Prostatepedia[1]

[1]expert insight + advice

Cholesterol + Statins

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In this issue....

It is almost impossible to think of prostate cancer without considering cardiovascular disease. Cardiovascular disease is a major cause of morbidity and mortality in men over the age of 60—the age range in which prostate cancer is also most common. A significant proportion of men with prostate cancer, then, are also at risk for cardiovascular disease.

Hormonal therapy, the standard treatment for men with recurrent aggressive prostate cancer, increases the risk of cardiovascular disease.

The physicians who treat aggressive prostate cancer—medical oncologists and urologic oncologists—are often poorly informed about optimal cardiovascular risk management and commonly ignore it. Hopefully, the conversations we feature this month will encourage you and your physician to more aggressively manage your cardiovascular risk.

The Internet is often a source of information that is distorted or completely wrong. This is certainly true of statins. There are websites that portray statins as highly toxic drugs. Nothing could be further from the truth. While all drugs have side effects, statins are one of the safer drug families. Different statins also have different side effect risks. For example, the risk of muscle damage appears to be much lower with Livalo than with most other statins.

I should mention that I might have a bias on these issues. My team when I was at the National Cancer Institute was the first to report on the ability of statins to kill prostate cancer and the first to note that this might involve targets other than cholesterol. We were also the first to note that statins block the synthesis of coenzyme Q10 and linked this to Statin-induced muscle damage.

Charles E. Myers, Jr., MD Pg1

(Borner, et al. Cancer Research 55: 2122, 1995; Danesi, et al. BBRC 206:637, 1995 and Thibault A, et al. Clin Cancer Res 2: 483, 1996).

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Michael Freeman, PhD

Cholesterol + Prostate Cancer

Dr. Michael Freeman is the Director of both the Division of Cancer Biology and Therapeutics Research in the Department of Biomedical Sciences and the Division of Basic Science Research in the Department of Surgery at Cedars-Sinai in Los Angeles.

Much of his work and the work of his laboratory at Cedars-Sinai focuses on prostate cancer progression.

Prostatepedia spoke with him recently about cholesterol, statins, and prostate cancer.

How did you come to focus on prostate cancer?

Dr. Michael Freeman: My post-doctoral fellowship at the MD Anderson Cancer Center was my first introduction to cancer research in the late 1980s. Then I went to Harvard University, where I took a faculty position. While I was at Harvard, I focused for the most part on urologic research—reproductive biology, cancer of the urogenital tract, and benign diseases of the urogenital tract. My post-training professional career concentrated on organs of the genitourinary tract and diseases that are associated with them.

Over time, my lab became more and more focused on prostate cancer because people joining my laboratory were interested in prostate cancer. Over time, we developed into a prostate-cancer-focused lab. Today, most everything we do is related to prostate cancer.

"The tumor can make its own androgen from cholesterol."

What do we know about the link between cholesterol and prostate cancer—from epidemiology, the lab, and the clinic?

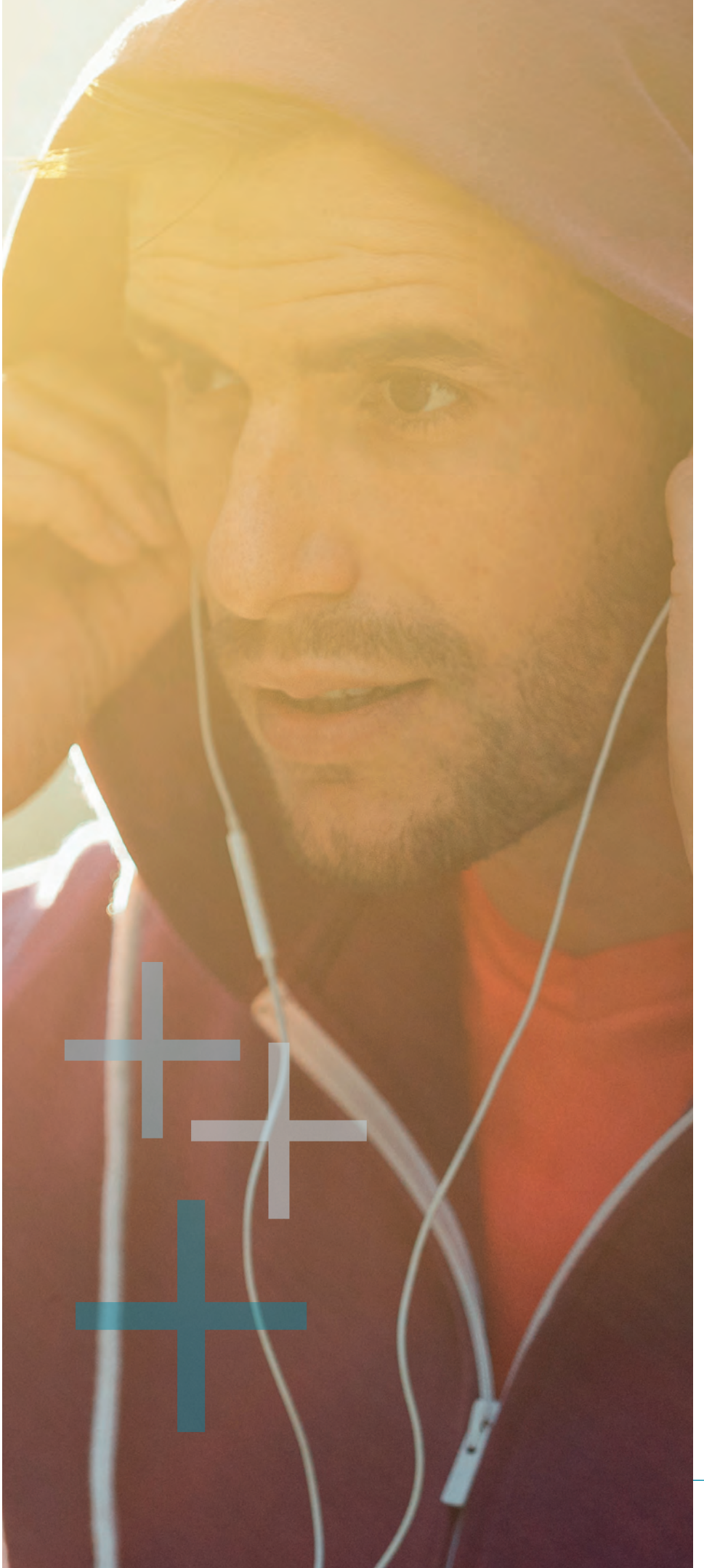
Dr. Freeman: We know some things from three different areas. There is evidence from population studies that high cholesterol is a risk factor for prostate cancer. There is fair agreement in published studies in humans that high cholesterol is a risk factor for aggressive prostate cancer.

The second type of information that we have is an emerging consensus from epidemiologic studies on the impact of statin drugs, which are HMG-CoA reductase inhibitors that lower levels of circulating cholesterol and other lipids. These drugs, which are commonly prescribed for cardiovascular health, seem to have a protective effect against aggressive forms of prostate cancer, but probably not for prostate cancers that either progress very slowly or would not be clinically relevant during a patient's lifetime. There is a little bit of a mystery as to why you wouldn't see a protective effect with indolent prostate cancer, but that is what the data show. There is not a very strong signal that statins protect for indolent prostate cancer, but for aggressive prostate cancer, the drugs appear to be protective.

