Informed Prostate Cancer Support Group Inc.
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Tuesday, November 16, 2021

NOVEMBER 2021 NEWSLETTER

P.O. Box 420142 San Diego, CA 92142
Phone: 619-890-8447 Web: http://ipcsg.org

STREAMING ONLINE LIVE

Volume 14 Issue 11

- **Saturday, Nov 20, 2021 IPCSG - Live-Stream Event, 10:00am PT**

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- Dr. Robert Pugach is the Medical Director of Western States HIFU. He has one of the largest prostate cancer practices in California and treats patients from all states and internationally. Dr. Pugach has devoted his career on effective minimally invasive technologies and procedures that treat a variety of urological conditions
- One remarkable treatment for prostate cancer is High Intensity Focused Ultrasound (HIFU). He is one of the world's most experienced HIFU practitioners and is in a select group of urologists certified to teach other doctors how to perform HIFU. Additionally, Dr. Pugach is one of the most experienced urologist in cryoablation – prostate freezing – for cancer.

- 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://ipcsg.blogspot.com/**
- **For Comments, Ideas and Questions,** email to Newsletter@ipcsg.org

October 2021 Informed Prostate Cancer Support Group Meeting

Summary by Bill Lewis

Recent in Advances in the Care of Patients with Prostate Cancer

Rana R. McKay, MD is an Associate Professor of Medicine and Urology, UCSD. She is a board-certified medical oncologist who specializes in treating people with urogenital cancers, including bladder, kidney, prostate and testicular cancer. Dr. McKay leads a multi-disciplinary prostate cancer clinic, focused on delivering advanced cancer care through a coordinated team approach. This clinic enables men diagnosed with aggressive prostate cancer - either early-stage or metastatic - to see her and a team of doctors including a urologist and radiation oncologist to obtain highly specialized care.

Genetic testing for patients with prostate cancer

Genes are pieces of DNA inside our cells that tell the cell how to make the proteins the body needs to function. DNA is the genetic "blueprint" in each cell, from which RNA is made, which then directs the formation of proteins – the building blocks of each cell in the body. Genes include inherited traits that are passed from a parent to a child, such as hair color, eye color, height range and susceptibility to disease.

Mutations are changes in genes that can promote the development of cancer. Mutations can cause a call to make (or not make) proteins that affect how the cell grows and divides. There are two types of mutations. *Inherited* (**Germline**) mutations are less common. A mutation in the egg or sperm that unite, leads to every cell in the child having the mutation. This can lead to "cancer family syndrome" or other inherited disease susceptibilities. The other, more common mutation type is **Somatic** – mutations that are *acquired* somehow during an individual's

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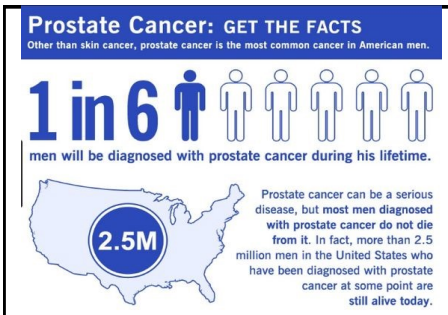

Organization

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

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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://ipcsg.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://ipcsg.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:

First we have Bill Lewis's summary of Rana McKay's presentation from the last meeting on recent advances in the state of the art. Then we have the following Articles of Interest:

1. Registration for major active surveillance (AS) research conference now open *If you are on AS, they want your participation*
2. Shock, Disbelief as NCCN Changes Prostate Cancer Guidance *The powers that be seem to have gone back in time for low risk PCa (Gleason 6) recommending radiation and surgery as alternatives to AS.*
3. Are the Right Men Getting Screened for Prostate Cancer? *when will the message get through to the public, clinicians, and health care professionals that inappropriate PSA testing outside evidence-based recommendations should cease?*
4. The Paradox of a Man's Most-Feared Test, the PSA *the prostate-specific antigen test — a simple blood test — is one of the most lauded yet also most controversial tests for prostate cancer.*

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life. Unless they are in cells that give rise to egg or sperm cells, they cannot be passed on to a child. They can arise in any type of tissue, leading to or affecting the course of various diseases, such as the various kinds of cancer – including prostate cancer.

Genetic testing is the use of medical tests to look at inherited and/or acquired mutations in a person's genes, using tissue sampling, blood, saliva or urine. Inherited (germline) testing is "clinically indicated" for metastatic; regional; very-high or high-risk localized cancer; or due to a family history (by specific cancer, relative degree, and age). It may be considered for intermediate-risk with intraductal or cribriform lesions (both implying a negative prognosis), or for prostate cancer with a personal history of other cancer.

Genetic testing can suggest targeted therapy options for patients tested with advanced disease. There has been a paradigm shift in selecting treatments for cancer. The early "one-size-fits-all" approach gave way first to "stratified medicine," where one takes into account disease subtypes, risk profiles, demographics, socio-economics, clinical features, biomarkers and molecular sub-populations. Now, "**precision medicine**" seeks to tailor treatments to the individual patient level, including genomics, lifestyle, personal preferences, health history, medical records, compliance, etc. Genetic testing can also point to other cancer screening options for patients tested (e.g., skin examination, mammograms for women, colonoscopy) and can suggest cascade testing for first degree relatives.

Most of the time, **germline testing** yields negative results (i.e., no useful information). Sometimes, especially for non-white, non-European males, the results show a "VUS" (a variant of uncertain significance). This means that we don't know what the genetic variation implies, but 95% of the time it is concluded to be benign with respect to cancer. However, it may become significant if there is a family history of cancer. The least common result from germline testing is a positive (significant) genetic variation, and the patient is then referred for genetic counseling.

Somatic testing (of tumor tissue) may likewise lead to three categories of results. Biologically relevant, "actionable" variations may point to ("predict") appropriate precision therapies and even be prognostic about likely outcomes. Biologically relevant, but nonactionable variations may provide prognostic information about the likely course of the disease. And there may be "VUS" results, whose clinical significance is unknown.

The most commonly found somatic variations are in the **androgen receptor pathway** (involving receptor amplification, mutation or deletion), which are treated with various ADT (androgen deprivation therapy) drugs. There are also occurrences of variations in the **DNA repair pathway** (i.e., BRCA and other mutations), for which drugs for treatment are emerging. Less common variations are found in the P13K (including PTEN gene) and WNT pathways. There were 99 prostate cancer genetic variations shown on a slide, with decreasing frequency of occurrence, but in the aggregate, comprising significant but mostly (as yet) nonactionable variations.

Novel imaging for patients with prostate cancer

PET imaging is a test that can reveal the metabolic or biochemical function of tissues or organs. It detects pairs of gamma rays emitted indirectly by positron-emitting radionuclides (also called radiopharmaceuticals, radionuclides or radiotracers). The radionuclides used so far include C-11, gallium-68, fluorine-18 and copper-64. These are attached to a molecule such as choline (participates in membrane lipid biosynthesis), fluciclovine (an amino acid analog), or PSMA (prostate specific membrane antigen, a transmembrane protein of cells), except in the case of sodium fluoride (which specifically targets bones). The half-lives vary widely, from 20.3 minutes for C-11, to 67.7 for Ga-68, to 109.8 for F-18 and 762.1 for Cu-64. All can be produced in a cyclotron, but Ga-68 can alternatively be produced in a lab using a "generator," making it potentially more widely available.

PSMA is especially of interest because it is overexpressed in prostate cancer – a hundred to a thousand times more than in benign tissue, with the greatest expression in high grade and hormone resistant prostate cancer. A small percentage of prostate cancer patients do not have this over expression, so PSMA imaging cannot be used with them.

PET data is usually overlaid on a CT scan, though sometimes on an MRI, to provide the anatomical location of the bright spots the PET agent produces.

There are some causes of false positive spot in PSMA imaging, including rib lesions, various nerve ganglia, and other tumors such as lung cancer, thyroid cancer or hepatocellular carcinoma.

Both Ga-68 and F-18 PSMA agents have been approved by the FDA [and since this talk was given, both are

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approved by Medicare. Ga-68 is available at UCLA and UCSF, and F-18 PSMA (known as Pylarify or Pyl) is available at UCSD and at Imaging Healthcare Specialists in San Diego].

Recent therapeutic advances for patients with prostate cancer

Lutetium-177-PSMA-617 is a new treatment agent, with combines a beta-particle-emitting radioligand with a PSMA-binding protein, that delivers the lutetium-177 to and into the cancer cell, where it damages DNA sufficiently to cause cell death of that cell and neighboring cells.

The VISION study showed that the cohort (advanced disease; prior chemo and hormone therapy) receiving the treatment lived 15.3 months on average, vs. 11.3 for the cohort. About one-third of the patients had their PSA continue rising despite the treatment. [This writer is not terribly impressed, given the cost. Combined therapy and/or more restrictive patient selection will probably be needed.] See the video or buy the dvd for the slides, to see more detailed data, including side effects.

PARP inhibitors have shown effectiveness in patients with a BRCA mutation, by preventing repair of DNA breaks and leading to death of the cancer cell. The PROFOUND study showed Olaparib gave 7.4 vs 3.6 months of disease "progression-free survival" and improved overall survival from 14.7 to 19.1 months. [Again, is the benefit worth the cost?] Another study with Rucaparib also showed some benefit, so the FDA has approved both drugs.

GnRH targeting drugs are the backbone of treatments for advance prostate cancer. Traditionally, LHRH (luteinizing hormone-releasing hormone) **agonists** such as leuprolide ("Lupron") have been used, which overstimulate the anterior pituitary gland, causing it to stop signaling for the production of LH, which is needed for testosterone production – which then is needed by most prostate tumors for growth. More recently, LHRH **antagonists** such as degarelix ("Firmagon") have been developed, which directly block the production of LH and therefore of testosterone. The HERO trial tested a new ORAL antagonist, relugolix ("Orgovyx") vs the traditional Lupron (injected) for 48 weeks, and found testosterone was suppressed even slightly better. Also, after the treatment was stopped, the patients' testosterone level recovered much more quickly (to 280 ng/dL vs 50 after 90 days). Side effects were very similar for the two cohorts, except there was a bit more diarrhea with relugolix, and about half as many major cardiovascular events. There is only limited data yet for combining relugolix with enzalutamide ("Xtandi"), abiraterone ("Zytiga") or apalutamide ("Erleada").

