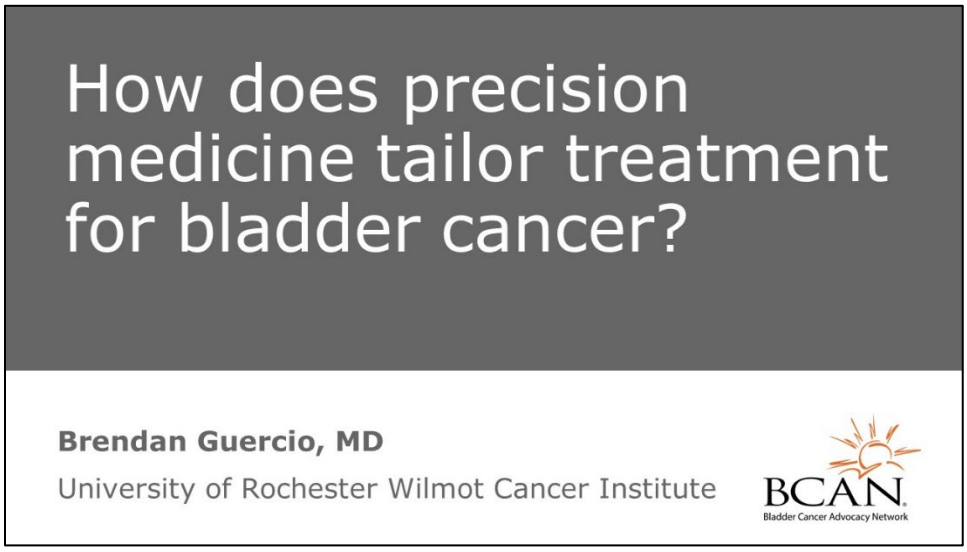


Stephanie Chisolm:

How Does Precision Medicine Tailor Treatment for Bladder Cancer Treatment? A Patient Insight webinar from the Bladder Cancer Advocacy Network. Before I begin today's program, I do want to thank our sponsors of the Patient Insight Webinar series, Merck and UroGen. We're really going to get off in just a few minutes talking about medical decisions and interventions that are really now being tailored specifically to you as a unique individual patient. What one patient gets for precision medicine is not going to be what the other patient gets in the next bed at the hospital. Precision medicine in bladder cancer involves really tailoring treatments based on specific characteristics of your cancer.

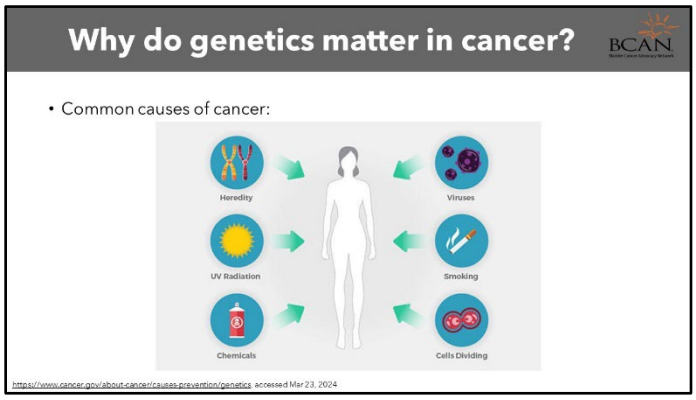
BCAN is delighted to welcome medical oncologist, Dr. Brendan Guercio from the University of Rochester Medicine, and he's going to guide us through a comprehensive review of the current and promising precision medicine initiatives that we're seeing out there. Dr. Guercio is an assistant professor at the University of Rochester Medical Center in Rochester, New York. He completed his medical oncology fellowship at Memorial Sloan Kettering Cancer Center and received his MD from Harvard. His areas of expertise include using cutting edge immunotherapy, chemotherapy and hormone therapy in the treatment of genital urinary cancers, with a focus on the development of new forms of therapy through clinical trials.