The third domain of information comes from preclinical models. We've developed a number of preclinical models that showed cholesterol-lowering in mice can be protective against prostate cancer growth. Those are experimental models.

There has been quite a lot of study of prostate cancer cells manipulated in various ways in the laboratory setting treated with statin drugs and other types of approaches showing that cholesterol can be a factor promoting prostate cancer growth.

Those laboratory studies are coupled with laboratory studies of human specimens that have shown that a number of genes are linked to



cholesterol metabolism. These genes that we, and others, have found are components of normal cholesterol metabolism; expressions or other genomic changes in these genes support cholesterol as a promoter of cancer growth.

The final set of evidence comes from the fact that prostate cancer, even its later stages, is driven by the androgen receptor, a protein that regulates gene expression and which is under the control of circulating androgens made in the testes. Somehow this nuclear protein becomes uncoupled from particular androgens and can then drive prostate cancer growth even when there is very significant pharmacologic depression of androgen. This is how aggressive prostate cancer is treated with drugs.

"Statins could be an important tool for secondary therapy."

In that instance, cholesterol has been shown to be a precursor for androgen synthesis within the tumor. The tumor can make its own androgen from cholesterol. Even in the face of androgen ablation, or a treatment that blocks the male sex hormones, the tumor can make its own androgen from cholesterol.

If you look at all of that evidence, it suggests that high cholesterol is bad and that lowering cholesterol is good. There are various qualifications to that and there are still a lot of things that we don't know about the detailed mechanism.

Are statins then a possible tool for preventing recurrence?

Dr. Freeman: Definitely. Statins could be an important tool for secondary therapy. There is evidence in the literature that suggests that is true.

For example, radiotherapy patients on statins after primary treatment seem to do better with respect to recurrence. There is not a lot of that data out there, but the data we do have suggests that statins could be beneficial in that setting. Statins could also be beneficial as a general preventive measure. This is controversial. People who resist this idea say everybody is on statins and yet people still get prostate cancer. The epidemiologic data showing that long-term statin therapy can reduce the likelihood of aggressive prostate cancer is pretty strong.

"Statins are considered very safe drugs."

Part of the problem with the interpretation of the literature on statin use is that we still don't understand on a molecular level less aggressive prostate cancer, or a cancer that is not going to be clinically relevant in a patient's lifetime. The incidence of that type of prostate cancer may not be affected by statin use.

But the idea of being able to prevent aggressive prostate cancer is attractive.

Dr. Freeman: It is attractive. That is why there is still a lot of interest in statins.

Is there also a lower incidence of aggressive prostate cancer in men who have very low cholesterol due to dietary and lifestyle habits and not statin use?

Dr. Freeman: There is such evidence. Unfortunately, that data is confounded by older evidence that suggests that low cholesterol can be a risk factor for prostate cancer and other types of cancers. My interpretation of that evidence is that it's mostly from the older literature in which patients presented with a greater cancer burden and that what is likely happening is that the cancer itself is scavenging cholesterol. The circulating cholesterol levels then go down, making it look like low cholesterol is a risk factor for cancer. But I don't think that is actually true. I think that for prostate cancer, lower cholesterol is beneficial.

Is there anything else going on with statins other than their cholesterol-lowering ability that could account for the lower risk of aggressive prostate cancer?

Dr. Freeman: There is. Statins inhibit the enzyme HMG-CoA reductase, which is in a metabolic pathway leading to cholesterol. There are many steps after that single step inhibited by statins before you get to cholesterol along that pathway. Within that pathway, there are other organic molecules produced called isoprenoids which can be used to modify certain types of signal transduction proteins also involved in cancer.

Statins can suppress the synthesis of these isoprenoids and thereby affect oncogenic signal transduction completely independently of cholesterol. There have been a lot of studies done and now a lot of people think statins' primary effect on any tumor may be this inhibition of isoprenoid synthesis.

The problem with that idea is that the liver is the principal target for

HMG-CoA reductase inhibitors. Cells in the liver make most of the circulating cholesterol. Most of the HMG-CoA reductase that is inhibited when you take a statin will be in the liver. Statins don't have great penetrance into the peripheral tissues, which is where the tumors are. Tumors also have a problematic blood-vessel structure. It's hard to get any kind of drug into tumors, which is one of the reasons why cancer therapy is so challenging. When there are protective effects against cancer in humans, the primary effect is on the liver, not on the cancer. In this case, that effect would be lowering circulating cholesterol.

There are a number of laboratories making modified versions of statins more likely to penetrate tumors, but those are experimental agents. We don't have very much information on how they work or their toxicity profiles.

Certainly, in laboratory experiments, statins can be very potent killers of cancer cells. If we could get statins into the tumor more effectively, then there would be a chemical effect independent of cholesterol that may be very important or maybe even more important than lowering cholesterol synthesis in a tumor. I think most of the protective effects we see in the epidemiologic literature come from effects from the liver.

There have also been reports of a potential synergistic effect between statins and metformin. Do you have any thoughts about that combination?

Dr. Freeman: I don't really have any opinions about it. Metformin is an interesting drug. It affects a signal transduction pathway that feeds into multiple metabolic pathways that can drive cancer growth. It's reasonable that there could be some sort of synergy, but that isn't anything that we've looked at in my lab.

"This is an emerging area."

Is there anything else patients should know about cholesterol, statins, and prostate cancer?

Dr. Freeman: At our center we have a number of different projects related to cholesterol, statins, and prostate cancer that look promising. This is an emerging area. New data will come out in the near future.

Is there any reason for men not to approach their doctors about going on a statin? Are there any downsides to statin use for men with prostate cancer?

Dr. Freeman: I don't think there is any reason not to do that. Statins are considered very safe drugs. The primary side effects are muscle pain, but most people are not susceptible to that. Just be aware that muscle pain is a possibility. But I don't think there is any reason not to go on a statin if a patient and his physician are concerned about a risk of prostate cancer. Most physicians are probably not going to prescribe a statin for the specific purpose of prostate health, but they would certainly be willing to prescribe in the context of cardiovascular health. You would have to work that out with your own physician, but I don't see any downside in going on a statin based on the broader literature or on the prostate cancer literature. Pp1

Alison M. Mondul, PhD, MSPH

Epidemiology's Story: Cholesterol + Prostate Cancer

Dr. Alison Mondul is an Assistant Professor of Epidemiology at the University of Michigan in Ann Arbor.

Prostatepedia spoke with her recently about what epidemiology tells us about the link between cholesterol, statin use, and aggressive prostate cancer.

What is cancer epidemiology?

Dr. Alison Mondul: Epidemiology is the study of how diseases occur in different groups of people and why. Basic scientists do a lot of work in animal models or in cell lines, but animals and Petri dishes aren't people. We need to also do research in real humans.

A lot of the work that epidemiologists do is what is called *observational*, meaning we look at groups of people, but the independent variable (in this case high or low cholesterol) is not under our control. We take a group of men and look at those who have high cholesterol and those who have low cholesterol and compare them to see how often they get prostate cancer. You can do this for all kinds of different exposures.

