Stephanie Chisolm:

We did have a few questions come in, and then somebody retracted their question because you already answered it. But one question is, why isn't somatic testing done when a tumor is profiled otherwise? If they're going to do pathology, why don't doctors just have somatic testing at least to find out what's going on in mutations?

Dr. Sonpavde:

So, somatic testing essentially is tumor testing. So, we do somatic testing quite routinely in metastatic urothelial bladder cancer, especially because we want to detect the FGFR3 three mutation or fusion, because for that mutation found in the tumor, we have actually a drug approved [inaudible 00:46:27]. The germline is where we are not doing it routinely in everybody at the moment, and this is where we want to select patients for it. And this is where, as you heard, approximately 15% of... If you select everybody and do it, you'll see approximately 15% have a germline mutation that they were born with. So, that's not just a tumor, but they were born with it. Again, if you choose younger patients or other families tree that's known multiple cancers, previous cancers, then you increase, you enrich your population for the presence of germline mutations. I don't know if you want to add to that, but yeah.

Dr. Dubard-Gault:

Well, I also find that it's access to it, right? Even when that that's true, you have to find the right person to help you through the process, right? So, that's why I'm so glad. Thank you, BCAN, for doing this because the awareness is one step to the process that makes all the other parts maybe easier.

Stephanie Chisolm:

Yeah. Well, our goal is to at least give patients some good questions to ask their providers so that if it is appropriate, they can get access to genetic testing. So, I think that's a big deal. And this is a common question that we see in here. Someone is concerned for their children. Her husband lost his bladder cancer battle in 2014 after 18 months of muscle invasive diagnosis. He was 54 years old. His younger brother has urothelial carcinoma in the kidney, and he's a survivor. He was diagnosed at 46. What screening would you recommend for her children going forward?

Dr. Dubard-Gault:

I would start with testing the person who's alive with germline genetic testing to identify if there is a common thread, right? Coming up with a positive result, there will give an answer as to why, and then a helpful tip as to what to do about the potential risks of either the bladder, the kidney, or other cancers like colorectal cancer where we would start a colonoscopy screening protocol sooner than age 45 or 50 or 40 if we didn't know that information. And each person, I would also say, would be able to have their own genetic testing. Every person can have genetic testing, but having the first person who's had a diagnosis of cancer be tested is useful as to make sure we can identify what it is we're looking for because the screening protocol sometimes is based on the risks that are not only the familial risks, but also what is present in the genetic testing results. Does that answer the question?

Stephanie Chisolm:

Yeah, this is great. This is so informative. And here's a question. Does all circulating free DNA in serum originate from tumor tissue? In a given patient, do tumor and cell-free DNA all match? Can there be heterogeneity in that?

Dr. Dubard-Gault:

I can take that one, and then you can add to it maybe. So, you can have a benign tumor shed in the blood the same way the cancer malignant kinds of tumors would. We don't know as much about what benign tumors shed or what we come up with if we were to test people with those. But uterine fibroids, for example, would shed things in the DNA, in the circulating blood. And then I find that the testing is not always done correctly, meaning that you may not always have enough coverage of everything to be consistent or be comprehensive of all the information, right? So, I don't know if I would trust it completely, but I know that there are other things that can shed in the blood that would make it so you would want to pay attention. And Dr. Sonpavde can add to that.

Dr. Sonpavde:

I agree with everything Marianne said, and I think Bishoy has done a lot of work in ctDNA probably wants to add to that. But essentially, most of the DNA in the blood is actually not tumor DNA, right? It's a very small component. Most of it is from all these other cells in the body, all the blood cells shed DNA. So, it's actually very, very challenging to find circulating tumor DNA that's originating from the tumor. And that's actually why we don't actually find it in a lot of patients at all. So, Bishoy, you want to add to that?

Dr. Faltas:

Yeah, so I completely agree. So, actually, most of the cell-free DNA... So, cell circulating tumor DNA is a very small fraction of the cell-free DNA. The majority of cell-free DNA actually comes from, as Dr. Sonpavde said, from peripheral mononuclear blood cells, so essentially white blood cells that we have. And that's essentially why when we do the slide that you showed earlier, why we can detect germline mutations in cfDNA, it's actually that those are coming from the white cells, which are normal cells. And based on frequency, we can actually tell if these are germline or somatic mutations. In terms of the heterogeneity aspect, so that that's a little bit more complex. So, there's somatic heterogeneity, which we call mosaicism, which is essentially, I could be born with a mutation, but then not all cells in my body. So, actually... Well, not born, but a germline mutation could develop at a later stage, but I'm born with that mutation, so maybe I didn't inherit it, or maybe I did, but then some of the normal cells in my body have these mutations and some others don't.

The same in terms of cancer and heterogeneity. There's also the definitely process of cancer heterogeneity, and that could result in differences in terms of the alterations that we observe in the circulating tumor DNA as well.

Stephanie Chisolm:

Great.

Dr. Dubard-Gault:

I will just add, this is why the plug of doing it paired, even though the blood and the tumor at once rather than having to chase one or the other is most useful. So, if we can do it all at one time, it's better.

Stephanie Chisolm:

Very, very helpful information. So, here's a question I think more for the oncologists. If erdafitinib and PARP inhibitors didn't work, could that mean that the patient didn't have the right mutations?

