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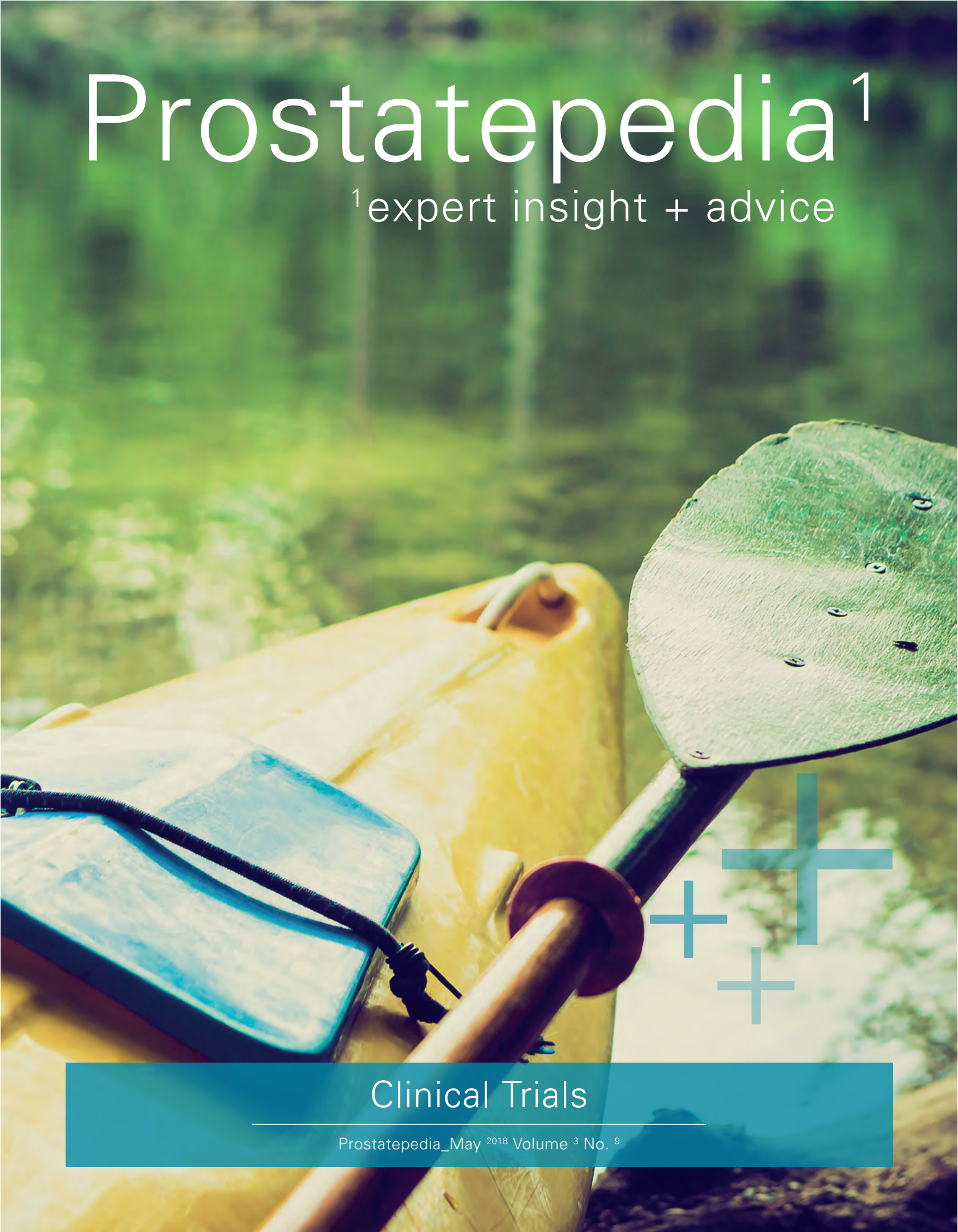

Clinical Trials

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In this issue....

Over the past ten years, the management of prostate cancer has been revolutionized by the appearance of new drugs and new concepts using established drugs as well as surgery and radiation. Every one of these advances only exists because of clinical trials. This is the only path forward. This month, we discuss many of the issues patients face when they consider entering a clinical trial.

The fact that most large clinical trials include a randomization to a control arm is often a major source of patient concern, especially if the control arm uses a placebo. When the control arm involves an active treatment, that treatment will typically represent current state-of-art care that you might receive if you do not enter a clinical trial. However, the cost to you will be less because the clinical trial sponsor will commonly cover the cost of care. The financial benefit to you could easily reach thousands of dollars.

What if the trial includes a placebo arm? First, the existence of a placebo arm commonly indicates that no existing treatment has proven to be of benefit. As a patient, you should do your due diligence on this point. Second, there are strict rules in place to protect patients on the placebo arm. You should know these rules and make sure you are comfortable with them.

Patients on a trial's placebo arm commonly do better than similar untreated patients not on a clinical trial. There is actually a large literature on why the Placebo Effect exists. One explanation offered is that patients on the placebo typically get better standard care, and I think this is a major factor. It may also be that patients on placebo do better for psychological reasons or a mind-body effect. The latter might be particularly relevant for the treatment of nausea, pain, anxiety, or depression.

Finally, many patients enter clinical trials for altruistic reasons. By entering a well-designed clinical trial, you will help answer questions that will benefit future patients. The progress we have made over the past decade only happened because patients who came before you chose to enter clinical trials.

Charles E. Myers, Jr., MD

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Clinical Trials + *You*

This month, *Prostatepedia* asks doctors, advocates, and patients why men with prostate cancer should consider joining clinical trials. Chances are you've never thought about entering a clinical trial. You and your doctor have hammered out a prostate cancer treatment plan that takes into account your particular cancer and which side effects you're willing to live with and which you're not. But a clinical trial? Most men never really think about joining a trial unless their own doctor brings it up—if he or she does at all.

"Most men never think about joining a trial."

But there are clinical trials available to men at every stage of the prostate cancer journey from new diagnosis to active surveillance to monitoring for potential recurrence to advanced disease. Some trials offer men access to a drug or therapy that they might not otherwise be able to get. Other trials help scientists learn about prostate cancer biology or genomics. All are important and all advance our understanding of prostate cancer with the aim of eventually eradicating the disease all together.

Understanding clinical trial terminology will be important as you evaluate whether or not you're interested in joining a particular trial. A Phase I clinical trial generally looks at drug safety and includes a smaller number of patients. A Phase II trial collects preliminary data on whether a given drug works in men with prostate cancer. A Phase III trial collects further information about drug safety and effectiveness—usually in different populations, different dosages, and in combination with other drugs. Phase III trials can lead to a drug's FDA-approval.

"Forwarding this issue of Prostatpedia to your doctor is a great way to start."

Forwarding this issue of *Prostatepedia* to your doctor is a great way to start a discussion about clinical trials. Be sure to take notes and do your own research afterwards until you're sure you understand the pros and cons of each trial you're considering.

"It is worth investigating."

Support groups—online and in-person—can be wonderful resources as you evaluate your options.

The bottom line is that it's worth investigating if there is a clinical trial available for you at this time whether or not you decide to join one in the end. You'll learn a lot about your options moving forward and may just find one that's a fit. Pp1

Fred Saad, MD
How I Talk To My Patients About Clinical Trials

Dr. Fred Saad, MD, FRCS is Professor and Chairman of Urology, and Director of Genitourinary Oncology at the University of Montreal Hospital Center.

Dr. Saad's main research interests include novel therapies for advanced prostate cancer and molecular prognostic markers in prostate cancer.

Prostatepedia spoke with him about how he talks to patients about clinical trials.

Why did you become a doctor?

Dr. Fred Saad: I really never had a second choice. I was really quite young, and for some reason, I was attracted to medicine and caring for patients. It sounds ridiculous, but it started when I was eight years old. It's a little weird for an eight year old to say that's what he wants to do, but for some reason it was an obsession of mine. Fortunately, it worked out the way I had hoped because I never even thought about what else I could do in my life.

Like a calling?

Dr. Saad: I don't know if it's a calling or an attraction to the challenge of the human body and how it works, seeing if you can do something to improve people's lives. At eight years old you really don't know what you're getting into. The older I got the more convinced I was that this was what I wanted to do. Fortunately, somebody accepted me into medical school. The rest is, as they say, history.

> *"We can only answer those questions through clinical trials."*

Two out of my four kids have decided to become doctors, so my example wasn't all bad I guess. One is already a doctor. One is starting medical school.

A family business.

Dr. Saad: I'm married to a doctor. So yes, I guess medicine is part of the family, part of us.

What are some of the pros and cons a prostate cancer patient might want to consider before joining a clinical trial?

Dr. Saad: Depending on what state or stage of the disease you're at, it wouldn't be a reflex of most patients to think about a clinical trial. When you've reached the very latest stage of the disease and you're told there are no other options, then I think most patients would ask if there are no other options available that are standard of care, is anything going on in research. In that situation, patients are sometimes the motor: they ask their physicians about what is available and many don't accept an answer of nothing else.

Unfortunately, in all the other stages of the disease, it is on those who face the unanswered questions of the disease every day to explain to patients the importance of answering those questions. We can only answer those questions through clinical trials.

