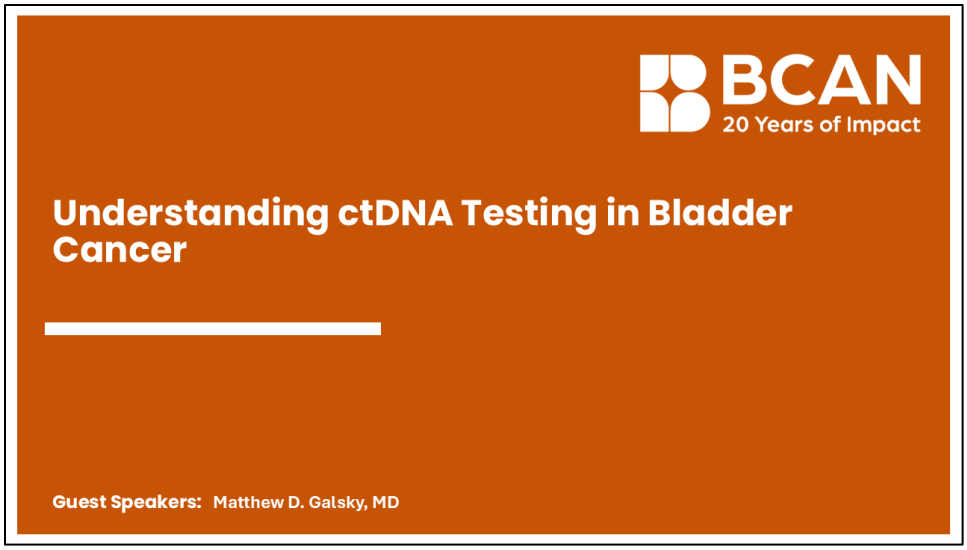

Patricia Rios:

Excellent. Okay. Well, and this relates to a couple questions relates to I believe the MODERN trial. With the MODERN trial, is it also testing the need for both ctDNA plus the CT scan? The CT scan is much more invasive than a blood test?

Dr. Matthew Galsky:

Yeah, that's a fantastic question as well. Really great questions and things that we think about a lot. So yes, so for that study during the monitoring phase, patients get standard of care monitoring, so they get CAT scans or other types of scans plus ctDNA. In the IMvigor011 results that I showed you, I showed you that slide where patients had ctDNA monitoring for that year, and the likelihood of seeing something on a scan before the ctDNA test became detectable was really quite low. So I don't know if the person who's asking the question is really getting at this that is, could we just use blood tests and not do scans anymore? And that's something that we think about. Is the data strong enough that we should think about testing that question? I think it's a great question.

Patricia Rios:

Great question. Well, the other question sort of follow up to the study is you mentioned that the study's currently recruiting, and so when will this trial end and what other information do you have for folks that are in that trial?

Dr. Matthew Galsky:

Yeah, so MODERN has been enrolling for about a year and a half. We expect it to enroll for several more years or a few more years at least. It's a very large phase three study. It's really two phase three studies in one, it's being done throughout the United States because it is a

trial that's being supported through a national clinical trials network. And so many sites in many cities throughout the US and Canada are participating. And in most, most cities, certainly not all, but most places rather, there is a site that offers MODERN likely not too far away.

Patricia Rios:

Thank you for answering that. You mentioned, and you had a beautiful slide of what ctDNA can and cannot tell us. Can you remind us, can ctDNA tell us how long to stay on immunotherapy after surgery?

Dr. Matthew Galsky:

Another fantastic question. We don't know the answer to that question yet. What we do know from data that I didn't show you is that if you have detectable ctDNA and it becomes undetectable on treatment that's associated with a very favorable outcome, that might not be surprising, but that the data really do support that. So we know that if it converts from detectable to undetectable, that's good. Whether or not that tells us that we can stop and at what point how long it needs to be undetectable after having been initially detectable, how long it needs to be undetectable, where we can be comfortable stopping. We don't have data to guide that yet.