CAR-T therapy involves reengineering T-cells harvested from a patient, to produce a PSMA protein, P-PSMA -101, which the immune system considers an invader, and attacks it, and then also attacks cells that have endogenous PSMA in their cell membranes – i.e., prostate cancer cells. It is a non-viral gene insertion technology that enables efficient and stable integration into the T-cell DNA, with "multiple safety, timeline and cost benefits," including more than 20X loading into the T-cells vs. insertion via viruses. This is part of a study at UCSD, which is still recruiting patients, and the initial results with 9 patients are encouraging.

CCW702 is a "bispecific antibody" to PSMA. One end of the large molecule binds to PSMA on cells, and the other end targets a certain type of T-cell, bringing it in close proximity to the cancer cell. This trial is also open at UCSD.

Cirmtuzumab + Docetaxel is to be tested soon in a trial at UCSD. WNT5A initiates a proliferatory pathway associated with cancer growth and metastasis, by binding to ROR1. ROR1 is also important in the progression to neuroendocrine prostate cancer. Cirmtuzumab (a monoclonal antibody) binds to ROR1, thereby blocking the WNT5A pathway and inhibiting cancer growth and metastasis.

COSMIC 021 is now an ongoing Phase 3 study using Cabozantinib ("Cabometyx;" an oral tyrosine kinase inhibitor) + Atezolizumab (an immunotherapy drug). In the small Phase 1 study, tumor regression was seen in 70-77% of patients as "best change from baseline in sum of target lesions."

VERU-111, an oral microtubule inhibitor similar to Docetaxel, targets the cytoskeleton and disrupts microtubule assembly. Ten men reached at least 4 cycles of continuous dosing, with most having a decrease in PSA and achieving stable disease. It is now being tested in a large Phase 3 trial.

Summary:

There have been advances in genetic testing for patients with prostate cancer, and testing is recommended for

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select patients. New PET imaging tools are available to aid in prostate cancer detection. Many therapeutic treatments are currently in development and have demonstrated early efficacy in select patients.

Questions:

Is UCSD involved in trials for prostate cancer through the Alliance Cooperative Group? The PREDICT trial is being prepared, but is a year away from enrollment.

Will Ga-68 PSMA scans be offered at UCSD? Probably, but Pylarify is already available, and the agents are essentially equivalent (except for the longer half-life of the F-18 Pylarify agent).

What about metformin to reduce metabolic syndrome in connection with ADT? There is a lot of mixed data, but in patients without metabolic syndrome risk factors (i.e., good health, low cholesterol, good hemoglobin values, regular exercise, etc.), adding metformin has been shown to not improve prostate cancer treatment outcomes, and has some side effects such as fatigue and GI toxicity. But if there are risk factors such as obesity or prediabetes, she believes metformin would be useful.

What about cases in second-generation ADT, in which PSA decreases but the cancer progresses? In advanced, castrate-resistant prostate cancer, there are many other pathways beside the androgen receptor pathway that can promote cancer growth. About 15-20% of these advanced-disease patients develop neuroendocrine-differentiated cancer. But overall, it is rare that PSA decline does not prevent cancer growth. If it occurs, it is in the late stages of the disease after many kinds of treatments.

What about use of chemo as a primary treatment after recurrence, in conjunction with ADT? In addition to the CHAARTED and STAMPEDE studies, a recent study of newly-diagnosed, high-risk patients showed a clear benefit for "early chemo." In the case of recurrence, it would be important to consider the individual case (disease burden, aggressiveness, etc.).

What is the wait time and cost for Pylarify at UCSD? The wait time currently is 2-3 weeks. Cost can be covered by Medicare, but with private insurance, the cost is quite variable.

What are the requirements to qualify to receive a Pylarify scan? It depends on the insurance company. A rising PSA after definitive treatment is the usual qualification.

Is C-11 used anymore? Not really.

Is SBRT (short-course radiation therapy) used to treat oligometastatic disease at UCSD? Yes, even though they don't have data on long-term outcomes.

Which vendors does she recommend for genetic testing? She favors Caris (wide range of genes tested) or Tempus, for somatic testing. Invitae and Ambry or others for germline testing.

Is there a periodic review of new information relating to a genetic test done in the past? Yes, though it doesn't happen often, the company will issue a new report.

We recommend that you watch the video online for more definitive information about the talk and slides: https://www.youtube.com/watch?v=kVREitV7VWU

A DVD of the talk and Dr. Mckay's slides will be available for purchase from the IPCSG about one month after the meeting.

On the Lighter Side

Articles of Interest

onlinelibrary.wiley.com

Registration for major active surveillance (AS) research conference now open

Registration is now OPEN for the upcoming conference on future research into the use of active surveillance for men with favorable-risk forms of localized prostate cancer:

Developing Provocative Questions: The Prostate Cancer Active Surveillance Research Initiative

Click on the link above for more information and to register.

The conference will take place **from 12:00 pm to 4:00 pm Eastern time on Monday, December 13** AND on **12:00 pm to 4:00 pm on Thursday, December 16**.

Registration for the Monday session will automatically register an individual for the Thursday session as well. The Thursday session will bring the group back together to review the findings from the Monday sessions and the recommendations for research based on those findings.

The registration page also provides core information about the agenda for the main input portion of the meeting on the Monday, when there will be an introductory overview session followed by a series of workgroup sessions on a variety of different topics designed to ensure input from patients, patients' spouses/partners and supporters, advocates, clinicians and researchers.

For patients in particular, **this initiative offers the opportunity for input on critical research into the use and application of AS for favorable-risk forms of prostate cancer for years to come**.

If you are man who

Is currently on AS for a favorable-risk form of localized prostate cancer

Was initially managed on AS for a favorable-risk form of localized prostate cancer but subsequently received active treatment (of any kind and for any reason)

Was initially told that AS was a reasonable possibility for initial management of your prostate cancer, but you decided to turn this opportunity down

Was never told about AS as a reasonable possibility for initial management of your prostate cancer, but realized, after first-line treatment, that this may have been a good opportunity for you

then **your participation and input to this initiative is potentially important**.

This initiative is supported by a grant from the Patient-Centered Outcomes Research Institute (PCORI). It has been organized and coordinated by the University of Maryland with input from multiple patient advocacy groups; a spectrum of specialists in the diagnosis and management of early-stage prostate cancer; and the American Urological Association. An initial survey about areas of interest for research on AS was completed by more than 350 patients and others.

medscape.com

Shock, Disbelief as NCCN Changes Prostate Cancer Guidance

Mick Mulcahy

For over a decade, the influential National Comprehensive Cancer Network (NCCN) has been recommending that men with low-risk prostate cancer be offered active surveillance as the lone "preferred" initial treatment option.

But the NCCN has now reversed this long-standing recommendation in the latest revision of its prostate cancer guideline.

The organization now recommends that low-risk disease be managed with either active surveillance or radiation therapy or surgery, with equal weight given to all three of these initial options.

The change is seen by some as a retreat to the past and was harshly criticized by many experts on Twitter. The complaints were voiced in unusually blunt and strong language for physicians.

"This is a terrible step back that impacts every urologist," commented John Griffith, MD, of Hartford Healthcare, who practices in New Britain, Connecticut.

Griffith explained that he prints out the NCCN guidance with "every patient newly diagnosed" and that the preferred designation is a "huge help" in reassuring them about not treating low-risk disease initially.

In a Twitter thread, Benjamin Davies, MD, of the University of Pittsburgh, Pittsburgh, Pennsylvania, facetiously wondered if a time warp was at play: "To suggest for a millisecond that active surveillance isn't the preferred method for low-risk men is bizarre thinking…Is this 1980?"

"I'm baffled," said Brian Chapin, MD, of MD Anderson Cancer Center, Houston, Texas, in another Twitter thread.

"This is ludicrous," said Andrew Vickers, PhD, of Memorial Sloan Kettering Cancer Center in New York City in a tweet.

Alexander Kutikov, MD, of Fox Chase Cancer Center in Philadelphia, Pennsylvania, commented on Twitter that the change "seems off the rails…a bit stunned by this."

Matthew Cooperberg, MD, of the University of California San Francisco, and Minhaj Siddiqui, MD, of the University of Maryland in Baltimore both called the move a "step backward."

Many others also expressed disappointment in the NCCN, whose guidelines are hugely influential because of the role they play clinically as well as with payors and the legal system.

"A huge setback & frankly a disgrace for @NCCN and its processes," commented Fox Chase's Kutikov.

Stacy Loeb, MD, of NYU Langone Health in New York City, suggested the new guidance may stunt use of active surveillance in the United States. She tweeted: "The updated NCCN guideline certainly won't help the lagging and heterogenous uptake of active surveillance in the US. We should be carefully expanding the pool for active surveillance, not narrowing it."

The purpose of active surveillance is to avoid adverse events from treatment, which can be life-changing as they include incontinence and erectile dysfunction.

The rationale is that many men with low-risk prostate cancer may not need treatment for their disease, as the disease may be slow-growing and may never threaten their life. With active surveillance, men are instead monitored with blood tests, scans, and biopsies to watch for worsening disease, and treated only when there are signs of disease progression.

medscape.com

Are the Right Men Getting Screened for Prostate Cancer?

by Mike Bassett, Staff Writer, MedPage Today November 11, 2021

Urology > Prostate Cancer

— Increases in PSA testing seen in age groups for which screening is not recommended

Prostate-specific antigen (PSA)-based screening for prostate cancer increased after the U.S. Preventive Services Task Force recommended individual decision-making for men ages 55 to 69 in 2017, reversing its 2012 guidance that advised against PSA screening in all men.

Now, a retrospective cohort study found that from 2016 to 2019 the overall mean rate of PSA testing increased from 32.5 to 36.5 per 100 person-years, a relative increase of 12.5% (95% CI 1.1-24.4), reported Michael Leapman, MD, of Yale University School of Medicine in New Haven, Connecticut, and colleagues.

Among men ages 55 to 69 specifically, the mean rate of PSA testing increased from 49.8 per 100 person-years in 2016 to 55.8 per 100 person-years in 2019 (relative increase 12.1%, 95% CI -0.2 to 25.2), they noted in *JAMA Oncology*.

Increases were also observed among men ages 40 to 54 and in those 70 and older -- age groups for which screening is not recommended.

"Increasing rates of PSA testing in age groups for whom screening remains explicitly discouraged highlights the need to enhance the quality of decision-making for early detection of prostate cancer given downstream consequences, such as unnecessary biopsy and the overdetection of low-grade disease," wrote Leapman and colleagues.

