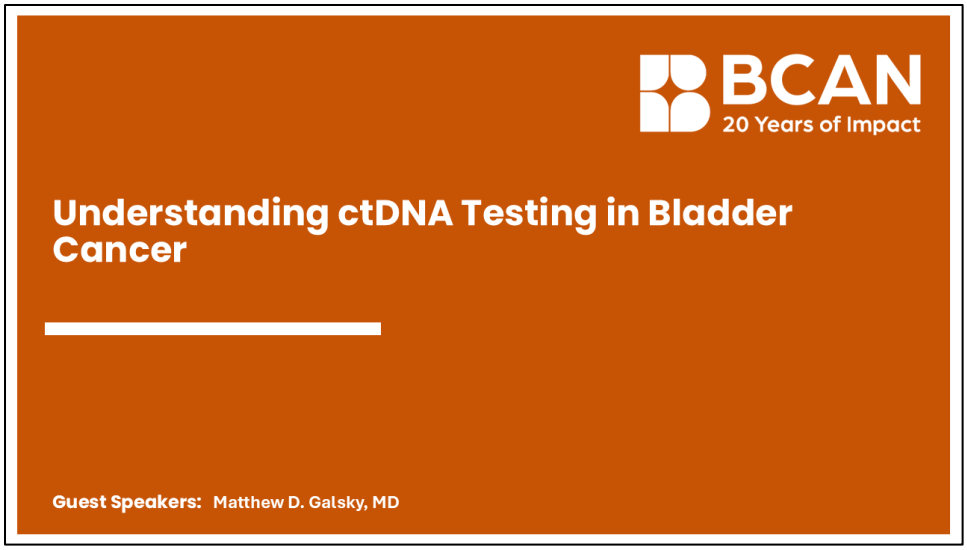
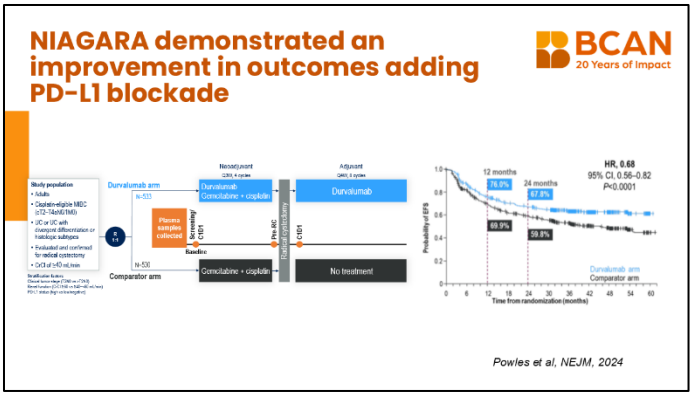


Dr. Matthew Galsky:

I'm just going to spend a few minutes talking about what we know about this testing in the neoadjuvant setting, and then I'll wrap up and happy to answer questions.

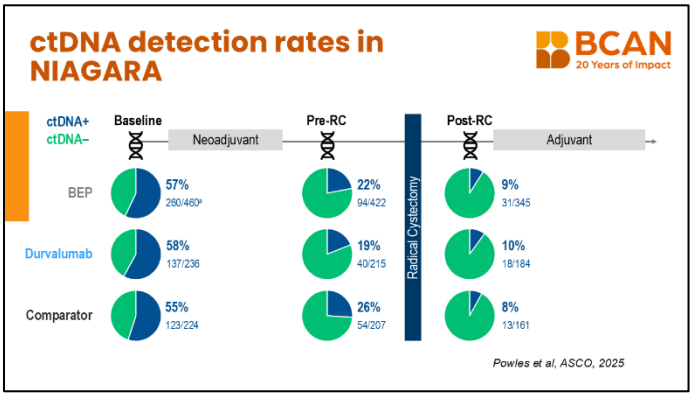
Dr. Matthew Galsky:



So we have one large data set so far that tells us a little bit about ctDNA testing in the neoadjuvant setting. And this is from a study that's called NIAGARA. In this clinical trial asked the question, should we add immunotherapy to standard chemotherapy prior to surgery to remove the bladder prior to cystectomy? And this study showed that the addition of immunotherapy improved event-free survival, decreased the risk of cancer coming back and increased overall survival. And so this has become a very commonly used treatment regimen.

