Hello. Good evening, everyone. My name is Zach Klaassen. I am a urologic oncologist at the Georgia Cancer Center in Augusta, Georgia. And I'm pleased to be joined with a couple of panelists who I'll introduce in a minute for this Prostate Cancer Foundation webinar looking at guiding treatment choice in localized prostate cancer. Thank you so much for joining us today.

We have a few folks still joining…..We have an action-packed program for you this evening. And I'm going to kick things off by going over a few introductory slides. First, we'd like to thank Veracyte for their sponsorship of this event tonight. All views from myself and from the speakers in the webinar are our own opinions and expressions and not influenced by the company. But we certainly thank Veracyte for their sponsorship of this event.

So a little bit of background about the Prostate Cancer Foundation. This foundation was founded in 1993 with the mission to reduce death and suffering from prostate cancer. PCF funds the most promising research toward treatment and cures with a global footprint in 28 countries, with now multi-millions of dollars in grant funding, particularly for young investigators as well as for established collaborations. Many of these therapies used today, that we use every day in the clinic were early stage funding from the Prostate Cancer Foundation.

So in terms of resources, I encourage the folks on the line to visit PCF.org. There's tremendous resources there in terms of updates, guidelines. You can view past webinars that we've put together and join online support groups as well as a new initiative through the Prostate Cancer Foundation called Prostate Cancer Patient Voices. This is an excellent website which has now been running for about six months, and this is really patients, their families, the caregivers explaining their patient journey, and a lot of excellent literature written by physicians at the level of the patient. And this is a great resource. So I encourage those on the line to also visit Prostatecancerpatientvoices.com.

So in terms of our panelists, we have two excellent panelists, both from the University of California at San Diego. The first is Dr. Aditya Bagrodia, who's an associate professor in the Department of Urology. He's a board certified urologist. He treats all aspects of genitourinary cancer and has conducted extensive research in urologic oncology, specifically looking at biomarker profiles and molecular signatures of urologic tumors as predictors of clinical outcomes. His focus, his clinical and research interests, understanding the molecular attributes of germ cell tumors with the goal of ultimately improving patient care. He also treats prostate cancer and has been the principal or coauthor of more than 150 articles in peer-reviewed publications.

So welcome, Dr. Bagrodia. It's great to have you this evening.

Thanks, Zack. Absolutely a pleasure. Educating patients is something I'm passionate about. I work closely with my partner Tyler, and for any of those in the Southern California region, we have a prostate cancer patient summit which is geared towards patients and caregivers running through elements of prostate cancer diagnosis and management that many of you all may be contending with on the day to day.

And that's February 10th, Prostate Cancer Patient Summit at UC San Diego, which is done in conjunction with the Prostate Cancer Foundation.

Fantastic.

So I'll introduce Dr. Seibert next. And Dr. Seibert is also, as I mentioned, from the University of California, San Diego. He is a radiation oncologist, assistant professor, Department of Radiation Medicine. He treats patients with a wide variety of tumors, including brain tumors and prostate cancer. He's a clinical translational scientist and does a lot of work from the engineering approach.

His research projects include development and validation of genetic risk models to identify men at risk of developing aggressive prostate cancer, much of which we'll touch on this evening, and also is a two-time

recipient of the Prostate Cancer Foundation Awards, including the Young Investigator Award in 2020 and the PCF Challenge Awards. So certainly somebody familiar with our foundation and a recipient of several awards.

Welcome, Tyler. Great to have you as well.

Thank you so much. Happy to be here. Excellent panel and great topic. So let's do it.

So the way we'll open things up tonight, we're going to spend a decent amount of time talking about several cases and sort of working through how molecular biomarkers and genetic biomarkers can help us stratify patients and help with discussions in the clinic about treatment options.

And certainly from a little bit of background perspective, sort of the nuts and bolts of how we diagnose patients is with PSA, prostate biopsy. At some point in time, usually there's an MRI involved as well, but these biomarkers do give us additional information, whether they're negative or positive, high risk, low risk that may help us with stratifying patients. And certainly we hope to highlight those in the cases and certainly we're going to sort of run a tight ship.

It's a busy program, but we want to spend time for Q&A at the end. I know we've had lots of questions submitted in the lead-up to this webinar and also I encourage folks to go through the Q&A and we'll try to get through as many as we can. Obviously, we can't get through all of them, but we're going to try to focus on biomarker-directed questions.

So without further ado, I'm going to roll through the first case here. Let me just pull up my screen. So this is the first of the five cases. And so this is a 62 year old healthy male. PSA is 8.7. He's got biopsy Grade Group 1, 2 out of 12 cores, 50% of the core. So on paper, a good candidate for active surveillance.

And he had an MRI, as we can see here on the right, with a PIRADS score of 4 in the right peripheral zone as highlighted with the arrows, a rather large prostate, at 100 cc's. So may explain some of the elevated PSA as well. So Aditya, are you counseling this patient on treatment, active surveillance? What are your thoughts on this case?

Yeah, I think, you know, the first major step in the road fork in the road is, Do we have enough information that compels us to treat this cancer now, sooner rather than later? We're taking into account life expectancy. I think this patient seems healthy [inaudible] the imaging reports, the PSA. And when we look at these, you know, in my mind at first pass, most things are generally looking favorable.

As the biopsy score is low, I think active surveillance is kind of the default. The PIRADS score is the one thing that's a teeny bit unsettling but not overly problematic. The PSA density, when we indexed the PSA to the size of the prostate is favorable. So surveillance is kind of where I'm heading. I want to make sure I get it right in a young, healthy male.

And then we don't, you know, we haven't missed a wolf in sheep's clothing. But I'm typically thinking surveillance in this context.

Excellent. And, Dr. Seibert, any additional information that would be helpful for for this patient to surveillance versus treatment?

No, I think I think that's been covered pretty nicely. I mean, I think that the PIRADS 4, as you mentioned, research area of interest for me is MRI.

