



Diane Z. Quale: Welcome to Conversations About Bladder Cancer. I'm Diane Zipursky Quale, the co-founder of BCAN, the Bladder Cancer Advocacy Network. Over the past 10 years, we've seen great changes in cancer treatment, largely due to the emphasis on precision medicine, personalized medicine that allows doctors to treat each cancer patient based on their own specific cancer and their own specific genetic background. And a large part of that personalized medicine, precision medicine is based on biomarkers.

And so joining me here today are two bladder cancer experts who are going to help us understand the role biomarkers play in bladder cancer treatment. Dr. Piyush Agarwal who is a urologic oncologist at the National Cancer Center in Bethesda, Maryland and Dr. Matt Galsky, a medical oncologist at Mount Sinai Hospital in New York City. Thanks to both of you for being here today.

Dr. Matt Galsky: Thank you.

Dr. Piyush Agarwal: Thank you.

Diane Z. Quale: So I think the best place to start with is can you provide our viewers with a very basic, simple definition of biomarkers?

Dr. Piyush Agarwal: So that's a tough question to answer, Diane. Biomarker, way I interpret it, is something measured in the blood, the urine, or at the tissue level in a patient that can give us a sense of whether the patient's disease is present and it can also be used to determine if the disease has a chance of recurring or coming back and ultimately give us a prognosis.

- Diane Z. Quale: So biomarkers have been used in cancer for a long time. What's a current biomarker that bladder cancer patients would know about?
- Dr. Piyush Agarwal: So if I were a bladder cancer patient, I probably have been tested with urine cytology, which is probably the most common urinary biomarker that there is. And every patient with bladder cancer, regardless of where they're treated, has probably had a urine cytology test done and that biomarker is essential for not only diagnosing bladder cancer but then monitoring a patient's response to treatment for localized, non-muscle invasive bladder cancer.
- Diane Z. Quale: And so for urine cytology, then they're looking at the urine for the cells to see how your cells look and how normal or abnormal they may be. Is that correct?
- Dr. Piyush Agarwal: Right. And a pathologist will be looking at it to determine are they high-grade cells and if so, can the pathologist tell us how it compares to normal cells because a problem is the urine will have at any moment both normal cells and in a patient with bladder cancer, abnormal cells. And the challenge for the cytopathologist is to determine is there a cancer there or not. So cytology is a very good test if you have a high-grade bladder cancer because it's likely to be picked up. But if you have low-grade bladder cancer, the test may not be able to pick it up because it may not see the difference between the normal cells and the slightly abnormal cells that are seen in the low-grade bladder cancer.
- Diane Z. Quale: So we have cytology as one of the basic biomarkers for bladder cancer. Matt, I also know that urologists do biopsies of tumors and in bladder cancer, we talk about it as a TURBT, a resection of bladder of tumor. So is that another form of a biomarker, getting that tissue from the tumor?
- Dr. Matt Galsky: It is a form of a biomarker. That tissue can be used to look at different biomarkers. Traditionally, when a biopsy is done, when a patient has tissue that's removed from the body, a pathologist looks under the microscope and really what they're doing is describing architecture. So if you think of a row of houses, you can describe how the houses look and they can all look the same and that provides one level of description of what's going on with the cancer. And then one can think about going into those houses and each individual house probably has something different on the inside. And that takes the description of the cancer to another level and that's usually what we're talking about when we think about biomarkers, trying to describe in much more detail when two things might look alike, why they might behave differently.
- Diane Z. Quale: So when I'm looking at the tissue, I'm going to be looking to see whether or not the tumor has invaded other layers of the bladder.
- Dr. Matt Galsky: That's correct.
- Diane Z. Quale: So does that tissue also tell me what the grade of my bladder cancer is?
- Dr. Matt Galsky: The tissue does and what the grade really means is when the pathologist looks

under the microscope. Again, it's really a descriptive term used to describe how aggressive the cells look under the microscope, how immature they look really.

Diane Z. Quale: Before the onset of precision medicine, doctors relied on cytology and biopsy to determine the proper treatment for patients. But now with the onset of genomics, there's a whole new level of understanding and opportunity. Is that right?

