Risk Stratfiied Treatment and Active Surveillance in Prostate Cancer

Should you opt for active surveillance when diagnosed with prostate cancer or Does your PSA test warrant more aggressive therapy instead? Tune in to hear Dr.Matthew Cooperberg's views on the controversial PSA testing and hear him talk about treatments based on risk assessment being the need of the hour. "

Full Transcript:

Priya Menon : Hello, everyone and welcome to the Cure Panel Talk Show on prostate cancer. I am Priya Menon, Scientific Media Editor at Cure Talk and along with the Cure Talk team of Sharib Khan and Chintan Patel, I welcome all of you this evening to a discussion on prostate cancer. We will be moderating the call and bringing people live on the show.

This is the eighth episode of the Cure Panel Talk Show and first Cure Panel discussion on prostate cancer. Our panel discussion broadcasts have received over 29,000 new listens until date. Today's panel is very unique. While I am calling in from India where its already the 29th around 3:30 a.m. in the morning, our co-host Dan Zenka, Senior Vice-President – Communications, Prostate Cancer Foundation, has called in from California. Dan was diagnosed with prostate cancer in 2010 at the age of 51 and you can follow Dan's prostate cancer experience on his personal blog MyNewYorkMinute. Welcome to the show, Dan!

On the panel we have Terry Herbert, calling in from Australia. Terry is a prostate cancer survivor who has been on active surveillance for over 10 years. He is also the Founder of the website Yananow or "You are not alone now." We have Dan Hennessey calling in from Canada. Dan is a prostate cancer survivor and author of With The Snap Of A Glove, which outlines Dan's prostate cancer journey. Gary Petersen, Editor, myelomasurvival.com has called in from Florida. Gary is a multiple myeloma survivor and part of our Myeloma Cure Panel.

A hearty welcome to all the panelists. The expert on the panel is Dr. Matthew Cooperberg, Assistant Professor of Urology, UCSF Helen Diller Family, Comprehensive Cancer Center, California. Dr. Cooperberg, on behalf of the Cure Talk team, I welcome you to the Cure Panel Talk Show.

All the listeners of the Cure Panel Talk Show on prostate cancer, I would like to read out a couple of things which will make your Cure Panel experience smooth. If you are listening in to the panel through your phone as well as a computer, please mute or stop the online broadcast on your computer for better audio quality. Callers will be invited to ask questions at the end of the discussion. You can let us know by pressing 1 on the keypad and we will bring them online live.

The topic for today's discussion is risk stratified treatment and active surveillance in prostate cancer. I invite Dan Zenka to talk about, tell us all about the Prostate Cancer Foundation and his experience with prostate cancer. Dan, you are on air now.

Dank Zenka : Okay, thank you, Priya. Ahh… The Prostate Cancer Foundation was founded in 1993, when there was very little research for prostate cancer going on. Since then, we have raised 530 million dollars to fund innovative research to find the diagnostics and treatments for advanced prostate cancer. As the result, we are very pleased and very proud to say that the death rate currently is 40% less than what was once predicted. Ironically, after being here with prostate cancer for two years, I was diagnosed with my own case. It appeared at that time that it was an aggressive genotype of cancer. I underwent a radical prostatectomy and the postsurgical pathology showed that the cancer had spread to my lymph system. So, I

then had seven weeks of IMRT or radiation therapy and two years of androgen deprivation treatments, which I am just coming off of at this point. So, I shared a lot of that on my blog MyNewYorkMinute.

At this point, though, it is my great honour to once again introduce Dr. Matthew Cooperberg. He is a distinguished physician scientist in addition to the credentials you mentioned. He earned his Doctorate in Medicine and his Masters in Public Health from Yale University; and we are very proud to say that in 2011, he was the recipient of a TCS Young Investigator Award, which is a three-year award, specifically designated for a young investigator, investigating a specific area of prostate cancer. At this point, Dr. Cooperberg, I would like to invite you to do an introduction, provide an introduction to the topic of risk stratified treatment and active surveillance.

Dr. Cooperberg : Sure. Thank you very much to both Priya and Dan for the invitation to speak today and I would really stress it really has been a tremendous honor to work with Prostate Cancer Foundation and really express my gratitude for my own career and on behalf of all of us at UCSF and elsewhere for the support that the organization has given us over the years and really it has made a tremendous difference for men diagnosed with the disease around the world. At this dimension, the very good news in prostate cancer is that since the start of the PSA screening era in the 1990s, we have seen a drop in mortality rates for this disease of actually more than 40% by the most recent data and this is not just the percentage of men who die with it, this is the age-adjusted population rate at the sort of highest at the immunologic viewpoint and this is the time when men are living longer. They are dying less of cardiac disease. If anything, there should be more a risk of prostate cancer mortality and yet we have seen the steady inexorable decline in mortality rates. So, this is a tremendous victory by any account. What exactly explains it remains pretty controversial, but the best analyses suggest that it is a combination of both early detection with PSA and better treatments, improvements in surgery, radiation therapy, medical therapy, etc.

So, how did we wind up from, you know, like you said, very good news with respect to prostate cancer , how did we wind up going from there to the decision by The US Preventive Services Task Force in 2012, recommend against PSA screening and you know, we should remember that that was not a recommendation to only screen some men or to screen for high-grade prostate cancer or to screen selectively. The recommendation was to screen nobody ever and I think it reflects a real disconnect between the way we think about the disease from the screening perspective and the epidemiologist's perspective and the way it actually has been managed in the US and the problem is that prostate cancer kills more men than any cancer except lung cancer and that is still true despite the improvement in mortality rates. However, its actually a small minority of men diagnosed with the disease who actually die of it.

