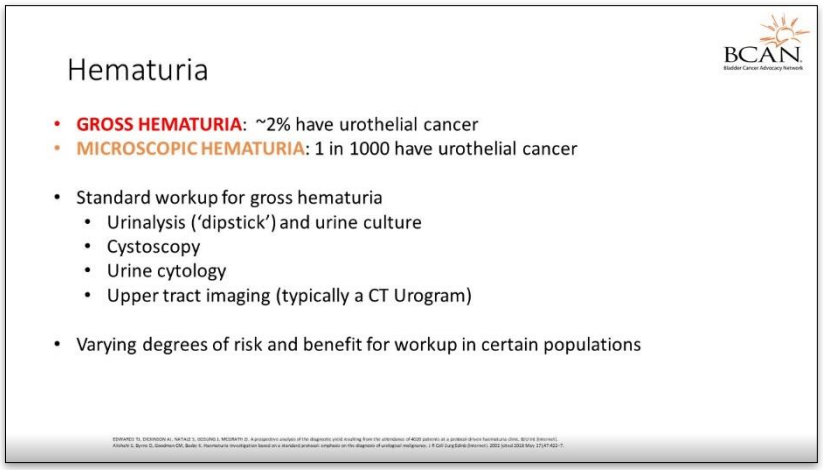
Stephanie Chisolm: My name is Stephanie Chisolm, and I'm the Director of Education and Research at BCAN. Most of us have provided a urine sample to our doctors at some point in time, but what are they looking at? Urine cytology is a test to take a look at abnormal cells in your urine. Your doctor might use this, along with other tests and procedures, to diagnose bladder cancer and other urinary concerns. Urine cytology may also be used in people who have already been diagnosed with bladder cancer and have undergone treatment. In these cases, urine cytology can be a way to help detect bladder cancer recurrence.

Meet Our Presenters:

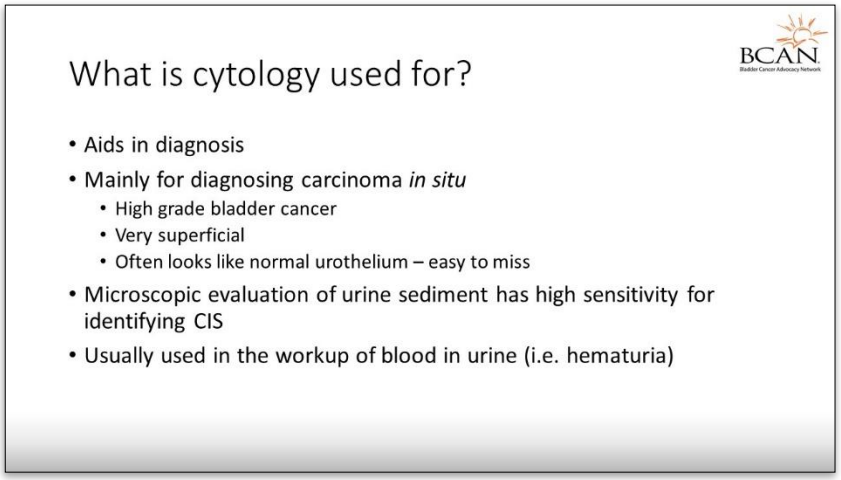
Dr. Max Kates: Dr. Max Kates is an assistant professor of urology and oncology with the Brady Urological Institute. He's got expertise in all areas of urologic oncology. His surgical philosophy is to assess the unique needs of each patient and develop the right treatment plan for them. His research interests parallel his clinical practice, with an emphasis on novel treatments for cancers in the urinary tract.

Dr. Phil Abbosh from Fox Chase Cancer Center to discuss what doctors are looking for in a urine cytology test and what exactly those tests are going to reveal. Dr. Abbosh is a board eligible and urology physician. He's received both his doctorate of medicine and doctorate in cellular integrative physiology from Indiana University. Dr. Abbosh continued his medical training with a fellowship in urologic oncology at Fox Chase Cancer Center. With a special interest in kidney and bladder, Dr. Abbosh is a recent recipient of Urology Care Foundation research scholar award and the winner of the 2018 Young Investigator Research award.

Dr. Phil Abbosh: All right. Welcome, everyone. So, we'll just kind of start right off the bat here. Most patients with bladder cancer at one point or another had a clinical condition or a symptom called hematuria, which is basically blood in the urine. Gross hematuria is when you can see the urine, it's visible. About 2% of patients with gross hematuria will have some kind of urothelial cancer diagnosis.



