Prostatepedia[1]

[1]expert insight + advice

Prevention + Screening

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In this issue....

In June, we're talking about screening and stratifying patients after an initial prostate cancer diagnosis. Why? Most of you have already been diagnosed with prostate cancer: that's why you're reading this. All of you are in contact with men in your families and communities who desperately need the information that follows. Share it with them.

Several of our conversations focus on controversies surrounding prostate cancer screening. I have long been highly critical of the US Preventive Services Task Force's (USPSTF) former, and now revised, recommendations. I object to more then their specific recommendations for prostate cancer: I believe the Task Force's decision-making process is fatally flawed. I also think that the organization is sufficiently insular that it cannot be reformed. The only effective solution is to replace it with a Task Force that has a sounder basis in both biology and statistics.

How can we effectively diagnose and treat prostate cancer? We need three steps for screening to favorably impact survival. The first step is to diagnose. As readers of *Prostapedia* know, advances in prostate cancer imaging, such as the fusing of MRI imaging with ultrasound, now allow us to locate and biopsy aggressive cancers. In a conversation that follows, Dr. Crawford reviews the molecular markers that allow us to better identify patients likely to harbor prostate cancers that need treatment—while stratifying those that don't. After a man has been diagnosed with prostate cancer, the second step is to determine the risk the cancer poses to him, as this determines the appropriate treatment. Traditionally, this risk stratification was done using nomograms like the Partin tables or the Prostate Health Index. Our understanding of the molecular changes that determine prostate cancer aggressiveness has advanced rapidly. We now have tests such as the Oncotype DX, Prolaris, and Decipher that improve our ability to predict disease aggressiveness.

The third step after diagnosis is to offer therapy based on the threat posed by a man's cancer. One benefit of determining risk based on molecular biomarkers is that we can also better identify patients appropriate for active surveillance. This directly addresses the problem of overtreatment.

As a medical oncologist, I have been concerned with finding the best management for men with the most aggressive forms of prostate cancer. There are multiple well-done randomized trials that show improved survival in men with high-risk prostate cancer if they are treated appropriately while the cancer is still organ-confined.

Without screening, we are much more likely to diagnose the high-risk patient only after his cancer has become metastatic. The USPSTF effectively chose to ignore the fate of these patients, condemning them to an early death. This is especially hard to accept because the Task Force had this evidence on hand at the time they gave screening the original D rating and has not adequately revised those recommendations.

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June Chan, DSc
Diet + Lifestyle's Impact on Prostate Cancer

Dr. June Chan is a Professor in the Departments of Epidemiology and Biostatistics and Urology at the University of California, San Francisco.

Her research focuses on how diet, exercise, and lifestyle factors contribute to prostate cancer aggressiveness, progression, and death.

Prostatepedia spoke with her about the impact of diet and lifestyle on prostate cancer.

What do we currently know about the relationship between diet, lifestyle, and prostate cancer?

Dr. Chan: We have observed that there are some relationships between diet and exercise and the risk of clinically relevant prostate cancer. As our studies evolved—and the field evolved alongside the development of PSA screening in the United States—it became important to define and focus on clinically relevant prostate cancer as an outcome.

Back in the early to mid-1990s when some of our first studies came out, we were just looking at specific dietary factors and the risk of overall development of prostate cancer. With PSA screening came the understanding that there are indolent tumors and overdiagnosis; we needed to adjust to that in the field.

Part of my work as a postdoctoral fellow was to collect detailed data in large cohort studies so we could classify men in a more clinically meaningful way. We collected details on stage, grade, and subsequent PSA values so that we could try to distinguish more indolent tumors from more aggressive tumors.

"Exercise may be important for deterring the risk of having recurrent or fatal prostate cancer."

Once we started to do that, it became more interesting because we really started to refine our questioning. The question isn't just, "Is vegetable intake associated with overall risk?" The question becomes: "Is vegetable intake associated with the risk of having bad prostate cancer? A cancer that will do harm." As studies have matured, we've focused on the risk of developing metastases and prostate cancer-specific mortality.

The field had to change as we started to understand the biology of prostate cancer better. Some of that early observational data that came from us looking at total prostate cancer risk needed to be looked at again. That is the stage we're in now. We look at those questions differently now that we have more clinically relevant outcomes with more time.

What do we know about the impact diet and lifestyle have on the risk of developing prostate cancer? What do we know about the impact diet and lifestyle have on progression? About the risk of developing aggressive versus low-risk disease?

Dr. Chan: I'll focus on what we know about clinically relevant cancer or, at least, some of the findings that have persisted over time.

The first thing, which is not discussed as much, is that smoking is potentially related to the risk of fatal prostate cancer. Some of the earliest data come from autopsy studies. They looked at people who had not necessarily been diagnosed with prostate cancer but had died for some other reason. They were able to correlate smoking history with a worse-looking grade and worse-looking features of prostate cancer.

Dr. Stacy Kenfield published a paper looking at the risk of fatal prostate cancer and smoking history. Her work showed that smoking has a broad effect —not just on respiratory cancers. Smoking elevates your risk of other cancers as well.

Some of our work indicates that exercise may be important for deterring the risk of having recurrent or fatal prostate cancer. The story started with two reports that we put out in 2011. Dr. Kenfield led one team and Dr. Erin Van Blarigan led the other. (I was mentoring both researchers.) We had the opportunity to ask about exercise and prostate cancer survivorship in two distinct populations. The results were somewhat complementary.

In one study, it appeared that vigorous physical activity was associated with a benefit or reduction in the risk of metastatic fatal prostate cancer among men diagnosed with localized disease.

The other study had a shorter follow-up, so we weren't able to look at metastasis and death, but we did look at a combined outcome of recurrence, metastasis, and death —or the initiation of secondary treatment after primary therapy in prostate cancer survivors.

While there was a trend toward a benefit for physical activity, what was particularly interesting was that we saw a benefit from brisk walking versus slower walking pace. It suggested that there was something specific about aerobic exercise, or cardiopulmonary exercise, that offered a benefit. We've been pursuing that in other studies.

What do you mean by benefit?

Dr. Chan: In one study, there was a reduced risk of prostate cancer

recurrence. In the other study, there was a reduced risk of prostate cancer death.

What impact do diet and lifestyle have on side effects of prostate cancer treatments?

Dr. Chan: That is not an area that we have focused on specifically, but historically, there have been quite a few papers on the potential benefits of exercise among men who are receiving androgen deprivation therapy (ADT) for prostate cancer. There have been a number of clinical trials documenting quality-of-life benefits. Exercise seems to help with quite a few side effects from ADT.

Do you think it's appropriate to recommend that men at high risk for recurrence pay more attention to diet and lifestyle modifications?

Dr. Chan: The way you're phrasing that question suggests that we know there is more of a benefit for people at higher risk.

In our studies, we looked at men with localized disease. We looked at men with localized disease at the time of diagnosis and at the potential benefit of different exercise or dietary factors on the risk of recurrence or death. We don't necessarily separate out men at higher versus lower risk and did not look to see if there is more benefit for them.

The way our results look right now, there is a potential benefit to exercise and diet for anyone diagnosed with prostate cancer. The nice thing is that a lot of the diet and lifestyle factors that we are seeing as potentially impacting prostate cancer progression would also be recommended for reducing one's risk of several other chronic diseases, such as heart disease and diabetes.

What type of diet do you recommend?

Dr. Chan: There have been a number of risk factors that have been studied. Some of the things that seem to be more consistent in the literature would be the intake of plant-based fats, as opposed to other types of fat.

Meaning limiting meat?

Dr. Chan: Correct. Plant-based fats, or vegetable-based fats, seem to be particularly beneficial—nuts, vegetable oils, avocado. We published a paper a couple of years ago that particularly showed that vegetable-based fats offer a benefit.

"We do not recommend specific supplements unless there is another medical indication or you've discussed it with your physician."

Limiting processed meat is generally recommended for many cancer types. There is some evidence of a potential benefit for prostate cancer.

Intake of tomatoes has been in the literature for a very long time. The benefit from tomatoes might be more from a general intake of carotenoids. Some people speculate it has to do with lycopene; lycopene is highly concentrated in tomatoes.

Some people are studying the intake of fish for its potential benefits. Some of the hypotheses surrounding that have to do with potentially beneficial anti-inflammatory effects.

We've reported on cruciferous vegetables in the past. I think we'd like to update those analyses because there haven't been too many other studies that have reported on it, but we did report a benefit specifically from cruciferous vegetable intake in the past.

Can you talk a bit more about omega-3 fatty acid supplements versus getting your omega fatty acids from eating fish?

Dr. Chan: A lot of the focus on omega-3 is generated from the original food-based data looking at benefits of fish. In general, we—our group, our team, and some of our publications—do not recommend specific supplements unless there is another medical indication or you've discussed it with your physician.

> *"If you have a decent diet, going overboard with a single supplement is not necessarily helpful."*

There are supplements that, when tested further in clinical trials, have not really panned out to offer a benefit. In fact, Dr. Kenfield published a paper not too long ago observing that men taking higher supplemental selenium actually had a higher risk of fatal prostate cancer.

Yes, selenium was recommended for a while.

Dr. Chan: There was some very early secondary data analysis from two trials that were not originally focused on prostate cancer. These studies looked at other cancers, but the investigators had the opportunity to look at prostate cancer.

There are many reasons why their results could be different. It's possible that in the populations they were studying men had lower baseline selenium levels. It could be that you get harmed when you supplement over and above the recommended level. I do believe that in some of the trials, the baseline circulating selenium levels were actually quite different.

There were two studies not focused on prostate cancer followed by the SELECT trial, which was focused on prostate cancer. SELECT did not see a benefit specifically for prostate cancer. But the study populations themselves could have had different baseline selenium levels.

All of this suggests that if you have a decent diet, going overboard with a single supplement is not necessarily helpful. Discuss supplements with your healthcare provider, because they can do a more individualized assessment and tailor the recommended supplement and dose.

In terms of lifestyle, do you have any recommendations other than don't smoke?

Dr. Chan: You mean not smoking, exercise, and diet?

Diet and exercise are two separate things. We always say diet, lifestyle, and exercise. When you say lifestyle, what do you mean?

Dr. Chan: I use lifestyle as a way to refer to diet and exercise together.

I know some have talked about meditation and stress relief…

Dr. Chan: We have had some studies looking at meditation and stress relief in conjunction with diet and exercise. We have a couple of studies that have done comprehensive interventions: one getting advice on nutrition, exercise, stress reduction, and meditation, but we have not looked at stress relief and meditation by themselves. I can't say that we can really tease it apart. Certainly, on an anecdotal level, I see the importance of all of that for a healthy state of mind and well-being.

Do you have any open and enrolling clinical trials now that men might be able to participate in?

Dr. Chan: We have two exercise-based interventions open now, and we have three likely to open later this year. (See https://urology.ucsf.edu/lifestyle-studies for a list of open trials.)

Is there anything else you think patients should know about the impact diet and lifestyle can have on prostate cancer?

Dr. Chan: At the University of California, San Francisco (UCSF), we have a comprehensive guide, which we produced in conjunction with the Prostate Cancer Foundation. It nicely summarizes in patient-friendly language the majority of what we just talked about. (See https://www.pcf.org/guide/ to download the UCSF guide.)

