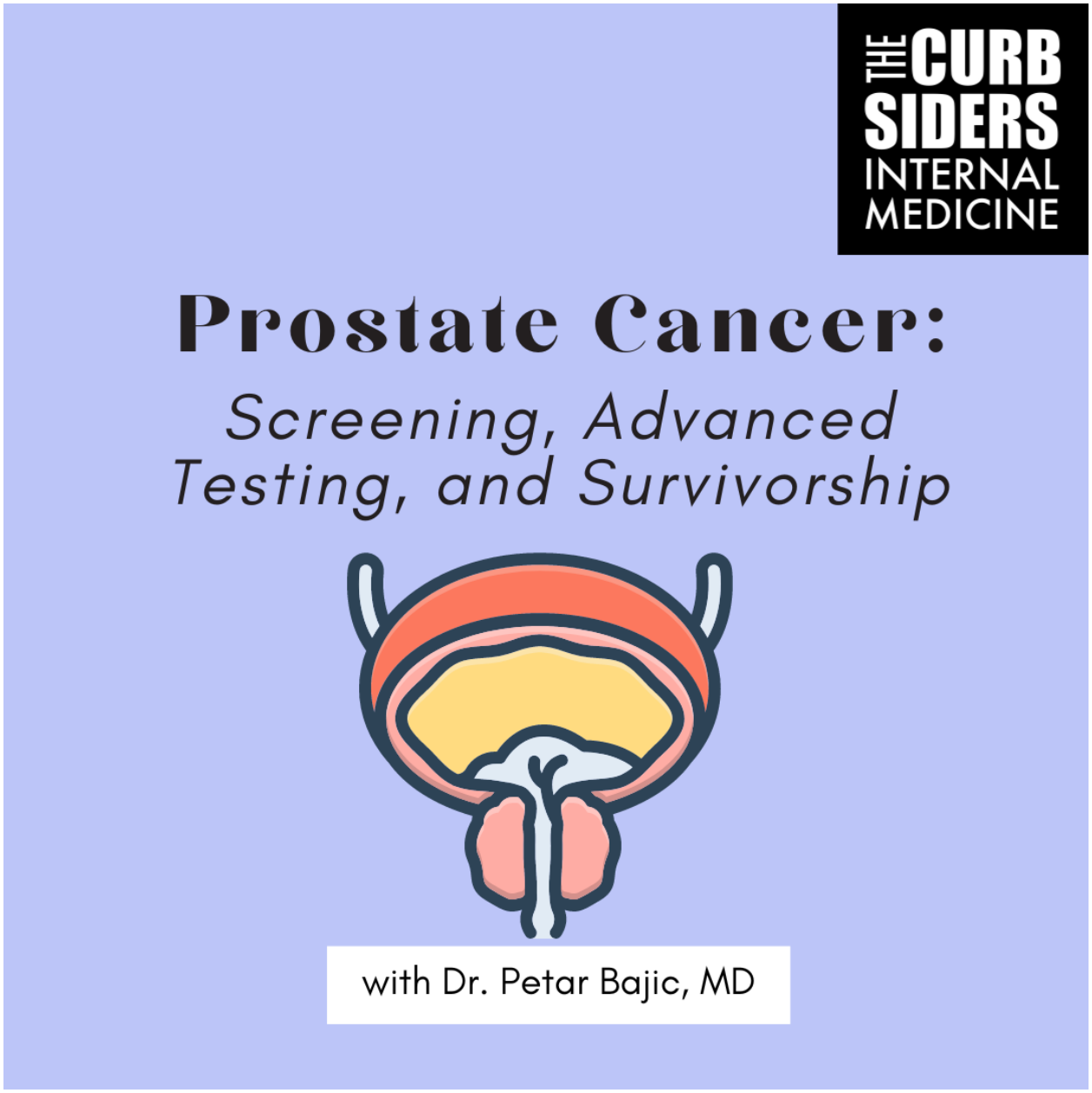
#371 Prostate Cancer:

Screening, Advanced Testing, and Survivorship

Navigating guidelines, parsing through the PSA, Survivorship, & More!



[Disclaimer]

Matt: Welcome back to the Curbsiders, I'm Dr. Matthew Watto, just furiously rifling through a set of urology puns here because, of course, on tonight's episode, we are talking about screening for prostate cancer, a very serious topic. But we always like to have at least one pun on the show, so I got to look them up, Paul, and why not do it last minute?

Paul: Just right.

Matt: Yeah. With me, if you're watching the video, you can see I have my great friend, Dr. Paul Nelson Williams, and a mystery cohost who we will announce in a minute. Paul, before we tell them about our cohosts and read their bio, can you tell the audience what is it that we do on the Curbsiders?

Paul: Happy to, Matt. As per usual, we are *the* Internal Medicine Podcast. We use expert interviews to bring you clinical pearls and practice-changing knowledge. As you mentioned tonight, we'll learn all about prostate cancer and primary care. To tell us more about our guests, about what we talked about, I am thrilled to ruin the mystery immediately and say that we are joined by wonder kid, producer extraordinaire, Dr. Beth Garbitelli. Garbs, how are you doing?

Beth: Doing great. Yeah, we had a fantastic discussion today with Dr. Petar Bajic. He's a urologist and a sexual medicine specialist at the Center for Men's Health in Cleveland Clinic's Glickman Urological and Kidney Institute. He earned his medical degree from the University of Toledo College of Medicine and completed his urology residency at Loyola University Medical Center. He followed this by completing a fellowship in andrology and male genital reconstructive surgery at Rush University Medical Center. So, before we get to that discussion, do we have any good uro puns, Matt?

Matt: Sure, I got some good ones, Paul, let's see what you think. So, Paul, you know what they say when you get accepted to urology school? Let's just pretend that's a thing.

[laughter]

Paul: No, tell me.

Matt: You're in.

