



# Informed Prostate Cancer Support Group Inc.

"A 501 C 3 CORPORATION ID # 54-2141691"



Saturday, April 16, 2022

## APRIL 2022 NEWSLETTER

P.O. Box 420142 San Diego, CA 92142

Phone: 619-890-8447 Web: <http://ipcs.org>



Volume 15 Issue 04

- **Next Meeting Saturday, April 16, 2022 IPCSG - Live-Stream Event, 10:00am PT.**
- **Dr. Richard Lam MD, Prostate Oncology Specialists 2022 Update on Prostate Cancer**  
A double board-certified internist and oncologist, Richard Lam, MD, has been specializing full time at Prostate Oncology Specialists in the treatment of prostate cancer since 2001. Dr. Lam will be discussing the latest news about Prostate Cancer, treatments and clinical trials. As always, his presentations will be very informative and presented in an easily understood format. He also brings a great wit with a touch of humor..
- Due to COVID-19, no in-person meetings at the Sanford Burnham Prebys Medical Discovery Institute will take place until further notice. This meeting will be live-streamed and will also be available on DVD.
- **For further Reading:** <https://ipcs.org.blogspot.com/>
- **For Comments, Ideas and Questions,** email to [Newsletter@ipcs.org](mailto:Newsletter@ipcs.org)
- **If you would like some copies of our new brochure by mail for distribution to your friends or physicians, please send email to [Newsletter@ipcs.org](mailto:Newsletter@ipcs.org) or call Gene at 619-890-8447**

## March 2022 Informed Prostate Cancer Support Group Meeting Summary by Bill Lewis

### Roundtable: Member Experiences

Speakers:

1. Mike Rogers - 17 year survivor
2. Keith Jameson - 4 year survivor
3. Bob Cruikshank - 18 year survivor

**Mike Rogers** had an elevated PSA in 2002 but was told it was BPH (enlarged prostate, a normally benign condition). A biopsy showed no cancer. He was put on Proscar (finasteride) until 2005, and then his PSA jumped from 5 to 15 in six months. Radiation was not recommended, but robotic surgery on the East Coast was said to be what he needed. By the time of the surgery, his PSA was 25. The surgeon did not take any lymph nodes (a giant mistake), saying that they were "nice and pink and rosy." The pathology report showed Gleason 3+4. When his PSA started to rise again, he went to Kansas City for a C-11 acetate scan to find where the cancer was. Radiation and Casodex (bicalutamide) brought his PSA to near-negligible, but after a couple of years it rose back to 4. Another C-11 scan and more spot radiation brought it down again – and, later, a third time. He used the Casodex intermittently through this period. After constant Casodex use was recommended, it eventually quit working and he is now on Xtandi (enzalutamide). His PSA has gone down from 13 to 3. He has "all the side effects" except seizure

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**Prostate Cancer: GET THE FACTS**

Other than skin cancer, prostate cancer is the most common cancer in American men.

**1 in 6**   
men will be diagnosed with prostate cancer during his lifetime.



Prostate cancer can be a serious disease, but most men diagnosed with prostate cancer do not die from it. In fact, more than 2.5 million men in the United States who have been diagnosed with prostate cancer at some point are still alive today.

**Organization**

a 501c3 non-profit organization - all positions are performed gratis



**Officers**

Bill Lewis President

**Additional Directors**

Gene Van Vleet

Aaron Lamb

Bill Manning

**Honorary Directors**

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Aaron Lamb, ..... Facilitator

Bill Manning, ..... Videographer

John Tassi, ..... Webmaster

Bill Bailey, ..... Librarian

Jim Kilduff, ..... Greeter

Aaron Lamb, ..... Meeting Set-up

Stephen Pendergast ..... Editor

**NEWSLETTER**

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**PROSTATE CANCER—2 WORDS, NOT A SENTENCE**

**What We Are About**

Our Group offers the complete spectrum of information on prevention and treatment. We provide a forum where you can get all your questions answered in one place by men that have lived through the experience. Prostate cancer is very personal. Our goal is to make you more aware of your options before you begin a treatment that has serious side effects that were not properly explained. Impotence, incontinence, and a high rate of recurrence are very common side effects and may be for life. Men who are newly diagnosed with PCa are often overwhelmed by the frightening magnitude of their condition. Networking with our members will help identify what options are best suited for your life style.

**Meeting Video DVD's**

DVD's of our meetings are available for purchase on our website at <https://ipcs.org/purchase-dvds> and are generally available by the next meeting date.

**Join the IPCSG TEAM**

If you consider the IPCSG to be valuable in your cancer journey, realize that we need people to step up and HELP. Call **President** Bill Lewis @ (619) 591-8670 ; or **Director** Gene Van Vleet @ 619-890-8447.

**From the Editor**

Due to COVID-19, no in-person meetings will be held until further notice. We will continue to post and distribute the newsletter in the interim. Our speaker this month will be broadcast via the IPCSG website at <https://ipcs.org/live-stream> and can be watched by scrolling down and clicking on the "WATCH THE PRESENTATION" button. The broadcast will begin approximately 10 minutes before to the listed start time.

**In this issue:**

Bill Lewis produced a summary of the last stream video, .

**Articles of Interest:**

1. \$150K Prostate Cancer Drug Draws New Attention to 'March-In' Rights — Advocates want Biden administration to enable Xtandi generics; industry warns against it
2. New FDA approval renews hope for advanced prostate cancer patients— Lutetium ready to grab and zap cancer cells
3. Personalized Medicine in Localized Prostate Cancer: Are We There Yet? - not yet but we're close.
4. Yes, Nodal Recurrence of Prostate Cancer is Potentially Curable—modern imaging and targeting radiation can zap it.
5. Cause of metastasis in prostate cancer discovered: MedUni Vienna study generates new momentum for diagnosis and treatment— Austrians may have solved mystery of why cancer spreads in the body. If so, existing medications may convert cancer to a chronic rather than fatal disease.

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and stroke, but overall, it's tolerable. He hopes never to have to take Lupron, anticipating that he would get all its side effects. He recommends getting the best supplement plan available if on Medicare, as that saved him a lot of money and allowed him to go to any doctor he chose. He also strongly recommends exercise for any prostate cancer patient. There are programs to help pay for Xtandi, so instead of \$14,000 per month, he paid \$3,000 the first month and \$700 per month thereafter. The IPCSG has been a huge benefit in his journey.

**Keith Jameson's** family background: His father was diagnosed with prostate cancer (PCa) at 52, and had hormone therapy for six years, but was getting blood clots as a side effect. Discontinuing the therapy led to rapid growth and spread, and he died two years later. Due to this family history, Keith went for a prostate checkup at his HMO -- but after a minimal check, the doctor told him to come back when he was 50. Procrastination extended this to age 54. Then his father-in-law, initially misdiagnosed, went to Scripps and was found to have pancreatic cancer. He died three weeks later. This prompted Keith to get that postponed PSA test. His first PSA was 4.7, and the biopsy had 3 of twelve cores positive with PCa of grades 6, 6 and 7 (4+3). He immediately searched on the internet, and found the IPCSG. He got very helpful information from Gene VanVleet, followed by attending meetings and reading information. Helpful books were the Key to Prostate Cancer (Dr. Mark Scholz), which indicated that Gleason 4+3 often metastasizes. A Guide to Surviving Prostate Cancer by Dr. Patrick Walsh, who pioneered nerve-sparing surgery, was helpful in pointing out that the prostate is expendable. He went to the Mayo Clinic and they said that with his family history, there would be a definite chance of recurrence if he chose focal therapy. He chose surgery there. At the time, they were doing a clinical trial of sprinkling the patient's own platelets in the wound area (obtained from a small amount of blood collected just before the surgery), and that seemed to hasten his recovery. He used Viagra for a few months as recommended, but then was able to discontinue. The PSA went to 0.01 and has since crept up to 0.07 and now 0.1. He slacked off on diet changes and exercise but is going back to them.

His brothers have also been diagnosed with PCa: one at age 63 (Gleason 6; active surveillance), two brothers with PSA's below 3.5 and his youngest brother was diagnosed at age 49 (got surgery at Johns Hopkins, has negligible PSA).

Member suggestions: Watch the testosterone level in addition to the PSA. As soon as practicable, get a PSMA scan to know where there is recurrence.

**Bob Cruikshank** had a PSA of only 2.2 in 2004 (age 55), but the DRE (digital rectal exam) indicated irregularities. A "random" biopsy found Gleason 3+4 PCa in 10 of the 12 cores. Diet and exercise pushed his PSA down to 1.4. In 2005, a targeted biopsy also gave Gleason 3+4, and the stage was T3c (ie, outside the prostate). He had ADT (hormone therapy) for 28 months, but no radiation due to a perceived lack of expertise in the San Diego area. He went off ADT, then another biopsy gave Gleason 4+4, so in 2008 he had ADT again for six months, then 39 days IMRT (intensity-modulated radiation therapy) with Dr. Mundt, a new expert at UCSD. The PSA was 0.2-0.3 for 11 years, but then rose to 0.75 in 2020. So, he recently had an MRI and targeted biopsy, and is waiting for the results. Then he expects to get a PSMA scan to find if the cancer has remained in the prostate area.

Member suggestion: Consider genetic testing.

Questions:

Cost of Medicare supplement plan? Bob chose plan F, which is no longer available. He's coming up on 84, and the cost will be \$480 per month. Best now is "G." Two advisors (no charge) are Patricia DeLeo, 858-231-6025 and Doug Kerr, 760-473-7721.

For comments about Kaiser vs. other options, see the video.

When do you take action when PSA starts to rise? See last month's talk by Dr. Metzger and also the October 2019 talk by Phranq Tamburri. Each is summarized in the following month's IPCSG newsletter.

Charles asked about BAT (bipolar androgen therapy). For info, see the internet or call Bill Lewis, 619-591-8670.

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His PSA was 1300. Firmagon (degarelix) dropped his PSA to 800 in ten days so far. Seeing doctors at Cedars and at UCLA (he lives in Santa Monica). It was noted to him that Dr. Rana McKay at UCSD may be doing a trial on bone metastases.

What PSA should one expect after radiation only? It may drift down over a period of months or even years because the radiation damages the cancer DNA, preventing it from replicating, and leading to cell death over time. As to ADT before, during and/or after radiation, see last month's talk in which Dr. Metzger said "Neoadjuvant use of antiandrogens means using them prior and during radiation treatment. Adjuvant use is during and after treatment. The gold standard was before and after, but now is during and after. This is a game changer for radiation patients."

Best doctors/teams in San Diego? UCSD and Scripps were most recommended.

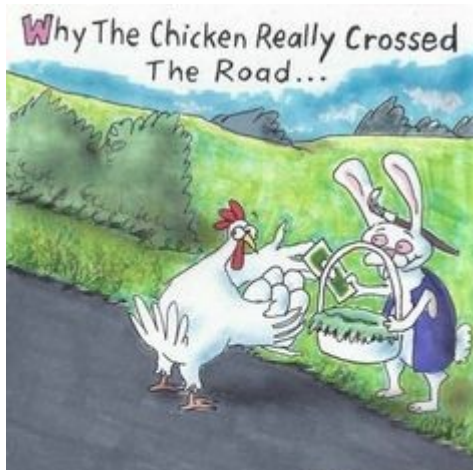
Has anyone in the group "waited too long" in taking action, and had negative consequences? Aaron Lamb shared his experience. It was also recommended that the patient get to a medical oncologist, and look into getting imaging.

What about diet and exercise? Aaron and others avoid red meat, refined sugar, dairy, many eggs. Good: fruits and vegetables. Hoppy beer (common in San Diego) is bad for PCa. Exercise is very helpful (extends life after diagnosis by 2X on average). Dr. Gordon Sacks at UCSD is a proponent of good diet. He is in the integrative medicine department. Do what you need to, to maintain a happy life. The Mediterranean diet is good, the vegan diet is more strict, and going beyond that is possible (ask Bill Lewis). Also, there are books listed on the IPCSG website that are helpful. A final note: excessive tofu, normally a healthy food, can work against ADT.

We recommend that you watch the video online for more definitive information about the talk and slides: [https://www.youtube.com/watch?v=o\\_n4UCtj13U](https://www.youtube.com/watch?v=o_n4UCtj13U)

A DVD of the talk will be available for purchase from the IPCSG about one month after the meeting.

## On the Lighter Side





## Articles of Interest

### **\$150K Prostate Cancer Drug Draws New Attention to 'March-In' Rights**

[medpagetoday.com](https://www.medpagetoday.com)

Jennifer Henderson

— [Advocates want Biden administration to enable Xtandi generics; industry warns against it](#)

by [Jennifer Henderson](#), Enterprise & Investigative Writer, MedPage Today April 6, 2022

In the ongoing debate about how to address skyrocketing prescription drug prices, experts are at odds over whether the federal government should grant "march-in" rights for patents on the prostate cancer drug enzalutamide (Xtandi).

