How Genomic Testing Can Help Guide Your Treatment Choice

Phillip Koo, MD [00:00:00] We're focusing on genomic testing. So, before we dive into that, I think it's important to sort of clarify some terms just so we're all on the same page. So, Jim, I'm going to start with you. What is the genome?

Jim Hu, MD, MPH [00:00:15] Sure. So, the genome is a collection, the complete collection of the DNA that really responds to, as we are speaking about cancers in terms of tumor behavior. And so, one can certainly profile genes and do what's called genomic testing to assess risks for cancer, for example. And you know, you're going to get to germline versus somatic, as well as what we term precision medicine, right? Whether some of these treatments can be started earlier or late, you know, or whether they need to wait later if someone is low-risk in terms of testing.

Phillip Koo, MD [00:00:51] All right, so today we're focusing on genomic testing, which also it's referred to by other names as well. I've heard like biomarker testing and things of that sort. But this is going to be very different from germline and somatic testing. Zach, can you sort of just give us a quick overview there just to make sure simplify that for all of us?

Zachary Klaassen, MD, MSc [00:01:13] Yeah, it's a great question, Phil. And thanks as always for the invite to come on these webinars. I think when we think about germline testing, this is the DNA that you're born with. You can't change it. This is what you pass on to your kids. And so, this is in every cell in your body, whether that be blood, whether that be saliva, whether that be in your liver, your kidney, any part, any cell that belongs to you has your germline DNA. And so that's what you pass on. We talk about heritable risk. This is the germline testing that we're talking about. So, people talk about what's the risk to my children? That's what you're passing on your DNA to your children, half of your DNA from the dad or the mom, and the other half from the other, the other parent. So that's a very specific, we can't change that. We just need to know about that if you have a risk factor that needs to be assessed.

Somatic testing is what specifically is going on in the tumor. So, we're talking about prostate cancer. That prostate cancer has an inherent genetic profile that is characterized by a certain set of genes. So, it's that may be different than the germline. So, there's heritable risks, which are germline, and the tumor specific is what we may be targeting with specific treatments. When you talk about genomic testing or biomarker testing, that's what we'll be talking about tonight, as you mentioned. This is different tests we can order as clinicians to assess risk based on what that tumor is. So, it's almost like a snapshot of the somatic testing, if that makes sense.

Phillip Koo, MD [00:02:35] Alright, great. So, germline is what you inherit and what you could potentially pass on to, you know, your children. Somatic is the tumor, and then genomic testing, which is what we're talking about tonight, is a subset of kind of somatic testing. So different tests and algorithms and protocols that give us different information. So, Jim, from your perspective, why is genomic testing important and in general, when do you utilize genomic testing?

Jim Hu, MD, MPH [00:03:05] Sure, absolutely. So, I think increasingly in prostate cancer, we recognize that it's a what we call a heterogeneous disease, or that it behaves very differently. And so, one of the terms I'll throw around that I think many patients have heard about is, for example, when someone is diagnosed, first it's localized versus metastatic,

and we're going to spend a lot of time on metastatic and high-risk localized disease tonight.

But then second, that term risk comes in, right? And so, risk just refers to some clinical information that we have collectively looked at to try to catalog or classify based on the risk of recurrence, right? Or, you know, how aggressive is this cancer? And so, the precision medicine or genomics tests that we're talking about here is based on sampling the tissue and running some tests. In the case of Decipher, which I think is just a preview of things to come, it's looking at RNA sequencing or a fingerprint of what that looks at. And so that improves our ability to predict the behavior of the tumor on top of, say, for example, PSA, clinical staging, as well as the grade of the cancer.

Phillip Koo, MD [00:04:23] So, that's really helpful. So genomic testing is able to help us understand your disease better and sort of risk, which we hear that often, risk stratification. So, it gives you know the physician more information to understand, alright, is their biology more aggressive, maybe less aggressive? And I imagine that's going to have a huge impact on how you manage those patients. So, Zach, to you, once you sort of order these tests, get those results, talk about the different disease states and how it might impact your treatment decisions, your management decisions.

Zachary Klaassen, MD, MSc [00:04:57] Yeah, no, I think we're gonna talk about two important areas where we use biomarker genomic testing tonight, as Jim mentioned. One that we're not gonna talk about, but where we use it quite a bit is in sort of localized prostate cancer, where we have a patient, they may be a candidate for active surveillance, which is just watching PSAs, MRIs, subsequent biopsies, et cetera. Or they may be a candidate for active surveillance, but we're not sure if they really are, maybe we need a little more information. Decipher really helps us sort of as another variable in that discussion point. So, I wanted to bring this up because we're not gonna specifically hit on it tonight, but really deciding who may be a candidate for active surveillance, who may on paper look like they need treatment, but then you look at this genomic score, it's low risk, and maybe we can do active surveillance for a period of time. So, this is something where Jim and I, as urologists, use Decipher all the time and in sort of this active surveillance question. And then we move into situations where we're taking out the prostate, we're doing a radical prostatectomy, the removal of the prostate and the seminal vesicles, and we get some higher risk features back, and we are trying to decide are we should we do radiation right away? Is there a period of time that we can wait and see what the risk of the tumor is based on that? Decipher also plays an important role in that situation as well. So, those are the two that we're not gonna talk about. Important to highlight. And then clearly, we're gonna talk about tonight the high-risk localized as well as the metastatic setting as well.

Phillip Koo, MD [00:06:28] Great. So, Jim, from your perspective, how have these genomic tests, these biomarker tests, changed how you've practiced over the years?

