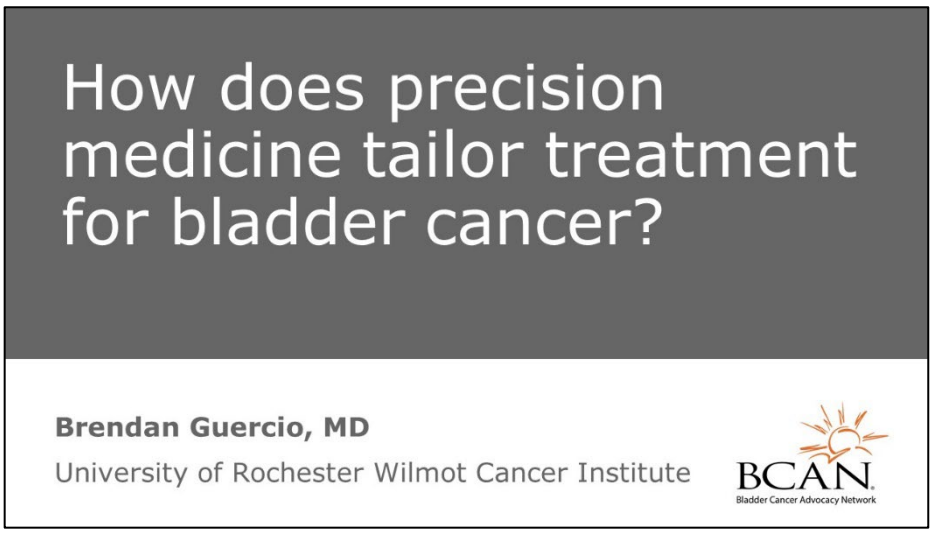

Stephanie Chisolm:

Thank you so much, Dr. Guercio. I think you can all agree that that was a very comprehensive review and definitely stimulated a number of questions. And I also think you can all agree with me that with talented clinicians like Dr. Guercio, who's also a prolific and talented researcher, the future is really bright for bladder cancer right now for patients who are newly diagnosed and even those facing the potential of a recurrence, there are now more options than ever before. I know one of the things that we discuss at our scientific meeting is really how do you sequence these different treatments? With so many different varieties, is it worthwhile to have your tumor genetic profile documented just in case you need to go to one of these precision medicine treatment options down the road? Is that something you would recommend to somebody who might be newly diagnosed?

Dr. Brendan Guercio:

That is a really great question, and I think that the answer is sometimes yes, that it's helpful to have that information in advance before you get to the point where you need to make a new treatment decision. For example, in advanced bladder cancer, the first treatment we often turn to is not a precision medicine. It's often immunotherapy or Enfortumab or chemotherapy. But I often will try to get genetic sequencing information from the time of initial diagnosis for advanced bladder cancer because it could help us know what options we have for the future. It could help us identify clinical trials. And it's also helpful because the genetic tests that are needed for precision medicine sometimes can take a long time. We often have to send a piece of tumor to a company. The company may take several weeks to analyze it and get the report back to us. So it's helpful to have that information ahead of time so that you're not rushing to get it when you actually need it later on.

Stephanie Chisolm:

That's really wonderful information to be considered. I think across the board, whether you're seen at a large academic hospital, some of them actually, for all patients coming in, they do offer genetic testing. And for others, especially for patients that are being seen in a smaller community practice or a smaller community hospital, that may not be an option. So I think if you're really interested, you should ask your doctors about that and see what they think about it. There is a question that has come in on the Q&A. Is there a registry that collects samples to study so that you can keep learning more?

Dr. Brendan Guercio:

That's a really good question, and there are actually a lot of registries that collect samples from different institutions. Sometimes these registries are parts of clinical trials that collect specimens on the trial and then add them to large banks of specimens that the National Cancer Institute can make available to researchers across the nation, which is really great because then any investigator with a really good idea can go to the National Cancer Institute and basically make a pitch to say, "I think this is a really great research question that we can use these samples for it to hopefully make things better for patients in the future." There's also large institutional efforts to do that. A lot of large cancer centers routinely bank samples from patients, with patient permission, to be used for future research studies to try to make precision medicine and cancer care in general better. So I guess the answer is that there's a lot of them around and certainly if a patient is interested in allowing for their tumor tissue to be used for that sort of purpose, letting their physician know that is a good idea.

