Stephanie Chisolm:

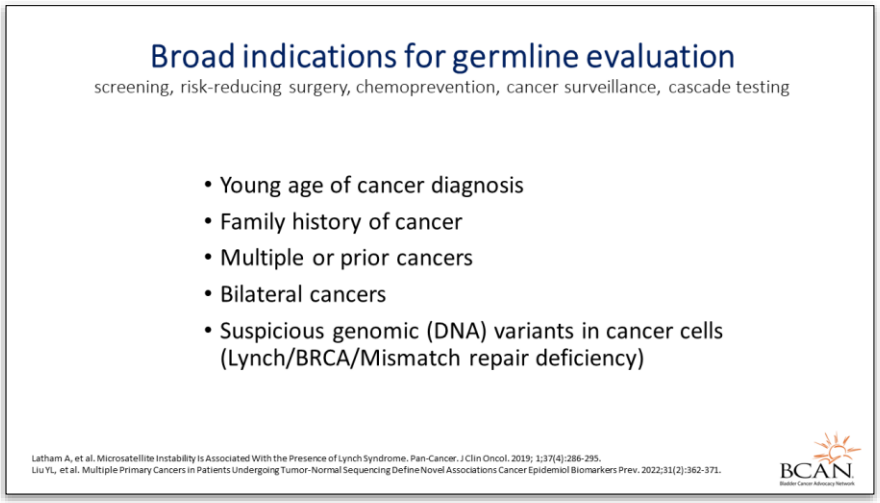
So, welcome to Treatment Talk: Genetics and Bladder Cancer Treatments. My name is Stephanie Chisholm, and I'm the Director of Education and Advocacy at the Bladder Cancer Advocacy Network.. We often hear that many patients patient have no known exposure risk factors to bladder cancer, such as smoking, and they wonder how they develop bladder cancer, and should they be worried about their siblings or their children being diagnosed at some point. BCAN is really pleased to welcome Dr. Guru Sonpavde, Director of GU Oncology at Advent Health Cancer Institute in Florida, Dr. Marianne Dubard-Gault, Director of the Cancer Genetic Service at Seattle Cancer Care Alliance in Washington, and also delighted to have the director of bladder cancer research at Wheel Cornell University, Dr. Bishoy Faltas with our patient advocates, Melanie P. and Ken D., on our Treatment Talk program.

Today's program, our presenters will share the clinically significant genetic changes known as germline variants that exist in some bladder cancer patients, but not all. And our patient advocates are going to share their experience with finding out about their own germline variants. So, Dr. Sonpavde and Dr. Faltas, welcome. You both are doing a lot of research on what is known as germline variants in bladder cancer, so we're really looking forward to finding out what some of the most common genetic alterations are in the disease and how they impact the treatment for bladder cancer. So, Dr. Sonpavde, I know you had some slides, so if you want to share your screen, you can help explain it with your slides first, and then we'll let Dr. Faltas add any comments at the end.

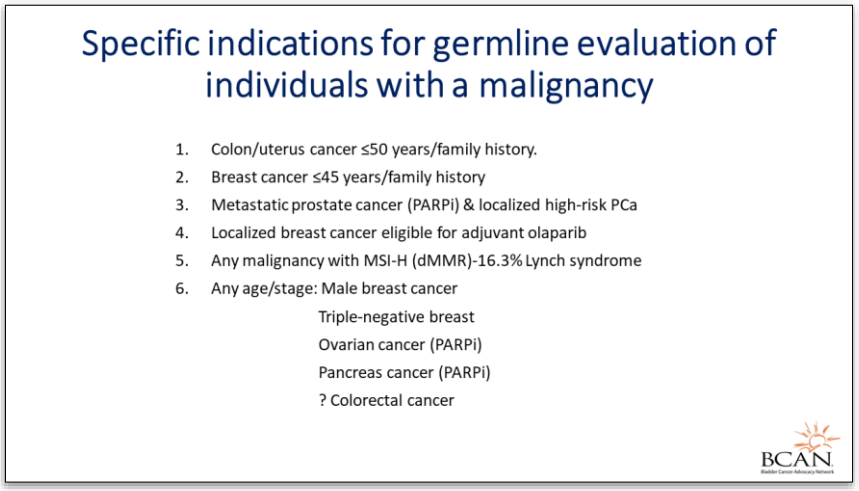
Dr. Sonpavde:

Thank you, Stephanie. Thanks for the invitation to give a brief lecture on the genetics of bladder cancer. So briefly, we are going to be talking about inherited mutations in this talk. So, we are not really talking about mutations found on profiling and studying the tumor tissue itself. I'm at the Advent Health Cancer Institute in Orlando. There are some broad indications for germline evaluation to see if the patient has

any mutations they were born with that makes them susceptible to cancer. And this is of course, young age of cancer diagnosis. When you suspect this, if you have a family history of cancer, especially in a first degree relative, if you have multiple or prior cancers, if you have bilateral cancers, or if you have some suspicious DNA mutations in the cancer cell itself when you are studying the cancer biopsy specimen. And of course, you do this because you want to see if you can help with risk-reducing surgery, chemo prevention, cancer surveillance, and cascade testing in other people in the family if a patient has a mutation that might increase the risk of cancer.