Some of those questions come at the very beginning. Screening for prostate cancer: Who should we screen? Who should we diagnose? What should we do once we have a diagnosis? Those questions continue through to localized disease: what is the best treatment for that patient at that time? What is the best approach once a patient fails therapy?

We have clinical trials at every single step of the prostate cancer journey. It's up to doctors to inform patients

that the reason we're still asking ourselves questions is because we don't have all the answers. We're going to get those answers through clinical trials. It becomes our responsibility to tell patients that clinical trials are available, that they're of minimal risk to the patient, but could actually help him and especially help future patients.

"Ask if there are any trials."

I explain to patients that breast cancer is way ahead of prostate because of clinical trials. There are other diseases, that we've almost cured because of clinical trials. We've got a ways to go with prostate cancer, but fortunately, we've made a lot of progress over the last 25 years.

Why do you think clinical trial participation isn't as common in the prostate cancer population as it is in the breast cancer population? Do you think doctors aren't bringing up the subject with men or there is some reluctance on the part of prostate cancer patients?

Dr. Saad: When I bring up clinical trials to my patients, over 80% agree to be a part of a clinical trial. Part of that may be our way of presenting the pros and cons of a clinical trial. But some patients may be uncomfortable or unwilling to be a part of a clinical trial even if there is one that might be appropriate for him. If presented in a proper way—honestly, transparently—the vast majority of patients accept.

Unfortunately, many patients aren't offered clinical trials, whether their physicians aren't involved, might not be convinced of the importance of the question, or are reluctant to refer a patient to another physician. Also, in general, men with prostate cancer are not as proactive as women with breast cancer in pushing for research and clinical trials. This has some effect on the speed at which we make progress.

There are unfortunately a lot of roadblocks that lead us to having less than 5% of patients in clinical trials. This is really unfortunate because we've got a lot more questions than answers in prostate cancer. It's critical that more patients join clinical trials. At my clinic we don't ask why a patient is in a clinical trial, but why *isn't* a patient on a clinical trial?

We have to think of clinical trials every time we see a patient with prostate cancer if we want to advance our understanding of the disease as fast as possible.

Not all clinical trials would change a patient's treatment path, per se. For example, an active surveillance or imaging study wouldn't necessarily change paths?

Dr. Saad: Absolutely. It's not a question of changing the patient's treatment path. It's about making an active effort to put patients in clinical trials. It is more work. I hear many of my colleagues say that we already do a really good job. We don't need to put a patient in a randomized clinical trial. That's unfortunate because it slows down the speed with which we get answers. Given the number of men with prostate cancer, we should have answered a lot of these questions a long time ago.

There are some institutions that have a long and very strong history of putting patients on clinical trials. Those institutions are the ones that are contributing a lot to our knowledge of prostate cancer. We need more physicians and centers committed. For individual patients, a clinical trial may or may not make a huge difference, but for the patients who come after him in that same situation it will.

Clinical trials do not always imply that more is better. Sometimes in trials we do add more treatments to have a better chance at curing that patient, but sometimes we reduce the intensity of treatment to determine if outcomes are similar but with improved quality of life. We're learning slowly through clinical trials what are the most appropriate approaches for different scenarios.

What would you say to a man who's reading this whose doctor perhaps isn't bringing up clinical trials or doesn't necessarily think finding a trial is a priority? Would you encourage patients to take the initiative?

Dr. Saad: In my experience, when a patient asks about clinical trials that triggers some effort on the physician to check. Usually that will trigger at least an honest answer from the physician. *Yes, I'm aware of a clinical trial, or no, I am not aware of any clinical trials. We can both look.*

Patients like to take a proactive approach to their treatment. Just bring it up when you're faced with a decision. When there are decisions to be made, usually there is a clinical trial linked to that.

If a patient faces a recurrence after surgery, the physician could rightly explain to him that we can give him radiation plus hormones or radiation alone. If we're presenting different options, that usually implies that there should be a clinical trial

available. At that point, ask if there are any trials. If we're giving you a choice it's because we honestly believe that those options are viable. Which choice is better is a clinical trial question.

Any time you are faced with a choice is a good time to talk to your doctor about trials that may be appropriate for you?

Dr. Saad: Or any time there is a change in the status of your disease. There are patients who are very proactive in looking for clinical trials. More and more patients are realizing that, because of the rigor with which we follow patients in clinical trials, most—if not all—patients come out winners, regardless to which arm they're randomized. Even if you're on the placebo arm, in many studies, your outcome seems to be even better on a clinical trial because you're followed so regularly that at the very first sign of a change you're offered the very best available therapy.

Some patients are apprehensive about clinical trials because they're afraid that they're going to be given a placebo.

Dr. Saad: We have to compare a new treatment with the standard of care. In some cases, the standard of care is to do nothing. But you're going to be followed much more closely in a clinical trial. If your disease changes, we might have the opportunity to go to the treatment arm. We might go on to something that might be most appropriate for you at the appropriate time.

A placebo is not all bad. Sometimes we've had clinical trials where the placebo patients actually do better in terms of the quality of life, sometimes even in terms of survival. Getting something that is unproven is not always better than getting nothing. Some people think it's

unacceptable that you're not going to get a treatment. I personally don't think a treatment, if it's unproven, is better than holding off until we know if that treatment is better or not more harmful than the alternative.

"The very best discoveries that we've had in the recent years are all due to clinical trials."

Right. Active surveillance trials might be an example.

Dr. Saad: When we started the active surveillance trials, patients were reluctant to be on the active surveillance arm. Then patients wanted to be on active surveillance. They refused to be randomized to treatment. Sometimes it becomes very difficult to do some clinical trials because patients and physicians come to us with a predetermined outcome in their mind. That harms clinical trials. If we start intervening too early, if we don't let the clinical trial go on, we actually do a disservice to patients in the long term.

The very best discoveries that we've had in the recent years are all due to clinical trials. Patients on clinical trials have led to tremendous improvements in the way we manage prostate cancer today. Researchers, clinicians, and especially patients with prostate cancer thank them! Pp

Jonathan Simons, MD
Funding Clinical Trials

Dr. Jonathan Simons is the driving force behind the Prostate Cancer Foundation (www.pcf.org), one of the leading funders of prostate cancer research worldwide.

Prostatepedia spoke with him about what clinical trial participation can do for your own prostate cancer journey.

How did you become involved with prostate cancer advocacy and the Prostate Cancer Foundation (PCF)?

Dr. Jonathan Simons: When I joined the Johns Hopkins faculty in 1993 as a young assistant professor, perhaps six laboratories in the world had prostate oncologists trained in molecular biology. Johns Hopkins did not have even one clinical trial in advanced prostate cancer using a medicine actually designed to fight the disease.

Then I met Mike Milken. He'd been diagnosed with advanced prostate cancer and was seeking third and fourth opinions—not only about his own case, but the state of prostate cancer research in general. Mike wasn't new to medical philanthropy; he'd been funding a broad range of research for decades before his diagnosis. But he was new to prostate cancer, so it was encouraging when he left our meeting saying there would be an infusion of research funds and a foundation to make progress against this disease. My mentor and research director at Johns Hopkins, Dr. Donald Coffey, told me, "If anyone's going to change this field, he's the guy.

I didn't realize that later I'd end up being PCF's CEO and President.

You were quite young.

Dr. Simons: I was an Assistant Professor eight months on the Johns Hopkins faculty, and I had a six-year-old and a four-year-old son running around in my office with coloring books on weekends while we set up experiments in my small laboratory. Back then, I was funded by PCF from across the hallway. They were within shouting distance. I have now a 30-year-old and a 28-year-old who do not use crayons.

What year did you officially join PCF?

Dr. Simons: I was there at the beginning in 1993 and was invited to the inaugural celebration of the founding in Washington, DC. Early funding from PCF allowed me as a physician-scientist to train in my laboratory another generation of young investigators who have gone on to become chairpersons and full professors at leading cancer institutions. Today they work toward better precision treatments and cures for prostate cancer in fields ranging from molecular biology to drug development, early clinical trials and nanotechnology. In 2007, I was recruited from the Emory University

> *"Spark, instigate and cultivate scientific proof-of concept."*

Cancer Center as its Founding Director and appointed CEO and President of the Foundation. I feel an awesome responsibility and the privilege to continue to serve the field in this way.

PCF funds quite a bit of research, both in United States and abroad. Is there a theme behind the kind of research you fund? What is your overall strategy?

Dr. Simons: The overall strategy is to fund the world's best, most innovative ideas early enough to reduce deaths from prostate cancer, reduce suffering from prostate cancer, and ultimately eliminate prostate cancer as a plague on humanity. What that means,

though, is that we fund mostly laboratory-to-clinic, game-changing, early-stage research in university and cancer center laboratories. We find partners to leverage this funding with additional government or biopharma support. We also fund research to help guide those therapies into the clinic to test whether they are successful or not.

"There are a lot of ways to innovate around digital healthcare."