Microscopic hematuria is when the patient can't see the blood, but the doctor will either do a dipstick test or a microscopic test, or typically both ideally, and see microscopic red blood cells in the urine that are not visible to the eye. Only about one in a 1,000, or maybe a couple in a 1,000 patients, will have urothelial cancer with microscopic hematuria.



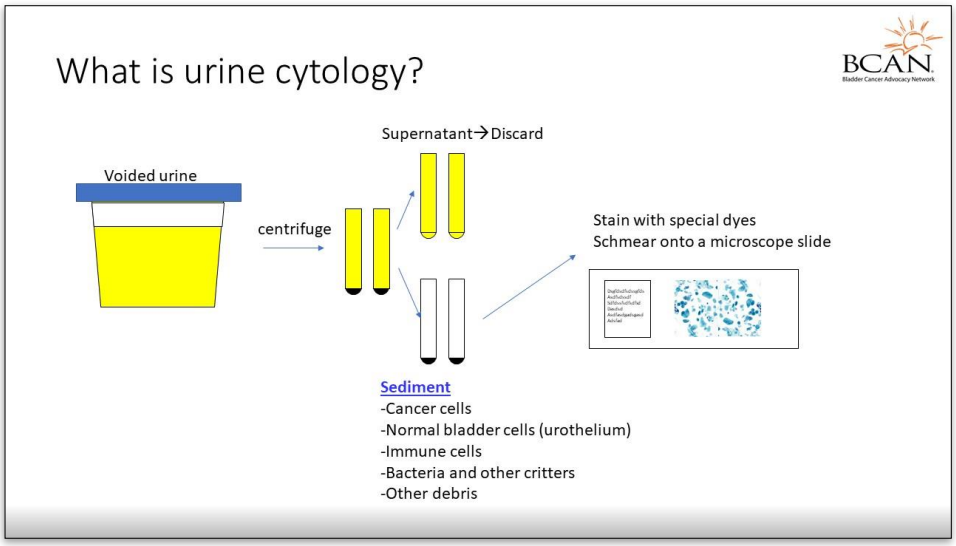
When someone shows up to their doctor with blood in the urine, there's sort of a diagnostic algorithm that a doctor should abide by. It's a standard of care. Typically patients will have a dipstick test, which is something that can be done in the office, kind of a quick and dirty urine test, and often a urine culture to determine if there's bacteria growing in the urine. Often the patient should be referred to a urologist for what's called a cystoscopy or a telescopic camera test where the camera is passed into the urethra and inside the bladder to look on the inside. The urologist for gross hematuria workup will typically order a urine cytology, which is sort of the focus of our talk today, and there will usually be some kind of an imaging test of the kidneys, ideally a special kind of a CT scan with contrast called a CT urogram. Next.

There are some nuances to the workup of hematuria with varying degrees of risk and benefit for workup in certain populations. So, in other words, a 29 year old female with hematuria during the time of a menstrual cycle might get a different workup than a 65 year old person who had been smoking two packs a day for 40 years. So, we try to consider some of these factors when we do a workup as a urologist. So, cytology is basically, in essence, it's an aid in diagnosis. It's a urine test which we use to enhance our assessment of what we see with our eyes. Next.