Dr. Guercio, I'm so thrilled to say he was the recipient of our 2021 BCAN Young Investigator Award for his research focused on the impact of diet on immune checkpoint inhibitors, therapeutic response and tolerability in bladder cancer patients. He's also received a young investigator award from ASCO, the American Society of Clinical Oncology Conquer Cancer

Foundation, and has been a recipient of research support from the NIH, the National Institutes of Health and the National Cancer Institute, the NCI. I'm now going to direct your attention to Dr. Guercio and you're going to share your screen. So welcome, Dr. Guercio, I'm going to turn it over to you. And then we will answer all the questions at the end of today's program. So don't forget to drop your questions in the box. Thanks so much, everybody. Enjoy the program.

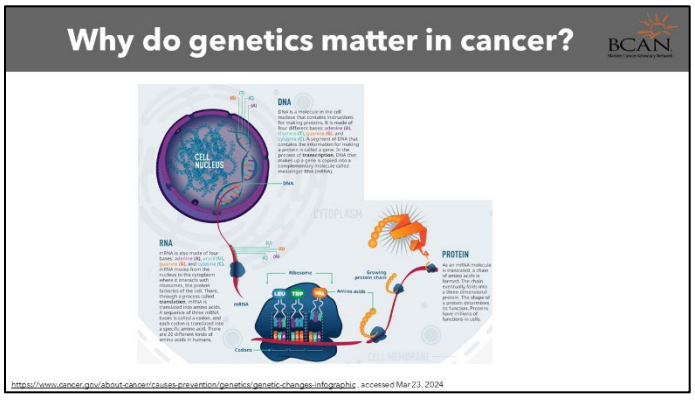
Dr. Brendan Guercio:

Thank you so much and thank you to the whole organization for inviting me to give this talk. Very excited to speak with everyone today. If you have any trouble seeing my slides, let me know. But exactly as Stephanie described, the goal of today's talk is to discuss precision medicine in general in oncology and how it pertains to bladder cancer specifically. And she did a great job explaining that precision medicine is really all about tailoring the treatment to an individual patient and that patient's individual cancer's characteristics. And oftentimes when we're talking about precision medicine, we're talking about targeting genetic characteristics or characteristics that are closely connected to genetics and the DNA of the cancer and the tumor that that cancer is made of.



So why do genetics matter in cancer? Genetics and DNA are really important to cancer and why cancer happens in the first place and how we can best treat it. We all know that there are lots of common causes of cancer like smoking, ultraviolet light from the sun, certain kinds of chemicals, and even some viruses that are known to cause cancer. And one of the common ways that most of these causes lead to cancer in the first place is by causing damage to DNA and mutations in DNA, mutations in genes that lead to cancer development and growth in the first place.

And so DNA is obviously essential to every form of life because it's basically the genetic code and blueprint for every cell in our bodies.



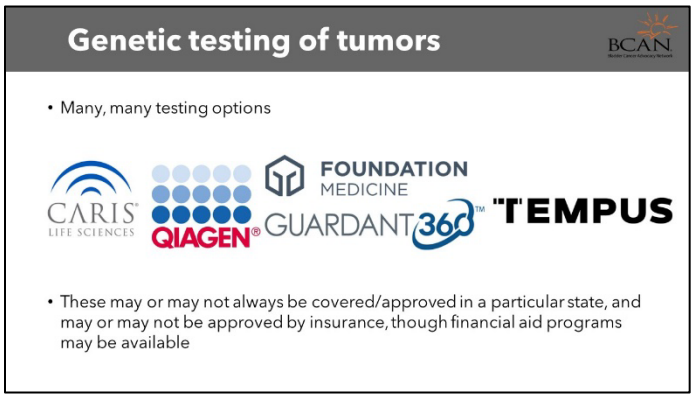
Dr. Brendan Guercio:

It basically tells our cells how to work and what to do, and the cell uses the blueprint from that genetic code to basically print out proteins.

Proteins are basically the workhorse of the body. They're like little machines that conduct all the activities that our cells need to do to survive. So when

cancer cells develop mutations, they use these mutations in their genes to create new proteins that don't behave appropriately and allow the cancer cell to grow out of control in ways that are harmful to us. And so that's really what causes cancer to occur in the first place in many cases.