And the PIRADS 4 certainly can give you a reason to biopsy, but is not proof at all that there's going to be a high grade disease. And he also has this giant prostate, 100 cc's, with a PSA that's fairly you know, it's elevated, but relative to that, it's not too bad. So I'm pretty happy with the Grade Group 1, small lesion.

Even with the MRI, I think this is a solid case for surveillance right now.

For sure. So some additional information we could get is a Decipher score. This is one of the genomic biomarkers that we do have approved in this setting for candidacy for active surveillance. So this patient did have a Decipher. He was actually considered high risk.
So the score was 0.85. You can see here his risk of prostate cancer mortality at 15 years with treatment is still 10%, and he has more than 50% risk of adverse pathology.

So, Dr. Bagrodia, in this situation, everything looks great on paper, but we have new information looking at this Decipher score with the with a pretty significant high risk score based on what we see here.
So is this changing your treatment plan in this healthy 62 year old patient?

Yeah. So nearly certainly the fact that this patient was young, he was actually of African-American ancestry. There were a couple of things that just made me a little bit more cautious and diligent about my approach. For instance, if this patient was substantially older, significantly sicker, I almost can't imagine I would have gotten a Decipher score because in some form or fashion, I don't know that I would have been ready to make a decision.

We didn't really dig into it, but with this patient, he also had substantial lower urinary tract symptoms. He's got a large prostate. So when we took all of these elements into account, I think that we're heading towards treatment. And we talked about the options of either doing a bladder outlet procedure followed by radiation, or surgery. The patient wasn't sexually active and was more interested in having it removed.

So absolutely, this kind of impacted my decision making and at the very least, it would have influenced me to get a early confirmatory biopsy. Sure,
If not, move straight to treatment.

And so it looks like he did have his prostate removed. And this is a phenomenal example of the wolf in sheep's clothing in terms of the Decipher score, high risk showing that this was clinically significant disease.

His lymph nodes were negative at the time of surgery, but he was T3 and was upgraded to Grade Group 4 with Gleason 4+4, tertiary pattern 5.

So I think let's let's pause here. I think just for our listeners' sake, you know, there's a lot of information about biomarkers and the way I explain it to my patients is: we can get a lot of information based on life expectancy, age, risk factors, family history, etc. you know, PSA, what the biopsy shows, fusion MRI in there….

When are you guys using biomarkers? And we've discussed Decipher but there's Oncotype DX GPS score. There's 4k score, there's urinary biomarkers, PCA3. We now have artificial intelligence biomarkers as well. There's a lot of information and there's a lot of heterogeneity in how we as clinicians use these additional tests. So maybe I'll start with Tyler. What are you considering and what do you use in your in your practice?

Yeah, So in my practice, I mean, as a radiation oncologist, most of the patients are coming to me, they, all of them already have a diagnosis and they've been worked up. So probably I'm using it pretty differently than the urologists are when they're trying to make an initial decision. This kind of example, which is a really striking case, I think is one that could get to me.

They might be referred to consider radiation. Patient really wants treatment, even though we were thinking active surveillance, and and this is an example of where….when you think when you have kind of an intuition or there's some things just…. you can't even put your finger on it, you know, Aditya was talking about this. He's younger. You know, I just there was some there were some things that concerned me. I at least wanted to be sure that we were doing really close surveillance. Maybe I should just double check

something else, get a new piece of information. That's when for me, this is useful in the intact… I mean, sorry, in the decision making of surveillance or not.

I think later we'll talk about where it comes really more into play for a radiation oncologist and how do we decide about systemic therapy.

Yeah, for sure. And Aditya. How about yourself? When are you considering this and what what biomarkers are you typically leaning on?

Yeah, I mean, from from the onset, you know, the the initial decision to treat or not, I think is a perfect example.

And these are incredibly complex for a urologic oncologist, radiation oncologist, you're taking in the health of the patient, their family history, their ancestry, their PSA, their MRI, their biopsy score, how much of a core was involved, if it's got two different components, Gleason Score 3 + 4 equals 7, what proportion of those are making up the core? Are these fragmented cores or complete cores? Their lower urinary tract symptoms, their sexual function? You're taking all this information and you're trying to somehow synthesize it into a binary treat or not to treat. And those decisions aren't easy. They're not easy for us. And I can't imagine they're easy for the patients. Sometimes I think that these biomarkers help provide clarity, but they also are just a bit of information. They're not the source of truth. There's not a neon light that says this is actually truth.
Hard to kind of bucket it, but younger, healthy patients, high volume Gleason score 3+3 equals 6, 3+4 equals 7 in reasonably healthy patients considering surveillance. If I had to give you something concrete, I think that's where biomarkers can help stratify on the front end.

Yeah, I like that. 3+4. With 3+4, we should be doing more surveillance in 3+4 than we did historically. That's clear from the ProtecT trial that was, you know, results were published recently, but we still are a little nervous about some of those. So that's a great case. We're getting additional genomic information on the tumor can help us feel reassured.

Yeah, I think those are great points and will be highlighted in some of these upcoming cases too. I think the one thing I'll add is, I'm a big fan of active surveillance. I trained at the University of Toronto, which is one of the first places that that really sort of honed in on active surveillance and decreasing the overtreatment for clinically insignificant prostate cancer and avoiding those side effects, which we all know.

And I think….I'll use this oftentimes when I'm trying to convince somebody that needs active surveillance that they should be on active surveillance. I think that's one way that I've used it in my practice as well. So. Okay, fantastic discussion.

Let's move on to Case 2. And this is a 63 year old healthy male. He does have a history of metastatic prostate cancer, his father. So I think that's a significant point right off the top. His PSA was 6.5. He had an MRI done, PIRADS 3 in the right peripheral zone, smaller prostate, kind of in line with his age, roughly 40 cc's. He did have biopsy Grade Group 1, but it was high volume disease, 12 out of 16 cores. And so, Dr. Bagrodia, this patient comes to your clinic and he's got Gleason 3+3 equals 6, but it's high volume 3+3.
What are you counseling this patient on at this point?