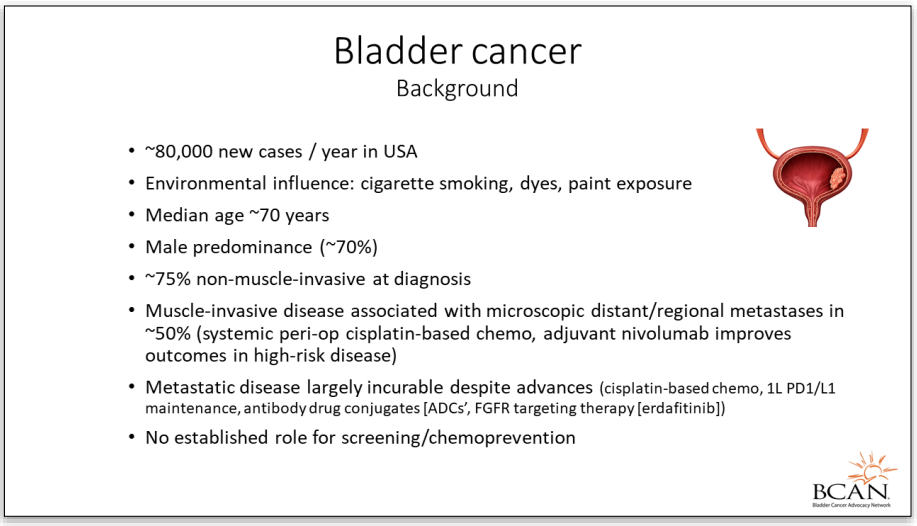


So, there are some specific indications for germline evaluation of patients to see if they were born with certain mutations that lead to cancer. So, this includes patients who are younger with colon or uterine cancer, younger breast cancer patients. Now, we do it in metastatic prostate cancer patients and localized high risk, high Gleason score prostate cancer because there are therapeutic implications with PARP inhibition treatment.

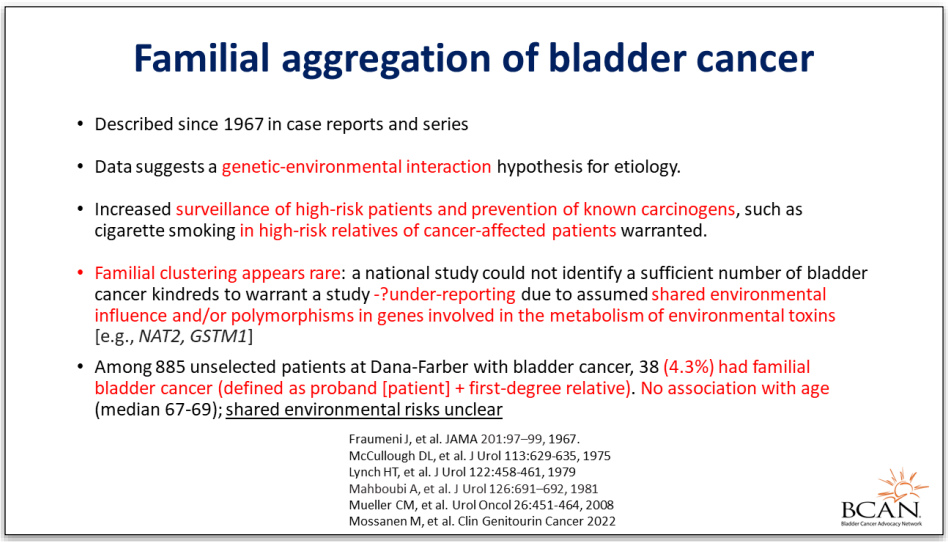


Localized breast cancer that is now eligible for adjuvant olaparib PARP inhibitor where it's approved in patients with germline alterations. And also, any malignancy where you have something called MSI high or a deficient mismatch repair, you want to look at whether these patients have a germline alteration because some of these syndromes, especially the Lynch syndrome, is associated with MSI higher deficiency in mismatch repair. Also, in certain cancers, germline testing of patients is done in any stage of cancer with male breast cancer, triple negative breast cancer, ovarian cancer, and pancreatic cancer, and perhaps colorectal cancer is now the emerging cancer where we are thinking of doing it in everybody regardless of stage.

Dr. Sonpavde:



Now, just a little bit of background on bladder cancer, we see approximately 80,000 new cases a year in the US. There is a strong environmental influence. We know about cigarette smoking, dyes and paint exposure that increases the risk of bladder cancer. It's an older person's disease. The median age is almost 70 years. There is a male predominance of the disease, approximately 70% are male. We don't really understand why, but this is a field for study. Approximately three-quarters of patients have non muscle invasive disease, so still not invading the muscle, deeper layer of the bladder or beyond. And we know that once it invades the muscle, it becomes very aggressive. You can have microscopic distant disease, and this is difficult to cure. Once it metastasizes and it becomes visible on scans or clinically, then you are really facing mostly incurable disease, unfortunately. There is not an established role for screening and chemo prevention medical therapy to prevent cancer at the moment in all patients with bladder cancer.