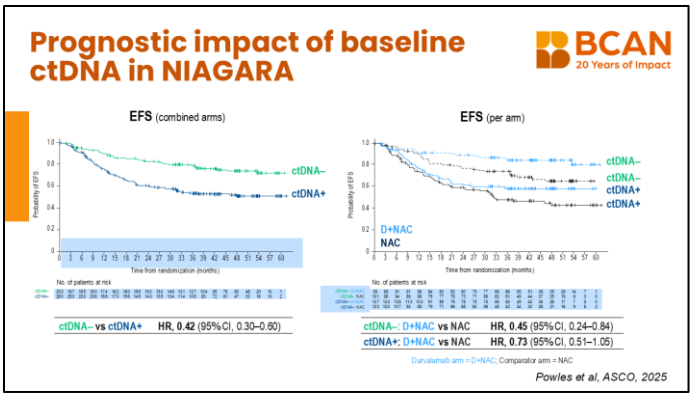
Dr. Matthew Galsky:

In this study, the investigators looked at the role of ctDNA using the same test that I just mentioned with the other studies, the Signatera test. And you can see here that at baseline prior to any treatment, about 57% of individuals have detectable ctDNA in the blood after getting neoadjuvant therapy. That decreases a lot, which is what you would want to see if chemotherapy and immunotherapy are having a favorable effect in this setting. And then you can see after surgery it drops much lower. So starting with about 57% to 9% after surgery in individuals who have had neoadjuvant therapy, chemotherapy, immunotherapy and, and surgery.



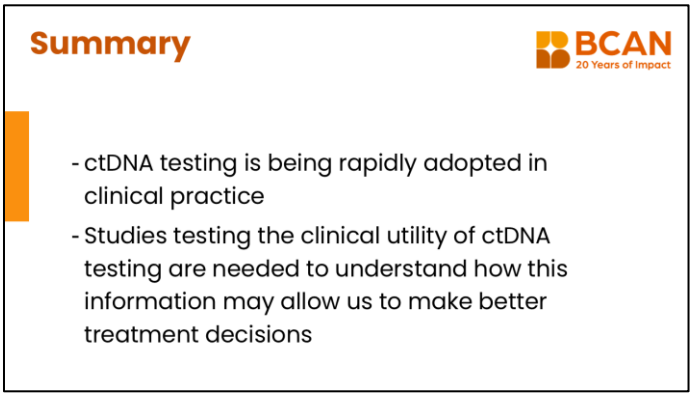
Dr. Matthew Galsky:

This is what the baseline test tells us in this situation that if the baseline circulating tumor DNA is detectable, there's a higher risk for cancer coming back than if it's not based on that single test. But what this data also showed was that even if the blood test is undetectable, a subset of individuals do have recurrence suggesting that we can't use this test definitively to omit chemotherapy.



And this is an analysis that's also retrospective. And so that has to be taken with a grain of salt. But it also showed that the addition of immunotherapy seemed to provide a benefit beyond chemotherapy alone, even if the baseline ctDNA test was undetectable. Again, reinforcing the potential role for treatment with systemic therapies like chemotherapy and immunotherapy, even if that baseline test is undetectable. Again, the potential information that's derived from the test when the primary tumor is present is a little bit different than when a primary tumor is removed with cystectomy. And we really expect there to be no detectable DNA in the blood.

Dr. Matthew Galsky:



So, in summary, ctDNA test saying being rapidly adopted in clinical practice, however, we do need studies demonstrating clinical utility. We need studies demonstrating that this information is really helping us make this information is really going to help us make good clinical decisions without relying solely on retrospective data to guide those decisions. And I think that we're seeing, we're seeing, evidence generation happen in both ways, what's happening in real-world practice, what's happening based on clinical trials. And I think in the next few years, this is really going to be part of our standard collection of data and it's going to be used to at least inform many of the treatment decisions that we make and that we help individuals with bladder cancer make. So I'm going to stop there and happy to answer questions.

Patricia Rios:

Thank you, Dr. Galsky. That presentation was very educational, very comprehensive, and it's very exciting to see the research that's being done in the space and the findings and what that means for patients. So I want to remind folks that you can use the Q&A button at the bottom to submit your questions. We have some already submitted, which I will filter for Dr. Galsky. So, Dr. Galsky, I want to begin by talking a little bit about access. Is this testing available through urologists or is it only through a clinical trial? What is the access to this kind of testing at the moment?

Dr. Matthew Galsky:

So this is commercially available technology, and as mentioned before, there are some different commercial laboratories that do this type of testing. And so not the ability to have the testing and the reimbursement policies are not uniform, but depend a little bit on the test. But the Signatera test, which was used in most of the data that I presented that does have a Medicare approval, and so it is widely available in the United States. What that means in terms of the financial implications of the test, I'm not the best person to, to, answer that question, but there is a Medicare approval specifically in individuals with bladder cancer for recurrence monitoring.