Jim Hu, MD, MPH [00:06:40] For sure. I think it just allows A is, you know, a very common question, I'm sure that Zach, myself, and you see in terms of your patient facing role is anyone diagnosed with cancer, you know, it's a scary term and people want to try to map out what their future looks like. And so, the precision medicine test and/or the Decipher test, for example, and Zach, you know, not to overlap with what he just very eloquently talked about, you know, it just gives you a sense if you're treated, you're given standard treatments for prostate cancer, for example, in the localized space, what's the chance of metastasis in five and 10 years and what's the risk of death in 15 years, right? And so, you

know, I think on top of that, for example, for the radiation oncologists, it's helpful because it they can decide if you have, we're gonna use the terms risk again, unfavorable intermediate risk or high risk, do we add androgen deprivation therapy, right? And then of course, I think how Zach and I see it most commonly is that we, in the men who have, let's say, low risk prostate cancer that are candidates for active surveillance, you know, it just gives us confidence, right? And the patient confidence when they come back as Decipher or you know, choose your precision medicine test, if it also just affirms that that molecular fingerprint has a less aggressive behavior, it just gives us confidence to do active surveillance.

Phillip Koo, MD [00:08:00] Alright, good. So there seems to be some questions. So just to summarize, we are not talking about germline testing today. We're not talking about the genetic things that you inherit and pass on. We're not talking about somatic testing. We are talking about that subset of genomic/biomarker testing. And, you know, as we discussed, it's more about sort of understanding the biology, understanding the risk. And the way I like to think of it is there's a lot of gray in medicine. I think a lot of times we try to simplify things, it's black or white, but there's a lot of gray. And then having this extra additional information can really change how you know you manage and treat these patients, which can be really important and is really heralding this idea of precision medicine. So hopefully this clarifies it, but we are focusing on genomic and biomarker testing. So, let's go right into case one, and I'll turn it over to you, Zach.

Zachary Klaassen, MD, MSc [00:09:00] So yeah, this is a case of essentially high-risk localized prostate cancer and where we may use Decipher genomic classifier to help us make some decisions. And we'll go through what Decipher is in a little bit more detail. We'll talk about a case and then Phil will have a discussion about where, depending on what this score is, what could the discussion be with the patient?

So, the Decipher prostate test is as Jim mentioned, it's a 22-gene genomic classifier. And it basically is looking at what are the long-term endpoints. So, if we take a whole bunch of patients and we have metastasis as an endpoint, what are the different risks for developing metastasis? And we know based on other studies that metastasis or disease that spread outside the prostate is a good surrogate endpoint for overall survival. It means that if you have metastasis, the likely of mortality is much higher.

And so, this Decipher test was developed at the Mayo Clinic. You can see here 1987 to 2001, 639 patients that had their prostate removed. Among those patients, 426 never developed metastases, and 213 patients did develop metastases. And these were higher-risk patients with higher Gleason score, higher PSA. What they did is, Jim eloquently said as well, there's a fingerprint of these 22 genes that then allows this to develop a risk score. And these genes, without getting into too much detail for Decipher, these are cell proliferation genes, genes that are involved in differentiation of tumor, immune modulation, androgen signaling. And so, to select those genes, a lot of work was done to get to those 22, but that's sort of the basis of what that fingerprint looks like.

And so, then once you get that Decipher score, you can see in the middle of the slide here: high-risk, intermediate, or low-risk, and this is really what we're discussing with the patient. If we look at Decipher prostate today, this is one of the most robust tests that we have in clinical practice. You can see here, it's been assessed in over 200,000 patients that have been subsequently included in studies. 25+ prospective randomized clinical trials that have included the Decipher prostate test, and 90+ publications demonstrating clinical validity and utility of this test. And so, there's a lot of tests out there. They're all kind of similar. I

think from my standpoint, I like Decipher because it's been so robustly analyzed, and we call it validation. We have it in a lot of different areas. We know that it works well. And as Jim mentioned earlier, this is about confidence in having these discussions with our patient. That validity, that robustness of the test really helps us with that confidence to have these discussions with patients and their families.

So, when we're looking at risk stratification, this case is on high-risk prostate cancer. This is the NCCN guideline. This is sort of one of the main guidelines that we use for a lot of different cancers, including prostate. And so, I've circled in the box here what high-risk prostate cancer is, has one or more of the following high-risk features: Clinical T3 to T4. So maybe a little bit aggressive in the prostate, into the capsule, maybe into the seminal vesicles, which sit behind the prostate. Gleason grade group 4 or Gleason grade group 5, this is on biopsy. And this also could be a PSA greater than 20. So, this is truly a high-risk patient with localized disease.

Phillip Koo, MD [00:12:37] Great, Thank you, Zach. So, you know, I do want to clarify. So, these tests are run in patients who have a diagnosis of prostate cancer. So there really is no age requirement or whatnot. And either you could send the biopsy sample or sometimes you could send a prostatectomy sample. Is that correct?

Zachary Klaassen, MD, MSc [00:12:52] Yeah, generally speaking, without getting too much in the weeds, some of them are for biopsy tissue, some of them are biopsy or prostatectomy tissue, Decipher's either one.

Phillip Koo, MD [00:13:01] Great. So, we're going to go through a case in this clinical scenario with I think which I think will help all of you sort of understand what goes through the mind of the urologist and sort of how this impacts how you might be managed. So, this case that we have today, a 69-year-old white male who had a screening PSA with the primary care physician, and it came back at 25 nanograms per milliliter. So that is high. Symptomatically, he's getting up one to two times a night to urinate, and he's not having any bone pain. So, his medical history is high blood pressure, high cholesterol. He's had his inguinal hernia repaired in the past, and he does have a positive family history, a brother and uncle with prostate cancer.