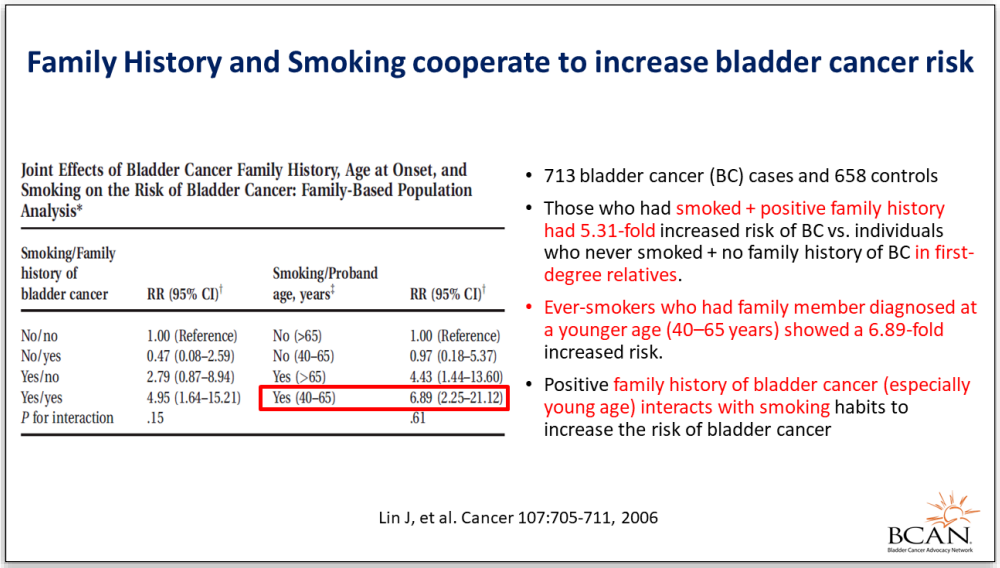
So, we have known that there is a familial aggregation of bladder cancer. When you see historically back in the 1960s, we've had case reports and series which described families with the concentration of bladder cancer in several people in the same family. So, there seem to be a genetic and environmental interaction. In most cancers, we think there is an interaction, of course, of something the patient was born with and interaction with something in the environment. For example, cigarette smoking could be that risk. There is also, we know that there would be a role for surveillance of high risk patients and prevention of known carcinogen. So, if you know somebody's at high risk cause they have a born with their mutation, you might want to surveil them and keep a closer eye on them. And also, in high risk relatives of cancer affected patients, you want to keep a closer eye on them.

Now, one study found that familial clustering is rare. Now, one of the problems is there might be underreporting of familial clustering because it first felt that if many people in the same family develop cancer, it might be because they shared the same exposure. So, if somebody smokes in the family, for example, everybody in the family is exposed to second hand smoke. Is it because of that, or is it because they were born with a certain mutation that led to and increases SC bladder cancer? Or were they born

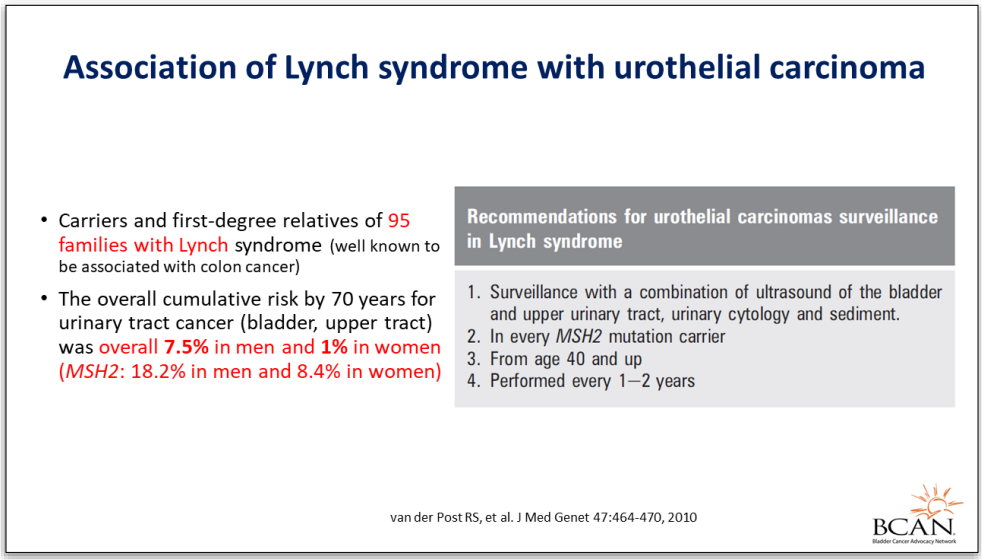
with some mutations and some genes that slows down the metabolism of some toxins and therefore increases the risk of cancer? So, not directly causing cancer, but slowing down the metabolism of certain toxins. So, we found, in Dana Farber, that there was a 4.3% incidence of familial bladder cancer defined as bladder cancer in a person and one more first degree relative with bladder cancer.

Dr. Sonpavde:

And we found interestingly, there was no association with age. So really, it was not like older patients had a higher risk of family through bladder cancer in a first degree relative, but the shared environmental risk was unclear in the study. Now, what we know interestingly is that a family history of bladder cancer and smoking in the person cooperate to increase the risk of bladder cancer. So, interestingly in the study, those who smoked and had a positive family history had a much higher risk of bladder cancer, and especially those who smoked, and had a family member diagnosed at a young age, that really increased the risk, 6.894, as you see here. So, really looked like family history of bladder cancer and smoking, cigarette smoking cooperate to increase exponentially the risk of bladder cancer, really suggesting that smoking is never good, but smoking, especially with the history of bladder cancer in the family is even much worse.