I do think it is important for patients to recognize that there are some things related to diet and exercise that can offer a benefit for prostate cancer, as well as for several other chronic diseases. One can think of the evidence for prostate cancer as underlining the importance of making healthy food choices and finding opportunities to exercise. Pp[1]

Jeffrey Swensen, PhD
Prostate Cancer Screening + BRCA2 Carriers

Dr. Swensen is the Associate Director of Molecular Genetics at Caris Life Sciences in Phoenix, Arizona.

Prostatepedia spoke with him recently about prostate cancer screening for men with BRCA2 mutations. (See *Prostatepedia* March 2017 for a discussion with Dr. Swensen about molecular profiling for prostate cancer.)

> *"At this time, though, screening is not warranted."*

Should a man with a BRCA2 inherited mutation be screened earlier for prostate cancer?

Dr. Swensen: Carrying a pathogenic BRCA2 mutation increases the risk for prostate cancer, and that cancer is more likely to be aggressive and earlier onset. There are recommendations that suggest male BRCA2 carriers should be screened more aggressively for prostate cancer. Male BRCA2 and, to a lesser extent, BRCA1 mutation carriers are also at increased risk for other cancers, including male breast cancer and pancreatic cancer. Screening male BRCA2 mutation carriers for breast cancer is generally recommended; screening for pancreatic cancer is generally not unless there is a family history of that cancer.

Would it make sense to offer prostate cancer screening to male children of a prostate cancer patient earlier?

Dr. Swensen: No. A man with a BRCA2 mutation tends to get prostate cancer at an earlier age than the standard person in the population. But it's generally not really early onset.

A female with a BRCA1 or BRCA2 mutation is at higher risk for breast and ovarian cancer and the onset can be at a considerably younger age. However, screening is typically not performed on these women until they're adults.

Male BRCA2 mutation carriers are at increased risk for cancers, but the risk is not the same magnitude as the risk for the women. The lifetime risk has been estimated to be around 20% for prostate cancer in a male BRCA2 mutation carrier; a female carrier of a BRCA2 or BRCA1 mutation has a lifetime risk of breast cancer that may be up to 80%.

A female BRCA1 or BRCA2 mutation carrier will be counseled and followed extensively. After they reach a certain age and have had children, they can have their breasts and ovaries removed to significantly reduce their risk. That is what Angelina Jolie did.

Are there any other mutations that are significant for prostate cancer?

Dr. Swensen: There is a mutation in another gene that has been shown to be a risk factor for prostate cancer: G84E in the HOXB13 gene.

This mutation is carried by about 0.5% of individuals of European ancestry. It is not a high-risk mutation. Male carriers have a two to threefold increased risk of prostate cancer. The mutation is not known to be therapeutically significant.

Is that mutation associated with an increased risk of getting prostate cancer or of getting aggressive prostate cancer?

Dr. Swensen: That has still not been clearly defined.

Does it make sense to offer prostate cancer screening earlier to men with the G84E germline mutation in HOXB13?

Dr. Swensen: It is one of many genetic factors that will influence an individual's risk of cancer. At this time, though, screening is not warranted. Pp[1]

GeneReviews

GeneReviews offers a good resource on cancer risks associated with BRCA1 and BRCA2.
https://www.ncbi.nlm.nih.gov/books/NBK1247/

Per-Anders Abrahamsson, MD, PhD

PSA Screening in Europe

Per-Anders Abrahamsson is the Chair of the Department of Urology at Skåne University Hospital at Lund University in Sweden and the Secretary General of the European Association of Urology (EAU).

Prostatepedia spoke with him about European urology and lessons learned from the randomized European screening trial.

How did you come to focus on prostate cancer?

Dr. Per-Anders Abrahamsson: I was trained in southern Sweden at Lund University, which is one of the oldest universities in Scandinavia. In our healthcare system, surgery is mandatory for doctors: for two years you practice as an internist. You do some psychiatry, general medicine, and surgery. I wasn't going to be a surgeon, but I changed my mind because I had a fantastic chief of surgery in a small hospital in southern Sweden.

I became a general surgeon. I had a good relationship with the university hospital and had just paid a visit to the Department of Urology at Lund University where I met two professors of chemistry and pathology. I started to do some research in prostate cancer. That was in the early 1980s. I finalized my PhD a few years later. At that time, only two researchers in the world were focused on a very special type of prostatic cell, the neuroendocrine cells, and neuroendocrine differentiation. There were only two of us publishing about neuroendocrine cells which most urologists, even oncologists, were not aware of at the time.

> *"Collaboration is critical and crucial."*

I ended up in Rochester, New York, working as a researcher in 1991. At the time, Abraham T.K. Cockett was the chief of urology and the secretary of the American Urologic Association; he eventually became president. He opened a lot of doors for me.

In a few months, I became laboratory director of his department. We were very fortunate because we had a lot of endowments, mainly from Eastman Kodak Company, Bausch & Lomb, and so forth. I recruited a lot of very good researchers from India, Japan, China, and Scandinavia. I stayed in Rochester for almost three years doing research focused on prostate cancer.

What was your role at the European Association of Urology (EAU) and the vision that you pursued while you were there?

Dr. Abrahamsson: I became a member of the EAU Scientific Committee in 1998 and, in 2004, I was selected as adjunct Secretary General responsible for science. In 2007, I had the opportunity to become Secretary General when professor Pierre Teillac from Paris stepped down to join industry. I served for eight years. (You could only be Secretary General for eight years.)

I didn't plan to become Secretary General, but you never know, things happen overnight. It was, of course, a major change in my life. The EAU started to grow exponentially—not only in Europe but globally.

My vision was to reach out to urologists across the world—in the Middle East, Far East, Latin America, and so forth. That we did quite rapidly.

The first thing we did was recruit a very good chair for our Guidelines Office. At present, the EAU has the most comprehensive urology guidelines in the world. Our guidelines

are translated into more than 50 languages.

Secondly, we invested in our journal, *European Urology*, and recruited a very good editor-in-chief, Professor Francesco Montorsi from Milan, Italy. Now it is the world's leading urologic journal.

We've been extremely successful in terms of our guidelines and scientific journal, as well as with our European School of Urology, which educates urologists in Europe, the Far East, and Latin America.

How does the European approach to prostate cancer differ from approaches in other parts of the world? Or is there even a specifically European approach?

Dr. Abrahamsson: Yes, absolutely. In Europe in the 1990s, we were very conservative, with few exceptions. We didn't really introduce early detection or screening programs whatsoever. In 1991, when I was working in the United States, the American Congress, American Cancer Society, and American Urologic Association all launched screening programs for prostate cancer.

At that time, Bob Dole was a Republican in Congress. He underwent surgery for prostate cancer. All of a sudden, you found advertisements in all the American airports for early detection (screening) of prostate cancer.

That was totally different from what we experienced in Europe at that time. We were a little bit more strict and conservative.

On the other hand, we knew for sure that we had a very high mortality rate for prostate cancer, especially in Scandinavia and Sweden, where I come from. In fact, we had the highest mortality rate in the world at that time.

Of course, we started to wonder what could we do about it.

That is why Sweden and Finland joined the European Randomized Screening Trial in the early 1990s.

How important are international collaborations for prostate cancer research?

Dr. Abrahamsson: Extremely important. I realized that when I was doing my PhD thesis in the 1980s, but even more so when I ended up in Rochester. As I said earlier, in Rochester, I had the opportunity to recruit good researchers from all over the world and to interact and collaborate with a number of leading centers in the United States and Canada. That sort of international collaboration was critical and crucial—and is even more important now in 2017.

You cannot do it alone. Collaboration is the key, especially if you look at patient-oriented research, what we call *clinical research*. You need increasing numbers of patient cohorts to study and follow over time in order to find out whether or not, for instance, screening can make a difference in terms of reducing mortality. Also to evaluate new treatment options, not only in surgery or radiation, but also for drugs and gene therapy coming out of vaccines, etc.

Collaboration is critical and crucial.

Are there any current international collaborations you think patients should know about?

Dr. Abrahamsson: I think the most successful initiative came when Movember started in Australia. (See May *Prostatepedia* for a conversation with Movember's Dr. Mark Buzza.) Movember is a worldwide phenomenon that is delivering a lot of money to research.

"In the United States, there has been a competition between radiation oncologists and urologists over whether surgery is better than radiation or vice-versa."

What about European collaborations?

Dr. Abrahamsson: The European Randomized Study of Screening for Prostate Cancer (ERSPC) included seven Western European countries. It was not possible in the early 1990s to include Eastern European countries. They were still struggling after the Soviet Union and World War II. It was only possible to include countries in western Europe, including Scandinavia.

Could you tell us a bit more about the screening trial? Not all of my readers are familiar with it.

Dr. Abrahamsson: It was initiated by one of the giants in prostate cancer research, Professor Fritz Schröder, who is now retired. He was eager to start a European randomized trial in the 1990s. He recruited over 162,388 men between the ages of 55 and 69. Half of them were randomized to screening by digital rectal examination (DRE) and the PSA blood test, and the other half were randomized to a control group.

The good thing about the European screening trial was that it was not contaminated in the control group by PSA testing. In the 1990s, it was not that common for European patients to undergo PSA testing. That worked in favor of our randomized screening trial: we didn't have any contamination in the control arm. It made a difference. In a similar study in the United States —Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial—more than 50% of the patients were PSA-tested before they were randomized to join the trial. It means that they were probably examined by a doctor before randomization. In addition, the number of patients included in the trial was not sufficient to make any statistically significant difference as to whether or not PSA testing would affect survival rates. In other words, it was an underpowered study.

What are your more recent findings?

Dr. Abrahamsson: The most recent findings were published almost three years ago in the *New England Journal of Medicine*. We announced that we could reduce mortality by 28%. We recently published online the results of the Swedish arm of the trial: we can reduce mortality by 72%. We have a slightly different protocol and a longer follow-up of over 18 years.

Why was the Swedish arm able to present data like this when no one else could? We did something different in Sweden: we screened every two years. We had no contamination in the control arm by patients who underwent PSA testing. We had a longer follow-up and full control of all our patients. We performed patients' surgeries with skilled surgeons in the treatment arm. That's the way to do it in order to optimize the outcome. If you really want to make a difference in terms of reducing mortality, you need a strict protocol and to follow patients for a long period of time—up to 20 years.

What do the findings tell us? Anyone reading this would think we should all be screening for prostate cancer.

Dr. Abrahamsson: No. If you really wanted to screen, it has to be early, fully controlled screening. Uncontrolled doesn't really make that kind of a difference.

The Swedish healthcare system is in favor of a screening program because all people in Sweden have government-provided healthcare. We don't need any private insurance.

Our healthcare system favors registered studies and other types of studies.

We also have probably the best cancer registry in the world, launched in 1959. By following each individual patient, we know why they die—whether it is from cancer, cardiovascular disease, or any other disease.

Do you think the growing acceptance of active surveillance, in addition to the results of this study, will impact the screening debate?