If the treatment shows promise, we try to leverage further the tens of millions of philanthropic dollars that we put in at the beginning with hundreds of millions more from Department of Defense, National Cancer Institute, Stand Up 2 Cancer, the V Foundation, and private foundations. About 80% of what we fund is precision treatment science, 10% basic biology, and perhaps 10% prostate cancer prevention including precision nutrition research.

Additionally, PCF was established with more in mind than accelerating cure for prostate cancer. From the beginning, we aspired to change the face of cancer research and to produce results that could help people suffering from a broad range of serious diseases. We never saw the process as a zero-sum game where increased funding for one disease diminished support for others. Rather, it has always been one of our key goals to increase the size of the research pie in ways that would benefit the greatest number of people.

Your organization funds the beginning idea—sparking research—and then other organizations like pharmaceutical companies or research institutes take the ball and run with it?

Dr. Simons: That's exactly so. Spark, instigate, cultivate scientific proof-of-concept, and convene stakeholders to ensure there is a strong ecosystem to take those concepts forward for patients.

You partner with pharmaceutical companies. You partner with medical institutions and the United States government. What about other countries? Do you work with groups in other countries?

Dr. Simons: We fund research in 21 countries. We have working partnerships with five foundations. We usually lead invest, but we are delighted to co-invest in research, particularly new kinds of treatment. We should really be called the *Global* Prostate Cancer Foundation.

"Your instinct should be: where is the right clinical trial?"

It has been difficult for researchers to get patients to enroll in clinical trials. Why do you think that is? What has been the obstacle to getting men to participate?

Dr. Simons: It is complex. I wish I knew all the answers. I think one reason is that patients feel fear about receiving a placebo and about being a guinea pig. That almost never happens in the kind of treatment research that we fund.

But I also think there is a lack of access to information about trial availability. I still think patients aren't empowered to ask which clinical trials could help them have a better outcome and also help others. I don't think the system is proactive. (Crate and Barrel bothers me a lot more about their products than the National Cancer Institute bothers patients about whether or not they might be eligible for a precision medicine trial.)

We're trying to increase awareness of these newer precision medicine clinical trials that have a much higher probability that the drug will work because the target gene is expressed or mutated. Basically: your tumor is vulnerable now and we're getting access to it, so the investigational drugs have a real chance of getting you back into remission. I think those are the major challenges.

Another issue is distance and travel time and associated costs. Clinical trial participation goes way down if it takes the patient more significant time to get to the hospital. If you are enrolled in a clinical trial, you have to go back and forth more often to see the doctor and nurses monitoring you. With a longer commute, participation rates fall.

We're therefore very interested in telemedicine, or using the internet, so patients don't have to drive as much. That's still experimental. Dr. Matthew Galsky, from Mount Sinai, is working on that problem.

Using telemedicine in clinical trials?

Dr. Simons: Yes. Most everything in the clinical trials world is still analog, and yet we live in this extraordinarily digital age. I'm talking to you on my phone—a piece of glass with some metal off ultra high frequency radio waves. Right before this call I was

looking at an MRI scan on my iPhone. I can do that, but we still make patients drive 90 minutes to see a doctor when we could probably use a smartphone.

There are a lot of ways we could very reliably take care of patients in an outpatient fashion. We just haven't fully digitized clinical trials, particularly for patients at a distance. There are a lot of ways to innovate around digital healthcare that would help make clinical trials easier for prostate cancer patients.

I think some men assume that a clinical trial might not be an option until their cancer has advanced. They wait until things have gotten really bad and then they look for a trial. I don't get the impression that many people think about trials when they're first diagnosed.

Dr. Simons: No.

But there are trials for the newly diagnosed, aren't there?

Dr. Simons: Absolutely. And a lot of them offer the possibility of much greater longevity and survival. Your instinct should be: where is the right clinical trial? But you're still processing, thinking, "My God, I have cancer!" We could do a much better job of educating patients.

How do most people find out about clinical trials? Just waiting for your doctor to say that she has found a trial you might want to consider? Or is the burden on the patient to find the trial?

Dr. Simons: Most of the time, if your physician isn't a real champion, it's just not a part of the consultation. Most clinical trial enrollment happens because you have a urological oncologist who believes in putting patients on clinical trials and is probably participating in one.

We'd like patients at every stage in their journey to look for a clinical trial with the idea that it might offer a better plan of care than they would otherwise have.

We could also do a better job of encouraging nurses to talk with patients about clinical trials.

How would you suggest men look for trials?

Dr. Simons: The site www.clinicaltrials.gov is an excellent place to look. I think www.PCF.org is an excellent place to look as well.

Making a habit of asking your doctor if there are any new clinical trials for where you are is also a great idea. Create the expectation that your doctor has to pay attention to potential trials.

The site www.clinicaltrials.gov tends to be a little bit technical. I would think it might be difficult for the average person to sort through.

Dr. Simons: You can always just ask your nurse or doctor about it. But I agree. We put more than 82 cents on the dollar into our research mission every year. But we wish we had the resources to create an incredibly patient-friendly, readable, real-time, digital website for clinical trials.

Until somebody does that, clinicaltrials.gov and pcf.org are good places to find the really important trials.

I suppose you could always come up with a list of trials and then bring it to you doctor and ask if any are appropriate for you.

Dr. Simons: Yes. For right now, that is the best thing to do. The first thousand men cured of advanced metastatic prostate cancer will all be

on a clinical trial. That's a true thing. This is how we talk to lymphoma patients. It's just more and more possible to talk about it for prostate cancer.

Prostate cancer is undergoing a revolution that other cancers have already gone through?

Dr. Simons: We've cut the death rate down by 52%. That's incredible. For the last 48%, we're going to need clinical trials. We need patients on clinical trials to take the death rate to zero.

Sometimes prostate cancer, unfortunately, escapes surgery or radiation and comes back. While we've significantly increased the overall survival rate, we're not yet able to cure the majority of men. We think we can. We *know* we can, but we have more work to do.

What does the financial end of clinical trial participation look like? Do men have to pay a fee for the therapies?

Dr. Simons: In clinical trials, research drugs are always free. Medical care is always free. The inconvenience is what is costly. Some employers are very difficult about you missing work for a clinical trial. There is a lot of going back and forth. They call it wage and financial toxicity. One of the effects of the experimental drug is toxic to job security. (It's hard enough when you're a cancer patient and worried about your employer.)

But the drugs, the pharmacy, the medical care, and the scans are all free.

Is there anything else you think patients might want to know about clinical trials?

Dr. Simons: The misperception is that patients will be treated like guinea pigs. But the first thousand patients cured of prostate cancer will all be on a clinical trial. Every major clinical trial is changing prostate cancer patient survival.

For example, in the SPARTAN trial for Erleada (apalutamide), the drug was so effective that within two weeks of presenting the results, it was FDA-approved. That's a record. Data was presented showing that 800 patients were benefitting from the drug, and then it was approved. The only drug that gained approval that quickly in all of oncology was Soltamox (tamoxifen) for breast cancer. We think this is going to happen all the time now.

The SPARTAN Trial focused on patients for whom previously there were no treatments. They saw their PSAs going up, but they were not metastatic. There was really nothing for them to do except wait until we started seeing metastases. Now, with Erleada (apalutamide) there is a chance that they're not going to see metastases for years. They've got hope. For that first group of men, all of this is possible because they found that clinical trial. Hundreds of men who participated in the SPARTAN trial are going to have a prolonged time without metastases.

Would you encourage newly diagnosed men to seek out clinical trials, even if their cancer is under control?

Dr. Simons: Yes. I encourage every patient to think about joining a clinical trial. It's not an easy message, but there are many studies showing that you get better nursing just by being on a clinical trial. You just get more attention. You can be there for the cure. Pp1

Ravi Madan, MD
Clinical Trials + Prostate Cancer

Dr. Ravi Madan (@Dr_RaviMadan), the clinical director of the National Cancer Institute's Genitourinary Malignancies Branch, focuses on immune stimulating therapies. In particular, he's interested in how we can combine these approaches with other therapies to improve patients' lives.

Prostatepedia spoke with him about clinical trials for prostate cancer patients.

Why has it been difficult for doctors to enroll patients in clinical trials?

Dr. Ravi Madan: The reasons vary from case to case. Sometimes physicians don't mention relevant trials at the right time for patients (when they're making treatment decisions). Sometimes patients don't want to go through the process of enrollment because of the perception that it delays their care and that delay will somehow impact their outcome. There is also personal preference. Some patients really don't like the uncertainty of a clinical trial—uncertainty in terms of what their treatment will be if there's a randomization or uncertainty about the outcome.

Trials should be discussed with patients when they're making a decision to change therapies. While enrollment does take time, it's usually only a few weeks, and for the most part, that doesn't impact the patient's outcomes or overall course.

Ultimately, patients need to have a risks/benefits conversation with their doctor to determine if a clinical trial fits into the personal treatment strategy that they've developed with their doctor and their family.

Perhaps many people assume clinical trials aren't really available until you have advanced disease, but that's not really true is it? There are trials available at all stages along the journey.

Dr. Madan: Correct. Trials exist in all stages of the disease. The ones that often get the most notoriety, either on television or in the news, are the ones for late-stage patients. But for example, here at the National Cancer Institute (NCI), we have trials for every stage of prostate cancer, from patients who are newly diagnosed to early recurrence to non-metastatic, and then ultimately, late-stage disease.