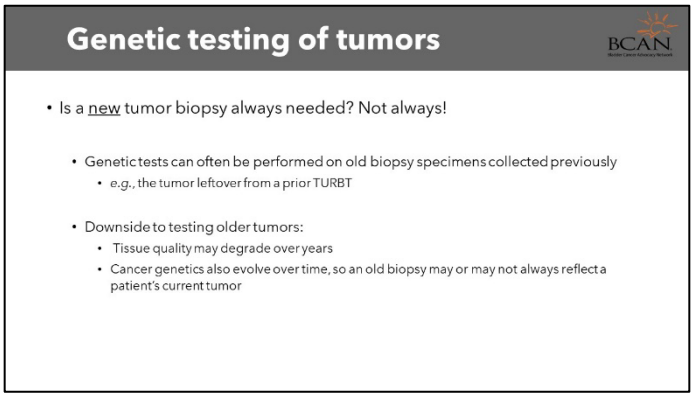
Dr. Brendan Guercio:



So it's obviously important to have good tests to be able to analyze the DNA and genes of cancer so that we can understand what these mutations are and help use them to tailor treatment for individual patients. And fortunately, genetic sequencing and testing has been around for a while now, so many different companies have now developed really good tests that can be used to analyze pieces of tumors from cancers to understand what their genetic code is saying.

This is just a list of some of the more prominent companies that have developed really good genetic tests. A lot of them have various pros and cons, but there's probably more similarities than differences in most cases. Which genetic test a physician might recommend in a specific circumstance may depend on the clinical situation, but it also may depend on the state where they're practicing. Some of these tests might be approved in certain states and not others, and it may also be related to insurance requirements and sometimes insurers will cover certain tests but not others. One thing that's fortunate in our modern era is that for many situations now where insurance won't cover a genetic test that's desired by a physician and their patients, there are sometimes financial aid programs that are available that can help get those tests done so that patients and their physicians can have that helpful information.

Dr. Brendan Guercio:

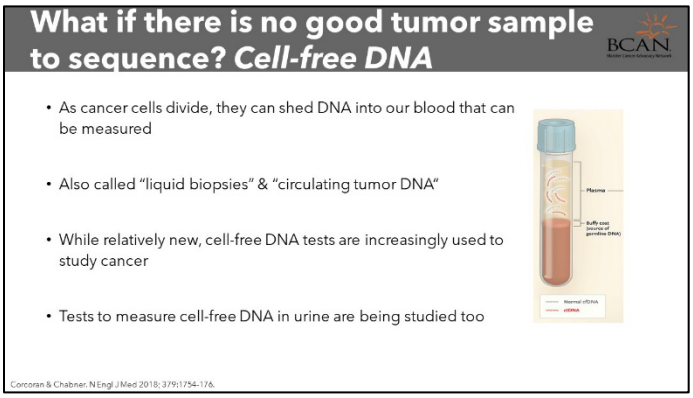


So one of the important things to know about precision medicine and genetic testing to allow for precision medicine is that often times the genetic tests that we use need a piece of the cancer or a piece of tumor to analyze in order to know what genetic mutations are present and what aren't. So often times that means getting a biopsy. One question that comes up a lot is, "Do we need to put a patient through a new

procedure to get a piece of tissue from their tumor or not?" And fortunately, the answer is we don't always need to put someone through an invasive procedure because sometimes we can actually just use an old biopsy that was already collected through a surgery or at the time of initial diagnosis to look at the genetic mutations in a patient's tumor. That makes things much more convenient for patients because otherwise it means putting a needle into a patient to get a piece of the tumor to analyze freshly, which is a good idea sometimes, but not always.

There are some downsides to using older tumors to guide precision medicine. Basically if the tumor is very old, the DNA can actually degrade over time if it's been many years. And so sometimes the results may not be very high quality. And then the other limitation is that cancers actually evolve over time and their DNA can change over long periods of time such that a very old biopsy of a cancer may not actually accurately reflect the genetic characteristics of a patient's current tumor. But most of the time sequencing an old tumor that was collected previously is okay.