Prostate cancer is extraordinarily common, even more than the published numbers would really suggest, you know. There are over 200,000 men who are diagnosed with the disease every year in the United States alone, but the actual prevalence is even higher. If you look at men who die in car crashes and things in their 30s and we do an autopsy and look hard enough, we can find a couple of cancer cells in about 30% of men. You are into your 50s, its about 50%. You are into your 80s and its just about everybody will have a couple of abnormal-looking cells on their prostate if we look hard enough and of course, most of these would never go on because any symptoms or any loss of life or any threat having ever been diagnosed and many of them frankly probably shouldn't be called cancer because they don't behave like what we think of a cancer doing in the body.

So, our challenge has really been separating out which ones need treatment and you know, which ones we can treat and continue to push the mortality down while avoiding over diagnosis and subsequent overtreatment for the many, many men with low-risk prostate cancer and we have changed the nature of the disease because of screening. You know before the PSA screening era really took off and got underway, prostate cancer was often found at late stage. It would show up with symptoms of either urinary obstruction or ureteral obstruction or bone pain and the majority of prostate cancers that were identified either were already advanced and incurable or had fairly high-risk disease characteristics. I will get into more later as to what that really means to be high risk.

Over the years, prostate cancer has become much more common because its found more in them, but we have also seen this profound risk migration so that whereas before ’99, almost a quarter of prostate cancers were advanced to metastatic at time of diagnosis, now that number is about 2% to 4% depending on which series you look at and nearly half of all men diagnosed with prostate cancer have low risk, relatively indolent tumors, which on many occasions again would never cause any problems have we not gone looking for them. And again, the challenge for us at the treating community is figuring out which ones need to be treated and which ones don’t and its actually, you’ll sometimes hear, especially those who are close to screening make the statements that we can’t tell which ones need to be treated from which ones don’t need to be treated. That’s simply not true and there are a number of clinical parameters that we can look at to try to identify which prostate cancers are more aggressive and which are not.

The first is actually again the PSA and PSA is controversial as a screening test for prostate cancer but is actually a very good tool for risk stratifying cancer once it has been diagnosed. We like to see the PSAs under 10, even more to see them under 6 and those are the ones we consider relatively low risk PSAs in the 10 to 20 range or intermediate, over 20 we start to think of that as somewhat higher risk and of course men who have advanced disease can have PSAs in the hundreds and thousands and actually if you look, speaking of which if you look at an unscreened population, a relatively unscreened population, you see a pattern which looks very much like the US used to look. We have had this fascinating collaboration with database in Japan which is still a relatively unscreened population, though things are changing there with respect to screening and its a completely different story, a completely different situation. Most men there are still diagnosed with advanced prostate cancer with PSAs in the hundreds and thousands. So, PSA is the first risk factor.

The second is the Gleason’s score and that is a measure of how the cells look under the microscope. When a prostate biopsy is done and the pathologists look at the tissue, they determine whether or not there is cancer and then if there is, they assign a grade and that’s called the Gleason grade. The Gleason grading system is a 1 to 5 grading system, but the standards have changed over time, so the patterns 1 or 2 really don’t exist any more, so pragmatically pattern 3 is relatively low grade, nonaggressive. Pattern 4 is intermediate and then pattern 5 is high grade, more aggressive. But, prostate cancer can be heterogeneous even with indicative prostate and with indicative tumor and in many cases what we will see is a combination of patterns. We might see a tumor that’s mostly pattern 3 with a little bit of pattern 4, that gets called a 3 + 4. Others will be mostly 4 with a little bit of 3, that gets called 4 + 3. So, you will often hear a Gleason’s score or Gleason’s sum reportedly, Gleason’s 6 or Gleason’s 7 and that’s, you know, summing the Gleason like that is that gives some information, but it also loses lot of the detail because there is a big different between the 4 + 3’s and 3 + 4’s. We think when we see these tumors where the primary pattern is 4 or 5, those are the ones that seem to be more aggressive. Conversely, we are starting to realize that there are many prostate cancers which have just a little bit of pattern 4, so 3 + 4’s where only 5% is cancer, for example is pattern 4. Those often behave very much like 3 + 3’s, the truly low grade ones.

And then, finally, there are so, we have got the PSA, the Gleason’s score, and then there are measures of how much cancer is in the prostate, so you can look at stage which is just whether we can feel the tumor on additional exam or whether we can see it on an ultrasound or an MR and better than that, a better prostate for tumor volume is how much cancer there is on biopsy. So, if we take a systematic biopsy of the prostate and take 10, 12, 14 cores, how many of those have cancer and how much of the tissue is actually involved with the cancer. So, we can put those parameters together, things like the stage, the grade, and the PSA and group the patients into low, intermediate, high risk groups or we can go one step better and use a multivariable model to really try to give a better or more accurate estimate of where again the patient falls on the risk spectrum and there are many, many ways to do this. Perhaps the best known are the nomograms and there are tables, there are nomograms, there are multivariable risk grouping systems and there is a common, for anyone familiar with this field, there is a common misnomer actually which calls any multivariable model a nomogram. Now, the nomogram is really just a graphical representation of a model which statistically combines these different parameters – the PSA, the Gleason’s score, etc., and one way to summarize that information is with a graphical illustration, that’s the best nomogram. You could also do this as a series of lookup tables like the Partin tables. At UCSF, we developed the CAPRA Score, which is the

Cancer of the Prostate Risk Assessment Score, a number of years ago. This has now been validated in tens to thousands of patients around the world in four to five continents and again this combines the PSA, the Gleason's score, and the extent of biopsy involvement to give a 1:10 score, which is the risk stratification, which can predict prostate cancer outcomes with high reproducibility and reliability and does so across treatments, across surgery, radiation therapy, and can predict both whether the cancer will come back after primary treatment and also give an estimation of what the risk that the patient will actually die of disease.