Dr. Abrahamsson: To a certain extent. The founder of active surveillance is Professor Laurence Klotz from Toronto. He has been able to show, with a 15-year follow-up, that less than 2% of men on active surveillance die of prostate cancer. It's good proof that one-third of a population being screened for prostate cancer are candidates for active surveillance over active treatment. Of course, some of his patients over time change from being low-risk to intermediate- to high-risk prostate cancer, but that is more or less an exception to the rule.

Most men diagnosed with low-risk prostate cancer—a Gleason 6—do not have a cancer that becomes more aggressive within the first five or 10 years. Adding newer imaging techniques like MRI gives you even more information about whether individual patients are at risk of having more aggressive cancers or not. Therefore, active surveillance has generally been accepted worldwide.

Some patients find cancer very worrisome and don't accept active surveillance. They want active treatments. I think it's easier to persuade a patient to go on active surveillance in Europe than in the United States. Based on my own experience, patients want active treatment more often in the United States than in Europe. There are also differences between northern and southern Europe: patients have different attitudes and preferences.

Do you think that is just a cultural difference?

Dr. Abrahamsson: Definitely. But the type of healthcare system has an impact too. It's easier for us in Scandinavia to tell a patient that he is not in danger at the present time, that we will follow him on a regular basis, and that he shouldn't be worried. Most accept that.

Why do you think that is?

Dr. Abrahamsson: In the United States, there has been a competition between radiation oncologists and urologists over whether surgery is better than radiation or vice-versa.

In low-risk prostate cancer patients, radiation therapy has been quite successful in the United States because brachytherapy is quite common. A few years ago, at least 50% of patients with low-risk prostate cancer were treated with brachytherapy. That has decreased more recently, but it is still a substantial number of patients.

Brachytherapy is not that common in Europe, especially now. Robotic surgery was launched in the early 2000s. Since then, we have seen reduced numbers of radiation, both in Europe and in North America.

Do you think focal therapy will emerge as an option for men who don't want to go on active surveillance?

Dr. Abrahamsson: I do believe in the future there will be an opening for focal therapy, but we still have certain limitations in terms of imaging. What you want to achieve by using focal therapies is to kill all the cancer cells, but we have not really been able to show that result so far.

There are limitations with focal therapy, but we've improved imaging techniques and new focal therapeutic options.

I would say, in the not-too-distant future, it would be an option for low-risk and intermediate-risk prostate cancer patients. I don't think there is a future for focal therapy for high-risk patients, honestly, because those men should have their entire prostate gland removed—and their regional lymph nodes as well.

Theoretically, our imagining techniques will only improve.

Dr. Abrahamsson: Yes, there is a very rapid improvement in all imagining techniques, but there are still limitations even with PET/CT scanning with tracers (Choline, PSMA, etc.) in terms of specificity and sensitivity.

It is exciting, though. I attend many meetings per year and there are always new reports, but as for using imaging to target and destroy 100% of cancer cells using focal therapy, we are not there yet. Unfortunately. Pp1

E. David Crawford, MD

To Biopsy or Not To Biopsy?

E. David Crawford is the distinguished Professor of Surgery, Urology, and Radiation Oncology, and head of the Section of Urologic Oncology at the University of Colorado Anschutz Medical Campus as well as the driving force behind http://www.pcmarkers.com/.

Prostatepedia spoke with him about how practitioners can fine-tune prostate cancer screening.

Why did you become a doctor?

Dr. Crawford: I got my interest in medicine from my family. They had a nursing home. I worked there when I was in high school and college, so I was around patients and doctors. I saw the compassion the doctors had and really liked it. I got to know a few of them.

Even though that was only a snapshot, I thought medicine would be a good thing to do. Then I got a job during college doing evaluations of people before surgery. That was how I got interested in urology.

My interest in prostate cancer began when I was at the University of California, Los Angeles, as a Fellow. I was dumbfounded that most of the patients we saw with prostate cancer were advanced and incurable.

"I saw the compassion the doctors had..."

I had an opportunity to work with Schering Corp. I did a study and got one of their drugs called Eulexin (flutamide) approved.

A man named Perry Lieber from Las Vegas came to see me. The only way he could get Eulexin (flutamide) was on my Phase III trial. He was a spokesman for Howard Hughes. He wanted to get the word out about early detection for prostate cancer. We started some of the early screening back in the 1980s in Las Vegas and in Colorado. Unfortunately, he died of prostate cancer.

This was in 1988. We didn't know what we were doing. We had PSA; we were testing and biopsying a lot of people. At first, that was good because we found a lot of aggressive prostate cancers.

Once we filtered through those, though, we were biopsying people at lower and lower PSAs and finding prostate cancers that didn't need to be found. There was a lot of overdiagnosis and overtreatment.

That went on for a while. Then the US Preventive Services Task Force said they think screening does work, but that it does more harm than good, so they couldn't recommend it. (They have more recently changed their recommendations.)

That put the brakes on things, but I think it was needed. When we do too many biopsies and rebiopsies and overtreat people, we have no way to restratify them.

I think the way forward is pretty simple. It involves prostate cancer markers: blood, urine, and tissue-based markers.

But first consider who orders PSA tests in the United States: family practice doctors order 92% of PSA tests. We have to educate these family practice doctors.

I did a study a few years ago that looked at the PSA cutoff of 1.5 ng/ml. What if you find prostate cancer in that zone of 1.5 to 4? We found that 70% of men who had their PSA analyzed had a level of less than 1.5 ng/ml and, therefore, could come back in 5 years for another one.

That's an easy message: a PSA above 1.5 to 4 ng/ml is a danger zone. Prostate cancer marker tests

come into play in men with PSAs in that gray zone of 1.5 to 4 ng/ml.

Everyone is talking about informed decision-making with these tests before a PSA is performed, but this is not going to happen. Family practice doctors have more significant things to talk about with their patients: obesity, hypertension, or diabetes. They don't get informed decision to check your cholesterol, your blood pressure, or your weight. They get informed decision after the fact.

I think you should do the same thing with PSA. Doctors should order the PSA tests in the right group of people. If the PSA is less than 1.5, no discussion is needed. Tell the man to come back in five years.

If his PSA is greater than 1.5, we need the next layer of testing and discussion. The goal right now is simple.

PSA is a frontline test to help identify people at risk for having prostate cancer. PSA doesn't tell us what kind of risk. It doesn't tell us if the man has low-grade or high-grade prostate cancer. That is where some of these new tests come in. PSA screening by itself, without any further testing, is gone. PSA is just the first test.

If a doctor were considering doing a biopsy and worried about prostate cancer, the next step would be genomic testing.

What sorts of genomic testing would be appropriate in this setting?

Dr. Crawford: The tests fall into three buckets: blood-based, urine-based, and tissue-based.

The ones I'm working on now are either blood- or urine-based tests. The prostate health index (PHI) is a formula that looks at several forms of PSA to come up with the relative risk of having prostate cancer. Phi is FDA-approved in the US for use in men with a PSA above 4: it gives their relative risk of having prostate cancer.

There are two issues with PHI. First, in Europe, the PSA cutoff is 2. In the United States, the PSA cutoff is 4. But we still have a lot of prostate cancer in men with a PSA between 1.5 and 4. We published a paper that showed a 10-13% higher risk in men with a PSA between 1.5 and 4.

Second, we need more data on PHI levels and high-grade cancers. We've done some studies that show that there seems to be a good correlation between high PHI levels and high-grade cancers.

"The way forward is pretty simple. It involves prostate cancer markers."

The other test is 4Kscore, which looks at the four prostate-specific kallikreins in the blood: Total PSA, Free PSA, Intact PSA, and Human Kallikrein 2 (hK2). The company adds their secret sauce and gives your relative risk of having high-grade prostate cancer.

If your 4Kscore is less than 7%, you don't worry. Above 7%, you do. Still, some people have high-grade cancer when their 4Kscore is below that—you have to account for other risk factors—but it's another good blood test. It's easy to do. The cost is down to less than $700 now. They're trying to get Medicare coverage.

Another test is the urine-based test SelectMDx. This test is done after a digital rectal exam. It is based on two genes that are overexpressed in high-grade prostate cancer. You measure the messenger RNA in urine.

What I like about SelectMDx is that if the test comes back negative, it has a 99% negative predictive value that you don't have a high-grade cancer like a Gleason grade 8, 9, or 10 and a 98% chance you don't have a Gleason 7 or above cancer.

If the SelectMDx comes back negative, it makes you feel really good. If it comes back positive, it gives you a relative risk of low-grade and high-grade cancers. The aim is to find the higher-grade cancers.

Right now, I think one of the more promising genomic tests is the SelectMDx.

Why so much of a push to develop these molecular markers?

Dr. Crawford: It's time. This is the era of personalized medicine. This is a way of addressing the issue of overdiagnosis and overtreatment.

There are approximately 1.4 million prostate biopsies done in the United States every year, but we only diagnose a couple hundred thousand people with prostate cancer. Many get rebiopsied and rebiopsied and rebiopsied.

If your biopsy is positive and you've picked up a low-grade cancer, you might then choose a molecular marker to determine your cancer's aggressiveness. These are the tissue-based genomic tests, such as Oncotype DX, Prolaris, and Decipher.

Another is called ConfirmMDx. This is a tissue-based test that looks for genetic changes called methylation genes around the cancer. (These are areas of *cancerization*.)

If the biopsy is negative and we order ConfirmMDx on the tissue and that test comes back as positive, it means we've widened the target area: we may have missed something and need to go back and look again with another biopsy.

Are prostate cancer markers covered by insurance?

Dr. Crawford: Only PHI and PCA3 have been approved. (PCA3 has pretty much gone by the wayside, though, after the introduction of SelectMDx.)

It happens this way: the company does some clinical trials, they bill insurance, and then they submit to Medicare. They get local coverage determination in which the test will be covered for a period of time while they continue to investigate.

"I think one of the more promising genomic tests is the SelectMDx."

The companies who make these markers are not big companies with deep pockets. They have a limited budget.

If we wait for an endpoint of death on some of these studies, none of us will be around to see the results. We need to think about other endpoints. We are looking at these other endpoints.

I'm excited about all this. I think we've got a way forward now. Most family practitioners believe that screening does do some good, but they know that it also does some harm. Now that we've got the tools to deal with screening, let's deal with it. Patients believe in screening. We don't want to go back to where we were with metastatic disease being the norm.

Do you think the former recommendation against screening ended up having a positive impact? That it forced the prostate cancer community to reevaluate the issue of overtreatment?

Dr. Crawford: A lot of people don't think that, but I do. There was a lot of overdiagnosis and overtreatment.

Sometimes when you tell a man he has cancer, he wants it taken care of yesterday. Many don't understand that some prostate cancers are like skin cancers. You don't cut off your arm because you have a small basal cell cancer on your wrist. It's the same way with prostate cancer. There are low-grade, nonthreatening Gleason 6 cancers.

Are these prostate cancer markers now widely accepted among family practitioners?

Dr. Crawford: No. Family practice doctors don't know much about these markers at all. Urologists don't either. This is the beginning of a long educational process. It'll take patients asking about the tests. Often, patients drive change: that's just the way things happen.

Many of our readers are influential in their communities. What would you say to those men about getting the word out about prostate cancer markers?

Dr. Crawford: There are a lot of hereditary and germline mutations being put forth in prostate cancer: as many as 5% up to 20% of prostate cancer patients will have some of these mutations.