Paul: That was not bad.

[laughter]

Matt: Paul, I did go to school for many years studying urology. There are many parts of my life, Paul, that you don't know about. You know what they gave me after all that school?

Paul: I do not.

Matt: A Pee-HD, Paul.

[laughter]

Matt: A reminder that this and most episodes are available through VCU Health for free CME at *curbsiders.vcuhealth.org*. Paul, it's late. I did want to mention that Dr. Bajic mentioned that he had consulted for Endo Pharmaceuticals as an advisor and for Coloplast Corporation receiving

consulting fees. Those relationships have ended, and they were not relevant to the topics discussed on tonight's episode.

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Matt: So, Peter, thank you so much for joining us. It's time to bring the audience in. I know we've been talking for a while off the air. Tell them about yourself and give them a hobby or interest that you have outside of medicine.

Petar: Sure, my name is Petar Bajic. I'm a urologist in the Center for Men's Health at Cleveland Clinic. The primary focus of my practice is male urinary and sexual dysfunction, and as part of that, I see a lot of men who are prostate cancer survivors. I also do a fair bit of general urology. As far as hobbies and things I like to do outside of work, my wife and I are avid travelers, so we

try to take at least one international trip a year and enjoying now, starting that up again after a couple of years of not getting to because of COVID.

Matt: Yes, thank goodness. Largely, we've been unlocked again, which is fantastic. Well, I know we have a limited amount of time with you, so instead of our normal getting-to-know-you stuff, maybe the audience can seek you out elsewhere. But we want to get to a case because I know they really want to hear a lot about prostate cancer screening. So, Garbs, would you do the honors?

Beth: Absolutely. So, this case is from Kashlak Memorial. Theo is a 61-year-old man who comes into your clinic for a checkup. His medical conditions include hypertension, hyperlipidemia. He takes an ARB and a statin. He has not been in the clinic for an annual since he's been in your patient panel, and you don't really know much about him as he was a patient inherited from a retired physician. He wants to know if he can get a PSA. His friend recently got diagnosed with prostate cancer, and he's been concerned about his own risk. To kind of kick it off, I just wanted to know if you could tell us about the incidence and burden of prostate cancer in the United States. Is the epidemiology for this disease changing?

Petar: Yeah, that's a great question. Prostate cancer is one of the most common cancers that men can get. Most men will get some prostate cancer if they live long enough. So, the vast majority of those are non-life threatening. I tell my patients that they're more likely to die with it than from it. But what's really important to know is that there is a smaller but very significant subset of prostate cancers that are life threatening. We'll talk more about what populations I recommend screening in, based primarily on our urologic guidelines, and we'll talk about some of the differences between that and other statements that have come out in the past 10 years.

Matt: Yeah, that's a big part of what we want to know about because I think if we could select-- we can know who was going to have prostate cancer that was going to matter as far as their quality of life, their mortality, that would be great. Hopefully, you'll be able to give us of a better idea of how to do that. I guess we should just jump right into the fact that we were mentioning earlier that a lot of primary care doctors have maybe given up on screening or are screening way less than they were 20 years ago and not being comfortable with the PSA test, the sensitivity, specificity. So, how should we go about selecting groups? I know that the USPSTF is recommending shared decision-making, but what about the Urology Society? What are the recommendations there and how do you select?

Petar: Yeah, our guidelines recommend for men aged 55 to 70 who are of average risk, meaning that they do not have a strong family history of prostate cancer and also, they are not African American, that those men should be screened with a yearly PSA or potentially every two years. For men under age 55, we typically recommend screening starting at age 40 for a subset of men who either have a strong family history or are higher risk for the more dangerous types of prostate cancer, like African American men. In general, for men over age 70, we do not recommend routine screening. Now, as we'll also talk about, I think, a little bit more, one of the most important factors to consider when considering a man for screening is his ten-year life expectancy is. Because as I tell my patients, prostate cancer is a condition that changes and evolves in general at a slow rate on the order of 5 to 10 years, not 5 to 10 days.

If a man in his 70s develops prostate cancer and otherwise dies from cardiovascular disease, it's unlikely to impact his lifespan or his quality of life. But if that same man has a strong family history of living to his nineties, and he's fit and otherwise healthy, it might even be considered in

that patient. So, it really is individualized, but in general, 55 to 70 is the age in which we screen with PSA.

Beth: Just to interject, we do want to emphasize that the AUA, like USPSTF, does have the same emphasis on a shared decision-making approach for deciding to screen a patient with a PSA. So, going into that discussion for patients between the ages of 55 and under 70, so 55 to 69, emphasizing that there are harms, there are risks, explaining what those are, and then from that point, also emphasizing that the greatest benefit for screening would be in that age range.

Paul: Petar, I think what we're talking about, at least in this particular discussion, screening for prostate cancer, we're talking about using the PSA. I just feel like it's a weird test. I don't know. I would be curious to know how you discuss with your patients in terms of exactly what it's looking at and what its significance is.

Petar: Yeah. PSA, or prostate-specific antigen, is a substance naturally secreted by the prostate. The purpose of PSA is actually to liquefy the semen. After ejaculation, the semen is a little bit more viscous and solid, and then the PSA actually liquefies it into a less viscous fluid, which facilitates fertilization, etc. This substance, PSA, like I said, is naturally secreted in the prostate but in a variety of disease states and conditions, the PSA may be elevated. So, for example, in prostate cancer, there's an overproduction of PSA. In other states, like infection, or after instrumentation of the prostate, let's say a catheterization or things like that, it may be also elevated transiently. So, there is some nuance on how to interpret it, and I'm happy to get into a little bit more detail, but that's generally how I explain it to patients.