Supporters, including prostate cancer patients who are currently [petitioning HHS for a hearing on the matter](#), say granting march-in rights to allow other manufacturers to produce a generic enzalutamide would [reduce its price substantially](#), allowing greater access to a life-saving treatment.

However, those who oppose the move, such as a group of research and scientific organizations and [those involved in commercializing new products](#), argue it [goes against longstanding legislation](#) designed to foster innovation.

The back-and-forth centers on the Bayh-Dole Act, a federal law enacted in 1980 to use the patent system to promote inventions arising from federally supported research or development, such as enzalutamide. But the Bayh-Dole Act also grants march-in rights by specifying that the federal government protect the public against "unreasonable use" of such inventions, and that particular language has inspired differing interpretations.

Enzalutamide, an androgen receptor inhibitor developed by Astellas Pharma, has been on the market for about a decade, first approved by the FDA in 2012 for treating metastatic castration-resistant prostate cancer. It was subsequently approved to treat non-metastatic castration-resistant prostate cancer in 2018, followed by an indication for metastatic castration-sensitive prostate cancer in 2019.

It was invented with NIH funding, and the FDA's Orange Book currently lists three patents for the drug, which are set to expire between May 2026 and August 2027, according to the petition.

Enzalutamide currently costs more than \$150,000 per year in the U.S., according to the petition, which holds that the price is "demonstrably unreasonable." However, those who oppose granting march-in rights for the patents on enzalutamide state that the Bayh-Dole Act was "never intended as a means for the government to impose arbitrary price controls on resulting products."

Though petitions for march-in rights have been brought, unsuccessfully, many times before, the arguments on either side of the current case appear to be heating up. For one, experts told *MedPage Today*, enzalutamide is a clear example of an invention developed from federal research that is now commercialized to meet a huge public health need. (In 2022, there are [estimated to be nearly 270,000 new cases of prostate cancer](#) in the U.S., according to the American Cancer Society.)

#### [Medical News from Around the Web](#)

Additionally, political pressures continue to mount for the federal government to address excessive prescription drug prices. Some say the Biden administration has signaled subtle support for hearing out the case on march-in rights, including through issuing an executive order on competition, which [opposes narrowing Bayh-Dole march-in rights](#).

"The fact that you're getting this amount of attention suggests to me that people are worried," Liza Vertinsky, PhD, JD, an associate professor at Emory University School of Law, told *MedPage Today*. "This is a huge industry where one could dig in and find some problems with pricing."

Earlier this week, Vertinsky [published a piece in Health Affairs](#) arguing that, "Biomedical public-private partnerships will only achieve their potential as vehicles for transformative change in public health if they are structured in a way that allows for the robust balancing of public interests with private incentives."

The current petition to have a hearing on granting march-in rights for the patents on enzalutamide would signal a "more balanced conversation on innovation," Vertinsky said. Though any potential impact would be small on companies, it could provide "significant cost savings for individuals who can't afford to pay their cancer bills," she

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added.

Peter Arno, PhD, a health economist at the University of Massachusetts-Amherst, concurred. Arno, who co-authored [an op-ed in STAT](#) on march-in rights along with one of the petitioners, told *MedPage Today* that the issue affects not only taxpayer dollars, but also the approximately 25% to 30% of people who don't take their medication because of the costs.

"That has very adverse health effects for people," Arno said. "It's one step in the long-term battle to get some control over drug pricing like they do in every other developed country."

In contrast, Joseph Allen, executive director of a group called the Bayh-Dole Coalition, which was formed in 2019 in support of the federal law, said the issue of drug pricing is a separate one altogether.

The federal law has been successful in commercializing technologies for 42 years, Allen explained. The group isn't arguing in favor of high drug prices, he said, rather that the law shouldn't be used for a purpose that it wasn't intended.

In response to the petition to HHS requesting that the federal government grant march-in rights for the patents on enzalutamide, the Bayh-Dole Coalition [submitted its own response](#) to the agency. It reads in part: "The Bayh-Dole Act laid the groundwork for the unprecedented partnerships between your department and the private sector, including those that helped lead to the development of life-saving vaccines and therapies to fight COVID-19. Misusing the law as the critics are now urging in the pending march-in petition threatens these relationships, as the government would appropriately no longer be viewed as a trustworthy partner."

Allen told *MedPage Today* that the coalition is hopeful that the federal law is upheld. Many people are nervous, he said, "because once you misuse this, you lose that confidence and you will never get it back again."

The companies "bet the farm" to commercialize technologies, Allen said. If that is made "even riskier," he added, "they're just going to walk away."

Astellas declined to make Mark Reisenauer, president of U.S. commercial operations, available for an interview. However, Reisenauer [wrote in an op-ed for STAT](#) that "despite the clear health benefits and broad availability of Xtandi, some individuals and organizations want to use it as a test case for disrupting the technology transfer and medical innovation ecosystem that is the pathway to the treatments of tomorrow."

Reisenauer noted that in 2021, "the majority of Medicare beneficiaries paid \$20 or less per month out of pocket for Xtandi," and that, "Retired military service members and their families enrolled in TRICARE can access Xtandi for co-pays ranging from \$0 to \$14 per month, with active-duty TRICARE members having no co-pay."

In response to *MedPage Today's* request to HHS regarding consideration of the petition to grant march-in rights for patents on enzalutamide, the NIH -- to which the request for analysis has been delegated -- responded that the petition is still under analysis.

NIH further noted that, depending on the facts and circumstances that are reviewed, the federal government's march-in right allows the funding agency to conduct an administrative proceeding. If the government finds that one of four criteria are met, it can grant additional licenses to other applicants. The most common considerations are failure to take "effective steps to achieve practical application of the subject invention" or failure to satisfy "health and safety needs."

[Jennifer Henderson](#) joined *MedPage Today* as an enterprise and investigative writer in Jan. 2021. She has covered the healthcare industry in NYC, life sciences and the business of law, among other areas.

### **New FDA approval renews hope for advanced prostate cancer patients**

[kgun9.com](#)

US Food and Drug Administration (FDA) has approved a new therapy, Pluvicto, for the treatment of adults with a certain type of advanced cancer called prostate-specific membrane antigen–positive metastatic castration-resistant prostate cancer (or PSMA-positive mCRPC)

US Food and Drug Administration (FDA) has approved a new therapy, Pluvicto, for the treatment of adults with a certain type of advanced cancer called prostate-specific membrane antigen–positive metastatic castration-resistant prostate cancer (or PSMA-positive mCRPC). This type of prostate cancer has spread to other parts of

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the body (metastatic), and is progressing after treatment with other anticancer therapies<sup>1</sup>.

Pluvicto (lutetium Lu 177 vipivotide tetraxetan) is the first FDA-approved targeted radioligand therapy (RLT) and is an important clinical advancement for patients with prostate cancer<sup>1</sup>. Data shows it can significantly improve survival rates for those with progressing mCRPC who have been treated with other therapy options<sup>1</sup>. Pluvicto works by targeting cells with the PSMA receptor, which is a biomarker located on the outside of cells and is highly expressed in more than 80% of patients with prostate cancer, making it an important way to assess the progression of metastatic prostate cancer<sup>1,2-8</sup>.

Pluvicto contributes to a patient's overall long-term cumulative radiation exposure, which is associated with an increased risk for cancer. Ensure patients increase oral fluid intake and advise patients to void as often as possible to reduce bladder radiation. Minimize radiation exposure during and after treatment with Pluvicto consistent with institutional good radiation safety practices and patient treatment procedures. Pluvicto is associated with other risks; please see the Important Safety Information at the end of this communication

### **Why this matters:**

Prostate cancer is the second most common cancer in Americans with a prostate gland. The American Cancer Society's estimates for prostate cancer in the US for 2021 are<sup>9</sup>:

1. About 248,530 new cases of prostate cancer
2. About 34,130 deaths from prostate cancer

10%-20% of patients with prostate cancer develop CRPC within 5 years of diagnosis and over 80% of these cases are metastatic at the time of CRPC diagnosis<sup>10</sup>. In CRPC, the tumor stops responding to hormonal therapies and in metastatic CRPC, the tumor spreads to other parts of the body, such as neighboring organs or bones<sup>10</sup>. Presently, patients with metastatic prostate cancer have a less than 3 in 10 chance of surviving for 5 years<sup>11</sup>.

FDA approval of Pluvicto is based on the Phase III VISION trial. **Participants treated with Pluvicto plus SOC had a 38% reduction in risk of death; both alternate primary endpoints of overall survival and radiographic disease progression free survival were met<sup>1</sup>.**

PLUVICTO™ (lutetium Lu 177 vipivotide tetraxetan) is a radiopharmaceutical used to treat adults with an advanced cancer called prostate-specific membrane antigen–positive metastatic castration-resistant prostate cancer (PSMA-positive mCRPC) that has spread to other parts of the body (metastatic), and has already been treated with other anticancer treatments.

### **Important Safety Information**

Use of PLUVICTO involves exposure to radioactivity. Long-term, accruing radiation exposure is associated with increased risk for cancer. To minimize radiation exposure to others following administration of PLUVICTO, patients are advised to limit close contact (less than 3 feet) with household contacts for 2 days or with children and pregnant women for 7 days, to refrain from sexual activity for 7 days, and to sleep in a separate bedroom from household contacts for 3 days, from children for 7 days, or from pregnant women for 15 days.

PLUVICTO may cause low level of blood cell counts. Patients should tell their doctor right away if they develop any new or worsening symptoms, including tiredness or weakness, pale skin, shortness of breath, bleeding or bruising more easily than normal or difficulty to stop bleeding, or frequent infections with signs such as fever, chills, sore throat, or mouth ulcers. PLUVICTO may also cause problems with kidneys. Patients should tell their doctor right away if they develop any new or worsening symptoms, including passing urine less often or passing much smaller amounts of urine than usual.

Before receiving PLUVICTO, patients should tell their doctor if they have low level of blood cell counts (hemoglobin, white blood cell count, absolute neutrophil count, platelet count); if they have or have had tiredness, weakness, pale skin, shortness of breath, bleeding or bruising more easily than normal or difficulty stopping bleeding, or frequent infections with signs such as fever, chills, sore throat, or mouth ulcers (possible signs of myelosuppression); if they have or have had kidney problems; if they have or have had any other type of cancer or treatment for cancer, as PLUVICTO contributes to long-term cumulative radiation exposure; and if they are sexually active, as all radiopharmaceuticals, including PLUVICTO, have the potential to cause harm to an unborn baby. Patients should use effective contraception for intercourse during treatment with PLUVICTO and for 14 weeks after the last dose. PLUVICTO may cause temporary or permanent infertility.

Before administration of PLUVICTO patients should drink plenty of water in order to urinate as often as possible during the first hours after administration.

The most common side effects of PLUVICTO include tiredness, dry mouth, nausea, low red blood cell count,

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loss of appetite, changes in bowel movements (constipation or diarrhea), vomiting, low blood platelet count, urinary tract infection, weight loss, and abdominal pain.

Please see full Prescribing Information for PLUVICTO, available at <https://www.novartis.us/sites/www.novartis.us/files/pluvicto.pdf> [novartis.us]

[cancerabcs.org](https://cancerabcs.org)

### **Personalized Medicine in Localized Prostate Cancer: Are We There Yet?**

**Robert T. Dess, MD**

Editorial | [Volume 113, ISSUE 1](#), P77-79, May 01, 2022

DOI: <https://doi.org/10.1016/j.ijrobp.2022.02.001>

Localized prostate cancer is in urgent need of personalized medicine. It is a disease with heterogeneous outcomes and multiple curative treatment options with variable effects on urinary, bowel, and sexual quality-of-life domains. The goal is clear: to offer a treatment strategy that maximizes benefit while minimizing harm. Currently, clinical factors alone, at least when used to formulate 3- and 4-tier National Comprehensive Cancer Network (NCCN) risk groups, have suboptimal discriminatory ability to accurately identify those at lower or higher risk of disease recurrence, metastasis, and death from prostate cancer.

Thus, there is a strong interest in prognostic molecular markers to aid in evaluating the tumor aggressiveness of newly diagnosed localized disease to best tailor treatment intensity with disease risk.

In this issue of the Red Journal, Tward et al evaluated the role of one such prognostic tool: a clinical cell-cycle risk (CCR) score. Prior studies, often in surgical cohorts, have demonstrated that the CCR score is prognostic in localized prostate cancer.

To date, however, there are limited data on the use of the CCR score based on pretreatment biopsy samples from men receiving curative-intent external beam radiation therapy (EBRT) with or without androgen deprivation therapy (ADT) for intact disease. Thus, this study represents an important contribution to the field.