So, because of that high PSA, you know, a referral was made to urologist, and the urologist performed a digital rectal exam, which felt a smooth prostate gland with no nodules. And then a recommendation for prostate biopsy was given because of that high PSA level of 25. So, 12 cores were taken. Eight out of 12 of those were positive for Gleason grade 4 prostate cancer. And given that, it makes sense to go ahead and get a PSMA PET CT, which did not show any prostate cancer getting outside of the prostate and metastasizing, which is great news. So, he would be characterized as localized high-risk prostate cancer because of the Gleason grade 4 and the PSA that was high at 25. So, what to do next? Obviously, that's going to be the big question. And you have multiple different options. So, Zach, bring us home. How does that test sort of what are you thinking in terms of treatment options? And then we'll get to the test results and see how that impacts that.

Zachary Klaassen, MD, MSc [00:14:49] Yeah. So, I think, you know, when we're sitting with a patient, we're really thinking about the three options. Sort of there's some other options, focal therapy, et cetera. We're just going to keep it at active surveillance, surgery, or radiation plus or minus hormone therapy. This patient clearly is not a good candidate for active surveillance. He's got high-risk disease, his PSA is 25, his Gleason grade group

score is 4. He's I believe he's 69, if I'm not mistaken. Otherwise, reasonably healthy. This is not an active surveillance candidate in probably 99.99% of cases. So, then you think about the two sort of classic treatment options: radical prostatectomy, radiotherapy plus hormone therapy. You know, I think there's certain places where maybe a radical prostatectomy would be okay. This PSMA PET scan is negative. But based on that Gleason grade group score, based on his PSA of 25, there's a higher likelihood of either having a PSA persistence, which means the PSA does not go down to zero after surgery, or a biochemical recurrence, the PSA goes down to zero initially, but then goes back up afterwards. So, then you're looking at probably radiation after the prostatectomy. So that's important for the patient to understand when you're talking about these two options.

The other option is radiotherapy, given the fact that this is external beam radiotherapy or brachytherapy, given the fact that it is high-risk disease, majority of folks would be candidates probably for 18 to 24 months of hormone therapy. This sort of helps the radiation work a little bit better as well as help that PSA come down a little bit quicker as well.

Phillip Koo, MD [00:16:23] So in your mind, what are you thinking the biomarker genomic test, the Decipher test, how is that going to impact your thinking? If it comes back high versus low, we'll go through those scenarios, but what's sort of the big concern here? Because you're also balancing what the patient wants and what their goals are.

Zachary Klaassen, MD, MSc [00:16:41] Yeah. No, I think really, you're, you know, Jim said it earlier, you're looking for a little bit more information. All the things we've talked about today are sort of the classic things we look at. You're looking at the PSA, you're looking at the clinical stage, and you're looking at the biopsy Gleason grade. And so, it's that one extra variable that maybe just helps you lean one way or the other. And that's really what it comes down to.

Phillip Koo, MD [00:17:05] So we'll go to the next slide and a Decipher test was sent off, I believe. Those show through shared decision making with the patient and family, patient elected for radiotherapy and ADT, was interested in other tests that may help with treatment decisions like somatic testing. No mutations were identified, and then a Decipher test was also performed. Talk us through this sort of graphic here in terms of how it might impact your thinking.

Zachary Klaassen, MD, MSc [00:17:36] Yeah. So, once you've gone through that shared decision-making process and you know that you're gonna do radiotherapy as a primary therapy, our radiation oncology colleagues have done a lot of really nice work, and they should be congratulated for the trials they run and for incorporating some of these analyses with Decipher afterwards. To sort of figure out how long we should be giving hormone therapy. Is it okay to give 6-12 months, or should we be leaning a little more towards 24 months of hormone therapy? And hormone therapy is not without its own risks and complications in terms of bone issues, muscle loss, fatigue, there's some cognitive disorders as well. So, I always think that with incremental ADT, we are at risk of higher risk of all those things. And so, if we need to do it based on what the cancer is telling us and what the genomic test is telling us, that conversation is either easier if you have a little more confidence that this is the right thing to do. And so, I think that in this conversation, we've decided on radiotherapy, how long should we be thinking about giving the hormone therapy for?

Phillip Koo, MD [00:18:42] You know, that's such an important question and I think oftentimes we talk about ADT and we sort of throw it out there like it's a benign type of treatment, which we know it isn't, and patients don't like it. And it's important for us to be able to figure out, alright, we don't want to give people too much, nor do we want to give them too little. And clearly the Decipher test in this scenario will give us the scientific backing to figure out, alright whether they should be on longer term or short term. So, let's go on to the next slide. And this is what was returned after the sample was sent and analyzed. So just sort of explain sort of this scoring system and what it means.

Zachary Klaassen, MD, MSc [00:19:22] Yeah, so we put together two sort of scenarios here because I think it's important to sort of see what whatever this test shows, what's the conversation after that? So, in this situation, Decipher prostate is low-risk, which is great. And so, when we're sitting down after getting that result, so usually what happens is we have the initial conversation, and we send off the Decipher. There's a follow-up visit to go over those results. Typically, it takes about two, maybe three weeks to get that result back. And so, when we have a low-risk score, as you can see here, perhaps there's less of a benefit for this long-term radiotherapy. Perhaps it's okay to give sort of a six-to-twelve-month course rather than an 18 to 24, even some would advocate up to 36 months. And so, I think the implications is to discuss with your treatment team whether you're a candidate for radiotherapy plus short-term ADT. I think a low-risk score sort of puts you perhaps in that short short-term ADT box. And if we don't have the Decipher test that says low-risk, we don't really know if that's even a feasible conversation. And so, I think, these conversations are always very different depending on how these tests come back because again, we have the confidence based on a lot of validation of this test to be able to get that, you know, low, intermediate, or high-risk back and then have that conversation with the patients.