Patricia Rios:

Wonderful, thank you. And we can certainly, I think there's also some of these companies that offer this testing may have some sort of financial resource page on their website. If folks are interested in learning more, I'm also curious to know how wide is the knowledge around the different testings are available? I see some question in the chat around lack of awareness

among providers. Is that because it's used in this space? In your presentation you talked about non-muscle, what about advanced disease or non-muscle invasive bladder cancer?

Dr. Matthew Galsky:

Yeah, great question. And so for advanced disease, there's more and more data being generated. There is probably the most robust data related to the use of circulating tumor DNA in patients with more advanced disease in terms of monitoring response to immunotherapy. And so there is data and a potential role in that setting in patients with non-muscle invasive bladder cancer. One of the challenges of course is that tumors are smaller and oftentimes behave less aggressively, and there is that correlation that I showed you on one of those earlier slides between tumor size, volume stage, and likelihood of detecting ctDNA. This in part might be a technological issue and with better and better testing, the ability to detect ctDNA even in the setting of non-muscle invasive disease might be better. We know that some of the commercially available tests, there is data that's been published on the use of on the use in non-muscle invasive bladder cancer, and there are certainly clinical correlations that one sees, but there's just, we have less information so far on how that testing might be helpful in terms of clinical decision-making in non-muscle invasive bladder cancer.

Patricia Rios:

Great, thank you. You talked about the testing and mutations, there's a lot of question about the HER2 mutations. I was wondering if you could speak a little bit about what that is and what role that plays in ctDNA testing.

Dr. Matthew Galsky:

Great question as well and reminds me to clarify something. And what I want to clarify is that even though this testing is based on identifying alterations in DNA in an individual's tumor, this tumor informed testing based on the intent of the test, which is really to find a needle in the haystack essentially to find this abnormal tumor DNA in this pool of liquid and normal cell-free DNA. So it's really a needle in the haystack problem. And because of that, the testing really isn't focused as much on what those mutations are from a cancer pathogenesis standpoint. What I mean is that when these mutations are selected for testing in the blood, they're not, they're not selected based on what might be mutations related to what's driving an individual's cancer or what might be targets for treatment, but they're selected based on other characteristics that might make them most likely to be detected.

When we're looking for these minute amounts of DNA in the blood, there's other technology, similar technology, but designed slightly differently. That is really focused more on the other question that's often referred to as a liquid biopsy. In this term, it's pretty nonspecific. And so essentially looking for a panel of cancer genes, if you will, in the blood and looking for specific alterations in those genes that are sometimes implicated in driving cancer growth. It might be targets for cancer therapies. There's other testing that's really good for that. And these tests are not necessarily the same tests.

With regards to HER2, so HER2 is a gene, it's a receptor found on cells. It's pretty well known because it's a target for drugs in many different types of cancers like breast cancer where it's most widely known. HER2 mutations are found in bladder cancer. That is an alteration in the actual gene, whether or not those mutations can be used to identify which patients should get which treatments. That's been a hard nut to crack so to speak. But increased amount of the HER2 protein, which is a different type of test that probably has more implications in terms of cancer treatment. So HER2 mutations still trying to figure out what we might learn from those in terms of cancer treatment, HER2 protein overexpression, which can be tested in a different way, that's important information potentially for treatment decisions.

Patricia Rios:

Wonderful. Thank you for clarifying. I can see where that needs some clarification. So there is a question about asking about studies being done to compare ctDNA versus, excuse me, ctDNA status in radical cystectomy versus trimodal therapy. Any insights on that?

Dr. Matthew Galsky:

Yeah, so there's a few publications with the use of ctDNA, even with the same platform, the same test that I had showed you that was used to generate all the other data. There's some studies using that platform in the context of trimodality therapy that looks interesting from the standpoint that it seems to line up in terms of providing prognostic information. But the data sets are much, much smaller than we have with cystectomy data sets. And you know that's in part related to where a lot of the big phase three studies have been done recently. So we just haven't had the big phase three trimodality studies to then go back and use specimens from those studies to ask these really important questions. That's probably going to change a little bit in the next year as some of these big studies that assess trimodality therapy and the role of adding immunotherapy to that. We're going to start to see the results of those studies and those studies will provide a really rich resource for asking questions about biomarkers like ctDNA.

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