Now, instruments like this, the CAPRA score, nomograms, etc., have about a 70% to 75% accuracy rate depending on which specific cohorts you are looking at and that's not bad in the spectrum of things. Of course, we are always pushing to do better and the whole rapidly evolving field of biomarkers for prostate cancer is really intended to improve the accuracy. There was actually this story in the New York Times about this yesterday, looking at the rapidly, really fairly rapidly evolving field of biomarkers intended to improve risk stratification for prostate cancer, but the fact of the matter again is that we can do pretty well with the current state of the art. We can identify with above 75% accuracy which tumors are low risk and which tumors are high risk. The problem is that we have not done a very good job as a treating community in targeting treatments to the men who are most likely to benefit from treatment.

So, we have a number of studies now, not randomized trials, but a number of studies looking at surgery versus radiation therapy versus other interventions and we do have few randomized trials looking at surgery versus no treatment for men with prostate cancer and it turns out if you look at the Scandinavian trial which came out originally in 2002 and was updated in 2011 or more recently the Tibet trial from the UCSF VA population that men with low-risk prostate cancer in many cases do not need treatment and they are no more or less likely to live a full life if they are treated or if they are not treated. Conversely, men with high-risk disease benefit tremendously from early treatment and are much more likely to die of prostate cancer if they are not treated. It is worth remembering that this is often not… Its not the best way to go. Its a slow painful process, dying of prostate cancer and there are, you know, many endpoints that we seek to avoid in treating prostate cancer besides simply lowering the death rate. But, again, if you look at the practice pattern across the US, we have not really targeted treatments in the right way. We tend to overuse treatment for low-risk disease and we under use treatment for high-risk disease. There are a number of studies suggesting we should be using more surgery for high-risk disease, often as multi-level therapy. Many men with high-risk prostate cancer should get surgery and radiation therapy and systemic therapy and frankly this is no different from breast cancer, rectal cancer, or other cancers, where we have known for many years that this is the answer and yet in prostate cancer, we still tend to have these debates about surgery versus radiation, focusing on low-risk disease where the question is really about quality of life, which brings me to the point of an active surveillance.

So, active surveillance, we are increasingly recognizing is an answer, if not the best answer, for many men with low-risk disease and what this implies is that we can look at these criteria, the PSA, the Gleason's score, etc., and predict with reasonably good accuracy which prostate cancers are unlikely to progress in the near term and what we can now tell men, we have nearly 1200 men that have gone down this pathway at UCSF and if you look across the various cohorts that have been published now, many thousands, seven or eight thousand at least. We can predict with it which men are likely to need treatment within the first three to five years. This is different from watchful waiting, which is an older concept where one would say you have got a low-risk prostate cancer, but you also have heart disease and other problems, go home, don't worry about this. We can give you hormonal therapy if you get symptoms of an advancing cancer in the future. Active surveillance is different. It entails a recognition that most of these cancers don't progress but some do and that if we see any signs of early progression, which we will detect with serial PSA assessments and repeat biopsies, we can intervene at that point with surgery, radiation, standard treatments with every intention of cure and, you know, our growing experience in the US and Europe and elsewhere really suggest that this is in most cases quite safe and a very effective way of avoiding the potential side effects of surgery and radiation and other treatments for men with low-risk prostate cancer, who again never really would have known that they have the disease had we not gone looking for it.
Active surveillance remains relatively underused in the United States. Most publications would suggest under

10% of men with prostate cancer and even when you look at older men with low-risk prostate cancer who are almost certainly going to die of something else long before prostate cancer. Even in that situation, only about 25% of them are managed with active surveillance, most are treated. There are many reasons for this and many incentives in the US and elsewhere that favor treatment rather than the surveillance, but as I said I think we are increasingly realizing that this is the preferred initial strategy and we need to do better with risk stratification. We do need to push the field for biomarkers to really try to determine which prostate cancers look low risk but might progress in the future versus which are so indolent, not only at the clinical level but also at the genetic level that we really should not call them cancer and we are rapidly making progress toward that goal and our hope is that we can continue to reduce prostate cancer mortality rates while simultaneously reducing the morbidity that we have caused from overtreatment of low-risk disease and I think if we can do that, then the screening debate really evaporates and, you know, whether that message will then actually reach the preventive services task force, I don't know, but I think that, you know, that goal continuing to reduce mortality while continuing to abate overtreatment rates really needs to be the over-arching theme for ongoing research and progress in clinical management for localized prostate cancer for the coming future.

Dan Zenka : And thank you, Dr. Cooperberg, for that very comprehensive overview. Before we continue with the panel some of the discussion, I would like to ask our panelist, Terry Herbert, Dan Hennessey, and Gary Petersen to tell us a little bit about their own personal journeys with prostate cancer. Why don't we start with you, Terry?

Terry Herbert : All right. Well, I am a 16-year survivor. I was 54 years of age when I was diagnosed in 1996. Even then I had to log on to the internet soon after I was diagnosed and discovered that even then concern was being placed about unnecessary treatment of men who had been diagnosed with variants of the disease that were largely to be indolent. Doctors were already saying that far too many men who were having therapies that provided no benefit but literally associated with a loss of quality of life. So, I chose not to have invasive therapy despite the advice of the doctors I consulted in Australia, the US, and South Africa where I was living at the time. Part of my active surveillance as I thought it was then was to have in 2007 the radiologist highlighted as the cancer lesion. Since my PSA was then 42, I reluctantly met the oncologist who advised to start intermittent ADT, androgen deprivation therapy. My latest PSA is 16. To try and help other men through this process, I established a website back in 1998 which provides basic information to newly diagnosed men and collectively shares the experience of men who had been diagnosed with cancer. We have now got over a thousand stories on that from the survivors. We get 300,000 visitors a year and you can search the stories by diagnosis so you can find a matching story to your diagnosis.