Dr. Matt Galsky: So that's really getting back to this issue when we rely on traditional pathology, which has been used for hundreds of years. It's really based on description and it's part in art based on looking under the microscope describing what the pathologist sees and very important information about cancer can be conveyed that way, but there are limitations and there's some subjectivity involved in looking at something and describing it.

With these new generations of biomarkers that involved DNA testing or RNA testing, we're really taking the description to a deeper level that not only might provide more information again when things look the same but behave differently. Why is that? Well maybe because there are aspects to those cancers that really are different that we can't describe just by looking at it. So that's one aspect of newer biomarkers that is promising. And the other aspect is that these newer biomarkers do have less subjectivity than just looking and describing.

Diane Z. Quale Quale: So you can be more certain that what you are seeing is an actual indication of what is the genetic makeup of my cancer?

Dr. Matt Galsky: That's right. And with any test including biomarkers and particularly new biomarkers, there is always an aspect of how accurate the test is in describing what it's supposed to measure. But test that can be described as being present or absent rather than having gradations like some traditional pathology measures do are a little bit more subjective in terms of our confidence that that test or that protein is present or not.

Diane Z. Quale: I've read a lot about determining whether there are alternations in a particular tumor. Are those alterations considered a biomarker, Piyush?

Dr. Piyush Agarwal: They could. This is really exciting time in bladder cancer because we are finding that there are some mutations that are associated with low-grade, non-muscle invasive disease and other mutations that are associated with more aggressive forms of non-muscle invasive disease or even muscle invasive high-grade disease. And one can think of a few examples where you might be able to identify whether a patient has high-grade non-muscle invasive disease or low-grade based on one or several mutations.

And so there are some testing being done in different gene panels looking at 12 or more genes and using that to predict what a patient's tumor might be and whether it would be likely to recur or progress. So we are getting closer to where we can use this information. Before, it was more characterizing a tumor but now, we might be able to, for each individual patient, give some sense of the prognosis and whether

that patient will respond to therapy.

Diane Z. Quale: So understanding whether or not it's a high-grade or a low-grade tumor in the non-muscle invasive world may impact how patients are treated.

Dr. Matt Galsky: Right.

Dr. Piyush Agarwal: Right. Right now, we can determine from pathology if someone has low-grade or high-grade disease. Typically, the high-grade patients will get some form of intravesical therapy like BCG. And we have a plethora of trials for patients who may not be able to tolerate BCG or in situations where BCG doesn't work for the patient, other drugs are being evaluated. But with the knowledge of some of these mutations being present, there are people who are finding some immune-related genes that are present in tumors and these immune-related genes might indicate whether a patient would respond to BCG or not. So if we fast forward a couple of years, maybe we'd be able to look at the immune-related genes at the very diagnosis and determine whether or not it's worthwhile to treat a patient with BCG because if they don't have those set of immune-related genes, they may not respond to that therapy.

Diane Z. Quale: So fast forward a few years, I think what most bladder cancer patients would like to see is that they no longer have to have as many cystoscopies as is required now since they are followed so long for recurrence. So are there studies underway that would reduce the need to have as many cystoscopies as is currently required?

Dr. Piyush Agarwal: Yes. So right now, we are using urine cytology. Urine cytology can help determine whether a patient gets a cystoscopy in the office or whether they're getting a cystoscopy in the operating room under anesthesia where they might get a biopsy. So for example, if a patient's receiving BCG therapy and their cytology comes back normal or negative from malignant high-grade cells, that patient may just undergo an office cystoscopy and does not need to be put under anesthesia. Whereas if the cytology is positive, then that patient likely has some disease that's there and so that patient might just go straight to the operating room for a biopsy because there's a strong suspicion that there may be tumor there. In terms of eliminating cystoscopy entirely-

Diane Z. Quale: And I'm saying not entirely but I'm talking about monitoring for recurrence because currently, patients could be on ... It might be every three months, it might be every six months that they have to come back and have undergo the scope and I'm just wondering if I'm certain from a perspective one of priorities in terms of treatment advances is to be able to reduce the need to come back so frequently.