Phillip Koo, MD [00:20:37] Great. So, this comes back and the scenario is it's high-risk. So how does that change what you're doing?

Zachary Klaassen, MD, MSc [00:20:46] Yeah, so this is, I would say, it's a harder conversation, but at least it gives us some clear goals that okay, we're gonna have to think about doing a longer-term course of radiotherapy. If I don't have this test and I say you need 18 to 24 months and really, they only needed 6 to 12, that's overtreatment by maybe a year or so. And so, while this is not what the patient or we want, we're grateful for because we know that we should be thinking about that longer-term radiotherapy at least 18 months, probably 24. And so, I think in those situations, then we focus on: how do we get through those 18 to 24 months?

I tell people the first thing is you keep exercising. If you're exercising already, continue to exercise. It's even more important on that long-term ADT to continue exercising. If you're not exercising, start exercising. And I think exercise really does do a really good job of certainly maintaining bone mineralization, muscle mass, but also just that cognitive aspect that is sometimes overlooked with long-term ADT. It's also important, you know, even for short-term ADT, but certainly for long-term ADT, that vitamin D, calcium supplementation is really important. Just naturally, that the way ADT works, hormone therapy is it's gonna decrease those levels, and it's important to supplement with the with vitamin D and calcium.

Phillip Koo, MD [00:22:09] So hopefully all the viewers sort of can see the value of this test, especially when you're trying to figure out whether you're getting longer term ADT or shorter term, and it really can inform that decision to make the decision that's best for you

personally. Obviously intermediate risk, it might come back intermediate risk sometimes and that's a little tricky.

Zachary Klaassen, MD, MSc [00:22:28] That's a harder conversation because then you really have to go back to shared decision making, right? So, then it's okay, are they on the younger side, are they healthier? Perhaps we maybe lean towards the high, the longer-term ADT, or maybe we try to get to 18 months, see how they're feeling, and then see if we can get to 24-ish months. But it's a harder conversation intermediate because we're kind of in the middle, you know, by definition.

Phillip Koo, MD [00:22:51] Great. So, let's go to the next slide and I think we have the take home messages.

Zachary Klaassen, MD, MSc [00:22:55] Yeah. So hopeful as you mentioned, Phil, hopefully that was helpful to the audience just to sort of see how this test can be helpful in this high-risk localized setting. And we know that, as we mentioned several times now, this is a validated genomic classifier for these patients and sort of delineating how long we should be giving hormone therapy for. And so, I think the NCCN, as I said, this is sort of the golden guideline that we often come back to. It's updated, you know, two to three times a year. It's certainly robust. And so, it's recommended in the NCCN guidelines to use this test in this setting. Again, I think it's important. The Decipher test is one factor among many. You should discuss this with your treatment team. Again, coming back to shared decision making, I think we had several points along that journey with the patient where shared decision making is super important for these patients.

Phillip Koo, MD [00:23:49] Great, thank you. So, let's go on to the next case and we'll turn it over to Jim. And this case will be for patients with metastatic prostate cancer. So, Jim, take it away.

Jim Hu, MD, MPH [00:24:06] Sure. Thanks so much. And so, this is just showing some of the work similar to what Zach showed earlier in terms of the foundational work for Decipher coming from the Mayo Clinic looking at the radical prostatectomy specimens. This just shows the scientific foundation of the use of Decipher now in the metastatic prostate cancer setting. And so, the STAMPEDE and CHAARTED trials refer to two large you know, what we term randomized trials. And in these trials, for example, in the STAMPEDE study, it was really the randomization of men with newly-diagnosed metastatic prostate cancer to traditional hormone therapy alone, or the addition of abiraterone with the hormone therapy. And the CHAARTED study is looking at men with metastatic hormone-sensitive prostate cancer and looking at whether or not adding docetaxel had some benefit to survival. And in in the charts, the figures we're looking at, for example, you can see that on the y-axis or up and down, that looks at overall survival. So, if you're straight across at 100 at the top, or one here in this example, that means everyone's still alive. And as you move to the right, that gives you the time frame.

And so, what you can see is that in both of these studies, that is on the left side with the addition of the abiraterone and on the right side the addition of docetaxel, which shows the green curve, if you're shifting those curves higher, that means that there was a survival benefit. People lived longer. And so again, I mentioned that this is the foundational work that was done by Veracyte or Decipher in this example, is that they went back and they had tissue from the men when they were diagnosed, and they ran the Decipher test. And similar to the scale, and we'll see later, they were classified as either high or low-risk. And so therefore, this is just showing you that in an observational way, when they looked at the

results of these randomized trials, they could go back and look at the classification of the tumor based on that Decipher score and then correlate it to their survival.

So, for example, in the CHAARTED study, again, this is high-volume disease, metastatic disease. This may show you that someone with a high Decipher but a low volume or low number of metastatic disease would still benefit from Decipher. Or, for example, the same thing can apply to the STAMPEDE study, where, for example, when they were newly diagnosed with metastatic prostate cancer, again, the burden of metastasis may be high, but if they come back low-risk, that particular patient may, again, through shared decision making, which Zach emphasized earlier, is there some benefit not to escalate to abiraterone because of a more favorable side effect profile. That you'd have less side effects just staying on hormone therapy alone.

And so that's really the gist is that the Decipher was run after the results of these randomized controlled trials where you had long-term survival data where they classified as Decipher high versus low risk, and then correlated to looking at the benefit of the intervention arm where abiraterone was added, for example, in STAMPEDE and docetaxel was added in CHAARTED.