Dan Zenka : That sounds like an excellent service. Thank you for creating that and certainly thank you for talking about your experiences. I still believe many men, too many men, don't talk about their prostate cancer. Dan Hennessey, how about your journey?

Dan Hennessey : Hey, thanks, Dan. Thanks very much. This certainly proves the fact that prostate cancer is not a Canadian or a United States issue. It actually is a global men's health issue and I am certainly honored to be part of this. I started my journey with prostate cancer in 2007 at the early age of 49. After urging from my wife to go get checked, I finally listened to my wife, which most of us don't do and had the test and in fact it came back that it was positive. I had a Gleason's score of 6 and after the biopsy, they felt that it was probably T2 prostate cancer. My urologist at the time considered my age and my activity. I had a young child. They felt that radical prostatectomy was the avenue to pursue, which I went through in 2007, followed up with 35 radiation treatments because when the surgery was performed, there was a sense that it may actually have moved to a T3 length of prostate cancer, so just wanted to make sure and that was seven years ago and my PSA is tested quite often and its undetectable and, you know, it's certainly an ongoing journey. I have had a couple of other surgeries to offset some of the potential side effects on the incontinence aspect, one actually as early as three weeks ago and so, it is a constant journey, a constant battle. It's a life-changing event, but it's certainly one that all men need to be aware of and it has to be something that everybody feels comfortable in talking of it.

Dan_Zenka : Right, and any cancer, prostate cancer or others, are certainly life-changing events. Gary Petersen, you are not a prostate cancer survivor, but you are a myeloma survivor. Can you tell us about your story?

Gary_Petersen : Yes. Actually, Priya asked me to participate in this and I urgently thought that, you know, there is probably a lot of other people who might be better. However, I think that the people who have stage IV prostate cancer are the ones that I am probably most similar to because they have a five-year life expectancy of 27%. When I started out with dialysis-dependent kidney failure, they had indicated that I had a three-month life expectancy and so here I am seven years later and still kicking after two stem cell transplants, but I do have cancer and I do have a prostate, but that's about as far as I can go as being eligible to participate, but as I went through it I had thought that, you know, there are some similarities at least in the stage IV and I was just shocked to find out that end-stage IV cancer, that there's twice as many people who die than with multiple myeloma, which is incurable. As a matter of fact, the five-year survival rate for multiple myeloma is like 37% and so, you know, I did some research on it and I had a few questions for the doctor, which would help to satisfy some of my questions with regard to it because ultimately they say everybody will end up with some level, just like the doctor had said.

Gary : So, that's kind of the, you know, the angle that I am coming from.

Dan Z : Okay

Gary : And I think where the stage IV guys, they are in the same situation that I was. Its that there is just no data out there as to who is good and who is not good at treating. Right. Right. stage IV prostate cancer, at least I haven't found.
Dan Z: Okay. Well, thank you, Gary, for sharing that. I will start the question. Dr. Cooper, you did touch upon… Dr. Cooperberg, sorry. You did touch upon the problem of overtreatment. You know, I hear numbers in the US alone, we spent two billion dollars in overtreatment. This week alone I heard one that was more than four times that amount. Its a real question. Patients hear the "cancer" and they panic and, you know, the first reaction is often I want this out of me. PSA test, I believe its one of the best tools we have today. I believe that saved my life and will continue to check my disease, but what new tools are coming down the line that will give patients perhaps greater surety as they say, okay, I am comfortable with pursuing active surveillance or I am okay with this mid-level treatment.

Dr. Cooperberg : So, there's a number of things in the pipeline and I think the first point though is to stress again that we are not bad already with the clinical information. The problem is we don't use it consistently. And, like I mentioned, there are a number of incentives, non-medical incentives, lined up against surveillance in favor of treatment, but there are a personal phenomenon, the psychological phenomenon, associated with the "C" word and with cancer diagnosis is a huge part of the problem and, you know, that's really our fault as the entire medical profession from pathology to urology to oncology, we use the same word "cancer" for a tremendous spectrum of biology, ranging at the one side to pancreatic cancer and much more aggressive malignancies where people really do have months to live and prostate is at the absolute other end of the spectrum where most people diagnosed literally would have decades to live, even doing nothing about it, not even surveillance and then even within prostate cancer, there is tremendous heterogeneity of, you know, of behavior and biology. So, men with what looks like low-risk prostate cancer, you know, we again can say with pretty good accuracy today what the behavior is likely to be at least in the next few years.

Now, there's a number of tests in late stage development, genetic tests that can be run on prostate tissue, a variety of tests that can be run on void samples or urine samples, and Novel imaging tests, things like functional MRI, MR spectroscopy, Novel PET tracers. There's a whole, you know, emerging field in biomarker development and these tools will all help. I mean none of them is going to be the sober bullet by themselves and none is going to give you a green light, red light. This needs to be treated, this one doesn't and one of the unanswered questions for all this is, like I said, I can tell you with 75% accuracy today how this is going to behave. If I can tell you with 90% accuracy how this is going to behave, would that make the

difference? Would that convince people that they do or do not need treatment and we don't really know the answer. We actually just got a large grant from the department of defense to actually ask exactly that question, to build a very comprehensive risk model that will incorporate genetic information, lifestyle information like diet and smoking. Two different genetic assays on the tumor. genomics really help with a truly personalized risk assessment that we will be able to give every patient that comes to UCSF, but the whole second part of the project is figuring out how this will actually change decision making. Will this actually result in more men being comfortable with surveillance and avoiding treatment and we don't really know the answers to that yet. Really more tools in the box.