Stephanie Chisolm:

That's really good information to have. Again, as you just mentioned, some of the larger places actually have a place where they can store all of those samples, both tumor samples, urine samples, blood samples. And then do you see a lot of corroboration in those three? If you were to look at a tumor and then also look at a urine sample, are you also seeing similar things in a blood sample? Is that something that you all look at when you're doing these research projects?

Dr. Brendan Guercio:

Definitely. Definitely. One of the very exciting areas is using these liquid biopsies to look for the DNA of cancers and tumors in the urine and in the blood and compare them to the genetic features in DNA that we find in pieces of the tumor itself. And we often find that there is good matchup. Sometimes, interestingly, we find that there are important differences because it turns out that when cancers evolve and change, sometimes different parts of a cancer can have different genetic features. And so if you only take a small piece of a tumor with a needle, you might pick up some genetic features that are important, but you might miss others that were present in other tumors in the body, which looking at DNA in the blood, which gets DNA from all over the body can sometimes be more informative in those circumstances.

Stephanie Chisolm:

How did you read my notes that I was taking? Because that was a question I came up with. Does tumor genetics change in recurrent tumors? You knew exactly what I was thinking. This is awesome. I really appreciate that. From your recommendation, are there particular urine tests, I think more than just a simple detection of bladder cancer overall? Because it really does benefit from having that cystoscopy where somebody's going in to look. But are there urine tests for monitoring that you think seem to be better than others?

Dr. Brendan Guercio:

I think the old standard that we've been using forever is urine cytology, which is still really important and a go-to test there, which is basically just looking for the cancer cells in the urine after you spin the urine down and just looking at it under a microscope. And obviously if you see cancer cells there, that can be really important for cancer detection. But there are more sensitive tests that are being developed. Some are commercially available that look for certain proteins or FISH, special kinds of DNA tests to detect cancer. I think the most exciting ones are still in the research phase. A lot of those other tests haven't really caught on in clinical practice because I don't think doctors have found them as helpful yet. But going forward, there are some tests that are in development that are much more sensitive, can detect very small amounts of DNA in the urine and can even tell us what genetic mutations are present in the cancer just from a urine sample. And I'm definitely optimistic that those will become an important part of standard care for bladder cancer over the next several years to decades.

Stephanie Chisolm:

Well, we have a great question that came in here, and this is almost looking for a little bit of suggestion as far as advice. "I'm awaiting results of my second round of BCG treatments. The first round did not work. I've been told that if it does not work, I should have a radical cystectomy to remove my bladder. I'm 49 years old and wondering if I should move forward with a radical cystectomy or explore other options?" And perhaps you might talk a little bit, this is my adding, some comments, talk a little bit about clinical trials.

Dr. Brendan Guercio:

Yeah, I think that's a great point. That's definitely a difficult situation to be in and I'm very sorry that you find yourself in that situation. Clinical trials are definitely actively looking at ways to help patients keep their bladders for longer. They're open at a lot of centers, especially large academic centers. In that space specifically, those are usually trials by urologists, although some of them might have involvement by medical oncologists too. But I think it might be reasonable if you're really concerned about keeping your bladder, which a lot of patients are, looking around to see if there are trial options is always a good idea. And there are other treatments other than BCG that are recently approved. Some of them are not always available, but your doctor will definitely know about them. So they're not the right choice for everybody, but you should be able to ask your doctor those questions because they know you the best and can tell you if those options might be reasonable for you.

Stephanie Chisolm:

Again, you jumped ahead, you read the question list. Can you comment on the efficacy of Adstiladrin? So since Adstiladrin is indicated for patients that did not respond to BCG, you need to have BCG first and if you don't respond, can you talk about Adstiladrin and maybe just highlight how that works? We have a webinar on that, and Patricia can drop that into the chat as well as she can drop our clinical trials search feature that we have on our website that lists all of the open clinical trials for your diagnosis across the country. So we'll get those in the chat box for you, but can you talk a little bit about Adstiladrin as if BCG doesn't work, what do you do next?