Yeah, I mean, generally it's the grade more than the volume that's catching my attention. So I really don't have a problem watching people with higher volumes of grade group 1, Gleason score 3+3 equals 6 disease. But then again, we're looking at his overall young age, his family history. So I'm a bit more diligent in this context. I still think that surgery is the default until something can kind of convince me otherwise. But I'm thinking surveillance. I'm thinking close surveillance, and I want to make sure that I've performed a biopsy and feel quite comfortable that I haven't missed anything.

For sure. Tyler, this guy comes to your clinic. He's getting all his options. How are you counseling this gentleman?

The same. I think that…..with that history of metastatic prostate cancer in his dad, you've got to also address the psychological issue of, you know, this is something he's seen. So it's scarier for this patient perhaps than for another one that doesn't really know much about the disease and hears, “I've got this very low grade cancer that probably isn't very threatening.” The volume of grade group 1 is something that I would note. I think these are things, though, that solidly in the category of active surveillance. However, history of metastatic prostate cancer, lots of cores and things. You know, PIRADS 3, which is a little bit equivocal.

It could be either way. I would just… I would encourage active surveillance because there's not much harm, I think, for him in waiting. But I would tell him, you're probably going to need treatment eventually. It might not be that far away. We're going to watch you very closely.

Yeah, a great point. I think a lot of the counseling with active surveillance is: you may not need treatment today. You may not need it tomorrow, you may need it in five years. Or three years. We're going to try to spare you side effects of treatment if we can safely.
In this gentleman, based on the history of his father with metastatic prostate cancer, is anybody jumping to germline testing at this point in time?

Absolutely. I mean, I think it's a guideline-directed standard. We're pretty proactive about, you know, higher grade disease, intraductal carcinoma, strong family history, not just of prostate, but breast, endometrial, ovarian and other familial cancer syndromes. Just get into it. And, you know, Tyler's really been a world expert in helping define some of the genetic risk factors.

Yeah, I agree. I mean… the history is concerning. And he's 63 and he clearly has a lot of disease. There's no particular reason why we can assume that this Grade Group 1 won't eventually become something else. As mentioned, advising the rest of the family or looking for other cancers, but in particular for prostate cancer.

If there was a BRCA2 mutation, that would give me a lot of pause. I'm a very big proponent of active surveillance, but I don't know that we really know what to think about BRCA2, where there is an association with more aggressive disease, that would change my conversation.

Sure. So this patient did have a Decipher score and his is low risk. So despite his family history and despite his high volume, Gleason 3+3 equals 6, his Decipher score is low. His risk of adverse pathology at the time of radical prostatectomy is only 16.8%. With this information, Dr. Bagrodia, what are you what are you counseling of at this point in time?

Yeah. So first I just have to piggyback off Tyler's last comment. So, BRCA mutations, we’re aggressive about screening for BRCA mutations. And we actually have a clinical trial here at UC San Diego for patients with high risk localized prostate cancer who should be getting germline testing as a standard of care to get olaparib, which is a medication that's highly effective in people with BRCA mutations prior to prostatectomy. Rana McKay is one of our phenomenal colleagues that spearheaded the whole effort.

Tyler and I are intimately involved, so it's worth mentioning that we're trying to do better for this disease. You know, we're talking about low risk cases, but if you are BRCA-mutated, or know people that are, there may be a clinical trial at sites such as Michigan, Penn, and others that could be available for you. But getting back to your questions, Zach, sorry, I couldn't take that opportunity…I digressed.

You know, I feel a little bit take a little bit of a sigh of relief here. You know, I feel a little bit better that there's nothing that's imminently dangerous for this patient where we need to jump into talking about treatment. And I would typically recommend a confirmatory biopsy within the next 12 to 18 months. And so

long as there's nothing dangerous there, plan on going on a surveillance program and get his germline testing for sure.

Absolutely. Tyler, any other comments on the Decipher score?

I agree. I think I would just one caveat is just that it would help me also feel more relieved and assured that this is fine. Active surveillance was already the plan. It's a good plan. We're fine. I just would like to remind everybody that the Decipher is not evaluating the entire prostate. It's only evaluating the bit that was tested. And if you have 12 cores and they all look kind of the same, you know, you're probably fine. But I would still keep a close eye on him. And this is where we don't really know what the most appropriate role of MRI is in active surveillance right now. But in a patient with kind of global disease, it's all over his prostate.
It's in all the cores. It would be a priority for me to make sure that we're looking everywhere before we do any kind of biopsy in the future.

Yeah, absolutely. Okay. So this patient was placed on active surveillance based on this Gleason grade group 1. He was germline testing negative. So watch him closely and follow a active surveillance protocol.

And without getting too much in the weeds for the for the listeners, there is several sort of renditions of active surveillance protocols, but typically including repeat biopsies, serial PSAs and MRI's at least every two years or so.

So good, we'll move on to case number three. So this is a 68 year old African-American patient and he had a PSA of 4.8. His MRI showed a PIRADS 3 in the left peripheral zone, 45 cc prostate. He had a biopsy Grade Group 2, 2 out of 12 cores, 40% core involvement, 10% pattern 4. So this is getting back to Tyler's previous comment about consideration for active surveillance in Gleason 3+4 patients. So I'll start with Tyler. How are you counseling this patient in your clinic given his low volume pattern 4.

Yeah, I would…I think that from what we have right here is 3+4, it's not very much 4. So it's important, I think, for the patients to understand that when we talk about 3+4, which is a confusing system, we're saying that there's more of this pattern 3, which is better, than there is of the pattern 4, which is worse.

In fact, the pattern 3, we don't really worry too much about. It's kind of a risk factor for something to happen in the future. It's not something happening right now. It's a risk that you might get a cancer that's threatening in the future. You don't have one yet. But 4, we consider that's something that can matter. 3+4 with only 10% pattern 4 means it's just not a whole lot of that 4, and it can be mixed in with the 3.