Dr. Sonpavde:

So, maybe I'll start and Bishoy can add. So, erdafitinib is approved in patients with FGFR3 activating or FGFR two activating mutations effusions in the tumor, so that's somatic. So, the response rate in the, these were post platinum chemotherapy exposed patients with progressive disease, the response rate was 40%. So, having the mutation seems to be necessary for the activity, but is not enough for the activity. So, obviously that's why we don't have a hundred percent response rate, right? So, having the mutation increases your vulnerability to FGFR inhibition, but is obviously not enough. So, we really need some better combinations of the FGFR inhibitors plus something else to improve the response rate, obviously. And this drug also does not cure these patients. So, really we have a long way to go to understand the genomics and the genetics that lead to the very high response rate and curing these patients with targeted agents. PARP inhibition is very...

It's still not approved in bladder cancer, so we only have trials showing that PARP inhibitors are active and improve outcomes in the short run in patients with a mutation in a DNA damage repair gene, mostly the BRCA genes, the combination deficiency positive patients with these mutations in the tumor. Mostly these were patients with mutations in the tumor in these trials. Germline patients, they were hardly any or none in these trials, but you can expect patients with the germline BRCA deficiency to have that in the tumor also. At the end of the day, there is some activity of PARP inhibition, but they're not approved yet, and it needs more work to get these drugs into the clinic for these patients.

Stephanie Chisolm:

Great. Thank you so much. Okay, we have time for two more questions. I was recently diagnosed with adenocarcinoma bladder cancer. That's more of a rare type of bladder cancer. Does any of this testing have any kind of impact? Is it going to be something he should do for his siblings to find out if there's anything in there that is a variant?

Dr. Sonpavde:

All of the work, as I understand it, has been done in urinary trial or urothelial carcinoma. Adenocarcinoma is such a rare entity. It is really not been that much germline work done on unless Marianne or Bishoy know anything about it.

Dr. Faltas:

No, I agree. I think the short answer is that we don't know, and I would say probably the same that applies to conventional urothelial carcinoma applies to these variants at this point, but we need more research.

Dr. Dubard-Gault:

And I would add that genetic testing can always be done later again. So, repeating testing is always a possibility, even if the person has had genetic testing already and was negative for it, for example. It's sometimes because it's inconclusive. It's not because there wasn't something to be found. And doing the genetic testing again in a year, two years or three years may very well bring an answer that we would've not been able to identify otherwise.

Stephanie Chisolm:

Right. And you bring up a good, another question that is here. Somebody had a radical cystectomy in 2017. Is it too late to get tumor tested for genetic mutations? Does pathology preserve the tissue for that long, or is there another way that they could find out if they have a genetic mutation or a variant?

Dr. Dubard-Gault:

I think at this time, given from what I'm hearing, the person's is NED no active evidence of disease. Correct? I would start with the germline testing, because that would be more useful for the explanation or what to do if something was identified as a positive result, because the tumor testing may not be as useful for the time being. It doesn't mean it's not something interesting or important to look for finding the answer, but it may not be as useful high yield than the germline testing on the blood or saliva. And that could be done with a genetic counselor.

Stephanie Chisolm:

Okay. One last question. The mother was a smoker and had lung cancer, sister had lung cancer and also bladder cancer, but was a non-smoker, and this person had bladder cancer. Should they get genetic testing?

Dr. Sonpavde:

And how old was the... I guess we don't know. I guess especially... I think in a non-smoker, I would have a low threshold to do it. One of the problems with a family this is this some kind of smoking exposure in the family as they were growing up, or is it some inherited mutation that led to bladder cancer and all these people in the family? So, I think when in doubt, I would lean towards doing it.

Dr. Dubard-Gault:

And if you have two relatives with lung cancer, we tend to say why not? Right? The testing would be covering the gene called EGFR. It's a vascular growth factor may not be covered by the insurance, because as Dr. Sonpavde mentioned, you may not have enough to bring that threshold for genetic testing for criteria, but it never hurts, no.

Stephanie Chisolm:

Okay, great. So, one more question. While I was getting chemo, my oncologist asked if I would agree to genetic testing, I agreed and was told the results were good, no need to do more work in this area. Does that mean that they don't have a gene that could cause their bladder cancer?

Dr. Dubard-Gault:

I can let Melanie answer that.

Melanie:

I felt like I was being asked it. Yeah. So, no, it doesn't mean that necessarily. I mean, the number of genes that they can look at to see if you have an inherited form of cancer is a set number right now. And that number is changing all the time. And in another five years, another few years, there may be a new set of genes. And especially if they have a positive family history, it's probably worth revisiting. But yeah, for now, I think you could be somewhat reassuring. Don't you think?

Stephanie Chisolm:

Yeah. And thanks in part to phenomenal researchers who are doing all of this amazing research going on going forward. The next five years might shed even more lights on all of these different mutations and variants and what their influence is both on developing disease, but also on treating disease. So, this has been a fabulous program. I'd like to thank Melanie and Ken for sharing their stories. This has been so wonderful. I really think it adds so much to the whole discussion. And Marianne, thank you so much. Providing all this genetic information has been phenomenal, be a great resource. Dr. Faults and Dr. Sonpavde, again, thank you. This has been fabulous.