Matt: I think this is a tricky thing. Generally, in the past couple of years, the way it's been going, patients ask me, "Do I need to be screened for prostate cancer?", largely, I've been saying, "Well, there was a time where everyone was getting prostate cancer screening with PSA testing. We found out that the test isn't as good as we would like with identifying who's going to have significant cancer, and there are some risks associated with even just getting a biopsy to find out if you have cancer or not." With that discussion, do you talk about, "Okay, so if we get the test and it's above this level, then this may happen"? Can you tell us how that part of the discussion goes? Do people have follow-up questions for you when you're telling them about the PSA?

Petar: Yeah, the first thing I always do is consider the patient's age and whether or not they meet the general screening criteria, and then I consider their 10-year life expectancy. If they seem like somebody that's likely to be around beyond 10 years, that all factors into my counseling. I think that whether or not they choose to be screened depends on a lot of things. Some of it may be their threshold to live with something going on in their body that they don't know about. Some people, they very much want to know if there's any possible thing going on. There are other people that say, "If it's not causing me some symptom, I don't even want to know about it." So, part of that conversation that I have may also entail asking them whether or not they would want to do something about it if it was detected.

It's not the easiest conversation to have, but in general, particularly if they have a strong family history, did their father or uncle have prostate cancer? How old were they when they were diagnosed? Did they die from prostate cancer? All those things are important to determine kind of how worried we should be. I think that it's a mistake to just say we should never check it, and it's a mistake to say that we should biopsy every single person with a PSA elevation. I can kind of walk you guys through a little bit of how I manage patients in certain scenarios. Happy to

discuss the cases that we have here, but yeah, it's a very individualized discussion that takes a lot of the patient factors into consideration.

Matt: I was going to ask Paul, do you want to throw out any scenarios? How do you think is the best way to approach this? Like less than four? Four to ten? Greater than ten? I'm not sure if you have a way that you split it up or if you think we should approach it.

Paul: No, I would love to hear Petar just for a broad framework for actually how he deals with it. I think, [unintelligible 00:15:53] expert on the show.

Petar: Sure. Let's say a patient walks in who has a single PSA value of 4.5, and it's flagged on your computer as elevated, and you don't have any other records. I think that's one patient where we may want to do a little further investigation and see if this is a change or if maybe they had a PSA a year ago somewhere else, we want to try to get their records. We also may want to consider repeating a PSA after about a month to see if it was just some transient increase. If it goes back down, then that is, to me, not concerning and would not merit a biopsy. When we look at the overall trends over time, we don't want to see a rapidly rising PSA. There are some varying opinions on what is considered abnormally, quickly rising, but I would say, in general, if a PSA is rising into that elevated range and continues to rise, that may be somebody you may be more worried about. If it's flagged elevated, but it's been stable for several years, and let's say they have known BPH, that can be a potential reason why it may be elevated. That's somebody we may be less worried about, particularly if they don't have a strong family history. So, it's never wrong to repeat it. There are some additional tests that we can use in certain men if we want a little bit more information.

A little bit about prostate biopsies, I can get into that. The traditional way of performing a prostate biopsy to rule out prostate cancer is by a transrectal approach. This is an office-based procedure that takes about two to three minutes. We insert an ultrasound probe into the rectum and give local anesthetics to the prostate. It's generally not painful, it just kind of feels like they're getting their prostate checked. We take twelve samples from the different areas of the prostate where cancer is most likely to appear. Risks of that procedure are bleeding, which is generally pretty mild. They typically hold their blood thinners. So, there is some risk to stopping blood thinners for a period of time in those patients. There's a risk of urinary tract infection, probably about 10%, despite the fact that we give antibiotics during. And there's a low but serious risk of sepsis, which is probably in the range of 1 to 5%. You see some rare reports of things like erectile dysfunction. I would say that is exceedingly rare, definitely less than 1%. Really, those are the main risks that I think patients need to be aware of. There's no risk of permanent incontinence or anything like that. There may be some transient worsening of lower urinary tract symptoms due to may be some swelling of the prostate, but that's pretty uncommon.

It's not something we want to take lightly. We want to carefully select the patients that undergo biopsy, but it's really important to know that there are some safer alternatives, both currently available, kind of also on the horizon at certain places that may not yet be offering it. Probably, the main option there to be aware of is a transperineal prostate biopsy, which is also performed with an ultrasound probe in the rectum but instead of passing biopsy needles through the rectum and into the prostate, which runs the risk of introducing rectal bacteria into the urinary tract, this type of biopsy passes the needles percutaneously through the skin. So, the risk of sepsis, although it's not zero, is almost zero and it really removes a lot of that infectious risk.

Now, there's still some risk of bleeding, some of those other risks we talked about, but in general, it's considered a much safer procedure. I think probably 5 to 10 years from now, the vast majority of biopsies in the US are going to be done that way.

Matt: I want to swing back to PSA for a minute just because I have a lot of patients, PSA comes back 0.5, I'm like, "Great, PSA is 0.5." Sometimes, you get 2.5 a year later, 3.5. Okay, still less than 4. We have some international listeners, but in the US, generally, 4 is considered our cutoff, like above 4, you consider biopsy. I think what I was seeing in the literature a lot is like 4 to 10 is where this gray area, you're not sure if you should biopsy or not. Above 10, it seems like most people would be worried enough to biopsy, I guess, depending on what else was going on, clinically. This is my understanding as a primary care who has not been doing as much PSA testing just because it just seemed out of like-- when I came up, they were telling us really not to do it too much. Now, I'm starting to hear again that and my urology colleagues, I'm noticing they're doing a lot more. They're being much more thoughtful about who they biopsy and another prebiotic testing, which I do want to talk about. Can you shed some light on that spectrum?

Petar: Yeah. Well, first of all, I think you're not alone. What we've seen is a lot of folks just don't check it at all. Either that's because that's the way they were trained to do it, or maybe they don't feel comfortable with some of the nuance related to it. The original USPSTF Task Force recommendations were to just not use it at all. What we saw after that, we did see an increase in the number of patients that were presenting with advanced prostate cancer. Since then, those recommendations have been modified to more of a shared decision-making approach in certain populations. Like, I said, there are some differences there with our urology guidelines where we do recommend screening for men in those age groups.