Dr. Piyush Agarwal: Absolutely. Patients don't like cystoscopy and it is one of the major reasons why bladder cancer is the most expensive cancer to treat because of the routine need for cystoscopy. So there are some of us, myself included, who will decrease our surveillance in patients with low-grade disease by incorporating other biomarkers. So for example NMP22 is a biomarker where it can pick up low-grade cancers quite well. And so if its normal in patients with a history of low-grade bladder cancer, we

can substitute an annual cystoscopy with that simple urinary biomarker test. And those of us that practice that are quite comfortable and do that approach. Some of us alternate each year with the cystoscopy versus the NMP22 biomarker test and that is a way where the patient can actually only have a cystoscopy every other year as opposed to having it once a year.

Diane Z. Quale: Well, that would be great if that's something that could be more widely accepted and practiced as we develop better biomarkers for that. So Matt, when we talk about muscle invasive disease, I know one of the challenges has been with patients who ... The standard of care for patients with muscle invasive disease is to have chemotherapy prior to having their bladder removed. Not all patients will respond to that chemotherapy and I know that you've been looking at ... There have been trials and studies going on looking at trying to determine who would respond to that chemotherapy so that those patients who might not don't have to undergo it in the first place. So can you tell us a little bit about what's been happening there and the use of biomarkers in that area?

Dr. Matt Galsky: So if your patient with muscle invasive bladder cancer, with cancer invading into the muscle layer, then removing the bladder is one of the standard treatments, cystectomy. And with the biomarker questions, the questions that can help us guide a patient's care in that setting are really two major questions. One is will that patient benefit from chemotherapy because if they're not going to benefit, then to expose someone to the potential side effects of treatment is a disservice. So that's one key question. And the second key question is do I have to have my bladder removed in the first place and if we could develop tests to answer either of those questions or maybe both together, that would clearly be a change in the way we treat bladder cancer.

Diane Z. Quale: So your point is we would be able to save more biological bladders.

Dr. Matt Galsky: That's right. Currently, when a patient has chemotherapy prior to surgery to remove the bladder and the bladder is removed and looked at under the microscope and there's no cancer in the bladder, we're all very excited. That's called the pathologic complete response.

Diane Z. Quale: But the patient might say, "Why is this good news? You removed my bladder."

Dr. Matt Galsky: Patients look at us very funny when I say it's good news, rightly so. The problem is that we don't have any reliable way prior to removing the bladder of knowing for certain that every last cell has been killed because even if we look in the bladder, even if Piyush looks in the bladder with a cystoscope after chemotherapy and doesn't see anything or does a biopsy and there's no cancer under the microscope, that really doesn't give us a sampling of the whole wall of the bladder. So currently, removing the bladder is the standard.

If we can develop biomarkers to say after receiving chemotherapy, if we don't see any cancer in the bladder on cystoscopy and if there's no cancer on a biopsy and that biomarker is associated with a very high likelihood that if that bladder was

removed, it wouldn't have any cancer in it, then maybe the bladder doesn't have to be removed in the first place. And in fact, there are studies going on right now testing that concept.

Diane Z. Quale: So I'll ask you because people would ask, okay? How long is this going to take?

Dr. Matt Galsky: So like anything in medicine, things move slower than we would like them to. And because this is such a shift in paradigm and because there is the risk that we might need bladders intact that can have cancer in them, we need to proceed very cautiously and conservatively and make sure these tests are measuring what we think they're measuring and make sure we're ultimately benefiting patients. So we have to go through the rigors of clinical trials to really show that this works. But I think we're talking about years, not decades. These trials are going on right now. This is not science fiction, this is something that we're really doing now.

Diane Z. Quale: So that's very exciting, too. Do biomarkers play a role in the use of immunotherapy today?

Dr. Matt Galsky: It's really a great question, Diane, because these immunotherapy drugs, specifically immune checkpoint inhibitors of PD-1 or PD-L1 inhibitors as they're called, these are really the perfect class of drugs for a biomarker. Why is that? Well, they work in a subset of patients but when they work, they work really well. So identifying that subset who's going to benefit is critically important. The tests that have been developed so far are mostly based on looking at the expression of a certain protein on the cancer cell that can be done on a biopsy specimen. Those tests initially showed some promise in terms of increasing our ability to predict who might respond to the medicines. However, they're not good enough to be able to be used in the clinic for decision making because even patients who don't have that protein present respond to these drugs.