For men ages 40 to 54, mean rates of testing increased from 20.6 to 22.7 per 100 person-years (relative increase 10.1%, (95% CI -2.8 to 23.7). And for those ages 70 to 89, these rates increased from 38.0 to 44.2 per 100 person-years (relative increase 16.2%, 95% CI 4.2-29.0).

The largest increase was observed in men ages 70 to 74, from a mean of 50.0 per 100 person-years in 2016 to 58.3 per 100 person-years in 2019, they noted.

Leapman and colleagues suggested that the increase in PSA screening among younger men may be the result of emerging evidence about the prognostic value of a patient's baseline PSA level at middle age.

"Further study is needed to understand patient perspectives and potential quality-of-life outcomes associated with screening younger men," they wrote. "These results should also strengthen efforts to align PSA testing with best practice, particularly for those least likely to benefit, such as men older than 75 years or those with significant medical comorbidity."

In a commentary accompanying the study, Freddie C. Hamdy, MD, of the University of Oxford in England, noted that the prostate cancer screening landscape is continuing to evolve -- as illustrated by the emergence of prebiopsy imaging with multiparametric MRI -- and suggested "the long-term practice of a PSA test followed by systematic biopsies of the prostate is antiquated."

He added that the use of imaging and targeted biopsies, as well as the potential demonstrated with genomic testing as a risk stratification approach to screening, means the field will continue to progress by mini-

mizing the risks of overdetection and overtreatment, and focusing on identifying early disease and tailoring treatments that can improve outcomes.

"But when will the message get through to the public, clinicians, and health care professionals that inappropriate PSA testing outside evidence-based recommendations should cease?" Hamdy asked.

For this study, Leapman and colleagues used de-identified claims data from Blue Cross Blue Shield beneficiaries ages 40 to 89 (median age 53) from Jan. 1, 2013 through Dec. 31, 2019 to calculate age-adjusted rates of PSA testing in 2-month periods, and then compared testing rates in 2016, which was before the guideline change, versus 2019, which was after the change.

One limitation to the analysis, the authors acknowledged, was that the Blue Cross Blue Shield database may not be generalizable to all populations, since it includes mostly younger and more socioeconomically advantaged patients with employment-based insurance.

medscape.com

The Paradox of a Man's Most-Feared Test, the PSA

By: Ericka Johnson

The prostate-specific antigen test is one of the most lauded tests for prostate cancer. It's also controversial and fraught with uncertainty.

"Should I get a PSA test?" During the course of researching my book, I heard this question a *lot*. Even when it wasn't asked straight out, I could feel it in the air, hovering above my conversations with men about their prostates.

"Is the test any good? What sort of number *should* I have? What sort of number do I *want* to have? Could I have cancer, or is it a false positive? Do I really need to take the test?" These questions were often asked through a haze of worry — so much so that I started to think of PSA as prostate-specific angst instead of prostate-specific antigen. And that the PSA *test* is causing the angst, not the prostate.

As it turns out, the prostate-specific antigen test — a simple blood test — is one of the most lauded yet also most controversial tests for prostate cancer.

But before I get into the social complexity of a simple blood test, let me provide a bit of background: prostate-specific antigen (PSA) is a proteolytic enzyme (an enzyme that breaks down proteins), secreted by the prostate into the ejaculate, that liquefies the seminal plasma, thereby allowing sperm to swim more freely. Small amounts of it also leak into the blood. Measuring this amount in the blood can indicate if there is an increased risk of cancer in the prostate.

The PSA test was first experimentally used to detect prostate cancer in the late 1980s, and in the mid-1990s it was approved for this purpose in the U.S. However, it is notoriously difficult to interpret, and can be connected to prostate size and age, and to other diseases like benign prostatic hyperplasia (BPH), inflammations, and infections. It can also be prone to false positives. Coupled with the digital rectal examination (the other dreaded test that involves feeling the prostate with a gloved finger), its reliability can be improved — a bit.

Results of PSA tests can — often do — lead to the next step: biopsy, which is often experienced as unpleasant, sometimes painful, and can lead to blood in the urine and, in some cases, infection. Biopsy following elevated PSA is, however, increasingly being replaced by MRI scans which are less cumbersome and might decrease the risk of unnecessarily detecting small, clinically insignificant, cancers. Nevertheless, results of PSA tests can also — and again, often do — lead to years of repeated, regular testing for the individual patient. And to years of repeated, regular PSA angst. Of course, the test can also lead to the detection of significant, potentially lethal, cancer, and the chance to save a life.

The angst I see men experiencing seems specifically generated by the threat of prostate cancer that the PSA test awakens.

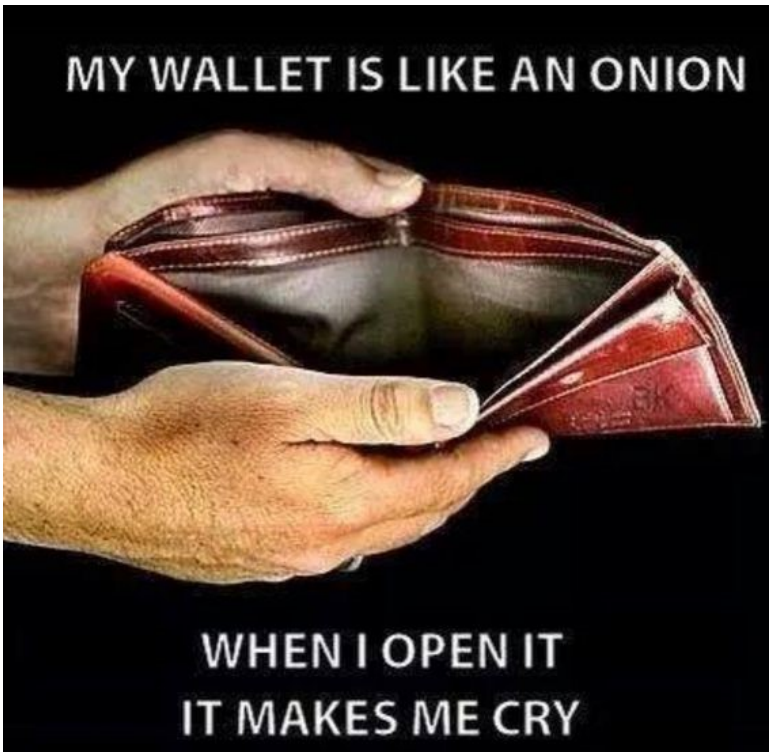
NETWORKING

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 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

Continued Editors Notes:

5. A New Blood Test Has Been Shown to Detect More Than 50 Types of Cancer—But Who Can Get It Right Now? *Galleri, looks for Circulating DNA unique to tumor cells*. Not covered by insurance, $1500, Dr. Fabio is offering it https://www.drfabio.com/healthblog/new-test-for-cancer-detection
6. Urine Test for Prostate Cancer Signals Amount of Aggressive Tumor—*researchers found that the multigene Prostate Urine Risk-4 (PUR-4) signature was strongly associated with the presence and amount of Gleason pattern 4 tumors, but not tumors of less aggressive histology*
7. Prostate cancer research in the 21st century; report from the 2021 Coffey-Holden prostate cancer academy meeting
8. Cleveland Clinic Study Links Gut Microbiome and Aggressive Prostate Cancer—*diet-associated molecules in the gut are associated with aggressive prostate cancer, suggesting dietary interventions may help reduce risk*.
9. Disparities in germline testing among racial minorities with prostate cancer *shortage of genetics professionals, disparities in care, medical mistrust, misinformation, and misunderstanding regarding germline testing, costs, and the understudied link between PCa and breast/ovarian cancer.*
10. Vitamin D deficiency increases prostatic megalin expression and globulin-bound testosterone import, increasing prostatic androgens in African American men— *Vitamin D deficiency associates with an increased risk of prostate cancer (PCa) mortality and is hypothesized to contribute to PCa aggressiveness and disparities in African Americans*
11. PFAS exposure, high-fat diet drive prostate cells' metabolism into pro-cancer state: Dietary fat synergizes with PFAS to trigger cancer in benign cells, accelerate tumor growth in malignant cells *Exposure to PFAS – a class of synthetic chemicals utilized in food wrappers, nonstick cookware and other products -- reprograms the metabolism of benign and malignant human prostate cells*
12. Virtual Prostate Cancer Clinic: Thumbs Up From Patients and Docs—*got high marks from patients who used its services.*
13. Five Percent Overall Medicare Reimbursement Cut Estimated for Medical Oncology in 2022 *Cancer Oncologists get pay cut for Medicare patients.*
14. Stereotactic Ablative Radiotherapy for High-Risk Prostate Cancer—a Prospective Multi-level MRI-based Dose Escalation Trial *SAbR dose for HR-PCa was safely escalated with multi-level dose painting of 47.5Gy to prostate, 55Gy to mpMRI-defined intra-prostatic lesions, and 25Gy to pelvic nodal region in 5 fractions*
15. New strategy against treatment-resistant prostate cancer identified: RNA molecule suppresses prostate tumor growth -- *restoring long noncoding RNA could be a new strategy to treat prostate cancer that has developed resistance to hormonal therapies*
16. High-Intensity Interval Training in Prostate Cancer *A high-intensity interval training (HIIT) aerobic exercise program improved cardiorespiratory fitness and suppressed prostate cancer progression*
17. HYPORT in Prostate Cancer: New Standard After Surgery?
18. Biomarkers Associating with PARP Inhibitor Benefit in Prostate Cancer in the TOPARP-B Trial

This is one of the paradoxes of the PSA test: People want it to find cancer and save individual lives, but they also critique it for finding too much cancer and destroying lives when applied across a whole population. If it is detected, the man and his family are placed in the shadow of cancer, faced with decisions about (and, in many countries, costs of) treatments with life-changing side effects. The man and his family are also thrown into a period of worry and anxiety, none of which would have occurred without the PSA test. For many individual men, even though they know that it might be the beginning of an extended rollercoaster ride of testing and more testing, there is still an almost irresistible impetus to know — and the hope that the test will prove they are — still — cancer-free.

It is this oscillation between hope and fear, combined with the continuous discursive shifting between the PSA as a test for individuals and the PSA as a screening tool for public health at the level of the population, that produces much of the debate about the PSA.

Complex, Confusing . . . Collective?

The preoccupation with mortality that emerges in the face of a blood test is not uniquely related to the PSA test — we are, after all, mortal. And especially at a certain age, most of us start to reflect upon this. However, as a medical sociologist, the angst I see men experiencing seems specifically generated by the threat of prostate cancer that the PSA test awakens. It is a test that congeals that angst into a worry which eats away at many of them.