In general, I would say that anybody with an elevated PSA should be evaluated by a urologist. Simple as that. It's good for you to know what some of the nuances are as far as when we biopsy and when we don't. But at the end of the day, you don't need to feel like you necessarily need to be a master of that. That's our job.

I generally consider anybody with a PSA above 4 or in certain populations that are abnormal may even come lower, but I would say definitely anybody over 4, you may want to think about whether or not they need further evaluation. Once you're getting above 10, that's kind of the danger zone. You need to be worrying about the possibility of, if they have prostate cancer, maybe it's even outside the prostate. If we can get these guys earlier when their disease is organ confined, it's a much better prognosis if they do have the real deal prostate cancer that we want to treat.

I can talk about some of the additional tests that are useful. First of all, I want to talk about some of your comments about the PSAs that we get sometimes are really, really low, 0.1, 0.09, sometimes even lower in guys who have not had prostate cancer treatment. It's important that folks know that the prostate is an androgen-sensitive organ. If a guy has hypogonadism, his PSA is actually going to be falsely low. This is extremely important. For anybody managing hypogonadism when you start testosterone replacement, if you see the PSA jump suddenly, it does not mean that you have caused that patient prostate cancer. Because like I said, prostate cancer is a slow-forming, slow-growing type of cancer. It didn't form overnight. But you are now replacing or repleting that testosterone that was absent and all of a sudden, the prostate, that

PSA factory, is back in business, so that level is naturally going to go up. This is something we call the saturation hypothesis for testosterone and PSA.

The way I manage it, and I manage a lot of men with low testosterone is whatever their new PSA is after they're eugonadal is their new baseline for future comparisons. If it really jumped up, I do short-term follow-up, two to three months. If it's stable, we continue to monitor it. I think the gut reaction a lot of times is to stop it. "Oh my God, you don't need a biopsy or you're never going to be on testosterone again." That's generally the principle. When I see a PSA of 0.5 or whatever, I'm thinking, "Does this guy have any symptoms of hypogonadism?" That's kind of where my mind starts going.

Matt: Very cool.

Petar: There's a lot of active investigation going on in that area. I don't want to say that is necessarily an accurate biomarker for low T, but just so you know, sometimes we find guys that maybe had prostate cancer, but their PSA was falsely low. That's why although it is not in any guideline that I am aware of, I still do find a digital rectal exam to be extremely useful and I have diagnosed men with really bad, poorly differentiated prostate cancers that are non-PSA producing by digital rectal exam. So, I do think that's a valuable tool. It may not be something that every primary care doc incorporates into their practice, but I think for my practice, it is something that I do on all new patients with a concern about PSA.

Okay, now that I've given that little detail about the androgens, I think it's worthwhile talking about some of the additional tests that we may consider unless you have any questions about that.

Matt: I just had a comment, which is, Paul, this is kind of neat. Every primary care knows that if someone's on finasteride, dutasteride, that you should consider that their PSA is going to be lower and that if they stop it, it will go up. I just hadn't thought about the person with hypogonadism, just because they have hypogonadism, not because we've given it to them iatrogenically. I hadn't considered that converse situation. So, pretty cool that you pointed that out.

Paul: Can I ask you a very basic question?

Petar: Yeah, please, go ahead.

Paul: This is more along the lines of that the test comes back normal. This is very basic, but what is the recommended interval for at least your end of things? Like how often-- if it comes back, do we just say, "Shoo, we're done"? Or is this an annual test or where do we go from there?

Petar: Annual test is my opinion. Our guidelines say that an interval of every two years may also be acceptable. I think logistically, in my clinic, it's harder to get somebody on a two-year schedule, and maybe more likely that they had missed and fall through the cracks. I generally do yearly prostate cancer screening if they're in that population and if they don't have a less than 10-year life expectancy.

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Beth: I had a question about the cancer history in families. I know folks will ask about prostate and I was kind of surprised at the BRCA connection. I just wanted to know if you could speak to that. Do you recommend getting a full cancer history or at least an expanded cancer history when you're trying to figure out who you should recommend more aggressively to actually get the PSA test if they're on the fence?

Petar: Yeah, absolutely. I generally focus my family history questioning on urologic cancers as a urologist, but it is important also to know about any significant another family history. BRCA is a big one that there is an association with. Anybody that has a lot of cancers in their family, I may be a little me more aggressive with asking them those questions or screening them if they answer those questions in a way that makes me more concerned.

Matt: I want to get back to the other test because we've teased it a couple of times now. You were going to say, okay, we're talking about some cases of PSA and how to interpret that based on their hormonal status. Tell us about what other tests can we use to try to figure out that person we should be biopsying if we're not sure.

Petar: If somebody comes in with an elevated PSA, you want to think about what other reasons there might be for PSA elevation. Do they have an indwelling Foley catheter? Did they just have a urologic procedure? Do they have a UTI? A simple test that you could check in somebody with an elevated PSA, particularly if they have some urinary symptoms, is a urinalysis, or urine culture, to make sure they don't have a UTI. If they don't have any of those other symptoms. You think this might be the real deal, always reasonable to repeat the PSA. Give it at least two to four weeks or so.

There are a lot of thoughts about certain things potentially causing the PSA to rise transiently. For example, some people recommend to patients not to ejaculate for 24 hours prior to getting their PSA checked or to avoid long bike rides and things like that. There's generally not a uniform consensus on these things, but if it was a really unusual rise, it's not wrong to ask them, did you just have sexual activity shortly before then? I've definitely had some patients that had it repeated, and it ended up being normal. So, no reason that you shouldn't just repeat it.