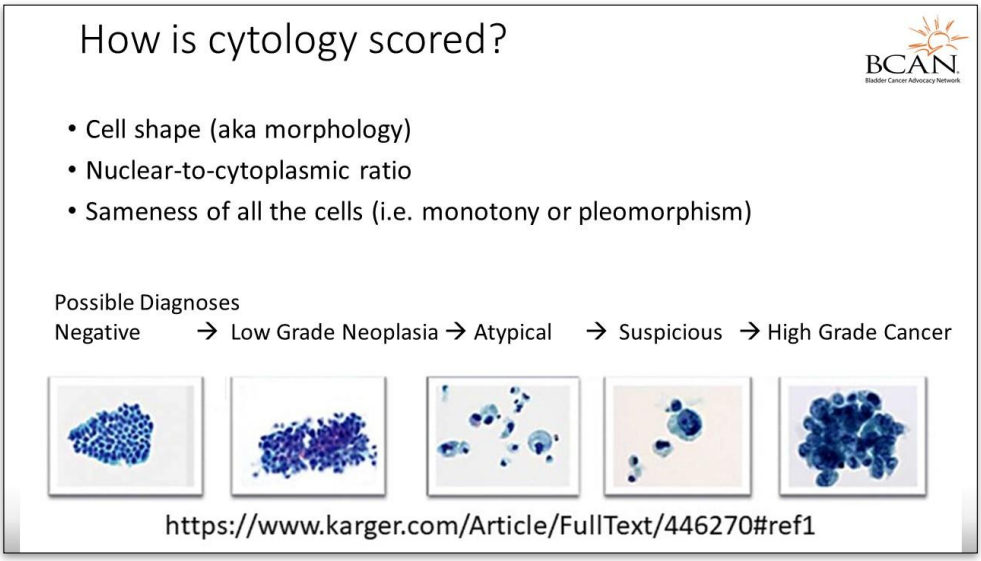
It is especially useful for diagnosing what's called carcinoma in situ, or CIS. This test, it kind of enhances what we see visually. CIS is considered a high-grade superficial type of a tumor. It often can look like normal urothelium, so it's easy to miss on a cystoscopy test. It's much harder to miss on a microscopic test, like a cytology. So, a cytology is a microscopic analysis of the urine that's excreted from a patient when they void.

Dr. Phil Abbosh: When we use a microscope to identify CIS, we have a very high sensitivity for picking it up with a urine cytology. And as I mentioned on the first slide, we typically use cytology in the workup of blood in the urine, and then in some additional clinical scenarios, which Max will talk about here in a couple slides. Next.

What is urine cytology? So, this is sort of just a quick graphic that describes what's done here. So, you'll go to the doctor's office. You will pee in a cup. The urine gets sent to a lab where the urine is poured into a test tube essentially that is centrifuged so that any pellet or sediment or cellular material, with gravity, will go down towards the bottom, which is that little sort of black part of the test tube there. And then the supernatant, which is the yellow part, the fluid part, will typically get discarded. And those cell pellets, the sediment at the bottom, is what we're interested in for pathology.

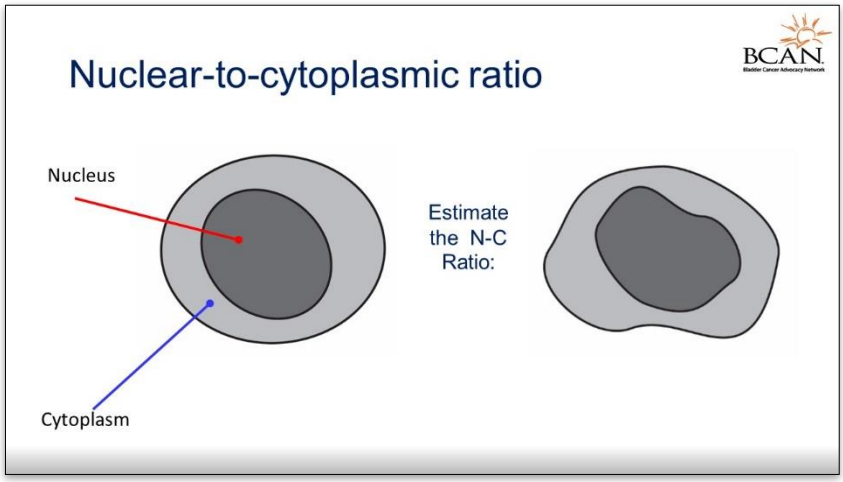


So if there are cancer cells, they'll be down there. Normal bladder cells, which can be exfoliated under normal processes from the bladder, will also be there. Immune cells, such as macrophages, lymphocytes, things that protect your bladder from infections are there. If there's any bacteria or other critters, such as yeast, those things will be in the sediment of the bladder. And then any other debris or cellular parts will be down there as well. That sediment is then stained with a special dye and then smeared onto a microscope slide with your identifying information. And then a pathologist called a cytopathologist will actually do, perform the microscopic examination of that smear that's on your slide. Next.