Epidemiology is like a toolbox you can use to investigate lots of different research questions in human populations. There is a lot of statistics involved. You might imagine that men who have high cholesterol are different in lots of ways from men who have low cholesterol other than their cholesterol level. Men who have higher cholesterol might eat different foods than men with low cholesterol. They might have genetic factors that lead to high cholesterol that are different from men with low cholesterol. They might exercise less. They might have a higher Body Mass Index. They might be unhealthier in other ways. They might tend to smoke more. Any number of things.

> *"A lot of the work that epidemiologists do is what is called observational."*

Epidemiology tries to deal with those kinds of factors using statistics, whereas in animal studies, the scientists control those aspects. You put one set of mice in a cage on the left and the other set of mice in a cage on the right and you determine everything. But people don't have one exposure in isolation of everything else.

Science works best when epidemiologists, basic scientists, and clinicians all work together. I might say we saw that higher cholesterol seemed to be associated with prostate cancer, but we don't know why. A basic scientist will then say, "That's really interesting," and go look at what cholesterol does to prostate cancer cells. It's easier to do that in a Petri dish than it is to do in a person.

What does epidemiology say about the link between cholesterol and prostate cancer? About cholesterol and aggressive prostate cancer?

Dr. Mondul: If you look at cholesterol and overall prostate cancer, the evidence isn't especially strong. But when you start to look at higher-grade or more advanced prostate cancer, it starts to become a little bit clearer. Higher cholesterol seems to be associated with higher risk of more aggressive prostate cancer, or prostate cancer with a worse prognosis.

The evidence is not uniform. In epidemiology, one study never gives you the answer. You look in one group of men and see one thing, but if you look in another group, you might see something a little bit different in some way. When we see something in one study, we don't really trust it. We like to see that same result, or a similar

result, in a lot of different studies. If we don't see the same thing, we'd like to be able to know why.

One of the complexities is that each study may define high-grade or aggressive or advanced differently. It's not a hard-and-fast definition. Also, how the study authors choose to categorize high and low cholesterol can be different from study to study. These are general difficulties in comparing across epidemiologic studies, but they're particularly true for studies looking at cholesterol and prostate cancer.

"Higher cholesterol seems to be associated with higher risk of more aggressive prostate cancer, or prostate cancer with a worse prognosis."

There have been multiple studies now looking at cholesterol and prostate cancer that show there doesn't seem to be a lot going on for overall prostate cancer. Several studies have seen a higher risk of either high-grade or more advanced disease with higher cholesterol. There are hints that higher cholesterol may be associated with more aggressive disease.

Meaning men who have high cholesterol tend to get more aggressive prostate cancer?

Dr. Mondul: Yes. Most of the studies have looked at cholesterol levels *before* diagnosis in healthy men and subsequent risk of developing prostate cancer. These studies have shown that men who have higher cholesterol tend to be diagnosed with more aggressive cancers. Very few studies have then looked at what happens after you've been diagnosed: what does your cholesterol level have to do with recurrence, or progression? Or your risk of dying from prostate cancer? Would lowering your cholesterol after diagnosis impact these outcomes? That is an area of research that people are very interested in.

What about men who have had high cholesterol and are now on a statin? Do those men still have a high likelihood of aggressive prostate cancer?

Dr. Mondul: The statin story is a lot clearer than the cholesterol story. There is good agreement across studies that statins appear to be protective for more advanced disease. In fact, there have even been a handful of studies looking at statins and fatal prostate cancer that have seen protection for this most clinically relevant outcome. This could be for a couple of reasons. Statins obviously lower cholesterol. It could be that statins protect against more aggressive prostate cancer by lowering cholesterol.

Statins do other things that may also be protective: they are anti-inflammatory. They act through other pathways that may also have an important role in preventing more progressive disease.

I said before, how you categorize high versus low cholesterol can vary. But you're either taking a statin or you're not so that categorization is clearer, although you still have to consider factors like dose and duration of use. Also, cholesterol can fluctuate over time. You can measure a man's cholesterol at one point in time before he was diagnosed, but perhaps the very next day he went on a diet and his cholesterol changed. Once a man goes on a statin, his cholesterol is pretty consistently lower. Also, once men start taking statins, they usually don't stop, presuming the statins are well tolerated, which they are in most people. As prescription medications go, they're fairly well tolerated in the population.

What does all this mean for men who have already been diagnosed with prostate cancer?

Dr. Mondul: The evidence that we have is a lot stronger showing that taking a statin before you're diagnosed with prostate cancer might prevent development of more aggressive disease.

There have been fewer studies looking at whether lowering cholesterol or taking a statin after diagnosis may also prevent a worse outcome. There are some suggestions that post-diagnosis statin use may have some impact on preventing death. More work is really needed here.

In general, we know that maintaining healthy cholesterol improves all kinds of different outcomes, not just prostate cancer. It can't hurt your prostate to maintain a healthy cholesterol level and to adopt the good lifestyle habits that go along with it. Prostate cancer might just be the latest entry on a long list of things improved by maintaining a healthy cholesterol level.

There is no downside to lowering your cholesterol?

Dr. Mondul: No. Lower cholesterol is obviously important for cardiovascular health. We've known that for a long time. If it helps your prostate too, that would be great. Pp[1]

Clinical Trial: Hyung Kim, MD Statins Before Prostatectomy

Dr. Hyung Kim is a urologic oncologist at Cedars-Sinai in Los Angeles.

Prostatepedia spoke with him recently about a clinical trial he's running that looks at the effects of cholesterol-lowering therapy before radical prostatectomy.

How did you come to focus on prostate cancer?

Dr. Kim: By training, I am a urologic oncologist. I treat all urologic cancers, but prostate cancer was a natural area for me to focus on since it is the most common of the urologic cancers. Prostate cancer is a disease with many unanswered questions. We clearly need ways to identify which cancers are potentially lethal and need to be treated and which do not need to be treated.

What do we know currently about the connection between cholesterol, statins, and prostate cancer?

Dr. Kim: A lot of our data comes from epidemiology studies in which statins were used to lower cholesterol to improve cardiovascular health. In many of these studies, the observation was made that patients with prostate cancer who were on statins were less likely to die of their cancers.

The other line of evidence comes from basic science research. People like Dr. Michael Freeman have done preclinical laboratory studies showing that lowering cholesterol levels in mice can slow down the growth of prostate cancer. (See page 4 for an conversation with Dr. Michael Freeman about his work.)

> *"We need stronger data in patients showing that lowering cholesterol has an effect on prostate cancer tissue."*

We have epidemiology data. We have preclinical data. The missing piece is prospective data in patients to help establish a firm cause/effect relationship between lowering cholesterol and favorable prostate cancer outcomes.

The epidemiology data is interesting because the link between statin use and the incidence of prostate cancer is weak, but there is a stronger link between statin use and the likelihood of dying from prostate cancer.

This suggests the possibility that statin use targets the lethal form of prostate cancer. It also suggests that statin use may not lower the likelihood of developing prostate cancer. However, if you develop prostate cancer, perhaps statin use will improve your likelihood of surviving the disease.

Mouse studies are controlled experiments where you do see a clear cause/effect relationship. You lower the cholesterol level in the mice and the tumors you implant in them grow more slowly. We have some idea of the basic mechanism behind this observation, but does this cause-and-effect relationship carry over to patients? Does that cause/effect relationship explain the epidemiology data that we see? Those are the unknowns. This is why we're conducting our trial.