Other options are things like checking a free PSA. A free PSA is indicated for men that have a PSA between 4 and 10. If they're outside of that window, the PSA is not validated for those PSA levels. What it's going to tell you is, it's going to give you a percent free PSA, and then it typically comes with a kind of risk of prostate cancer based on that, so it's more useful information. However, I find that this test is becoming less and less used, and part of that is because it does not differentiate between the low-risk, low-grade types of prostate cancer, which generally, as we'll talk about, are managed with active surveillance and do not necessarily require invasive treatment, and more serious types of prostate cancer.

A newer test that I use in my practice that does differentiate those is called IsoPSA. IsoPSA similarly tries to risk-stratify patients who have a PSA over 4. The way it does so is by looking at different isomers of PSA, and the ratio of those isomers to each other. What it'll tell you is, does this IsoPSA risk threshold fall above or below the danger level? If they're in the high-risk category, there's about a 50% chance that they have a real deal prostate cancer, at least intermediate or potentially high-risk cancer. If it's below that, then it's a pretty good indicator that they do not have a serious type. It's not perfect, but it's a useful tool.

The last one that I'll mention that I think is used quite a bit is the prostate MRI. In general, in my practice, I use prostate MRI more to determine where to biopsy, rather than whether or not to biopsy, because it isn't perfect. You can get a prostate MRI that might be normal, and there's still probably about a 25% chance of prostate cancer even in those patients.

Beth: I'm just going to say on a radiology rotation I was on last year, I shadowed with a fellow who's doing prostate MRIs, and I was, like, shocked at how heterogeneous they looked. It just seemed really challenging to read them. I mean, I know they're really good at that, but I could just imagine that it just shows you areas of abnormality that might be worthy of a biopsy. I can definitely see it can be some gray area.

Petar: The prostate MRIs, there's a category system called PI-RADS, where the higher the number, the more scary the lesion is. In general, PI-RADS 4 and 5 lesions we find concerning. 1, 2, and 3, we don't really worry about as much. These assessments are best done by a radiologist very experienced with prostate MRI. There's been some publications that show that lower-volume centers that don't do a lot of these types of studies may be more likely to miss clinically significant lesions. It's not a perfect test, just like many of these other tools, but in the right patient, it is very useful. I primarily use it in patients who have already been biopsied. Despite the PSA being elevated, we didn't find any cancer. A lot of times, it ends up that there is a lesion in an area that we otherwise wouldn't be checking, or maybe it's something small that we might have missed. And then later, we can come back and do a focused biopsy on that.

Matt: I wanted to just bring us back to our case here. We had this 61-year-old guy coming in for a checkup asking about PSA testing because he had a friend who was recently diagnosed with prostate cancer. He's in the range if you go by the AUA, he's in that 55- to 69-year-old range. We haven't told you anything about him to make us think his life expectancy is less than 10

years. I think he's someone it would be reasonable to get a PSA test for. I think that probably the audience is just going to wonder about like, "Well, how do I know?", because some guidelines are saying shared decision-making. The AUA guidelines are saying to do it. There. were some kind of dueling articles in the New England Journal in April 2020 and June 2020 which I can link to in the show notes, I read them. And even the one that was more on the side of being against PSA testing was just like, "I can tell you there is no right answer to this. What we should be trying to do is find the people that are most likely to benefit and try to find who's going to have the high-grade cancers that should get a biopsy and should get treatment." I'm just thinking the audience is going to be like, "I'm confused, what should I do?" Paul, we always ask for a test that tells us exactly what to do.

Paul: One test, yeah.

Matt: Just tell me what to do. I just want to know what to do. It seems like maybe there's not for this situation either. I think maybe we should move on. Should we give this patient prostate cancer so that we can talk about it-- I mean, I do want to talk about active surveillance because I know that's something that I don't understand so well, and I would love to talk about that, but, Paul, I tend to jump the gun on these things. Am I missing any big things that we need to get to before? We talked about biopsy, complications of it. We pretty well talked about some of the pathways. Do you want to biopsy this patient or what should we do next with this?

Paul: [laughs] I love that you told me to skip ahead. We still didn't actually diagnose him. So, we're just going to [unintelligible 00:36:59] biopsy then?

Matt: No, I'm saying, well, we could move the case. Let's say his PSA came back at 7 and we did an IsoPSA and were worried maybe that he could have a high grade-- and maybe just for good measure, we also got an MRI of his prostate to figure out where we wanted to biopsy. Now, Petar is seeing you. What if he came back with a lower-grade prostate cancer? What might that discussion be like? And talk to us about active surveillance.

Petar: The first thing I'll say is that you may have a hard time getting insurance to pay for an MRI in somebody who has never had a prostate biopsy unfortunately. It seems like it's getting better. What I found, at least where I practice, is that a lot of times they won't reimburse for that if it is done in somebody just for an elevated PSA. If you had that information, it's useful because it may allow us to do a targeted biopsy and increase our confidence that the biopsy result is accurate. But in this patient with an elevated PSA, elevated IsoPSA, I would definitely proceed with a biopsy. I would personally counsel him on the option of transperineal biopsy which, like I said, is a safer option that may not be available everywhere. It is a little bit more involved in the amount of time that it takes and the potential for discomfort. So, we typically do those with nitrous oxide in the office.

Anyhow, that's the way I would do it. If I had the MRI ahead of time, great. If there's any suspicious lesions on that, we would target those, and in addition to that, do a standard template of random biopsies just in the event that there's some prostate cancer in areas that did not show up on the MRI.

Matt: If he came back with a concerning Gleason score-- Actually, I don't know the Gleason score well enough to say what would be a borderline score-- So, can you maybe talk about that? What would be a Gleason score that might warrant active surveillance? Like, let's say this

person really didn't want radiation or prostate surgery, but we're going to give them prostate cancer. Can you tell us what would a low-risk score look like?