When I am having these conversations — with friends, with colleagues, and with men I have interviewed — I tend to remember a urologist I met early on in this study, who admitted slyly that he didn't get the PSA test for himself, to avoid, as he called it, "starting down that slippery slope." He wasn't the only urologist who admitted this to me during the course of my study, and his comment articulated a well-known phenomenon: that testing and screening can lead to a series of further tests, and a future of uncertainty. And sometimes it can generate pre-illness, proto-illness, or the idea of being a patient-in-waiting; even if you are not sick now, testing and screening can produce the feeling that you might become sick, that you might develop symptoms, and that in the future you will be struck by, in this case, prostate cancer. Then, once you have been tested, you as a patient are responsible for getting tested again, and keeping track of your numbers, following their ups (ideally not) or downs, or just their steady onward march through time.

The numbers become a visible way of knowing what is happening in your body, of trying to pin down risk and uncertainty. But because the PSA test can also be the first step in a series of more invasive tests, it is also cracking open the door to a future that threatens the side effects of prostate treatments, like impotence and incontinence and the feelings those possibilities evoke. It raises the specter of cancer and death.

Medical experts and policy-makers are aware that PSA testing is a source of anxiety for patients, but there is scant research on this, and what little there is tends to be mentioned but not considered seriously in debates about screening and testing decisions. This seems particularly poignant in recommendations that, more recently, have encouraged patient participation in deciding whether to test or not, a situation in which anxiety over results and potential false positives conflicts with the anxiety about refusing available medical tests and thereby missing a cancer.

This is amplified by the fact that the PSA test is purported to save lives by identifying tumors early, allowing for more successful treatments of smaller, contained cancerous tumors, and ultimately helping to reduce the number of men who die of prostate cancer every year. Public discussions about the PSA test are filled with survival stories from men who have found their cancer (often early, often when they were relatively young) and been successfully treated, so that they are alive today because of it. In these narratives, early detection is considered a good thing, because one is still alive; discussions of side effects are minimal. The PSA test allows medicine to come in and save a life rather than watching impotently by the patient's side through the advanced stages of cancer.

Survival rates for prostate cancer *have* improved significantly over the last 30 years, but it is not clear if this is because of better treatment and primary care, or because of wider screening practices that allow earlier detection, or a combination of both. And while there is agreement that screening could save lives by detecting and treating prostate cancer earlier, it appears to entail the overtreatment of large numbers of men. This means that many men are unnecessarily subjected to surgery or radiation, and thereby have to deal with the severe side effects of treatment: pain, incontinence, bleeding, fistula formation, bowel trouble, sexual dysfunction, as well as the status of patient (including repeated PSA tests post-treatment to monitor if the cancer returns) for years to come.

The concept of watchful waiting or active surveillance, however medically justified it might be, could quickly become an emotional nightmare.

And while the medical community is generally in agreement that many prostate cancers do not need to be treated (especially in men over 75), while others can benefit from active surveillance instead of immediate treatment, it can sometimes be hard to convince a patient of that. Cancer is terrifying. A patient who finds out they have cancer wants to get rid of it, and as quickly as possible. The concept of watchful waiting or active surveillance, however medically justified it might be, could quickly become an emotional nightmare.

The controversy about screening has become entrenched, as many national healthcare policy-makers have suggested that men should *not* be screened for prostate cancer with the PSA test. Pushing back against these decisions are national and international patient activism campaigns that try to raise awareness of the importance of screening, and encourage men to get tested. The importance of being tested — and possibly of screening populations of men — is a popular cause, for example, for many national prostate cancer patient groups — Europa UOMO; the French Association Nationale de Malades du Cancer de la Prostate; the German Bundesverband Prostatakrebs Selbsthilfe; the international Movember Foundation; the Swedish Prostatacancerförbundet — even if some countries' patient groups are more reticent (like British Prostate Cancer UK), and even as the medical debate about its validity is still ongoing. Collectively, there are groups of men (and women, and cancer industry interests) promoting PSA and prostate cancer screening and testing, collecting research money for technological development, lobbying for screening programs, and enrolling men to participate in support groups and patient activism. And, of course, encouraging them to get tested.

All these voices, interests, and opinions are debating, promoting, rejecting, and encouraging the PSA test as a screening tool in the media around us. Especially in November. November — or Movember — has been the internationally successful flagship promotion campaign of a prostate cancer charity, encouraging men to get their PSA tested and asking them to take individual responsibility for the test rather than relying on national screening policies.

This is the message behind the mustache campaigns in November, for example, often fronted by famous people wearing mustaches, that pop up everywhere each winter. But notice the shifts I have made: from talking about individual men and their feelings about a simple PSA test to a discussion about the statistical life-saving it might achieve, to the response of governments and professional associations, to patient groups and charities who return the question to individual men and ways of encouraging them to be tested. The shifts from individuals to collectives and back to individuals in the debate can make one dizzy. It is no surprise that people become confused about the value of the PSA test, and its benefit to men.

How to Embrace Complexity

Healthcare as we know it today is governed with information sheets and short, simple sentences that simplify and flatten complexity in an attempt to achieve clarity. Often, this does away with complexity altogether. A lot of healthcare practice and policy is uncomfortable with recognizing death, fear, and vulnerability. And not just healthcare providers and policymakers: also people, us, everyone we know — the users and patients of modern healthcare are uncomfortable with recognizing death, fear, and vulnerability.

But how do you take something complex and make it simple, while maintaining the complexity? And how do you warn about the completely rational and expected worry about death that testing might trigger?

The PSA test involves many voices, perspectives, concerns, and stances. And there is no closure to the debates about its usefulness, even when there is a policy decision. This is because the medical evidence, should it ever become clear, is only one part of the answer. But this means that the question of PSA screening and PSA testing is more complicated than merely a question of whether the test is good enough or not. It is not only about the risk of false positives — though it *is* about that. It is not only about the risk of overtreatment — though it is about *that*, too. It is not only about the impossibility of screening men, finding cancer, and then being able to know which cancers are dangerous enough to warrant treatment and which are harmless enough to not bother about or embark upon active surveillance. And it is not only about the impossibility of reassuring someone with cancer that they can continue living with it, that they shouldn't worry. It is about all of these things, entangled together.

The decisions about screening that we are living with today are historically formed and culturally embedded, and will always be so.

Judging by the countless discussions I had with men when I wrote my book, and the voices raised for and against PSA screening in the media, it would seem as if our responses within this regime of anticipation are (at least also) colored by strong feelings of fear and worry about our mortality and vulnerability. They are emotional. And we are often caught in these knots of emotion, statistical risks, and prevention discourses, aided and abetted by well-meaning health promotion campaigns and evidence-based anticipation regimes, a situation that can easily become affective and infected. And a state of affect is not necessarily the most productive place in which to make a rational, calculated decision.

We assume that we are rational, calculating agents, making decisions based on objective facts, and we would like to believe that the answers to our screening questions could be based only on objective medical knowledge, because that would suggest that there should be a correct answer out there to questions of screen or test, when and how. But as the very idea of pure medical facts becomes tainted by the undercurrent of social context within which they are being produced, that option fades away. Those decisions about screening that we are living with today are historically formed and culturally embedded, and will always be so. They will engage our feelings of fear and worry specifically because they address mortality and death. This is the unavoidable "affective." But instead of seeing that as a starting point for an infected debate, I suggest we embrace it. Perhaps recognizing those feelings and other social considerations in our decision-making will produce more humane, and ultimately more caring, policies for those we are trying to help.

A New Blood Test Has Been Shown to Detect More Than 50 Types of Cancer—But Who Can Get It Right Now?

health.com

By Elizabeth Narins November 08, 2021

Cancer is the second leading cause of death in the US—and it has been for years, according to data from *JAMA* published in March. And while a large number of people often survive the disease, thanks to ever-evolving medical treatments, many people are still diagnosed too late for treatment to be effective.

Enter: Galleri, a multi-cancer, early detection blood test, manufactured by the company GRAIL. The test isn't brand-new—biotechnology company Illumina Inc. announced the formation of GRAIL back in 2016 with the intent of creating a pan-cancer screening test to help detect early signs of cancer in asymptomatic patients—something that could "decrease cancer mortality," according to a press release at the time.

Five years later, in June 2021, GRAIL announced that Galleri is now available nationwide, as a prescription-only cancer screening test. The announcement was the culmination of years of research, backed by notable institutions like the Mayo Clinic, Cleveland Clinic, Dana Farber Cancer Institute, and more.

Of course, any advances in cancer detection or treatment are welcomed news—but what else is there to know about Galleri, and who can benefit from the test right now? Here's what you need to know about the science behind the test, and what it can—and can't—tell you about your health.

How exactly does Galleri work?

In its first-ever press release, GRAIL touted the early cancer-detection test—which would later be named Galleri—as a "simple blood test," but the science behind that simple test is quite complex.

Ask a doctor and they'll tell you the Galleri test detects circulating tumor-derived, cell-free DNA (cfDNA) that could indicate the presence of cancer using a targeted methylation bisulfite sequencing assay and machine learning techniques.

That's kind of a mouthful—in order to begin understanding what that means, it's important to understand that cancer is a disease of the genome, or all the the genetic information of an organism, made up of DNA.

Nearly all of the cells in your body have the same DNA, according to the US National Library of Medicine. But unlike the DNA in healthy cells, the DNA in cancer cells carry cancer-specific signals; tumors shed this DNA into the blood. Multi-cancer early detection testing looks at blood samples for DNA fragments and their cancer-specific signals to identify cancer and where that cancer signal originated in the body.

The Galleri test requires a prescription from a licensed health care provider—telemedicine or otherwise—who can request a testing kit on your behalf by ordering it electronically through Galleri's provider portal or by completing a test requisition form available on their website. Next, you bring your unopened Galleri specimen collection kit to your doctor's office or a lab where you'll have two vials—about 1.5 tablespoons—of blood drawn from a vein in your arm before it's shipped off to a GRAIL lab for processing that can take up to 10 business days.

The results go directly to the healthcare provider who ordered the test for you. They'll either read "Cancer Signal Not Detected" or "Cancer Signal Detected" with "Top Predicted Cancer Signal Orgin(s)" which predicts where the cancer may be coming from. Your doctor can use these results to order further testing to make a formal diagnosis.