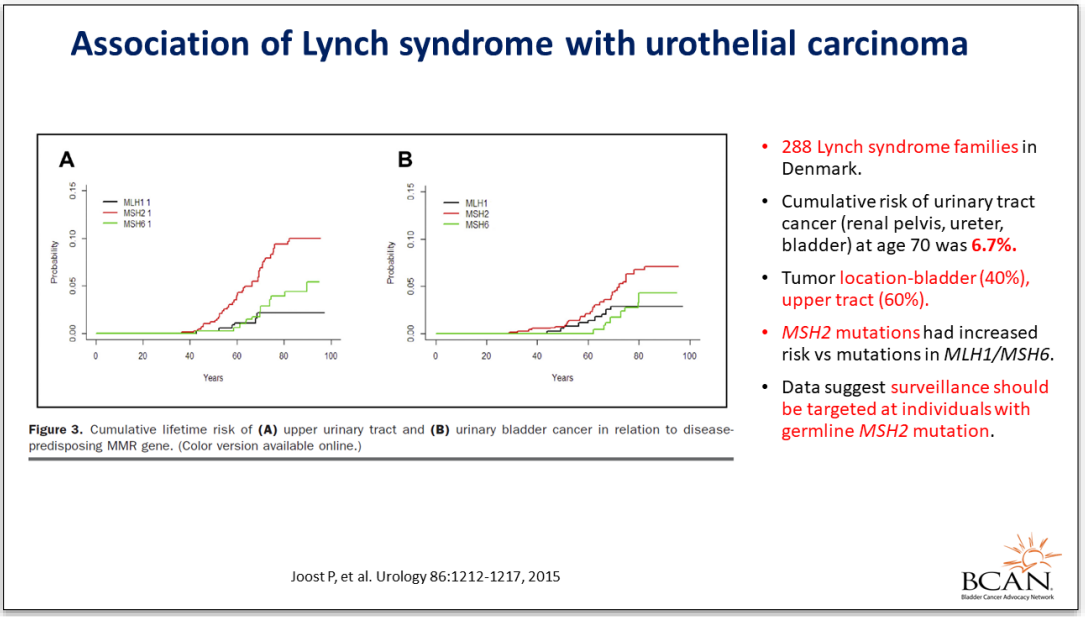
So, Lynch syndrome is a syndrome. It's a hereditary predisposition syndrome with certain mutations I show you here that patients are born with, and we know that this is a syndrome well known to be associated with colon cancer. However, we also know that this is associated with bladder and urinary tract, upper tract urinary tract cancer. So, approximately 7.5% of men and 1% of women with Lynch syndrome developed urinary tract cancer over a long period of time by age 70. So, really the author here suggested that, based on these findings, patients

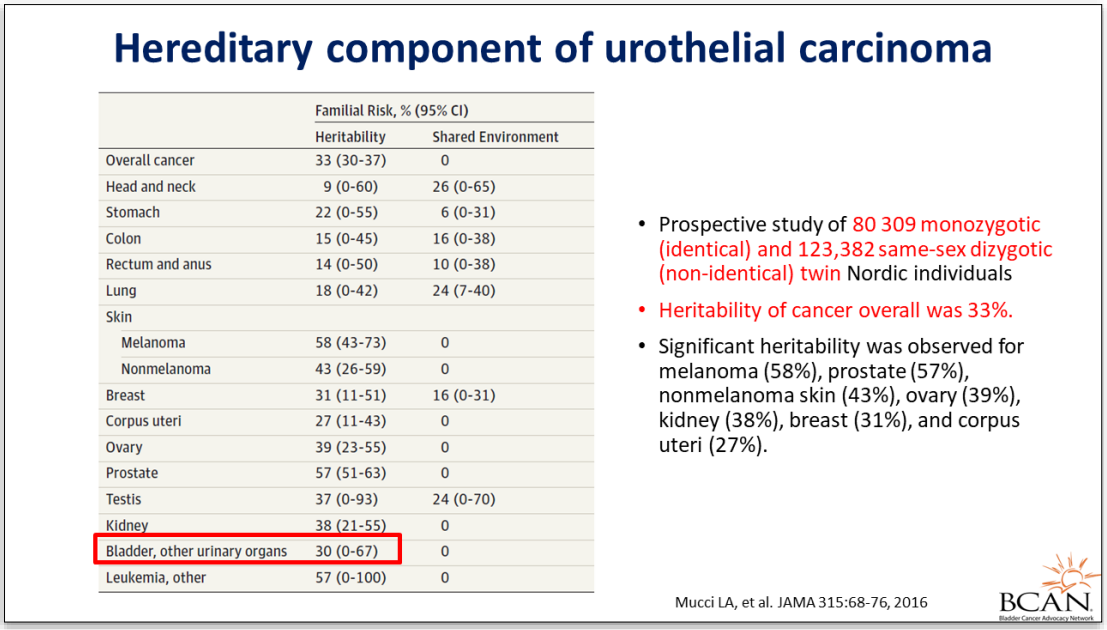


who have a known Lynch syndrome, especially the MSH2 gene, perhaps they should consider surveillance from age 40 and up every one to two years.