Dan Z. : Its very complex and we know there are about 27+ varieties of this disease. That's something most patients don't understand… Correct…. as they enter into their journeys.

Dan Z. : Right. Terry, do you have a question for Dr. Cooperberg?

Terry Herbert : Well, my first question was along the lines that we covered pretty well with Dr. Cooperberg's pattern, was that doctor has been saying for years that we should call the low risk prostate cancer something else… Yes. …and his most recent letter, open letter, he suggests that we should call it prostatic tubular neogenesis because none of the words we use – tumor, cancer, or malignant – really apply to low risk prostate cancer (yeah) and he says we should about calling it potentially malignant. Now, I wonder because that's what leads to a great movement like the Gleason migration which follows when they decide that Gleason 2's were no longer to be. If we call this as something else, would we find more people with malignant disease, whether that would go up 7b and 8's?

Dr. Cooperberg : Yeah. Look, I am aware that there is this controversy and there have been a lot of labels proposed out there. Ian Thompson at UT Southwestern and Laura Esserman who is a breast surgeon wrote a terrific editorial a couple of years ago post the term idle tumor. Other people, you know, in bladder cancer we have something called a papillary urothelial neoplasm of unclear malignant potential and there's a lot of these suggestions out there. I personally am in support of, I think, that a change in nomenclature would be very beneficial, that you call these low-grade ones something else that would imply that it needs surveillance but avoid using the word "cancer." However, you know, that requires a tremendous consensus among not just urologists but oncologists, pathologists, policy makers. It changes, you know… There is an incredible amount of inertia against that sort of a change. I think it may be a direction that we will eventually head as we get these markers online, but I can tell you that not only do all the clinical features look low risk but so do the genetics. Maybe that's what it will take to start changing these changes. Jonathan Epstein who is one of the best known prostate pathologists at John Hopkins, just had an editorial out in the journal "Clinical Oncology" at the end of last year, addressing this question and they were talking about a change in the way we think about the Gleason's scores. They stop short of suggesting that we stop calling the lowest grade 1 cancer, but they are raising these issues. Now, that is the title of the editorial and its "Should we be calling Gleason's 6 cancer?"

Dan Z. : Oh! We have been touched upon about that thing, you know, how can we take the C arm cancer, the big C?

Right. Dan Hennessey, what have you got for Dr. Cooperberg?

Dan H. : Well, I know in Canada the elephant in the room has become the word "PSA" and I know this is an issue that we are trying to encourage men to talk about. We are trying to raise awareness and then all of a sudden the word "PSA" becomes like the mark of death and its not something that people should look at. Its not something and it has a very negative connotation that I developed a video to hopefully empower our young people to take an active role in raising awareness by talking to the men in their lives – fathers, sons, uncles, grandfathers and encourage them to talk to their doctor and the urologist that actually took part in it, gave a call of action at the end of the video and mentioned the word "PSA" and a governing body here on the East Coast of Canada, Canada Care Nova Scotia, all of a sudden put a stop to the video going into the high schools which was the audience that was intended because of the word PSA and all of the controversy

around PSA. Now, let's face it. PSA is a test. It's not a be-all end-all as you have mentioned, but it will give you an indicator of the abnormalities in the prostate. So, I guess the question I have is why are we putting this elephant in the room when it is a proven test to give us at least some parameters at the starting point to start the investigative aspect of dealing with prostate cancer.

Dr. Cooperberg : And the answer to that question is honestly probably more political than it is scientific and its sad and I need to, you know, I can talk for hours on this subject and I want to get too far into the weeds, but the study compliments, you know, there has always been some controversy across different guideline bodies as to what the recommendations are. The urological societies and the cancer societies generally have been supportive. The internal medicine society is intended to be a little bit more cautious and the US preventive services task force who, for better or worse, are perceived as the gold standard have always been either slightly hostile or neutral and they generally have not made a strong statement in one direction or another. In 2009, they came out with the recommendation of an "I" which is indeterminate except for men over 75 for whom they recommended broadly against screening. I think it is important to recognize who is on that panel. These are some respected epidemiologists who have had, you know, very successful careers in internal medicine, looking at things like vaccination policy, things like, you know, cardiac disease. There's not an oncologist to be found and, you know, quite honestly you can look at the entire membership of the task force with one exception they have never published in prostate cancer and if you read their evidence study, evidence or view, it is a deeply, deeply slow document and truthfully at the end of the day, they do not understand the data to the depth that is required and what it really comes down to are two large trials done, one in the United States and one in Europe, the PLCO and the ERSPC, and these studies are frequently cited as providing contradictory evidence with respect to the benefits of screening and this is just simply not true. So, you know, again staying very brief about this, the American trial which is the PLCO, intended to randomize men to have PSA screening versus no PSA screening. The problem is there were so many logistical problems getting the study off the ground. By the time it actually launched, PSA screening had become incredibly prevalent in the United States and if you look at the final analyses, in some of these…, you know, unfortunately people tend to only read the abstract of the original paper or they only read the New York Times headline. If you actually read some of the secondary papers and, you know, some of the details here, 79% of the men that were supposed to be in the control arm actually got their PSA checked at least once in the PLCO trial. So, the only thing the PLCO trial tells us is getting your PSA checked every year for six years is no better than getting it checked sometimes when you happen to show up at your primary care doctor's office and that's certainly true, but the PLCO trial tells us absolutely nothing about whether PSA versus no PSA is beneficial. These are statements made by the authors of the PLCO trials, not a controversial statement.