What Galleri can tell you about your health—and what it can't

As of right now, the The United States Preventive Services Task Force (USPSTF) only recommends routine screenings for colon, breast, cervical, prostate, and lung cancers for those with risk factors (age, family history, personal history, etc.). But those cancers account for just 29% of all cancer deaths according to the American Cancer Society—that leaves a large chunk of cancer deaths due to disease for which screening tests aren't available.

Galleri, on the other hand, has been shown to detect more than 50 types of cancer—45 of which don't have a recommended screening test available.

The research has been thorough: A group of researchers from Cleveland Clinic, The US Oncology Network, and several additional well-respected institutions joined GRAIL to complete the The Circulating Cell-Free Atlas Study (CCGA), which was designed to develop and validate multi-cancer early detection blood tests in 15,000 subjects with and without a known cancer diagnosis. The tests delivered negative readings to 99.5% of participants who did not have cancer using a measure known as "specificity," and served up false positives to just 0.5% of participants.

What's more, researchers were able to detect cancer in 51.5% of cancer patients using a measure known as "sensitivity." The blood tests were more likely to detect more advanced cancers, and was most accurate in detecting 12 kinds of cancer—including liver, head and neck, esophagus, pancreas, and ovarian—for which there are no routine screening tests.

In a separate PATHFINDER study, when researchers looked at 6,629 asymptomatic subjects over 50 years old, an earlier version of Galleri detected 13 types of cancer across 29 participants. About 44.6% of positive test results led to a cancer diagnosis, and nearly 40% of those cancers were stage 1 or stage 2—a good thing because early detection is pivot for improving cancer outcomes. What's more, in 96.3%t of cancer cases, Galleri was correct on its first or second guess at where the cancer originated.

So all in all, how promising are these results? "The test is a step forward and very important for early detection of certain cancers that we don't typically screen for," Christian Rolfo, MD, professor of medicine and associate director for clinical research at the Center of Excellence for Thoracic Oncology at Mount Sinai's Tisch Cancer Institute, tells *Health*.

But, while Galleri can help send your doctor in the right direction to conduct further testing and determine whether cancer is indeed present, he stresses that these new blood tests cannot diagnose cancer and should not replace routine cancer screenings—rather, they should compliment them. "We need to continue to use imaging for diagnostics," Dr. Rolfo says.

GRAIL is on the same page: "Galleri is not a diagnostic test and is intended to be used as a complement to existing cancer screenings," a GRAIL spokesperson tells *Health*.

Dr. Rolfo's biggest concern is that on average, the tests pick up just 51.5% of cancers. What's more, the test's sensitivity, or ability to detect cancer, varies based on cancer type and cancer stage, which isn't optimal. For instance, Galleri has been shown to detect just 18.2% of kidney cancers compared to 93.5% of lung cancers; while overall, it picks up 90.1% of stage 4 cancers, it only detects an average of 16.8% of stage 1 cancers. "The test sensitivity is still low among people with stage 1 cancer, which is when we want to detect it since we can detect bigger tumors with imaging," Dr. Rolfo says.

Another way Galleri falls short, so far as innovation is concerned: It can't help predict your cancer future. Unlike the BRCA blood tests, which measure your genetic risk of developing cancer at some point, Galleri simply tells you whether cancer DNA is currently present in the blood at any given moment—not whether you have a higher risk fo developing it in the years to come.

"It's still good to have a method to detect certain cancers at an earlier stage," Dr. Rolfo says.

Who can (and should) use the Galleri test?

At the moment, Galleri is only recommended for people with a heightened cancer risk—being older than 50 and having a family history of cancer are both qualifiers. Because your eating habits, lifestyle, home or work environment, or genes could also increase your cancer risk, it's best to talk to your doctor about whether you're a candidate for Galleri testing.

While GRAIL is careful not to prescribe its tests to any particular demographic, in clinical testing, their researchers enrolled participants who had a history of

smoking, documented genetic cancer predisposition, or personal history of cancers that affect the blood, a GRAIL spokesperson told *Health*.

If this doesn't sound like you, and yet you've already begun to dial your doctor's number, slow down. "We don't want patients with no known risk factors coming in asking for tests because they are afraid of cancer—we're not there with the technology yet," Dr. Rolfo says.

And of course there's a chance you might not want this kind of testing in the first place. After all, facing your medical fate can be super scary and disruptive, particularly in the absence of symptoms—something GRAIL has already thought about.

"We know that a cancer diagnosis can affect the mental health of patients, families and their caregivers; feelings of depression, anxiety and fear are not uncommon," wrote a GRAIL spokesperson via email. "We believe that early detection provides hope and information that patients deserve."

Galleri, which costs $949, isn't currently covered by insurance, although you might be able to use your FSA or HSA dollars to pay for it. And while the tests are available in all 50 states, GRAIL is still working toward an FDA approval.

The fact remains that early cancer detection can reduce cancer mortality rates—and beating cancer begins with knowing you have it, as Galleri notes on its site. With the average person undergoing multiple routine screenings as they get older, be it a mammogram, pap smear, or colonoscopy, soon, Galleri testing—or other modes of early cancer detection—could be just as commonplace.

Urine Test for Prostate Cancer Signals Amount of Aggressive Tumor

Frederik Joelving

A potential new urine biomarker for prostate cancer not only spots the presence of aggressive tumors, it also indicates the amount of these tumors, according to a recent report.

In a study of biopsy and prostatectomy samples, researchers found that the multigene Prostate Urine Risk-4 (PUR-4) signature was strongly associated with the presence and amount of Gleason pattern 4 tumors, but not tumors of less aggressive histology.

Given that increased Gleason pattern 4 tumor burden is associated with disease progression in men at intermediate risk, the results suggest that "PUR can show us which men at intermediate risk may require treatment and which may instead be managed conservatively with surveillance," said senior author Jeremy Clark, PhD, of Norwich Medical School, University of East Anglia, in the United Kingdom. "PUR will also be useful for monitoring disease in men that do not currently require treatment and flag up the emergence and expansion of aggressive disease," he said.

The study by Clark and colleagues was published online on November 3 in *Life*.

Tests using the traditional blood-based biomarker for prostate cancer — prostate-specific antigen (PSA) — have limited sensitivity and specificity, leading to unnecessary biopsies and overtreatment.

The PUR biomarker, one of several emerging alternatives to PSA, is a four-group classifier based on 36 genes, Clark and his colleagues explain. Its categories correspond to the probabilities of the presence of normal tissue (PUR-1), and D'Amico low-risk (PUR-2), intermediate-risk (PUR-3), and high-risk (PUR-4) prostate cancer.

Clark's team found in earlier research that the PUR-4 signature was able to predict disease progression in men on active surveillance for prostate cancer up to 5 years after a single urine sample. For their latest study, they sought to understand the relationship between PUR-4 and the amount and grade of tumor.

On the basis of biopsy samples from 215 men with prostate cancer, the researchers found that PUR-4 signature values correlated significantly with increasing Gleason grade.

There was no significant difference in PSA level by tumor volume for Gleason grade 1, 2, or 3. The same was true for PUR-4 and Gleason grade 1 tumors, which only contain less clinically significant Gleason pattern 3 cancer. However, PUR-4 values in men with Gleason grade 2 tumors larger than the median were significantly greater than for smaller tumors. PUR-4 values for large Gleason grade 3 tumors were also greater than for smaller ones, although the difference did not reach statistical significance.

"Since [Gleason grade] 2 and [Gleason grade] 3 contain both Gleason Pattern 3 and 4 cancer these ob-

servations suggest that Gleason Pattern 4 cancer may be contributing to PUR-4 status," the authors write.

The researchers also examined radical-prostatectomy specimens from nine men — three with Gleason grade 1, four with Gleason grade 2, and two with Gleason grade 3 tumors, as determined on the basis of presurgical biopsy.

There was no significant correlation between PUR-4 and PSA levels, nor were PUR-4 values linked to total tumor area or Gleason pattern 3 tumor area. But the amount of Gleason pattern 4 tumor showed a strong correlation with PUR-4 values, which did not change after adjusting for total prostate size.

"Our study shows that the PUR test can assess the amount of Gleason pattern 4 without the need for a biopsy," Clark told *Medscape Medical News.* "It could therefore be a very useful tool indeed for assessing a man's risk of dying from prostate cancer."

Jack Schalken, PhD, a professor of experimental urology at Radboud University Medical Center, in Nijmegen, the Netherlands, called PUR "another test" for prostate cancer the performance of which is in the same range as that of existing products.

"In fact, several tests are commercially available, but the clinical use is surprisingly low," he told *Medscape Medical News* by email. Schalken, who was not involved in the new study, has reviewed several biomarkers for prostate cancer.

The PUR test is now undergoing validation in an international study that is expected to last another 2 years, Clark said. If successful, the test would stand out for several reasons.

First, it is based on many genes, so it is able to spot malignancies that other tests, which rely on just a few genes, may not pick up. In addition, although it is sensitive to the amount of Gleason pattern 4 tumor, it does not seem to detect the clinically less significant Gleason pattern 3 cancers.

"We have an at-home collection kit — the men do not have to come to a hospital to provide a urine sample," Clark said.

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Prostate cancer research in the 21st century; report from the 2021 Coffey-Holden prostate cancer academy meeting

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Abstract

Introduction

The 2021 Coffey-Holden Prostate Cancer Academy (CHPCA) Meeting, "Prostate Cancer Research in the 21st Century," was held virtually, from June 24–25, 2021.

Methods

The CHPCA Meeting is organized by the Prostate Cancer Foundation as a unique discussion-oriented meeting focusing on critical topics in prostate cancer research envisioned to bridge the next major advances in prostate cancer biology and treatment. The 2021 CHPCA Meeting was virtually attended by 89 investigators and included 31 talks over nine sessions.

Results

Major topic areas discussed at the meeting included: cancer genomics and sequencing, functional genomic approaches to studying mediators of plasticity, emerging signaling pathways in metastatic castration resistant prostate cancer, Wnt signaling biology and the challenges of targeted therapy, clonal hematopoiesis, neuroendocrine cell plasticity and antitumor immunity, cancer immunotherapy and its synergizers, and imaging the tumor microenvironment and metabolism.

Discussion

This meeting report summarizes the research presented at the 2021 CHPCA Meeting. We hope that publication of this knowledge will accelerate new under-

standings and the development of new biomarkers and treatments for prostate cancer.

nature.com

Cleveland Clinic Study Links Gut Microbiome and Aggressive Prostate Cancer

Tracy Wheeler

Cleveland Clinic researchers have shown for the first time that diet-associated molecules in the gut are associated with aggressive prostate cancer, suggesting dietary interventions may help reduce risk. Findings from the study were published in *Cancer Epidemiology, Biomarkers & Prevention*.