Dr. Sonpavde:

There is a different study here also that looked at several Lynch syndrome families and found an approximately 7% risk of urinary tract cancer by age 70. Now, 7%, just to put it in perspective, it's higher than baseline of course, but it's not as high as the penetrance of Lynch syndrome for colon cancer. So, if you have Lynch syndrome, the risk of colon cancer is perhaps approximately 50%, while bladder cancer is much lower, 7%. So, really the penetrance is not high, fortunately, but there is clearly an association with urinary tract cancer. So, what is the hereditary component of urothelial carcinoma? This is essentially the most common cell type of cancer of the urinary tract. We know, in a large study that I show you here, the heritability of cancer, overall, what is the hereditary component of cancer, approximately 33%. And as you can see here, bladder cancer is right there in the middle of that range. So, really the heritability of bladder cancer is about average when you compare across different cancer. So, it's not at the highest. You see here, prostate cancer is much higher, 57% inheritability, for example. Now, this is a study that looked at patients who were unselected, so any urinary tract cancer patients, urothelial carcinoma patients who were selected, close to 600 patients. And they found that 14% of

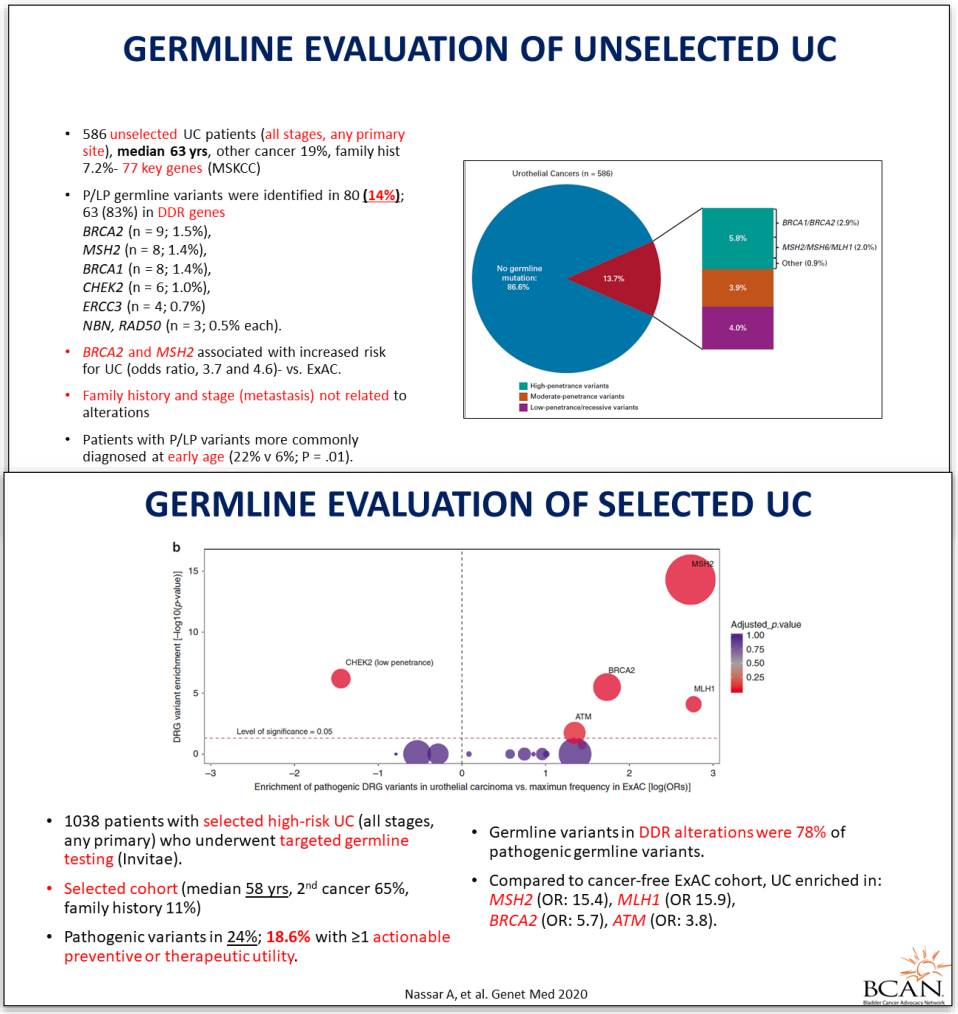




patients had one of these DNA damage repaired gene mutations.

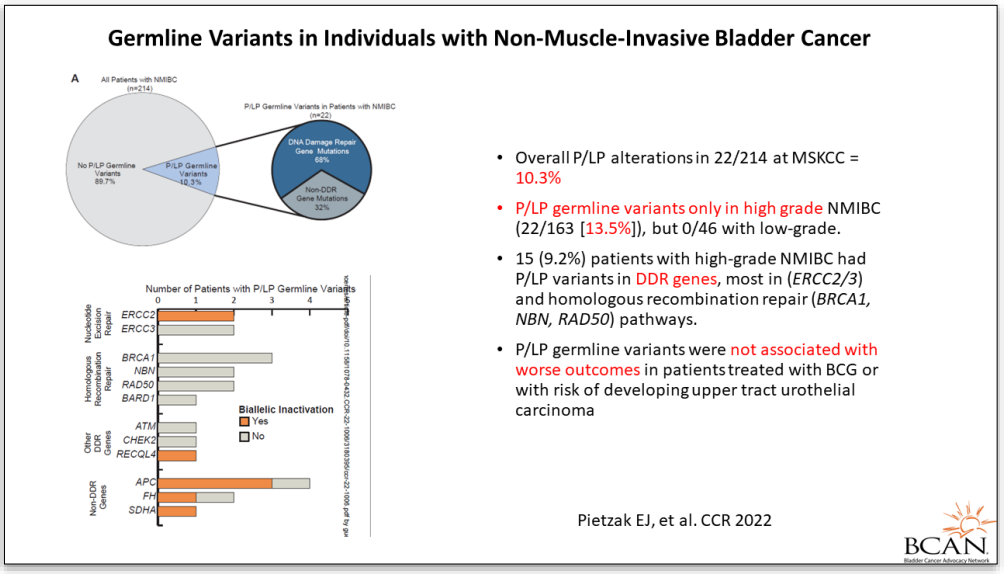
Dr. Sonpavde:

You see here, some of the Lynch genes are in there, the BRCA genes are in there, well known to be associated with breast cancer. And what was found was that younger age was enriched for these alterations. So really, again, suggesting that perhaps in younger age patients, you should have a lower threshold to test for germline mutations that these patients may have been born with. This is a different study we did at Dana Farber, which is from a commercial company, and more than a thousand patients. This was a somewhat more selected group. So, we sent patients blood for germline testing if we think they're at high risk for some inherited gene mutation. So, this was somewhat more selected, somewhat younger population, 58 years. So, you can see here 24% of patients had a pathogenic mutation they were born with, and 18.6% of them overall had an actionable, so-called actionable mutation, again, enriched for some of the Lynch genes and the BRCA genes.

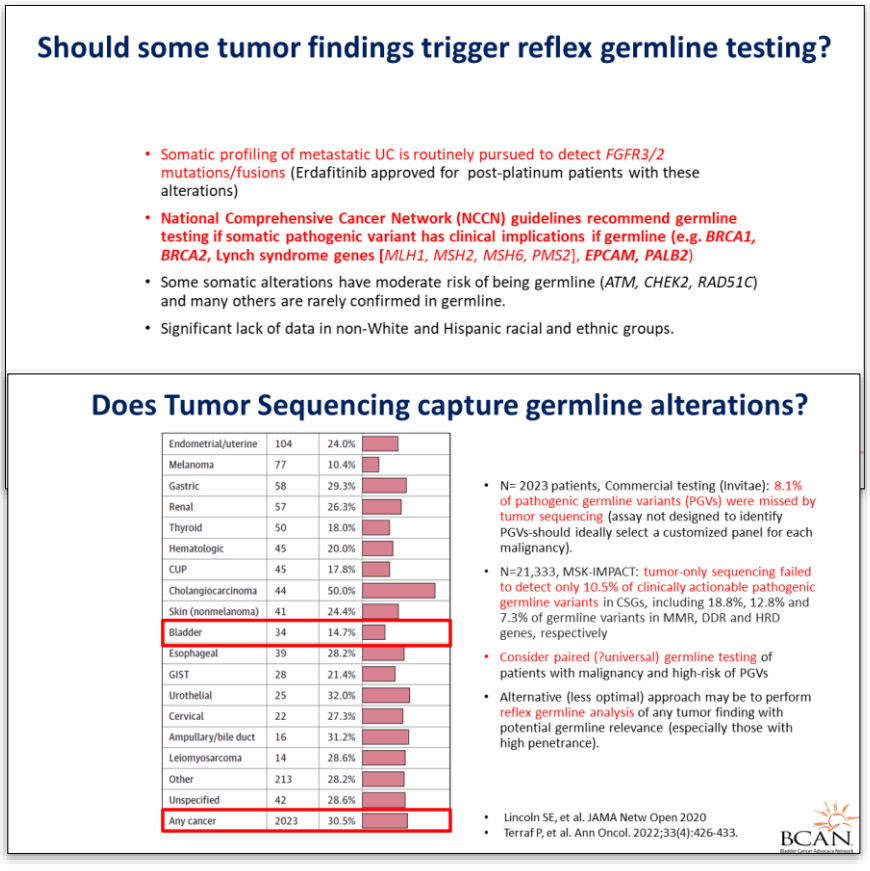


Dr. Sonpavde:

Now, there's a recent study that looked at patients, specifically patients who had non-muscle invasive bladder cancer, so cancer that was not yet invading a muscle and beyond. The interesting finding here, was that patients with high grade non-muscle invasive cancer were enriched for germline mutations, 13.5%, while the low grade patients did not have this mutation. So, this is somewhat interesting, suggesting some association of higher grade non-invasive disease with these mutations. So, as you know, we are doing tumor tissue testing a lot these days to select patients for certain drugs based on mutation found in the tumor. So, not germline, not what you were born with, but in the tumor. So, one of the questions that arises is, should you do germline testing if you find certain mutations in the tumor? So, in fact, the NCCN suggest that in patients who have certain mutations that would be high risk if they were germline.