Patricia Rios:

Thank you for answering that. And during your presentation, you used the phrase detect cancer aggression, and one of our listeners would like for you to elaborate on that phrase, please.

Dr. Matthew Galsky:

Yeah. Can you tell me the phrase again?

Patricia Rios:

Detect cancer aggression.

Dr. Matthew Galsky:

So I'm trying to think of where I might've used that. We can detect cancer aggressiveness, or maybe not detect is the right word. We can try and assess cancer aggressiveness by looking at features under the microscope, like the stage of the cancer. That tells us a little bit about aggressiveness and a little bit about risk of recurrence, but of course it doesn't tell us everything, and that's why we need these additional technologies.

Patricia Rios:

Thank you. There is lots of great questions and words expressing how outstanding your presentation has been. There's a question about patients who had radical cystectomies done in the past without the benefit of having the tumor being evaluated for tumor-informed ctDNA. Is there any opportunity to use blood samples alone to perform tumor-agnostic ctDNA testing to provide surveillance for recurrence cell bladder cancer in those patients?

Dr. Matthew Galsky:

So there are some commercial vendors who have ctDNA who have blood-only ctDNA tests. The tumor-informed tests can also be done on archival tumor specimens that from a surgery that was done years ago, someone could take a blood test now and the tumor that was removed a few years ago and generate this assay. That's something that's technically achievable in those situations. Of course, the question becomes, if it's been long enough from the time of surgery, then we know that the risk of recurrence becomes markedly lower as well. And so the information that's derived when you do it five years after surgery, it might not provide so much additional information because the prognosis at that point is really quite good. But from a technical standpoint, yes, there are tests that can be done without the tumor, but the test can be done with the tumor as well, even if the surgery was done a few years ago.

Patricia Rios:

Excellent, thanks. And there's a question about ctDNA testing being effective at detecting plasmacytoids that spreads along the facial planes. Can you speak to that?

Dr. Matthew Galsky:

Yeah, another very insightful question. So somewhat more limited data about variant histologies of bladder cancer and the role of ctDNA testing. We know from one, at least one publication that when there's urothelial cancer with components of other appearances under the microscope, ctDNA seems to perform pretty similarly. Plasmacytoids specifically or pure plasmacytoids specifically, there's limited data, but with most variants it seems to line up pretty well with what we see with a, a more pure urothelial cancer.

Patricia Rios:

Something related to that question is what about small cell neuroendocrine bladder cancer? Could this help with ensuring metastasis is not occurring after cystectomy?

Dr. Matthew Galsky:

Yeah, so similar, similar to the plasmacytoid question, more limited data, but the data that are available suggests that the performance in variant histologies is pretty similar to a, to pure urothelial cancer.

Patricia Rios:

Thank you for addressing that. And there's a question that needs a little clarification around ctDNA testing being tied specifically to the initial tumor but does not detect any other cancers which might be present. So recurrence refers to the initial cancer, not a new type of cancer. Is that correct? Can you elaborate on that?

Dr. Matthew Galsky:

Yeah, yeah, thank you. Thank you for raising that point as well. So because this is a bespoke test being made on a tumor specimen that was removed in the past, it's really intended to try and identify recurrence of that cancer. And so when we talk about recurrence of cancer after cystectomy, I should have probably been a little bit more specific. Really the main thing that we're trying to detect is microscopic spread of cancer or microscopic metastatic cancer before that becomes macroscopic metastatic cancer that we could see on a scan. That's a different situation than a recurrence within the urinary tract, which of course we know sometimes occurs in individuals with, with urothelial cancer.

Those cancers, depending on the situation, can sometimes be a different clone of cancer cells that wouldn't necessarily be detected with that test that was built based on that primary tumor that was removed in the past. So might not be helpful in that situation is unlikely or almost certainly unlikely to be helpful in detecting a different type of cancer. So ctDNA surveillance after cystectomy does not replace colonoscopy because it's not going to detect a completely unrelated colon cancer that could develop, but it is really meant to try and detect that cancer that was removed, try and detect whether or not those cancer cells are still in the body.