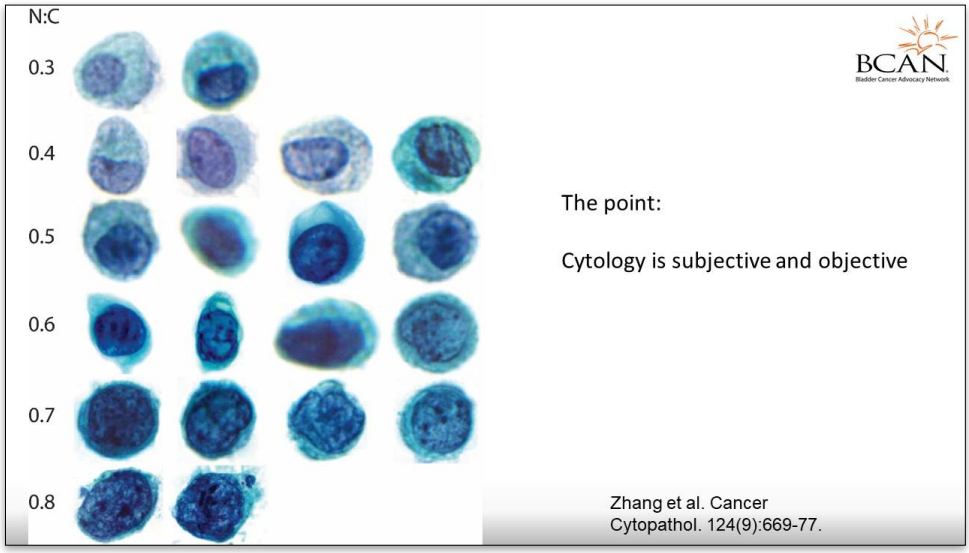


Dr. Max Kates: So, a lot of patients, we have the amazing ability to gather some initial questions from many of you, and I see the Q&A is already very active, and we'll try to respond as a team to the Q&A.

But many of you asked the very basic question of, what is cytology and what is the difference between all of these diagnoses that you can get on a cytology? And so essentially, a cytology is an analysis, as we just discussed, of cells in the urine. And by far, the most important aspect of the cytology is the combination of the cell's shape, or what pathologist's would call the morphology, and the nuclear to cytoplasmic ratio. What does that actually mean? That actually means the amount of the cell that is made up by the nucleus, or the nuclear material, versus the surrounding fluid, or the cytoplasm. And a the amount of nuclear material increases, the likelihood of cancer greatly increases.



But as you can imagine, this is not an objective test, okay? And that's something that Phil and I will try to drive home to all of you as much as possible. What does that mean? It means we have some tests, for example, a PSA, okay? It's a number, right? It's a blood test that comes back as a number. Now, how we interpret that number varies, but by and large, you get a number back. With something like a urine cytology, it's what we would call a qualitative test that's judged by an expert, and that expert is not just somebody who's a pathologist, but usually somebody who's gotten specialized training in cytology. So, they're a cytopathologist, and what they do is they basically look at these slides of urine and look at these cells and try to assess the nuclear to cytoplasmic ratio and the cells shape and whether basically all the cells look the same, monotony would be the pathologic term.



So, the possible diagnoses are from something called the Paris criteria, okay? And this came out a couple years ago, and this is how pathologists judge a cytology. And it can be either negative, which means these are all perfectly normal

cells. They all look the same. They all have a small nuclear to cytoplasmic ratio, so mostly the fluid surrounding the nucleus, not the cell dominated by the nuclear material. That would be negative.

Dr. Max Kates: They can come back as low-grade neoplasia, which to be honest, we don't see very often. I can't remember the last time I saw low-grade neoplasia, and I don't put a ton of stock into. The big one that patients always ask about is atypical. And this is, would be atypical here in the middle. And basically what atypical means is that the nuclear to cytoplasmic ratio and the morphology, it's all completely... It works as something that's not normal, right? It's not normal, but it certainly does not look like cancer cells, and it certainly is not consistent with cancer cells.