Phillip Koo, MD [00:27:49] Great. So, this is interesting. It's a new indication. So we go to the next slide, but it's a new indication where patients are going to be metastatic. And then this test basically just tells the physician and helps inform the physician whether maybe they should get more aggressive therapy or potentially less aggressive therapy. People can see how valuable that type of information would be.

So, I think going through this case will hopefully highlight that for everyone as well. So, we have a 77-year-old African-American male on PSA surveillance with his primary care physician. So, it went from 7 nanograms in 2023, went up the next year to 11, and then went up pretty rapidly the next year to 45. So obviously this is concerning. He's getting up two to three times a night to urinate, is having hip pain, no blood in the urine. High blood pressure, high cholesterol, has had a heart attack, so clearly it has a lot of cardiovascular risk factors, has had knee replacement and gallbladder removal in the past, and has a mother with breast cancer.

So, this patient obviously would get referred to a urologist. And I will say that you know the screening, the PSA screening is just a blood test. After they're sent to the urologist, oftentimes they will get a digital rectal exam to help characterize the disease. So, it's not really necessarily part of the screening protocol, but this follow-up protocol is where the DRE comes into play. And the urologist noticed some nodules on both sides of the prostate. It was recommended to get a prostate biopsy. And 11 of the 12 cores came back with Gleason grade 4 to 5 prostate cancer, so high grade. Makes sense to get a PSMA PET in that scenario. And what they saw was that there were pelvic lymph nodes, there were this disease in the left hip and also the spine. So, this clearly got outside of the prostate and has spread to other parts of the body.

So, what does the patient have? The patient has what we would call high-volume metastatic prostate cancer. So, a decent amount of lesions outside of the prostate, more aggressive, obviously not a good prognostic indicator. So, what to do next? You have multiple different treatment options, which includes systemic therapies, but the question becomes how much systemic therapy and which ones. So, let's go to the next slide. So, patients interested in other tests that might help with treatment decisions. They did somatic and germline testing, which is very applicable because the patient has metastatic disease,

but we're not going to talk about that. Also had Decipher testing done. So, Jim, talk us through the Decipher test and how that's gonna change how you might manage this patient.

Jim Hu, MD, MPH [00:30:38] Sure, absolutely. And so, when we go back and think about the medical history, for example, right? I think you had a history of a heart attack. And so, we know that, for example, if someone and Zach mentioned the duration of hormone therapy or androgen deprivation therapy you can be on if you get radiation. But in the case of metastatic disease, hormone therapy is basically the gold standard, right? You're gonna stay on hormone therapy, whether you know, a newly diagnosed person like this is hormone-sensitive or you can turn into castrate-resistant prostate cancer after some time. But the hormone - the androgen deprivation therapy or hormone therapy remains something that you stay on, right? And so that's number one.

But going back to the heart attack history, we know that there is an association of hormone therapy and the intensity of hormone therapy with other side effects like metabolic syndrome, like coronary artery disease, or worsening the risk of strokes and so forth, right? And so, when we talk about treatment intensification and the use of Decipher and how it may be beneficial, again, the STAMPEDE trial showed, I think largely that that if you have newly diagnosed high-volume metastatic disease, that certainly the addition of abiraterone is gonna improve overall survival. But then again, we talk about the burden in terms of side effects and some of those undesirable aspects of increasing your risk of a heart disease and metabolic syndrome, diabetes as well. And so that's where, again, if someone comes back as Decipher low-risk, that's a discussion to be had with the urologist, the prostate cancer specialist, in terms of whether or not it makes sense to try to delay treatment intensification with the abiraterone or what's seen as the ARPI, the antigen receptor pathway inhibitor in this case. For example, then if someone had a much higher, again, in this case, a high burden or even higher burden of metastatic disease.

If someone came back as Decipher high risk, you see the plus-minus docetaxel. You know, docetaxel, I didn't, I think, go into it in greater depth earlier, but it's actually a form of chemotherapy that basically inhibits cell division, right? And so, some of the undesirable side effects of inhibiting cell division, which will slow down or kill some of the prostate cancer cells, though, is that cells that turn over rapidly are also affected, right? Because typically chemotherapy, you kill the cells that are dividing quickly, like cancer. But typically, for example, side effects such as your hair falling out or diarrhea or an upset stomach, you know, we know also the hair cells turn over quickly, or the cells in the gastrointestinal tract turn over. There's also neurotoxicity where you get numbness, tingling. And so, there's a lot of undesirable side effects.

And so, it's basically tailoring whether or not you know someone with Decipher high risk in which there may be greater benefit of adding triplet therapy or all three, the ADT, the androgen receptor pathway inhibitor, the abiraterone in this case, and or the docetaxel if someone is high risk.

Phillip Koo, MD [00:33:58] Great. So, let's go to the next slide. So, the Decipher was sent off likely using their, I believe the biopsy samples, and it comes back low-risk. Take it away from here.

Jim Hu, MD, MPH [00:34:13] Sure. So, if you think back to the figure in which - it was on the far right - from the CHAARTED study where there was no, you know, in someone who was that's Decipher low-risk, if you added docetaxel, right, the green and the red curves

did not change. Okay, meaning that there was no difference in overall survival. So, in that particular instance, again, the addition of docetaxel did not affect survival, but certainly it has treatment side effects, right? And so that's an example where, I think I mentioned, someone may have a high burden of disease based on their PSMA PET CT. But yet, on a personalized medicine or on a genomic medicine basis, a genomic testing basis when you looked at the biopsy and it's Decipher low-risk, then that person would not benefit in terms of overall survival from the addition of the docetaxel.

Phillip Koo, MD [00:35:07] Let's go to the next slide and it's the same idea. Like if it came back high-risk, then clearly adding the docetaxel would be beneficial.

