Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/gi-insights/improving-detection-of-lynch-syndrome-key-strategies/13943/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Improving Detection of Lynch Syndrome: Key Strategies

Dr. Buch:
Lynch syndrome is the most common cause of inherited colon cancer. Unfortunately, a large number are underdiagnosed. This is *GI Insights* on ReachMD. I'm your host, Dr. Peter Buch. Joining us today to discuss how we can improve detection of Lynch syndrome is Dr. Bryson Katona. Dr. Katona is Director of the Gastrointestinal Cancer Genetics Program, Director of the Gastrointestinal Cancer Risk Evaluation Program, and Assistant Professor of Medicine at the Hospital of the University of Pennsylvania.

Welcome to the program, Dr. Katona.

Dr. Katona:
Oh, well, thank you so much for the invitation. It's a real honor to be here, and I'm really excited to talk about Lynch syndrome.

Dr. Buch:
Perfect. And that's a wonderful segue to our first question. Dr. Katona, let's begin with some background. When should we suspect a patient of having Lynch syndrome?

Dr. Katona:
Well, it's a great question, and let me just give a couple facts about Lynch syndrome that I think it's really important to appreciate. So, Lynch syndrome is actually, incredibly common from a genetic syndrome perspective. It's estimated that about 1 in 270 individuals have Lynch syndrome, which means that in the US there's approximately 1.2 million Americans who are living with Lynch syndrome although the vast majority have not yet been diagnosed.

When should you look for Lynch syndrome or think about it? I think the biggest tipoff that most clinicians in practice will run into is a concerning family history. So, we know that Lynch syndrome increases risk of colorectal cancer, endometrial cancer—those are the two big ones—but also many other cancers outside of those two classic cancers.

There are a few criteria and tools out there that can kind of help you sort through the family history. One that's been used for a long time is the Amsterdam II criteria. There's also a really cool tool called the PREMM 5 tool. This is an online tool that was developed by the Dana-Farber Cancer Institute, and its P-R-E-M-M 5. This is an online tool that just with some very simple personal and family history can help you determine what your patient's risk of having Lynch syndrome actually is, and so I encourage everyone out there that may be listening to check out this tool and try it out.

Now, you know, apart from family history, I think the other big place where we have a really great opportunity to identify individuals and families with Lynch syndrome is through doing mismatch repair immunohistochemistry on cancers. Now, technically, or hopefully, mismatch repair immunohistochemistry is done universally on all colon cancers and endometrial cancers, and it really should be done universally regardless of age at the time that the cancer was diagnosed. And abnormalities in the mismatch repair staining on cancers really should prompt, again, an evaluation for Lynch syndrome, and I know that's one of the major ways that in our practice we're picking up patients and families with newly diagnosed Lynch syndrome.

Dr. Buch:
So, can we do a deeper dive, Dr. Katona, into what exactly is DNA mismatch repair and micro satellite instability, so our audience really gets a good perception of what this is all about?

Dr. Katona:
Certainly. So, you know, Lynch syndrome really results from a pathogenic mutation in one of the DNA mismatch repair genes. And so,

there are actually four genes that are involved in Lynch syndrome—MLH1, MSH2, MSH6 and PMS2—that are all involved in the DNA mismatch repair system. However, there's another gene, a gene called EPCAM, which sits right upstream of MSH2. EPCAM is not involved in mismatch repair per se, but mutations in EPCAM can cause Lynch syndrome due to silencing of the MSH2 gene. But what the mismatch repair system really is, its importance is in recognizing and repairing areas within the DNA, specifically small insertions, or deletions, and these areas typically occur naturally during DNA replication, and the mismatch repair system does a great job of repairing those areas when they do occur.

So, in Lynch syndrome, you're basically one of these mismatch repair genes, you know, has a loss of function mutation to begin with. What that can lead to is actually small insertions and deletions throughout the genome. Of course, if these insertions and deletions hit the right genes that can then be carcinogenic and can promote the carcinogenesis process, but these small insertions and deletions also frequently hit the microsatellite regions of DNA, which are these areas where there are multiple, small, identical DNA repeats, and so that's one way that tumors can be tested for concern for Lynch syndrome is they can look for instability of these microsatellite regions, meaning these microsatellite regions have a lot of either small insertions or deletions.

Dr. Buch:
Thank you. And further follow-up on that, are mismatch repair genes and microsatellite instability unique to colon cancer, or is that related to other cancers as well?

Dr. Katona:
Yeah, that's a great question. So, it can be seen in other cancers, as well, and so, within colorectal cancer, we think probably about 15 percent of colorectal cancers have a mismatch repair defect, but we certainly see it in endometrial cancer and then other cancers outside of these two classics. Lynch syndrome cancer as well.

Dr. Buch:
And you led me to another thought. So, let's say God forbid there's a patient out there who has a family member who had an early-onset colon cancer but that mismatch repair genes, and microsatellite instability was never done. Can that be done on formalin-fixed material?

Dr. Katona:
Yes, it sure can. And we do, often times, we'll go back to older colon cancer samples to do that testing. Universal screening of all colon cancers and endometrial cancers has really only been something that's come about over the last 5 to 10 years, and so, you know, prior to that most colon cancers didn't have mismatch repair IHC performed. Nowadays, genetic testing has become so easy and so cheap to do. In many of these cases, it's almost easier to just go ahead and do the genetic testing rather than to try to dig up old tissue samples to do mismatch repair staining.