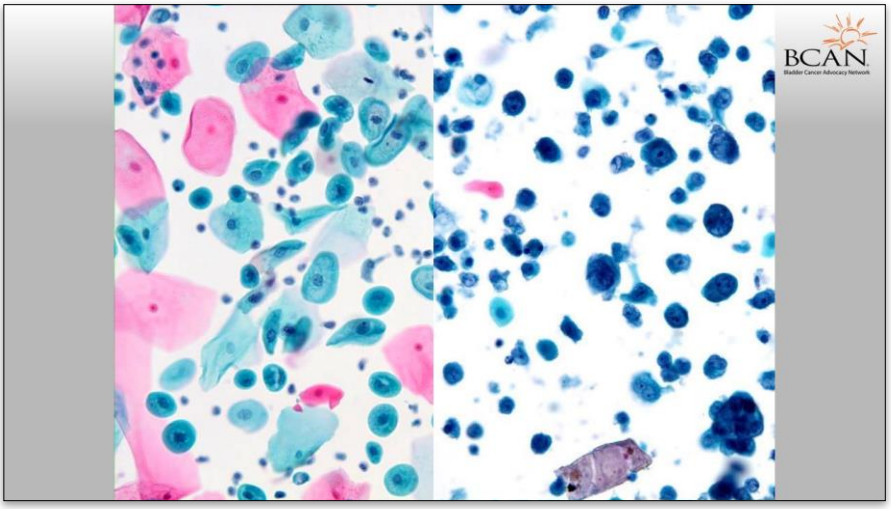
So, that's a hedge. It's basically the pathologist saying, this is really just indeterminate. These are abnormal cells, but they certainly don't look like cancer cells. And when we get to the clinical aspects, I'll tell you how I interpret that, but basically, I interpret that as being more commonly than not nothing. Usually inflammation, usually benign inflammation. I do not consider an atypical cytology to be diagnostic of cancer at all, and that's something I spend a lot of time talking to my patients about.

Suspicious is really... In talking to cytopathologists, it's maybe one of the cells looks like it is pretty good to be a cancer cell, but that's one cell out of many, many, many, and so most pathologists are not going to say that this is high-grade cancer. They're going to say, "Wow, one of those cells looked very abnormal, but it was really just one of these cells. I couldn't really make that diagnosis on all of the cells, so I'm going to call this suspicious."

And then there's high-grade cancer, which are multitude of cells that are clearly cancer. So I wanted to spend a good amount of time kind of going over this so that we could all kind of fundamentally work from the same language, and we can get in the questions and answers, and I see we went from four in the Q&A to already nine. So I'm sure this... I'm not reading them yet, but I'm sure this already incited a lot of questions. But I wanted us all to use the same nomenclature before we kind of go on. I can tell you that this nomenclature is from a standard called the Paris criteria that the pathologists are trained to use. All right, next slide.

So, this is a little bit of repetition, but really just talking to you about how they make these judgment calls. Basically, the larger, the more nuclear material you have, the more likely it is to be a cancer cell.

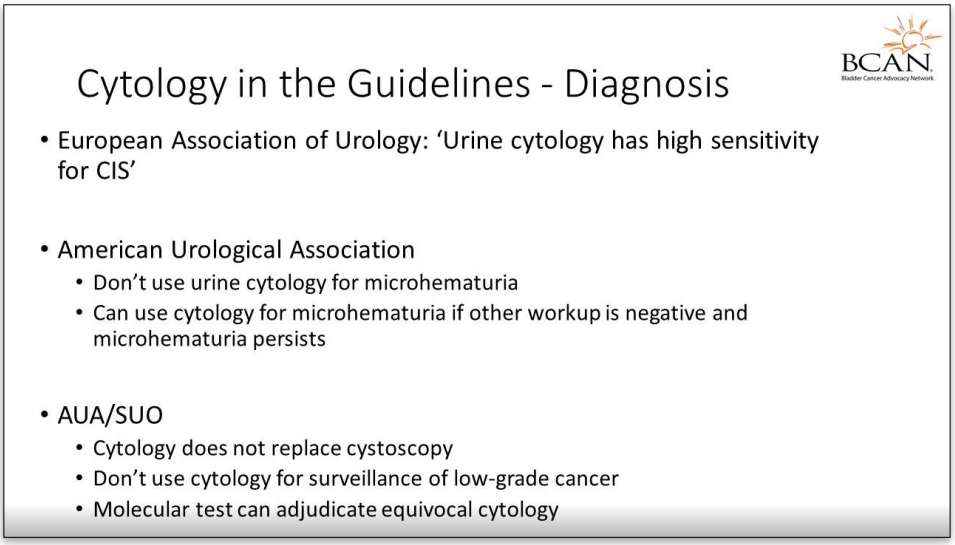
Dr. Max Kates: And once again, these are very different degrees of... I think there's an animation on this you can click on. Maybe not. So, you can see there's varying degrees if you go from top to bottom. At the top, you go from... That's perfect. At the top, you go from a lot of cytoplasm to a small amount of nuclear material, compared to all the way to the bottom, you see that cell is almost all nuclear material down here and very little of that light blue cytoplasm. But the real point is that this is a very subjective process. We can try to bring in objective criteria like this ratio, but ultimately it's going to come down to a lot of expertise. Next slide.