To keep abbreviations straight, the CCR score is a mathematically derived score that combines the University of California San Francisco Cancer of the Prostate Risk Assessment (CAPRA) score—a validated prognostic tool based on readily available clinical and pathologic variables

—and a commercially available cell cycle progression (CCP) score based on RNA expression of cell-cycle progression genes (Prolaris).

Based on the current study, the authors conclude (1) that CCR accurately provides prognostic information using cumulative incidence of distant metastasis as their primary endpoint and (2) that a threshold score (CCR  $\leq 2.112$ ) may identify men suitable for EBRT alone without ADT. Before discussing the results supporting these conclusions, it is important to understand the underlying cohort.

The present CCR cohort was assembled retrospectively by pooling data from men treated with external beam RT (greater than or equal to an equivalent dose in 2 Gy fractions of 71.8 Gy) at 15 institutions from 2003 to 2017 (n = 1683). Of these, 55% (n = 936) of men were excluded, primarily due to missing clinical information, a common limitation of retrospective data sets that can introduce bias.

Eighty-seven percent (13 of 15) of centers over the 14-year period contributed <100 patients (7 patients/year), and 60% contributed <50 patients (4 patients/year). The final cohort of 741 men had Gleason Score  $\geq 7$ , prostate-specific antigen >10 ng/mL, or  $\geq$ cT2b disease. The median follow-up was 5.8 years, and there were 47 metastatic events within 10 years.

Does CCR provide prognostic information regarding distant metastasis risk? Yes, the CCR was prognostic for metastasis in the full cohort (hazard ratio, 2.2 [95% confidence interval, 1.7-2.9]) and remained so after accounting for multiple definitions of ADT use and duration. As for measures of discrimination, the C-index of the CCR score was 0.72 (0.65-0.79), and the time-dependent area under the curve AUC was 0.69 (0.61-0.77). It is important to note, however, that CAPRA alone had C-index of 0.68 (0.60-0.76) and time-dependent AUC of 0.68 (0.59-0.76). Moreover, as shown in supplementary Table E2, the CCP gene expression biomarker itself had a time-dependent AUC of 0.52 (0.46-0.58), or not significantly different from a coin flip. Thus, although CCR had the highest nominal

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prognostic performance of all models evaluated, CAPRA may provide a large component of the discriminatory ability of CCR. CAPRA is readily available based on clinical variables, and additional commercial tests such as the CCP have associated costs.

Based on NRG/RTOG 0815, and the Meta-Analysis of Randomized trials in Cancer of the Prostate consortium, ADT consistently reduces the risk of biochemical recurrence, distant metastasis, and prostate cancer-specific mortality across the disease risk spectrum.

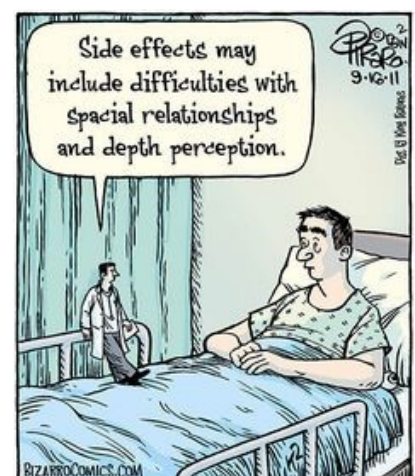
Absolute benefit, however, is a function of baseline risk. Stated explicitly, the 30% to 60% risk reduction benefit from adding ADT to EBRT is quite different for a man with a baseline distant metastasis risk of 5% versus one with a 20% baseline risk. This supports the rationale behind discussing EBRT alone with those with more favorable-risk disease. Does the CCR threshold score of  $\leq 2.112$  provide actionable information regarding patients who may be selected for EBRT *without* ADT?

As expected, ADT in the CCR cohort was not standardized; treatment and duration were based on physician and patient preference. Notably, only 40% to 60% of men with unfavorable intermediate- and high-risk disease received guideline-concordant ADT duration. Although patients below the CCR threshold score did not benefit from ADT, those above the threshold also did not appear to derive a benefit from ADT. In supplementary Figure E2, the RT-alone group had equivalent or superior outcomes compared with those receiving ADT. This is the limitation of retrospective comparative effectiveness research; the rationale for omission, receipt, and duration of ADT is often not available, and it is difficult to demonstrate the established benefits of ADT with non-standardized treatment due to confounding by indication. Those limitations aside, we can review how the CCR threshold could be applied across the current NCCN favorable-, unfavorable-, and high-risk groupings.

For men with NCCN favorable intermediate-risk disease, 95% (161 of 169) were at or below the  $\leq 2.112$  threshold. Recall, however, that the same favorable clinical factors (eg, Gleason 3 + 4, low percentage of cores positive, single risk factor) are incorporated into both NCCN favorable/unfavorable risk stratification and the CCR (by virtue of CAPRA). It follows that most men with favorable intermediate-risk disease have a lower CCR score. Thus, CCR may be of limited value for most of these men with favorable-risk disease who already consider RT alone with omission of ADT based on clinical factors alone. Of the 8 patients with NCCN favorable intermediate-risk disease with a CCR score above the threshold, 4 men were at risk beyond 5 years of follow-up, and 0 men were at risk at 10 years of follow-up, limiting meaningful analysis.

For men with NCCN unfavorable intermediate-risk disease, 52% (184 of 351) had a CCR score below the threshold. Of these men, 112 received RT alone with a distant metastasis risk of less than 5%. Notably, only 56 men treated with RT alone were at risk beyond 5 years of follow-up. Given the heterogeneity of this group, and the promising metastasis outcomes, this may be an area for further prospective studies with standardized treatment and follow-up.

## On the Lighter Side



## NETWORKING

Please help us in our outreach efforts. Our speakers bureau consisting of Gene Van Vleet is available to speak to organizations of which you might be a member. Contact Gene 619-890-8447 or [gene@ipcsg.org](mailto:gene@ipcsg.org) to coordinate.

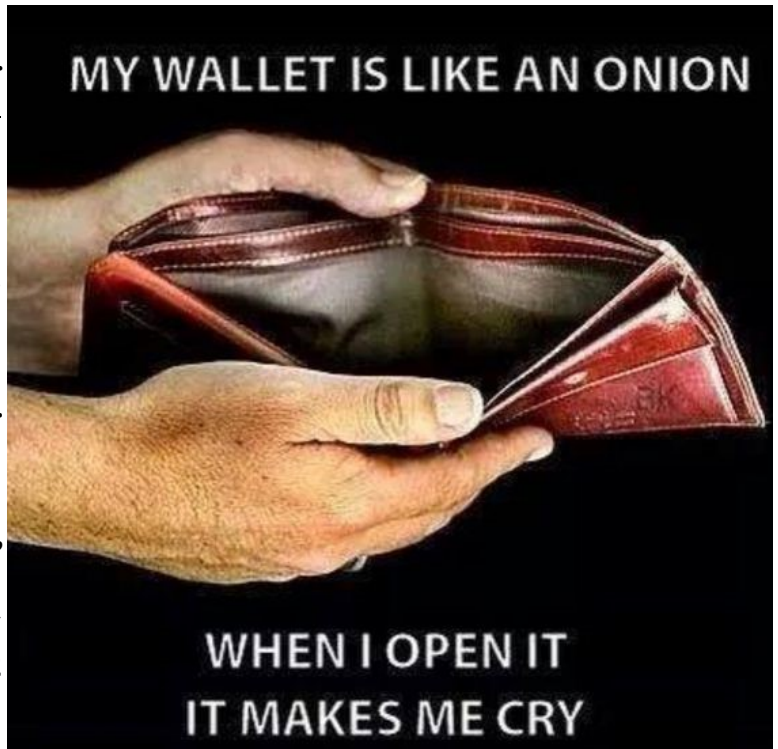
Member John Tassi is the webmaster of our website and welcomes any suggestions to make our website simple and easy to navigate. Check out the Personal Experiences page and send us your story. Go to: <https://ipcsg.org/personal-experience>

Our brochure provides the group philosophy and explains our goals. Copies may be obtained by mail or email on request. Please pass them along to friends and contacts.

## FINANCES

We want to thank those of you who have made special donations to IPCSG. Remember that your gifts are tax deductible because we are a 501(c)(3) non-profit organization.

We again are reminding our members and friends to consider giving a large financial contribution to the IPCSG. This can include estate giving as well as giving in memory of a loved one. You can also have a distribution from your IRA made to our account. We need your support. We will, in turn, make contributions from our group to Prostate Cancer researchers and other groups as appropriate for a non-profit organization. Our group ID number is 54-2141691. Corporate donors are welcome!



**While our monthly meetings are suspended, we still have continuing needs, but no monthly collection. If you have the internet you can contribute easily by going to our website, <http://ipcsg.org> and clicking on "Donate" Follow the instructions on that page. OR just mail a check to: IPCSG, P. O. Box 420142, San Diego CA\_92142**

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For men with NCCN high- and very high-risk disease, long-term ADT consistently improves cancer-related outcomes and overall survival.

In the CCP cohort, 89% of men with high-risk disease were above the CCR threshold, including 99% of those with very high-risk disease. Only 25 men with high- and very-high-risk disease had CCP risk below the multimodality threshold, and only 7 received RT alone, with 1 patient at risk beyond 5 years of follow-up. The authors note there are no distant metastasis events in this group, but there were also virtually no men with long-term follow-up. This data set is not able to inform the utility of CCR to personalize treatment in high- and very-high-risk disease.

In summary, Tward et al should be congratulated for assembling a 15-institution consortium and analyzing this data set with transparency. CCR provides improved prognostic information above and beyond NCCN intermediate- and high-risk designations. Given the contribution of CAPRA to the overall CCR score, more work is needed to determine when to optimally consider the CCP gene expression biomarker run on pretreatment biopsy samples, or when CAPRA itself or other similar clinical prognostic groupings may be sufficient. Simon and others have proposed criteria to evaluate tumor biomarkers.

Based on the limitations of the retrospective design, the nonstandardized treatment and follow-up, this study represents Level IV-V evidence. ADT remains a standard of care with high-level randomized evidence supporting its use and should be discussed with men as such. The validation of the CCR threshold within the context of men receiving EBRT with or without ADT, although important, is not yet actionable. Given the limitations, a data set with nonstandardized ADT use, CCR is unable to identify patients who can safely omit ADT, particularly those with unfavorable intermediate-, high-, and very-high-risk disease, and more prospective evidence is required.

Above all, the authors should be commended for focusing on what matters: absolute risk reduction. This estimation along with a detailed understanding of our treatment-related side effects are critical components of patient-centered, shared decision-making. Ongoing studies within the NRG Oncology/RTOG are testing deintensification and intensification hypotheses in unfavorable

## Articles of Interest continued from page 9

intermediate-risk (GU010) and high-risk (GU009) disease using the Decipher genomic classifier as a stratification variable, and we should encourage accrual to these and other future potentially practice-changing trials. We are on our way, but we are not there yet.

### **Yes, Nodal Recurrence of Prostate Cancer is Potentially Curable**

[edjournal.org](http://edjournal.org)

Gray Zone| [Volume 106, ISSUE 2](#), P238, February 01, 2020

[Rahul D. Tendulkar, MD](#)

[Omar Y. Mian, MD, PhD](#)

DOI: <https://doi.org/10.1016/j.ijrobp.2019.07.016>

Advances in positron emission tomography (PET) imaging with prostate-specific tracers allow more sensitive and specific detection of low-volume recurrences that were previously indiscernible using conventional imaging. Retrospective data in patients presenting with NIM0 prostate cancer support combined-modality therapy with radiation and androgen deprivation therapy, and preliminary data from the Radiation Therapy Oncology Group 0534 randomized trial suggest that salvage pelvic nodal radiation therapy with androgen deprivation therapy is safe and effective for patients with biochemical recurrence after prostatectomy.

<sup>1</sup> A proportion of patients enrolled on Radiation Therapy Oncology Group 0534 would likely have had PET-detected nodal metastases, if PET imaging had been available. It is reasonable to extrapolate that salvage pelvic radiation therapy would be effective in a patient whose primary tumor has been controlled with prior prostate radiation therapy..

[nature.com](http://nature.com)

### **Cause of metastasis in prostate cancer discovered: MedUni Vienna study generates new momentum for diagnosis and treatment**

Prostate cancers remain localised in the majority of cases, giving affected individuals a good chance of survival. However, about 20% of patients develop incurable metastatic prostate cancer, resulting in approximately 5,000 deaths each year in Austria alone. Medical research has not yet adequately explained why metastases occur in some people and not in others. A research team at MedUni Vienna has now discovered specific changes in a protein that drive the growth and spread of prostate cancer. The study was recently published in the journal *Molecular Cancer*.

In the study, the researchers broke new ground and investigated the role of the protein KMT2C in prostate cancer. KMT2C is a genetic component that essentially functions as a regulator of central cellular processes. If KMT2C loses this regulatory ability due to typical cancer-related mutations, this encourages the proliferation of the cancer gene MYC. This in turn causes cells to divide at an increased rate, driving both growth and spread of the cancer.