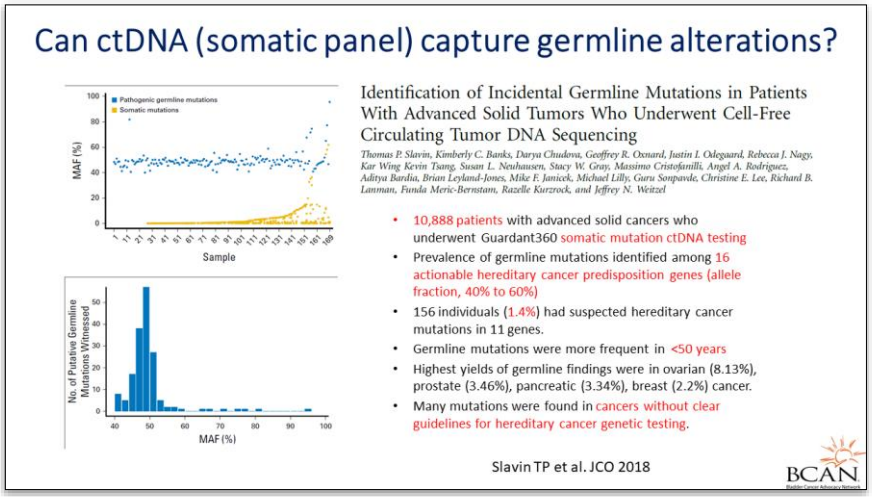
For example, the Lynch genes, the BRCA genes, when you find them in the tumor, should you be doing a germline test of the patient's blood or saliva to see if they were born with some of these mutations? So, this is what the NCCN suggests, at least to consider this in patients who have this high risk mutations in the tumor itself. And in fact, there is a different study here that found that tumor sequencing is actually pretty good at catching germline mutations, but it does not catch everything. So really, the author suggests that really to capture all the patients with germline mutations, you would have to do germline testing in everybody and not do it as a reflects based on tumor testing. So, this is one direction the research and the body of research is going, is to do universal testing in everybody regardless of what mutation is in the tumor. One other question that arises is we are doing circulating tumor DNA testing, so this is



DNA in circulating freely in the plasma, in the blood, not in the blood cells.

Dr. Sonpavde:

So, when we do this, we are looking at really... We are trying to look at whether the patient has mutations in the tumor that are detected in the blood. So, it turns out that if you have a high threshold and you try to catch these mutations with a high, so-called high allele fraction present in a high fraction, then you can actually catch hereditary DNA mutations that the patients may be born with, even in circulating tumor DNA. So, you should pay attention to what mutations are seen in the allele fraction, even in the circulating tumor DNA, which we do usually just to look for mutations as a reflection of mutations in the tumor itself.



So, the universal germline testing is emerging. We know that when you look at across different studies, when you just test everybody with any solid tumor, you see between five and 15% of patients having some germline mutation that is relevant. And in fact, many of these have therapeutic implications. We know that many of these drugs here are approved based on germline mutations in these BRCA genes, the MSI high tumors with the deficiency in mismatch repair. So, as you can see here, several therapeutic implications based on germline mutations. And in fact, in bladder cancer, there's a study that looked at rucaparib, a PARP inhibitor in patients with metastatic cancer as a maintenance following chemotherapy setting. And it turns out that patients with either tumor or germline mutations, most of them had pretty much tumor actually, but germline mutations

Universal germline testing in unselected patients with solid tumors

summary

Study	Panel	N	% with germline alterations
TCGA	WES	10,389	8%
Mayo	Panel	2984	13.3%
MSKCC	Panel	1566	15.7%
Indiana University	WES	1028	12.8%
U. Michigan	WES	1015	15.8%
MDACC	Panel	1000	4.3%

Huang KL, Cell 2018; Samadder NJ, JAMA Oncol 2020; Schrader K, JAMA Oncol 2016; Schneider BP, ASCO 2020; Cobain EF, JAMA

Therapeutic implications of germline alterations

Role in precision medicine

Interpretation of germline variant pathogenicity for cancer risk has been well-established; however, focus on determining therapeutic actionability is still emerging.

Cancer	Germline alteration	Setting	Therapy approved
Prostate	Germline or somatic *BRCA* (rucaparib), HRR/*BRCA* genes (olaparib)	Metastatic, castration-resistant, pre-treated	Olaparib, Rucaparib
Breast	*BRCA*	Metastatic Her2-, pre-treated	Talazoparib, Olaparib
Breast	*BRCA*	Adjuvant, Her2-	Olaparib
Pancreas	*BRCA*	Metastatic, maintenance	Olaparib
Ovarian	*BRCA*	Metastatic, pre-treated Maintenance	Olaparib Olaparib, Niraparib
Any	MSI-H, dMMR (Lynch syndrome)	Any cancer	Pembrolizumab

Richards S, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 17:405-424, 2015