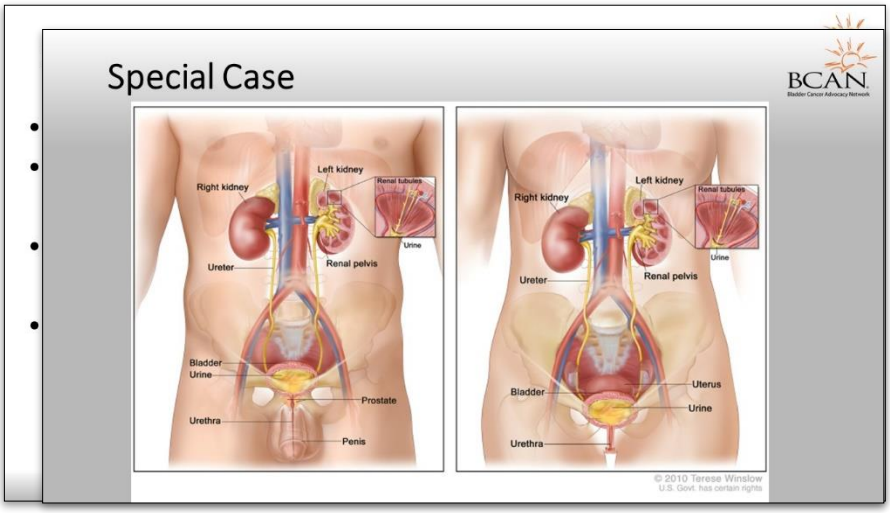
And I think this really drives this home, is these are two examples of basically cytologies that can be difficult to figure out. One of them on the left is really benign coming from benign shedding of kidney cells, of cells from in the upper track. And on the left are really... And on the right are inflammatory cells from BCG. And neither of these are really diagnostic of cancer for sure. So, I just wanted to give you that to show you that it's a very sort of subjective process. Next slide.

So, what is cytology? What does our guideline say about cytology? So basically, as Phil mentioned, cytology is highly sensitive for CIS. Next.

The American Urologic Association basically says we should not be using cytology for the work above microhematuria. Why? Because it has very poor diagnostic accuracy in the workup of microhematuria. We can use it if the rest of the workup is negative and the microhematuria persists, but more times than not, we don't use it. And then additionally, we really don't use cytology to replace cystoscopy, and we don't use it for surveillance of low-grade cancer. It's much better for that CIS, or that high-grade cancer, than it is for detecting low-grade cancer.



Dr. Max Kates: And molecular tests, of which Phil will be talking about some different options, can help adjudicate cytologies that might atypical or suspicious, if there's concern on the part of the patient and the clinician. Next slide.



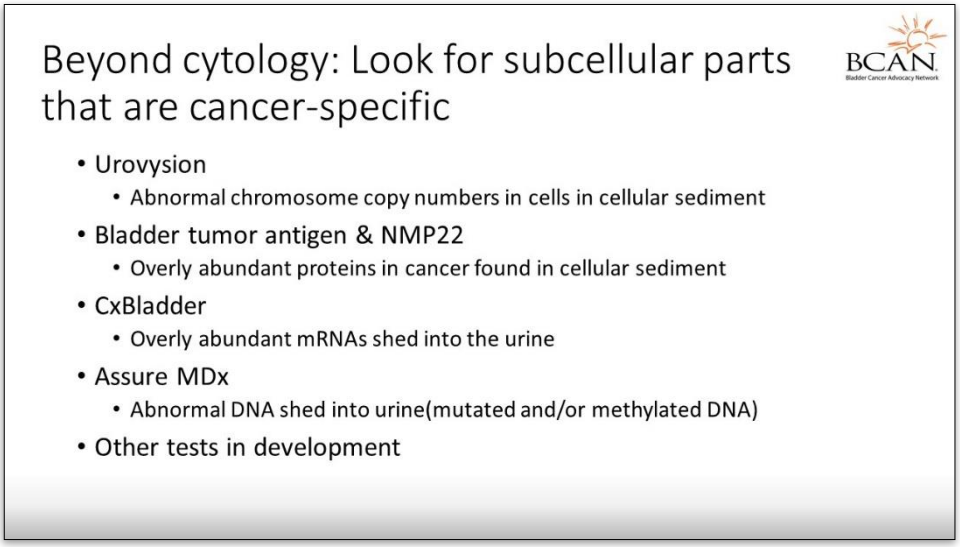
Okay, so let's go over a case. I think these are always fun to do for everyone, and I say fun because they kind of bring to life some of the points we're kind of making. So this is a 62 year old gentleman. He presents to his urologist with gross hematuria. His cystoscopy and his CT of his abdomen and pelvis show no evidence of a tumor. His urine cytology then comes back as high-grade urothelial carcinoma. So, basically we do the classic workup. We get a CT of the abdomen and pelvis. It doesn't really show anything obvious. We put a camera in the bladder. It doesn't really show anything, but yet the cytology comes back as concerning for high-grade urothelial carcinoma. And this is a pretty common scenario. It happens. And in this situation, many of us, this is expert opinion, so you'll get different answers from different urologists, but many of us have the philosophy of essentially looking elsewhere, being on a little bit of a treasure hunt as I tell my patients.