So until we have a test that either tells us that the majority of patients are going to benefit or the majority of patients aren't going to benefit, it's of little clinical use because if it only tells us that some patients with the test, a higher proportion will benefit but there are a lot of patients who are going to benefit even if they don't have the test, it doesn't help us that much.

Diane Z. Quale: So right now with these new immunotherapy drugs, it's available to all patients.

Dr. Matt Galsky: That's right.

Diane Z. Quale: Regardless of whether or not they test positive for a specific biomarker.

Dr. Matt Galsky: That's right. In this specific biomarker, this specific protein that we're really talking about is PD-L1 testing and that testing is available in many centers, in many commercial laboratories. Some of these drugs are actually approved with the test linked to the drug but even in those settings, it still isn't useful enough to be implemented widespread in the clinic.

Diane Z. Quale: What would you tell your patient with non-muscle invasive bladder cancer what they have to look forward to in the future?

Dr. Piyush Agarwal: So Diane, if you are my patient, I would say there are a lot of exciting developments for bladder cancer that might directly help you. I would say the first thing to ask your doctor is are they involved in any clinical trials or do they know of any clinical trials that might pertain to your situation where you could benefit from the trial or we could, as a community, learn more about bladder cancer from that? A lot of these technologies are emerging and I would say that there's nothing that I can tell you right now that is standard of care but things become standard of care after being investigated and that investigation time is now.

So I think that it's exciting for patients because there are other things that they can participate in and specifically for non-muscle invasive, our ability to detect cancers through imaging, through localized cystoscopy, the use of blue light cystoscopy, the use of certain new technologies is allowing us to really do a better job of picking up tumors, detecting tumors, and resecting tumors. So I think there's already some improvement in their clinical trials in those areas as well as in more novel areas, specifically looking at mutations and responses.

Diane Z. Quale: Matt, for the patients you treat with muscle-invasive bladder cancer, what should they be asking their doctors about biomarkers and bladder cancer treatment?

Dr. Matt Galsky: If you're a patient with muscle invasive, very advanced bladder cancer even today, I think it's work a discussion with your physician about whether or not there's additional testing beyond just routine pathology that can be used to inform treatment decisions. Most of the tests are now being studied in the setting of clinical trials to establish their utility. But some of these tests are commercially available and are being utilized and in certain instances that is appropriate so that-

Diane Z. Quale: And you're talking about where I would get my tumor genomically tested.

Dr. Matt Galsky: That's right. That's right. Genomic testing of tumors and that testing can be done in academic laboratories or commercial laboratories and that testing can sometimes provide useful information, but it really warrants a discussion with one's physician as to whether or not it's the right time to use that testing and if that testing is ordered, how will it be used to impact care.

Diane Z. Quale: In the muscle invasive and advanced disease space, what else do you see on the close, near term horizon?

Dr. Matt Galsky: So in the near term, and I think we're talking about three to five years, I believe we'll see the first drugs approved in bladder cancer that are linked to a specific mutation in the tumor. What do I mean by that? When there are mutations in tumors and those are detected based on looking at the DNA in tumors, sometimes they act like light switches that are turned on all the time and are keeping the cancer cells growing all the time. And if we could identify what those light switches are, then we can pair those to drugs that turn off those light switches. This has

been done in other cancers. Lung cancer is really the model for this with multiple drugs approved that are linked to these specific tests. We don't have one yet in bladder cancer but within the next few years, we likely will have an approval based on some very promising results.

Diane Z. Quale: So there are clinical trial looking at those questions?

Dr. Matt Galsky: There are clinical trials ongoing and clinical trials already completed really setting the stage for the trials that could lead to FDA approval of these types of drugs.

Diane Z. Quale: And compiling that information is going to help researchers like both of you help improve treatments for bladder cancer patients. Thank you both very much for joining me today. It's an exciting time, I think, for our bladder cancer community and every reason for patients and their families to be hopeful that doctor specialists such as yourselves are spending so much time on these very important issues and looking to improve treatments and improve the lives of the patients you serve. So thank you very much.

Dr. Piyush Agarwal: Thanks for having us.

Dr. Matt Galsky: Thanks, Diane.

Diane Z. Quale: For more information about biomarkers or other bladder cancer issues, please go to www.BCAN.org.