Patricia Rios:

Thank you for addressing that. During your presentation you talked about identifying, talking about whether is it best to treat, are we over treating, under treating and the opportunities to be able to have answers to those questions through this testing. So, there's a question from one of our listeners who says, is there a danger in just being monitored and waiting for a detectable test result versus going ahead and doing immunotherapy to treat undetectable ctDNA since this does not have a high recurrence rate?

Dr. Matthew Galsky:

So that's, that's a major question and that's what we're trying to answer based on MODERN. We know that the likelihood of having cancer recur on a scan metastatic recurrence when a ctDNA test is serially negative is low. But in the data that I showed you before, the risk of having the ctDNA convert from undetectable immediately after surgery to detectable is, is, not insignificant. That occurs in a decent of individuals. And so whether or not a watch and wait sort of approach is non-inferior to a treat immediately after surgery approach, we really need to know the answer to that question from a study that asks that specific question

comparing those two treatment approaches. And that's really what we're trying to do in MODERN.

Patricia Rios:

Thank you for explaining that. Can you clarify, so there was a lot of good information about studies and our listeners want to know if there are recommendations in terms of what time period ctDNA will be helpful.

Dr. Matthew Galsky:

So the bulk of data suggests that after cystectomy for muscle invasive bladder cancer, there's a role and there's a role for monitoring ctDNA after cystectomy for serial monitoring for recurrence, along with other conventional types of testing like CAT scans, the interval of that testing, oftentimes we'll do every three months for a period of time and then stretch it out to six months and then once a year at a similar interval then at a similar interval that we do CAT scans after surgery, there's not great data to identify the best surveillance strategy yet or the best interval for surveillance. Unfortunately, we really don't have that data for CAT scans either, which we do all the time in terms of what's the right interval, there's an interval that became a pretty standard approach and that's what everyone really sticks to.

Patricia Rios:

I want to go back to the access and awareness theme. There's a lot of questions here in the chat around how widely used this is. Is this testing available beyond academic centers, say with local community hospitals, urology centers? Do you have any insight to share with us on that?

Dr. Matthew Galsky:

Yes. So it is, it's available throughout the United States being an assay that's performed in a commercial laboratory. A clinician can order this test and doesn't have to be in a, an academic medical institution.

Patricia Rios:

Excellent. And would a patient know that the test is being offered

Dr. Matthew Galsky:

In general when, when a test is ordered it that should certainly be discussed with an individual for whom it's being ordered for in terms of being able to contextualize and discuss the results.

Patricia Rios:

Excellent, thank you. And I know you mentioned that information about coverage and not having that information available at the moment, but any sense in terms of how much this

test would cost out of pocket if someone wanted to have the test and but insurance doesn't cover it?

Dr. Matthew Galsky:

Yeah, it's information that I should have for you, but I don't and I don't want to give you misinformation.

Patricia Rios:

That's okay. Thank you for addressing it. We'll try to find that and send it out to folks. Let's see. I think we are at the top of the hour. Thank you so much for the presentation and for addressing all the questions presented today by our listeners. I want to end with one last question and that is what would be your, your takeaway message for our listeners today? What is that one thing you want them to remember from today's presentation?

Dr. Matthew Galsky:

So I think ctDNA testing is going to have an evolving role for treatment decision making. I think it has a role potentially already in the post cystectomy setting, and it's something that's commonly being done. And so it's important to be aware of it, what it means, what it can tell us, what it can't tell us, and I think that we need to generate these. We need to generate data from these prospective studies that are ongoing to really know how we should use this information to inform clinical decisions.

Patricia Rios:

Thank you. Thank you again for our fabulous presentation. I hope you'll come back and present on any other findings and important information for our community to be aware of.