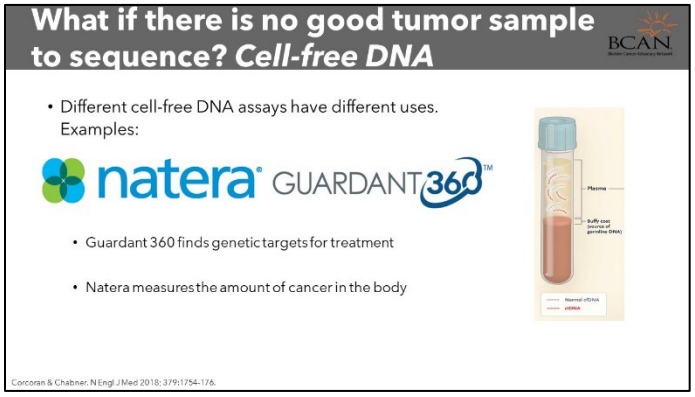
Dr. Brendan Guercio:



So another issue that comes up is what if there is no old piece of tumor available for precision medicine genetic testing, and what if that we don't have a way to safely get a biopsy now? Well, fortunately in that case, new technologies have developed to allow us to look at the genetic code in cell-free DNA. Basically, cancer cells when they divide shed DNA naturally and some of that DNA actually makes it into patient bloodstreams or other fluids even like urine. And so scientists have gotten so good at measuring and detecting genes and DNA in very small amounts that they can now even measure some of the cell-free DNA in the bloodstream of patients with cancer. And these tests are often referred to as liquid biopsies that are analyzing circulating tumor DNA, because it's often circulating in our bloodstream.

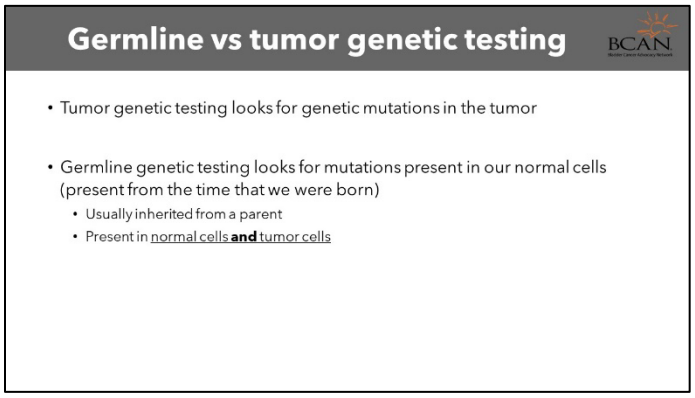
And while these tests are still relatively new, they are becoming increasingly utilized in the field of oncology in a way that's very helpful and allows us to much less invasively understand what kinds of genetic features might make a person benefit from a specific precision medicine. And the tests that are being developed for self-radiating in urine are especially exciting for folks with bladder cancer because the bladder when there's bladder cancer in it obviously leaks cell-free DNA into the urine, and that's probably going to be a very important thing for bladder cancer treatment in the future. At this point, cell-free DNA in urine is not used to guide precision medicine very often yet, but it's a very active area of research that's very exciting.

Dr. Brendan Guercio:



Another important thing to know is that there are many different types of cell-free DNA tests with different kinds of uses. They aren't all the same. So for example, two of the more prominent tests that are often used are Natera and Guardant360. They're both very good tests, but they're used in very different ways. Both used on blood samples. But when Guardant360 is used, it's very good at identifying specific mutations or genetic targets in cancer that might be targetable with a precision medicine. While Natera is actually very good at measuring the quantity of DNA from cancer in the bloodstream and how that quantity changes over time, which can actually be used to help track treatment response. So very different tests, but both are very good in specific circumstances.

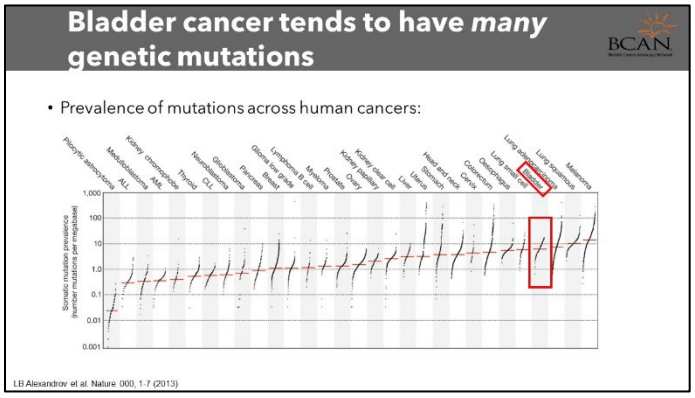
Dr. Brendan Guercio:



Another important thing to know about the kind of testing that can help guide precision medicines is the difference between germline genetic testing and tumor genetic testing. So far I've mostly been focusing on talking about tumor genetic testing where we take a piece of the tumor and analyze its DNA or look for DNA from the tumor in the bloodstream. But something else that is important in certain situations is looking at germline genetic testing, which is the genetics from the normal cells in our body because sometimes we actually have mutations in our cells that we were born with because we usually inherited them from a parent. And those mutations are therefore present in every cell in the body, both the normal cells and the tumor cells. And those can be important in certain situations.

