HOW TO GET IN FRONT OF PROSTATE CANCER

Learning about patients' experience on therapy informs scientists' use of ADVANCED DIAGNOSTIC TECHNIQUES, DESIGN OF CLINICAL TRIALS, AND EVALUATION OF BIOMARKERS.

Preventing or delaying prostate cancer from metastasizing may determine whether a patient lives or dies. One of the issues is that once prostate cancer is metastatic, it can rapidly gain resistance to many treatments. "So, one goal for us is to continue to find real treatment options for people who progress on available therapies," says prostate cancer expert and medical oncologist Margaret Yu, vice president, disease area leader, prostate cancer, at the Janssen Pharmaceutical Companies of Johnson & Johnson (Janssen).

Rather than considering only overall survival, the field is turning to patient-centric outcomes, such as metastatic-free survival (MFS). Keeping the disease local gives patients more options. "When the disease is caught early, we think about developing treatments that help maintain the person's quality of life," Yu says.

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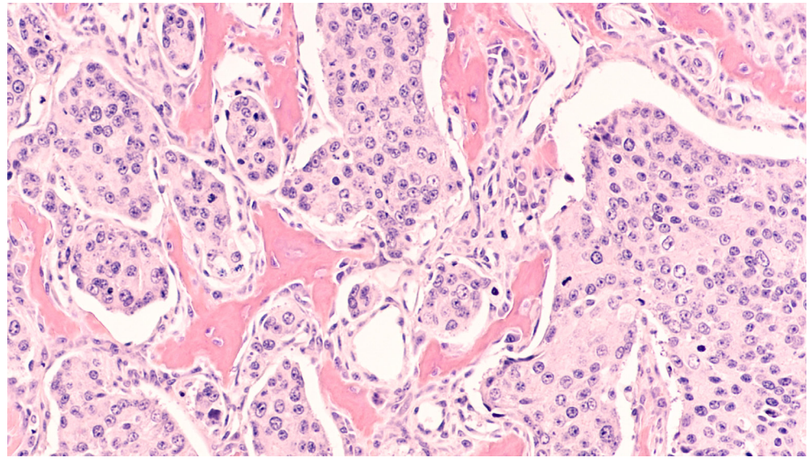
Improving outcomes for people with prostate cancer, therefore, requires developments on several fronts:



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▲ **Once prostate cancer has metastasized (here shown invading bone) it is much harder to treat**

a better understanding of the biology behind the progression of the disease, and a broader view of what treatment success looks like. For Janssen, when using existing treatments and in the creation of new ones, this involves focusing on the patient. Janssen's scientists are testing their new investigational products using innovative clinical trials that explore new biomarkers, some created through artificial intelligence (AI), as well as incorporating more advanced forms of imaging in clinical trials.

TARGETING TESTOSTERONE

In 1941, University of Chicago surgeons, Charles Huggins and Clarence Hodges, developed what remains one of the most common prostate cancer treatments, androgen deprivation therapy (ADT), which is used for treatment of both local and metastatic disease. ADT can be performed surgically by removing the testicles, or chemically by pharmacologically reducing production of testosterone. "When people get ADT as the first treatment for prostate cancer, 30–40% have a very deep response," Yu says. "The rest have a limited duration of response, and some don't really respond at all."

To improve outcomes, physicians often combine different types of therapies. For about 50 years, scientists have known "when you add ADT to radiation therapy, patients live longer than with ADT alone", Yu says.

At some point, a patient's disease can grow resistant to ADT. "Castration-resistant (also referred to as hormone resistant) prostate cancer remains a clear challenge," says medical oncologist Emiliano Calvo, director of clinical research at START Madrid in Spain. For these patients, oncologists can try an androgen receptor inhibitor (ARI). "ADT reminds me of a dripping faucet, because there are still some hormones like testosterone being made by the tumour. We have clinical evidence that treating prostate cancer with ADT alone is no longer enough," Yu explains. "With today's ARIs, there's so little testosterone in the blood that you have to use very sensitive methods like mass spectrometry to find it."

Still, if someone develops hormone-resistant disease, "that's a whole other set of challenges", says urologist Neal Shore, medical director of the Carolina Urologic Research Center in South Carolina. "What becomes important is the appropriate sequencing of therapies throughout the course of the patient's prostate cancer journey." Managing this journey requires understanding the therapies that can help prolong survival, while minimizing complications and optimizing quality of life. "You absolutely have to personalize the treatment journey," he adds. "Which is why the treatment for patients with prostate cancer has become very complex and sophisticated."

NOVEL TARGETS AND TARGETING STRATEGIES

Learning more about the biology of prostate cancer reveals potential targets for treatments that don't directly involve hormones like testosterone. One such approach is to target the interactions between androgen receptor signalling and other molecular pathways involved in both tumour pathogenesis and treatment resistance. This could lead to treatments that target molecular defects in prostate cancer. For example, around 15–20% of patients with prostate cancer lack the tumour-suppressor gene PTEN, which result in disease that is difficult to treat. PTEN serves largely as a biomarker of prostate cancer, but preclinical research proposes potential PTEN-based treatments, such as gene therapy, to restore the nonfunctioning gene.

Another potential target is PARP-1, which has a role in DNA repair. Patients lacking PTEN might rely on PARP for DNA repair; PARP inhibitors could therefore block the ability of prostate cancer cells to repair their DNA, causing them to die. Studies already show the benefits of PARP inhibitors in breast, ovarian and pancreatic cancers, and multiple clinical studies are evaluating when to use them in prostate cancer.

Several other, next-generation treatment approaches are in early development. Janssen is targeting prostate lineage antigens, using techniques such as chimeric antigen receptor therapy (CAR-T), bispecific antibodies, radio conjugates, antibody-drug conjugates and vaccines, as well as investigating combination approaches with surgery and external beam radiation therapy.

PATIENT-CENTRIC CLINICAL TRIALS

To reach as many people as possible, clinical trials must also evolve to be more inclusive. As noted by the US Food and Drug Administration (FDA): "Ensuring people from diverse backgrounds join clinical trials is key to advancing health equity."

Shore, who with his colleagues has worked on about 400 clinical trials, agrees. "One of the things that's of paramount importance is making sure we have a diverse population entering trials," he says. "Enrolling a diverse population enables the investigation of treatment safety and efficacy for different racial or ethnic groups."

Janssen also strives to expand the diversity of patients in its clinical trials. "You really have to be very intentional to do that, because you can't open clinical trials in places that may be challenging to access for some patients," Yu says. Janssen uses demographic data to select clinical-trial sites in areas with highly diverse populations, to improve its ability to recruit patients from different ethnic and cultural backgrounds.

In running those trials, Janssen scientists also explore new endpoints that provide more insight into a patient's disease. Traditionally, prostate specific antigen (PSA) has served as the key biomarker in this cancer. The course of a prostate tumour and PSA, however, do not always correlate. As Yu says, "PSA is not always a reliable measurement for benefit or progression in patients on treatment, because one value is just a snapshot in time and can change quickly when used to monitor disease progression."

So Yu and her colleagues develop clinical trials to incorporate longitudinal changes in PSA with MFS and progression free survival (PFS) endpoints. In patients with nonmetastatic castration-resistant prostate cancer, a long time to MFS indicates how long a patient's disease will remain contained on treatment. The FDA has even developed guidelines for using MFS as an endpoint in such trials, noting that it "would be useful in assessing the treatment effect of products in patients with nonmetastatic castration resistant prostate cancer". MFS does not, however, account for patients who experience a rise in PSA, which often occurs before metastatic disease and is indicative of inadequate disease control. "PSA monitoring is an important

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▲ **1. Who might benefit from radiation therapy can be determined with the help of artificial intelligence**
2. Diversity in clinical trials is key to ensuring new treatments work for more people