Why would someone want to join a trial? Just to gain access to a treatment he may not otherwise have access to?

Dr. Madan: Sometimes you get access to treatments earlier than they may be available to the general public. People should understand that clinical trials often involve the standard of care they would get anyway plus an experimental agent.

There is an altruism component to a lot of this as well. It never ceases to amaze me, but when I deal with the patients here at the NCI, so many of them tell me: "If this helps me, that's great, but I just want to help someone else later on." It's not like everybody has to have that reason, but it's remarkable how many do.

So, the reasons are variable. Sometimes it's because there aren't other options, but sometimes it's because it adds options or adds cards to the playing deck, if you will, and sometimes it's just pure altruism.

I guess that's especially true in earlier-stage diseases, where you don't necessarily need experimental treatment or access to something that you wouldn't otherwise get access to, such as those on active surveillance.

Dr. Madan: Correct. We have patients in studies who just have rising PSAs where we're trying to evaluate the potential of immunotherapy in that setting, but the alternative therapy is just really observation for a lot of those patients. For them, the trial

is an opportunity to do something when the standard of care might be to do nothing.

What about the concept of the placebo? I've heard patients say they're afraid of getting a placebo, which could make their cancer worse. Is that still a part of the clinical trial world?

Dr. Madan: It is part of the clinical trial world. Many trials require a placebo because in order to scientifically answer a question, there may have to be a group of patients who are untreated. In those circumstances, the protocol (a document that is often over a hundred pages) is designed to protect those patients. Whenever patients are on placebos, there are very strict guidelines about how they're watched and the parameters used to remove them if there's evidence that their cancer is getting worse. In some cases, they have scans very frequently. They're not left unminded, and it's usually for a short time.

But many trials don't involve placebos. We conduct trials to see if we can take a standard therapy that's in use and add something to it to make it better, and this is especially true in this new age of immunotherapy. In that process, everybody will get the standard therapy, and some of the patients will get the experimental therapy in addition.

They're not just getting a placebo, and then left unmoored.

Dr. Madan: Right. There are very strict criteria about how patients are monitored so that, if there is evidence that the cancer is getting worse—regardless if it's standard therapy or placebo—then they move onto something else. In many trials with placebos, oftentimes the physicians don't even know what the patients are getting, so the physicians often treat them all like they're getting the placebo because that's really the safest thing from a patient's standpoint.

"Trials exist in all stages of the disease."

That's interesting.

Dr. Madan: We need to monitor placebo patients closely in case they are getting nothing, and we need to move on to something else.

But if a trial involves placebo, patients should be comfortable with that and comfortable with the relationship with their doctor who's going to help them make these decisions. Otherwise, it creates a lot of stress, whether in the initial process with the randomization or while they're on the study.

What about the financial end of trials? Do patients have to pay to participate in clinical trials—for the therapy itself, the procedure, the scan, or more? Or are the costs just travel expenses and time away from work?

Dr. Madan: Generally speaking, patients don't pay the price for the drug treatments on a clinical trial. Sometimes trials are billed so the insurance company will cover standard costs that would be covered anyway. But for the most part, the patients do not incur the cost of the clinical trial. Costs are borne out by the companies or research bodies that conduct the trials.

Here at the National Cancer Institute (NCI), we are able to conduct trials that are completely free of charge to the patients. And in addition to that, because we are a government entity designed to really benefit the entire country, once patients are enrolled in our trials, we are able to fly them in from different parts of the country. We can incur the travel costs for patients who travel from anywhere in the United States. That's part of our mission here: to bring the benefits of this institution to everyone in the country.

Wow! So your clinical trial patients only have to pay for their hotel and time away from work?

Dr. Madan: Correct. And most patients qualify for a subsidy toward their hotel.

That's unusual, isn't it? Most non-government-funded trials don't offer things like that, do they?

Dr. Madan: Yes. It's an unusual circumstance. It allows our institution to address diseases that may not affect many patients within one geographical area. It's a unique opportunity to conduct studies on rare diseases, but we also use it for studies in more common diseases.

"Patients don't pay the price for the drug treatments on a clinical trial."

You don't want to just study prostate cancer in men in the metropolitan D.C. area, right?

Dr. Madan: Correct. For example, I have studies with medullary thyroid

cancer, which is a very rare disease. But we're able to get people from across the country and do it in a way that no other institution can because our catchment area is the entire country.

How can men find out about clinical trials? My impression is that the usual path is that their doctor brings it up, or perhaps they hear about it in a support group, but what are some ways that men can find out about trials? Just by visiting clinicaltrials.gov?

Dr. Madan: I would actually recommend https://www.cancer.gov/about-cancer/treatment/clinical-trials/search because clinicaltrials.gov is more for clinicians. One of the greatest features of cancer.gov is you can search by zip code or city, and it tells you trials within 25, 50, 100 miles, or whatever you like.

But either website has a great patient-based resources. I encourage patients to bring up clinical trial options with their doctors and get their doctors' thoughts on what they find.

Patient support groups are another excellent resource. Depending on the cancer, there are also online support groups that are more prevalent and will probably become more so. Over about a third of our patients are self-referred from around the country, and not just referred by doctors, so it's common for patients to advocate for themselves in this manner.

I was under the impression that if, for example, a man found one of your trials on clinicaltrials.gov and thought he was a perfect fit, he had to go back through his doctor to get involved in the trial. Is that true? Or can he contact you or the researcher directly?

Dr. Madan: Yes; he or she can contact the researcher directly. I get some calls directly from patients saying they saw this on the internet. We also have a clinical trials contact, so no, they don't have to go through their doctor.

I often encourage patients to speak to their doctor just to get an impartial perspective or additional perspective. Also, patients and doctors have very good relationships usually, and it's important to get a second opinion before you embark on the clinical trial journey.

But certainly they can contact us directly, and they very frequently do.

When studies are finally completed and published in academic journals, are patients informed, or do they have access to those results?

Dr. Madan: There's not often a direct mechanism by which patients are informed about the results of the trial. But often, through the course of a study, patients will ask about the experiences so far. We'll certainly fill them in, and then we have had patients call us up for results. We certainly publish the results and can share them, but there's not a direct mechanism.

Interesting. There probably should be.

Dr. Madan: That's an interesting idea. It's possible some institutions have that. I'm not aware of any at this time.

But patients can always ask their contact directly, right?

Dr. Madan: Yes.

What else should patients know about joining clinical trials?

Dr. Madan: Clinical trials can be an important part of each patient's individual treatment strategy. Especially for patients with cancer, it's important for them to develop

these strategies in conversations with their doctor and their families, and to develop that strategy based on personal preferences.

"Clinical trials can be an important part of each patient's individual treatment strategy."

Clinical trials are a way to get additional treatment options over time, options beside the standard options that are generally available. Being on a trial requires a little additional time, and there is potential for side effects. If there's a randomization process, patients should be comfortable with that, no matter what they get.

As the patients who come to NCI from all over, consider local trials and those around the country. Sometimes travel is not optimal, but we've had patients come in from as far away as Hawaii and Alaska. Take advantage of the opportunity if you can.

The pace of cancer research today is remarkable, especially in immunotherapy, which is one of the biggest focuses here at NCI. All of us should remember that none of these advances would have happened without remarkable patients who decided to enroll in clinical trials. I consider it an honor to be able to work with the types of people who enroll in trials here at NCI and around the country. It's really an extraordinary and humbling experience for me. Pp1

How To Get Involved…

Find A Clinical Trial
1-800-4-CANCER (1-800-422-6237)

Paul Nguyen, MD and Marie Vastola: Trial Eligibility + Black Men

Ms. Marie Vastola is a Clinical Research Assistant in Radiation Oncology at Dana-Farber/Brigham and Women's Cancer Center. She works on Dana-Farber-led and international clinical trials that accrue men with multiple stages of prostate cancer. She is an author on six research articles focusing on prostate cancer and has presented her research at a national conference.

Dr. Paul Nguyen is an internationally recognized expert in prostate cancer clinical care and research. He has published over 250 original research articles and has various national leadership roles and is the Dana-Farber Cancer Center Genitourinary Clinical Center Director for Radiation Oncology, Vice-Chair for Clinical Research in the Department of Radiation Oncology, and Associate Professor at Harvard Medical School.

Prostatepedia spoke with them about how eligibility requirements for prostate cancer clinical trials may unfairly exclude African American men.

Why did you become a doctor?

Dr. Paul Nguyen: I've always wanted to be there for patients at the most important time in their lives. For that moment following a cancer diagnosis, all of a sudden that diagnosis becomes the most important thing in your life, and I really wanted to be there for people at that time.

This became personal because my father was diagnosed with prostate cancer. He got surgery. When it recurred, he got radiation, and so the radiation management of prostate cancer became something personal for me as well. That's how I became involved in this field.

> *"All of a sudden that diagnosis becomes the most important thing in your life."*

Interesting. That happened when you were already working on prostate cancer, or when you were younger?