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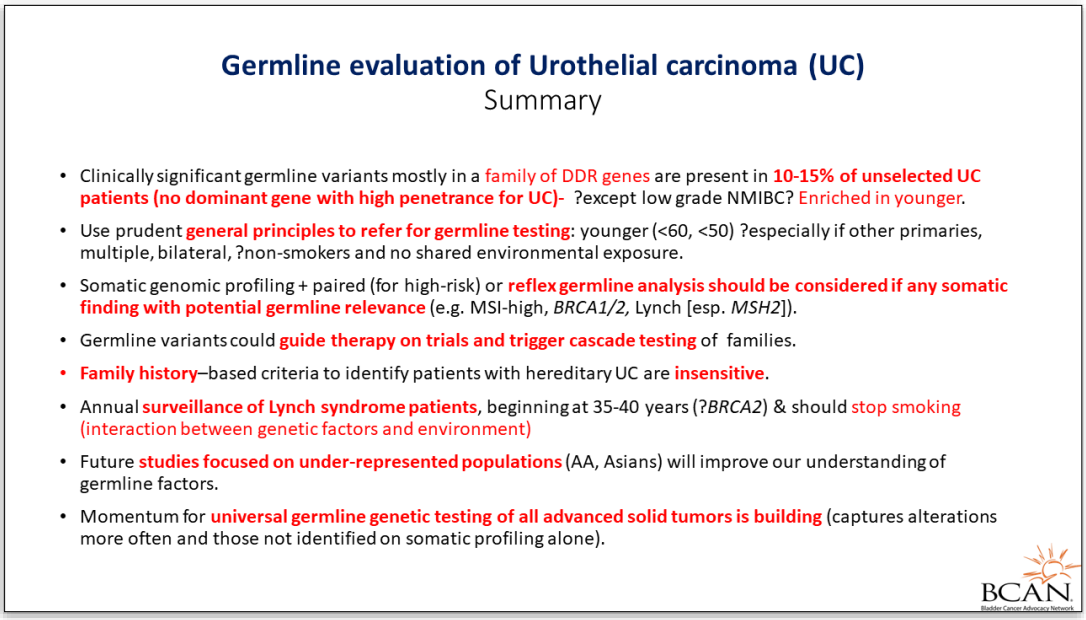
were allowed on this study, there was an improvement in outcomes in patients with a DNA damage or pain mutation at the tumor level of the germline. So, I'll just give you quickly, a summary conclusion slide. So, clinically significant germline variants found in mostly DNA damage repair genes are found in approximately 15% of all patients with urothelial carcinoma, but there is not a single dominant gene with a high penetrance that causes cancer. As I said, Lynch syndrome, only 7% penetrance.

Dr. Sonpavde:



So, we should really use general prudent principles to refer patients for germline testing, younger patients, other primaries, bilaterality. Especially non-smokers with cancer, there is no known environmental exposure, really should have a low threshold to test these patients. If you have done tumor profiling, you should consider germline analysis, especially if you see a mutation that is of significant relevance if it's present at the germline, for example, a BRCA gene or a Lynch gene found in the tumor testing. And some of these variants in mutations, of course, could guide therapy on trials and trigger cascade testing, the so-called cascade testing of other people in the family, especially the first-degree relatives, if the patient has one of these mutations. Family history is insensitive. Family history is something that patients don't usually recall very well, occasionally, and actually, quite commonly, upper urinary tract cancer is frequently misrepresented as kidney cancer, which is it's not. It's a urinary tract cancer. So, that is a frequent source of confusion for family history. And surveillance, although it's not done in everybody, surveillance and Lynch syndrome, patients starting in the mid thirties to 40 should be considered.

And patients with these germline mutations, especially Lynn syndrome, should, of course, stop smoking because of the cooperation of an environmental insult and a germline alteration. And studies should really focus on underrepresented populations. All of these germline studies that I showed you, they were really studied for Caucasian population. So there was not much for Asian population or African American population. And then finally, the momentum for universal germline genetic testing of all patients with advanced solid tumor building, because this can capture alterations that will not be always captured on tumor testing. So, this is where the field is going, but this need for the thought and for the study. With that, I ended in my talk here.

Stephanie Chisolm:

So, Dr. Faltas, I know you're doing a lot of research. Do you have any comments to add about some of the work that you're working on in this particular germline area?

Dr. Faltas:

Thank you, Stephanie. Dr. Sonpavde is always a very hard act to follow because I think he's covered all the important points. Just a couple of points that he's already mentioned that I would like to touch on briefly. So, I think family history is actually quite an important point. And this is an example... This whole topic of joint line mutations of bladder cancer is an example of a topic that the more we ask about family history and the more we look for these mutations, the more we find them. And as clinicians, we haven't necessarily been trained as genitourinary medical oncologists treating bladder cancer. To be very specific, so far, we haven't generally been necessarily focused on the family history because up until the last few years, most of us haven't really known that. Before this research came about, research from our group, Dr. Sonpavde's group, Dr. Carla's group, and many others, that these germline mutations are actually prevalent in patients with bladder cancer.

And we're still debating what really to do about them, what are the implications that are empirically implications for cascade testing, and so on and so forth. And I know we're going to discuss that today with Dr. Dubard. So, I think these are important points. Just to summarize this point, I think we're all on a mission here to increase awareness of the high prevalence, relatively high prevalence of these alterations. And it's very important to ask because although I agree with Dr. Sonpavde, the history is in insensitive tool, but sometimes also very important in terms of raising the red flags or the suspicion for testing. The second point I think that Dr. Sonpavde also touched on is that most of our knowledge about these germline mutations is coming from Caucasian patients, and specifically when it comes down to a point related to variants of unknown significance, which are essentially classification of these alteration that could come back.

So, yes, there is an alteration on genetic testing or a mutation, but we don't know its clinical significance. And these VOSs or variants of unknown significance are a lot more prevalent in non-Caucasian patients, the patients from other diverse ancestry, mostly because we really haven't been studying these patient populations in the past. We're working to correct this in our own research, but that's an area that I think we all need to be aware of and to continue to work on, both to study these variants of unknown significance and reclassify them to try to understand really what their clinical significance is for patients from all ancestry. I'll stop there.

Stephanie Chisolm:

Yeah, you guys are doing some amazing work, and I know that the future is going to look brighter because you're digging deep or into so many of these things.