Dr. Buch:
Thank you for that. And with all of that in mind, what are the limitations of our current testing options?

Dr. Katona:
So, I'll go back to the mismatch repair immunohistochemistry. So that testing actually does not actually pick up all cases of Lynch syndrome. So, it's pretty good, but it's not perfect. I think the other main limitation of testing is that, you know, even when you're considering family history we know that there are some families that have Lynch syndrome, that may not have a dramatic family history of cancer, and so it wouldn't be picked up by, say, the Amsterdam Criteria or wouldn't be picked up by the PREMM 5 model. And so, there are many factors that can contribute to this, such as potentially it's one of the Lynch syndrome genes that has a lower penetrance and so lower cancer risk, and so maybe there aren't that many family members who have been affected. Sometimes people have very small families, so maybe, you know, an only child of only children, and so you may not have as many at-risk family members, or people also may, you know, have died for other reasons and may have died early, such as potentially like an accident or something like that. And in those cases when you have people dying at younger ages, they may not reach an older age at which time, you know, they may have developed a cancer.

And so, you know, mismatch repair immunohistochemistry isn't perfect, and family history, certainly isn't perfect as well, and so, you know, again, I think given that genetic testing is so easy to do now. I think, you know, even if people have even a low suspicion or a mild suspicion of Lynch syndrome, and if the patient is motivated, it's totally reasonable and worth it to send the patient for evaluation.

Dr. Buch:
And that leads me to another question, because I'm sure a lot of practitioners are thinking out there. Is there protection for patients out there when they get their genetic testing and, they are positive? So, will that count against them for insurance?

Dr. Katona:
So, there's an act out there called the GINA act, or the Genetic formation Nondisclosure Act. This was a law that was passed years ago that really prevents discrimination based on genetic testing results in the health insurance marketplace and also within the workplace. So, you know, patients are protected from those, in those two arenas. However, what the GINA act does not cover is it does not cover protection for life insurance discrimination, for disability insurance discrimination nor does it cover long-term care insurance discrimination. Now, in my practice, personally, I haven't seen a whole lot of insurance companies heavily discriminating against patients with Lynch syndrome who haven't had a cancer, but it's certainly possible under those circumstances.

And so, before someone does go to get evaluated for Lynch syndrome, it is important for them to meet with a genetic counselor.

Dr. Buch:
That's really useful information. For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Bryson Katona about Lynch syndrome.

Dr. Katona, how should we approach family members of a Lynch syndrome patient? We've talked a little bit about that but tell us a little bit more.

Dr. Katona:
Yeah. So, if you have a patient in a family where there's a known, gene mutation, testing family members is some of the most powerful genetic testing that we can possibly do because, you know, if a patient does have the gene mutation, they're going to of course need intensive screening. But if the patient doesn't and tests negative for that familial mutation, then in most cases, they can just be screened at average risk.

Dr. Buch:
Thank you for that. So, how do family colorectal cancer type X and Lynch syndrome compare?

Dr. Katona:
So familial colorectal cancer, type X, for those who aren't familiar with this syndrome, basically is a family that has a lot of colorectal cancer in the family such that they meet Amsterdam Criteria, but the big difference is that the colorectal cancers and familial colorectal cancer type X are not mismatch repair deficient. They're actually mismatch repair proficient or microsatellite stable. So, while years ago many of these families were getting screened as if they had Lynch syndrome, now we can do genetic testing in them and demonstrate that they don't have Lynch syndrome. And there's been an increasing body of literature to show that these individuals do have increased colon cancer risk, but they don't have all of the other extracolonic cancer risks that we see in Lynch syndrome. And so, individuals who fall under this familial colorectal cancer type X really should just be screened with more frequent colonoscopy and should really not undergo all of the other Lynch syndrome-related, cancer risk management that Lynch syndrome patients go through.

Dr. Buch:
Thanks for filling us in on that. So, before we conclude, are there any other thoughts you would like to share with our audience today?

Dr. Katona:
You know, I think as we study Lynch syndrome more and more, you know, what we're realizing is that management and care of patients with Lynch syndrome really needs to be individualized. I think, you know, 5 or 10 years ago, everybody with Lynch syndrome was kind of getting put into the same bucket and getting managed the same, but now we really tailor management of Lynch syndrome to the particular gene that the gene mutation is in, to the family history, as well as other personal factors. And I think the other important thing is that identifying Lynch syndrome patients really should be on the top of every physician's mind because knowledge is very powerful in Lynch syndrome. It allows these patients to make proactive choices about their health get involved in aggressive screening programs that, you know, ultimately will improve long-term survival from cancer. And so, I do encourage all the listeners to, you know, keep an eye out for patients who may be at risk for Lynch syndrome and, and refer them for evaluation.

Dr. Buch:
With those interesting insights in mind, I want to thank my guest, Dr. Bryson Katona, for sharing his insights on diagnostic challenges Lynch syndrome.

Dr. Katona, thanks so much for joining us today.

Dr. Katona:
Well, thank you again. I really enjoyed our conversation.

Dr. Buch:
For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit ReachMD.com/GIInsights where you can be Part of the Knowledge. Thanks for listening, and looking forward to learning with you next time.