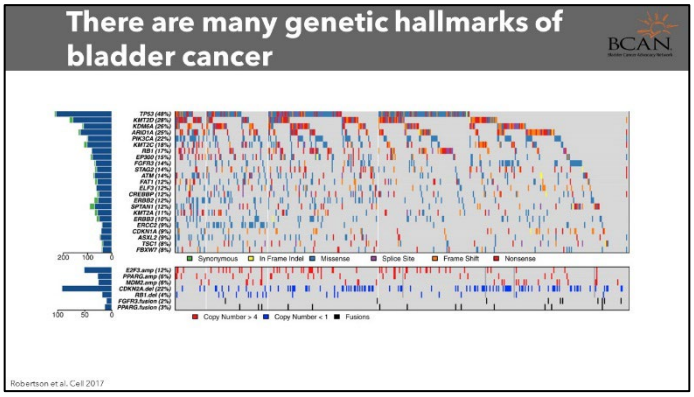
There's many different germline genetic tests that are now available. What's nice is that they're generally very easy to do. They usually require a cheek swab or maybe a simple blood test. You don't need a piece of the tumor to do this kind of testing when we're just looking for DNA in the normal cells of the body. But one of the reasons germline testing may matter to folks with bladder cancer in particular is because in a small percentage of patients with bladder cancer, patients may have bladder cancer because they have Lynch syndrome. Lynch syndrome is a hereditary syndrome that's due to a defect in DNA repair due to a problem in the DNA from time of birth. And it actually increases the risk for multiple types of cancers, not just cancers of the urinary tract, but even more often cancers of the colon and the uterus.

Dr. Brendan Guercio:

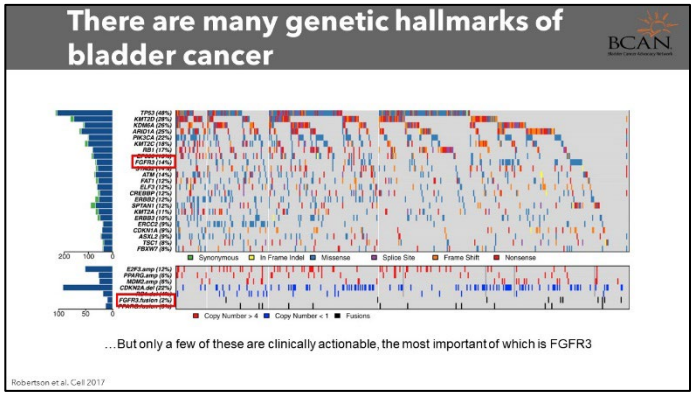


Bladder cancer is really interesting in the realm of precision medicine because in precision medicine we're usually trying to target mutations. And it turns out that bladder cancer is a cancer that has many different types of genetic mutations. This is a graph showing the average number of mutations for different types of cancer. And you can see all the way on the left, there are some types of cancer that don't have many mutations, like certain kinds of leukemia or certain kinds of kidney cancer. And then all the way on the right, there are other cancers that have many, many mutations on average like melanoma and lung. And then just below those is bladder cancer. So there's certainly a lot of mutations to potentially target.

Dr. Brendan Guercio:



And a lot of these mutations occur in genes that pop up again and again such that we know since they are so common in bladder cancer, they must be really important to how bladder cancer develops and grows like TP 53, for example, at the top of this chart of genetic mutations.



But because precision medicine is still a pretty young field, only a few of these genetic hallmarks are actually clinically actionable at this point in clinical practice, although many of them are the subjects of active research and are promising for future treatments. But in terms of genetic markers that are common in bladder cancer that are important in standard treatment today, the most important one is probably FGFR3.

Thank you to our sponsors: