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Understanding ctDNA Testing in Bladder Cancer

Guest Speakers: Matthew D. Galsky, MD

Patricia Rios:

I want to welcome all of you to the Bladder Cancer Advocacy Network Patient Insight webinar series. My name is Patricia Rios, director of Education Advocacy, and your host for today's program on understanding ctDNA testing, what it means for you, and is it ready for prime time in bladder cancer.

So, researchers and doctors are learning more about how to use a new kind of lab test called circulating tumor DNA or ctDNA to help monitor bladder cancer. To help us understand and learn more about this, we have invited Dr. Matthew Galsky, a leading bladder cancer researcher and medical oncologist who will explain what ctDNA testing is, how it works and what it can and can't tell us. Dr. Galsky will also discuss the latest research and how ctDNA testing may be used in the future.

A little background on our guest speaker Dr. Matthew Galsky is a medical oncologist focused on the care of patients with bladder cancer. He completed his medical oncology training at Memorial Sloan Kettering Cancer Center. After completing training, he joined the faculty at Sloan Kettering to pursue focus on clinical care and research related to bladder cancer. In 2010, he was recruited to the Tisch Cancer Institute, Mount Sinai School of Medicine as director of genitourinary medical oncology, where he's currently a professor of medicine, and associate director for translational research and co-leader of the Cancer Clinical Investigation program.

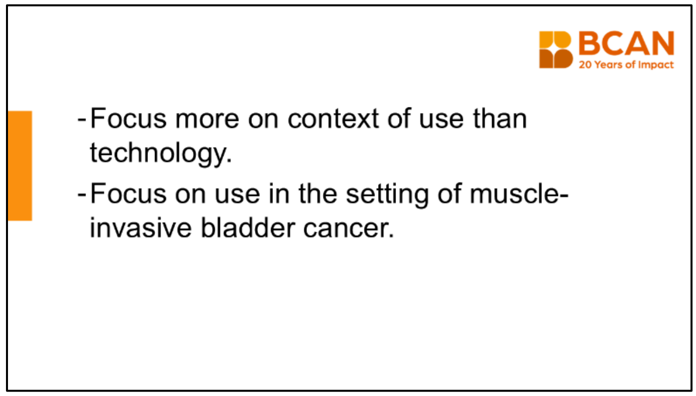
Dr. Galsky's research focuses on the development of new approaches to treat bladder cancer. And without further ado, I'm going to hand over the screen to Dr. Galsky for today's webinar on understanding ctDNA testing, what it means for you, and is it ready for primetime and bladder cancer. Dr. Galsky, It's a pleasure to have you, and the screen is all yours.

Dr. Matthew Galsky:

Thank you, and thanks for that really nice introduction. So I'm going to share my screen. Thanks to everyone for joining today. I'm excited to talk about this new technology. I think there's a lot that we don't know. We're learning a lot every day, and it seems like at every meeting there's more data on ctDNA. So I'm going to talk to you a little bit about this technology, how it's evolved, what we know today in terms of clinical decision making, what we don't know and where we think this technology might be going in the future.

Dr. Matthew Galsky:

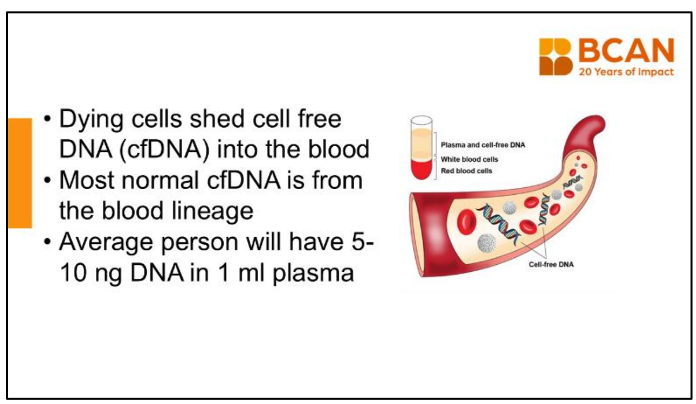
A few disclaimers maybe I'm going to focus more on context of use than technology. And what I mean by that is that we say ctDNA stands for circulating tumor DNA, but of course there's bunch of different tests that can be done to detect ctDNA and there are new tests being developed every day.



And so those tests aren't necessarily equivalent. And so when we talk about these tests, we really have to specify which test we're using and that's the case for any medical test. And then the second disclaimer is that I'm really going to focus on muscle invasive bladder cancer because that's where most of the data has evolved. We will see data in other clinical disease states of bladder cancer with ctDNA evolving, but right now, this is where the emphasis has been and it's been on muscle invasive bladder cancer from for some fairly straightforward reasons, which I'll touch on.

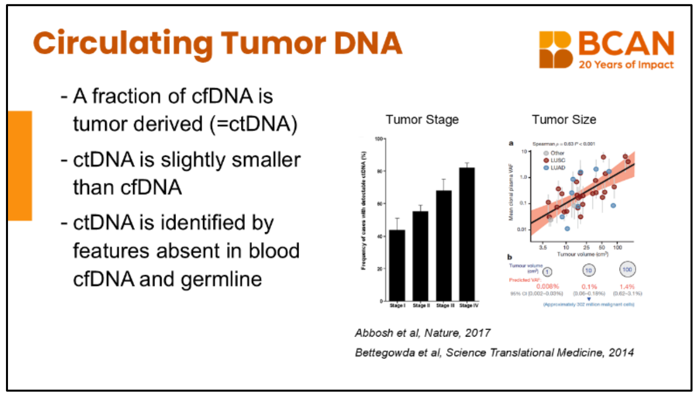
Dr. Matthew Galsky:

So cells in the body when they die, they shed DNA into the blood. As you know, DNA is the genetic material inside of all of our cells. It's the cookbook, if you will, for determining how cells should make proteins and then determines function of cells in our body.



And so when cells die, that genetic material gets released into the blood and that can be measured and that's referred to as cell-free DNA, just because it's DNA, that's free from a cell cell-free DNA, so that can be detected in the blood. And that's been known for some time. And I'm actually going to show you one slide on some historical data in terms of when these discoveries were made.

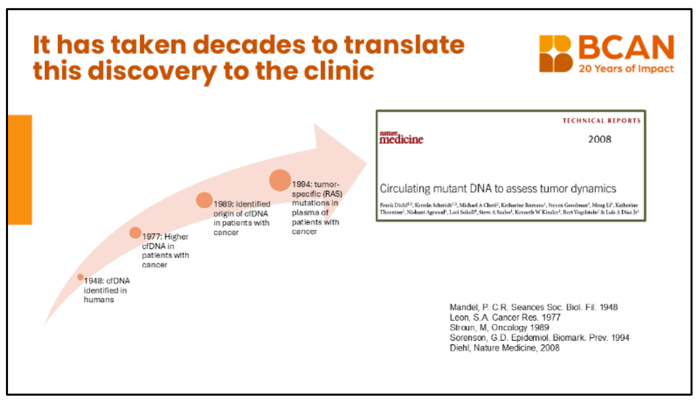
Dr. Matthew Galsky:



But that's been known for some time and it was only later that it was determined that a fraction of that DNA that's normally present because it's released from dying cells, a fraction of that in individuals who have cancer is released from cancer cells.

And so the idea here is to be able to pick up or pick out rather that DNA that's being shed from cancer cells rather than normal cells. And that's been a major technical hurdle for many, many decades. But now we're seeing this become reality in terms of the ability to test for this DNA shed from cancer cells within the blood. You can see in these two figures here that there is some correlation between clinical features in the ability to detect circulating tumor DNA in the blood in general, and this is not an absolute, but in general, larger tumor size or higher tumor stage is associated with a higher likelihood of being able to detect abnormal DNA in the bloodshed from cancer cells.

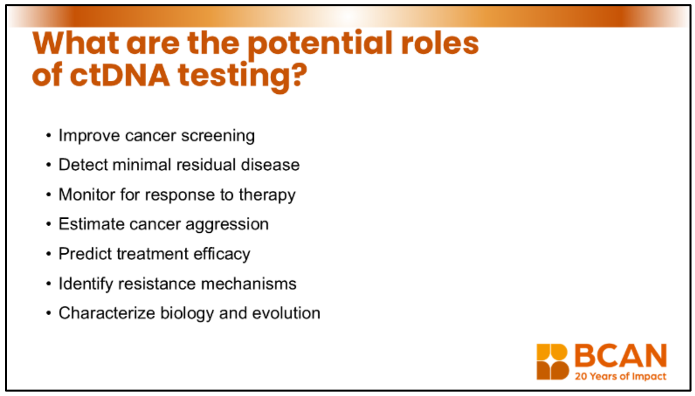
Dr. Matthew Galsky:



So, as I mentioned before, it's been known that cell-free DNA is present in the blood for a long time. In fact, there was a paper in 1948 that described that. And then in the 1970s there was a paper that showed that individuals who have cancer generally had a higher load or a higher amount of cell-free DNA in their blood than patients without cancer. And then later what that DNA was, the precise DNA that was found to be abnormal shed from cancer cells was determined and described in a paper. So you can see here that this is not necessarily a new concept, but it's a concept that's evolved over decades of really innovative and careful work to be able to translate this scientific discovery into potential clinical action ability. And one of the reasons that I show this slide is just that it, you know, takes time. Scientific discoveries take time.

Of course, we want them to move faster and faster. No question about it. We all do. But some of the major advances that have occurred over the years are built on the backs of other discoveries that have been made over decades.