Now, the European trial when it was originally published in 2009, these papers came out with the same issues in internal medicine in 2009. The European trial showed that you had about a 20% to 30% reduction in prostate cancer mortality depending on some of the statistical adjustments that they made, but, you know, in the initial report, they were predicting mortality events up to 11 years after screening and the numbers that have re-picked up on there were that you had to screen 1400 men and treat 48 to save one life. Now, that's to save one life at 9 to 11 years of followup and if you are screening a 50-year-old man, 9 or 11 years of followup is not in any way the relevant time frame. This is one of the big challenges in prostate cancer, is we screen men decades before they would essentially die of the disease. Because of the nature of the disease if you wait until you know you have it, its far too late to cure it, but that means that you need literally decades of followup to make meaningful statements and there have been some very, very careful extrapolations from the ERPC data that suggests that if you project four over the course of the man's lifetime the number you need to treat actually falls substantially, something like 6:1.

Then, actually, there is a Swedish study too which gets less that shows a number needed to manage, not necessarily treat everybody, of about 12:1. So, again, now recognize that those were still treating a lot of, you know, a lot of people to avoid one death. That's even 6:1 means we treated five men who didn't need it, but you have to recognize that that compares to just about anything else that we do in preventive medicine, whether we are talking about cholesterol management, mammography, what have you. So, you know, at the end of the day, you have got a very heterogeneous primary care provider. Just don't forget its

not urologist that decides whether or not the man gets a PSA check in most cases, its the primary care doctors. They hear contradictory evidence and they hear different things from different guideline organizations and for better or worse, the preventive services task force has the perception, they have the implementary of the government and they are perceived as being the most objective. I actually believe that they are not, but they have the sort of stamp of governmental approval, so lot of primary care doctors just sort of assume that they are correct and rates of screening are falling and its a problem because it's completely You know, we screen… So, I mentioned that we don't treat very reliably according to risk. We also don't necessarily screen the right people. There is a great study that came out from the VA population a couple of years ago, looking at screening rates for older men in the VA and if you look at men in their 70s in the VA population and this is not the healthiest population in the United States. These are the veterans, most of who have multiple medical problems in this system. You know, the rates of screening for men in their 70s was around 60%, but the healthiest men were a little bit more lucky to screen than the least healthy men. When you get up to men who are over 85 and most of us will say that the only time we should check a PSA in an 85-year-old is if both his parents bring him to the exam.

(Laughter)..You will see 30% screening rates and what's worse is among those men over 85, the men who are most likely to get screened were the ones who had the most co-morbidities, you know the men who had the most heart disease, lung disease, etc., because basically their doctor is just checking a box and every time they come in, they get 50 lab tests and the PSA is one of them. That's not the right way to use PSA screening. We should be screening young men, healthy men and screening less frequently. If you get it, there's another yard. Again, I don't want to just get in studies, but another great study from Sweden, this is actually a terrific study where they looked at men in the city of Sweden who in 1981, long before PSA was on anybody's horizon, they just drew blood on these men and stuck in the freezer and the men who went on and lived out their lives. About 3% of them have actually died of prostate cancer and they went back years later, once PSA was broadly available, and they ran PSAs on at least our tidal blood specimens. It turned out that if you had a PSA of less then 1 at age 60 and never had another PSA screening for the rest of your life, that predicted that your likelihood of dying of prostate cancer was infinitesimally low and that's just for the single screen. So, you know, we should be screening men at a young age, screening less often. For the men that have low PSAs, they should not necessarily get a PSA every year, but we should be screening because there are men that have aggressive prostate cancers which start young and by the time they show up, you know, they are in their mid 60s and get their first PSA check, its often too late. So, there's no question we should be using the test better and most importantly we should be targeting treatments appropriately to the right patients that have the higher risk tumors. So, you know, all of us in academic urology sort of have the same message. The problem is, you know, no specialists, you know, oncologists, urologists, not even specialist vital statisticians are invited to participate in these dialogs with the task force and so ultimately you get a lot of confusion in the public and primary care doctors either decide they are going to screen everybody or they don't screen nobody and increasingly its the latter and most men come in and specifically request a test. Its not even being discussed with them and I think that's a huge disservice.

Dan Z. : Okay. Thank you. Thank you, Dr. Cooperberg.

Dan Z. : Gary Petersen, do you have a question?

Gary : Yes, I do have and first and foremost, Dr. Cooperberg, Sir, certainly learned a lot from your presentation and I can also see that, you know, there is a heck of a lot of things yet to do and that you have got a real fight on you and it seems for something that seems so life saving and something that should be done and it doesn't seem to have, you know, that common acceptance by everybody, but there are a few things that I have noticed, one of which is that there are the four different stages of prostate cancer and the National Cancer Institute states that the five-year survival for the 93% of the people who are either I through III in the staging have words, which means that it hasn't reliable, basically 100%, but I think its fantastic and you guys have apparently come a long way to get to this point, but if it does metastasize the five-year rate is just 27.8%, which is really worse than the incurable cancer that I have.

Yeah.

And can't these cancers, you know, and you have talked a little bit about that, but I just… It also seems beyond understanding why, you know, you can't find these cancers before they get to the stage IV…

Right, right…. where, you know, people die.

Dr. Cooperberg : So, you know, I mean there's multiple reasons for that and so remember first of all if that rate does continue to fall, the proportion that you have incurable prostate cancer, but, I mean not all men get screened. Its only about 40% to 50%. You know, its a ball park guess of, you know, how many men actually get PSA test at some point in their lives. You know, many men never get a PSA test and they show up with or they get one relatively late and by the time the prostate cancer is found its incurable. Now, one point I will make about stage IV prostate cancer is that there is this incredible amount of progress being made here as well. We have gone from a situation where in 2004 we got the first chemotherapeutic, which is Taxotere, which had excellent survival benefit and from 2004 to 2010 really nothing happened and in the last three years we have gone from one effective drug to seven and that number is going to continue to increase very rapidly, so the many who have options of effective and very, very promising medications for men with advanced prostate cancer continues to grow all the time and this is a very exciting time for advanced prostate cancer as well, but obviously as you say, the best way to manage stage IV prostate cancer is to catch it before it gets to that point and I absolutely believe that if we used screening more effectively, you know, more broadly and more effectively, we can continue to drop that rate without increasing the overtreatment rates.