So that's just saying that it's kind of doing something, but it's not really aggressive at all yet. Still a candidate in my mind for active surveillance. If the patient is insisting on treatment, you know, they're uncomfortable with active surveillance, I would try to be reassuring. But, you know, we start to have a different kind of conversation because once you're in intermediate risk, it's probably better for you to do… to wait to be treated when we see that something's happening, you know, there's no rush. Let's see what happens with your PSA in the next six months, right? Yeah, but but you're really - what I was saying before is, you're probably going to need treatment in the future. With the 3+4 at 68 and you're healthy overall. There's a really good chance that you're going to need treatment in the future.

So don't disappear is my main message. Right? Don't say you're on active surveillance, but really mean you're not showing up again. We really need to watch you.

Yeah. How are you guys at UCSD doing your active surveillance program? What's sort of your protocol there you guys follow, Aditya?

Yeah. I mean, I don't want to kind of get too far in the weeds. I think it does involve you know, there's a lot of factors. You're again, look at the patient comorbidities. Biopsy tolerance, MRI findings. When I started out -

maybe this will be easier - it was diagnostic biopsy…within a year, confirmatory biopsy; PSAs at six month intervals; 18 months are getting an MRI. If the MRI look clear, continue on with PSA at six month intervals, three years, second MRI, and almost reflexively, barring any major change in something, they're going to get another biopsy at three years.

Yeah.

As I've evolved, I think it's a bit more individualized where you're looking at all the different elements: the cores, the Gleason score, the PSA density, the family history, the genomic classifiers and you know, it loosely kind of fits that. But in general, I would say it's been a little bit de-intensified in my hands.

Yeah. Tyler, how about yourself?

No, not really any additional comments other than to say that the best trial we have looking at this did PSA every six months. So I consider that the the minimum. You can't get away with not doing that. Anything beyond that is, you know, as clinically indicated if …. you're looking at the patient, you think that they're very high risk, that confirmatory biopsy can be really important.

MRI is another tool that we have. But at minimum, the PSA. The other biomarkers, everything…but just cannot stop getting the PSAs. That's the minimum for us.

I agree. I think MRI for active surveillance is probably one of the most useful tools we have. And I know this is a biomarker discussion, but I think MRI is one of the best biomarkers we have in the sense that if you have a initial biopsy and the confirmatory biopsy that are in line and the MRI is relatively clean, I think that's a good indicator that you're probably going to have a period of time where you're safe on active surveillance, so to speak.

So yeah, always would want an MRI starting out because I do see patients that are coming, especially - not from UC San Diego - but from outside that have had a systematic biopsy only, with no MRI. And that makes me very suspicious. Right. I think, OK, do we know if there was an anterior lesion or something that wasn't sampled that could change the entire situation.

We've seen that. We've all seen that many times. Right. That's a classic. So you must, in my clinic, you must have an MRI if you're going on active surveillance. I just want to be sure that we're not missing some high grade, very obvious lesion on MRI when you start out. Yeah, And as you were saying, a normal MRI as you go feels reassuring.

We don't have a great clinical trials to tell us that that's true. But but what we're really pretty confident about is if that MRI goes from normal-looking to not normal at all, that's bad news and you definitely need a biopsy.

Yep. Totally agree. Well said. Okay, so this patient 3+4 low volume does have a Decipher score.

And this is where a lot of clinical decision is made in terms of, it's **not** obvious. And we have an intermediate risk score for this Decipher score. So 68 year old healthy gentleman African-American, PSA is relatively low, some low-volume 3+4. We don't get a ton of help necessarily from the Decipher score. So, Tyler, how are you counseling this patient?

I think that we do cautious active surveillance. We start with, let's see how things go over the next several months. We're not dedicated to ten years. Obviously, with all active surveillance we're planning to treat as soon as there's an indication. I think that we start by seeing how things go. It's not really high risk, clinically seems okay, seems appropriate for active surveillance. That would be my recommendation, but I'd want to intervene before he gets to, you know, unfavorable intermediate risk.

Would you change your active surveillance follow up for this gentleman versus somebody, let's say with three cores of 3+3 in a low risk Decipher score?

Intermediate risk versus low, I don't know if we know exactly what to do with it, but yeah, I'd probably pay a little bit more attention. The low risk with just a tiny bit of ….Certainly versus 3+3, …3+3. low risk. I'm not very excited at all. We probably wish we hadn't found it in the first place. Patient would be better off not knowing, because it's not likely at all to do anything to him. This guy, as we've already said we'd want to watch closely. This is somewhat reassuring. I mean, you look at this 15 year risk of mortality from prostate cancer, it's minuscule.

You know, in the big picture, 68, something else is probably going to end his life, not prostate cancer. But he's got a few risk factors. So we should keep an eye on him.

Yeah. How about you, Aditya, how are you counseling this patient?

Yeah, I mean, sort of two things. One, I think, you know, getting that biomarker can actually help decide if and when a confirmatory biopsy should be performed. I think as urologists and doctors, sometimes we trivialize what that could mean to any given patient. Second thing, I think for patients, it's important if a test is going to be ordered, that the ordering provider, at least in some form or fashion shares with you what that readout is going to look like, and has almost a preemptive discussion on what they plan on doing based on the results of that test. Because these are, you know, you look at the readout for this, it's a little confusing.

So you got a test. It's intermediate risk. Okay. Let's just say it's low risk. What are you going to do? How is that test going to impact your decision making? I think that's helpful for patients and for providers because now we had a gray zone scenario. We're still in the gray zone.

If it had been plotted out, you know: if it's low risk, let's plan on checking the PSA in six months, a PSA in 12 months with an MRI and repeating an MRI and some fusion biopsy. Great.
If it's high risk. All right. Now we're really thinking about treatment. Let’s have you come to our multi-D [multi-disciplinary] clinic. Meet with the rad oncs, the med oncs, the uro oncs and come up with a plan.