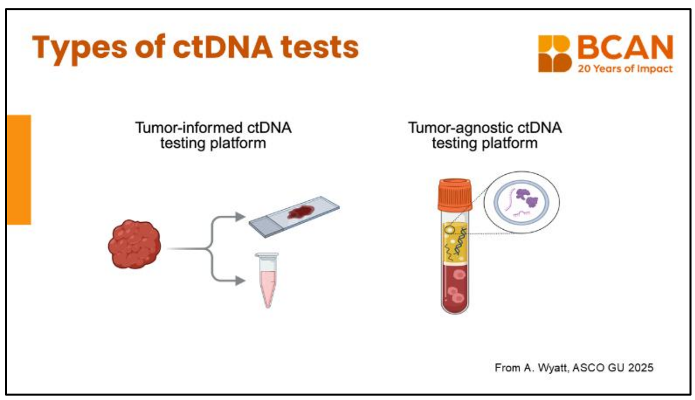
Dr. Matthew Galsky:



So now we have this technology in the clinic, and I'm going to describe what that is a little bit more. But when we think about the potential roles of being able to test for DNA shed from cancer cells in the blood, there's a number of potential roles one could potentially think about using this to screen for cancer and individuals who don't have cancer. And there are some commercial tests being developed specifically for that reason. There's the ability to monitor response to treatment. So that's particularly useful in situations where we can't see cancer on a scan to determine if the treatments that we're giving are having a beneficial effect.

But the role that I'm going to talk about mostly today is the second bullet point here, which is detecting minimal residual disease. And I'm going to explain what I mean by that.

Dr. Matthew Galsky:



There's two main types of ctDNA platforms that have been developed to test for microscopic amounts of cancer in the body, and those really fall under these umbrellas of what we refer to as tumor-informed or tumor agnostic. And what that means, this is just two very different approaches, each with some different pros and cons. Tumor-informed platforms essentially take a tumor sample that was removed as part of clinical care, that tumor specimen undergoes DNA sequencing to find the abnormal DNA patterns in an individual patient's cancer. And then those patterns, those abnormal DNA findings are translated into a bespoke test that can check for the presence of those mutations within the blood. So these tumor-informed tests are bespoke tests that are designed for every individual patient based on their individual cancer, and that's very different than most of the tests that we use for cancer.

There's also tumor agnostic platforms and tumor agnostic platforms referred to tests that try and detect abnormal DNA in the blood without having the tumor to guide what we're looking for. And that can be done in a number of ways. One is to look for just cancer, just DNA abnormalities that are commonly found in a certain type of cancer like bladder cancer. The potential benefit of that approach, of course, is that one could think about doing this much more quickly than having to go through the process of doing all the work on the primary tumor first and then developing the test for the blood. The downside potentially to date is that it might have a little bit more hard time detecting in an individual abnormal DNA in the blood because it’s not, it might not be quite as sensitive in picking up abnormal DNA. But those are the two platforms that have generally been pursued.

Dr. Matthew Galsky:

Today I'm going to be talking mostly about a tumor-informed platform and because one, that's the test that's been used to generate virtually all of the clinical trial data that I'm going to show you. And two, it's a test that's commercially available too. So it's frequently being ordered by clinicians. And so I want to start with this slide as an overview of what we know from the clinical trial data today for muscle invasive bladder cancer. Then I'm going to go through some of the data and then happy to answer questions. So right now, I think based on what we've seen in the past several years from clinical trial data sets is that ctDNA probably gives us a good idea about who should receive additional medications, chemotherapy, immunotherapy, those types of medications after having surgery to remove bladder cancer. That is cystectomy. Potentially there's a role for this technology or this testing after radiation for bladder cancer as well.

Most of the data so far has been generated in the context of cystectomy for bladder cancer after surgery to remove bladder cancer with a cystectomy. Of course, the notion would be that you shouldn't be able to detect any circulating tumor DNA in the blood if the primary tumor is removed and there's no residual cancer in the body. And so that's really what this test is trying to achieve. And obviously the ability to do that after the primary tumor is removed has maybe different implications than when the primary tumor is present. And that's why the adjuvant setting has really been the clinical disease state where most of the data has been generated to date because that's really where we have the toughest time determining whether or not an individual should receive additional treatment or not. And I'm going to come back to that point and maybe explain it a little bit better and in a different way.

What I think we don't know for sure yet is if you have a DNA test after cystectomy and it doesn't show any detectable tumor DNA, I don't know that the data so far tell us definitively that we can avoid giving medications after surgery and I'll show you the data in why I am coming to that conclusion. And then finally, of course, giving systemic treatment like chemotherapy and immunotherapy prior to cystectomy, what we refer to as neoadjuvant treatment has become a very standard treatment. And so that raises the question, can we use this testing to decide who should get neoadjuvant therapy before surgery versus just have surgery alone? And I don't think the data are quite there that we could use this test to not give neoadjuvant therapy. I'll show you why we need more data. As the tests get better and better, maybe we will be able to address that question more definitively.

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