How do you hope this trial will fit into the conversation about statins and prostate cancer?

Dr. Kim: Statins may have an effect on prostate cancer. However, a clinical trial to explore this possibility will require a long treatment period and many years of follow-up, given the long natural history of the disease. Such a study is going to be very expensive. It's going to take lots of patients.

"We're taking men who are already scheduled to undergo a prostatectomy and lowering their cholesterol."

Before we embark on such a costly study, we need stronger data in patients showing that lowering cholesterol has an effect on prostate cancer tissue that would suggest a clinical benefit.

In order to get that early clinical data to hopefully justify a large Phase III clinical trial, we're taking men who are already scheduled to undergo a prostatectomy and lowering their cholesterol using a medication that is already on the market called Vytorin (ezetimibe and simvastatin).

Once the man's prostate is removed, we take some of the leftover tissue and molecularly analyze it to see if there has been any effect.

For how long will you lower the cholesterol?

Dr. Kim: We're lowering cholesterol for two to six weeks. In the cardiology literature, where statins have been extensively studied, blood cholesterol lowering was achieved by two weeks. In animal studies, if the serum cholesterol is lowered, you see a molecular effect within 24 hours.

Our study has a molecular endpoint. We're not looking for survival. We're not looking for disease shrinkage. We're looking at molecular changes. Because we see these changes very quickly in mice, we think that a short treatment period will allow us to determine if lowering cholesterol is having a cellular effect in men.

Are there any eligibility criteria? For example, are you not interested in enrolling men who have been on statins for years for other reasons?

Dr. Kim: Men scheduled for prostatectomy can enroll whether they are on a statin or not. We're taking men who have not been on statins, but we're also taking men who have been on a standard statin. The reason for that is that, in the epidemiology studies, there seems to be a link between stronger, more potent statins and a greater benefit. We're arguing that maximal cholesterol lowering is the best way to go.

Instead of using a standard statin, in our trial we use a medicine called Vytorin (ezetimibe/simvastatin). Vytorin (ezetimibe/simvastatin) has two different medications in a single tablet: a statin (simvastatin) and another medicine called Zetia (ezetimibe). There are two sources of cholesterol in the human body. The liver makes cholesterol; statins shut down cholesterol production in the liver.

The other source is from the gut or the diet. Zetia (ezetimibe) essentially binds the cholesterol in the gut and prevents its absorption. Then the cholesterol and Zetia (ezetimibe) simply pass through the intestines and never make it into the bloodstream.

We believe this strategy will maximally lower serum cholesterol. Patients on statins can enroll, but they need to stop their statin and go on Vytorin (ezetimibe/simvastatin) until after surgery. We measure cholesterol levels before and after starting treatment.

How To Get Involved…

Patients who are interested in participating should call Jenny Park, MPH at 310-423-8762 or email jenny.park@cshs.org for more details.

Is there anything else men should know about the trial?

Dr. Kim: We don't know if statins, or lowering cholesterol, is targeting low-grade tumors or high-grade tumors or perhaps both types of tumors. We want patients with both low- and high-grade tumors, so Gleason grade 3 and 4 tumors.

This is a low-risk study in the sense that we're not using an experimental medication. This is a drug already in use by millions of people for cardiovascular health. We're testing it for an experimental indication.

For most patients, the primary motivation to participate in this study is to help us answer an important scientific question, however, there is the possibility that lowering serum cholesterol may slow prostate cancer growth which could benefit patients while they are waiting for surgery. If we can show some molecular effect, then the next study will randomly assign patients to statin versus placebo. Perhaps men on active surveillance can enroll to see if cholesterol-lowering therapy decreases their risk of progression so that they do not require surgery or radiation. This might be a follow-up trial if our study is positive.

The other point I'd like to make is that our study is funded by The Alliance for Clinical Trials in Oncology, which used to be called CALGB. It is one of the major National Institutes of Health (NIH)-funded cooperative groups. Pp1

Neil Fleshner, MD
The Metformin Active Surveillance Trial

Dr. Neil Fleshner, Chair of the Clinical Division of Urology at the University Health Network and Professor at the University of Toronto, Canada, is a urologic oncologist with a special interest in active surveillance for prostate cancer.

Prostatepedia spoke with him recently about his Metformin Active Surveillance Trial.

How did you come to focus on prostate cancer?

Dr. Neil Fleshner: For 15 years, I've been studying how to prevent prostate cancer.

A lot of our work over the years focused on specific micronutrients. More and more, as some of the science in our lab and other labs expanded, it became obvious to me that the problem was not a lack of antioxidants, or a lack of this or that, but just caloric excess and insulin-driven factors. We published some work in the *Journal of the National Cancer Institute* years ago that proved this.

Those results gave us a reason to look at metformin in a variety of studies. We gave men metformin prior to prostate cancer surgery and showed that tumor growth was stunted. Then we did some large database-type studies, which we published in the *Journal of the National Cancer Institute* and in the *Journal of Clinical Oncology*, which showed that if you were a diabetic male in Ontario, Canada, and by happenstance your doctor gave you metformin, your risk of dying of prostate cancer was significantly less. Those results led to the conception and funding of this trial.

> *"The idea is that the men getting metformin would have a lower chance of their cancers getting worse."*

What is metformin?

Dr. Fleshner: Metformin was developed to treat Type II diabetes. It's one of the oldest treatments around for Type II diabetes. It's generic. It's cheap: it costs 13 cents a day. There are many mechanisms by which it works.

Prostate cancer has a unique metabolism. For example, we don't use FDG-PET scans to image prostate cancer. That tells us, right away, that prostate cancer doesn't use glucose the way regular tumors do. Prostate cancer is more avid for choline and other carbons. Glucose utilization in non-prostate cancers tends to be quite colitic (causing inflammation of the colon), whereas in prostate cancer it is more what we call *oxidative phosphorylation*.

It turns out that metformin is a significant oxidative phosphorylation inhibitor and seems to poison the way by which prostate cancer uniquely uses fuel.

You have a trial looking at metformin in men on active surveillance. What is the thinking behind the trial?

Dr. Fleshner: We know that many men on active surveillance don't die of prostate cancer, but that up to a third eventually need treatment. We're trying to lower the chance that men on active surveillance would need treatment for their prostate cancer, or delay progression in other words.

In this trial, we're taking 408 men at 15 Canadian centers and randomizing them to metformin or placebo. We repeat their biopsies 18 and 36 months after their entry into the study. The idea is that the men getting metformin would have a lower chance of their cancers getting worse.

A lot of men on active surveillance end up dying of other diseases—like cardiovascular disease—and not prostate cancer. Is that phenomenon playing into the trial?

Dr. Fleshner: This is only a three-year trial, so we're focused on metformin's influence on prostate cancer, but there is no doubt that metformin may have other potential mechanisms or benefits to general health. I say *may*, because it obviously requires further study.

If you look at the diabetes literature, all the oral treatments for Type II diabetes lower sugar levels about the same, but only metformin has been proven to improve survival rates. This is interesting. It makes some investigators wonder if metformin's effect has anything to do with diabetes at all. Some people are studying metformin as an overall life-extension type of drug.

What are the patient eligibility requirements for your trial?

Dr. Fleshner: You have to have a Gleason 6 prostate cancer with low-volume disease, so three cores or less.