Dr. Nguyen: I was in medical school when my father was diagnosed. I didn't know anything about prostate cancer at the time. He had surgery, and the cancer came back. The surgeon at the time was just going to manage him with hormone therapy. I had no idea at the time, but that was not an appropriate recommendation.

I talked to an expert at my medical school, someone who knew prostate cancer, and asked him what my father should get, was his doctor's recommendation the right management? He said no. He said my father needed radiation because the hormones won't cure him. He'd just be on them for the rest of his life. He needed radiation to get rid of it, which was standard, and so that really opened my eyes.

That doctor became a mentor for me. He was a radiation oncologist, and I followed him into the field. His name is Anthony D'Amico. That's how I became a prostate cancer expert myself. I now work in that same department.

Dr. D'Amico really is an amazing guy.

Dr. Nguyen: He is. He's a very special guy.

Ms. Vastola, how about you? What path led you to what you're doing now?

Ms. Vastola: I'm not a doctor, but I'm on that path. I majored in biology in college, and I really liked it. I liked learning about all the mechanisms of disease and how different parts

of the body reacted and responded to disease. I worked in labs, and then I realized that the projects I liked the most were the ones closer to the patient because I've always liked helping people. Medicine combines that scientific research and discovery that I love with helping and connecting with people, which is very important to me. You can do research in medicine but never connect with anyone, and I don't think I would be happy with just that. I love going to clinic and working with patients.

Like Dr. Nguyen, I like being there for people on some of their worst days. It's not only one of the most important days, but it's also one of the worst days when they learn that the MRI showed something new, or their PSA is rising again. It's very meaningful to me to be there with patients during that experience.

Then, if we can't help them completely with their treatment if they're recurring, we can still help them with other aspects of process, and all of that is worth it to me. It combines things that are emotionally and personally gratifying with something that's very intellectually stimulating.

How have black men been underrepresented historically in prostate clinical trials? What are some of the prevailing theories or ideas about why that might be?

Dr. Nguyen: It's multifactorial, and that was something that our research aimed to get at. Because of the historical experiences like the Tuskegee experiment, some African-Americans may have been more leery of engaging in clinical trials. Because trials require certain costs and extra time away from work, this can be more difficult on certain populations. Or it could be from the doctor side. Some doctors may not be as willing to engage African-American patients to enroll them on trials. There are multiple factors, so it's hard to know exactly what is the main driver.

Ms. Vastola: We have patients come from long distances to Dana-Farber, and they do that because they know that Dana-Farber is a good place for them to get treated. Many patients, especially ones who travel long distances, either have connections in the medical field and that's how they found out about this, or they're highly educated and they have the resources to look into research and potential treatments themselves. These are tools that only people who are a little more privileged have.

Why did you zero in on eligibility criteria? What were you looking at?

Ms. Vastola: Actually, a patient is what started this research project. I had been screening an African-American patient for one of our open trials, and filling out the paperwork to determine if he was eligible. Most of this paperwork is related to the cancer, to make sure that patients have the type of cancer that we're studying. But other sections of the checklist establish that the patient is otherwise healthy. We wouldn't want to give an experimental treatment to a patient who wasn't healthy for their sake and for the research's integrity. He didn't meet the criteria for one of those health checks.

One of the ways we determine that a patient is otherwise healthy is to look at their immune function, and his white blood cell count was too low. I hadn't seen that before, and we ran his blood test again. His medical oncologist said the patient had benign ethnic neutropenia, which I had never heard of it until then. Because of that he couldn't go on the trial that we had. It wasn't a trial that we were running out of this hospital, but we talked to the sponsors. And as with many big trials, they don't allow exceptions, no matter what.

He didn't get the opportunity to be on a trial that was designed for men just like him, and that was really frustrating. Everyone involved with his treatment was frustrated with that, and so we looked into if that could be happening to other men.

We also looked at creatinine. It's well known in the medical field that black patients have a higher serum creatinine, and so you have to use a special formula that accounts for race when you're looking at their kidney function. We looked at benign ethnic neutropenia because that's what started it, and it was something that people seemed unaware of.

Dr. Nguyen: In a research group, the ideas usually come from the lab principal investigator (PI), and then the junior people carry it out. In this case, Marie actually came up with this idea herself because of a patient experience that she had, seeing an African-American patient not be able to get on one of our trials. It's what led to this *Journal of the American Medical Association Oncology* paper, which is impressive.

That is. What did you look at?

Ms. Vastola: We wanted to know how often this happens. Was this a fluke, or does this happen to other African-American men? The best way to find out was to look at the eligibility criteria of other trials. Every trial records when people don't meet the criteria. They don't often record why though, so we couldn't just look at the internal records of our trials. The website clinicaltrials.gov lists all trials available to patients in the United States and also a lot of international trials, and it usually lists the eligibility criteria.

Not all the trials go into detailed criteria, but many do. We went through 401 trials that had endpoints that we thought meant that they had the potential to reach large audiences and change practice. We looked at all of them and pulled the eligibility criteria to see how many of them had this white blood cell criterion. We expected some would have it. We did not expect that almost 50% of trials would have either of these two criteria. We were also surprised that the serum creatinine criterion was so common that a quarter of the trials have it.

"A patient is what started this research project."

People are aware of this, and they know to calculate kidney function accounting for race. A lot of trials would use serum creatinine, which is just the blood test, but then they would also say that if a patient meets formula criteria (based on race), then they're okay, which is what we want to see. Not all trials do that, and that's the issue. Every single lab result you look at that measures creatinine says at the bottom that if the patient is African-American, apply this formula. But over 25% of these trials weren't including that formula.

What else did you find?

Ms. Vastola: Those were the two criteria that we looked at. We also broke it down by year, size of the trial, the phase, and toxicity of the

therapy. We were glad to see that, over time, people are using the serum creatinine eligibility criteria less and less, which may mean that more people are aware of it. That's not the case for the white blood cell criterion though.

Dr. Nguyen: We looked only at trials that have survival as an endpoint, so these are trials looking to make people live longer. We think it's especially important that all patients have equal access to these kinds of trials.

There are a few consequences of not having African-Americans on these trials. Patients who go on trials can sometimes get access to new drugs, so it's a problem if African-American patients aren't getting on trials. We also don't get to learn enough about whether certain drugs perform particularly well in African-Americans, and so we don't get to learn about the specific benefits or lack of benefit of certain agents for African-American patients. We wind up extrapolating from the larger patient pool, which probably works most of the time, but perhaps there's something special that we can learn from having African-American patients on trials so that we could find better cures that can be tailored for African-American patients.

Ms. Vastola: Exactly. Not having access to these clinical trials hurts the individual because they don't have access to treatment that could potentially help them. But the lack of access also hurts the whole population.

It also skews your results, so that what you're learning about isn't really prostate cancer in all men, just prostate cancer in a subset of men.

Ms. Vastola: Exactly.

"It's especially important that all patients have equal access to these kinds of trials."

What do you hope this will mean for clinical trial design and eligibility recruitments?

Ms. Vastola: We presented this research letter at the Prostate Cancer Symposium of the American Society for Clinical Oncology in poster form. We got a lot of feedback from academic investigators, people who devote their lives to this. Their papers define the field. They said they'd never thought of this, and that some didn't know benign ethnic neutropenia existed. This section of the eligibility criteria—the part that defines whether a patient is healthy—is just carried over from trial to trial because it's so standard. It's not something people think about when they design trials because it's so standard. It's textbook.

We hope that, as more people understand this, they will consider it when they design their trials.

Dr. Nguyen: We were guilty of it in our own trials, and that's how this all came about. We just used standard entry criteria copied over from previous studies. We were surprised to learn that this could disproportionally disadvantage African-American patients from being able to enroll in our trials. Given all the barriers that African-American patients face in getting on clinical trials in the first place, the last thing that we need is yet another barrier. Pp1

Jan Manarite: Clinical Trial Tips

Jan Manarite joined the prostate cancer community in 2000 when her husband Dominic was diagnosed with advanced prostate cancer. She has gone on to become one of the most recognized advocates in the prostate cancer community today.

Prostatepedia spoke with her about questions prostate cancer patients may want to ask when considering joining a clinical trial.

How did you become involved with patient advocacy?

Ms. Jan Manarite: My husband was age 58. He was in a lot of pain. He was one of those men that would not go to the doctor. He had to have a physical for his charter captain's license down here in Florida, and they told me he was healthy as a horse. I'll never forget it. Nobody took a PSA.

One thing led to another, and he was in so much pain that he finally agreed to go to a pain doctor, (which was a big deal for him). The pain doctor treated him a little bit, but said, "I really need to know why you're having this pain. I have to do some kind of imaging."

Unfortunately, to do the imaging, he had to lie down. He hadn't laid down in two months. He had been sleeping sitting up in a recliner. They had to give him general anesthesia and completely sedate him to do an MRI.

He was out for quite awhile. They wheeled him into a bone scan. Finally, someone did a PSA, and his PSA was over 7,000. As you can imagine, his imaging was full of cancer throughout his entire skeleton. That's how we started.

You're the wife of a patient, and you went through this journey with him. But how did you start volunteering and working with other patients?