One of my recommendations is that if you have germline mutations of prostate cancer like BRCA2 (and others) your family members should get tested.

The PSA cutoff of 1.5 falls in very nicely with this. If your PSA is 1.5 or above, get the tests we discussed—like the SelectMDx or the 4K.

What about repeating these tests? If a man consistently has a high PSA, would it make sense to keep repeating these tests?

Dr. Crawford: He should be referred to a urologist.

Are these tests at all useful in men on active surveillance or with low-grade cancers?

Dr. Crawford: Thirty percent of patients fail active surveillance. When these men eventually have surgery, sometimes they have adverse pathology. Why did that happen? It happened because when we did the biopsy, we missed the bad cancer—the Gleason 7s, 8s, 9s, and 10s. Some of these tissue markers, like Prolaris and Oncotype DX, can help in that scenario.

Part of the follow-up for men on active surveillance is a repeat biopsy. I haven't met a lot of men who like to have biopsies every year, but they do it.

After a while, doing repeat biopsies and monitoring gets to be more expensive than treatment. A urine test like SelectMDx or 4K can help you determine who needs to be rebiopsied.

What I'm looking at now is whether or not doing the SelectMDx every other year can eliminate the need for biopsies. And I'm finding the answer is yes. Pp

Douglas Payne
Living With Metastatic Prostate Cancer

Mr. Douglas Payne talked to *Prostatepedia* about his experiences with metastatic prostate cancer and the importance of helping other men in his local support group.

How were you diagnosed with prostate cancer?

Mr. Douglas Payne: I had no idea that I had prostate cancer. I wasn't even having any of the normal symptoms of prostate cancer. I had to get up in the middle of the night to pee, but it wasn't that big of a deal. I had yearly physical exams; everything was always normal. I wasn't concerned.

Through that summer, I noticed that I was having a lot of pain in various places. I didn't know why, but I thought: I play hard. I live hard. I work hard.

When you play hard, you figure that as you get older, you don't heal quite as quickly.

Then I started having night sweats that were unbelievable. I would wake up just soaking wet. The bed would be soaked. We would have to get up and change the sheets and put towels down just to get back to sleep.

It got to the point where my back hurt really badly. I thought it was some kind of muscle thing. (It turns out it was cancer in my ribs and back.)

The back pain forced me to go to the doctor. I said, "I don't feel good." He said, "Well, what's the matter?" I said, "I don't really know what's the matter. I just don't feel very good. I'm kind of tired. My back hurts. I've been having night sweats."

He checked me and said, "You appear to be fine." He then did blood work. My PSA came back at 1100. He thought it was outrageously high. He said, "I've never even heard of anybody having a PSA this high." He thought I must have a bad prostate infection. (My wife and I had been traveling in the Middle East.) He thought maybe I'd picked up a disease from a sheep. We had been camping out in the desert with sheep and goats.

Was this a family physician?

Mr. Payne: This was my family physician. He didn't know what it was.

I was 58 years old and in very good health. I work hard at staying healthy and in shape. It was quite surprising when the PSA came back that high.

He had done a rectal exam and didn't feel anything wrong.

He thought it must be an infection, so he put me on antibiotics. It took two weeks for me to get in to see him again and then another two weeks for him to diagnosis prostate cancer.

During that four-week period, I went downhill fast. I was losing more than a pound a day. It was just bad. My wife was freaked out. I was freaked out.

They sent me in for a bone scan. I didn't know why they were sending me in for a bone scan because I didn't know that prostate cancer metastasized to bones.

"The back pain forced me to go to the doctor."

I knew I had a problem when the doctor called me back in the same day as the scan. He sat down and said, "You've got Stage IV metastatic prostate cancer. I'll make an appointment with the oncologist for you."

That was it. That was the last I heard from him.

Two days later I went to a urologist for a biopsy. Before we even had the results of the biopsy, I went to see the oncologist.

What kinds of treatment did he put you on?

Mr. Payne: I told him that I wanted to fight this thing as aggressively as I could. I'm young, healthy, and strong.

This would be the time to do it rather than down the road when the treatments could wear me out more. Immediately, he put me on androgen deprivation therapy: two shots of Firmagon (degarelix) in the stomach. I started chemotherapy about a week later.

Did you have any side effects?

Mr. Payne: Yes, I had a lot of side effects. The chemotherapy has immediate short-term side effects and then longer-term side effects. I had the usual ones: nausea and my hair fell out. I ended up having to have two blood transfusions. (I had neutropenia, or abnormally low white blood cells, and my hematocrit levels went down really low.)

All in all, I have to say that I dealt with it pretty well. It wasn't as bad as I thought it would be, although it did get considerably worse over time. Chemotherapy builds up. I got mouth sores, which weren't really that bad.

I don't know really how to describe the worst part. A couple of days after getting the chemotherapy, I would go through this really dark psychological period. I just felt really dark. Not really depressed so much as I didn't want talk to anybody. I just sat there. I didn't do anything. It lasted several days.

During the last three treatments, my wife took off from work and just stayed home with me; we watched movies.

Now that it's over, the only lasting effect is neuropathy, or weakness and numbness, in my feet.

Do you think the chemotherapy caused your dark mood?

Mr. Payne: I believe it was clearly related to the chemotherapy. I could feel it for about two days afterward. Then it would go away after four or five days.

When you were first diagnosed, did you reach out to other men with prostate cancer? How did you find out information about the cancer? Or process what was happening to you?

Mr. Payne: I'm a scientific-thinking type of person by nature. I like to reason things out and think about stuff.

Of course, the Internet is amazing. Whether for good or bad, I ended up going home and researching cancer. I read right away that I had less than a 30% chance of a five-year survival.

I've learned a lot since then. But at the time, knowing that my Gleason score was 9 and I was metastatic, I thought, "I'm not going to survive a year." That's what I first thought. I was a little bit concerned about that, as you might imagine.

I was fortunate. Through a couple of people, I found out about a prostate cancer support group at a local hospital that I started attending right after I was diagnosed. I've attended ever since. The emotional support is completely invaluable to me.

What has your experience with the support group been like?

Mr. Payne: A retired prostate cancer doctor runs the group. He is devoted to the cause. He runs several in the Seattle, Washington, area.

I go to a Thursday morning group. We generally have between 10 and 20 people there. Mostly men, but occasionally someone will bring his wife. At first, I was a bit discouraged, because most of them had localized disease.

I showed up and thought, "Oh my God! I'm going to die. I've got Stage IV cancer! It's already metastasized and here they are talking about active surveillance. I'm going through

chemotherapy and androgen deprivation therapy." (I think the side effects from androgen deprivation therapy are worse than the side effects from chemotherapy).

Really? I've never heard anybody say that.

Mr. Payne: I'm on Lupron (leuprolide) now. They started me on Firmagon (degarelix) because they didn't want a spike in my testosterone levels.

When you take away someone's testosterone, it changes a lot about him. I've had a hard time dealing with those changes: the loss of intimacy with my wife, putting on weight. Now my breasts are growing. I am fatigued. I've got bone density loss.

The worst thing about it is that this is not going to end. It's just going to go on and on and on.

Do the same people come every week to the support group?

Mr. Payne: There are regulars, but almost every week someone new shows up. Most of the new guys are newly diagnosed. Some are people who have had cancer for quite some time but are now recurrent.

The new person always talks first: tells his story and asks questions. Then everybody offers their perspective.

The doctor does a good job of bringing the latest prostate cancer news: new treatments, new diagnostic methodology. He talks about where you can find more information.

I've heard a lot of men say that their prostate cancer diagnosis changed how they saw themselves and their lives. Did you experience anything like that after diagnosis?

Mr. Payne: I don't think it changed the way that I see my life. I've always tried to live my life with passion and purpose. I don't feel that the diagnosis changed me in that regard, but it did sharpen my focus. I reprioritized: now I know I have a lot less time. Nobody knows when they're going to die, but now I'm thinking, "I've got a very limited lifespan left. I have to make the most of that time."

Do you have any advice for men in a similar situation to yours?

Mr. Payne: Get into a support group of some type. I found it to be invaluable.

Ideally, you could find a support group like the one I have that offers emotional support and knowledge.

In the end, no one is going to care about your healthcare as much as you. You've got to advocate for your own healthcare.

Here's a good example. Early on through my research, I read about a clinical trial in *Prostatepedia*. I went to my doctor and asked what he thought. He said, "There is absolutely no clinical evidence to show that this is going to do you any good." I said, "Does it make sense?" He said, "There is some logic behind it." I said, "Then I want to do it."

Had I not brought that article up with my doctor, it never would have happened. Did it make a difference in the end? There is no way to know, but it gave me the satisfaction of knowing I'm not leaving anything on the table. I'm not leaving any stone unturned. I'm doing everything I can to advocate for my own health.

I go to my doctor and we talk about clinical studies being run all over the country. I go see him with a spreadsheet of all the different drugs available and how they're used. He looks at me and rolls his eyes,

but he'll discuss it all with me and answer all my questions.

I'm glad you found someone who is listening to you.

Mr. Payne: I suggest to anybody that if you're not happy with the doctor you have, find a new one. Not all doctors are the same.

Do you share your clinical trial spreadsheet with your support group?

Mr. Payne: I do.

What would you say to a man living in a community without a support group like this?

Mr. Payne: That would be really hard. I'm fortunate to live in Seattle where we have a lot of resources.

I would say information is out there. It takes some effort, but you can figure it out.

Do you have any other advice for men who have just been diagnosed or are facing recurrence?

Mr. Payne: If you have just been diagnosed, figure out how aggressive your cancer is and what you can do about it. Are you an active surveillance candidate? Should you be looking at surgery? Should you be looking at radiation? There are all kinds of opinions out there. In the end, you have to decide what is right for you.

You have to figure out what the answer is. You can't just be told.

For someone who is recurrent, the question becomes, "What do I do from here?" It's the same educational process, but the standardized treatment protocols are pretty well spelled out. You don't have a whole lot of choice.

"Cancer sucks, but you've got to deal with it.."

Once my PSA started to rise again, they put me on Zytiga (abiraterone). Fortunately, it's been effective for me. This is my third month on Zytiga (abiraterone) and my PSA has come back down. I'm happy about that. I'll ride the wave as long as I can.

I continue to go to every support group meeting because every once in a while I bring something to the discussion that is helpful, especially for new people. If they're in advanced stages or recurrent, they need someone to talk to. They need someone to listen. That is why I keep going.

Are you saying you mainly go to the support group to help other men and not to get help for yourself?

Mr. Payne: Yes. I'm to the point now where I know a lot. It's ridiculous the amount of information that I have in folders on my desk. I don't always have the information right off the top of my head, but I know how to find it.

Androgen receptor variance is a pretty esoteric topic. A lot of people don't want to get into it. For whatever reason, I do.

And I'm not afraid to say anything. A lot of guys don't want to talk about some of the stuff that is inevitable. I can't have sex anymore. It sucks. Cancer sucks, but you've got to deal with it.

I'm stunned when I hear about guys who go to the doctor and find out they have cancer and don't want treatment. I don't understand that at all.

A few months ago, I interviewed a man from Oregon. He said that when some people find out they have cancer, they grab a shovel and start digging a grave in the backyard. Others grab a sword and start fighting.

Mr. Payne: Which one is he?

He grabbed the sword.

Mr. Payne: I'm glad to hear that. You have to fight.

It's hard when you are afraid or overwhelmed, though.

Mr. Payne: Yes. It took me awhile to get over being overwhelmed. But I can't change the facts. It is what it is. All I can do is make the smartest decisions that I can.

I never allow myself to feel sorry for myself or to complain. My wife and I have traveled around the world. We've been to a lot of third-world developing countries, seen how other people live. My life is full of all the things that are important. I have a great family, great kids, and great grandkids. I don't ever complain. I don't let anybody tell me how unfair it is. It is what it is. You have to learn to live with that.

Every day is a challenge. I balance spending time learning about prostate cancer while not dwelling on it. I still have to live. I have to earn a living. I still need my health insurance. (I can't even imagine what I would do without insurance.)

It's a bit of a paradox. I'm always looking forward to my next blood test: what are my numbers are going to be? But once that week or month is over, I can't focus on it. I have to focus on making my days last as long as I can. Enjoying each one. Pp1

J. Renee Savickas Lindsay McBride Free Screening Events

Ms. J. Renee Savickas is the Vice President and Director of Early Detection and Awareness Programs and Ms. Lindsay McBride is the Development and Education Programs Manager at the Prostate Conditions Education Council (PCEC) in Denver, Colorado.

Prostatepedia spoke with them about the free education and prostate testing events they host in September of each year as well as the importance of advocacy.

How did you become involved with prostate cancer advocacy?

Ms. Lindsay McBride: When I moved to Denver, I was hired by PCEC to lead awareness and education events. I'm so thankful; the education has been incredible. I have enjoyed working in the prostate cancer space and working with a leading patient advocacy organization.

Ms. Renee Savickas: I've been with PCEC for seven and a half years. About the same time that I joined the organization, my husband's father passed away from prostate cancer. He was only 73 years old. He never went to the doctor for check-ups. He thought he was invincible. He walked every day, but never went to the doctor. He was finally forced to go in because he had really bad back pain. They started running all kinds of tests and found out he had prostate cancer. By that point, the cancer was advanced. He had bone metastases. He didn't live for very long. There was not much they could do for him because it had spread all over his body. I ended up working here around that same time. Now, I'm super worried about my husband and my son. When I advocate to patients about how important early detection is, I really empathize.

So then the importance of early detection isn't abstract for you? It hits close to home?

Ms. Savickas: Absolutely.

Do you share your father-in-law's story with men at screening events?

Ms. Savickas: I do. Sometimes my husband volunteers with me and shares his story.

Can you talk to my readers a bit about how PCEC started and its current mission?

Ms. Savickas: Our group was founded in 1989 by Dr. E. David Crawford and a group of leading urologists and oncologists. At that time, prostate cancer was most commonly found in the advanced stages.

We developed Prostate Cancer Awareness Week as a flagship national

> *"We work with all members of the prostate cancer team."*

screening program. We worked to help diagnose prostate cancer earlier and at the most treatable stages and conduct research to help improve prostate cancer diagnosis and detection. Over the last three decades, we have grown into a key education and awareness organization.

We also offer life-saving prostate health assessments year round. Men can come to one of our free testing, education, or awareness events for a quality prostate health assessment. Our services give men the opportunity to talk to a urologist, get a PSA, and/or digital rectal exam. Some sites offer general men's health testing, which includes a lipid panel, testosterone, and cholesterol levels.

Are these events only in Colorado?

Ms. Savickas: No. We certainly have a large number of events in Colorado because this is where we are based, but our programs and initiatives are available across the country. We also

have a great network of hospitals, academic centers, and urology groups that participate in our programming to enhance the reach of our programs. (See www.prostateconditions.org for a list of participating sites.)

We also have an international presence. We are proud of our most recent addition of Prostate Cancer Awareness Week in Japan.

What are PCEC's other programs?

Ms. McBride: We offer prostate cancer patient education events throughout the year in different cities across the country. Leading physicians offer talks to patients and caregivers on advanced cancer topics and markers in prostate cancer. Some events focus on aiding in the decision-making process after initial diagnosis.

It is also important to ensure providers have access to cutting-edge information. Therefore, we work to educate medical professionals with nursing education events across the country.

One of the things that makes PCEC unique is that we work with all members of the prostate cancer team: patients, caregivers, physicians, nurses, patient advocates, and navigators.

Men encounter a variety of different health professionals as they move throughout their prostate cancer journey, don't they?

Ms. McBride: Exactly. Managing prostate cancer can be very difficult.

Why—and how—should patients become their own prostate cancer advocates?

Ms. McBride: Simply put, men will get better care if they are their own advocates. It is important that men are empowered to be in charge of their treatment.

How?

Ms. Savickas: We encourage men to get second opinions and to consult with a variety of different physicians throughout their prostate cancer journey. We also encourage them to bring a family member or friend to appointments to help take notes. It helps to have someone there with a clear mind and to have an extra set of ears. Other important components are to get educated and to ensure you discuss not only your treatment options for today, but plan for the future.

Do you think it's important for men with prostate cancer to participate in outreach programs? For patients to reach out to other men?

Ms. Savickas: We love to work with prostate cancer patients. It's very powerful to have a prostate cancer patient speak to newly diagnosed men about his experiences. We would love for even more patients to engage with us to help at our patient education events. Any way patients can volunteer at health fairs or screenings is great, even if it's on social media spreading the word about how important the work is.

Ms. McBride: Men have to speak up and speak out. I know a lot of men don't like to talk about being sick and don't want to talk about their prostates, but the only way to help anyone is to talk about their experiences with prostate cancer.

Ms. Savickas: No taboos.

Like you having your husband come speak at screening events about his father's prostate cancer…

Ms. Savickas: Right. I like for him to share his story. Pp[1]

Clinical Trial: Preston Sprenkle, MD Screening Men With BRCA2 Mutations

Dr. Preston Sprenkle is an Assistant Professor of Urology at Yale University.

Prostatepedia spoke with him about a trial he's running on targeted prostate cancer screening.

Why did you become a doctor?

Dr. Preston Sprenkle: My father was a physician. I liked the idea of helping people and doing something that was both intellectually challenging, yet also socially and intellectually rewarding.

I wasn't sure, though, so after college I worked in consulting for a little, while also volunteering in an ER and in some free clinics. I really valued those experiences with patients and the one-on-one interactions. I recognized how much good you can do and how much you can help someone by just listening and being attentive to their needs and concerns. Those experiences solidified my desire to go into medicine.

When I started medical school, I quickly realized that I really enjoyed anatomy and surgery. Urology is a fantastic specialty because you come in contact with a wide variety of patients—from children to very old patients, men and women. Even though most people think urology just centers on men, we actually take care of a lot of women too.

Urology involves a lot of surgeries that can be complicated and take a lot of time and energy, but there is also a lot of one-on-one patient-based care dealing with very personal things like sexual function or urinary function. Urology is somewhat unique among surgical specialties in that we not only operate on patients, but very often follow them for many years, allowing for long-term relationships with our patients.

I then became interested in cancer care. The current challenge is to improve the way we take care of cancer patients. Cancer is scary. Fortunately, in many cases it is is very treatable and even curable. But hearing the C-word can be terrifying. Most people shut down and don't really hear much after learning they've been diagnosed, so it can be a little longer process to help them understand that there are opportunities for cure.

What is the thinking behind the clinical trial you're running?

Dr. Sprenkle: We opened this trial to better understand the relationship between the BRCA2 mutation, or BRCA2 deletion, in men and the incidence of prostate cancer.

There have been several studies showing that men with prostate cancer who have a BRCA2 mutation have a more aggressive prostate cancer more likely to have lymph node positivity.

What we have not been able to identify is where that starts. These men were arguably diagnosed with prostate cancer because they had an elevated PSA. Is their risk higher because they were diagnosed later in the course of their prostate cancer, or is their risk higher because the BRCA2 deletion causes them to have higher-grade prostate cancer?

When we started this trial, there was no information and no long-term prospective studies. (I believe there recently has been a trial that suggests that on a stage-for-stage basis it actually may not be much worse to have BRCA2, but that was not around when we started this trial.)

We are trying to understand the incidence of prostate cancer in this population of men with the BRCA2 mutation. This is, in part, a registry for all men who have a known BRCA2 mutation. We offer them prostate cancer screening with standard techniques: PSA blood tests, DRE, etc. But we also offer an MRI and MR-targeted biopsy to evaluate if there are any radiologic characteristics that could be used.

If 28-30% of men in a general population have prostate cancer with a PSA cut-off of 4, is that the same for men with a BRCA2 mutation? Or should we be screening men with this mutation earlier? Or biopsying them with a lower PSA? Do men with this mutation have a 30% rate of prostate cancer with a PSA of 2?

There is a famous trial called the Prostate Cancer Prevention Trial that used a medication to shrink the prostate. During the trial, they biopsied men if they had an elevated PSA and then at the end of that trial. Even men who didn't get treatment were biopsied at the end, independent of what their PSA was. The trial gave a tremendous amount of information about what the likelihood is of developing prostate cancer when your PSA is as low as 1. Based on the results of this trial, we know that approximately 8% of men with a PSA of 1 or less have prostate cancer on a random biopsy– even though we typically don't biopsy those men.

This current trial is an opportunity for us to gain information about how—or if—the incidence of prostate cancer is different in a population of men with a BRCA2 mutation.

Are you just looking for men without prostate cancer with the BRCA2 mutation?

Dr. Sprenkle: Yes. Any man who has at least a 10-year life expectancy qualifies to be screened. The biggest challenge is identifying men with the mutation. Most people find out they have the mutation because their mom, sister, or father was tested and found to have the gene delete mutation. They then screen the family, because there is an increased risk of breast cancer in men and a few other things that are much less common.

Like what?

Dr. Sprenkle: Melanoma and pancreatic cancers. BRCA2 is a DNA repair gene. In some of these areas that have cell turnover, it can result in cancer.

So you'll offer prostate cancer screening to men who carry the BRCA2 gene. What else do you do? Offer biopsy? MRI?

Dr. Sprenkle: The trial is actually very simple: we're offering more aggressive screening than basic standard of care to men with the BRCA2 mutation. Standard care would be to do a PSA and a prostate exam; if those were both normal, screening would stop. But in this trial, we also offer an MRI—which is a higher tech way of screening for prostate cancer—and a biopsy. (In the UK, they're evaluating using MRI as a screening tool independent of PSA.)

What we are doing is an aggressive evaluation to establish how many people with a BRCA2 mutation have cancer.

So then this is an effort to figure out if a targeted screening makes sense in this population of men?

Dr. Sprenkle: We are hoping to identify *how* we should do targeted screening, so yes. Pp1

How To Get Involved…

For more information, contact Dr. Preston Sprenkle by emailing preston.sprenkle@yale.edu or calling 203-785-2815.

Paul Schellhammer, MD
A Urologist's Personal View of Prostate Cancer

Paul Schellhammer, MD is a urologic oncologist who has been involved in key clinical trials for the treatment of prostate cancer, including studies that led to the FDA approval of Provenge (sipuleucel-T). He has served as President of the American Urologic Association, Chair of the Department of Urology at Eastern Virginia Medical School, and has also been on the editorial boards of several journals.

The following is an excerpt from an article Dr. Schellhammer wrote for the *Turkish Journal of Urology* (2016 Sep; 42(3):121-6. DOI: 10.5152/tud.2016.50318) about his own prostate cancer journey. (See http://turkishjournalofurology.com/sayilar/163/buyuk/121-1263.pdf)

Emotions

The emotional impact of a cancer diagnosis is quite profound regardless of how well educated or well informed the patient. I will describe my mindset with a cardiovascular event which I experienced two years before the diagnosis of prostate cancer—a mindset that I have discussed and confirmed as similar to the experience of others in the same situation. Certainly the coronary occlusion, which fortunately was promptly treated with two stents with good results was sobering. Total occlusion of the left anterior descending coronary artery, as was my case, has been dubbed the "widow maker" for good reason.

Nevertheless, there was optimism. Plans for better diet, more exercise, and healthier lifestyle would allow me to partner with my heart with anticipation of a productive future. The emotional impact of the cancer diagnosis was quite different—a visceral reaction, almost a sense of betrayal and fear—a desire to rid myself of the alien invader by whatever means was my primary thought and plan of action. This, despite the fact that I knew very well that the greatest risk for future morbidity and mortality rested with cardiac disease–I have had six additional stents placed as a reminder of this–and that any prostate cancer morbidity and mortality were certainly many years into the future. With the encouraging recent advances in knowledge about treatments for advanced prostate cancer, morbidity and mortality will decline even further. As powerful as my initial emotional reaction to the cancer diagnosis was, the news, as I've mentioned, of PSA failure one year after radical prostatectomy was perhaps more profound. A positive spin that I can place onto the roller coaster ride of PSA recurrences that were to follow is that the human psyche turns resilient and tolerates each iteration of "treatment failure" with a greater degree of equanimity.

I will paraphrase here an observation made by Wendy Harpham, a physician and medical writer, who was faced with one of many recurrences of a hematologic malignancy. She observed that cancer did not make her life uncertain but exposed her to the uncertainties of life. She put aside her fears, apprehensions, and concerns about tomorrow and appreciated what she now had in a way never before possible.

Clinical Trials and Hope

Intertwined with the disappointment of PSA recurrences is the hope that rests with new effective and approved therapies and the promise of new therapies that are in the process of clinical trial testing and that might be even more effective. The promise of investigative therapies certainly provides hope.

However, the time, testing, and travel that clinical trials often demand are daunting and often frustrating. Patients are prepared to participate in and take risks that trials may present in hopes of deriving benefit. They are essential partners in the team moving cancer

therapy forward. We must remember that the term "team" implies facilitation of opportunity for all members of the team and, in the case of the clinical trial team, specifically the patient. The time has arrived to fulfill the promise that trials must be more patient-friendly. I have entered many patients into clinical trials, and have personally participated in two trials (one after PSA failure following salvage radiation plus androgen deprivation therapy, and one upon developing castration-resistant metastatic disease) and can attest to the difficult regulatory gauntlet they present.

Androgen Deprivation Therapy

The four letter word that best describes the state of androgen deprivation therapy is "LOSS"—loss of energy; interest; vitality; mental and physical activity; muscle mass and strength; cardiovascular health; bone health; and, most overtly, sexual health, including erectile dysfunction and diminished libido. I believe the global effect of androgen deprivation is underappreciated and that the debilitating effects of impaired sexual health are often inadequately addressed. They present a challenge to the physician, the patient, and the patient's partner. The long-term strain placed on relationships can be as significant as the strain of the initial prostate cancer diagnosis. A manual recently published, entitled *Androgen Deprivation Therapy: An Essential Guide for Prostate Cancer Patients and Their Loved Ones*, in my opinion, is just that—essential! It deals with problems and possible solutions. As I wrote in my evaluation of this manual, "It was only when I began my personal journey with androgen deprivation therapy that I was able to appreciate the profound impact this treatment has on daily life. Even with my real-life experience with androgen deprivation therapy (ADT) accumulated over decades, I know I cannot, within the limits of one or even several office visits, begin to prepare and educate patients for their new reality. I could not even do that for myself! If only a complete user-friendly manual existed. Now it does."

The Lexicon of Cancer

The world of cancer has developed its own vocabulary. And words matter. When used in certain contexts they deliver a specific message. Three of these words are *survivor, cure, and war*.Soldiers persevering through battle, just as cancer patients enduring chemotherapy or a surgical procedure, consider themselves survivors. One of the major differences, of course, is that in medicine survivorship is a time-limited event usually measured by three, five, or 10-year survival curves. Survivorship is not a one-time event as there is always the possibility of subsequent cancer recurrences and further treatment. I am certainly thankful and delighted to be surviving at the present, but I consider my pathway better described by the word *participant*. I say this because I have, with my physicians, partnered and participated in a number of decisions and then participated in the treatment process whether standard of care or clinical-trial based.

Another gold standard word is cure. Certainly every cancer patient looks for a procedure or pharmacologic agent that will rid him of disease and restore life, and hopefully quality of life, as experienced prior to the diagnosis. Cure promises to relegate the cancer experience to the past tense. However, cure is often evanescent. Dormancy may be recognized in the future as an accepted temporary pattern of cancer behavior. I think it is important to note that the Latin root of the word cure is curare which means "to care for". Again, against the background of persistent/recurrent disease, caring for the patient through a series of treatments is more realistic and supportive than the promise of final/complete obliteration of the disease.

Lastly the word *war*. The war metaphor has entered almost all aspects of our lives. It is commonly used in competitive sports, business, and politics. War became closely associated with cancer when, in 1971, President Nixon, as part of the National Cancer Act, officially declared war on cancer and aimed to defeat cancer in what is now recognized as a very unrealistic timeline. War is energy depleting, resource consuming, and long wars all the more so. Prostate cancer is a disease of long natural history. Patients who enter into a daily battle with the disease forfeit the state of living well with their cancer. Siddhartha Mukherjee, in his biography of cancer, The Emperor of All Maladies, discussed his concern with the cancer war metaphor. He suggested that the war on cancer may have to be won by redefining the meaning of victory. For prostate cancer patients this may involve a state of negotiation whereby they learn to live well and hopefully long with their disease. The emphasis is on thrival as well as survival. This mindset has been described by others as, "When there are clouds on the horizon, one learns to dance in the rain," or those patients do best who learn to dance with their disease. Again, as stated earlier, the appreciation of "today" is affirming and healing.

It has been my privilege to share my story with men receiving the unwelcome news of a prostate cancer diagnosis and also my privilege to witness the courage and strength they demonstrate as they face a future with this disease. I appreciate the opportunity to share my story with you. Pp[1]

Merel Grey Nissenberg
Changing Screening Recommendations

Ms. Merel Grey Nissenberg, a California attorney specializing in medical malpractice cases, is the President of both the American-based National Alliance of State Prostate Cancer Coalitions (NASPCC) and the California Prostate Cancer Coalition (CPCC).

Prostatepedia spoke with her about the recent proposed changes to the US Preventive Services Task Force (USPSTF) recommendations on screening.

How did you become involved in prostate cancer advocacy?

Ms. Merel Grey Nissenberg: I'm a trial attorney. I handle medical malpractice cases.

Obviously, I don't have a prostate. I don't have anybody in my family who passed away from prostate cancer, but I'm very interested in prostate cancer and in cancer advocacy.

In my law practice, I've handled a lot of prostate cancer cases with inexcusably late diagnoses. Just shabby care. A lot of those clients have passed away because of that.

In 1994, I handled a case that had a surgical oncologist as one of our experts. He recommended that I start working on the California Division of the American Cancer Society's Prostate Cancer Task Force, which I did.

I then went on to co-chair the task force. In 1997, there was a California-wide American Cancer Society meeting on prostate cancer. We thought it would be great to have a statewide California coalition for prostate cancer. Everybody said we couldn't do it because California is too big. We heard that challenge. The California Prostate Cancer Coalition is now 20 years old!

Was this the first American statewide prostate cancer coalition?

Ms. Nissenberg: At that time, Pennsylvania had a coalition and Massachusetts had a fledgling coalition. A few other states were just starting coalitions.

In 2001, I went to a meeting with 20 state leaders in Washington, DC, at the former National Prostate Cancer Coalition (NPCC.) NPCC is now ZERO. We wanted to see how the states could help their organization—and how NPCC could help the states with *their* missions.

At that meeting, I met a lot of people from other state coalitions. I said I'd like to set up coalitions in all 50 states. Jan Marfyak, a prostate cancer survivor who was co-chair of the Pennsylvania coalition at the time, thought that was a great idea. Together, we started raising money to set up state coalitions.

In 2004, we decided to set up a national alliance, an umbrella organization, which would allow states to network with each other and to share best practices. This is now the thirteenth year of the National Alliance of State Prostate Cancer Coalitions.

Our original goal was to make prostate cancer a national healthcare priority by becoming a collaborative force that developed and mentored state prostate cancer coalitions.

In 2014, we added two core priorities: awareness and education, and public policy advocacy. To address awareness and education, we created a guide on prostate cancer screening aimed at patients and primary care physicians alike. (See https://tinyurl.com/nycvrr6).

How have the United States government's recommendations on prostate cancer screening changed?

Ms. Nissenberg: When I first got involved with prostate cancer advocacy, the recommendation was inconclusive whether you should screen or not. In fact, in our work, we

use the word 'testing' because the term "screening" is so controversial.

In 2012, which was the most recent USPSTF Recommendation, the US Preventive Services Task Force announced a straight across-the-board D recommendation: do not screen. Most physicians saw the "D" at the top of the page and never read beyond that.

But then we went back and looked. In the middle of the middle sections of the recommendations, in the Clinical Consideration section and in the Reply to Public Comments section, the Task Force clearly says that if a man wants to have an informed discussion about prostate cancer, his physician must—this is mandatory language—have that discussion with him. It is then the patient's decision based on his own values and preferences whether or not to get tested. It was buried in the guidelines, but it's there.

I know a lot of men have since gone for their regular physicals and have not been offered PSA testing, even though they're getting blood drawn for other things. The issue of prostate cancer screening is not brought up. They're not even offered digital rectal exams (DRE).

There was a huge outcry after the 2012 Guidelines became final; they did not take into account your family history, if you're African-American, or if you have been exposed to Agent Orange or any other type of banned chemicals. (Agent Orange is a huge risk factor for Vietnam veterans.)

The 2012 recommendation scared men away from asking for testing. Later the California Prostate Cancer Coalition and the American Cancer Society worked together briefly to get some language into the ACS guidelines that we could both live with. We did not like the way ACS used the phrase *potential* benefits and harms instead of *potential* benefits and *potential* harms. (The word "potential" only referred to the benefits, not the harms.) It made the benefits only potential, but the harms certain.

Precision in language is important…

Ms. Nissenberg: Exactly. But the USPSTF proposed changes to the guidelines in April of this year; it would still be a D recommendation for men 70 and over (with no regard to life expectancy), but a C for men 55 to 69. They're recommending that a man speak with his physician and that the physician offer the man an informed discussion about prostate cancer testing.