Who should patients contact if they think they may be eligible?

Dr. Fleshner: They can contact Miran Kenk (416-946-4501 ext. 3431, miran.kenk@uhn.ca) or myself at neil.fleshner@uhn.ca.

Is there anything else patients should know either about metformin or prostate cancer?

Dr. Fleshner: I think we have to embrace trials like this one, but not rush to start taking metformin. It's extremely important that we put good science to this first. Pp[1]

Jamie Bearse
What Does Trump Mean for Prostate Cancer?

Jamie Bearse is the CEO of ZERO — The End of Prostate Cancer (https://zerocancer.org/), a prostate cancer nonprofit organization that advances research, improves the lives of men and families with impactful programs, and inspires action.

Prostatepedia spoke with him about the changes President-elect Donald Trump's administration may bring to prostate cancer.

How did you become involved with prostate cancer advocacy?

Mr. Jamie Bearse: I've been with ZERO for about 15 years. It seems hard to imagine, but I have. When I started, ZERO was called the National Prostate Cancer Coalition. When I applied, I was the Press Secretary for a Massachusetts Congressman. Prior to that, I worked on his inaugural campaign and then moved to Washington, DC, to work on Capitol Hill.

When the opportunity to work in prostate cancer came up, I decided I wanted to be a part of doing for prostate cancer what had been done for breast cancer. Fifteen years ago, the breast cancer movement was in full momentum and began, in many ways, when Betty Ford started talking openly about breast cancer. When I started with ZERO, people like Joe Torri and Rudy Giuliani were just coming out about their prostate cancer diagnoses. That really helped push the dialogue forward, making it okay for families to talk openly about prostate cancer, rather than in whispers or not at all.

At a young age, I was impacted by cancer. I had family members who battled the disease and lost.

We didn't celebrate Mother's Day when I was growing up because my grandmother died on Mother's Day at 50 from colon cancer. My mom never wanted to celebrate Mother's Day. That is still the case to this day. My mom served as an emotional support to her siblings and my grandfather for a fair period of time. I spent a lot of time with my other grandmother until we learned that she had leukemia. She died not even a year later.

What is ZERO?

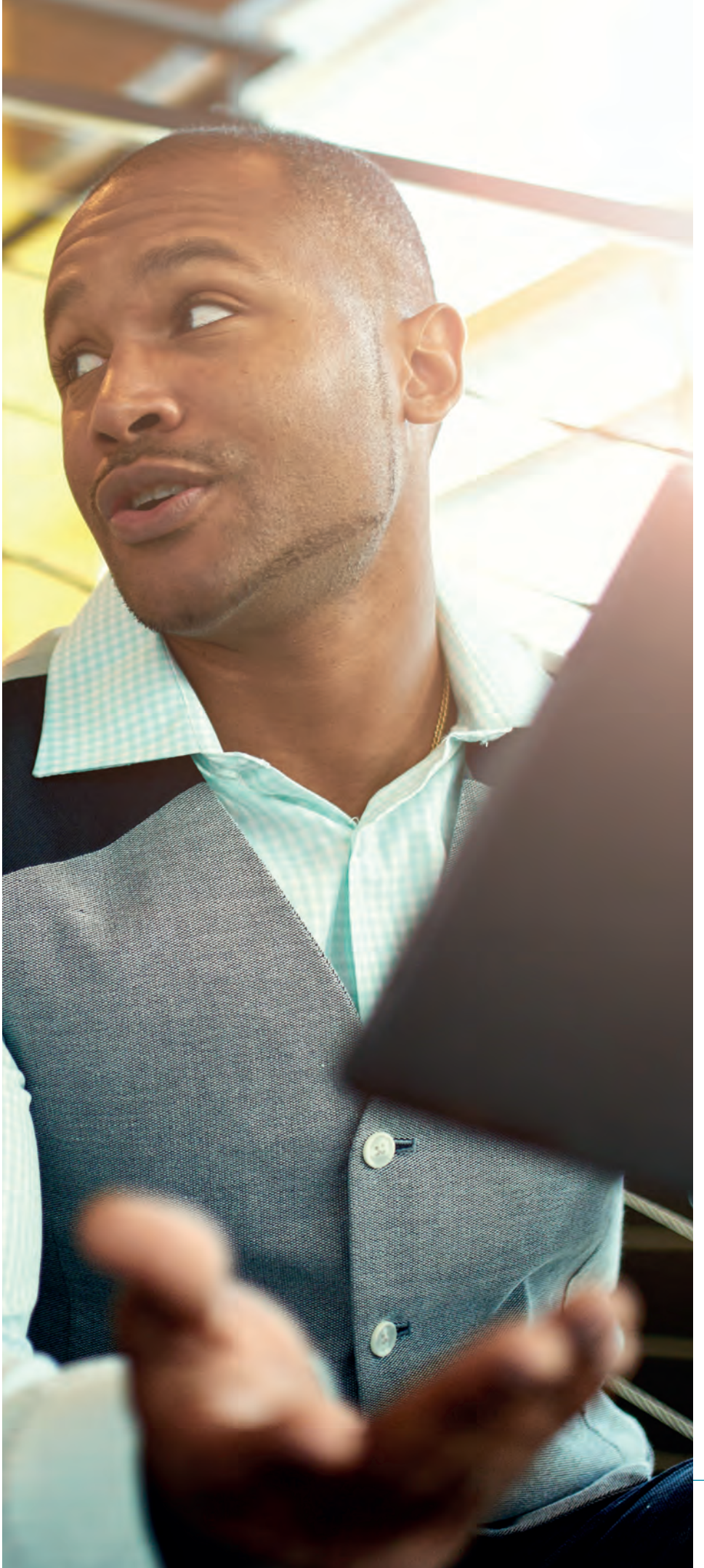
Mr. Bearse: ZERO's mission is to end prostate cancer. We do that by advancing research and improving the lives of men and families with impactful programs and inspiring action. We advance research by working with the federal government to protect and grow prostate cancer research funding. We work to to defend and expand patients' rights and access to care.

We also have a Run/Walk event series in about 40 cities across the country. We team up with doctors' offices and local nonprofit entities to host the events the events. These runs encourage men at risk for prostate cancer to pursue an active lifestyle as a way to battle and prevent cancer.

They are also a way for local communities to join forces and get involved in the cause. The Run/Walk is a conduit to connect people and move them forward down a path of awareness and advocacy. We provide education and support in many different forms.

We have also, for the last three years, provided about $183 million in patient copay relief to more than 48,000 patients across the country battling advanced disease.

We have a patient navigation program for prostate cancer patients looking for help in an era of unprecedented uncertainty in health care. This program connects prostate cancer patients and caretakers with a patient navigator, nurse practitioner, or social worker for help with matters as simple as getting a ride to their doctors' offices to more complicated matters like insurance reimbursement and appeals, enrolling in Social Security disability, supplying clinical trial information, and reviewing enrollment qualification.



We have monthly webinars and empower our advocates to organize health fairs to offer information and screening to their communities. We have local partners around the country that provide free early detection and mobile programs in California and Louisiana.

What does the Trump presidency mean for prostate cancer research?

Mr. Bearse: There are two different sources of government funding for prostate cancer research: the National Institutes of Health (NIH) and the prostate cancer research program within the Department of Defense (DoD).