So this has kind of got my attention. I'm not freaking out. I do think close surveillance, biopsy within a year would probably be where I land.

Is there any additional - other than maybe a repeat MRI down the road - is there any additional biomarkers you guys would get at this point to sort of help give you confidence one way or the other?

You mean in addition to now that we have the Decipher?

Yeah, yeah. In this situation, now that we know what we know with the Decipher.

Honestly, I wouldn't, I mean, I think that we've already got a fairly muddy pond and another bit of information is going to be…I think it's not going to be enough to tell me whether we should treat or not to treat in my hands.

There's also been some studies that are done that actually show that the various markers that are out there don't really correlate. So they're actually looking at kind of different things. And I'm not ready to hang my hat on one versus the other. I do think, you know, Decipher has been studied in the context of clinical trials more so than some of the others.

As an academician, I like that. There could be value added of sequential biomarkers. I haven't really gone that route yet.

Yeah. Tyler, any additional biomarkers, or are you pretty happy just kind of watching at this point with what we have?

Yeah, I usually don't order more than one for a given patient.

I think maybe it's a radiographic biomarker and I'm not suggesting that I would order it. Some people have already started ordering PMSA PET scans to get a little bit of a better understanding of what's going on within the prostate if they're considering focal therapy. I wouldn't do that. I think ideally it happens in the context of a clinical trial, but I don't know. What about you, Zach?

No, I think I'm happy with this. I answered one of the questions in the chat as we're kind of going along in terms of what your point about Decipher is arguably the best-studied biomarker that we have in the context of clinical trials, and we're going to go through some of those exciting ones in the next couple of cases as well.

And I think when we're looking at the milieu of options, you know, MRI, Decipher, all these are the ones you mentioned at the beginning of the session, it can make it muddier. And we have very good data for Decipher in various aspects. And we have it built into clinical trials and it's been evaluated and validated and revalidated. I think, you know, we as sort of academicians have to follow the evidence that we have. So I think we're all on the same page with that.

So, okay, let's move on to case number four. I actually will confirm this guy was placed on active surveillance, confirmatory with a Gleason grade group 2. So he's being followed closely and doing well.

Case four. So 68 year old gentleman, PSA 7.8, MRI shows a PIRADS 4 lesion left peripheral zone. He's got contact with the capsule so looking like clinical T3a disease potentially. Prostate is 28 grams, not oversized. He has a biopsy done which shows Grade Group 2 in 3 out of 12 cores; Grade Group 1 in 3 out of 12 cores so he's got 3+3 and 3+4. Unfavorable intermediate risk, 50% of the cores, so he's got some higher risk features there.

Next steps if he's going for radiotherapy, let's say. Tyler, are you considering this patient for ADT? What sort of counseling are you giving this gentleman?

Yeah, great. So this is an interesting case because it's not so different from one of the earlier ones we saw. Right. Again, it's 10% pattern 4 and we were saying active surveillance. But what's different in this one is two things. One is percentage of cores. I don't know how useful that is. All I know is in the guidelines, it puts you into the unfavorable intermediate risk category. And so a lot of people are going to be recommending six months of hormone therapy for this patient, if they go for radiation.

Right. Probably the majority will be recommending it and that would be concordant with guidelines. So so I'm not so sure, but it is there. Then you also have this broad contact with the capsule. Could mean nothing, could mean that there is a little bit of disease outside of the prostate and that would be a risk factor for recurrence with treatment.

So those two things make me, you know, they give me pause and and, you know, I would feel that I need to at least offer that patient the ADT. I'm kind of on the fence about, does he really need it? It depends on kind of the other factors. How are you… favoring quality of life or are you favoring, you know, maximal chance of cure? What is your overall function like? How much would this impact you? So it would definitely be a discussion. But six months of hormone therapy is for sure on the table. It would be wrong to not at least to have that discussion, I think.

For sure. And I think at 68 years old, I mean, if he's healthy, obviously candidate for surgery, correct?

Yeah. And I mean, you know, this gets a little bit nuanced, right? Like if this was a MRI ultrasound fusion biopsy and this region's been oversampled and it's those cores that kind of tips them into unfavorable intermediate risk land, that's something that is a detail worth spending a moment on.

I can just tell you, I'm familiar with this case. This is systematic only. There is a targeted biopsy as well. And it was the same grade group 2 in that lesion. But this is systematic only because I agree you can't…you don't want to weight too much the targeted cores.

Totally. So I, you know, for me it's not a dead ringer that we need to treat. Now I think our guideline directed option would be to treat. Standard options would be surgery or radiation with hormone therapy. I'm going to venture to say that we all feel like that today is a bit overkill. That's a sense. But yes, surgery, radiation with hormones I think would be guideline directed options.

Okay. So let's progress through this case. So patient declines ADT. If his Decipher is high, how would you interpret this situation, Tyler? So he has a Decipher score, low risk, he decides against ADT.

What evidence do we have for…. if he was high risk on Decipher in terms of the ADT option?

Right. So you ask the question about the evidence do we have. So what we have is this report and this is based on high quality evidence from clinical trials telling us that his risk is low. His risk of developing metastases with radiation or surgery is, you know, 1% at five years, 2.6% at ten years, it's very low.

So we were feeling like this was probably going to be overkill. And this is suggesting that in terms of absolute risk, like how much risk does he have, it probably is overkill. In terms of evidence, you know, we don't have any randomized trials based on Decipher that have completed. But in a second, we're going to get Aditya's opinion on this one.

But I'll tell you, the trial that we have ongoing right now that we are excited about.

Yeah, So let's go to that. So this is NRG-GU010 and take it away, walk us through this exciting trial.

So this is a trial by NRG Oncology, which is a national - actually multinational - cooperative group organization. So they run big trials that are sponsored, funded often by the National Cancer Institute.