#### **New insights into the transition to metastasis**

"Our study provides new insights into the previously poorly understood transition from localised prostate cancer to terminal metastatic prostate cancer," says study leader Lukas Kenner (Department of Pathology at MedUni Vienna, Comprehensive Cancer Center of MedUni Vienna and University Hospital Vienna, Department of Laboratory Animal Pathology at Vetmeduni Vienna and the KI Center CBmed), underlining the significance of the research work. In addition, the knowledge gained about the effects of KMT2C mutations may also generate new momentum for the diagnosis and treatment of prostate cancer.

#### **Diagnosing aggressive progression at an early stage**

KMT2C mutation status can be measured via a blood test, allowing early diagnosis of potentially aggressive progression in prostate cancers. In addition, MYC inhibitors could be used to prevent increased cell division, and hence metastasis, and it is hoped that further scientific studies will substantiate this. MYC inhibitors are essentially new cancer treatment drugs that have already been tested in clinical trials and -- if further studies confirm this -- could also be used in metastatic prostate cancer in the next few years. "Since a high level of KMT2C mutation characterises many types of cancer, such as breast, lung, colorectal, bladder and even skin cancer, our study results have a great deal of potential in the research, diagnosis and treatment of malignant cancers in general," says Lukas Kenner.

#### **Story Source:**

[Materials](#) provided by **Medical University of Vienna**. Note: Content may be edited for style and length.



## The Galleri Test: A New Blood Test for Cancer Screening

The Galleri test can detect more than 50 kinds of cancer

By the end of 2022, according to the American Cancer Society, there will be [an estimated 609,360 deaths](#) caused by cancer in the United States. As the second leading cause of death in the U.S., it's important that we catch, diagnose and treat cancer as early as possible. While there are standard screening tests for a handful of common cancers, most cancers, including rare cancers, don't have any tests that allow for early detection. Now, thanks to the Galleri test, there's [a game-changing technique](#) to catch more than 50 kinds of cancer in one simple blood test.

Emeritus Chair of the Glickman Urological Kidney Institute Eric Klein, MD, explains how the Galleri test works, why it has the potential to change the way we diagnose cancer and how it's different from other cancer screenings.

### What tests are done to check for cancer?

Currently, there are five cancers that are recommended for screening regularly in the U.S.:

[Mammographies](#) test for breast cancer, typically in people assigned female at birth (AFAB) ages 45 to 54.

[HPV tests and Pap tests](#) screen for cervical cancer, typically in people who are AFAB ages 25 and up. Colonoscopies test for colorectal cancer in people over 45.

Low-dose CT scans can be conducted on people who are at high risk for lung cancer if they're former smokers or have had occupational hazard exposure.

[Prostate-specific antigen](#) (PSA) tests screen for prostate cancer in people assigned male at birth (AMAB) 55 and older.

Each of these screenings test for a specific kind of cancer and is done on a semi-regular basis. However, there isn't currently a way to screen for more lethal cancers like pancreatic or [ovarian cancer](#). These cancers aren't usually caught until you start showing symptoms, and by then, the cancer has usually developed into stage III or stage IV and may have spread to other parts of your body.

"Currently, we don't detect the majority of cancers, including highly lethal ones, such as pancreatic or ovarian cancer, until symptoms are present," says Dr. Klein. "But Galleri can find those cancers at a time when they're in an earlier stage and before symptoms appear."

### What is the Galleri test?

The Galleri test may present a far [more efficient way](#) of detecting cancer. Instead of searching for any one type of cancer, it screens an individual for multiple cancers. Its potential is to change the current screening process from screening for individual cancers to one where individuals are screened for multiple cancers with a single blood test.

Many cancers shed DNA into your bloodstream, known as cell-free DNA or circulating tumor DNA. This DNA is usually shed as cancer cells die. Using what's called Next-Generation DNA Sequencing and machine learning, doctors are able to use a single blood draw (test) to look at various patterns in that DNA code and figure out two things: if a cancer signal is present, and from where the cancer likely started.

These patterns in your DNA are possible because of a biological process known as methylation. During this process, your body expresses certain genes but not others. You can picture it like a wall of light switches: for every switch you turn on, others might turn off, and different configurations produce different results. So, a skin cell will have one configuration, while a liver cell will have another. In the same way, healthy cells will have one configuration, while cancer cells will have a different one. And specific cancer types will have specific configurations different from other cancer types.

"It's like fingerprints and how fingerprints tell the difference between two people," explains Dr. Klein. "The methylation patterns are fingerprints that are characteristic of each kind of cancer. They look one way for lung cancer and different for colon cancer."

If you take the Galleri test, you can have two possible results:

No cancer signal detected means there's no cancer DNA detected in your bloodstream.

A cancer signal detected suggests you may have cancer.

If a cancer signal is detected, the Galleri test is able to identify which organ system the cancer is likely coming from with about 90% accuracy. If this happens, you would then have another test (like a blood test, CT scan or ultrasound of your kidneys, lungs, pancreas or other affected system) to verify the presence of cancer. Then, you can



determine what treatment is right for you. The key here is that you're catching cancer much earlier than you normally would have before you start showing physical symptoms.

### **What cancers are detected by Galleri?**

Galleri can detect [more than 50 types](#) of cancer, including: [Anal cancer](#). [Breast cancer](#). [Cervical cancer](#). [Esophageal cancer](#). [Kidney cancer](#). [Leukemia](#). [Liver cancer](#). [Mesothelioma](#). [Oral cancer](#). [Pancreatic cancer](#). [Stomach cancer](#). [Uterine cancer](#).

This is especially effective when you consider that some of these cancers are extremely rare and highly lethal. In the case of pancreatic cancer, which isn't normally detected until stage III or stage IV and has a one-year survival rate of 5%, it means you can catch at least some cases much earlier than normal.

"Twelve cancers, including anal, bladder, colorectal, esophageal, head and neck, liver/bile-duct, lung, lymphoma, ovary, pancreatic, plasma-cell neoplasm and stomach cancer, account for about two-thirds of all cancer deaths in the U.S.," says Dr. Klein. "For these 12, Galleri finds about 40% of stage I cancers, 67% of stage II cancers, 80% of stage III cancers and 95% of stage IV cancers."

Galleri can detect these cancers because of the DNA it sheds into your bloodstream. That means it **doesn't** detect cancers that don't shed DNA into your bloodstream, like brain cancer.

### **How accurate is the Galleri blood test?**

Depending on the test, traditional screening tests have a false-positive rate of 10% to 40%. Galleri has a 0.5% false-positive rate, which means it's highly accurate.

"It finds 51.5% of cancers," points out Dr. Klein. "If you look at the 12 cancers that account for two-thirds of all deaths in the U.S., it actually finds 67% of those."

And it's 89% effective in predicting where the cancer started.

Currently, the Galleri test is meant to be in addition to traditional screenings — so you should get screened for cancers [as you normally would](#) once you've reached the applicable age. But, Dr. Klein points out that as we develop more research and collect more data, it may be possible to test for most cancers in the future using a simple blood test without having to use screening tests of the past.

"This is theoretical, but in the future, all cancer screening could be based on a blood test. But we're not there yet," he notes.

### **Is the Galleri blood test FDA approved?**

Currently, the Galleri test isn't U.S. Food and Drug Administration (FDA) approved. For now, if you're over the age of 50 and have a family history of cancer, are at higher risk for cancer or you're immunocompromised and you're interested in taking the Galleri test, you should talk to your healthcare provider. They can [register with GRAIL and order the test](#) (the healthcare company responsible for developing the Galleri test).

## **CRISPR screens reveal genetic determinants of PARP inhibitor sensitivity and resistance in prostate cancer**

[biorxiv.org](https://doi.org/10.1101/2022.04.16.498888)

Takuya Tsujino

### **Abstract**

Prostate cancer (PCa) harboring BRCA1/2 mutations is often exquisitely sensitive to PARP inhibition. However, genomic alterations in other DNA damage response genes have not been consistently predictive of clinical response to PARP inhibitors (PARPis).

Here, we perform genome-wide CRISPR-Cas9 knockout screens in BRCA1/2-proficient PCa cell lines and identify novel genes whose loss has a profound impact on PARPi sensitivity and resistance. Specifically, MMS22L deletion, frequently observed (up to 14%) in PCa, renders cells hypersensitive to PARPis by disrupting RAD51 loading required for homologous recombination repair, although this response is TP53-dependent. Unexpectedly, loss of CHEK2 confers resistance rather than sensitivity to PARPis in PCa cells through increased expression of BRCA2, a target of CHEK2-TP53-E2F7-mediated transcriptional repression.

Combined PARP and ATR inhibition overcomes PARPi resistance caused by CHEK2 loss. Our findings may

inform the use of PARPis beyond BRCA1/2-deficient tumors and support reevaluation of currently used biomarkers for PARPi treatment in PCa.

### **Gut environment changes due to androgen deprivation therapy in patients with prostate cancer**

Fukuda, Shinji

#### **Abstract**

#### **Background**

It is estimated that by 2040 there will be 1,017,712 new cases of prostate cancer worldwide. Androgen deprivation therapy (ADT) is widely used as a treatment option for all disease stages. ADT, and the resulting decline in androgen levels, may indirectly affect gut microbiota. Factors affecting gut microbiota are wide-ranging; however, literature is scarce on the effects of ADT on gut microbiota and metabolome profiles in patients with prostate cancer.

#### **Methods**

To study the changes of gut microbiome by ADT, this 24-week observational study investigated the relationship between testosterone levels and changes in gut microbiota in Japanese patients with prostate cancer undergoing ADT. Sequential faecal samples were collected 1 and 2 weeks before ADT, and 1, 4, 12, and 24 weeks after ADT. Blood samples were collected at almost the same times. Bacterial 16S rRNA gene-based microbiome analyses and capillary electrophoresis-time-of-flight mass spectrometry-based metabolome analyses were performed.

#### **Results**

In total, 23 patients completed the study. The  $\alpha$ - and  $\beta$ -diversity of gut microbiota decreased significantly at 24 weeks after ADT ( $p = 0.017$ ,  $p < 0.001$ , respectively). Relative abundances of Proteobacteria, Gammaproteobacteria, Pseudomonadales, *Pseudomonas*, and concentrations of urea, lactate, butyrate, 2-hydroxyisobutyrate and S-adenosylmethionine changed significantly after ADT ( $p < 0.05$ ). There was a significant positive correlation between the abundance of Proteobacteria, a known indicator of dysbiosis, and the concentration of lactate ( $R = 0.49$ ,  $p < 0.01$ ).

#### **Conclusions**

The decline in testosterone levels resulted in detrimental changes in gut microbiota. This dysbiosis may contribute to an increase in frailty and an increased risk of adverse outcomes in patients with prostate cancer.

[sciencedirect.com](https://www.sciencedirect.com)

### **Radical prostatectomy findings and oncologic outcomes in patients with prostate cancer detected on systematic sextant biopsy only, MRI-targeted biopsy only, or both**

#### Highlights

- We assess unique cohorts: cancer on sextant (S-Bx) or targeted (T-Bx) biopsy only.
- Cases with cancer on T-Bx show larger tumor volume than those only on S-Bx.
- Compared with S-Bx only, cancer detection on T-Bx correlates with [tumor recurrence](#).
- There are no significant differences in cancers detected on T-Bx vs both S-Bx/T-Bx.

#### Abstract

#### Objective

Magnetic resonance imaging-targeted biopsy (T-Bx) has been shown to more accurately detect clinically significant prostate cancer. However, the clinical significance of cancer detection on T-Bx, followed by definitive treatment, needs to be further investigated. We herein investigated unique cohorts of patients with prostate cancer detected on systematic sextant biopsy (S-Bx) and/or T-Bx.

#### Materials and methods

We assessed consecutive patients who had undergone T-Bx with concurrent S-Bx (6 sites,  $\geq 12$  cores), followed by radical prostatectomy from 2015 to 2019. Within our Surgical Pathology database, we identified a total of 222 men who met the inclusion criteria for prostatic adenocarcinoma on either S-Bx or T-Bx, or both (B-Bx). Radical prostatectomy findings and oncologic outcomes were then compared among groups.

#### Results

Prostate cancer was detected on S-Bx only ( $n = 32$ ; 14%), T-Bx only ( $n = 40$ ; 18%), or B-Bx ( $n = 150$ ; 68%). Compared to cases with cancer detected on S-Bx only, those on T-Bx only or B-Bx showed significantly higher tumor grade (highest Grade Group in each patient) on biopsy and significantly larger estimated tumor volume on prostatectomy. There were no significant differences in tumor volume on biopsy, tumor grade on prostatectomy (except S-Bx vs. B-Bx), pT or pN stage category, surgical margin status, or preoperative prostate-specific antigen level between cases where cancer was detected on S-Bx only vs. T-Bx only or B-Bx. There were also no significant differences in any of these clinicopathologic features between cancers detected on T-Bx only vs. B-Bx. Kaplan-Meier analysis revealed a significantly higher risk of biochemical recurrence after prostatectomy in patients whose cancer was detected on T-Bx only ( $P = 0.020$ ) or B-Bx ( $P = 0.032$ ) than in those on S-Bx only. No significant difference in recurrence-free survival between T-Bx only vs. B-Bx cases ( $P = 0.601$ ) was seen. In multivariate analysis, cancer detection on T-Bx only (vs. S-Bx only) showed significance for recurrence (hazard ratio = 8.482,  $P = 0.045$ ).

#### Conclusions

Detection of prostate cancer on T-Bx, in addition to or instead of S-Bx, was found to be associated with larger tumor volume as well as worse prognosis. However, no significant clinicopathologic impact of simultaneous tumor detection on S-Bx was indicated in patients with prostate cancer present on T-Bx.

**Direct comparison of low-dose-rate brachytherapy versus radical prostatectomy using the surgical definition of biochemical recurrence for patients with intermediate-risk prostate cancer**

[ro-journal.biomedcentral.com](https://ro-journal.biomedcentral.com)

Ishiyama, Hiromichi

*Radiation Oncology* volume 17, Article number: 71 (2022) [Cite this article](#)

#### Abstract

##### Background

We compared the oncological outcomes of patients who received seed brachytherapy (SEED-BT) with those who received radical prostatectomy (RP) for intermediate-risk prostate cancer.

##### Methods

Candidates were patients treated with either SEED-BT ( $n = 933$ ) or RP ( $n = 334$ ). One-to-one propensity score matching was performed to adjust the patients' backgrounds. We compared the biochemical recurrence (BCR)-free rate using the Phoenix definition (prostate-specific antigen [PSA] nadir plus 2 ng/mL) for SEED-BT and the surgical definition (PSA cut-off value of 0.2 ng/mL) for RP. We also directly compared the BCR-free rates using the same PSA cut-off value of 0.2 ng/mL for both SEED-BT and RP.

##### Results

In the propensity score-matched analysis with 214 pairs, the median follow-up treatment was 96 months (range 1–158 months). Fifty-three patients (24.7%) were treated with combined SEED-BT and external-beam radiotherapy. Forty-three patients (20.0%) received salvage radiotherapy after RP. Comparing the BCR-free rate using the above definitions for SEED-BT and RP showed that SEED-BT yielded a significantly better 8-year BCR-free rate than did RP (87.4% vs. 74.3%, hazard ratio [HR] 0.420, 95% confidence interval [CI] 0.273–0.647). Comparing the 8-year BCR-free rate using the surgical definition for both treatments showed no significant difference between the two treatments (76.7% vs. 74.3%, HR 0.913, 95% CI 0.621–1.341). SEED-BT had a significantly better 8-year salvage hormonal therapy-free rate than did RP (92.0% vs. 85.6%, HR 0.528, 95% CI 0.296–0.942,  $P = 0.030$ ). The 8-year metastasis-free survival rates (98.5% vs. 99.0%, HR 1.382, 95% CI 0.313–6.083,  $P = 0.668$ ) and overall survival rates (91.9% vs. 94.6%, HR 1.353, 95% CI 0.690–2.650) did not significantly differ between the treatments.

##### Conclusions

The BCR-free rates did not significantly differ between patients treated with SEED-BT and those treated with RP for intermediate-risk prostate cancer even when they were directly compared using the surgical definition for BCR. SEED-BT and RP can be adequately compared for oncological outcomes.

**Accuracy of SelectMDx compared to mpMRI in the diagnosis of prostate cancer: a systematic review and diagnostic meta-analysis**

[nature](#)

[Reza Sari Motlagh,](#)

## Abstract

### Background

The SelectMDx test is a promising biomarker that is developed based on detecting urinary messenger RNA in combination with clinical prostate cancer (PCa) risk factors. We aimed to compare SelectMDx and mpMRI as a diagnostic test in detecting PCa and high grade(HG)-PCa in men suspected to have PCa.

### Methods

According to PRISMA, a systematic search was performed using major web databases for studies published before September 30, 2021. Studies that compared sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of SelectMDx and/or mpMRI were included. The bivariate random model that plotted sensitivity, specificity, PPV, NPV, and likelihood ratio (LR) for PCa and HG-PCa detection was applied to compare SelectMDx, mpMRI, and combination strategies (both positive and one or both positive).

### Results

Seven studies comprising 1328 patients who had undergone SelectMDx and mpMRI to detect PCa were included. Regarding PCa detection, SelectMDx had a pooled sensitivity of 81%, specificity of 69.8%, PPV of 64.7%, NPV of 85%, and LRs of +2.68 to -0.27, while mpMRI had a pooled sensitivity of 80.8%, specificity of 73.4%, PPV of 72.4%, NPV of 83.5%, and LRs of +3.03 to -0.26. The one or both positive strategy had the highest sensitivity (96.3%), NPV (95.7%), and the lowest -LR (0.06). While the both positive strategy had the highest specificity (80.9%), the PPV (76.5%) and +LR (3.68). In the scenario of PI-RADS 3 lesions not being biopsied in case of a negative SelectMDx ( $n = 44$ ), unnecessary biopsies would be reduced by 42% (44/105) while the risk of missing HG-PCa would be 9% (4/44).

### Conclusion

The performance of SelectMDx is comparable to that of mpMRI with regards to PCa and HG-PCa detection. In addition, this biomarker could help refine the clinical decision-making regarding the necessity of a biopsy in patients suspected to have PCa.

## For Men on ADT, Checking Bone Density May Thwart Fractures

[medpagetoday.com](https://www.medpagetoday.com)

Mike Bassett

[Oncology/Hematology](#) > [Prostate Cancer](#)

— But testing rates remain low among older prostate cancer patients on androgen deprivation therapy

by [Mike Bassett](#), Staff Writer, MedPage Today April 1, 2022

Bone density testing in older prostate cancer patients on androgen deprivation therapy (ADT) was significantly associated with a decreased risk for major osteoporotic fractures, but remains little used, a prospective population-based study found.

In the cohort of nearly 55,000 men treated with ADT from 2005 to 2015, those who received dual x-ray absorptiometry (DXA) screening had a 9% lower risk of major fractures compared with those who did not (HR 0.91, 95% CI 0.83-1.00,  $P=0.05$ ), after adjustment for previous fractures and history of osteoporosis, according to researchers led by Maria Suarez-Almazor, MD, PhD, of MD Anderson Cancer Center in Houston.

Over the study period, 17.5% of the men had fractures and 7.7% had major fractures, but just 7.9% received DXA screening, they reported in [JAMA Network Open](#).

"Given the deleterious impact of fractures for morbidity and mortality, implementation strategies are needed to increase the uptake of current guidelines for bone health management among men with prostate cancer," Suarez-Almazor and colleagues concluded. "Early intervention with bone-modifying agents could potentially reduce the burden of illness associated with fractures among older men who are survivors of prostate cancer."

The group found several factors associated with lower DXA screening rates:

Receiving nonsteroidal androgens (OR 0.57, 95% CI 0.39-0.84)

Being single (OR 0.89, 95% CI 0.81-0.97)

Black race (OR 0.80, 95% CI 0.70-0.91)

Living in small urban areas (OR 0.77, 95% CI 0.66-0.90)

Living in areas with lower educational levels (OR 0.75, 95% CI 0.67-0.83)

In an [accompanying editorial](#), Amar Kishan, MD, of the University of California Los Angeles, and colleagues noted that since the study's end, professional societies have updated their guidelines on DXA screening, suggesting that current bone density screening rates may be higher. Over the study period, screening crept up from 6.8% in 2005 to 8.4% by 2015.

However, the study "highlights the fact that there is substantial room for improvement in evaluating bone health among patients with prostate cancer receiving ADT," according to the editorialists.

"The low rate of DXA screening and the disparities in the use of DXA screening are concerning," wrote Kishan and colleagues. "It is particularly problematic that low rates of DXA screening were identified among men who were non-Hispanic Black, single, or residing in areas with lower socioeconomic status and lower educational levels, suggesting that more research into these patterns is needed to fully understand the associated dynamics and implement appropriate strategies to increase bone health screening when indicated in these populations."

#### [Medical News from Around the Web](#)

The study from Suarez-Almazor's group was based on data from the Surveillance, Epidemiology, and End Results database and the Texas Cancer Registry, which were linked with Medicare claims. It included 54,953 men 66 years or older with prostate cancer who were diagnosed between January 2005 and December 2015 and who initiated treatment with ADT.

Most of the men were white (75.4%), while 11.1% were Black and 8.5% were Hispanic. Of these, just 4,362 men received DXA screening, with rates among Black patients a particularly low 5.2%.

In general, DXA screening was more prevalent among patients with a diagnosis of osteoporosis (n=1,526) or fractures (n=1,426) in the year before ADT initiation.

In a multivariable model including propensity score adjustment, Suarez-Almazor and colleagues determined that previous DXA screening was not significantly associated with a risk of fracture.

#### **Genetic Score Shows Promise for Honing PSA Precision**

[medpagetoday.com](#)

Charles Bankhead

— [Fewer unnecessary biopsies projected with use of genetics-adjusted values](#)

by [Charles Bankhead](#), Senior Editor, MedPage Today April 12, 2022

NEW ORLEANS -- Adjusting prostate-specific antigen (PSA) levels for normal genetic variations showed potential for making PSA testing more useful, including reducing unnecessary prostate biopsies, a large genome-wide association study (GWAS) suggested.

A "polygenic score" (PGS) that accounted for noncancerous variations in PSA values explained 7.3%-8.8% of the variation in baseline PSA values in two large prostate cancer prevention studies. Correcting PSA values for noncancerous variations would have led to almost 20% fewer negative biopsies in men without cancer and 15.7% fewer biopsies in men with low-risk disease.

Genetics-adjusted PSA values also had a stronger association with aggressive prostate cancer than did unadjusted values, reported Linda Kachuri, PhD, of the University of California San Francisco, at the [American Association for Cancer Research](#) (AACR) meeting.

"I think our findings are exciting because we're able to show that we can use these genetic discoveries that are coming out of genome-wide association studies to actually improve, potentially, the detection of prostate cancer and hopefully try to make a PSA a more useful and accurate screening biomarker," said Kachuri, during an AACR press briefing. "This is only the first step. It's absolutely important to validate these findings in additional patient populations."

However, she cautioned that "the data that I'm showing really includes predominantly men of European ancestry. In our subsequent efforts, we're really trying to focus on having larger and much more diverse studies so we can really comprehensively examine PSA genetics and individuals of all ancestries to really represent our target patient population."

Though widely used in the diagnosis and management of prostate cancer, PSA remains controversial because



of its poor sensitivity and specificity, which leads to overdiagnosis and overtreatment of prostate cancer. Kachuri and colleagues hypothesized that the accuracy of PSA testing could be improved by accounting for inherent variations that are unrelated to prostate cancer.

Although GWAS investigations often focus on identifying genetic variations associated with a disease, Kachuri's group conducted a study to identify genetic changes in PSA values unrelated to cancer. The study involved more than 95,000 men from the U.S., England, and Sweden. The analysis identified 128 PSA-related variants, including 82 not previously recognized.

#### [Medical News from Around the Web](#)

Data from the analysis formed the basis for developing a PGS that accounted for the variants' contributions to PSA values. The score, individualized to each patient, represented the sum of genotypes across the 128 variants, weighted to reflect the variants' effect on PSA levels. A personalized adjustment factor was applied to a patient's PSA value, which was adjusted up or down to account for patient's unique PSA profile.

To validate the PGS, they applied the score to PSA values of participants in the [PCPT](#) and the [SELECT](#) prostate cancer prevention studies. The studies involved a combined total of almost 28,000 men who did not have prostate cancer at enrollment. The analysis showed that the score explained 7.3% of variation in PSA values in PCPT and 8.8% of the variation in SELECT. Moreover, the analysis showed the PGS was not associated with prostate cancer in the PCPT (OR 0.98) or SELECT (OR 1.04), confirming that the score reflected benign PSA variation.

The investigators used the individual PGS values to evaluate the potential impact on referral for biopsy. By substituting the PGS for patients' measured PSA values, Kachuri and colleagues estimated that 19.6% of negative biopsies potentially could have been avoided. In a separate analysis, the PGS was applied to men who had indolent, low-grade prostate cancer. The results suggested that 15.7% of biopsies could have been avoided in those men.

"This is another indication that genetically adjusted PSA could potentially be very useful for reducing overdiagnosis of prostate cancer," said Kachuri.