Congressman Tom Price, the nominee for secretary of the US Department of Health and Human Services (of which the NIH and the National Cancer Institute are divisions), is a medical doctor. We're hopeful disease research will remain safe and continue to move forward.

ZERO has a keen focus on DoD research. Many people don't know that the DoD plays a significant role in the War on Cancer. Within the DoD is a program called the Congressionally Directed Medical Research Programs (CDMRP) that has about two dozen cancer research programs. One of those programs is a prostate cancer program, earmarked at about $80 million. It focuses on taking new bright ideas from the scientific bench to the patient's bedside as rapidly as possible.

It has been a very successful business model that incorporates patient feedback. Peer-reviews by gold-star institutions around the country decide who gets grant funding. There have been three new treatments for advanced prostate cancer finalized in the last five years as a result of DoD prostate cancer funding: Xgeva (denosumab), Xtandi (enzalutamide), and Zytiga (abiraterone).

The presidential administration has historically not given much philosophical input into medical research funded by DoD, because the DoD's budget is largely created by Congress. Again, we're hopeful medical research is a cause that everyone can get behind regardless of politics.

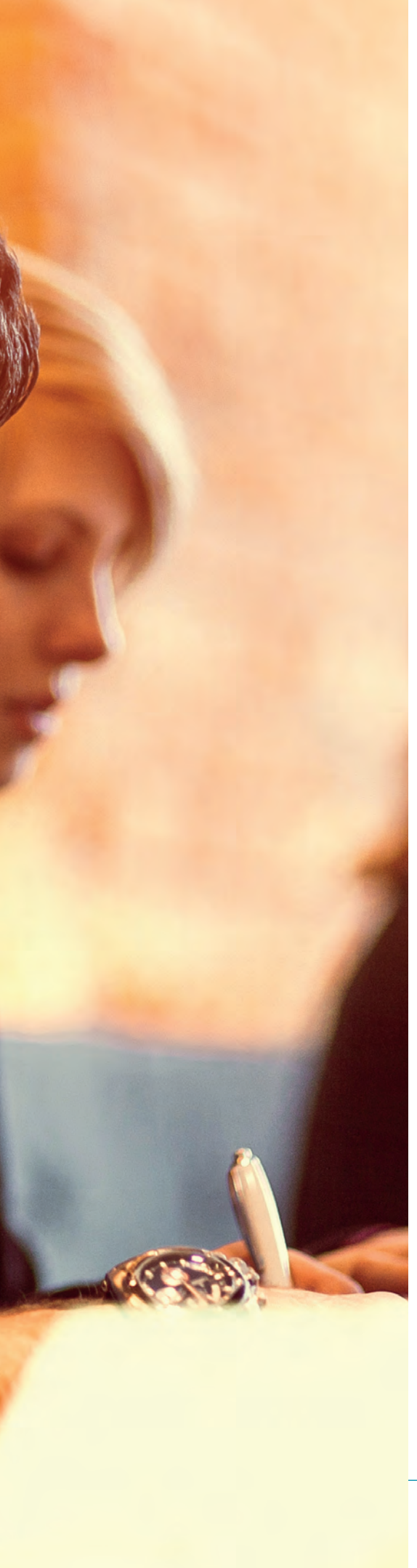
However, there is always a risk, predominantly because Senator John McCain, who was reelected, is an opponent of the CDMRP. McCain is not necessarily against cancer research, but he does not believe that medical research funding belongs in the Department of Defense and has continually tried to create bills to eliminate the program. He also continues to fall short on offering a solution; he just wants to eliminate the program. How many people will support the bills he introduces is a bit of an unknown, but I'm fairly confident that the bills will not pass.

What should patients do if they're concerned about the fate of prostate cancer research?

Mr. Bearse: At the end of February, we host our ZERO Prostate Cancer Summit in Washington, DC, during which we teach advocates from around the country to be the best advocate they can. We bring patient advocates to Capitol Hill to meet with their elected officials in an attempt to recruit these officials as champions for prostate cancer research. Joining us for that summit and getting on our advocacy email alert list are great ways to get involved.

How will the proposed modifications to the Affordable Care Act (ACA) affect prostate cancer patients?

Mr. Bearse: Opinions on what may happen with the Affordable Care Act (colloquially known as Obamacare) change every day. Repealing the ACA is at the top of the Republicans' list. However, it's very unclear if it will be replaced with a new plan.



Trump has signaled some interest in keeping parts of the ACA that seem to be popular around the country—covering existing conditions and allowing children up to the age of 25 or 26 to remain under their parents' health insurance. However, those two provisions of the ACA are tied into the overall funding mechanism. We may see a fight over the ACA continue for months.

What can patients do if they're nervous about implications for their own care?

Mr. Bearse: If you're unsure about what all this means for your own battle with prostate cancer, you may want to use ZERO's patient navigator program: ZERO360. Our patient navigator program pairs you with a case manager who will stay with you throughout your fight with cancer. This is not a one-and-done phone call. You will be assigned to a professional who will help answer all of your questions on a rolling basis.

As the ACA potentially changes or does not, as your health insurance potentially changes or does not, we will help direct you in the best possible way.

Is this a fee-based service?

Mr. Bearse: It is absolutely free and confidential.

Are there any other implications for prostate cancer patients during this transition?

Mr. Bearse: Many prostate cancer patients and advocates are very interested in early detection for prostate cancer. There is an agency Senator Jeff Sessions, and Congresswoman Marsha Blackburn called the United States Preventive Services Task Force (USPSTF) that states that the prostate cancer PSA test doesn't have any value in saving lives. We disagree.

"We may see a fight over the ACA continue for months."

We believe that PSA testing is the first step in identifying who has prostate cancer and who does not. There are other steps that help determine how widespread and aggressive a man's prostate cancer may be before he jumps into treatment.

The USPSTF argues screening men automatically leads to over-treating men. We disagree.

Congress has tied the USPSTF's recommendation to insurance coverage for screening and has had a great influence on general practitioners. A man will go in to see his doctor for an annual physical expecting the doctor to give him all the tests he needs to make sure that he is healthy. But more times than not, the general practitioner will cite the USPSTF's stance that prostate cancer screening has no value unless you are in a high-risk group like being African American or have a family history of the disease. We believe that is a problem.

But the election may have a positive impact on current screening recommendations if the ACA is overturned because the USPSTF recommendations are tied to it. Congressman Price, Sen. Sessions, and Congresswoman Blackburn, all part of the Trump government, have been friendly toward divorcing the USPSTF from screening recommendations. Pp1

Patients Speak
Depression + Cancer

Tom M. spoke with *Prostatepedia* recently about his prostate cancer journey and the depression he struggled with while on Lupron.

How did you find out you had prostate cancer? What was your initial reaction?

Mr. M: I was on vacation with my girlfriend's family about 700 miles away from where I live. I had problems urinating. Everybody was off somewhere, so I went into the little town and did what most men do. I started drinking beer. I figured that would help. It didn't.

Instead, I spent a really painful night. I ended up in the ER in agonizing pain. Fortunately, the ER doc knew exactly what it was. He said, "You have an obstruction in your urethra." He put in a catheter, which gave me instant relief, and sent me to a urologist.

The urologist said that I probably had prostate cancer. My PSA was 199. I spent four days there before they took the catheter out and I made the journey back home.