While more research will be necessary, the study's lead author Nima Sharifi, M.D., says findings from the team's analysis of nearly 700 patients may have clinical implications for diagnosing and preventing lethal prostate cancer.

"We found that men with higher levels of certain diet-related molecules are more likely to develop aggressive prostate cancer," said Dr. Sharifi, director of Cleveland Clinic's Genitourinary Malignancies Research Center. "As we continue our research in this area, our hope is that one day these molecules can be used as early biomarkers of prostate cancer and help identify patients who can modify their disease risk by making dietary and lifestyle changes."

In this study, Dr. Sharifi and his collaborators – including Stanley Hazen, M.D., Ph.D., and Eric Klein, M.D. – analyzed data from patients previously enrolled in the National Cancer Institute's Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.

They studied baseline levels of certain dietary nutrients and metabolites (byproducts produced when a substance is broken down in the gut) found in patients' blood serum prior to prostate cancer diagnosis. They compared serum levels between healthy patients and those who later received a prostate cancer diagnosis and died from the disease.

The researchers found that men with elevated levels of a metabolite called phenylacetylglutamine (PAGln) were approximately two or three times more likely to be diagnosed with lethal prostate cancer. This metabolite is produced when microbes in the gut break down phenylalanine, an amino acid found in many plant- and animal-based protein sources like meat, beans and soy.

In addition to PAGln, researchers also discovered that elevated levels of two nutrients abundant in animal products, including red meat, egg yolks and high-fat dairy products, called choline and betaine, also were linked with increased risk for aggressive prostate cancer.

While these nutrients and gut metabolites have been studied previously in heart disease and stroke, this is the first time that gut microbiome metabolites have been studied clinically in relation to prostate cancer outcomes.

Dr. Hazen was the first to identify PAGln's association with increased cardiovascular disease risk. The findings were published in 2020 in *Cell.* "Interestingly, we found that PAGln binds to the same receptors as beta blockers, which are drugs commonly prescribed to help lower blood pressure and subsequent risk of cardiac events," said Dr. Hazen, director of Cleveland Clinic's Center for Microbiome & Human Health and chair of Lerner Research Institute's Department of Cardiovascular & Metabolic Sciences. "This suggests that part of beta blockers' potent efficacy may be due to blocking the metabolite's activity."

"New insights are emerging from large-scale clinical datasets that show use of beta blockers is also associated with lower mortality due to prostate cancer," said Dr. Sharifi, who is a staff physician in Lerner Research Institute's Department of Cancer Biology. "We will continue to work together to investigate the possible mechanisms linking PAGln activity and prostate cancer disease processes in hopes of identifying new therapeutic targets for our patients."

The research team also will continue to explore the reliability of using choline, betaine and PAGln as biomarkers of aggressive prostate cancer and how dietary interventions can be used to modulate their levels and reduce patients' subsequent disease risk.

Chad Reichard, M.D., a urologic oncologist at Urology of Indiana and a previous urology resident at Cleveland Clinic, and Bryan Naelitz, previously a medical student in Dr. Sharifi's lab and now a urology resident, are co-first authors on the study. Dr. Klein is a urologist and emeritus chair of Glickman Urological & Kidney Institute at Cleveland Clinic. The research was supported by the National Cancer Institute and the National Heart, Lung,

and Blood Institute (both parts of the National Institutes of Health), as well as the Prostate Cancer Foundation.

jamanetwork.com

Disparities in germline testing among racial minorities with prostate cancer

McKay, Rana R.

Abstract

Germline testing is becoming increasingly relevant in prostate cancer (PCa) screening, prognosis, and management. A subset of patients with PCa harbor pathogenic/likely pathogenic variants (P/LPVs) in genes mediating DNA-repair processes, and these P/LPVs have implications for cancer screening, treatment, and cascade testing. As a result, it is recommended that all men with high-risk localized and metastatic PCa undergo routine germline testing. As more PCa patients undergo germline testing, it is important that clinicians and genetics experts recognize current disparities in germline testing rates among racial/ethnic minorities in the United States. The reasons for these disparities are multiple and require similarly manifold consideration to close the germline testing gap and reduce inequities in PCa screening, management, and treatment.

Conclusion

It is widely accepted that a subset of PCa susceptibility is attributed to inherited predisposition. Because the identification of alterations in PCa predisposition genes may help inform screening strategies for patients and family members, treatment options in the metastatic setting, and clinical trial enrollment, it will become increasingly important to bridge the gap for PCa patients who are underserved with regard to germline testing. Issues to be addressed include a shortage of genetics professionals, disparities in care, medical mistrust, misinformation, and misunderstanding regarding germline testing, costs, and the understudied link between PCa and breast/ovarian cancer.

sciencedaily.com

Vitamin D deficiency increases prostatic megalin expression and globulin-bound testosterone import, increasing prostatic androgens in African American men

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ABSTRACT

Vitamin D deficiency associates with an increased risk of prostate cancer (PCa) mortality and is hypothesized to contribute to PCa aggressiveness and disparities in African Americans. We reported a relationship between African-ancestry, circulating and intraprostatic vitamin D metabolites and prostatic expression of megalin, an endocytic membrane receptor that internalizes globulin-bound hormones. Here, we show that megalin imports sex hormone-binding globulin (SHBG)-bound testosterone, potentially regulating intraprostatic hormone levels. Vitamin D levels regulated megalin expression in cell lines, patient-derived prostate epithelial cells, and prostate tissue explants, and mice with prostatic knockout of *Lrp2* (megalin) showed reduced prostatic testosterone. Notably, prostatic 5α-dihydrotestosterone levels were higher in African American men and correlated inversely with serum vitamin D status, while megalin protein levels were reduced in PCa tissue. Our findings highlight the negative impact of vitamin D deficiency on PCa and the potential link to PCa disparities observed in African Americans.

medpagetoday.com

PFAS exposure, high-fat diet drive prostate cells' metabolism into pro-cancer

state: Dietary fat synergizes with PFAS to trigger cancer in benign cells, accelerate tumor growth in malignant cells

Exposure to PFAS -- a class of synthetic chemicals utilized in food wrappers, nonstick cookware and other products -- reprograms the metabolism of benign and malignant human prostate cells to a more energy efficient state that enables the cells to proliferate at three times the rate of nonexposed cells, a new study in mice found.

However, consuming a high-fat diet significantly accelerated development of tumors in the PFAS-exposed mice, said the scientists at the University of Illinois Urbana-Champaign and the U. of I. Chicago who conducted the research. PFAS is an abbreviation for perfluoroalkyl and polyfluoroalkyl substances, often described as "forever chemicals" because they don't degrade naturally and persist as environmental pollutants. Studies have associated PFAS with harmful effects in laboratory animals.

"Our data suggest that exposure to PFAS synergizes with dietary fat to activate the protein-coding gene PPARa, altering cells' metabolism in ways that escalate the carcinogenic risk in normal prostate cells while driving tumor progression in malignant cells," said food science and human nutrition professor Zeynep Madak-Erdogan, the principal investigator on the project.

"These alterations in cell metabolism that occur downstream of PPARa activation may underpin the increased prostate cancer risk observed in men who are exposed to PFAS," said Madak-Erdogan, who also holds an appointment as a health innovation professor with the Carle Illinois College of Medicine.

In their analyses of gene transcription activity, the scientists found that PPARa was expressed at significantly greater levels in the tumor cells of the PFAS-exposed mice that ate the high-fat diet. PPARa controls cell proliferation and differentiation, aids in immune and inflammatory responses and has been found to play a key role in the development of liver and kidney cancers, according to the study.

Previous studies, including some conducted in humans, linked PFAS with a range of serious health problems such as prostate cancer, the most common male cancer in the U.S.

Published in the journal *Nutrients*, the current study's findings are believed to be the first to shed light on the synergistic interactions of PFAS and dietary fat and the metabolic changes that shift benign prostate cells to a malignant state, triggering rapidly growing tumors.

The scientists injected an aggressive form of malignant human prostate cells into the flanks of male mice that were fed either a high-fat diet intended to mimic the typical Western diet or a control diet. Some of the mice also received oral doses of perfluorooctane sulfonate (PFOS), one of the most common forms of PFAS that has been associated with various cancers.

"We observed an increase in the tumors' volume when exposed to either the high-fat diet or the PFOS," said co-author Michael J. Spinella, a scientist in the Cancer Center at Illinois and professor of comparative biosciences. "However, at 40 days post-injection, we observed that the fastest tumor growth occurred in the group of mice that both ate the high-fat diet and received PFOS exposure, which suggested a synergistic interaction between the two."

In cell culture, the scientists exposed benign prostate cells and a derivative line of aggressive malignant cells to PFOS and found that the malignant cells replicated at triple the rate of the cells in the control group.

When the researchers exposed the benign and malignant cells to another form of PFAS, perfluorobutane sulfonic acid, the malignant cells' viability was five times greater than the cells in the control group.

Studies have associated PFBS exposure -- which can occur through polluted air or polluted drinking water -- with diseases of the thyroid and other organs.

The scientists hypothesized that metabolic energy pathways within the cells were undergoing changes to facilitate the rapid growth observed.

"We analyzed the metabolites that changed in response to PFOS treatment, and we found that the metabolic phenotype of the prostate cancer cells was altered, upregulating the proliferative energy pathways," said co-author Joseph Irudayaraj, the associate director for shared resources at the Cancer Center at Illinois and a founder professor of bioengineering at the U. of I.

"Exposure to PFOS significantly upregulated genes associated with metabolism, particularly the molecule

pyruvate, which is involved in glucose metabolism, and the precursor molecule acetyl-coenzyme A that facilitates the metabolism of fatty acids and steroids," he said.

Prior research, including a 2019 study led by Madak-Erdogan, found that changes in the metabolism of pyruvate and fatty acids were associated with various forms of cancer and other diseases. In that study, published in the journal Cancer Research, Madak-Erdogan's team found that free fatty acids caused estrogen-receptor positive breast cancer cells to increase cell proliferation and tumor growth.

Structurally, chemicals in the PFAS family resemble free fatty acids and bind to the same sites on serum proteins, Madak-Erdogan said.