A final objective of the study was to examine the PGS utility for recognizing aggressive prostate cancer. The results showed that the corrected PSA values outperformed (as reflected in area under the curve) measured PSA levels, as well as a validated PGS for prostate cancer, for identifying aggressive disease in both the PCPT and SELECT studies. Combining the PGS for PSA and the PGS for prostate cancer provided the best results.

If the promising preliminary results are confirmed by further evaluation, the PGS could establish a new paradigm for providing clinicians with useful information about prostate cancer, said press briefing moderator Louis Weiner, MD, of Georgetown Lombardi Comprehensive Cancer Center in Washington.

"I think the polygenic score, added to the information that we get from a variety of different PSA determinations...can create more precise knowledge or information," said Weiner. "It's important that all information be transmuted into knowledge, which then becomes actionable...How do you integrate this with issues such as environmental modifiers of PSA, like inflammation, prostatitis, or age? How do you integrate the polygenic score into a more holistic interpretation of what PSA might be?"

"This is a tool, and I think that tools that give us more precision typically turn out to have value," he stated. "If this is validated -- and it seems to be getting validated right now -- it could create a new paradigm for giving clinicians useful, actionable information to inform their patients."

[Charles Bankhead](#) is senior editor for oncology and also covers urology, dermatology, and ophthalmology. He joined MedPage Today in 2007.

#### **Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer — Cancer ABCs**

This week seems to be a Darolutamide (Nubeqa) celebration on our blog. On April 7th, we posted a blog post, "[Darolutamide Provides Additional Overall Survival And Safety For Men With Non-Metastatic Castrate Resistant Prostate Cancer \(CRPC\) Who Also Have Co-Morbidities](#)."

Today's post is also about darolutamide (Nubeqa). Nubeqa is a potent androgen-receptor inhibitor; this means that it prevents any hormones produced by the body from gaining access to and supporting the cancer cell. Nubeqa has been shown to increase the overall survival among men with nonmetastatic, castration-resistant prostate cancer.

The question has come up, would combining Nubeqa, androgen-deprivation therapy (ADT), and docetaxel chemotherapy increase survival among men with metastatic, hormone-sensitive prostate cancer?

There was an international, randomized phase 3 trial of men with metastatic, hormone-sensitive prostate cancer to gain insight into this question. The trial assigned some men to receive darolutamide (at the standard dose of 600 mg [two 300-mg tablets] twice daily) or a placebo, both in combination with androgen-deprivation therapy (ADT) and docetaxel chemotherapy. The primary endpoint was overall survival.

### RESULTS

The trial analyzed data from 1306 men (651 in the darolutamide group and 655 in the placebo group); 86.1% of the men had metastatic disease at the time of their initial diagnosis. Data showed that the risk of death was significantly lower, by 32.5%, in men who had received darolutamide than in those who received a placebo.

Adverse events experienced by both groups were similar. The frequency of grade 3 or 4 adverse events was 66.1% in the darolutamide group and 63.5% in the placebo group.

### CONCLUSIONS

The good news is that in this trial, in men with metastatic, hormone-sensitive prostate cancer, their overall survival was significantly longer with the combination of darolutamide (Nubeqa), androgen-deprivation therapy (ADT), and docetaxel chemotherapy than with placebo plus androgen-deprivation therapy and docetaxel. The frequency of adverse events was similar in the two groups. (This trial was funded by Bayer and Orion – [\(NCT02799602\)](#))

### **Randomized Trial of Conventional- vs Conventional plus Fluciclovine (18F) PET/CT-Guided Post-Prostatectomy Radiotherapy for Prostate Cancer: Volumetric and Patient-Reported Toxicity Analyses**

[Vishal R Dhere, MD #, 1](#)

Published: April 10, 2022 DOI: <https://doi.org/10.1016/j.ijrobp.2022.04.005>

[Abstract](#)

#### *Purpose/Objective(s)*

: Post-prostatectomy radiotherapy planning with fluciclovine (18F) PET/CT (PET) has demonstrated improved disease-free survival over conventional-only [CT or MRI-based] treatment planning. We hypothesized that incorporating PET would result in larger clinical target volumes (CTV's) without increasing patient-reported toxicities.

#### *Materials/Methods*

: From 2012-2019, 165 post-prostatectomy patients with detectable PSA were randomized (Arm 1 [no PET]: 82; Arm 2 [PET]: 83). Prostate bed target volumes with (CTV1 [45.0-50.4 Gy/1.8Gy]) or without (CTV2/CTV [64.8-70.2Gy/1.8Gy]) pelvic nodes, as well as organ-at-risk doses, were compared pre- v post-PET (Arm 2) using the paired t-test and between Arms using the t-test. Patient-reported outcomes (PRO's) utilized International Prostate Symptom Score (IPSS) & Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP). Univariate & multivariable analyses (MVA) were performed & linear mixed-models were fitted.

#### *Results*

: Median FU of the whole cohort was 3.52 years. All pts had baseline PRO's, 1 pt in Arm 1 & 3 pts in Arm 2 withdrew, & 4 Arm 2 pts had extra-pelvic uptake on PET with XRT aborted, leaving 81 [Arm 1] & 76 pts [Arm 2] for toxicity analysis. Mean CTV1 (427.6cc v 452.2cc [p=0.462], Arm 1 v Arm 2) and CTV2/CTV (137.18cc v 134.2cc [p=0.669]) were similar prior to PET incorporation. CTV1 (454.57cc v 461.33cc; p=0.003) and CTV2/CTV (134.14cc v 135.61cc; p<0.001) were modestly larger following PET incorporation. While V40Gy (p=0.402 & p=0.522 for rectum & bladder, respectively) & V65Gy (p=0.157 & p=0.182 for rectum & bladder, respectively) were not significantly different pre- v post-PET, penile bulb dose significantly increased post-PET (p<0.001 for both V40Gy & V65Gy). On MVA, Arm was not significant for any EPIC-CP subdomain. IPSS & EPIC-CP LMMs were not significantly different between Arms.

#### *Conclusion*

: Despite larger clinical target volumes after incorporation of fluciclovine (18F) PET, we found no significant

difference in patient-reported toxicities with long-term follow-up.

April 5, 2022 / [Cancer Care](#)

## **Real-World Effectiveness of Sipuleucel-T on Overall Survival in Men with Advanced Prostate Cancer Treated with Androgen Receptor-Targeting Agents**

[link.springer.com](https://link.springer.com)

McKay, Rana R.

[Abstract](#)

### *Introduction*

The treatment landscape for metastatic castration-resistant prostate cancer (mCRPC) continues to evolve. Sipuleucel-T was the first immunotherapy approved by the US Food and Drug Administration (FDA) to treat asymptomatic or minimally symptomatic mCRPC. The androgen receptor-targeting agents (ARTAs) abiraterone acetate and enzalutamide were initially approved to treat mCRPC. Looking at chemotherapy-naïve men with mCRPC, we compared survival outcomes between the sipuleucel-T + ARTA cohort (men who received either sipuleucel-T or an ARTA in the first line, and then the other in the second line within 6 months) and the ARTA monotherapy cohort (men who only received ARTA monotherapy).

### *Methods*

This retrospective cohort analysis used longitudinal, adjudicated claims data from the US Medicare Fee-for-Service 100% research identifiable dataset that includes both urologic and oncologic practice settings. Eligible men started their first mCRPC treatment with either sipuleucel-T or ARTA in either 2014 or 2015 and had continuous Medicare Parts A, B, and D eligibility for the subsequent 3 years. A multivariable Cox proportional hazards regression model was used to analyze overall survival (OS), both overall and by index year, and to control for differences.

### *Results*

The sipuleucel-T + ARTA and ARTA monotherapy cohorts comprised 773 and 4642 men, respectively, with different characteristics at treatment start. The most commonly used ARTAs were enzalutamide in the former and abiraterone in the latter cohort. Median OS was 30.4 and 14.3 months in the sipuleucel-T + ARTA and ARTA monotherapy cohorts, respectively, with the sipuleucel-T + ARTA cohort having a 28.3% lower risk of death than the ARTA monotherapy cohort (hazard ratio 0.717; 95% CI 0.648, 0.793;  $p < 0.01$ ).

### *Conclusions*

This real-world study of mCRPC treatment indicates that men receiving sipuleucel-T and ARTAs had a longer median OS than patients receiving treatment with an ARTA alone, suggesting that leveraging mechanisms of action can be beneficial in treating patients with mCRPC.

### [Plain Language Summary](#)

The treatment landscape for metastatic castration-resistant prostate cancer (mCRPC) continues to evolve. There are multiple treatments for mCRPC, including sipuleucel-T, the first US Food and Drug Administration (FDA)-approved immunotherapy, and the androgen receptor-targeting agents (ARTAs) abiraterone acetate and enzalutamide. Although sipuleucel-T uses a unique mechanism of action that may be useful in developing a treatment strategy for mCRPC, an optimal treatment algorithm for prostate cancer remains undefined. Therefore, survival was compared in men with mCRPC who received sipuleucel-T and an ARTA in the first 6 months of treatment with those who received only ARTA monotherapy. A retrospective longitudinal study was conducted using the US Medicare Fee-for-Service 100% research identifiable dataset linked to the National Death Index. Eligible men started their first mCRPC treatment with either sipuleucel-T or ARTA in either 2014 or 2015 and had continuous Medicare eligibility for the subsequent 3 years. Men who received treatment with both sipuleucel-T and an ARTA had a longer median survival (30.4 months) than men who received an ARTA without sipuleucel-T (14.3 months). This represents a 28% reduced risk of death with sipuleucel-T. This real-world study of mCRPC treatment indicates that men receiving sipuleucel T and an ARTA survive longer than men who only receive an ARTA, suggesting that changing the mechanism of action can be beneficial in treating patients with mCRPC.

## MedUni Vienna

[meduniwien.ac.at](http://meduniwien.ac.at)

Medical University of Vienna

(Vienna, 04-04-2022) Prostate cancers remain localised in the majority of cases, giving affected individuals a good chance of survival. However, about 20% of patients develop incurable metastatic prostate cancer, resulting in approximately 5,000 deaths each year in Austria alone. Medical research has not yet adequately explained why metastases occur in some people and not in others. A research team at MedUni Vienna has now discovered specific changes in a protein that drive the growth and spread of prostate cancer. The study was recently published in the prestigious journal "Molecular Cancer".

In the study, the researchers broke new ground and investigated the role of the protein KMT2C in prostate cancer. KMT2C is a genetic component that essentially functions as a regulator of central cellular processes. If KMT2C loses this regulatory ability due to typical cancer-related mutations, this encourages the proliferation of the cancer gene MYC. This in turn causes cells to divide at an increased rate, driving both growth and spread of the cancer.

### New insights into the transition to metastasis

"Our study provides new insights into the previously poorly understood transition from localised prostate cancer to terminal metastatic prostate cancer," says study leader Lukas Kenner (Department of Pathology at MedUni Vienna, Comprehensive Cancer Center of MedUni Vienna and University Hospital Vienna, Department of Laboratory Animal Pathology at Vetmeduni Vienna and the K1 Center CBmed), underlining the significance of the research work. In addition, the knowledge gained about the effects of KMT2C mutations may also generate new momentum for the diagnosis and treatment of prostate cancer.

### Diagnosing aggressive progression at an early stage

KMT2C mutation status can be measured via a blood test, allowing early diagnosis of potentially aggressive progression in prostate cancers. In addition, MYC inhibitors could be used to prevent increased cell division, and hence metastasis, and it is hoped that further scientific studies will substantiate this. MYC inhibitors are essentially new cancer treatment drugs that have already been tested in clinical trials and - if further studies confirm this - could also be used in metastatic prostate cancer in the next few years. "Since a high level of KMT2C mutation characterises many types of cancer, such as breast, lung, colorectal, bladder and even skin cancer, our study results have a great deal of potential in the research, diagnosis and treatment of malignant cancers in general," says Lukas Kenner.

### Service: Molecular Cancer

KMT2C Methyltransferase Domain regulated I INK4A expression suppresses Prostate Cancer metastasis  
Tanja Limberger, Michaela Schleder, Karolina Trachtová, Jiaye Yang, Sandra Högler, Christina Sternberg, Vojtech Bystry, Jan Oppelt, Boris Tichý, Margit Schmeidl, Anton Jäger, Ines Garces de Los Fayos Alonso, Heidi A. Neubauer, Monika Oberhuber, Belinda Schmalzbauer, Sarka Pospisilova, Helmut Dolznig, Wolfgang Wadsak, Zoran Culi, Suzanne D. Turner, Gerda Egger, Sabine Lagger, Lukas Kenner

doi: 10.1186/s12943-022-01542-8

[molecular-cancer.biomedcentral.com/articles/10.1186/s12943-022-01542-8](https://molecular-cancer.biomedcentral.com/articles/10.1186/s12943-022-01542-8)

### Relapsed Prostate Cancer Will Need Other Treatment Approaches

Mark Scholz, MD

[verywellhealth.com](http://verywellhealth.com)

The slow-growing [prostate cancer](#) is different from other cancers in one critical way: People with penises who experience a [relapse](#), or a return, of their disease after surgery are more likely to die from old age than from prostate cancer.