I got an appointment as soon as I could with a urologist near me. They said, "You have prostate cancer," and sent me for tests to see if it had spread.

I went on Firmagon for a month and my PSA dropped to 14.9. Then they put me on Lupron for about nine months. I had really bad side effects. The side effects didn't start out too bad, but they just kept increasing. I had unbelievable hot flashes and fatigue. Loss of concentration. Then I had periods of feeling like I had the flu for three or four days. My body would ache. And then I'd get depressed. It would go away and come back. It would come out of nowhere. I'd be fine one minute and the next minute, it was like I dropped into this deep black hole. I was in pain. I felt crappy and irritable and grouchy.

> *"I'd be fine one minute and the next minute, it was like I dropped into this deep black hole."*

I was suicidal at times. I was ready to die rather than deal with the side effects of the treatment. I'd go to bed and think, "I don't care if I wake up in the morning." There was a lot of anger. I didn't know who I was anymore. I didn't know what was going on. I didn't know why I was so angry. It just popped out of nowhere. My partner would say something and I'd just flash. Then I'd be embarrassed and sad and frightened myself.

I didn't know who I was for the longest time. I just knew this wasn't the *me* I used to know.

Were you exercising during that period?

Mr. M: I was living in Montana: in wintertime, it's 20 below with snow. I had some exercise equipment, but I had no motivation. I didn't know what to do. I didn't want to do anything, so I watched a lot of TV and read.

I was starting a long-distance relationship with my girlfriend in Southern California where I am now. I'd come see her and things would be fine for a few days and then I'd go back into this big hole of depression. It was miserable and it was getting worse.

Finally, when I saw my urologist she said, "Why don't we take you off treatment? That is the only way to stop the side effects." I went off treatment for almost four months and the side effects got better, but then my PSA went from 3.7 up to 19.7. She put me back on Lupron and said I was going to be on it for the rest of my life.

I tried to talk to her about my depression, she just said that it's part of the treatment and there was nothing she could do.

I went to see my primary care physician for my regular physical. She asked, "You're doing okay and then one minute later it's like you're hit with lightning and you're in this hole?" She knew exactly what I was going through. She really knew what was happening. She prescribed Effexor (venlafaxine) to help with depression and hot flashes. She gave me *Panax ginseng* to help with fatigue.

But she did something else: she gave me hope. I had hope for the first time in nine months. That really changed my attitude and outlook on my immediate life. I felt as though I could cope with all the negative side effects and continue treatment.

Later, I decided the long-distance relationship wasn't working so I moved to Southern California and got a new doctor there who added Casodex to the Lupron.

I wanted to come off the Effexor (venlafaxine) because it didn't seem to be helping with the depression or hot flashes anymore.

You have to ween yourself off Effexor (venlafaxine). I asked my new oncologist how to do that. He said, "We didn't prescribe this, so you have to go see your primary care physician."

After about six months with this doctor I was becoming a little disgruntled by the care I was not receiving. He was not answering my questions. He said, "I treat the disease. Nothing else."

Around that time, I found a support group called the Prostate Forum of Orange County (www.prostateforum.org). I started to get really good information

He said, "I treat the disease. Nothing else."

from them. There is so much confusing and conflicting information out there.

Last year doctors from Compassionate Oncology Medical Group came and gave a presentation about their clinic. I made an appointment for a consult after that.

So you found a new doctor through the support group?

Mr. M: Yes. I wouldn't have found them otherwise. I learned that you really need to talk with your oncologist. And I finally was able to come off Lupron. The depression and side effects have slowly abated to being tolerable.

You need to be able to trust your oncologist enough to really talk about what's going on?

Mr. M: Exactly. You do need to trust them and believe that what they're doing is right for you.

Would you suggest other patients shop around until they find the right doctor?

Mr. M: Yes. A lot of times people who have been newly diagnosed feel pressured to start treatment immediately. If they're seeing a urologist, they feel pressured to get surgery or if they're seeing a radiologist they feel pressured to get radiation treatment. They're so scared that they believe they have to start treatment right away.

When I was a new patient, I was totally overwhelmed. There was so much paperwork, so many tests. I didn't know what was going on. I was just trying to cope with living each day as best I could and adjusting to living with all the side effects of treatment and the medications. And trying to cope with the changes in the quality of life I was experiencing.

So about six months ago, after three years on Lupron, I finally decided that I was going to be more active in my own treatment and not just do what the doctors said. That made a big difference for me. I think it does for anyone going through the treatment process. You have to participate in your treatment. You have to be on top of stuff and talk to your doctors.

There are breakthroughs in prostate cancer treatment every week. Treatment has changed rapidly in the last five years. I know some people on active surveillance are just waiting for a new breakthrough to be approved. And some people leave the country for treatment that is not available yet here in the US.

What you learn at the support group is that you actually have time to sit down, get your information straight, and find the right treatment provider for you. You have to make a choice, not a quick choice, but a well-thought-out choice in talking with your partner about what the side effects are for the type of treatment you and your oncologist decided to implement. And what are, if any, the possible irreversible side effects?

And perhaps most importantly, carefully consider how the treatment and its side effects will affect the quality of your life and the lives of your partner, family, and friends. Ask yourself: "What am I (and my partner) willing to do and live with while undergoing treatment?" Pp[1]

Tom Michaels
Specialty Pharmacies

Tom Michaels is the Senior Vice President of Sales & Pharma Account Management for Diplomat (https://diplomat.is/), the largest independent specialty pharmacy in the United States.

Prostatepedia spoke with him recently about specialty pharmacies.

How did you come to work with a specialty pharmacy?

Mr. Michaels: I spent about 30 years in big pharma corporations —27 of those years with Novartis Pharmaceuticals. I've been in sales for about 35 years: I've been a sales rep, an account manager, a sales manager, and a sales director.

What I really had fun doing was building sales teams. At Novartis, I helped build and expand our hospital sales team. I built a gastroenterology sales team, then respiratory, dermatology, and primary care sales teams. I got a lot of experience in a broad array of therapies along the way.

My wife is also with Novartis in their oncology division. In my last years at Novartis, I had to downsize my teams five times in four years. I wasn't having as much fun at that point. During those last four years, my wife kept telling me about this specialty pharmacy called Diplomat in Flint, Michigan, that could really use my sales expertise.

> *"You can't go to the corner drugstore and pick up oncology meds."*

In June 2012, Diplomat's vice president of sales called her to say he was leaving and wanted to recommend her for his position. She said, "Thank you, but I'm not interested, though I know somebody who might be."

That is how I came over to Diplomat. When I started, Diplomat had about 22 sales reps and managers. Today, we have over 200 nationwide. We're really having an impact on the marketplace in rare disease, orphan drug, specialty infusion, and oncology spaces.

What does Diplomat do?

Mr. Michaels: Diplomat is the largest, independent specialty pharmacy in the country. We serve all 50 states and the US territories of the Virgin Islands and Puerto Rico. We are the fourth largest specialty pharmacy in the country, but the only one that is totally independent.

We earn all of our business. Our job is to earn every script that we get. We are focused on taking good care of patients and on high-touch, high-cost medications that need special handling. That is where we excel.

While there are big pharmacies out there, Diplomat is one of the top distributors of oncology drugs because oncologists and pharmaceutical manufacturers feel that we deliver higher-touch care than a big-box pharmacy.