And this one is interesting. If you go to the next slide, we'll show you kind of…this is a little bit of a weird schematic, I know, but you see that there are two arrows from the top. So the patient goes on the study and if you go to the left, if your Decipher is less than 0.4 like this patient's is, then we're asking the exact question that we were just debating.

Do they need the six months of hormone therapy or not? So we will randomize – a computer flips a coin, so to speak - and the patient either gets the six months of hormone therapy, which is consistent with today's guidelines, or we spare them the six months of hormone therapy, which we think is probably okay. And this trial will tell us the answer definitively.

If his Decipher had been higher, so intermediate or high, so higher than 0.4, then it would be randomized to say, well, hey, genomically, this tumor, in terms of the genes that it's expressing or like what it's doing are… it actually looks like it's behaving aggressively. So in that case, we're randomizing to the standard, which is the six months of hormone therapy OR adding another medication that we know works really well against prostate cancer and might give a better chance of cure.

That's great. So maybe if you can you give our listeners an update on where we stand with this trial in terms of accrual, when we might see some data from this trial?

Well, early stage prostate cancer, you have to be very patient because what we care about is metastatic disease. It takes a long time for that to happen, fortunately, but so we won't have definitive results on this study for quite a while.

But it's enrolling right now. It's open…if patients, you know somebody, it's open all over the place, including we're about to open it here, but it's open all over and it's enrolling very well. Patients are accepting this trial faster than we were expecting.

Yeah, I think this is a great example of incorporating Decipher into the trial design and then having basically, you know, two separate arms with two separate randomizations, right? So it's these trials - for the patient, for the listener standpoint - are always big trials and it's basically a 4-arm trial. And so it takes a lot of patients to to get the results that we're looking for.

Aditya, comments on this trial?

I love it. I mean, it's the sense is….that there's basically heterogeneity. On the one hand, we have this super common disease that's relatively slow moving. On the other hand, prostate cancer is responsible for the most cancer deaths among men. And even just among intermediate risk, this sliver, we're going to see a spectrum. Some that are going to be nasty players, aggressive, potentially lethal, and some that really never have the biological capacity to hurt somebody.

So a trial like this to me is phenomenal. We're trying to personalize medicine, you know, remove androgen deprivation and everything that kind of comes along with it for patients that aren't going to benefit. Add on additional life-preserving therapies for people that may have a bit more aggressive cancer. As a somewhat of an academic purist, I think doing this in the context of a clinical trial, so in five, ten years we can say: A patient like you walks in the door, got a Decipher test, half of them got this, the other half got this. This group lived longer. That's why you should get option B.

So I'm a huge fan, happy to be…have this trial up in our study and send patients to our multidisciplinary clinic to discuss all their options comprehensively.

Yeah I think the fact that we could potentially, if we're lucky, we get answer to maybe one question. If we're really lucky, we get answer to both sides of this of this coin, which would be fantastic for patients and for helping us counsel them.

Before we move on, Tyler, any other comments on the study?

No, that's good. I would go back. I actually just think…I hadn't realized that slide. I just want to note this. On the intensification and on both actually, with the radiation, it notes this “escalated RT boost,” which is talking about giving extra radiation to the visible tumor. And on the next case, I'll mention that a little bit more. So I wanted you to see, that's something that's being included in these trials now.

Excellent. All right. We're doing well on time. We'll probably spend about three or four or 5 minutes on this case, and then we'll finish up with the questions. So let's go through case five.

This is 71 year old patient, PSA is 18.3, he has an MRI, which we can see here on the right, PIRADS five lesion in the left peripheral zone, no extra capsular extension. Has a biopsy Grade Group 4, Gleason 4+4 and 7 out of 12 cores. He is high risk, so he gets a PSMA PET scan for staging.

He has no visible metastases. He's NCCN-classified as very high risk. Next steps, radiotherapy and long term ADT, 24 months. Should we add a new anti-androgen medication to this? So perhaps, Tyler, give us your thoughts on this case.

Yeah. So this is a this is one where there's there are a couple of things. We don't see ECE. That means extra capsular extension; doesn't look like it's gone out of the prostate. So that's good. The tumor is quite visible. And I'll say that this is a little different. The last one was on standard MRI, and I circled it for you in red so that people can see what we're talking about. Because I know that it's hard to see these if you're not used to looking at a prostate MRI.

This one has this color code on it that's showing you where it is. That's a quantitative advanced MRI biomarker that we work on in my lab at UC San Diego and that we use clinically. We just published a study showing that this helps radiation oncologists do the escalated dose, to increase the dose of radiation to the tumor, which has been shown to improve patients' chance of cure without increasing toxicities.

It's a total homerun, if you can do it. The challenge is, it's really hard to do it well. And we're bringing technology to make it easier for people to do it. And we've shown that that's possible. So here we have this tumor, we can see it, we can do radiation. We definitely need hormone therapy as high risk disease. In fact, very high risk with a Gleason 4+4, it's in seven cores. So I am concerned.

We see one part on this slice of MRI that the tumor is bigger if you go up and down. So, you know, and then there's other parts that obviously we're not seeing so bright on the MRI. But this gives me pause because I know that with this very high risk, even with radiation and long term hormone therapy, there's a reasonable chance that it will come back.

And it might come back locally. It might come back in the lymph nodes, it might come back distantly. I'm really worried about lymph nodes and distant disease in particular in this patient. That even if we get a PSMA PET scan, which we would, and in this case it was negative, you don't know if there might already be some cancer growing somewhere else that we haven't seen.

And if that were the case, we would certainly want additional medication. And we're just not really sure. So if we had a better way of predicting who are the patients that need an additional medication during those two years, that would be fantastic.

That's great. Aditya, any other thoughts on this patient? Any role for surgery or is this a radiation oncology patient?