With most common cancers—colon, breast, brain, [melanoma](#), lung—the cancer's return likely means a poor outcome and often leads to death. But with prostate cancer, remission can last up to 10 years. The overall survival rate is 98%. |

This article explains three types of prostate cancer relapse and how they are treated. It discusses the im-

importance of the [prostate-specific antigen](#) (PSA) test in assessing these relapses.

kupicoo / iStockphoto

### **PSA Doubling Time**

The PSA [doubling time](#) (PSADT) represents the amount of time it takes for the PSA level in the body to double. The PSA level may suggest a developing or fast-growing cancer, depending on how fast the PSA doubling occurs.

This matters because of the role that PSA plays. It is a protein produced by the [prostate gland](#) to create between 15% and 30% of the liquid found in semen. This liquid contains the sperm released during ejaculation.

The sensitive PSA test is able to detect a recurring prostate cancer with relatively few cells. This microscopic level of detection is key for those using the PSADT to see if prostate cancer comes back.

When prostate cancer does recur, the PSADT can guide your health care team in developing a treatment plan. These plans will differ, depending on what kind of relapse you may experience.

### **PSA Levels and Prostate Cancer Relapse**

For people with relapsed cancer, the threshold to determine relapse will change based on whether [surgery](#) or [radiation](#) was used to treat it:<sup>2</sup>

PSA levels drop to zero after surgery. The cancer has returned if PSA levels are over 0.2 nanograms per milliliter (ng/mL).

PSA levels are low but present after radiation. A relapse has occurred when the PSA levels rise 2 points higher than whatever the lowest score achieved after radiation.

### **Types of Relapse**

Three different grades are used to describe prostate cancer relapse: low, intermediate and high. Your treatment options will depend on which grade of relapse you experience.

Your healthcare provider also will consider the level of your original risk at diagnosis when developing a treatment plan.<sup>3</sup>

### **Symptoms**

In many cases, symptoms of a recurring prostate cancer are similar to those you experienced with the original diagnosis. They include:<sup>4</sup>

- [Urinary frequency](#), and/or the urgent need to urinate
- Urinary hesitancy, with delays in starting or stopping flow of urine
- Blood in your urine, called [hematuria](#)
- Bone pain near the prostate region
- Unintentional [weight loss](#)

### **Diagnosis**

After your initial treatment for prostate cancer, you will continue care with your healthcare provider, likely a [urologist](#) who specializes in urinary tract conditions. They will monitor PSA levels to watch for any recurrence, keeping a close eye on the PSADT.

They may want to do a [prostate biopsy](#) if the level reaches cause for concern or there are other signs of recurrence. A pathologist will view the tissue sample taken from the biopsy to see if cancer cells are again present. A [digital rectal exam](#) also may be part of your examination.

Imaging may be used to diagnose a prostate cancer relapse. These scans rely on positron emission tomography (PET) but may also include magnetic resonance imaging (MRI) or computed tomography (CT).

Some imaging tests used specifically for prostate cancer include:

- Newer F18 PET [bone scans](#) that detect much smaller cancers<sup>5</sup>
- [PET scans using axumin](#),<sup>6</sup> C11 acetate, or choline

MRI or [CT scans](#) that can show any spread to pelvic [lymph nodes](#)

Your treatment for prostate cancer relapse will depend on your PSADT and a number of other factors. Some relapses are so low-grade that no treatment at all will be required.

For example, someone with a PSADT of more than 12 months and a PSA level of less than 10 ng/mL may be



monitored with repeat PSA tests. Or, relapse may occur in an older person whose life expectancy makes treatment unlikely or unnecessary.

Treatments for prostate cancer relapse may include surgery, radiation, and medication. Keep in mind that the treatment strategy is tailored to the level of relapse: low, intermediate, or high.

It also will depend on whether your initial prostate cancer was treated with surgery or radiation.

Specific treatment strategies, such as radiation combined with a hormone therapy called Lupron, are often used to care for people who have had surgery to treat their prostate cancer radiation.

### **Low and Intermediate Risk**

Radiation to the [prostate bed](#), a common secondary site for prostate cancers, may be a treatment strategy for people who were low or intermediate risk before their surgery.

People in these risk categories also are likely to have a PSADT doubling time of 6 to 12 months or less. Their diagnostic scans show no evidence that the prostate cancer has [metastasized](#), or spread, to other parts of the body.

Hormone therapy is another treatment option, alone or after radiation. Lupron (leuprolide acetate) is the most commonly used of the hormone therapy medications, but others include:

Trelstar (triptorelin pamoate)

Firmagon (degarelix)

Zoladex (goserelin)

Hormone therapy medications work because prostate cancer cells need testosterone to survive. These drugs "starve" the cells by blocking the testosterone.

As with many types of cancer therapy, the earlier treatment is started the better it works.

### **High Risk**

People with prostate cancer relapse and a PSADT of less than six months are at much greater risk of the cancer's spread. Your healthcare provider will likely choose a more aggressive treatment approach as a result.

Radiation therapy may be combined with Lupron hormone therapy for as long as 12 to 18 months in these cases. Other powerful drug options, including those used to treat prostate cancer that may have spread, include:

Zytiga (abiraterone acetate)

Xtandi (enzalutamide)

Taxotere (docetaxel)

In some cases, your healthcare provider may combine one or more drugs and then treat with radiation a few months after the drugs are started. The radiation targets known sites where the cancer has spread. It also may target common sites of spread, such as pelvic lymph nodes and the prostate bed.

### **What Is Intermittent Therapy?**

In some cases, hormone therapy drugs can be used at intervals in order to reduce the effects of having low testosterone. The PSA usually drops to less than 0.1 within six months of starting therapy, so the drug treatment is then stopped. The drug is restarted after a "break" when PSA levels rise.

### **Milder Hormone Therapy**

Sometimes, when people are older or more frail, they may be given mild forms of hormone therapy such as Casodex (bicalutamide).

There is often less difficulty with common side effects, which include:

Fatigue

Weakness

Weight gain

Breast growth

### **Other Treatment Options**

There are other treatment possibilities for prostate cancer, and researchers are working to advance these options for people with an initial cancer or one that recurs. These options include:

[Chemotherapy](#) drug combinations

[Cryotherapy](#), a treatment that relies on extreme cold to freeze tissue

[Immunotherapy](#) drugs, such as Provenge (sipuleucel-T) and [Keytruda \(pembrolizumab\)](#)<sup>7</sup>

Targeted therapy drugs, including Olaparib ([lynparza](#))<sup>8</sup>

## Summary

Prostate cancer relapse happens when your previously treated cancer returns. How it will be assessed and treated depends on your initial cancer diagnosis, whether it was treated with surgery or not, your recent PSA doubling time, and factors including age and overall health.

Your symptoms may be similar to your initial cancer, and techniques used to diagnose prostate cancer relapse—like a biopsy or digital rectal exam—are ones you likely know.

Your healthcare provider can assess your recurring cancer as low, intermediate, or high risk. There are different treatments for each group, including radiation, hormone therapy, and other medications.

## A Word From Verywell

Treatment for prostate cancer relapse after surgery is never a one-size-fits-all approach. Be sure to follow up with your provider so that your PSADT times are closely monitored for signs your cancer has returned.

## Frequently Asked Questions

Is the PSADT Different From a Gleason Score?

Yes, very much so. The Gleason score is used to grade, or describe, existing prostate cancers and how advanced they are. Pathologists examine prostate cells under a microscope and assign a score from 1 to 5. The higher the score, the less the concern over prognosis and treatment.<sup>9</sup>

Is There a "Normal" PSA Level?

Yes — and no. Your levels may vary depending on age, level of sexual activity, what medications you take, or how much (and when) you engage in exercise, such as biking. Historically, a PSA over 4 ng/mL is associated with a higher risk of cancer, but some people with lower levels have cancer, and sometimes people with higher levels don't.<sup>10</sup>

Thanks for your feedback!

Verywell Health uses only high-quality sources, including peer-reviewed studies, to support the facts within our articles. Read our [editorial process](#) to learn more about how we fact-check and keep our content accurate, reliable, and trustworthy.

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[medpagetoday.com](#)

## Should We Use PSA to Find Active Surveillance Candidates?

Howard Wolinsky

7-9 minutes

— [Widespread testing can lead to overdiagnosis and overtreatment](#)

by Contributing Writer, MedPage Today April 3, 2022

As a patient on active surveillance (AS) since 2010, I always considered AS a solution for men like me with very low-risk prostate cancer. Is it time to rethink that?

E. David Crawford, MD, a urologist and a long-time prostate cancer researcher, surprised me when he explained that in his view, prostate-specific antigen (PSA) testing should *not* focus on finding men to go on AS.

Rather, he argues that PSA testing should be used to determine which men *do not* need PSA testing on an annual or more frequent basis, as this can help avoid unnecessary biopsies.

In [an interview](#) with *MedPage Today*, Crawford said that PSA used along with molecular testing can help many men stay off routine PSA for perhaps 5 to 10 years before repeating it, modeling it after colonoscopies. He said his approach will save many men from biopsies, which carry risks of sepsis and other infections, and also spare them years of worry from "anxious surveillance."

Back in the 1980s, Crawford started working with the then new test to effectively follow men with more advanced prostate cancer.

One of his patients with metastatic prostate cancer asked the urologist a simple question: *Why not use PSA testing to find prostate cancers early?*

The patient had some clout. He was Perry Lieber, operations manager for one of the world's richest men at the time, Howard Hughes.

Crawford said he was resistant to the screening idea at first because he didn't think men would go for it.

In 1986, the FDA approved the PSA test to monitor the progression of prostate cancer in men who had already been diagnosed with the disease.

The 2014 book, [The Great Prostate Hoax: How Big Medicine Hijacked the PSA Test and Caused a Public Health Disaster](#), spells out how the FDA, under pressure from the manufacturer and patient advocates, in 1994 approved the use of the PSA test with a digital rectal exam to test asymptomatic men for prostate cancer.

The controversy continues. Some lives were saved, but widespread testing was accompanied by an epidemic of overdiagnosis and overtreatment of low-risk prostate cancer.

Active surveillance was developed 30 years ago as a strategy for close monitoring of men with low-risk disease. Crawford said the arrival of molecular tests of prostate cancer tissue changed the game once again.

#### [Medical News from Around the Web](#)

PSA blood levels of 4.0 ng/mL sent men from the primary care physician to the urologist, with the consequence being in most cases, until recently, "definitive" treatment.

Crawford suggests a new cutoff of 1.5 ng/mL.

"I picked that cutoff because when you start going above that you do have a risk of prostate cancer that is significant. And if you let it get above a cutoff of 4, you'll find more cancers but you'll also miss some bad ones that might have been found earlier," he said.

His research showed that with this approach, 70% of men could bypass biopsies and avoid years of anxiety. He suggests follow-up in 5 to 10 years.

"This is where you get into trouble and that's where we started integrating what already had been done in a lot of other cancers -- molecular markers -- to find the people who had a problem. Everybody got very proud of themselves for finding all these cancers and putting patients on active surveillance rather than doing surgery or radiation," said Crawford, who runs the website [PCmarkers.com](#).

"My point is we don't want to find patients for active surveillance. It is an area that creates a lot of mental anguish. It creates a lot of follow-up biopsies. It generates a lot of MRIs. Markers can help us," he said, referring to such tests as SelectMDx, 4Kscore, and phi.

He contends that family practitioners, who order about 90% of PSAs, need a simple figure to focus on: 1.5 ng/mL.

"They can't remember all the nuances. They get turned off by it. When we find somebody is at risk,

we do a molecular marker,' said Crawford.

"It's amazing that doctors don't rely on markers to help them to make a decision on when to biopsy. And that's what my whole direction is about -- to eliminate active surveillance by not finding people that go on active surveillance. We want to find people that need active treatment, surgery, and radiation."

The proposal elicits mixed responses.

Family physician Stephen Spann, MD, founding dean of the College of Medicine and vice-president for Medical Affairs at the University of Houston, is concerned that the lower the cutoff of PSA, the greater the risk of increased false-positive rates and the greater the detection of "minimal cancer."

He said, "I would just want to know, what is the evidence that this is going to make a difference in patient survival or even quality of life. We don't even know -- we don't even have hard data today -- what early detection leads to if you get prostate cancer. The trials that were done on that 15 or 20 years ago were sort of a toss-up. It's a personal decision because we don't have really rock-hard, solid evidence that early detection leads to prolonged survival. And if you get early detected and treated, you have a pretty high chance of becoming impotent and incontinent."