Dr. Brendan Guercio:

Definitely, yeah. And I don't use Adstiladrin as a medical oncologist. I give medicines that are either oral or intravenous, but I work with urologists all the time that treat the earlier stage bladder cancers with medicines like Adstiladrin. And it's interesting, a lot of the really great treatments that we have for early stage bladder cancer, like Adstiladrin, BCG, they work basically by stimulating the immune system to try and fight the cancer and to break up the cancer. And it is a good treatment option. To my knowledge, it's still kind of hard to get your hands on it in a lot of places, so it may not always be available even though it's approved. But for specific patients, I think it's definitely worth a conversation with your urologist about whether or not that's a good option for you if you are one of those folks who has a BCG unresponsive, non-muscle invasive bladder cancer.

Stephanie Chisolm:

What are your thoughts on extending immunotherapy beyond two years of treatment with Pembrolizumab?

Dr. Brendan Guercio:

It's a really good question. We don't really have good data in bladder cancer to help us know whether or not treatment with immunotherapy should end at two years or keep going. It causes a lot of hand-wringing and headaches for folks trying to think about it just because we don't have good data. And there are efforts to basically create clinical trials that randomize patients to either continuing immunotherapy at two years or stopping if they have a really good response. But those studies either aren't completed or they've been really hard to do because, understandably, patients are hesitant to be randomized in that situation.

Some folks feel really strongly that they're responding to the immunotherapy, so why would they stop? And other folks say, "Well, I've been on this so long, I would love a break, so why not give it a try?" But those studies are really hard to do, but they are important. So if you run into a clinical trial like that, I think it's a good idea to participate to help the field move forward and get a better answer to that question. But I think the real best answer is we know some people can stop and do fine, some people do stop and then the cancer might start growing again, and we're not yet that good at telling which person is going to be which.

Stephanie Chisolm:

There's a question from somebody that's clearly reading the journals, and you may or may not have seen this right off the top, but the link to the journal is actually in here. But they're referencing, "As Clinton et cetera found, tumor genomics changed, meaning discordance, between cancer stages. Can you comment on that in terms of how that genomics is changing and evolving as your disease might progress?"

Dr. Brendan Guercio:

It is interesting because one of the ways cancer is so smart and learns how to overcome treatments that we use to control it is through genetic change. It's basically evolving on a cellular scale. And in order to do that, it basically changes its genetic code so that it's more unstable so that it's easier to mutate, it's easier to change, it will duplicate the number of genes it has in one part of the genome and it'll delete the parts of the genome in other areas that are meant to keep cell growth in check. And it will just kind of mutate more and more as time goes on in an effort to be able to grow faster and be harder to control. And so that's generally the trend that we see as cancers start as very early cancers with less mutations and more normal looking genomes. And then as things move along their genomes just start to look stranger and stranger compared to normal cells. I don't know if hopefully that answers the question.

Stephanie Chisolm:

It does, and it just makes you think that cancer is an elusive adversary, that it can disguise itself and change and work faster than what you all are doing. And there's so many of you brilliant people working on finding the answers, but it's like a moving target. It just doesn't give you a chance to do anything to really get one step ahead of the disease, which is really unfortunate. But the good news is we do have some really talented people working on this. We still have time for a few more questions. Is there a test similar to DDR that might predict response to BCG? Do you know of anything? I know you're not a urologist and you don't necessarily deal with BCG, but do you know of anything that's out there or coming?

Dr. Brendan Guercio:

There have been some interesting studies on gene expression patterns, which are not specifically mutations, but are looking at basically the pattern of genes that the cancer chooses to read. And it does look like some of those gene expression patterns might be associated with better or worse response to BCG. That's still very early research and definitely not used yet in clinical practice to guide treatment with BCG. I think one good thing about BCG is that the response rate to BCG is just really high. And so fortunately, even without knowing the genetic features of a patient's individual bladder cancer, the vast majority of folks who are treated with BCG actually do have a good response.

Stephanie Chisolm:

And it's also not super expensive, it doesn't have quite the impact necessarily because it's intravesical, it's in the bladder itself, it's not systemic, it doesn't go elsewhere in your body. So there's a lot of reasons why BCG is usually the starting treatment because around 60%, right,

65% is pretty good effect from BCG. But now that we have other options, the good news is even things like what you spoke about earlier with the TAR-210, the little pretzel device, they can put a number of different treatments into that dispensary. It's a little piece that goes in flat through the catheter, and when it goes inside the bladder, it curls around itself and turns into almost like a little pretzel so it doesn't come out. And I've seen them and they have little microperforations that just allow that medication to go out.

Because if you think about it, keeping medication in the bladder, it's hard because nobody can keep their urine in for hours. It doesn't happen. And so when you fill up, you fill up, you have to empty it out. So it's always going through. And so keeping medicine there at the site of a non-muscle invasive tumor is really challenging. And this is something really promising that they're working on delivering this medicine over a longer period of time by having this little pretzel. So it's not only the medicine itself, but it's how it's getting in there that is, I think, part of the promise of the future that there's great science that's going on.

Dr. Brendan Guercio:

Absolutely, and I would just add to that, that there is even some promising early data that's definitely not standard yet, suggesting that the pretzel, because like you said, it's delivering treatment around the clock for a long time just in the bladder, may actually even be helpful in patients with muscle-invasive bladder cancer, which we typically think of as something that's so advanced that it really needs more aggressive treatment than intra-bladder, intra-vesical treatments. So that might be an option that helps maybe other more systemic medications work even better by adding to them in the future, but those trials are still being done, so we'll have to wait to see what the results from the larger studies show.

Stephanie Chisolm:

Again, it's such an exciting time from the research perspective, from a patient advocate perspective, speaking up for patients. There are now combinations of therapies, and things that worked really well on their own are working better when you pair them in some combinations. So I think we just keep learning all the time. There's a question about maintenance treatment, somebody saying they think it's aimed to actively prevent metastatic cancer from getting started once a patient is in remission. Can you talk a little bit about maintenance treatment, what that's really intended to do?

Dr. Brendan Guercio:

Sure. And there's different kinds of maintenance treatment. There's BCG maintenance, there's also maintenance for advanced and metastatic cancer, like maintenance Avelumab and immunotherapy. Both actually have similar goals, just in very different contexts. But basically the goal of any maintenance therapy after a good response has been achieved with your initial treatment is to make sure that that treatment response stays in place and stop things from coming back or from growing again. And we know from many experiences with bladder cancer now that even if you get a good response to BCG upfront or if you get a good response to chemotherapy for advanced bladder cancer, waiting around after you get that good response to see what the cancer does, does not work as well as if you proactively give additional

treatment that's usually less intense, fortunately, and less demanding in terms of side effects, but still helps to keep any residual cancer cells in check or stop those residual cancer cells from developing.

Stephanie Chisolm:

I think we have time for one more question, and it's similar to something that was submitted, but you spoke earlier about Natera versus Guardant and how they're a little bit different. I think one of the biggest concerns I hear from patients all the time is this fear of recurrence. So is there one over the other that you suggest that would be better to use for surveillance, that you're going to get a better image of what's happening in your body where it might not even be seen on a routine scan, like a PET scan? Say you've had your bladder removed and you're looking for any kind of sign of recurrence elsewhere, is there something that makes one of those tests better than the other?

Dr. Brendan Guercio:

Absolutely, yeah. The Natera test is especially good at detecting very, very small amounts of cancer in the body. And the way it does that is actually they first take a piece of a patient's original tumor that was cut out through surgery usually, and they look for specific genetic mutations that are present in that person's tumor, and then they go back to the bloodstream and look to see if they can find any of those specific mutations in the bloodstream. And since they're looking at just a very specific small number of mutations, they can detect those mutations at very, very, very small levels. So as a result, they found that for folks who have, for example, had a cystectomy and their bladder cancer was removed, when they use the Natera test, that can actually detect any residual bladder cancer in the body after the cystectomy much better in a lot of cases than a scan can. It's not a perfect test. It may give a false negative maybe 10 to 20% of the time. But it's still a really, really good test that is usable now to help make sure there's no cancer left after a surgery like that.