Jim Hu, MD, MPH [00:35:15] That's right. So that's the, you know, in the people that were, if you think back to the figure, Decipher high-risk, that's where the curve separated, right? Those who got the intervention that is abiraterone in the STAMPEDE trial or the docetaxel in the CHAARTED trial, the curve separated more. So, there was a better overall survival benefit, looking at the fingerprint, the genomics, Decipher score, in this case that one is high-risk and you're more likely to benefit from the addition of the doublet therapy (that is the abiraterone) or the triplet therapy, the addition of docetaxel.

Phillip Koo, MD [00:35:53] So this is great. I think hopefully the viewers all see the benefit where, alright, if it comes back low-risk, it doesn't make sense to get that additional chemotherapy, which is going to be hard, without any benefit. And then clearly in those who come back higher risk, it makes sense to go forward with, you know, a triplet type of treatment with chemotherapy because you will benefit from that. So, you could hopefully see how powerful that type of information is in terms of treatment planning. So, give us the take home messages.

Jim Hu, MD, MPH [00:36:26] Absolutely. So, the Decipher test is a validated genomic classifier test. As we talked about, this isn't looking at, you know, germline testing. We're testing the prostate cancer biopsy tissue, which was sent out to this commercial lab. And based on that risk stratification, again, I'm trying to use all the terms that we've defined and that patients will become more comfortable with. The risk just basically increases your prognostic or predictive ability to help you better understand, in this case, overall survival implications of adding the abiraterone or adding the docetaxel doublet or triplet therapy in the setting of newly diagnosed metastatic prostate cancer. And again, the treatment intensification just means adding the abiraterone up-front or even more intense, adding docetaxel and the abiraterone in terms of triplet therapy. And as we mentioned earlier, of course, the goals of treatment for individuals vary, right? And everyone's different in terms of side effects and their desire to have certain morbidity or side effects. And that's why we talk about shared decision making where with the provider, with the healthcare provider, these discussions should be had.

Phillip Koo, MD [00:37:42] So we're gonna move on to some Q and A and we have a lot of questions coming in that were submitted before the webinar and we have a lot that were submitted during it, and I know Zach's been able to answer some of them. So, one question I'd like to ask is, you know, in this setting, so post-biopsy, you have a diagnosis of prostate cancer, you have Decipher, you have other tests that could be performed. What are some of the other tests? What are some of the pros and cons of those different tests? Maybe Zach, I'll start with you.

Zachary Klaassen, MD, MSc [00:38:13] Yeah, I mean there's tests sort of before diagnosis, there's tests after diagnosis. So, you may get the mumbo-jumbo of tests is

pretty vast. I think if we're talking about post-diagnosis, the sort of the main ones, Decipher, Prolaris, GPS [Genomic Prostate Score] or Oncotype DX are sort of the main ones. At a high level, they're all sort of….the goal is to see what risk is. And so, they may be testing slightly different genes. There may be different validation studies. Generally, I've developed a comfort level with Decipher. I think we talked about the robustness of the data and the validation of that test. So, we have our comfort level with the ones we use. You know, with those some questions about I had a Prolaris, should I get a Decipher? I think probably not. You know, it's one variable amongst many to sort guide a treatment decision. So, it's not an easy answer to give, but if you've had one, it's probably enough.

Phillip Koo, MD [00:39:14] Jim, in your practice, have you ever seen conflicting data points or results from these various tests? And if you do, how do you sort of reconcile that?

Jim Hu, MD, MPH [00:39:25] Sure, great question. In fact, I'll just you know, I think just using a real-world example, right? And so, you know, one of the tests that I don't think we've mentioned, but just to be fair, that we'll mention is the Artera test. And that's a new precision medicine test that is based on, again, the secondary analysis of randomized controlled trial data. And in this case, it's you know, men who had radiation therapy. Do you add androgen deprivation therapy similar to the example that Zach used in the first case? And so Artera, instead of running like the Decipher, the 22-gene pathway on a chip, Artera looks at artificial intelligence and looking at the slides and then correlating those slides to the long-term outcome of, you know, did they do better if you added androgen deprivation therapy or not?

And so, a recent patient, for example, we did that, right? Because they wanted to ask the question, should I get androgen deprivation therapy or not? And we had conflicting results. The Artera test said, you know, no, this is lower risk. The Decipher said it's higher risk. So, what do you do, right? And so, this gets to, I think, you know, Zach's point when he introduced Decipher earlier. In this case, I'd probably say that Decipher has been valid - Again, I have no just full disclosure. I, you know, I'm not an investor, don't have any shares in either of these companies. But in this case, Decipher has been through more validation studies, right? There's been more studies beyond, for example, that randomized controlled trial that Artera is based on.

And so, I think as a patient, you may want to, you know, and one of the things that is, you know, I think a sophisticated patient would recognize is there's a lot of statistical modeling, right? And so, we know that statistics is only as good as the data. It's kind of like junk in, junk out. And I'm not saying it's junk, but as your sample size increases, as you test this in other populations and find the same results, and that's what validation means, then I think you have more confidence in the outcome.

Now, having said all that, just to put a fine point on this, you know, one of the things we talked about is let's say you had a radical prostatectomy, seminal vesicle invasion, and you got a Decipher, right? Like we've seen patients where, you know, 10 years ago they had a Decipher and it said, oh, you know, it's Decipher is 0.96, your chances of dying are, you know, 20% at 15 years, right? But we see patients 10 years out and they have no cancer recurrence. And so, you have to understand that this is almost like looking for the weather report a year in the future, right? It may help you plan what you're gonna wear that day or you know, your travels, or looking at an almanac, for example, like a farmer does and says, hey, what do I plant this year? But it may not come to be. And so, I think that's the caveat in all these tests.