I would say yeah. I mean, assuming he has a greater than a ten year life expectancy, which I think they were, having, you know, getting a good assessment of urinary function, sexual function, understanding the patient's preferences. Surgery as well as radiation with hormone deprivation I think are standard guideline directed options. I do think it's important that you run through the very real possibility that they may require additional treatment in the future, whether that's radiation with or without hormones to the prostate bed.
But yes, I would say that, you know, this patient would likely be seen in our multidisciplinary cancer clinic where they visit with a radiation oncologist like Tyler, urologic oncologist like myself, a medical oncologist to talk about hormone therapy, specifically an intensification of it. And, you know, our job is to make sure they have a good, comprehensive understanding of their options and pick the best one for them.

Yeah. So this patient, the question is, should we have another medication? We're going to get into another exciting clinical trial that's coming up. And so, other medications, some of the listeners may be familiar with these. So this includes abiraterone, enzalutamide, apalutamide, darolutamide. This is sort of the second generation anti-androgens.

And we see that this patient does have a high risk Decipher score. So he's got a 0.92. This is potentially life threatening disease. In the interest of time, I want Tyler to walk us through this last trial that we have, which is another NRG trial.

Right. So this one is called NRG - GU009, very similar to the other one. But this is for patients with high risk disease. It is open here at UC San Diego. It's also enrolling much faster.

Most trials enroll patients slower than it was optimistically predicted. These trials are enrolling much quicker because they're so, everybody's so supportive. Patients get it, physicians get it. Everybody's wanting to put patients on these trials and get answers. So this one, that patient, it was….we were uncomfortable. We're uncomfortable. We know we have curative treatments. We could cure him, but we're uncomfortable because we're just not sure. We might have something better if we could offer it to him.

By what we know so far from clinical trials, he didn't meet the criteria to add an additional drug, abiraterone. Right. So, off trial, I'm not really convinced that we should be doing, you know, adding additional medications, because we might just be causing extra harm and not on average helping the patients. But on trial, I'm very supportive of this. The guy's Decipher was very high.

So for very high Decipher - notice that the numbers on this one are different than the other one. Very high, going to the right. then you're going to get radiation, two years of hormone therapy, and you get randomized to with or without an additional medication called apalutamide. Fantastic trial. I suspect that apalutamide would help this man, but I don't know it. And if we do the trial, we'll find out the answer for future patients.

Go down the other way. What if his Decipher had been low? That's telling us that his absolute risk is not actually as high as you were worried about. You remember, it wasn't…it's all in the prostate. It's not…we don't have any imaging evidence it's out. So maybe he doesn't even need two years. You know, we've seen people try one year, we've seen 18 months and things, right.

So this trial is saying, if your Decipher is low, maybe we can spare you a whole year of hormone therapy. So we'll randomize patients to either two years standard of care or only one year. And that would…either of these would just be a dream in the future to be able look at a patient and say, you know what, we can cure you better if we give you this additional medication or hey, we're going to save you a whole year of your life on this medication. You just don't need it. That's wonderful news.

Yeah. I think both of these trials we've discussed tonight, whether they're positive or negative, are going to tell us a lot about how we treat these patients in the future. Before I move to the Q&A, Aditya, any comments on this trial?

You know, it's again, I think it's a no brainer. It's an exciting trial. It's ushering in an era of personalized medicine. This patient would have received hormones with androgen deprivation 12 versus 24 months. These are not trivial if you're a lower risk. Adding on a life prolonging second medication is not trivial if you're high risk. So, you know, couldn't be more supportive. And, you know, really, I think it's worth mentioning that the immense amount of effort to get these trials open through the cooperative groups, accessible to patients is massive.

And, you know, hats off to the leaders in our community that are constantly pushing and striving to improve the standard of care.

Absolutely. Okay. So we have a few minutes left in our session. I do want to go through some of the questions. Unfortunately, we won't be able to get to all of them. I know there's a lot of great questions out there.

I'm going to focus a couple on genomic testing and certainly Decipher. So this patient is 68 years old. PSA is 5.7, Decipher is 0.35. One core of 4+3, Grade Group 3. Three cores of 3+3/Grade Group 1. MRI enlarged prostate, staging negative. So how are you counseling this patient with 4+3, some Grade Group 3, essentially a low PSA, 68 years old? Aditya?

Yeah, I mean, maybe a bit of a disclaimer that all of these decisions really should be made in conjunction with your urologist, radiation oncologist, primary team. But broadly speaking, I'm assuming healthy 68 year old. Some of the positives are, the PSA is not sky high. We do see scenarios where the PSA can be actually relatively low when you have tumors that have de-differentiated. But I'll take it, take it kind of at face value. PSA [inaudible] concerning. Sounds like he's got a relatively bigger prostate. The 4+3 equals 7. That's got my attention. I think the first default is treatment. I'm leaning towards standard options of surgery or radiation. If they're electing for radiation, I think this is the perfect type of patient to have Decipher testing, which could help maybe inform whether or not they would be benefiting from hormone intensification or deintensification in the context of the NRG-010 trial that Tyler discussed.

Yes, so, Tyler, this guy. 4+3. Decipher is low risk. If he's in your trial, he's getting deintensification. Is there any situation where you would watch this patient with active surveillance?

I mean, it would have to be that he has competing health problems, right? So if he's got a decent life expectancy, Gleason 4+3, I'm not really willing to watch, no, I would recommend treatment.

Let me see here. Here's a gentleman. PSA is 10. Gleason 4+4. 5% of 1 out of 25 cores. Getting PSMA scan. Let's assume his PSMA scan is negative. So he's kind of right on that cusp of high risk. But low volume, high risk. How are you counseling this patient? Let's say he's 56 years old, doesn't give an age, but let's say he's 56.

Yeah, I would I mean, for me, this is exactly why we have that deintensification arm on the second trial, where we're saying, look, that Gleason 4+4. You cannot ignore that. It's a problem. We don't know. But that's high risk disease by definition, means that we think there could be a big….Now he's got a low Decipher, he doesn't have a lot of 4+4.