Based on the 2012 guidelines, physicians didn't have to bring up testing at all. They were completely relieved of the responsibility of bringing up prostate cancer testing. Physicians felt that legally they didn't have to discuss testing with men.

An informed discussion is not the physician telling you why you don't want to be tested. Your physician is supposed to discuss the risks of being diagnosed with a cancer that doesn't need treatment. He or she should also discuss the benefits: if you have an aggressive disease, early detection is critical.

Men need to know that this is their decision to make, based on their preferences and values. It's not for someone else to say that you don't need to know about this.

I've dealt with cases in my law practice in which the doctors actually note in medical records that the patient wants a PSA. "Patient is worried about prostate cancer." And still some doctors have refused to test. Some of those patients are dead now.

People tend to trust whatever the physician says.

It's that old hierarchal relationship people have had with their doctors.

Ms. Nissenberg: Right. They just tend to think he or she has this superior experience, training, and expertise, so if the physician says don't worry, the patients won't worry.

But, as I said, physicians haven't even been bringing testing up—and have felt legally justified in not doing so.

The way I see it is that you have to educate, not just the primary care doctors, but also men—prospective patients—so they know to ask about prostate cancer screening. You can't ask for an informed discussion about something you don't know exists. We need to educate both groups.

So from the D recommendation of 2012, the proposed guidelines now say that physicians should discuss the potential benefits and risks associated with screening with men 55 to 69.

But the NASPCC and the CPCC have problems with the new proposed guidelines. First, why start at age 55? We advocate that a man get a baseline PSA in his early 40s. This gives a risk assessment; you can then personalize follow-up.

If you're at low risk based on your PSA reading, you don't have to come back for retesting for another five years. (No one is suggesting that men get yearly PSA tests.)

If you're at intermediate risk, you get retested every one to two years, depending on your other risk factors.

Men at high risk would obviously need immediate follow-up.

Even the Task Force itself acknowledges in the Frequently Asked Questions section of the new proposed draft guidelines that sometimes you don't see a benefit to screening for over 10 years. Sometimes 10-15 years. If you wait to get baseline tests until men are 55, you lose an opportunity to prevent some of them from developing metastatic disease.

Another change in the recommendations is that the Task Force now discusses active surveillance. The guidelines say that there are men who will choose active surveillance, so those men will not be overtreated by definition. But the guidelines did not also acknowledge the fact that we now have urine, blood, and tissue markers that can help determine whether or not a man is at risk for aggressive disease. Why worry about overtreatment if a man is diagnosed, but not acknowledge the availability of biomarkers to select those at high risk for clinically significant prostate cancer?

Lastly, NASPCC and CPCC believe that Vietnam veterans and others exposed to Agent Orange should be included in the Task Force definition of a high-risk group (that currently includes African-American men and men with a family history of prostate cancer).

We do applaud that the Task Force is now finally openly talking about informed decision-making.

It's important to remember that not everyone who is tested will be overtreated. (I don't believe there as such a thing as overdiagnosis.) Diagnosis is just information.

You can choose not to be treated once you have the information.

Ms. Nissenberg: Exactly. You wouldn't tell a woman, "You don't really want to know if you have breast cancer, *dear*."

After a certain age, women get mammograms yearly.

Ms. Nissenberg: Exactly. Physicians take that choice away from men.

We distribute our decision-making guide (see https://tinyurl.com/nycvrr6) to physicians as well as patients so that they know which questions the patient is going to ask. (Men aren't going to be coming in with 500 pieces of paper from the Internet.)

In the guide, we talk about things like baseline PSA, the importance of family history, ethnicity, and exposure to Agent Orange. Questions like: If I have a biopsy and it reveals cancer do I necessarily have to have treatment? What is active surveillance?

Good, basic questions-and-answers.

Why are they revising the guidelines now? Because of the outcry in the prostate cancer community? Or is this just part of the normal cycle of revision?

Ms. Nissenberg: It is part of the normal cycle of revision. The outcry probably helped precipitate it, but this is just their normal timeframe.

What do you feel are the greater implications of the guideline changes?

Ms. Nissenberg: The implications are that more men will hopefully be tested. More men will have that conversation and make their own informed decision about whether they want to be tested or not. The changes to the guidelines will raise awareness at the very least.

The changes are a good start, but we've got to go further. Pp[1]


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Who is XTANDI for? XTANDI is a prescription medicine used to treat men with prostate cancer that no longer responds to a medical or surgical treatment that lowers testosterone and that has spread to other parts of the body. (This is a type of advanced prostate cancer.)

Important Safety Information

Who should not take XTANDI?

XTANDI is not for use in women. Do not take XTANDI if you are pregnant or may become pregnant. XTANDI can harm your unborn baby. It is not known if XTANDI is safe and effective in children.

Before you take XTANDI, tell your healthcare provider if you:

- Have a history of seizures, brain injury, stroke or brain tumors.
- Have any other medical conditions.
- Have a partner who is pregnant or may become pregnant. Men who are sexually active with a pregnant woman must use a condom during and for 3 months after treatment with XTANDI. If your sexual partner may become pregnant, a condom and another form of birth control must be used during and for 3 months after treatment. Talk with your healthcare provider if you have questions about birth control. See "Who should not take XTANDI?"
- Take any other medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements. XTANDI may affect the way other medicines work, and other medicines may affect how XTANDI works. You should not start or stop any medicine before you talk with the healthcare provider that prescribed XTANDI.

How should I take XTANDI?

- XTANDI is four 40 mg capsules taken once daily.
- Take XTANDI exactly as your healthcare provider tells you.
- Take your prescribed dose of XTANDI one time a day, at the same time each day.
- Your healthcare provider may change your dose if needed.
- Do not change or stop taking your prescribed dose of XTANDI without talking with your healthcare provider first.
- XTANDI can be taken with or without food.
- Swallow XTANDI capsules whole. Do not chew, dissolve, or open the capsules.
- If you miss a dose of XTANDI, take your prescribed dose as soon as you remember that day. If you miss your daily dose, take your prescribed dose at your regular time the next day. Do not take more than your prescribed dose of XTANDI in one day.
- If you take too much XTANDI, call your healthcare provider or go to the nearest emergency room right away. You may have an increased risk of seizure if you take too much XTANDI.

What are the possible side effects of XTANDI?

XTANDI may cause serious side effects including:

- **Seizure.** If you take XTANDI you may be at risk of having a seizure. You should avoid activities where a sudden loss of consciousness could cause serious harm to yourself or others. Tell your healthcare provider right away if you have loss of consciousness or seizure. Your healthcare provider will stop XTANDI if you have a seizure during treatment.
- **Posterior Reversible Encephalopathy Syndrome (PRES).** If you take XTANDI you may be at risk of developing a condition involving the brain called PRES. Tell your healthcare provider right away if you have a seizure or quickly worsening symptoms such as headache, decreased alertness, confusion, reduced eyesight, blurred vision or other visual problems. Your healthcare provider will do a test to check for PRES. Your healthcare provider will stop XTANDI if you develop PRES.

The most common side effects of XTANDI include weakness or feeling more tired than usual, back pain, decreased appetite, constipation, joint pain, diarrhea, hot flashes, upper respiratory tract infection, swelling in your hands, arms, legs, or feet, shortness of breath, muscle and bone pain, weight loss, headache, high blood pressure, dizziness, and a feeling that you or things around you are moving or spinning (vertigo).

XTANDI may cause infections, falls and injuries from falls. Tell your healthcare provider if you have signs or symptoms of an infection or if you fall.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of XTANDI. For more information, ask your healthcare provider or pharmacist.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see the Brief Summary on the following page and the Full Prescribing Information on XTANDI.com.

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It is not known if XTANDI is safe and effective in children.

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Do not take XTANDI if you are pregnant or may become pregnant. XTANDI can harm your unborn baby.

What should I tell my healthcare provider before taking XTANDI?

Before you take XTANDI, tell your healthcare provider if you:

- have a history of seizures, brain injury, stroke, or brain tumors
- have any other medical conditions
- have a partner who is pregnant or may become pregnant. Men who are sexually active with a pregnant woman must use a condom during and for 3 months after treatment with XTANDI. If your sexual partner may become pregnant, a condom and another form of effective birth control must be used during and for 3 months after treatment. Talk with your healthcare provider if you have questions about birth control. See "**Who should not take XTANDI?**"

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. XTANDI may affect the way other medicines work, and other medicines may affect how XTANDI works.

You should not start or stop any medicine before you talk with the healthcare provider that prescribed XTANDI.

Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist when you get a new medicine.

How should I take XTANDI?

- Take XTANDI exactly as your healthcare provider tells you.
- Take your prescribed dose of XTANDI one time a day, at the same time each day.
- Your healthcare provider may change your dose if needed.
- Do not change or stop taking your prescribed dose of XTANDI without talking with your healthcare provider first.
- XTANDI can be taken with or without food.
- Swallow XTANDI capsules whole. Do not chew, dissolve, or open the capsules.
- If you miss a dose of XTANDI, take your prescribed dose as soon as you remember that day. If you miss your daily dose, take your prescribed dose at your regular time the next day. Do not take more than your prescribed dose of XTANDI in one day.
- If you take too much XTANDI, call your healthcare provider or go to the nearest emergency room right away. You may have an increased risk of seizure if you take too much XTANDI.

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- **Posterior Reversible Encephalopathy Syndrome (PRES).** If you take XTANDI you may be at risk of developing a condition involving the brain called PRES. Tell your healthcare provider right away if you have a seizure or quickly worsening symptoms such as headache, decreased alertness, confusion, reduced eyesight, blurred vision or other visual problems. Your healthcare provider will do a test to check for PRES. Your healthcare provider will stop XTANDI if you develop PRES.

The most common side effects of XTANDI include:

- weakness or feeling more tired than usual
- back pain
- decreased appetite
- constipation
- joint pain
- diarrhea
- hot flashes
- upper respiratory tract infection
- swelling in your hands, arms, legs, or feet
- shortness of breath
- muscle and bone pain
- weight loss
- headache
- high blood pressure
- dizziness
- a feeling that you or things around you are moving or spinning (vertigo)

XTANDI may cause infections, falls and injuries from falls. Tell your healthcare provider if you have signs or symptoms of an infection or if you fall.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of XTANDI. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XTANDI?

- Store XTANDI between 68°F to 77°F (20°C to 25°C).
- Keep XTANDI capsules dry and in a tightly closed container.

Keep XTANDI and all medicines out of the reach of children.

General information about XTANDI.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use XTANDI for a condition for which it was not prescribed. Do not give XTANDI to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about XTANDI. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about XTANDI that is written for health professionals.

For more information go to www.Xtandi.com or call 1-800-727-7003.