Stephanie Chisolm:

Well, if you have a few more minutes, I think we have time for maybe two more questions if that's okay?

Dr. Brendan Guercio:

Sure.

Stephanie Chisolm:

Somebody's on a course of Opdivo post cystectomy with an ileal conduit for one year. Is there some way that they should be monitoring that they would know if it's effective or not, or do they just have to wait for scans to see if their cancer recurs?

Dr. Brendan Guercio:

That is a really good question. Definitely one thing that's standard is monitoring with scans in that setting to make sure that nothing is growing. So that's definitely recommended at regular intervals. Other than that, typically folks just kind of follow the scans. You can use the Natera ctDNA test in that situation. Sometimes there could be issues with reimbursement, although Natera actually has been very good about making sure that patients do not get billed for their test, which is really nice. So there are some doctors and patients that decide to use the Natera test to see if there's any cancer there that the scans can't pick up.

But that said, the Natera test is so new sometimes we don't know what to do with that information. If you can detect a little bit of cancer in the blood, does that really mean that the immunotherapy is not working? It might still be working, and maybe you need to follow that test in the blood for a couple of months or six months to see if it maybe goes away on the Opdivo. Although it can be helpful in certain situations, sometimes having more information can even be confusing if you don't know exactly what to do with it. But it's worth a discussion with a physician who knows your case best to see if they think that's a reasonable option that might help in your specific situation.

Stephanie Chisolm:

Why is cyclophosphamide used in chemotherapy a risk factor from bladder cancer? Because we hear that, sometimes patients had another cancer and they were on chemotherapy and now they got bladder cancer. Why is that? Do you have any connection as to why or idea?

Dr. Brendan Guercio:

Yeah, it's interesting. The bladder, unfortunately, because it's kind of the exit for a lot of the toxins that our body is trying to get rid of through the kidneys, a lot of those products that our body wants to expel in the urine end up sitting in the bladder for a little bit. So the bladder kind of unfairly gets a high load of those potentially cancer causing agents, including cyclophosphamide, which leaves the body that way and unfortunately can be very irritating to the lining of the bladder. And since cyclophosphamide, like most chemotherapies, works by damaging DNA, if it's sitting in the bladder for a while and irritating the bladder and damaging its DNA, just like those other risk factors I talked about at the beginning of the talk, like smoking or ultraviolet radiation, if there's enough damage to the DNA done that can increase the risk of a cancer in that area developing unfortunately. That said, cyclophosphamide is a great medication and it does help cure some patients with certain cancers. So if a physician recommends it, the benefits of the cyclophosphamide probably outweigh the risks of a bladder cancer developing. But unfortunately, there are certain side effects from certain medicine treatments that can lead to other cancers down the road rarely.

Stephanie Chisolm:

Right, and it's all in that fine print of the consent form that you have to sign before you take anything. And it's overwhelming sometimes to think about, "Well, if you do this, then all these other things can happen." So this has been really phenomenal. Thank you so much for a brilliant presentation. I'm going to ask one last question. What would the single most important message you want our listeners to leave today's program with?

Dr. Brendan Guercio:

I think I would want them to leave with hope because there's a lot of really great scientific advances that are happening. And just in the past decade, we've had more progress in bladder cancer than there was in the past probably 30 or 40 years. So things are getting better, and I would encourage them, it's always a reasonable idea to ask about getting involved in research in clinical trials. And should never feel obligated to participate in research or trials, that's always voluntary. But it is the best way for us to move the field forward so that everybody who is affected by this disease has a better experience in the future.

Stephanie Chisolm:

I agree. No new science happens without clinical trials. And we are so fortunate that young investigators like Dr. Guercio are on this. This is what drives them every day. I hope everybody has learned a lot from today's program. And he was great, right? So I hope everybody's applauding back on their screens on the backside. But I also invite you to join our Ask the Experts Program on May 22nd when Dr. Guercio is going to join Dr. Matt Mossanen, who is a urologist from Boston, with our director of research, Rebecca Johnson, and really get into answering a wide assortment of questions across the spectrum of disease. That's all we have time for today.