We had a 99% patient satisfaction rate in the past year and a 94% satisfaction rate among prescribers. That speaks volumes.

What are the differences between a specialty pharmacy and a traditional pharmacy?

Mr. Michaels: Patients with diabetes, hypertension, and arthritis usually go to the corner drugstore to get their medicine. But for patients with chronic, complex illnesses like cancer, multiple sclerosis, cystic fibrosis, or hepatitis C, the journey is different. For the most part, you can't go to the corner drugstore and pick up oncology meds. They cost up to

$12,000 a month. They're not sitting on a shelf in the corner drugstore.

These medicines also require special handling. Dosing is complex. There are some that are injectables. Some have a lot of side effects that need to be managed. Patients need to be coached on why they're on the drug, how to take the drug, and who to call to help them navigate and manage side effects.

How do you believe Diplomat differs from other specialty pharmacies?

Mr. Michaels: The level of touch and care we provide to our patients. We're a nimble, not one-size-fits-all organization. These drugs are high efficacy, but often high side effects. We counsel patients about side effects before we ship medications.

We provide a CarePak customized to the patient with a tip card on how to manage side effects. We'll also include information about over-the-counter products that can help them, such as Imodium for diarrhea, cream, or sun block. We also have a 24-hour pharmacist and nurse on board so that if you have problems and your provider isn't available, we'll help you navigate any problems. We detail for the patient and caregiver which medicine they're supposed to take on which day so that they can be compliant.

With the CarePak, we've found that patients move from an average of eight and a half months of therapy to over 10.5 months of therapy. We help them stay compliant for an extra two months.

Do you offer any other kinds of support for patients?

Mr. Michaels: We work with manufacturers when we know certain drugs will cause certain side effects. One company had a drug that caused

stomatitis, or mouth sores, among other side effects. When we looked at our data we saw that the average patient only stayed on this drug for about 168 days. We felt patients could benefit by staying on therapy longer, so we looked for a way to help patients navigate these side effects.

We contacted the manufacturer and talked to them about our patient coaching on proper mouth hygiene and foods to avoid, only to discover that our average of 168 days was 100 days better than their own average fill rate. We made some additional changes and today our average fill rate for that medication is 258 days; the manufacturer's fill rate is still below 100.

The high-touch coaching and hand-holding that we do really makes a difference in patients' quality of life and their ability to stay on a medicine that is helping them.

But the biggest side effect patients face is the impact on their pocketbook. We have a strong funding department that does the legwork to obtain funding from third parties on behalf of our patients. Last year, our oncology patients had an average copay of $704. With the assistance of our dedicated funding team, we were able to lower that copay down to $7.22. Oncology patients with traditional insurance had an average copay of over $277. After we applied copay cards, we brought that down to about $21.

What other financial assistance programs do you offer?

Mr. Michaels: When we initially reach out to patients, we look at their copay amounts. We advocate on their behalf to enroll them in copay assistance programs, whether that is through a manufacturer copay card or a 501(c)(3) nonprofit organization.

You reach out to patients? You don't wait for the patient to ask you about potential financial assistance?

Mr. Michaels: Patients are already going through enough. We make sure we're upfront with any information so they don't have to actually say there is a financial hardship.

We build a packet on behalf of the patient that includes, among other things, proof of income, IRS statements, Social Security award letters, diagnosis, and chart notes from the prescriber. We then submit the application to the nonprofit on behalf of the patient. We call them back, sometimes the same day, to tell them if they've been awarded any money to help pay out-of-pocket expenses for their therapy.

Funds available wax and wane. If a patient has access to a manufacturer copay card, we use that before applying to a nonprofit. We also look for state programs that may be available.

But in prostate cancer particularly, funds come and go. A lot of organizations don't consider veterans' benefits. We may find there are no funds in the foundations, but a patient may qualify for a veterans benefit so that they don't pay out-of-pocket.

We also advocate on behalf of uninsured patients. We work closely with the manufacturer Patient Assitance Programs to ensure our patients receive the treatment they need.

Last year, we secured $71 million in third-party copay support. Forty-eight million of that was from foundation support and $23 million from commercial programs. We had hundreds of patients use Patient Assistance Programs to get support beyond that.

Which foundations do you work with?

Mr. Michaels: We work with various foundations. We also work with patient advocacy groups. We have a catalog of foundations and track them daily to see who is open and who is closed. We have to be on top of it.

If a man reading this is interested in using your specialty pharmacy, what would he do? Ask his doctor or approach you directly?

Mr. Michaels: He can do either. Typically, it is the patient's provider sending the prescription, along with the patient's insurance and clinical notes, which we can use to determine the patient's needs and direct him to the most appropriate resources. If a patient just has questions, he can certainly contact us directly through our main line here at Diplomat.

Is there anything else you think is important for patients to know about specialty pharmacies?

Mr. Michaels: Specialty pharmacies are very different from traditional or retail pharmacies. This isn't like getting an antibiotic at your local pharmacy. As a specialty pharmacy, we really position ourselves to be an extension of your main provider. We're tied intimately with your providers and their nurses to make sure that there is a strong continuum.

Some people use a pharmacy listed on the back of their insurance card because they think they have to. But you are the customer. You need to advocate for yourself. If you're not getting the service that you want or deserve, there are alternatives. Pp1

XTANDI takes on advanced prostate cancer while you take on what matters to you.

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.

FIND OUT HOW YOU CAN FIGHT BACK.

Talk to your doctor and visit XTANDI.com/info

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.

QUESTIONS ABOUT XTANDI? | **Call 1-855-8XTANDI (1-855-898-2634)**

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What is XTANDI?

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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.

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- 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.

What are the ingredients in XTANDI?

Active ingredient: enzalutamide

Inactive ingredients: caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, black iron oxide

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Marketed by:
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Medivation Inc., San Francisco, CA 94105
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WHAT IS ZYTIGA® (abiraterone acetate)**?**

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.

IMPORTANT SAFETY INFORMATION

Who should not take ZYTIGA® (abiraterone acetate)?

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.

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

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®?")**
- Take any other medicines, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ZYTIGA® can interact with many other medicines.

If you are taking ZYTIGA®:

- Take ZYTIGA® and prednisone exactly as your healthcare provider tells you.
- Take your prescribed dose of ZYTIGA® one 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 to 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.
- 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).**

He spent 35 years fighting dangerous fires.

RETIREMENT WON'T CHANGE WHO HE IS.
NEITHER WILL
ADVANCED PROSTATE CANCER.*

IF YOU THINK YOUR TREATMENT OPTIONS ARE LIMITED, THINK AGAIN.

***ZYTIGA® is a prescription medicine used along with prednisone to treat metastatic castration-resistant prostate cancer, a type of advanced prostate cancer that is resistant to medical (eg, hormonal) or surgical treatments that lower testosterone and has spread to other parts of the body.**

...talk to your doctor to see if ZYTIGA® is right for you.

once-daily

Zytiga®
(abiraterone acetate)
250 mg tablets

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

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

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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800 Ridgeview Drive
Horsham, PA 19044 USA

 08/16 038767-160817

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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Coming Up!

March
Using Genomics to Guide Treatment

April
Bone Metastases

May
Collaborations for a Cure

June
Prevention and Screening