Ms. Manarite: To be candid, this has become my career. But, going back to that first day, pacing the hallway with my cell phone asking friends to pray for me, quite frankly, that is how it started. Shortly after, I started digging and searching. The internet was still pretty new to me, so my nine-year-old son helped me on it. When he was in school, I spent time on his computer.

I found some resources online. Dr. Stephen Strum at The Prostate Cancer Research Institute connected with me and helped us out the most. He came from California to where we live in Florida a couple months after my husband's diagnosis. We went to hear him speak at a local support group.

Dr. Strum ended up driving back to Sanibel Island with us. We got him a hotel. It was all very surreal. He came to our house the next day and talked to us for free for three hours when other doctors shoveled us in and out because they were too busy. It was this long process of crisis and miracle.

Then, Dr. Strum offered me a job. There, I had access to information, Dr. Strum, and Dr. Scholz. Learning how to research and think objectively in a crazy emotional situation can do wonders for your situation. My husband lived for 13 years after that diagnosis. That alone was a miracle.

Since then, I've tried to help people get to a place where they're no longer overwhelmed. If they'll let me, the first thing we look at is their personal medical records because that's what tells them what kind of prostate cancer they have. Until they have a basic understanding of that, they're not even ready to ask questions. Even if we find three important clues in their recent bone scans, PSA pattern, or pathology report, they just learned something straight out of their own medical

records as opposed to all over the internet.

Which may or may not pertain to their precise situation.

Ms. Manarite: Yes. If you can just pull facts out of your medical records and research those personal facts, you're already cutting down your search. You are your own search engine.

I've been doing this for 16 years now, and no matter where people are in their journey, I try to narrow it down for them based on the available resources and direct them to the next important information. If they can see the next two or three steps and have a clearer understanding of what they have and what they can ask the doctor next, it's less overwhelming.

We've spoken so many times over the years, and you always bring it back to the medical records. Rather than spinning your wheels about what may or may not happen, you can hone in on what's actually happening.

Ms. Manarite: It's 100% true.

Why might a patient want to consider joining a clinical trial?

Ms. Manarite: A clinical trial decision is just another treatment option. That's all it is. It's still a risk versus benefit decision, just like choosing hormone therapy or surgery. That's what it has to be.

One of the risks involved in a clinical trial is that it can take you a month to get in. You should definitely plan on it taking three weeks, though it could be longer. There's a screening process. You have to fill out paperwork, make sure you qualify, get your medical records, check their boxes, cross their Ts, and dot their Is.

If your PSA is doubling every three weeks, and you're metastatic, you have to factor that in: is it worth it for you to wait three weeks to see if you even qualify? That's one of the risks. I don't think people know it takes awhile to get into a clinical trial.

No. I don't think they do at all.

Ms. Manarite: The other risk is the side effects. That's always part of your treatment decision. The side effects can be tricky if you're considering a clinical trial with a drug that we don't know a lot about yet. However, there is a way to dig for that information. I don't think patients realize this.

If it's in the early stages of the clinical trial, the name of the trial drug is going to be an acronym. For examples, MDV-3100 is now Xtandi (enzalutamide), and ARN-509 was apalutamide and is now Erleada. If you Google that acronym adding the words *discussion*, *forum*, and *side effects*, you'll find people who are on a clinical trial for this drug talking about the side effects in forums.

That's a fantastic tip.

Ms. Manarite: Adding the word *discussion* to Google searches directs your results to discussion forums, where probably you're going to find conversation. Data is important, but so is conversation. Honestly, if these are your peers, it's *your* own peer-review.

Data is never everything. Sometimes you find information through word of mouth. Sometimes you have to search discussions to dig up things to help you make your personal decision. No information is perfect, but sometimes that's what you need.

In an early clinical trial, this can be helpful. You need a basic understanding of the side effects. Ask your doctor about them. If something happens, knowing it was a side effect for someone else is helpful.

What about the issue of a placebo? Many patients are afraid that if they join a trial, they're just going to get the placebo.

Ms. Manarite: Great question. Placebo is another risk involved in a trial. You have to evaluate if you are willing to take that risk. But not every clinical trial has placebo. Let's look at them by phase.

Almost every Phase III trial has placebo. However, even then, sometimes two-thirds of the patients get the drug and only one-third gets placebo. That's kind of interesting, and right off the bat, it gives you a question to ask and clarify.

"Learning how to research and think objectively in a crazy emotional situation can do wonders for your situation."

Almost all Phase II trials have no placebo. There are always exceptions, but most of them do not. That would make Phase II really interesting to me if I were a patient.

No Phase I trials have placebo (that I've heard of) because they're busy doing things like giving patients the drug and kicking the dose up as high as they can to see what patients cannot tolerate. There is some risk involved in what they call *dose*

escalation. Again, you need to be informed about what that means.

That all being said, here's another thing patients don't realize. You can stop the clinical trial at any moment you want. You are 100% in control of whether and when you enter or exit. That makes it a little less scary.

"A clinical trial decision is just another treatment option."

Are there any other areas of misinformation that you feel are important to highlight?

Ms. Manarite: There are a few Phase III trials—not many, but a few—in which you may get a placebo. If, during the trial, your disease progresses on the drug, you may be able to come out of the placebo and get treatment. That's called a *crossover provision*. Unless you ask, you may not get that information up front. Again, that changes your perspective on the risk versus benefit.

A great example of this is the Erleada (apalutamide) trial. They had a crossover provision in the Phase III trial so that if your disease progressed on placebo, you got free Zytiga (abiraterone). At the time, Zytiga (abiraterone) cost maybe $5,000-$7,000 a month. That is a big benefit to a patient. "I'm going to get free Zytiga (abiraterone) if I fail the trial drug or placebo. I don't have to put it through Medicare or my insurance. That's kind of interesting. Now I'm listening." A crossover provision in a Phase III trial that has placebo is a great question to ask.

Do you have any thoughts or advice about the financial end of clinical trials?

Ms. Manarite: Yes. Make that a question. In most clinical trials, especially Phase III drug company-driven trials, the treatment is going to be free. You may also be covered for travel, including compensation for long drives. You can't assume you know the answer because they're all different. The point is: *ask*.

Is travel frequently covered?

Ms. Manarite: Frequently, yes, but not always. You have to ask. That becomes part of your decision, your risk versus benefit.

If you don't live in a town that has a large institution or university where they're more likely to be doing clinical trials, you may have to drive. There are exceptions. That's another good question to ask.

I drove my husband to Miami once every two weeks for a Phase II Xinlay (atrasentan) trial. He got sick of it. He really didn't want to do it, but I wanted him to do it. He didn't feel good enough to get in a car, travel for two hours, sit in the clinic for an hour, and drive back for two hours. We did it for a while, but then he'd had enough, and he pulled out.

Another question to ask is if the clinical trial requires a CAT scan, bone scan, or blood test to qualify. They almost always do, but they aren't always covered by the trial. Some are covered by your insurance, but if you don't have insurance, will you have to pay? Again, this is a good question to ask. For someone who does not have insurance, accessing a clinical trial with potentially free treatment can be a huge benefit considering the risk/benefit profile.

Especially for the imaging. That comes up a lot.

Ms. Manarite: That's why you have to ask if imaging is covered.

What about finding trials? Do you recommend patients go to clinicaltrials.gov and look through there?

Ms. Manarite: You can definitely search www.clinicaltrials.gov. It has the largest selection. And they recently made their website a little more user-friendly. But it's not easy.

Here's an example. I just went on clinicaltrials.gov and searched prostate cancer in Florida. Because I chose *recruiting* and not other criteria, I got 66 studies that are recruiting. Then I can filter down from there. That's definitely better than it used to be.

They also have an 800-number you can try, which is new. I'm not sure if it's general help or disease-specific.

Do you think if someone had a specific trial they were curious about, their experience might be different rather than just calling up and asking what's available?

Ms. Manarite: Yes. That may be a better question. I would try (800) 4-Cancer.

My feeling is that most people find out about trials through their doctors, if at all.

Ms. Manarite: Most of the time. I think that's fair. You're right about that.

This happens all the time: people will call me, and they'll say, "My doctor wants to put me in a clinical trial. I'm not sure if it makes sense, but he seems to like it. I'm going to try it."

I'll ask them for more information on the trial—what it's even called—and they'll have no idea.

So, if your doctor's talking to you about a clinical trial, walk out of there with a paper about it. Don't leave without some kind of paper that has the name of the drug, the name of the trial, or something because you'll never be able to research it when you get home. Walk out of there with a paper.

At least the name of the trial so you can go home and Google it.

Ms. Manarite: They should give you a 1-page printout at least.

Also, if you're going into a clinical trial, you will probably meet a new medical professional, such as a clinical trial nurse or the research nurse. It's a whole new person. If you develop a relationship with them in the beginning, it might help expedite your enrollment. One of the tips I always tell people is: hand the clinical trial nurse your medical records. They won't have to look for your information because you've given them your file already. It might speed things up.

Aren't most medical records electronic right now, or are you suggesting people keep a print copy?