Do you really need to put him on two years of hormone therapy? I mean, you might. You really might. We know that clinically, we didn't just make this up, right? There was 4 months versus 28 months. Clear advantage for survival. You were more likely to be alive if you got 28 months. Six months versus 36 months, you are more likely to be alive after 36 months.

So we can't just discount that off of a trial. But I think that we feel that now we have more information to tell us that this high risk patient doesn't have the same high risk as the guy we were talking about a minute ago. Yeah. So for this one, I think deintensification on a trial is a fantastic idea and really might change the standard of care in the future.

Yeah, it's a great point. Aditya, comments on that patient?

Yeah. So first off, I think when patients are confronted with the cancer diagnosis, there's a very natural immediate sense to panic and do something like…yesterday. Nearly certainly these tumors have been there for years, if not decades, certainly months, and getting comprehensive information about all the correct information before jumping into decisions is mandatory.

So if this patient came to see us in our multidisciplinary clinic, if they hadn't already, they certainly get an MRI. I think it's worthwhile to have the pathology re-reviewed. You really want to have a pathologist that's got expertise in looking at prostate cancer. You know, 1 out of 24 cores, maybe MRI shows an anterior lesion that's kind of tough to get to. And you're like, okay, cool. I buy it.

If there's something that's a little bit off. And another expert looks at this and now it's 4+3 equals 7, that could be a bit different. I think Decipher testing, clinical trials, I would absolutely get germline testing [inaudible] indicated. That could also make you eligible for like a neoadjuvant olaparib trial like I mentioned earlier.

So just kind of take a deep breath. Basic information to me is, you want to have an MRI, we'll take the kind of pathology at face value, get the staging PSMA scan. Ideally, these adjunct tests - Decipher and germline testing - could inform your actual treatment. So that's kind of how I'm thinking about it.

I like that idea. And I mean, we're doing a quick-fire kind of, you know, here, this situation, what do you want to do? But in real life, I completely agree. We're not trying to immediately start treatment. We're trying to figure out the best path forward for the patient. And I would never do, you know, I order MRI on every patient that I'm going to consider for, you know, we're talking about radiation or surgery. We want to know. We want to know if the MRI is still going to show us things that the PET doesn't. So I want to see if it's spread outside, if it's involving the neurovascular bundle. You know, these are things that would change…if it's already involving seminal vesicles, that's going to change this discussion. Right. Low Decipher. But it's already in the seminal vesicles.

I mean, you know, what has happened trumps what you're predicting might happen.

Very good point. I think you guys hit points about taking a deep breath and getting second and third opinions is tremendously important. This is, as I tell patients, is not pancreatic cancer. It's not brain cancer. You know, we really need to get all the information because the side effect profile – which we haven't gotten into in terms of treatment tonight - is massive, whether it's surgery or radiation or even the psychological side effects of active surveillance.

Right. I mean, it's important to get all this information. So we have about one minute left. I just want from a logistical standpoint, there's been some questions about…. "I've never heard about a Decipher test. My doctor has never talked to me about it." How would you counsel those patients? You know, most this is covered by insurance. Maybe just briefly in 20 seconds each talk about how you guys bring it up in your in your practice from a logistical standpoint
Aditya, you go first.

You know, I think the onus isn't on the patient, but there's no advocate quite like yourself, you know, educate yourself. Being on this webinar, Prostate Cancer Foundation is a tremendous resource. And like you mentioned, you know, we give the treating providers the benefit of the doubt that they're doing what's in the patient's best interests.

But you, you really want to be super well informed on all of your choices, including PSMA PET scans, MRI, Decipher tests. This is all part and parcel of what we do. But if you trained 30 years ago and this wasn't around and it's not available to you, you're not using it. And that's not like a nefarious omission. It's just lack of familiarity or access.

But broadly, I know it's generic. You got to be your own advocate, kind of educate yourself on the state of the art. You're never going to hurt somebody's opinion….any good doctor would encourage second, third opinions. If you've only seen a urologist, you really ought to see a radiation oncologist. If you only see a radiation oncologist you ought to see a urologist, ideally in a collaborative multi-D setting.

Kind of vague. But but I truly believe that.

Yep. Great points. Tyler, any additional comments?

Yeah, I think if you're if you're going to your doctor with an idea, like, totally fine, you know, I think that's it. Like Aditya said, this is important. You know, you're your best advocate. I think you're asking for a biomarker, I think the question should be, hey, I you know, I've got this biomarker idea. I heard about this on this webinar. You think, how would this influence your management? Because as you were saying earlier, both of you, right, if it comes back high, if it comes back low, what are you going to recommend differently, especially if it's going to cost you something out of pocket?

Because even if it's covered by insurance, you know, how much is it going to cost you? Is that going to help you? And so that you're on the same page about what the expectation is. If you just go in and ask for a new biomarker, the biomarker comes back and the doctor doesn't know what to do with it, and you haven't talked about it. It might be kind of a disappointing experience.

But I think having a plan: if it comes back high, we're going to do this. If it comes back low, we're going to do this. You know, this is how it's going to guide the situation for you, because you might be any one of these different five scenarios or something completely different that we talked about today, right? And the interpretation of that Decipher is totally different depending on which situation you're in.

Yeah, I think I'll end with a comment. We say to our residents all the time, Don't order a test if it's not going to potentially change your management. I think that's that sums up a lot of how we think about managing and working up patients.

And so I think that's it's a good, good sort of summary of our discussion.

Gentlemen, it's been a great evening. I hope our listeners enjoyed this. We'd like to thank both of you for your expertise and your time, the Prostate Cancer Foundation, for the opportunity to be on this webinar and Veracyte again for sponsoring. And we look forward to additional webinars and hope everybody has a safe, happy holiday.

Thank you very much. Thank you, everybody. Thanks, Tyler, thank you all for the audience. Appreciate it.