Co-authors of the new study include former nutritional sciences graduate student and first author Ozan Berk Imir; University of Illinois Chicago urology professor Wen-Yang Hu; UIC andrology lab director and urology professor Gail S. Prins; U. of I. Urbana-Champaign comparative biosciences research scientist Ratnakar Singh; graduate student Qianying Zuo; research assistant Yu-Jeh Liu; and undergraduate student Alanna Zoe Kaminsky.

The research was supported by grants from the National Institutes of Food and Agriculture in the U.S. Department of Agriculture, the U. of I. Office of the Vice Chancellor for Research, and an Arnold O. Beckman Award from the Campus Research Board.

prostatecancerinfolink.net

Virtual Prostate Cancer Clinic: Thumbs Up From Patients and Docs

Roxanne Nelson RN, BSN

CHICAGO — A virtual prostate cancer clinic (VPCC) got high marks from patients who used its services.

Of the nearly 1400 men who had completed active prostate cancer treatment and who were enrolled in the virtual clinic, 94% reported that they were comfortable with being monitored virtually.

In addition, most the patients said that using the VPCC saved them time (92.4%) and reduced out-of-pocket expenses (87.3%).

The study results were presented here at the American Society for Radiation Oncology (ASTRO) Annual Meeting.

"The number of virtual follow-ups increased steadily each year, with a spike due to COVID-19," said lead author Richard Boyajian, MSN, RN, NP, from the Dana-Farber/Brigham and Women's Cancer Center, Boston, Massachusetts. "During the pandemic, the VPCC allowed for very rapid switching of patients from in-person follow-ups to virtual monitoring."

Cancer Diagnosis Impetus for VPCC

Although telemedicine got a huge boost during the COVID-19 pandemic, some patients with prostate cancer at Brigham and Women's Hospital and Dana-Farber Cancer Institute have been using this approach for several years.

Boyajian, a nurse practitioner who works in radiation oncology, came up with the idea of a virtual clinic in 1996, when he was diagnosed with leukemia. "I was waiting to get a stem cell transplant and spending a lot of time at Dana-Farber — and I didn't want to," he said. "I wanted to come up with a way that I could stay out of the clinic."

After his curative therapy, Boyajian returned to school to become a nurse practitioner and then went to work at Dana-Farber — the place he credits with saving his life.

He joined the genitourinary radiation oncology team in 2013, and was caring for patients being treated for prostate cancer. Boyajian noted that these patients are regularly followed for PSA testing and with physician visits to report any symptoms.

A great deal of time was spent in the follow-up process on repetitive tasks for physicians and staff, he explained. "From a patient perspective, it is also very time-consuming as they have to travel to the clinic," he said. "They have to deal with traffic, take off from work — they probably spend more time in the waiting room and traveling than they do with the doctor. We decided that there's got a better way."

Boyajian received a grant from the Brigham Care Redesign Incubator and Startup Program (BCRISP) to create the virtual program. He then developed a software program that allowed patients to have their PSA levels drawn at an affiliated lab that reported directly into the electronic health record (EHR) or at a local lab,

and these results were combined with an electronically submitted questionnaire filled out by the patients. The digital health platform then analyzed PSA levels to indicate relapse or no relapse and provided symptom scores based on questionnaire responses.

Savings in Time and Money

Follow up was also virtual, either by telephone, secure email, or messaging through the electronic health record portal. Patients with posttreatment symptoms were generally managed virtually and those with evidence of PSA recurrence received appropriate scanning per guidelines along with discussions with the referring physician.

asco.org

Five Percent Overall Medicare Reimbursement Cut Estimated for Medical Oncology in 2022

On November 2, 2021, the Centers for Medicare & Medicaid Services (CMS) released the 2022 Medicare Physician Fee Schedule (PFS) and Quality Payment Program (QPP) **final rule**. The Association for Clinical Oncology (ASCO) will analyze the rule in greater detail in the coming days, while initial highlights from the rule are outlined below.

Medicare Physician Fee Schedule Updates

Conversion Factor

The 2022 Conversion Factor (CF) will be $33.59, a decrease of $1.30 from the 2021 PFS conversion factor of $34.89. This 3.7% reduction in the CF is largely due to the expiration of the 3.75% temporary payment increase provided by the Consolidated Appropriations Act (CAA) in 2021.

Specialty Impact

ASCO estimates a 5% overall reimbursement cut for the medical oncology specialty stemming from the fee schedule in 2022 based on updates to Relative Value Units (RVUs) and the updated CF. The actual impact on individual clinicians, however, will vary based on geographic location and the mix of Medicare services billed.

Additionally, that estimate does not include the expiration of the Medicare sequestration moratorium (an additional 2% overall cut) and the statutory sequestration (a further 4% cut overall) set to take effect January 1, 2022.

As 2021 comes to an end, so does the deadline for Congress to take action on the looming sequestration cuts to Medicare reimbursement. ASCO urges Congress to prevent this impending Medicare payment crisis through legislation. ASCO members are encouraged to **contact their lawmakers** and ask them to support providers, and patient access to care, by stopping additional cuts to Medicare reimbursement before the end of the year.

ASCO will complete a full specialty impact analysis in the coming weeks as the Association looks more deeply into the final rule.

Clinical Labor

CMS will move forward with updates to the Clinical Labor rates and will phase in the updates over four years to transition from the current rates to the final updated prices in 2025. CMS is following the same implementation methodology it did for updated supply and equipment prices.

Split or Shared Evaluation and Management (E&M) Services

CMS is updating the definition of split (or shared) E&M visits provided in the facility setting to include a physician and a non-physician practitioner (NPP) in the same group. The split or shared E&M visit is billed by the physician or practitioner who provides the substantive portion of the visit, which in 2023 will be more than half of the total time spent. Split or shared visits can be reported for new as well as established patients, and initial and subsequent visits, as well as prolonged services.

Telehealth

CMS finalized its proposal to allow certain services added to the Medicare telehealth list temporarily during the COVID-19 public health emergency (PHE) to remain until December 31, 2023. CMS will continue to evaluate whether the services should be permanently added to the telehealth list after the PHE is lifted. CMS also adopted permanent coding and reimbursement for a virtual check-in (audio-only) service.

CMS is implementing provisions of Section 123 of the CAA by removing geographic restrictions and adding the home of the beneficiary as a permissible originating site for telehealth services furnished for the purposes of diagnosis, evaluation, or treatment of a mental health disorder. CMS also finalized its proposal to allow audio-only communication for mental health services furnished

by practitioners who have the capability of furnishing two-way audio/video communications, but where the beneficiary is not capable of, or does not consent to, the use of two-way audio/video technology.

Billing for Physician Assistant (PA) Services

CMS is implementing section 403 of the CAA, which authorizes Medicare to make direct payment to PAs for professional services that they furnish under Medicare Part B beginning January 1, 2022. Medicare currently can only make payment to the employer or independent contractor of a PA. Beginning January 1, 2022, PAs may bill Medicare directly for their professional services, reassign payment for their professional services, and incorporate with other PAs and bill Medicare for PA services.

Colorectal cancer screening

CMS finalized implementation of Section 122 of the CAA, which provides a special coinsurance rule for procedures that are planned as colorectal cancer screening tests but become diagnostic tests when the practitioner identifies the need for additional services (e.g., removal of polyps). Beginning in 2022, the coinsurance required of Medicare beneficiaries for planned colorectal cancer screening tests that result in additional procedures furnished in the same clinical encounter will be gradually reduced from 20% on January 1, 2022, to zero percent on January 1, 2030.

Appropriate Use Criteria (AUC) Program

CMS finalized the proposal to begin the payment penalty phase of the AUC program on the later of January 1, 2023, or the January 1 that follows the declared end of the PHE for COVID-19. This flexible effective date is intended to take into account the impact that the PHE for COVID-19 has had and may continue to have on practitioners, providers and beneficiaries. Previously, the payment penalty phase of the AUC program was set to begin January 1, 2022.

Quality Payment Program Updates

CMS is finalizing its proposal to move to Merit-based Incentive Payment System (MIPS) Value Pathways (MVPs) in 2023. For performance year 2023, CMS finalized seven MVPs in the areas of rheumatology, stroke, heart disease, chronic disease management, emergency medicine, lower extremity joint repair, and anesthesia.

For the 2023, 2024, and 2025 performance years, MVP participants are identified as individual clinicians, single specialty groups, multispecialty groups, subgroups, and alternative payment model (APM) entities that are assessed on an MVP for all MIPS performance categories. Beginning in the 2026 performance year, multispecialty groups will be required to form subgroups to report under MVPs.

Other key QPP policy updates for 2022 include: revising the definition of a MIPS eligible clinician to include social workers and certified nurse mid-wives; setting the MIPS performance threshold at 75 points and the exceptional performance threshold at 89 points; weighting the cost and quality performance categories equally (as statutorily required) at 30%; and extending the CMS Web Interface as a collection type and submission type in traditional MIPS for registered groups, virtual groups, and APM Entities for the 2022 performance year only.

thereader.mitpress.mit.edu

Stereotactic Ablative Radiotherapy for High-Risk Prostate Cancer—a Prospective Multi-level MRI-based Dose Escalation Trial

Purpose

Radiation dose intensification improves outcome in men with high-risk prostate cancer (HR-PCa). A prospective trial was conducted to determine safety, feasibility, and maximal tolerated dose (MTD) of multi-level MRI-based 5-fraction stereotactic radiation (SAbR) in patients with HR-PCa.

Methods and Materials

This phase I clinical trial enrolled HR-PCa patients with grade group ≥4, PSA ≥ 20ng/ml, or radiographic ≥T3, and well-defined prostatic lesions on multiparametric MRI (mpMRI) into 4 dose-escalation cohorts. The initial cohort received 47.5Gy to the prostate, 50Gy to mpMRI-defined intra-prostatic lesion(s), and 22.5Gy to pelvic lymph nodes in 5 fractions. Radiation doses were escalated for pelvic nodes to 25Gy and mpMRI lesion(s) to 52.5Gy and then 55Gy. Escalation was performed sequentially according to rule-based trial design with 7-15 patients per cohort and a 90-day observation period. All men received peri-rectal hydrogel spacer, intra-prostatic fiducial placement, and 2 years of androgen deprivation. The primary endpoint was MTD ac-

cording to a 90-day acute dose-limiting toxicity (DLT) rate <33%. DLT was defined as NCI Common Toxicity Criteria for Adverse Events (CTCAE) ≥ grade 3 treatment-related toxicity. Secondary outcomes include acute and delayed gastrointestinal (GI)/genitourinary (GU) toxicity graded with CTCAE.