But Todd Morgan, MD -- chief of urologic oncology at Michigan Medicine in Ann Arbor, and principal investigator of two large randomized controlled trials evaluating tissue-based biomarkers in men with localized prostate cancer -- said he agrees with the idea that PSA can be used as a risk stratification tool. Morgan, who until last year served on the National Comprehensive Cancer Network guidelines panel for low-risk prostate cancer, noted that the NCCN guideline has a PSA cutoff of 1.0.

"If your PSA is really low, you probably don't need further PSA screening for 5 years. There are pros and cons because the higher the threshold you're going to start to miss a few cases of cancer, but you can rule out a whole lot more patients," he said.

*Howard Wolinsky is a Chicago-based medical writer. He has written the blog, "A Patient's Journey," for Med-Page Today since 2016. He is the editor of the Substack newsletter, [TheActiveSurveillor.com](https://www.theactivesurveillor.com).*

*Active Surveillance Patients International and the AnCan Virtual Support Group for Active Surveillance are holding a webinar with other groups, "Your Voice in the Future of Active Surveillance" at 11 a.m. Eastern Time on April 22. The free meeting features top physicians in the field internationally, including Laurence Klotz, MD, of the University of Toronto, and Peter Carroll, MD, of the University of California, San Francisco. [Register here](#).*

## **Grade and stage misclassification in intermediate unfavorable-risk prostate cancer radiotherapy candidates**

[Gabriele Sorce MD](#), [Rocco Simone Flammia MD](#), [Benedikt Hoeh MD](#), [Francesco Chierigo MD](#), [Lukas Hohenhorst MD](#), [Andrea Panunzio MD](#), [Armando Stabile MD](#), [Giorgio Gandaglia MD](#) ... [See all authors](#)

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[Abstract](#)

*Background*

We tested for upgrading (Gleason grade group [GGG]  $\geq 4$ ) and/or upstaging to non-organ-confined stage ([NOC]  $\geq$  pT3/pN1) in intermediate unfavorable-risk (IU) prostate cancer (PCa) patients treated with radical prostatectomy, since both change the considerations for dose and/or type of radiotherapy (RT) and duration of androgen deprivation therapy (ADT).

*Methods*

We relied on Surveillance, Epidemiology, and End Results (2010–2015). Proportions of (a) upgrading, (b) upstaging, or (c) upgrading and/or upstaging were tabulated and tested in multivariable logistic regression models.

*Results*

We identified 7269 IU PCa patients. Upgrading was recorded in 479 (6.6%) and upstaging in 2398 (33.0%), for a total of 2616 (36.0%) upgraded and/or upstaged patients, who no longer fulfilled the IU grade and stage definition. Prostate-specific antigen, clinical stage, biopsy GGG, and percentage of positive cores, neither individually nor in

multivariable logistic regression models, discriminated between upgraded and/or upstaged patients versus others.

### Conclusions

IU PCa patients showed very high (36%) upgrading and/or upstaging proportion. Interestingly, the overwhelming majority of those were upstaged to NOC. Conversely, very few were upgraded to GGG  $\geq$  4. In consequence, more than one-third of IU PCa patients treated with RT may be exposed to suboptimal dose and/or type of RT and to insufficient duration of ADT, since their true grade and stage corresponded to high-risk PCa definition, instead of IU PCa. Data about magnetic resonance imaging were not available but may potentially help with better stage discrimination

## **<sup>177</sup>Lu-PSMA-617 and Idronoxil in Men with End-Stage Metastatic Castration-Resistant Prostate Cancer (LuPIN): Patient Outcomes and Predictors of Treatment Response in a Phase I/II Trial**

[jnm.snmjournals.org](http://jnm.snmjournals.org)

Sarenya Pathmanandavel

Research Article Featured Article of the Month

, Megan Crumbaker, Andrew O. Yam, Andrew Nguyen, Christopher Rofe, Elizabeth Hovey, Craig Gedye, Edmond M. Kwan, Christine Hauser, Arun A. Azad, Peter Eu, Andrew J. Martin, Anthony M. Joshua and Louise Emmett

Journal of Nuclear Medicine April 2022, 63 (4) 560-566; DOI: <https://doi.org/10.2967/jnumed.121.262552>

### Abstract

<sup>177</sup>Lu-PSMA-617 is an effective therapy for metastatic castration-resistant prostate cancer (mCRPC). However, treatment resistance occurs frequently, and combination therapies may improve outcomes. We report the final safety and efficacy results of a phase I/II study combining <sup>177</sup>Lu-PSMA-617 with idronoxil (NOX66), a radiosensitizer, and examine potential clinical, blood-based, and imaging biomarkers.

**Methods:** Fifty-six men with progressive mCRPC previously treated with taxane chemotherapy and novel androgen signaling inhibitor (ASI) were enrolled. Patients received up to 6 doses of <sup>177</sup>Lu-PSMA-617 (7.5 GBq) on day 1 in combination with a NOX66 suppository on days 1–10 of each 6-wk cycle. Cohort 1 ( $n = 8$ ) received 400 mg of NOX66, cohort 2 ( $n = 24$ ) received 800 mg, and cohort 3 ( $n = 24$ ) received 1,200 mg. <sup>68</sup>Ga-PSMA and <sup>18</sup>F-FDG PET/CT were performed at study entry, and semiquantitative imaging analysis was undertaken. Blood samples were collected for analysis of blood-based biomarkers, including androgen receptor splice variant 7 expression. The primary outcomes were safety and tolerability; secondary outcomes included efficacy, pain scores, and xerostomia. Regression analyses were performed to explore the prognostic value of baseline clinical, blood-based, and imaging parameters.

**Results:** Fifty-six of the 100 men screened were enrolled (56%), with a screening failure rate of 26% (26/100) for PET imaging criteria. All men had received prior treatment with ASI and docetaxel, and 95% (53/56) had received cabazitaxel. Ninety-six percent (54/56) of patients received at least 2 cycles of combination NOX66 and <sup>177</sup>Lu-PSMA-617, and 46% (26/56) completed 6 cycles. Common adverse events were anemia, fatigue, and xerostomia. Anal irritation attributable to NOX66 occurred in 38%. Forty-eight of 56 had a reduction in prostate-specific antigen (PSA) level (86%; 95% CI, 74%–94%); 34 of 56 (61%; 95% CI, 47%–74%) had a PSA reduction of at least 50%. Median PSA progression-free survival was 7.5 mo (95% CI, 5.9–9 mo), and median overall survival was 19.7 mo (95% CI, 9.5–30 mo). A higher PSMA SUV<sub>mean</sub> correlated with treatment response, whereas a higher PSMA tumor volume and prior treatment with ASI for less than 12 mo were associated with worse overall survival.

**Conclusion:** NOX66 with <sup>177</sup>Lu-PSMA-617 is a safe and feasible strategy in men being treated with third-line therapy and beyond for mCRPC. PSMA SUV<sub>mean</sub>, PSMA-avid tumor volume, and duration of treatment with ASI were independently associated with outcome.

[jnm.snmjournals.org](http://jnm.snmjournals.org)

## **A Comprehensive Assessment of <sup>68</sup>Ga-PSMA-II PET in Biochemically Recurrent Prostate Cancer: Results from a Prospective Multicenter Study on 2,005 Patients**

Monica Abghari-Gerst

Research Article Clinical Investigation

, Wesley R. Armstrong, Kathleen Nguyen, Jeremie Calais, Johannes Czernin, David Lin, Namasvi Jariwala,



Melissa Rodnick, Thomas A. Hope, Jason Hearn, Jeffrey S. Montgomery, Ajjai Alva, Zachery R. Reichert, Daniel E. Spratt, Timothy D. Johnson, Peter J.H. Scott and Morand Piert

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## Abstract

We prospectively investigated the performance of the prostate-specific membrane antigen (PSMA) ligand  $^{68}\text{Ga}$ -PSMA-11 for detecting prostate adenocarcinoma in patients with elevated levels of prostate-specific antigen (PSA) after initial therapy.

**Methods:**  $^{68}\text{Ga}$ -PSMA-11 hybrid PET was performed on 2,005 patients at the time of biochemically recurrent prostate cancer after radical prostatectomy (RP) (50.8%), definitive radiation therapy (RT) (19.7%), or RP with postoperative RT (PORT) (29.6%). The presence of prostate cancer was assessed qualitatively (detection rate = positivity rate) and quantitatively on a per-patient and per-region basis, creating a disease burden estimate from the presence or absence of local (prostate/prostate bed), nodal (N1: pelvis), and distant metastatic (M1: distant soft tissue and bone) disease. The primary study endpoint was the positive predictive value (PPV) of  $^{68}\text{Ga}$ -PSMA-11 PET/CT confirmed by histopathology.

**Results:** After RP, the scan detection rate increased significantly with rising PSA level (44.8% at PSA < 0.25%–96.2% at PSA > 10 ng/mL;  $P < 0.001$ ). The detection rate significantly increased with rising PSA level in each individual region, overall disease burden, prior androgen deprivation, clinical T-stage, and Gleason grading from the RP specimen ( $P < 0.001$ ). After RT, the detection rate for in-gland prostate recurrence was 64.0%, compared with 20.6% prostate bed recurrence after RP and 13.3% after PORT. PSMA-positive pelvic nodal disease was detected in 42.7% after RP, 40.8% after PORT, and 38.8% after RT. In patients with histopathologic validation, the PPV per patient was 0.82 (146/179). The  $\text{SUV}_{\text{max}}$  of histologically proven true-positive lesions was significantly higher than that of false-positive lesions (median, 11.0 [interquartile range, 6.3–22.2] vs. 5.1 [interquartile range, 2.2–7.4];  $P < 0.001$ ).

**Conclusion:** We confirmed a high PPV for  $^{68}\text{Ga}$ -PSMA-11 PET in biochemical recurrence and the PSA level as the main predictor of scan positivity.

## New Trials in Prostate Cancer: Could Your Patients Benefit?

[medscape.com](https://www.medscape.com)

Helen Leask

A number of studies in [prostate cancer](#) have started enrolling in recent months. Perhaps one of your patients could benefit from enrolling in one of these trials?

**Unfavorable intermediate-risk prostate cancer.** Patients who have received this diagnosis in the previous 12 months can join a phase 2 study that avoids androgen-deprivation therapy (ADT). The usual approach for such patients is ADT plus radiation treatment. The trial is, instead, testing two different levels of stereotactic body [radiation therapy](#) (SBRT) guided by the [Decipher score](#), a genetic measure that assesses the likelihood of the tumor spreading.

All participants will receive SBRT to the seminal prostate and seminal vesicles every other day. Men with high-risk Decipher scores will also receive radiation to any dominant lesion within the prostate and to the lymph nodes in the pelvis. The sole outcome measure is progression-free survival (PFS) over 2 years as assessed by PSA. Overall survival (OS) and quality of life (QoL) will not be tracked. Memorial Sloan Kettering Cancer Center (MSKCC) has seven sites across New Jersey and New York that started recruiting 145 participants in December. [More details at clinicaltrials.gov.](#)

Commenting on the MSKCC study, Marc Garnick, MD, professor of medicine, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, who is not an investigator in the trial, said that the lack of randomization may mean that the study "may not move the field forward in helping determine if ADT is or is not needed in this population."

**Unfavorable intermediate-risk prostate cancer.** Men with this diagnosis can also join a National Cancer Institute (NCI)-partnered phase 3 study that takes a randomized approach to the question of whether ADT — along with its devastating side effects — can be avoided in men with low-risk Decipher scores. The trial will also hope to improve prospects for high-risk men by adding darolutamide (Nubeqa), a medication for castration-resistant prostate cancer, to 'usual therapy' of radiation plus ADT.

Low-risk participants will receive up to 11 weeks of radiation treatment plus up to 6 months of ADT (ie, usual therapy) or radiation alone. All men with high-risk Decipher scores will receive usual therapy; one group will also receive daily oral darolutamide. The study opened in November, hoping to recruit 2050 participants across 14 US states. Development of metastasis is the primary outcome; OS and QoL are secondary outcomes. [More details at clinicaltrials.gov](http://clinicaltrials.gov).

Garnick commented that this study is "potentially important" and "makes a lot of sense as long as the specific criteria for low- vs high-risk genomic classification is adhered to and homogeneous among the study populations." **Prostate cancer that has spread to the bones.** Adults with this type of prostate cancer who have already undergone a [prostatectomy](http://clinicaltrials.gov) or 'definitive radiotherapy' are sought for a phase 2 trial testing the addition of radium (Ra-223) dichloride to SBRT. One group of men will receive a 'sandwich' of two doses of Ra-223 over 4 weeks, followed by a week's worth of radiation, then four doses of Ra-223 over 16 weeks. Participants in the control group will have radiation only. The study opened in November and aims to enroll 136 participants across Colorado, New Jersey, New York, and Ohio. PFS is the only outcome measure. OS and QoL will not be tracked. [More details at clinicaltrials.gov](http://clinicaltrials.gov).

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### On the Lighter Side





# On the Lighter Side