Petar: Sure. For those that maybe don't know, the Gleason score is a scoring system that's based on the pathologic examination of prostate tissue removed during a biopsy. What they do is they look for the two most common patterns that are visualized in the sample, and that's where they assign the Gleason score, which is, let's say, for example, 3+3, 3 and 3 being the two most common patterns that they found, or 3+4, et cetera, up to 5+5. The higher the number, the more aggressive appearing the cancer is.

Generally, based on the Gleason score, we group into five grade groups. I tell patients 1 is the best one to have. Grade group 5 is the worst one to have. In general, grade group 1, which is basically Gleeson 3+3=6 prostate cancer is generally managed with active surveillance for the vast majority of men. People do not die from Gleeson 6 prostate cancer unless it converts to a more serious type. Or maybe there was a more serious type that was just missed on the biopsy and we didn't know it was there. But the actual Gleeson 6 prostate cancer does not spread or metastasize or anything like that.

The opposite side of the scale, so the grade group 4 and 5 cancers, those are the really nasty ones. Those are usually like Gleeson 8. 9, 10. Those are the ones that are the real deal. Those need to be treated. Active surveillance is not an option. Now, the ones in between are the ones where I think there's the most nuanced. Grade group 2 and 3 prostate cancers, or what we would consider intermediate risk, that's where we really factor in the patient factors. If it's a 70-year-old guy with other health issues who's a grade group 2, he might be more likely to be managed with active surveillance, than somebody who's 40 with high-risk cancer mutations and with the same Gleeson score. We factor all those things in in how we counsel the patient on the various treatment options. But in general, active surveillance is reserved for the less aggressive, less dangerous types.

Active surveillance, the key word there is active. That doesn't mean we're just watching it and not doing anything. We actually actively monitor the PSA, starting usually-- there's no universally agreed upon protocol, but for example, I check PSAs at the beginning of every three months. I typically check an MRI at the three-month mark, particularly if a patient has not already had an MRI to get an idea of whether or not there may be a lesion that I didn't sample with the biopsy to make sure I'm not missing something more serious. Typically, we repeat a biopsy every couple of years to make sure biologically that the cancer is not progressing or getting worse. So, there's a lot involved.

For a compliant patient who's going to show up to his follow-up and get the tests, it's a great option. But if you have a patient that just admittedly or maybe you don't think is going to follow up very well, it may not be the best choice, particularly if they have a higher-risk type of cancer. There are a number of treatment options depending on the PSA and the grade group, and those include things like surgery, radiation, etc.

Matt: This is great. I feel like I'm understanding this whole world a lot better already. Paul, any follow-up questions or comments?

Paul: No, I think I've got most of the script [unintelligible 00:43:01]. I would love to actually hear how you discuss, and I think you touched on some of this, if you don't have a lot more to add, that's okay. The lower risk cancers, because I feel like you hear and I've heard patients say the

C word, and I think a lot of our patients view cancer as the big, gigantic, and not so organ-specific process or a very nuanced thing, and they hear cancer, they fear the worst. I think you touched on being active about the surveillance probably provides some reassurance, but is there anything else that you add to that discussion to reassure them that it is not an insane thing to just watch things for now?

Petar: Yeah, there are a wide variety of different types of patients out there. There are some folks, it doesn't matter if they are the lowest risk type maybe they had-- and this is not an uncommon scenario. We do 12 biopsies, and maybe one of them showed if the one core there was like 5% of that one core had Gleason 3+3 prostate cancer, they are devastated and they want their prostate out. It can be a challenging conversation to have but really the thing that I emphasize in those patients-- and that specific patient I just mentioned, we would consider that very low risk, assuming that their PSA was also low. The likelihood of dying from prostate cancer in that scenario is very close to zero within the next 10 years. The thing that I emphasize is that people die with this type of prostate cancer, not from it. I talk to them about what the most common reasons that men die are and it's not Gleeson 6 prostate cancer.

The bottom line though is that some folks maybe are just not the best candidate for that frequent follow-up and the frequent PSA testing, and some of them may choose to have treatment. Now, that guy specifically who has very, very, low-risk prostate cancer, that would be somebody I would be trying very hard to talk out of having treatment. But a lot of times, it's more borderline. I think emphasizing, like I said, that it's not life-threatening cancer, that it changes and grows on the order of 5 to 10 years, not 5 to 10 months or five to ten days, really allows people time to think about it and just say that, "You can always change your mind. We're going to start with repeating another PSA in three months and then we'll see where things go." A lot of times when they see that maybe the PSA is stable or even goes down relative to the last one, they may be more reassured. It gives them more time to think about it, do research, etc. A lot of this is just reinforcing that nothing needs to happen as an emergency, take time to think about it, and do the research, give a lot of reading material, engage the family in the discussion I think is really important, and just really make sure they understand before they make a decision that may be irreversible.

Paul: Great, that's helpful. Thank you.

Matt: Should we move on to a case of more survivorship? Let's say we ended up choosing active surveillance for our patient, and you talked about following the PSA every three months, at least early on, repeating an MRI in three months, and biopsying again every few years. Let's say he does well and never ends up requiring treatment for it. So, let's move on to a case. Beth, do you want to give us a new case to go by?

Beth: Yeah, let's say that it's a few years down the road. We are taking care of Theo's friend who had cancer. Now, he is post cancer treatment for his prostate cancer. I guess I've been seeing this where sometimes folks in places where there are less specialists, they may have seen an oncologist or a urologist or a specialist for a period of time, and then they fall off and they're mostly being followed by primary care. I'm just really curious about how you approach general survivorship in folks who have had prostate cancer. Do you do more regular PSA screening for them post treatment and things like that?