Results

Fifty-five of the 62 enrolled patients were included in the analysis. Dose was escalated through all 4 cohorts without observing any DLTs. Median overall follow-up was 18 months, with a median follow-up of 42, 24, 12, and 7.5 months for cohorts 1-4 respectively. Acute and late grade 2 GU toxicities were 25% and 20%, while GI were 13% and 7%, respectively. Late grade 3 GU & GI toxicities were 2% and 0%, respectively.

Conclusions

SAbR dose for HR-PCa was safely escalated with multi-level dose painting of 47.5Gy to prostate, 55Gy to mpMRI-defined intra-prostatic lesions, and 25Gy to pelvic nodal region in 5 fractions. Longer and ongoing follow-up will be required to assess late toxicity.

sciencedaily.com

New strategy against treatment-resistant prostate cancer identified: RNA molecule suppresses prostate tumor growth

Many patients with prostate cancer are treated with drugs that lower or block hormones that fuel tumor growth. While the drugs are effective for a time, most patients eventually develop resistance to these therapies.

A new study from Washington University School of Medicine in St. Louis has identified an RNA molecule that suppresses prostate tumors. The scientists found that prostate cancers develop ways to shut down this RNA molecule to allow themselves to grow. According to the new research -- conducted in mice implanted with human prostate tumor samples -- restoring this so-called long noncoding RNA could be a new strategy to treat prostate cancer that has developed resistance to hormonal therapies.

The study is published Nov. 5 in Cancer Research, a journal of the American Association for Cancer Research.

"The drugs that we have to treat prostate cancer are effective initially, but most patients start developing resistance, and the drugs usually stop working after a year or two," said senior author Nupam P. Mahajan, PhD, a professor of surgery in the Division of Urologic Surgery. "At that point, the options available for these patients are very limited. We are interested in addressing this need -- developing new therapies for patients who have developed resistance -- and we believe the RNA molecule we've pinpointed may lead to an effective approach."

The key protein that drives prostate tumor growth, the androgen receptor, binds to testosterone and stimulates cancer growth. Studying the stretch of DNA that codes for the androgen receptor, the researchers discovered that a section of the DNA molecule next to the androgen receptor produced a molecule called a long noncoding RNA. They found that this long noncoding RNA plays a key role in regulating the androgen receptor and vice versa. Because of its position next to the androgen receptor in the genome, the researchers dubbed it NXTAR (next to androgen receptor).

"In prostate cancer, the androgen receptor is very clever," said Mahajan, who is also a research member of Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine. "Our research shows that it suppresses its own suppressor; essentially it binds to NXTAR and shuts it down. This means that in all the prostate cancer samples that we study, we rarely find NXTAR, because it is suppressed by the heavy presence of the androgen receptor in these types of tumors. We discovered NXTAR by using a drug that my lab developed that suppresses the androgen receptor. When the androgen receptor is suppressed, NXTAR starts to appear. When we saw this, we suspected that we had discovered a tumor suppressor."

The drug, called (R)-9b, was developed to attack a different aspect of prostate cancer biology, knocking down expression of the androgen receptor overall rather than just blocking its ability to bind to testosterone or reducing overall testosterone levels in the body, as currently approved drugs do. But in this study, (R)-9b ended up serving as a tool to reveal the presence and role of NXTAR.

Studying human prostate tumor samples implanted in mice, the researchers showed that restoring NXTAR

expression caused the tumors to shrink. They also showed that they didn't need the entire long noncoding RNA to achieve this effect. One small, key section of the NXTAR molecule is sufficient for shutting down the androgen receptor.

"We are hoping to develop both this (R)-9b drug and NXTAR into new therapies for prostate cancer patients who have developed resistance to the front-line treatments," Mahajan said. "One possible strategy is to encapsulate the small molecule drug and the key piece of NXTAR into nanoparticles, perhaps into the same nanoparticle, and shut down the androgen receptor in two different ways."

Mahajan worked with Washington University's Office of Technology Management to file a patent application on potential uses of NXTAR as therapeutics. In addition, the Moffitt Cancer Center in Tampa, Fla., where Mahajan was a faculty member before joining Washington University, has filed a patent application on the (R)-9b drug. The (R)-9b inhibitor has been licensed to a biotechnology startup company called TechnoGenesys. Mahajan and co-author Kiran Mahajan are co-founders of the company.

This work was supported by the National Cancer Institute (NCI) of the National Institutes of Health (NIH), grant numbers 1R01CA208258 and 5R01CA227025; the Prostate Cancer Foundation (PCF), grant number 17CHAL06; and the Department of Defense (DOD), grant number W81XWH-21-1-0202.

The (R)-9b inhibitor has been licensed to a biotechnology startup company called TechnoGenesys. Mahajan and co-author Kiran Mahajan are co-founders of the company. They also own stock and serve as consultants to TechnoGenesys.

Story Source:

Materials provided by **Washington University School of Medicine**. Original written by Julia Evangelou Strait. *Note: Content may be edited for style and length.*

newsroom.clevelandclinic.org

High-Intensity Interval Training in Prostate Cancer

Anita Slomski

News From the JAMA Network

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A high-intensity interval training (HIIT) aerobic exercise program improved cardiorespiratory fitness and suppressed prostate cancer progression in a phase 2 trial.

The trial involved 52 men undergoing active surveillance for localized very low risk to favorable intermediate risk prostate cancer at a single center in Canada. The group randomized to HIIT exercised on a treadmill at 85% to 95% of peak oxygen consumption (Vo_2) 3 times per week for 12 weeks. The control group randomized to usual care maintained their normal exercise level.

medscape.com

HYPORT in Prostate Cancer: New Standard After Surgery?

CHICAGO — The long-term side effects of hypofractionated postoperative prostate bed radiotherapy (HYPORT) for prostate cancer are similar to those of conventional radiotherapy, a new study concludes.

"Hypofractionation is a strategy for shortening treatment by giving larger doses per fraction and is an accepted practice standard for intact prostate cancer," commented the lead author, Mark K. Buyyounouski, MD.

NRG-GU003 is the first study to compare a short course of higher-dose radiotherapy with the well-established, standard 7-week course of radiotherapy for patients who have undergone radical prostatectomy, he noted.

The results showed no clinically or statistically significant differences between the two treatments on the Expanded Prostate Cancer Index Composite (EPIC) with respect to gastrointestinal (GI) or genitourinary (GU) toxicities at 2 years (P = .12).

Although patients who received HYPORT initially experienced more severe symptoms, "those symptoms resolved at 6 months and were identical to the other group — and stayed that way until the end of the study," Buyyounouski commented. He is a professor of radiation oncology and director of genitourinary cancers in the

Department of Radiation Oncology at Stanford University's School of Medicine, in Stanford, California.

"HYPORT is a new acceptable practice standard for patients receiving post-prostatectomy radiotherapy," he concluded.

There are advantages with this approach for all parties, he said. For patients, it requires a shorter time commitment, and there is less expense related to travel and co-pays. For healthcare practitioners, productivity is improved, and costs are lower.

The new study was presented here at the plenary session of the American Society for Radiation Oncology (ASTRO) 2021 Annual Meeting.

Practice Changing or Not?

"These findings are potentially practice changing," commented Sophia Kamran, MD, a radiation oncologist at the Massachusetts General Hospital Cancer Center and assistant professor of radiation oncology at Harvard Medical School, Boston, Massachusetts. She was speaking during an ASTRO press briefing at which the new results were highlighted.

"The field is moving toward hypofractionated radiotherapy for prostate cancer, and it really has been widely accepted in the intact setting," she commented. Now it should also be accepted in the post-prostatectomy setting, she suggested.

"Using contemporary radiation techniques and image guidance, we are able to target a volume and are able to safely deliver hypofractionated radiation therapy that allows for multiple benefits on multiple fronts for our patients, and for our physicians as well," she said.

However, the invited discussant at the plenary session said that more data are needed.

"The information I need before adopting HYPORT as a gold standard is longer-term recurrence data, long-term GU/GI toxicity data, and evidence in higher-risk patient populations that approximate current practice/treatment patterns," said Brendan Mahal, MD. He is an assistant professor of radiation oncology at the University of Miami Miller School of Medicine–Sylvester Comprehensive Cancer Center, Miami, Florida.

Biomarkers Associating with PARP Inhibitor Benefit in Prostate Cancer in the TOPARP-B Trial

Suzanne Carreira

, Nuria Porta, Sara Arce-Gallego, George Seed, Alba Llop-Guevara, Diletta Bianchini, Pasquale Rescigno, Alec Paschalis, Claudia Bertan, Chloe Baker, Jane Goodall, Susana Miranda, Ruth Riisnaes, Ines Figueiredo, Ana Ferreira, Rita Pereira, Mateus Crespo, Bora Gurel, Daniel Nava Rodrigues, Stephen J. Pettitt, Wei Yuan, Violeta Serra, Jan Rekowski, Christopher J. Lord, Emma Hall, Joaquin Mateo and Johann S. de Bono

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Abstract

PARP inhibitors are approved for treating advanced prostate cancers (APC) with various defective DNA repair genes; however, further studies to clinically qualify predictive biomarkers are warranted. Herein we analyzed TOPARP-B phase II clinical trial samples, evaluating whole-exome and low-pass whole-genome sequencing and IHC and IF assays evaluating *ATM* and RAD51 foci (testing homologous recombination repair function). *BRCA1/2* germline and somatic pathogenic mutations associated with similar benefit from olaparib; greater benefit was observed with homozygous *BRCA2* deletion. Biallelic, but not monoallelic, *PALB2* deleterious alterations were associated with clinical benefit. In the ATM cohort, loss of ATM protein by IHC was associated with a better outcome. RAD51 foci loss identified tumors with biallelic *BRCA* and *PALB2* alterations while most *ATM*- and *CDK12*-altered APCs had higher RAD51 foci levels. Overall, APCs with homozygous *BRCA2* deletion are exceptional responders; *PALB2* biallelic loss and loss of ATM IHC expression associated with clinical benefit.

Significance: Not all APCs with DNA repair defects derive similar benefit from PARP inhibition. Most benefit was seen among patients with *BRCA2* homozygous deletions, biallelic loss of *PALB2*, and loss of ATM protein. Loss of RAD51 foci, evaluating homologous recombination repair function, was found primarily in tumors with biallelic *BRCA1/2* and *PALB2* alterations.