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Developments in Colorectal Cancer Screening: Cell-Free DNA Blood Testing

Dr. Buch:
Welcome to *GI Insights* on ReachMD. I'm your host, Dr. Peter Buch, and joining us today to discuss a cell-free DNA blood-based test for colorectal cancer screening is Dr. William Grady. Dr. Grady is the Medical Director of the Gastrointestinal Cancer Prevention Program at the Fred Hutchinson Cancer Center and the Rodger C. Haggitt Professor of the Division of Gastroenterology at the University of Washington School of Medicine.

Thanks for joining us, Dr. Grady.

Dr. Grady:
Thank you, and thank you very much for inviting me. I'm excited to tell you about this new blood test, this new screening option for colorectal cancer.

Dr. Buch:
Perfect. As a prelude to our discussion, Dr. Grady, what percentage of the population who's eligible for colon cancer screening are adherent to the guidelines?

Dr. Grady:
Colon cancer is a major killer in the United States. It's the second most common cause of cancer death, and about 150,000 people are affected every year. We recommend people between the ages of 45 and 75 have colon cancer screening done, and what we know is, of that, about a third of people are not compliant with colon cancer screening. So depending on how you define compliance, the number falls anywhere between 60 to 70 plus percent of people aren't compliant with screening for colon cancer.

Dr. Buch:
So moving on, now, could you give us a brief overview of what cell-free DNA testing is all about?

Dr. Grady:
That's a great question. The thing that's really exciting about this blood-based test is it's ushering in a new era of cancer screening tests that I think we'll see emerge in the next five years or so for a variety of cancers, and colorectal cancer is the first one where we are seeing this move forward. What we're talking about here is there is DNA that's present in the blood that's not in the white blood cells, but it's actually DNA that's circulating naked, free of cells, in the plasma space of the blood, and that DNA comes from a variety of different sources. It comes partly from cells that have degraded in circulation. We also know that there are normal cells in the body that can shed DNA. But importantly, for this test, we know that tumor cells shed DNA at quite a high rate, and what this test can detect is the tumor cell DNA that's present in circulation in the plasma of blood, and there's a technology that's been developed, using something called next-generation sequencing, that can detect the tumor DNA present in the blood. This technology has been a major breakthrough because what it allows us to do is to detect the tumor DNA, which is present in very small amounts. It's somewhat akin to finding a needle in a haystack. And with this new technology that's been developed over the last 10, 15 years, it's now created this opportunity to create this new generation of cancer screening tests.

Dr. Buch:
Very exciting. And as a quick follow-up, what's the difference between the testing that we're talking about and Septin 9?

Dr. Grady:
That's a really great question. Septin 9 is also a tumor DNA test, and it was developed years ago. What makes it different than the

current generation of tumor DNA tests is that rather than looking at thousands of features—and when I say features, what I'm really referring to are specific alterations in the genomic DNA or in the epigenomic DNA that's present in the circulating free DNA—the Septin 9 test only detects one molecular feature that's present in the tumor DNA, and that's something that's called methylated Septin 9. It refers to a chemical modification of the DNA called methylation that occurs at the location of the Septin 9 gene. By using just that one feature, the Septin 9 blood test can detect about 60 percent of people who have colorectal cancer and does not detect people who have advanced colorectal polyps. So by increasing the number of molecular features that you can detect, that's dramatically improved the performance, the sensitivity, and the specificity of the new generation of cell-free DNA test. So the short answer to your question is, the big difference between the current test—the Shield test that was just recently published on in *The New England Journal of Medicine*—versus Septin 9 is that the sensitivity for the Shield test is much better than the Septin 9 test.

Dr. Buch:
So going into a little bit more in detail, what factors could lead to a false positive test when using a cell-free DNA test?

Dr. Grady:
That's a really good question and one that's under active investigation. One possibility would be that there's a different tumor than the colorectal cancer tumor, in this case, that's shedding the tumor DNA into circulation, and that's resulting in a false positive test. What we have found is that in follow-up studies from the multicancer early detection test is that doesn't seem to be a very common phenomenon, and so, instead, probably what's happening is that there are some alterations that are present in normal cells' DNA that is resulting in the false positive test result. That's the most likely scenario at this point. But one big question that is going to need to be figured out as we go forward with these tests is how often a false positive test is because there's another tumor that's present in the person that currently isn't appreciated, that's occult at the time that the cancer test is applied.

Dr. Buch:
For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. William Grady about a cell-free DNA blood test for screening patients for colorectal cancer.

So, Dr. Grady, how does the sensitivity and specificity of the cell-free test compare with FIT tests or multitarget DNA tests?

Dr. Grady:
Yeah, a really great question. So, if we think about the different screening options that are available, the one that's used predominantly is colonoscopy, and that's considered to be the gold standard in terms of the technical sensitivity and specificity of the assay. So colonoscopy detects essentially 100 percent of colorectal cancers, detects 95 percent roughly of advanced adenomas, and detects somewhere between 70 to 85 percent of nonadvanced adenomas. If we then look at the next most commonly used screening test, which is the FIT test, what we find is in a one-time use, the FIT test has a sensitivity for colorectal cancer that ranges somewhere between 70 to 85 percent with probably a most accurate assessment being somewhere in the high 70 to low 80 percent. For the advanced adenomas, it detects around 35 to 40 percent of those. And then the nonadvanced adenomas is in the low 30 percent. Now, if we then turn to the multicancer detection tests, their performance is around 75–83 percent for colorectal cancers, and we don't know how well they work for detecting colorectal polyps.

How does that compare to the cell-free DNA test that we have for colorectal cancer? So in the study in *The New England Journal of Medicine,* what we found is the sensitivity of that test can detect 83 percent of people with colorectal cancer and detected 13 percent of people who had advanced adenomas. One interesting aspect of that advanced adenoma data is that if we then looked at those advanced adenomas that have a histologic feature called high-grade dysplasia, the sensitivity of the assay increased to the low 20 percent range.

Dr. Buch:
And before we close, Dr. Grady, since this test is not yet FDA approved, what are the next steps prior to approval?

Dr. Grady:
In terms of the FDA approval process, it underwent a review by an advisory committee that the FDA had put together. That advisory committee was favorable with regards to approving the test. So then what happens is that the FDA is now reviewing the advisory committee's comments about the test and will be making a decision sometime probably in the next few months about whether that test will be something that they will approve or deny. Then the next step in terms of whether the test will be available and affordable will be whether CMS will approve payment for the blood-based test for using in colorectal screening. And then once that happens, usually—as I think most of your listeners know—then private insurers usually follow suit. That whole process probably will not complete until, I'd say, the end of this year or beginning of next year. So that's where we are with the FDA approval process. I do want to note that the test is currently available as a limited diagnostic test, so it can be ordered, and if an interested provider goes to the Guardant Health website,

there are instructions for how that test can be ordered and used for patients at this time.

Dr. Buch:
What a great discussion about a future option in colorectal cancer screening. I want to thank my guest, Dr. William Grady, for joining us today and sharing this important information. Dr. Grady, it was a pleasure speaking with you.

Dr. Grady:
Yeah, thank you. It was a real pleasure speaking with you and telling you about this really exciting development in colorectal cancer screening.

Dr. Buch:
For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit *GI Insights* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.