Petar: Yeah, great case, great question. First thing I want to emphasize is that anybody who's had prostate cancer should be having PSAs for life, because we do know that these cancers

can progress. They can recur even after treatment. So, it's not uncommon that I see a guy show up for another issue who had his prostate removed 25, 30 years ago and hasn't had a PSA in over ten years. Now, the vast majority of those guys are fine, but it's important to continue to monitor that and in anybody who's had their prostate removed, the expectation is the PSA should be undetectable. If it's detectable, even if it comes back as normal, because it's less than 4, if it's detectable at all in one of those patients, that's concerning that there may either have been a positive margin or some cancer in the lymph node. It's just something to be aware of.

Another thing that are important to know is that no matter what type of prostate cancer treatment a man undergoes, there are some similarities in the side effects that he might experience from that. I think most providers know that, let's say, prostate removal, for example, can impact sexual and urinary function, but some folks don't know that even radiation can affect those same things. The timeline of when those side effects may occur is different. With surgery, there's more upfront, and then for most men, there tends to be recovery of those things. Maybe not 100%, but 80% or more. The radiation is more likely to cause those same effects down the road, so it can take 5 to 10 years but I frequently see guys that had those types of treatments that now are experiencing those issues.

What does that entail? Well, erectile dysfunction is probably the most common sexual dysfunction that we see in this population. On the urinary side, urinary incontinence, is primarily for men who had their prostate removed. The radiated guys tend more likely to have overactive bladder-type symptoms. Frequent urgent urination, burning with urination, things like that, there can be acute toxicity and late toxicity. Those are all things that those men may experience. The reason why this population is different than your run of the mill blood pressure or cholesterol or diabetes guy that shows up with erectile dysfunction is that in the treated prostate cancer population this is neurogenic erectile dysfunction. Whereas the vast majority of other patients you see out there, it's arterial insufficiency that causes ED due to atherosclerosis of the penal arteries.

In this population, essentially the nerves that run alongside the prostate that are responsible for erectile function are damaged. Even if they don't have to be removed for cancer, they have to be moved aside to remove the prostate or when the radiation is delivered, those nerves are abutting the prostate, so they are bound to be damaged from the radiation therapy. If the signals don't get from the brain to the penis to tell those arteries to dilate and bring the blood in, Viagra is not going to work, Cialis is not going to work, Tadalafil, Sildenafil. This can be a pretty challenging population to treat. I generally recommend that if they're not responding to conservative therapies for their sexual or urinary issues that they be referred to a urologist for further management because they can be pretty difficult to treat.

Matt: I had not heard about neurogenic erectile dysfunction. I had no idea. So, that's a great pearl. And certainly, I will not be trying to treat that with phosphodiesterase inhibitors. Now, I understand why they wouldn't work.

Petar: It's not every patient. A lot of these guys have both issues. It's pretty uncommon to find a guy walking around there in his 60s that does not have some degree of cardiovascular disease, and they may or may not respond to a PDE5 inhibitor. But it's important to know that if these drugs are not working, you should be thinking, "Could this be neurogenic in etiology. Could it potentially be hypogonadism contributing?" We know that PDE5 inhibitors in a man who is

hypogonadal work better when combined with testosterone replacement therapy. So, if the T is low, they are less likely to respond to PDE5 inhibitors.

Beth Garb's: In addition to getting that referral to urology, do you recommend for any of these folks be sent to Pelvic PT? I'm just curious if that might be helpful as an adjunctive.

Petar: Great question. One of the other groups of patients I see in my practice regularly is men that have pelvic floor dysfunction that causes things like pelvic pain, genital pain, and sometimes stress urinary incontinence, particularly in the postprostatectomy population. A man in general relies on his prostate and his internal urinary sphincter for continence. Another name for the internal sphincter is the bladder neck. When the prostate is removed, the prostate is gone, and that internal sphincter or bladder neck is essentially gone. So, they are completely reliant on their external urinary sphincter, which is the voluntary one that we can control, and do Kegel exercises and things like that. Some men may not have adequate control of that muscle to be continent after prostatectomy. So, it's very common for there to be transient urinary incontinence after that type of procedure, which generally resolves for most men quite quickly, but in some men can persist and be permanent and require further treatment.

The other thing, those same nerves that I mentioned that run along the side of the prostate that can be damaged either during prostate removal or with prostate radiation are the nerves that innervate the external sphincter. If there's nerve damage and the sphincter muscle is denervated, it may not coapt sufficiently and they may leak urine. So, that's pathophysiologically what happens in those patients. Pelvic floor physical therapy can be very useful in helping to retrain that muscle and expedite that man's restoration of continents. It's not something we necessarily universally use for every single patient, I know some centers do, but in patients who are not making progress with the Kegel exercises that we teach them, we send them to PT to make sure they're doing them correctly. That's one population where pelvic floor training is valuable.

Another population I see not infrequently is men who have had radiation do tend to develop dysfunctional pelvic floor muscles later on. I find that some of those men can have things like burning with urination and pelvic pain. Sometimes, it may even contribute to some of their frequent and urgent urination. There are different types of pelvic floor exercises, more like stretching and lengthening types of exercises that could be beneficial for that as well.

Paul: I have to imagine, especially if they're in your office, you're screening and asking specifically about these symptoms, as I'm thinking things through, I wonder how often these are just volunteered and how often we should be asking more aggressively, at least in the primary care setting about symptoms like erectile dysfunction or urinary dysfunction, that kind of thing, because it may not come up, I think, unless you specifically ask, because some of these are such sensitive topics.

Petar: Yeah, and I mean, this is an area, obviously, that I specialize in, so I'm asking every single patient about it. I don't think that every single primary care doc out there needs to know the nuance of which prostate cancer treatment causes what specific type of dysfunction. Anybody that you see who has been treated for prostate cancer, two simple questions you can ask, are there any sexual issues that you're having that you're concerned about? Are there any urinary issues that you're having that you're concerned about? If they've had treatment for prostate cancer, they're by default a complex urologic case. I think that's a reasonable person to refer. You don't need to stress yourself out about trying to figure out what is the best solution.