Zachary Klaassen, MD, MSc [00:42:13] Phil, can I add one quick thing to Jim's comment? I think you know, there's a lot of, I think the Artera genomic discussion is important. There's some recent data that's come out that suggests they may look at different components. And so maybe, building a biomarker that has both of them, you know, maybe what we see in the next several years. But you could talk to probably a hundred different urologists. They're gonna have experience with one versus the other. They're all kind of the same in terms of the genomics, but I think with the artificial intelligence and Artera certainly is the most common. There's some other ones that are being developed. This is still playing out as we go. And I think, you know, AI continues to get better with more data. So, we'll see how that plays out. But I think at least it early on snapshot is they're maybe looking at different components of a pathology slide.

Phillip Koo, MD [00:43:04] You know, this is really exciting. It's almost like you're trying to predict the future and whatnot. It's almost like science fiction, but it's a reality. It's not perfect, but it's helpful. How do you sort of talk through patients where they might get something where, we've been talking about high-risk and metastatic today, but we'll just sort of take it more broadly. Patients with low-risk or intermediate risk, and all of a sudden, they get a high Decipher score, and that's gonna scare them to the nth degree. Zach, how do you counsel patients through that journey?

Zachary Klaassen, MD, MSc [00:43:36] Yeah. So, I again a real-world example from I believe this Monday's clinic or maybe last Monday, it doesn't matter. A patient with four cores of Gleason 3+3, so low-risk disease, interested in active surveillance, younger patients. So, I wanted to make sure we covered all our bases. We got a Decipher score. We discussed it recently, and it was, I think it was 0.8. So, it was in the high risk. So, I told the family, my recommendation is you can still do a period of active surveillance. It just, we may have a little tighter rein on a PSA going up or an MRI changing, or maybe a shorter leash on a repeat biopsy. So, it doesn't mean that you have to immediately jump to therapy. It just means that our threshold to do the next step in evaluation or eventually treatment may be a little bit lower based on what that test shows.

Phillip Koo, MD [00:44:28] So, you know, we're talking now about active surveillance. This is an interesting question that was submitted. Jim, do you ever do multiple Deciphers if patients are on active surveillance and then repeat it every time, they get a biopsy?

Jim Hu, MD, MPH [00:44:41] That's a great question. So, I think just to step back a little bit and just to make sure we're all on the same page, right? So, number one is, you know, everyone's prostate size is different, but as a rough rule of thumb, you can say that a biopsy samples 1% of the prostate, right? And so, you gotta understand that you're running that test, that test of the tumor, the tumor characteristics, from that particular sample. And so, you know, and typically our labs do not send out two separate cores of tissue for the precision medicine test or Decipher in this case, to be run, right? So, you're picking the highest. Let's say someone has grade group 1 and grade group 2, they should be sending out the grade group 2 prostate cancer, right? And so, you have to understand number one is that on repeat biopsy, even with MRI targeting, I would say, most of us who are honest about it, it's unlikely you're hitting the exact area over and over again, right? You know, with modern technology. And so, do you submit a Decipher when you're on active surveillance? I think I A. Yes, I would if someone had grade group 2 prostate cancer. If someone had grade group 1 prostate cancer in the earlier example that you and Zach were discussing, you know, I think overall, and Zach, Philip correct me if wrong, I think usually the discordance, meaning that someone's high-risk Decipher, low-risk prostate cancer under the microscope is pretty uncommon, maybe about 3%, right?

And so, the caveat with all of these tests, and I think, you know, and as a physician, is I think how the patients should think about this is, you know, let's order a test only if we're gonna do something with the results, right? Because the worst thing you can do is to order a test and you're not really gonna do anything with the result. Like, and again, just as a quick story, like I practice in New York, you know, people love there's a lot of finance people, they love predictability, so forth. But it's kind of like these days, get it, you had the prostatectomy, you're gonna get a Decipher, right? And we know now randomized controlled trials show that you should wait for PSA recurrence, you know, before you do radiation. And we didn't know that when Decipher originally came out, right?

But yet we still have people who want to get that just because they like the numbers. I personally don't like to do that because it gives you anxiety. If the test comes back, like I said, like the example of the weather report, if it says it's gonna rain, but it never does, to me, you know, we're not gonna do anything about it, right? 10 years from now, if it rains or not, but yet you're introducing a degree of anxiety. So again, I kind of, your original question do you repeat Decipher on a biopsy? I would only, again, do it for someone who's got, you know, intermediate-risk cancer or what we term clinically significant, because there is a component of that, right? The pattern for that can metastasize.

Phillip Koo, MD [00:47:20] So Zach, in terms of insurance coverage, what does that look like from your perspective?

Zachary Klaassen, MD, MSc [00:47:27] Yeah, it's a great question. I mean, I think I'm not an expert in insurance, and I think it probably varies by state. Generally speaking, Decipher has been well covered for my patients. And so, I like that aspect of it too. Yeah, I think for the most part, Medicare covers the majority of these. But there's always gonna be, you know, somebody has part this or part that in their insurance, and there's a secondary component that may give us a little bit of trouble. But generally speaking, well covered by insurance, particularly in those settings where we use it a lot in deciding on active surveillance or not. And so, I think I think it's gonna be very individualistic. It's gonna be state specific, probably, but majority of companies will cover it.

Phillip Koo, MD [00:48:13] So Jim, we probably have a lot of patients on the line right now who might be on active surveillance or might have had a prostatectomy for intermediate-risk prostate cancer who now are interested in getting this Decipher test. So how long does that sample last where they could run a test like this?