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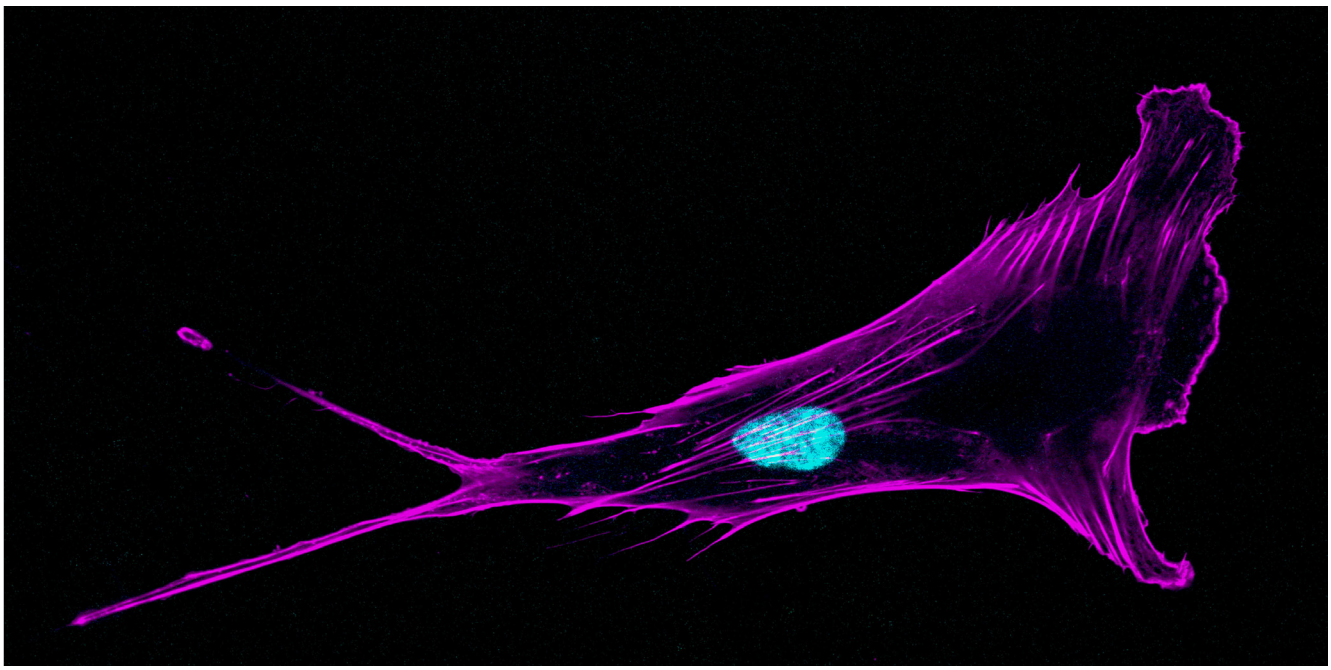

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▲ **A metastatic prostate cancer cell can easily invade other tissues, causing the disease to spread**

component of the patient journey, and it's something that physicians and patients pay close attention to," says Yu. "It's important that we account for this information in clinical trial endpoints."

ADDING AI-BASED BIOMARKERS

Applying AI might also reveal other information to describe the progression of a patient's disease. In February 2022, the American Society of Clinical Oncology's Genitourinary Cancers Symposium (ASCO GU) included an AI session.

At that meeting, radiation oncologist Daniel Spratt, of the University Hospitals Seidman Cancer Center in Ohio, presented findings on an AI-derived digital pathology-based biomarker for localized prostate cancer. Spratt and his colleagues digitized tumour biopsy slides from patients with localized cancer. Then they used the clinical and imaging data to train multimodal deep-learning AI to identify features that might predict the likelihood of metastasis. Spratt explained that a lot of this information is "nonhuman interpretable data" — information that only computers can differentiate. He showed that this AI-based tool can help determine which patients might benefit from radiation therapy with or without ADT. From the results of this work, Spratt described this tool as "the first predictive biomarker" to help oncologists determine who benefits the most from the use of hormone therapy with radiation therapy for people with localized prostate cancer.

Other scientists also use AI to predict the likelihood of prostate cancer progression from local to metastatic. A team led by computational pathologist Wouter Bulten, of the Radboud University Medical Centre, in the Netherlands, set a challenge to encourage the development of new AI-based algorithms. The aim was to categorize prostate cancer by Gleason gradings, which predict a disease's potential for spreading. From algorithms produced by 1,290 developers, Bulten and his colleagues concluded: "Successful generalization across different patient populations, laboratories and reference standards, achieved by a variety of algorithmic approaches, warrants evaluating AI-based Gleason grading in prospective clinical trials."

IMAGING FOR BETTER OUTCOMES

To manage a patient's health care more effectively, physicians need better tools to assess the impact of an ongoing therapy quickly. "You need to see some kind of change in the prostate cancer to distinguish between a clear response to a treatment or progression of the disease," Yu says

Tracking the state of a patient's disease more accurately would allow the treating physician to make better decisions. One way to do that is with prostate-specific membrane antigen (PSMA) PET imaging. "With PSMA PET," Yu says, "you can really see metastatic disease much earlier than with a CT, MRI or a technetium 99-bone scan." As a result, she notes that "the bar is even changing for who is metastatic and who isn't". Although Yu points out that PSMA PET has been used for nearly a decade in some countries, "the uptake and access has been much slower in the US".

The increasing focus on keeping a patient's prostate cancer from metastasizing leads to longer and better lives, but there's more work to be done. As Yu says, "Our mission is to cure prostate cancer, which is not easy, but we'll get there by focusing on getting in front of the disease." ■