So, we're trying to find this in places where it's not obvious, so that's going to be the prostatic urethra. We'll oftentimes, this is a great situation to perform blue light cystoscopy, particularly looking for small areas of CIS in an otherwise normal bladder. We may also want to do random bladder biopsies, and we may want to also visualize the upper tracts and certainly take at least washings from the upper tracts.

So, this is a scenario in which we're looking for subtle cancer, and the key thing is is that when we look at the urinary system, it encompasses the kidneys, the ureters, the bladder, and the urethra. And a urine cytology is shedding of a urinary tract cell, and it can be from any of those places. So, the obvious tumors oftentimes should be apparent on a CT scan and a cystoscopy, but sometimes we'll do a little more sleuthing. And that's how urine cytology can be helpful in this type of case.

Dr. Phil Abbosh: Thanks, Max. That was really good. I think that was a good summary. So, I'll talk a little bit about some of the other urine-based tests that we use as urologists sometimes. I really tend to just rely on cytology. I don't use a lot of these other sort of more novel tests. I think there's several reasons for that. But this is sort of my wheelhouse, so in addition to being a surgeon, I am also a scientist, and our lab is really focused on urinary biomarkers that aren't really even described here yet. We're still in the research phase of some of the things we're using.

Dr. Phil Abbosh: But the first one is what's called a FISH test, or the UroVysion test. This test measures chromosome copy numbers in the cells in the urine sediment. When the urine... When a patient has cancer, there are often chromosomal copy number changes. Your urine, all of the cells in your urine are supposed to have two copies of each of the four chromosomal areas that are tested on a UroVysion test. And if there's ever three copies or one copy or six copies, that's abnormal, and that would result in a positive UroVysion test. It's a specific test for bladder cancer, but it's not always positive when people have low-grade bladder cancers.



There's also a test called the BTA, or bladder tumor antigen, and also a test called the NMP22 test. These tests measure the amount of a protein which is over expressed or overly abundant in patients with bladder cancer in the actual cancer cells that are found in the urine sediment. They're often what's called a point of care test, which means it can be done in the office where a patient pees into a cup and it's almost like a dipstick test essentially where the test will be positive or negative in the office, as opposed to a cytology which has to be sent out to a lab where it's fixed and stained and then a pathologist interprets it under a microscope.

The Cxbladder is another new test which measures what are called MRNAs, which everybody probably has heard of the term MRNA now because of COVID vaccines, but MRNAs are, just like in COVID vaccine, there are pieces of genetic material that encode proteins. And those MRNAs can be measured very easily using a test called reverse transcription and polymerase chain reaction, or RTPCR. And Cxbladder measures I think five MRNAs that are shed into the urine.

AssureMDx. I'm not even sure if they still make this test, but it came out a couple years ago, and then i kind of stopped hearing about it. But it measures instead of MRNA, measures DNA that's shed into the urine, and it specifically measures changes in the DNA either by mutations, which are common in bladder cancer, or methylation of the DNA which causes silencing of genes that are encoded by that DNA which becomes methylated.

There are other tests in development I mentioned. That's one of the things we work on in our lab. Our lab is specifically working on a DNA-based urine test that we're really excited about.

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