Mr. Manarite: Either or. Whatever works for you. If you're going into a clinic for a doctor's appointment, and you have this specific question, having a printed medical record on you that you can ask about is exactly what you need to be doing. There's a time and a place for both types of medical records (online and printed) depending on what you're doing. Pp

Us TOO: Clinical Trials for Prostate Cancer Patients

Tony Crispino is the Us TOO Las Vegas Support Group Leader. Rick Bangs is a bladder and prostate cancer survivor and research advocate. They are both research advocates at SWOG and the National Cancer Institute. Tony and Rick outline for Prostatepedia the prostate cancer clinical trial process with commentary by prostate cancer warrior and clinical trial participant Bob Klingle and his wife Jean.

Clinical trials are key to the development of new (or proof for existing) drugs, processes, or methods in the treatment of prostate cancer, with many potential benefits for participating patients. Clinical trials exist to answer important questions about the care of patients or the experience of and outcomes from that care. Trials can test new therapies, compare therapies, test new drugs or surgical techniques, study cancer prevention, offer tools to make decisions, provide support resources—including people or software, further the knowledge about the disease, and much more. For the research community, the participation by patients in trials is extremely valuable in answering important questions that can lead to new standards of care.

Patients and caregivers should recognize that clinical trials ask and answer important questions that are not just targeted to late disease stages (such as metastatic prostate cancer). Many trials are done today for prevention and for early stages of prostate cancer. People should *always* ask about the possibility of participating in clinical trials. Bob Klingle, prostate cancer warrior and clinical trial participant shares, "At the time I found my clinical trial, there was really no one to help you. There might have been tons of opportunities that doctors might not have even known about, and you would need to do the research yourself. A friend recommended the Stand Up to Cancer website which listed numerous clinical trials that looked potentially applicable. I worked with my doctor to cut the list down and we selected the best trial for me."

The clinical trial process is a lengthy undertaking. Before a trial is open to patients and caregivers, planning and design of the trial has likely taken a year or more, sometimes several years. It requires experts to review and revise, along with government approval to assure that the design is solid and the implementation well planned to avoid wasting time and money. The only trials that can be labeled failures are those that do not get completed—even trials that do not get the expected or desired results help science move forward. A clinical trial is successful whether it proves a new drug or therapy works or does not work provided it is completed and gets reported. For patients and caregivers, this may be undesirable because they want to believe that they received the best care possible and got the best results possible. The current treatment may actually have been the best care possible even if the current treatment is to monitor the disease without administering a therapy. That can happen if no drug that had been studied improved patients' outcomes.

Patients and caregivers should understand the following about participating in a clinical trial.

1. It is a noble undertaking that will help many patients moving forward, but may or may not help them directly.

2. While their participation may have certain requirements for follow up and limit their control over decision-making, they always have the option of dropping out of a trial (even though that may seem to be an undesirable result for the researchers).

3. Patients and their caregivers own their own destiny and what is done to their body.

4. If the trial is negatively impacting their quality of life, they need to let their physician know and try to resolve the issues. But where it is too much to bear, they can stop participating at any time. There is no penalty for withdrawing from a study and when they do, they will be offered the best-known therapy currently available.

Klingle says, "Sometimes in a clinical trial, the doctor will see that the treatment did not achieve a desired outcome and when that occurs a patient is withdrawn from the study. Similarly, sometimes the patient will need to start another care program and will need to quit the program. People should keep in mind that the trial doctors often are not your *new doctors*. They will likely be helpful and will hopefully monitor your progress throughout the trial, but you cannot count on this. You need to watch your own progress with your primary care doctor and if the cancer is not being controlled, or there is a delay in treatment, you need to be the one to decide to *jump ship* and leave the trial. Do not wait around for a trial doctor to tell you if you need to leave, as they might not." However, this decision should be made carefully, as more time may be needed to prove that the treatment is not helping you. That is why each research protocol is designed with follow-up studies at specified times. If a person does decide to withdraw before those end-points are reached, they may be missing out on something that could help them.

Trial Phases

Trials are categorized within differing phases reflecting how much is known about the intervention as it moves

from the laboratory to individuals and then patient and caregiver populations. Phase I trials typically test the safety of a drug and expose potential side effects. Phase II trials test effectiveness of a therapy or drug and develop a hypothesis that can lead to a Phase III trial. This phase is designed to compare the new therapy to the best-known therapy at the time. A much greater number of patients participate in Phase III trials than the other two study phases. That is partly why Phase III trials offer the highest level of evidence and can change the standard of care or prove that a drug or procedure was or was not better than the standard of care.

Role of Caregivers

In most cases, trials are targeted to patients and not caregivers. Caregivers should always understand the details in the Informed Consent Form (ICF), which the trial participant signs before starting the trial. Caregivers can play a very critical role in identifying and immediately addressing possible adverse side effects and inform physicians where the patient cannot or does not recognize them. Caregivers are very important participants in any clinical trial. Jean Klingle, wife and caregiver of Bob, recommends, "Take great notes! You can't always remember everything that was said. If you can't be there, have your partner take video or record the conversations with doctors. You will have a fuller version of what is being said than would be possible based on memory. Depending on the results, you might not be in the right frame of mind to pay attention to or remember, some very important details."

Placebos

Placebos, which may be sugar pills or some other inactive agent, are used in trials where there is no treatment today as the standard of care. *If a procedure is being tested, often a sham or fake procedure is performed, which mimics the procedure without actually doing anything to the patient. Placebos are never provided as a substitute for an effective treatment.* If a new cancer treatment is being tested, the control group will still get the best-known therapy at the time. Patients who get a placebo typically don't know it and may never know if they received the experimental treatment or the placebo. But sometimes they may think they know, and that may cause them to withdraw from a trial as they search for an active agent. They should be aware, however, that sometimes not even the doctor doing the study will know whether someone is receiving a placebo. That is why follow-up testing is required to find out if the treatment is effective.

Some studies have a *cross-over* design, which means that if tests show the treatment is not working, patients are given the opportunity to take the other treatment. Remember, even if a treatment fails to improve the patient, that does not mean the person was taking a placebo, because even effective treatments do not help every patient. In randomized clinical trials (RCT) testing an experimental drug, a blind trial is where the patient does not know if they are receiving the drug or a placebo. A double blind trial is one where neither the patient nor the physician knows whether the patient is receiving the drug or the placebo. Typically, RCTs testing drugs are double blind unless there is a reason to know, such as when there are toxicities that need to be monitored.

Bob Klingle shares, "I have no experience with a blind trial involving placebos. I was told the drug that was to be used in my trial. This was a trial that was very appropriate for me, as that matched my chosen treatment option. In some cases, patients in trials are told they will be on the drug or placebo, and in some cases they will not be told. Once the trial ends, it ends. There is no immediate access to the new approach or treatment, and it might undergo more tests, or if submitted back to the FDA, subject to other approval processes before it can again be accessed on the market. As far as those requiring treatment that might be given placebos, ideally the doctors participating in the trial would be closely monitoring the situation, and if anything were to become needed in terms of treatment, that would be addressed and the patient might be let go from the trial. But there is no guarantee for this, so the patient must be sure to stay involved in the updates, and to keep his own primary care physician involved throughout the process."

Those interested in the possibility of entering a clinical trial should first discuss it with their doctors. If it is agreed upon that you might be a good candidate, a great place to start would be the Us TOO Clinical Trial Finder at http://www.ustoo.org/HCP-Clinical-Trials. This free, confidential clinical trial finder will help you to locate any matching clinical trial based on your location and medical profile. You can search online or by phone. Responses to a 10-minute questionnaire will generate a list of clinical trials within patient specifications that can include treatment preference, geographic area, medication type or brand name, and clinical trial phase (I, II or III). The patient questionnaire can be completed online or on the phone speaking with friendly, knowledgeable clinical trial navigators who speak English and Spanish. To search by phone, call 1-877-769-4830. Pp

Patients Speak
Tim B: The Erleada (Apalutamide) Clinical Trial

Tim B. talks about what it was like to participate in the clinical trial that led to Erleada's (apalutamide) FDA-approval.

How did you find out you had prostate cancer? How did that journey begin?

Tim B: In 2005, I had a rising PSA. Every year or so, we did a PSA test because the urologist was concerned about my rising PSA. I was over the limit for my age. I had three biopsies. Eventually, they found out I had cancer, which was a Gleason score of 7, a 3+4. Not a whole lot of cores were involved, which was good.

I thought that if I changed my diet, I would be able to do active surveillance, so I did. That lasted about nine months. My PSA kept going up.

Finally, I had a radical prostatectomy in 2013 and I had clean margins. There was nothing outside the prostate as far as they could tell. I continued on my healthy diet. I'm into heavy exercise; skiing, swimming, walking, and playing golf.

Unfortunately, about six months later, I had a PSA of 0.03, which meant there was still some cancer left. I was hoping it would die, but it didn't. My PSA was going up slowly. I waited around until it got to 0.5. Then at 0.5, I decided to do something and talked to my urologist. He told me I should go on hormone therapy and salvage radiation. What a terrible name!

I agree. It's a terrible name.

Tim B: I really didn't want to do the standard of care. So, I asked if I could join a clinical trial. I was open. If something were out there that could help me and the world, that's a pretty cool thing. He told me about a urologist down at UCSF, Dr. Eric Small.

I went to the website—and I'm sure other men would experience this—they've got all these clinical trials, but I couldn't figure out which trials I fit into. It's very confusing.

I live in Reno, so my wife and I drove down to San Francisco, and we met with Dr. Small. There was one trial he thought might work, but he needed to see me every month in San Francisco. I said, "If we can do something and get rid of the cancer in some way, I'm willing to drive from Reno to San Francisco once a month to meet with you." (Over 200 miles away).

Dr Small explained there were three segments to the trial: either I'd get only experimental drug, only hormone therapy, or a combination of the two. He said I could back out of the trial if I found it wasn't the right thing for me.

I was hesitant. The only two classifications I was really interested in were the experimental drug by itself and the experimental drug with hormone therapy. He understood, but encouraged me to sign up. I signed all the papers.

It turned out I got only the experimental drug, which was perfect. That began my journey.

Because experimental drugs are experimental, they don't know the right dosage. They have ideas. They know how it works. But in Phase II, you're a guinea pig. You've got to assume you're a guinea pig, and some men won't like that. I figured somebody's got to do it. It's a valuable thing for the rest of the men in the world.

My dosage was four pills a day. My PSA was up to 2.0 and the cancer was growing very fast. The doubling time was about two or three months when I started taking the drug. And the drug started working right away. After the first month, my PSA dropped down to 0.03. By the second month, it dropped to undetectable. I thought it was great!

During the third month, I got hives. The hives were so bad, I couldn't get out of bed. I was the first one in the trial that had gotten hives and rash because I was the first to get the new formulation unknown to me. A number of other men experienced the hives later because, in the midst of the trial, they changed the formulation. But it was only two weeks of agony and pain for me, as they eventually cut back the dosage by a quarter.

I also found out, fortunately, that Southwest Airlines had a really inexpensive flight down to Oakland. I could take the BART around to San Francisco. The flight was $49 each way, which was a no-brainer. It's less than I spent on driving. I could actually make a roundtrip to San Francisco in one day, and so it became much less expensive.

The whole time I was taking the drug, my PSA stayed undetectable. But then, unfortunately, the trial was over in August 2017. I had to go off the drug. My PSA started going up again, doubling every three or four months. My PSA is now up to over 1.2, and I've had to go to the standard of care. I'm on hormone therapy, and I start radiation in May.

I avoided the standard of care for two years, which to me was worthwhile. And, I helped get the drug through the FDA.

I loved the drug. I would love it if the FDA approved the drug. Right now, it is approved for a more serious metastasized cancer. But I'm hoping that it becomes available to all men because that would really improve their quality of life.

What would you say to other men who are thinking about a clinical trial?

Tim B: Because this is an experiment, it's going to be a bumpy road, and you've got to be ready for a couple of bumps along the way. Hopefully, you don't get a rash or anything negative. The nice thing was I knew what drug I was getting.

We decided that we didn't want to take a chance of being a placebo group, although trials are generally set up so that you can back out. So, if your PSA starts going up, you can get out.

I would say, get a good doctor who you can communicate with. I thought Dr. Small was a great doctor to talk and work with. His team was very helpful. Those were benefits. I couldn't have known beforehand, but the fact that they're a teaching university that does research helped a lot.

Don't expect that the trial will solve all your problems. Obviously, here I am two years later going down the path I didn't want to go down, but I can't find any other trials that fit me. If there were another trial, I know Dr. Small would tell me about it.

Your urologist becomes another advocate. You need to build your network of people. That's how I look at Dr. Small, as part of my support network.

You're a member of Silicon Valley Prostate Cancer Education and Support Group through El Camino Hospital, right?

Tim B: I was. I'm now a member of the Renown prostate support group here in Reno, now. But I stay on the Silicon Valley email list because they send out informative emails, and no matter where you are, you can't get enough information. I love the fact that new developments are going on to protect men.

Are clinical trials a subject matter that comes up in your Reno support group? Is it something that men are talking about?

Tim B: In my group, they do not presently, but when I was living in Silicon Valley, we did. I've done lots of the experimental trials (not FDA approved). I had an inter-rectal MRI once when I was in the Valley. I also had a PSMA PET scan, which showed that I have presently got lesions in my prostate bed.

I know I've got cancer, and I've got to do something about it. More trials are performed nationwide near teaching universities.

Trials are not for everybody, but if you're willing, the developments are happening so fast that you can't afford not to be thinking about clinical trials as an opportunity.

That's great.

Tim B: I'm very excited about the future. I hope that something like Erleada (apalutamide), which was ARN-509, becomes a standard of care. I think that these drugs have the potential to help a lot of men. Pp[1]

MAP YOUR PATH FORWARD

WITH ADVANCED PROSTATE CANCER

MyProstateCancerRoadmap.com is an online resource that can help patients and caregivers navigate through advanced prostate cancer topics such as:

UNDERSTANDING YOUR ROAD

You already know about prostate cancer. What is advanced prostate cancer?

CHOOSING YOUR ROAD

Explore your treatment options so you can partner with your doctor to decide what is best for you.

FINDING YOUR WAY

Learn how to adapt to changing relationships and begin to navigate other changes in your life.

VIEWPOINTS FROM THE ROAD

Educate and empower yourself with educational articles and real stories about people facing prostate cancer.

Visit www.MyProstateCancerRoadmap.com/start to stay in the know and subscribe to our newsletter.

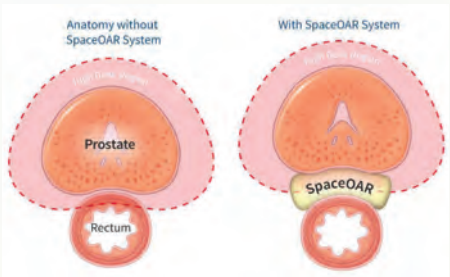
Janssen Oncology

Prostate Cancer Treatment Side Effects Aren't Side Issues When They Happen to You

According to the American Cancer Society, in 2018 over 164,000 men will be diagnosed with prostate cancer.1 For those men, treatment options range from surgery to remove the entire prostate, radiation to target the cancer in the prostate, or 'active surveillance', monitoring carefully over time for signs of disease progression. The quality of life issues that arise from surgery and radiation range from diarrhea, rectal pain and bleeding, urinary leakage and loss of sexual function that can last for years.

For men that choose radiation therapy to treat their prostate cancer, there is an innovative product that can minimize side effects caused by the treatment. Because the prostate is located near the rectum, unintended radiation damage to the rectum and surrounding tissues can occur leading to lifelong complications. In April 2015, a product called SpaceOAR® hydrogel became available for use during radiation treatment for prostate cancer. The gel acts as a protective spacer between the prostate and the rectum and has been clinically proven to reduce the risk of side effects from radiation treatment.2 In a prospective, randomized, multi-center clinical trial in the U.S., patients treated with SpaceOAR hydrogel prior to prostate cancer radiation treatment demonstrated bowel, urinary and sexual benefit through three years of follow-up. The study found that the patients that did not receive SpaceOAR hydrogel experienced a clinically significant decline in bowel, urinary, and sexual quality of life eight times more often than patients that received SpaceOAR hydrogel. 2, 3

SpaceOAR hydrogel is placed in a minimally invasive outpatient procedure with local or general anesthesia. Patients can immediately resume their normal activities. The gel stays in place for approximately three months and is then naturally absorbed and cleared in the urine in about six months.



As of 2018, SpaceOAR hydrogel is used in 19 of the Top 20 Cancer Hospitals in the United States and has been used in over 20,000 patients worldwide. To learn more about SpaceOAR hydrogel or to find a Radiation Oncologist or Urologist in your area, please visit SpaceOAR.com/prostate.

"The gel acts as a protective spacer between the prostate and the rectum and has been clinically proven to reduce the risk of side effects from radiation treatment."

1. "Key Statistics for Prostate Cancer | Prostate Cancer Facts." American Cancer Society, www.cancer.org/cancer/prostate-cancer/about/key-statistics.html.

2. DA Hamstra, N Mariados, J Sylvester, et al. Continued Benefit to Rectal Separation for Prostate Radiation Therapy: Final Results of a Phase III Trial. Int J Radiat Oncol Biol Phys; 2017 Apr 1; 97(5): 976-985

3. DA Hamstra, et al. Sexual Quality of Life Following Prostate Intensity Modulated Radiotherapy (IMRT) with a Rectal/Prostate Spacer: Secondary Analysis of a Phase III Trial. Published online: July 19, 2017 Practical Radiation Oncology. Pp1

Risks associated with the implantation of SpaceOAR hydrogel:

In addition to the risks associated with any medical procedure there are potential complications that may be associated with the use of the SpaceOAR System that include, but are not limited to: pain or discomfort associated with SpaceOAR hydrogel; needle penetration or injection of SpaceOAR hydrogel into the bladder, prostate, rectal wall, rectum or urethra; local inflammatory reactions; infection; injection of air, fluid or SpaceOAR hydrogel intravascularly; urinary retention; rectal mucosal damage, ulcers, necrosis; bleeding, constipation; and rectal urgency.

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June:
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