Dan Z. : Right. Thank you. Definitely use it more effectively. You know, as a stage IV patient myself, I say I have great confidence that, you know, if my PSA starts rising and then if I become treatment resistant, I see the next best thing there and the next best thing behind that, you know, any sequences and new combinations, so you know, from my perspective, I think that you just put it right and I think that if we get better at stratifying, even using the existing tools, in guiding men to proactive surveillance, they too should feel pretty confident, that is, they move out of proactive surveillance, that there is a lot of solutions and lot of very effective treatments for them.

Dr. Cooperberg : Absolutely. Well, and remember too that most men that move out of active surveillance, we expect to move to surgery or radiation, which we expect to be curative. You know, the number of men… So, that does bring up a good point that the million dollar question is always what are the odds that today we can cure this, next month or next year, it will be too late. Right? And that those odds are not zero, but they are extremely low. You know, we always we have to be careful that the number of men that will die of prostate cancer because they wanted surveillance instead of getting surgery or radiation is not zero, but its extremely low. Right. And we think the window of opportunity for cure is often probably measurable in years, if not decades.

Dan Z : Okay. Thank you. Priya, would you like to open up the call to questions from some of our listeners at this point?

Priya : Thank you, Dan. The person calling from 916-375, you may please ask your question now.

Caller : Hi! My name is Jeff McQuillan. I highly respect these panelists, particularly the Canadian fellow because I am formally from Montreal. Hello! Hello. I am starved for hockey but not to get more time. I also respect Dr. Cooperberg. I am a patient at UCSF and I was just diagnosed last week with a Gleason's 6, a PSA of 3.6. They have been tracking since 2009. Gleason's 6, as I mentioned, its focal, on the left side. I have decided to go with active surveillance with one of the young excellent urologists there. I had quite an experience, a wild time up here in the Sacramento Valley, where I had about four urologists when my PSA started to accelerate. Some of them wanted to do surgery immediately and I was not ready for the priesthood,
sorry for the pun. However, however, if this does begin to grow in me and the doctor wants to do treatment, I

am not sure surgery or radiation is what I would choose. Being a Berkeley graduate, I do tend to stretch from the letch. I push but due to the morbidity, I want to be realistic, particularly in respect to the doctors and you researchers, but I am really only looking at ablation. I wanted to ask particularly Dr. Cooperberg but others on the panel, hopefully if I could obtain ablation if this thing starts to grow.

Dr. Cooperberg : So, that is a great question and opens up a whole another realm of, you know, discussion and emerging possibilities in prostate cancer. I think, you know, there is a lot of interest in ablation and just for anyone who is not familiar with the idea there is why can't we just treat the tumor and leave the rest of the prostate alone, basically people talk a male lumpectomy or prostate lumpectomy or something similar to that and that the reason its difficult is that prostate cancers don't actually grow as lumps. You know, if you look at a kidney tumor, for example, its a little ball that grows on top of or inside the kidneys. You can see the ball very clearly on imaging. Prostate cancer tends to be more infiltrative. You get cancer cells right next to normal cells and many of them are not visible on imaging. So, the question is what one, you can ablate the entire prostate with things like cryotherapy or HIFU, but the side effects of those procedures are no better than surgery and brachytherapy and other things and I do want to be clear that treatments have also come a long way and we are very concerned with things like incontinence and erectile dysfunction, but the rates of those side effects in high-volume centers where these procedures are done routinely continue to fall all the time. Its far, far from the certainty that those side effects will exist long term even after the traditional therapies.

So, what's needed for focal ablation is reliable imaging, we need to be able to see the cancer with an ultrasound or an MRI or something similar to know that we know where to do the ablation.
We have lots of effective ways of destroying tissue. We can use cryotherapy, which ice. We can use HIFU, which is ultrasound. We can use laser. We can use all kinds of things and the question is do we know where to aim that ablative energy and the problem is some of these technologies have really been used without a lot of careful study, [start=51:35,51:37Dr._Cooperberg]particularly in Europe and some places in the US and you see some pretty bad stories out there of people that have been sold those goods here for these sort of unproven therapies and there are really inscrutable stories of companies paying urologists to take their patients to Mexico to treat them there and things like that. So, we are actually actively working to open up an ablation protocol here at UCSF, which will probably be based on focal cryotherapy. We are still working out some of those details. There is probably going to be a focal HIFU protocol opening here as well and other academic centers around the country are developing similar protocols and like I said, there is a lot going on in Europe and I believe Australia as well, but there is a great deal of caveat, I am told here. I really believe that these treatments for now should only be happening in the setting of clinical investigation and academic centers where the outcomes are being assessed and tracked very, very carefully because we are still not exactly sure how it should be done and how the men should be followed after treatment.

Caller : Thank you, doctor. I will be in line when you open up. (Laughter)

Dr. Cooperberg : Sure. Stay in touch with us.

Yeah

Dan Z. : Okay. I think we have time for maybe two more questions.

Priya : Ah, yes. Actually, Dr. Cooperberg, we have a participant writing in. When is repeat biopsy indicated for patients with low-grade, low-volume disease who are on active surveillance?