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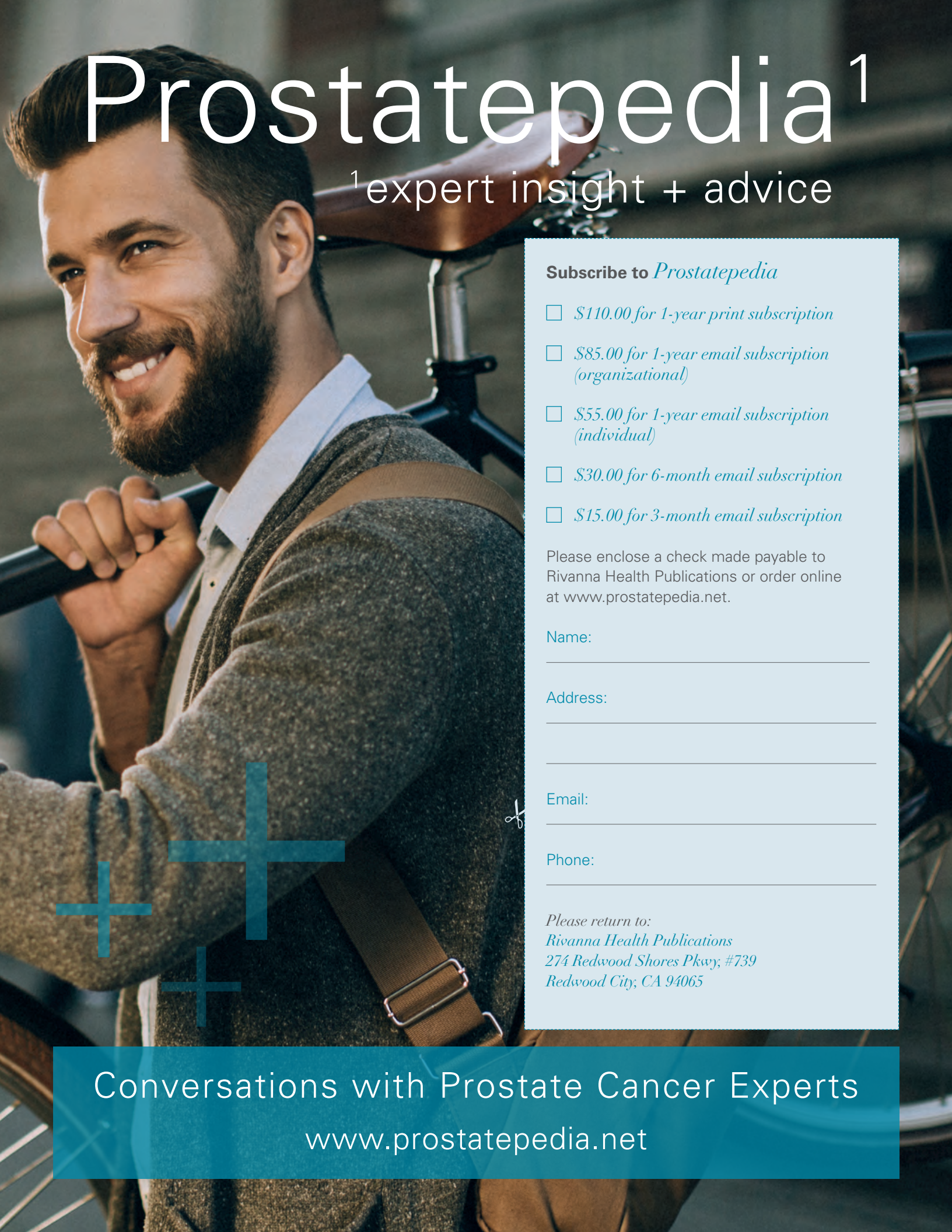

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ZYTIGA® is not for use in women or children. **Keep ZYTIGA® and all medicines out of the reach of children.**

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- Have heart problems
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- Have any other medical conditions
- Plan to become pregnant **(See "Who should not take ZYTIGA®?")**
- Are breastfeeding or plan to breastfeed. It is not known if ZYTIGA® passes into your breast milk. You and your healthcare provider should decide if you will take ZYTIGA® or breastfeed. You should not do both. **(See "Who should not take ZYTIGA®?")**
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- Take ZYTIGA® on an empty stomach. **Do not take ZYTIGA® with food.** Taking ZYTIGA® with food may cause more of the medicine to be absorbed by the body than is needed and this may cause side effects.
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- Swallow ZYTIGA® tablets whole. Do not crush or chew tablets.
- Take ZYTIGA® tablets with water.
- Your healthcare provider will do blood tests to check for side effects.
- Men who are sexually active with a pregnant woman must use a condom during and for one week after treatment with ZYTIGA®. If their female partner may become pregnant a condom and another form of birth control must be used during and for one week after treatment with ZYTIGA®. Talk with your healthcare provider if you have any questions about birth control.
- If you miss a dose of ZYTIGA® or prednisone, take your prescribed dose the following day. If you miss more than 1 dose, tell your healthcare provider right away.

ZYTIGA® may cause serious side effects including:

- **High blood pressure (hypertension), low blood potassium levels (hypokalemia), and fluid retention (edema).**

Tell your healthcare provider if you get any of the following symptoms:

- Dizziness
- Fast heartbeats
- Feel faint or lightheaded
- Headache
- Confusion
- Muscle weakness
- Pain in your legs
- Swelling in your legs or feet

- **Adrenal problems** may happen if you stop taking prednisone, get an infection, or are under stress.
- **Liver problems.** You may develop changes in liver function blood tests. Your healthcare provider will do blood tests to check your liver before treatment with ZYTIGA® and during treatment with ZYTIGA®. Liver failure may occur, which can lead to death. Tell your healthcare provider if you notice any of the following changes:
  - Yellowing of the skin or eyes
  - Darkening of the urine
  - Severe nausea or vomiting

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- Weakness
- Joint swelling or pain
- Swelling in your legs or feet
- Hot flushes
- Diarrhea
- Vomiting
- Cough
- High blood pressure
- Shortness of breath
- Urinary tract infection
- Bruising
- Low red blood cells (anemia) and low blood potassium levels
- High blood sugar levels, high blood cholesterol and triglycerides
- Certain other abnormal blood tests

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

THESE ARE NOT ALL THE POSSIBLE SIDE EFFECTS OF ZYTIGA®.

FOR MORE INFORMATION, ASK YOUR HEALTHCARE PROVIDER OR PHARMACIST.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

ZYTIGA® can interact with other medicines.

You should not start or stop any medicine before you talk with the healthcare provider who prescribed ZYTIGA®.

Know the medicines you take. Keep a list of them with you to show to your healthcare provider and pharmacist when you get a new medicine.

Call your doctor for medical advice about side effects. You are encouraged to report negative side effects of prescription drugs to the FDA.

Visit www.fda.gov/medwatch, or call 1-800-FDA-1088 (1-800-332-1088).

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Horsham, PA 19044 USA

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janssen

PATIENT INFORMATION
ZYTIGA® (**Zye**-tee-**ga**)
(abiraterone acetate)
Tablets

Read this Patient Information that comes with ZYTIGA before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is ZYTIGA?
ZYTIGA is a prescription medicine that is used along with prednisone. ZYTIGA is used to treat men with castration-resistant prostate cancer (prostate cancer that is resistant to medical or surgical treatments that lower testosterone) that has spread to other parts of the body.

ZYTIGA is not for use in women.

It is not known if ZYTIGA is safe or effective in children.

Who should not take ZYTIGA?
Do not take ZYTIGA if you are pregnant or may become pregnant. ZYTIGA may harm your unborn baby.

Women who are pregnant or who may become pregnant should not touch ZYTIGA without protection, such as gloves.

What should I tell my healthcare provider before taking ZYTIGA?
Before you take ZYTIGA, tell your healthcare provider if you:
- have heart problems
- have liver problems
- have a history of adrenal problems
- have a history of pituitary problems
- have any other medical conditions
- plan to become pregnant. See "**Who should not take ZYTIGA?**"
- are breastfeeding or plan to breastfeed. It is not known if ZYTIGA passes into your breast milk. You and your healthcare provider should decide if you will take ZYTIGA or breastfeed. You should not do both. See "**Who should not take ZYTIGA?**"

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ZYTIGA can interact with many other medicines.

You should not start or stop any medicine before you talk with the healthcare provider that prescribed ZYTIGA.

Know the medicines you take. Keep a list of them with you to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take ZYTIGA?
- Take ZYTIGA and prednisone exactly as your healthcare provider tells you.
- Take your prescribed dose of ZYTIGA 1 time a day.
- Your healthcare provider may change your dose if needed.
- Do not stop taking your prescribed dose of ZYTIGA or prednisone without talking with your healthcare provider first.
- Take ZYTIGA on an empty stomach. **Do not take ZYTIGA with food.** Taking ZYTIGA with food may cause more of the medicine to be absorbed by the body than is needed and this may cause side effects.
- No food should be eaten 2 hours before and 1 hour after taking ZYTIGA.
- Swallow ZYTIGA tablets whole. Do not crush or chew tablets.
- Take ZYTIGA tablets with water.
- Men who are sexually active with a pregnant woman must use a condom during and for 1 week after treatment with ZYTIGA. If their female partner may become pregnant, a condom and another form of birth control must be used during and for 1 week after treatment with ZYTIGA. Talk with your healthcare provider if you have questions about birth control.
- If you miss a dose of ZYTIGA or prednisone, take your prescribed dose the following day. If you miss more than 1 dose, tell your healthcare provider right away.
- Your healthcare provider will do blood tests to check for side effects.

What are the possible side effects of ZYTIGA?

ZYTIGA may cause serious side effects including:

- **High blood pressure (hypertension), low blood potassium levels (hypokalemia) and fluid retention (edema)**. Tell your healthcare provider if you get any of the following symptoms:
  - dizziness
  - fast heartbeats
  - feel faint or lightheaded
  - headache
  - confusion
  - muscle weakness
  - pain in your legs
  - swelling in your legs or feet
- **Adrenal problems** may happen if you stop taking prednisone, get an infection, or are under stress.
- **Liver problems**. You may develop changes in liver function blood test. Your healthcare provider will do blood tests to check your liver before treatment with ZYTIGA and during treatment with ZYTIGA.

  Liver failure may occur, which can lead to death. Tell your healthcare provider if you notice any of the following changes:
  - yellowing of the skin or eyes
  - darkening of the urine
  - severe nausea or vomiting

The most common side effects of ZYTIGA include:

- weakness
- joint swelling or pain
- swelling in your legs or feet
- hot flushes
- diarrhea
- vomiting
- cough
- high blood pressure
- shortness of breath
- urinary tract infection
- bruising
- low red blood cells (anemia) and low blood potassium levels
- high blood sugar levels, high blood cholesterol and triglycerides
- certain other abnormal blood tests

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ZYTIGA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZYTIGA?

- Store ZYTIGA at room temperature between 68°F to 77°F (20°C to 25°C).

Keep ZYTIGA and all medicines out of the reach of children.

General information about ZYTIGA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ZYTIGA for a condition for which it was not prescribed. Do not give ZYTIGA to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about ZYTIGA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ZYTIGA that is written for health professionals.

For more information, call Janssen Biotech, Inc. at 1-800-526-7736 (1-800-JANSSEN) or go to www.Zytiga.com.

What are the ingredients of ZYTIGA?

Active ingredient: abiraterone acetate

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

Manufactured by: Patheon Inc. Mississauga, Canada
Manufactured for: Janssen Biotech, Inc. Horsham, PA 19044

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: May 2016

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