Certainly, regular things like if they're having urinary symptoms, an alpha blocker, or something like that is very reasonable. Particularly, if they're not having the improvement that they're looking for, that would be a patient to refer.

Paul: You have the question about the hormone blocker, wonder if you could just [unintelligible 00:55:36] generally before we move past that. I know we're not expected to know the side effects of every medication, but I feel like that is a broad class we see fairly commonly. So, anything we should be specifically thinking about patients receiving those medications?

Petar: Yes. So, a little bit of background on when we use androgen deprivation therapy or hormone blockers, this is generally reserved for men that have advanced prostate cancer. The first group where you might see this is in men who have more aggressive types of prostate cancer that are newly diagnosed and who may have chosen to undergo radiation therapy. For the more serious types of prostate cancer, the radiation therapy is oftentimes combined with a limited-duration androgen deprivation therapy as a sensitizing agent or radiosensitizing agent to make the radiation more effective. Depending on the status of the cancer, that might be six months, it might be two years. During that time, as this is essentially chemical castration, you would expect all of the symptoms of hypogonadism. A lot of these guys get hot flashes, they have a lack of energy, lack of sex drive, etc. In that population, they get off of it, and depending on the patient, some people get their testosterone levels back and they don't have those symptoms anymore. But some people do actually have persistent libido issues, persistent sexual dysfunction, persistent things. So, that's definitely a population that if they're continuing to have issues, you may want to refer for further evaluation.

Another population is those who have metastatic or advanced prostate cancer who maybe have undergone treatment and have a continuously rising PSA, despite that. Those patients may be treated with lifelong androgen deprivation therapy. Some patients, unfortunately, the cancer may change or adapt and become nonhormone sensitive. We also call that castration-resistant prostate cancer. For those patients, it gets pretty complex but there's a variety of immunotherapy agents and chemotherapy agents that are definitely outside of my scope of practice but those are the situations where we may be turning off testosterone to try to help control the cancer. It's important to know that as a primary treatment is not considered curative but is meant to keep cancer at bay.

Matt: What are you following for side effects as patients are on those? Any tests in primary care that we should be ordering? I think bone density or metabolic labs of any kind, hormonal testing, or anything like that?

Petar: Yeah, great question. We could probably do an entire hour's talk on the treatment of advanced prostate cancer and all of the different agents that are used. It's hard for me to give just a blanket recommendation despite that but I think a lot of the things that we commonly see checked in those populations are things like bone density, liver function, and things like that.

Matt: With that, I think it's time to get take-home points. Let's get some take-home points, maybe a couple of things that you want the audience to remember from this talk tonight. Thank you again so much for all your time and teaching, this has been fantastic.

Petar: Yeah, it's my pleasure. It's really a great opportunity to chat about this stuff. I think as far as take-home points go, I think it's important for folks to know that although it didn't get as much publicity, those initial statements by the USPSTF task Force that said that we should not ever

check PSA, that is no longer the case. Those statements have been revised. They did not get as much news surrounding them. So, don't be afraid to order PSA. You don't necessarily need to know all the nuances of it, but if the patient meets those criteria for screening that we talked about today, and you talk to them about the pluses and minuses of screening if their life expectancy is greater than 10 years, you check a PSA and it's elevated, it's never wrong to send them to a urologist for further evaluation. That does not mean that they are going to undergo prostate cancer treatment and permanently negatively impact their quality of life or that they're going to become septic or something like that. If nothing more, it's just for the counseling and the pluses and minuses of proceeding with the biopsy, further testing, etc.

There's a lot of new things out there. The space is continuously evolving. Biopsies are becoming safer. Treatments are becoming safer. We now have focal therapy, which is an option that's gaining traction, that is also being investigated further. It doesn't necessarily have the same side effects as the treatments that we've done previously. The biopsies, like I said, are safer. There are other tests that can be used to increase our confidence about whether or not treatment is indicated.

The other thing I want to emphasize is that for any patient that you see in your practice who has been previously treated for prostate cancer, make sure you're asking those important but sometimes difficult questions. Are you having any trouble with urination or continence along with that? Are you experiencing any bothersome sexual dysfunction? You've got to make sure these people know that this is not the way they have to live their whole life. I cannot tell you how many patients that I've seen who spent decades thinking that they just had to live their life this way in diapers for the rest of their life. There are a number of effective treatment options available. We can restore quality of life to these patients. There's a lot of great options for them. So, it's just really important to know that.

Matt: We will start the outro music here. That is great. Thank you.

Paul: That was fantastic.

This has been another episode of the Curbsiders bringing you a little knowledge food for your brain hole.

Beth: Yummy.

Paul: [chuckles] Great. Get your show notes at *thecurbsiders.com* and while you are there. sign up for our mailing list to get your weekly show notes in your inbox. Plus, twice each month, you get our new Curbsiders Digest recapping the latest practice-changing articles, guidelines, and news in internal medicine.

Matt: Paul, we're going to have to make some promotional materials with Ali as part of our third recording, our third co-host, essentially because he's been on every episode recently. Ali the cat, that is, for the people not watching the video. We're committed to high-value, practice-changing knowledge, and to do that, we want your feedback. So, please subscribe, rate, and review the show on Apple Podcasts or on Spotify. You can also send an email to *thecurbsidersteach@gmail.com.* A reminder that most episodes are available through VCU Health for free CME at *curbsiders.vcuhealth.org*.

Wanted to give a special thanks to Beth "Garbs" Garbitelli for writing and producing this episode. And to our whole team. Technical production is done by Pod Paste. Elizabeth Proto

runs our social media. Stuart Brigham composed our theme music. With all that, until next time, I've been Dr. Matthew Frank Watto.

Beth: I've been Beth "Garbs" Garbitelli.

Paul: And as always, I remain Dr. Paul Nelson Williams. Thank you and goodbye.

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