis of specific features of CTCs could identify men who were less likely to respond to next-generation hormonal agents such as abiraterone acetate and enzalutamide (Xtandi, Astellas), and should be prioritized for chemotherapy or other nonhormonal treatments. Although this test is ordered infrequently because many providers and patients want to try next-generation

hormonal therapy regardless of the test results, it nonetheless represents a use for CTCs in prostate cancer.

We can potentially get more accurate results by searching for ctDNA, which is tumor DNA shed directly into the circulation. A challenge with this approach is that 99.9% of the DNA in the sample may be from normal tissue, and only 0.1% from cancerous tissue. Rather than trying to profile all the ctDNA, we can search for specific targets, such as *BRCA* mutations. This may not be a practical approach for getting a full picture of all the mutations that are present in the tumors, however.

Another potential use of ctDNA, which has been looked at in several studies, is as a biomarker of response to treatment. If the ctDNA volume decreases, this may be a sign that the tumor is responding. If the volume increases, it could be a sign that the treatment is not working. Early results from the IMvigor011 study, which Dr Thomas Powles presented at the 2021 annual meeting of the European Society for Medical Oncology (ESMO), showed that the use of a genetic assay by Natera called Signatera was able to predict which patients with urothelial cancer would relapse after immunotherapy, based on the presence or absence of measurable residual disease. A similar study by Christensen and colleagues also showed that monitoring of tumor-specific mutations after removal of the bladder can predict when patients will relapse, in that patients in whom ctDNA remains undetectable after definitive surgery are unlikely to relapse. We need further studies to determine whether detection of measurable residual disease could replace computed tomography to detect recurrence.

Disclosure

Dr Friedlander has received research support from Roche Genentech, Seagen, BMS, and Trishula Therapeutics; and honoraria from Astellas, AstraZeneca, EMD Serono, and Gilead.

Suggested Readings

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