Jim Hu, MD, MPH [00:48:33] Absolutely. So, I think, you know, there are situations where, for example, you mentioned biopsy active surveillance, right? If the core of tissue or the amount of tissue is very little, okay. And so, to answer that question fully, there's slides that are made of the cancer that the pathologist examines under the microscope. They look at the characteristics, they grade it, right? But they preserve what's in a paraffin block, and that's what's sent out to the third party in this case, Decipher or another precision medicine test, right? And so, you have to have adequate tissue to begin with. And it varies from test to test, like two, three millimeters of cancer, right? Number one. Number two, your question, do you send it for radical prostatectomy? As I mentioned earlier, I personally would not because you know the randomized trials have shown the addition of radiation therapy only benefits people if you recur, right? Because let's say you had a high-risk Decipher, but you never recur, you get radiation, then you've been overtreated, right? You get the side effects, but you're not getting the benefit because you wouldn't have failed anyway, right? And so that's where I typically, again, I don't get a Decipher in the post RP

setting because there's been several randomized controlled trials that have looked at, you know, irradiating someone right away for adverse - what we call adverse pathology, that is higher grade cancer, positive margins, or you know, seminal vesicle invasion, versus waiting until the PSA gets detectable to above 0.1, 0.2 and irradiating at that time. And the outcomes show that cancer control is about the same, but yet you're gonna have worse side effects, worse quality of life if you do the radiation up front before waiting for PSA recurrence.

Phillip Koo, MD [00:50:13] Great. Thank you. So, Zach, a lot of times, you know, patients will hear these things, read about different tests. They'll go to their doctor and say, hey, doc, I was reading about this. I think it makes a lot of sense. Can you get one for me? And then the physician may or may not be as up to date, or they might say, Oh, you don't need it. Don't worry about it. You know, you know, you're fine. What advice do you have? Because that's really a tough position for patients and their caregivers to sort of try to push back against a response like that.

Zachary Klaassen, MD, MSc [00:50:43] Yeah, great question, Phil. I mean, I think, especially in today's healthcare systems, patients have to be advocates for themselves. Whether that's themselves or their granddaughter or their significant other. And I think you bringing something to your physician, he may say it's not indicated, and it may not be indicated, but you don't know for sure. There's always an opportunity for a second opinion. And so, I think if somebody really thinks, you know, they're up to speed, they're a really intelligent patient and they think they do need it, and your current physician's not, second opinions are always good. And I think there's a lot of urologists, radiation oncologists that that see patients as second opinions. I know Jim and I both do. And so just getting a second opinion to make sure may truly maybe it is not indicated, but if it is and you believe in it, you know, be an advocate for yourself, seek a second opinion.

Jim Hu, MD, MPH [00:51:38] if I may, I think Zach answered that question great. But the other example I think that comes up in my mind, Phil, is also just understanding that, you know, I think Zach, you know, was good enough to comment further on Artera, that is artificial intelligence, right? Looking at slides. But you have to understand that there is a subjectivity component to a pathologist looking at the biopsy, right? And so, you know, Zach's saying, hey, you know, empower the patient, get a Decipher, that can also replace, you know, you, the patient, having to call the doctor's office and saying, hey, I want my slides sent to institution X or institution Y, right? Because on a molecular level, you're getting a molecular signature that has been, as we talked about, tested, validated to better improve the prediction of the tumor. And so, I think there's an additional component that you're also getting in terms of you know, a second opinion, but on a molecular level of what the what the pathologist may miss, right? Because of inexperience or just difference in interpretation.

Phillip Koo, MD [00:52:41] You know, there have been some questions submitted about like PARP inhibitors. That's gonna be related to germline and somatic testing, not this genomic testing that we've been talking about today. And we have some other webinars where we've covered that topic. So, we have a couple minutes left. Any final words? Let's start with you, Zach, about genomic testing and biomarker testing.

Zachary Klaassen, MD, MSc [00:53:03] Yeah. Again, I appreciate all the great questions. I tried to get through a few during the session, but hopefully this was helpful to everybody on the line. As always, I'm impressed by how many people attend these. I think my take home is genomic testing is super exciting. It can be very helpful. It's not a be all end all

test. There's a lot of factors that go into these treatment decision making. Again, PSAs, Gleason scores, patient goals, etc. etc. So, it's very helpful and in the right situation use with people who know how to use it, Jim mentioned, only order a test if it may change how you're gonna potentially treat somebody. I think that's wonderful words of wisdom because it's not a be all end all. It can help with the discussion and really, it's an individualistic decision between shared decision with the family, and the patient and the provider.

Jim Hu, MD, MPH [00:53:53] Yeah, I think you know, we've covered it very thoroughly. Great for the opportunity. I think just, you know, keeping it simple Decipher or genomic testing, reinforce the use of active surveillance. Figure out if you're going to do radiation therapy, do you need to add androgen deprivation therapy to decrease the risk of recurrence? And then as we've learned tonight, and the risk again, similar high-risk, you know, adding ADT how long, and then metastatic disease, doublet or triplet therapy based on high versus low risk Decipher.

Phillip Koo, MD [00:54:22] Wonderful. You know, I really appreciate you guys taking the time to do this. Hopefully all the viewers can see the nuances and how this test can really help you make a better decision for you and your family members especially because some of these treatments come with negative side effects as well and you want to sort of pick the package or pick the path that gets you the best clinical outcomes while minimizing those adverse events and I think something like this can be really powerful. Really appreciate all of you guys joining and staying on for this hour webinar. And again, it’s so important, a knowledgeable patient is an empowered patient. And hopefully everyone is more knowledgeable after spending this hour with us. So, thank you all and enjoy the rest of your evenings.

Zachary Klaassen, MD, MSc [00:55:12] Happy Thanksgiving.

Jim Hu, MD, MPH [00:55:14] Thanks everyone.