Dr. Cooperberg : So, typical active surveillance involves PSA check about every three months and, you know, we describe a biopsy every one to two years. Now I think in reality that gets a little bit customized depending on the patient, how old they are, how long they have been on surveillance, and how stable things are otherwise. So, you know, everybody will get a biopsy within a year and if there is reason to believe that the original diagnostic biopsy wasn't of high quality, we will sometimes repeat a biopsy immediately to make sure that we haven't missed an aggressive cancer and then almost everyone will get a biopsy at the one-

year mark and then beyond that if the PSA is absolutely stable and there was a low-risk, low-volume cancer, we can stretch out that interval because there is some risk with every biopsy and our goal with the biomarker development, imaging development, is to be able to say, okay, this is a low-risk prostate cancer plus the MRI is clean and the genetics look positive, we are going to do the next biopsy in five years. We will treat this more like a colonoscopy and we are hoping to move toward that sort of paradigm pretty quickly.

Priya : Thank you, Dr. Cooperberg. There's another question. I am 58 years old white male newly diagnosed, unsure of which option to choose. T1c Gleason 6 + 5, PSA 4.2. Considering proton but have a metal hip replacement that complicates proton treatment. Help.

Dr. Cooperberg : So, actually, I mean, not having seen the details and of course, you know, I can't get specific advice, but, you know, assuming that the cancer was not present in multiple cores, those actually are the criteria that we would consider perfect and, you know, certainly typical for surveillance. Proton therapy, I do have to say is one of the, you know, very few treatments that I tend to advise men to shy to away from, that is actually one of them, because of the way that has been advertised, its really troublesome. Its by far the most expensive treatment for localized prostate cancer by a factor of two. Its far, far, more expensive than surgery and brachytherapy and there's not a shred of evidence published anywhere ever that it improves any clinical benefits that it cures more cancers or causes less sexual and urinary dysfunction than brachytherapy or other forms of radiation therapy or at the end of the day, its better than surgery, but its advertised very heavily because its so richly reimbursed. So , you know, there are better ways to give radiation more effective and probably effectively as to give radiation therapy, but the answer to the question I think, you know, the short, you know, from that limited data probably surveillance is the reasonable first to pursue.

Priya : Thank you, Dr. Cooperberg. There's another one. He writes I am at stage IV. Currently, I am taking Zytiga. I have already done Taxotere and Provenge. What are my options after Zytiga?

Dr. Cooperberg : So, I would… That's a situation where your actually best option most likely is an academic center where you have access to clinical trials. There is Enzalutamide which is the most recently improved medication that was previously known as MDV3100. It comes under the trade name Xtandi. That might be a relevant option. There's another chemotherapeutic called Jevtana, I mean, there are actually, you know, few options and there are clinical trials for things like and other treatments which are coming down the pipeline in late stages of development. So, you know, presumably this person is under care of an oncologist if they have already received chemotherapy, but those are some of the medications that are worth discussing and if they don't have access locally, they should be seen at an academic center.

Priya : Thank you. There's this lady who writes in. My boyfriend has been diagnosed with low progression-type prostate cancer. What do I expect in the immediate future?

Dr. Cooperberg : So, again, it depends on the specific protocol, but if it is a low risk cancer and the friend has opted for surveillance, hopefully very little. You know, the PSA tends to be stable in the short term. Sometimes, you know, it really depends on… We get a lot of information the first year. If the PSA is really rising steadily and that really has to be steady, sometimes the PSA will blip up and then come right back down. Again, we always are careful not to panic over single PSA values. If the PSA is rising steadily and rapidly, if the repeat biopsy shows higher-grade cancer, that's one that needs to be treated, but if the PSA is stable or even declining, if the repeat biopsy is negative, which sometimes is, it doesn't mean the cancer went away, but it means it was so small that we couldn't even find it the second time. You know, those are signs that this is one that is likely not to progress in the short intermediate term, so it really sort of depends on what happens in the first year or two of observation, I think.

Priya : Thank you, doctor. I have a few questions for you. My first one would be when would a physician tell a patient who is on watchful waiting to undergo primary treatment?

Dr. Cooperberg : Yes. There's not an easy answer there. Generally, so that we use I would say steadily rising PSA and there's not a strict line. Its not like you are fine when your PSA is 9.7; when its 10.1, it needs to be treated. I think its when there are signs of a steady rise in the PSA and if there's a sign of real progression, either on imaging or on biopsy and, you know, I think we are increasingly comfortable with the idea that if we go from a 3 + 3 to a 3 + 4 with just a minimal volume of pattern 4, sometimes those men can stay on surveillance, but that is, you know, in other places that's often the trigger for treatment. The men that we see clearly go from one core positive to seven cores positive, we see multiple cores of 3 + 4 and 4 + 3, you know real change and aggressive and those are clear cancers that should be treated immediately and then there's a lot that are gray are and there honestly is a lot of, you know, medicine rather than hot lines there. Its always an ongoing discussion with the patient. There are patients that are… You know, there are men that, you know, really have to be talked into in the first place because they can't stand the "C" word and those men tend to want to be treated at a lower threshold. There's other men that really will do anything possible to avoid surgery and radiation and they are much more comfortable letting things right. So, it's always very individualized.

Thank you very much, Dr. Cooperberg. I think that was a wonderful discussion. We are almost coming to the end of our show time.
Okay
Dr. Cooperberg, thank you very much. It was an honor to have you here today. Terry Herbert, Dan Hennessey, and Gary Petersen, it was a pleasure to have you on the Cure Panel Talk Show. Thank you very much. Dan, it was a wonderful discussion. Thank you for co-hosting it with us.

Dan Z. : My pleasure.

Priya : Cure Talk thanks all its listeners and participants. Thank you all for your support and we look forward to having all of you join us for the next Cure Panel Talk Show. For more details of our upcoming shows, please visit trialx.com/curetalk. Thank you.