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Exploring Emerging Advancements in Early Cancer Detection

Announcer:
Welcome to ReachMD. This medical industry feature, titled “Exploring Emerging Advancements in Early Cancer Detection” is sponsored by GRAIL. Here's your host, Dr. Paul Doghramji.

Dr. Doghramji:
The war on cancer began 50 years ago. But despite significant advancements in therapeutics, the oncology community has not yet been able to declare victory. About 40% of Americans receive a cancer diagnosis in their lifetime, amounting to over 600,000 American deaths on average every year, or nearly 1,700 loved ones a day.[1,2] But technical developments in early cancer detection may lead to improved care and lives saved.

This is ReachMD. I'm Dr. Paul Doghramji. Joining me to discuss cancer screening methods and multicancer early detection is Dr. Joshua Ofman. Dr. Ofman is a gastroenterologist and a public health services researcher as well as the CMO and head of External Affairs at GRAIL. Dr. Ofman, welcome to the program.

Dr. Ofman:
Thank you very much for having me. I'm delighted to be here.

Dr. Doghramji:
Let's start with a high-level overview of early cancer detection. Dr. Ofman, keeping current screening guidelines in mind, how well can we detect cancer early?

Dr. Ofman:
Well, it's a great question. And I think what's been most interesting to me, as a public health-oriented physician, is just the lack of urgency that has been formed around early cancer detection and cancer prevention. You stated the numbers, you know, we're losing about 600,000 Americans every year to cancer.[1,2] And that's about a COVID-size pandemic, year after year after year. But you saw with COVID the level of urgency we're able to bring to that.

So, I think there's a real opportunity, first of all, to just increase our awareness and urgency around early cancer detection. And as you mentioned, we've made some progress with cancer. Therapeutics have made tremendous advances. And with screening technology, there's also been about a 20% reduction in cancer deaths over the past several decades.[3] And we have some wonderful screening tests, they screen for one cancer at a time, they look for single cancers, and they are finding cancer and saving lives. But, in reality, the majority of the cancer deaths, 70 to 80% of them are still occurring due to cancers that we're not looking for at all.[4] In fact, today, the majority of cancers still go undetected until it's simply too late, because there are not screening tests available for the majority of these cancers. So, we screen for five cancers today in the United States, breast, colorectal, cervical, prostate, and on an individual basis, and high-risk patients, lung cancer as well.[5]

And when I got to GRAIL, I asked a really simple question. I asked, ‘How good are those five tests, single cancer screening tests, how good are they at finding all the cancer?’ And it turns out that the picture isn't that great. You know, we've been fighting a war against cancer for decades. And it's just not a war we're winning, because these screening tests, while saving lives and they're remarkable, they're only finding about 15 to 16% of the incident cancers in adults between the ages of 50 and 80.[6] And that's just not going to be enough to really make a dent in the cancer mortality curve.

So, we happen to be in an era now due to great advances in genomics and machine-learning and artificial intelligence, where the

convergence of those technologies have really brought enormous technical advances to how we might screen for cancer in the blood, and also screen for many cancers at the same time. So, we can really introduce a paradigm shift to move away from only screening for individual cancers to a world where we're also screening individuals for cancer. And that's a big change.

Dr. Doghramji:
Now, what exactly do you mean by cancer detection rate?

Dr. Ofman:
Well, the cancer detection rate is really a public health-oriented measure that looks at the fraction of cancers that are actually detected from the total number of expected cancers in the population. So, when I said that the five existing screening tests only find 15 to 16% of cancers, that's really the cancer detection rate.[6] So just to take a single cancer screening example, if you look at mammography in adults over the ages of 50, between 50 and 79, there's about 107 million Americans.[6] And mammography is finding a cancer detection rate of about 9%.[6] So, of the 1.3 million cancers that are expected in the population, mammography finds about 9% of them.[6] So, you can look at how a multi-cancer early detection test might improve that over time. And it's a really important measure to see how are we doing in our efforts to try to find cancer early?

Dr. Doghramji:
Now, if we take a look at strategies to improve early detection, what are some of the key metrics that we need to focus on?

Dr. Ofman:
Well, the big idea here is to stop finding cancers in their late stages and really improve the percentage of cancers we're finding in their earlier, more treatable stages. Because when cancers are found, when they're already metastatic, and spread to distant sites, only about 2 of 10 people will live five years or longer.[7] But when cancer is found in its localized stage, before it's spread, about 9 out of 10 people will live five years or longer.[7] So, there's just an enormous opportunity.

And so, one of the most important metrics is how do you make that transition safely. So, you need a very low false positive rate. Because if you're looking like GRAIL's test does for over 50 cancers, you can't afford to have false positives like you do with the single cancer screening tests.[8] So, that would create an unbearable burden of healthcare resources. So, the false positive rate for a multicancer early detection test is really the most important. And for Galleri, which is GRAIL's test, it's about a half a percent.[8] And that compares to about 10 to 12% for single cancer screening tests.[9-11]

The second most important metric clinically is something we call the positive predictive value. And that's among those who have a positive screening test, what is the likelihood they actually have cancer. And single cancer screening tests have positive predictive values that are not that high. For example, mammograms, it's about 5%.[11] So, if a woman who has a positive mammogram, she only has about a 5% likelihood of being diagnosed with breast cancer, yet, she's going to go on that all-too-familiar journey of looking for that cancer.[12] Similarly, with stool-based colorectal cancer screening tests, and low-dose CT for the lung, these PPVs are in the single digits.[12]

And that really is very different with GRAIL's Galleri test, we have a positive predictive value between 40 and 50%.[7] So just an order of magnitude better than anything that's ever been seen before with cancer screening. So that's a critical metric.

And then finally, if you're going to look for many, many cancers, with signals in the blood, you need to be able to localize those signals to the tissue or organ of origin. And, that's a really important thing to do to tell the doctor where to go look for the cancer. And so, GRAIL's Galleri test does that with very high accuracy, well over 90%.[8,13]

Those are really the most important metrics as we think about transitioning into a world of multicancer early detection, in addition, or as a complement to our single cancer screening tests.

Dr. Doghramji:
For those just tuning in, you're listening to ReachMD. I'm Dr. Paul Doghramji, and today I'm speaking with Dr. Joshua Ofman about evolving technology in early cancer detection, and the role of multicancer early detection technology.

With those metrics in mind, let's dive into multicancer early detection, or MCED. Now, Dr. Ofman, how does this technology work?

Dr. Ofman:
Well, we know that, you know, we can see in circulation genomic material, so circulating free DNA in the blood. And it's been known that that circulating DNA in the blood can be read, and we can look for signals and patterns and fingerprints in that DNA.

Now, when cancer grows in the body, those cells are growing very rapidly, and they're dying very rapidly. And they're releasing their

DNA into the blood so that DNA can be found, it can be isolated, and it can be read. And the question that GRAIL asked was, what is the best way to analyze that DNA to find cancer and early cancer?

So, they did a head-to-head comparison of all of the relevant methods.[14] They looked at mutations, they look at chromosomal changes. They looked at fragmentomics, they looked at RNA, they looked at epigenetic markers. And epigenetic markers are really important. And they are these little methyl groups, which attach to the DNA, which turn cancer genes on and off. And it's been known for quite some time that these epigenetic changes are hallmarks of cancer, like mutations are as well, but they're much more prevalent in the genome than mutations are. So, the head-to-head study showed GRAIL that these methylation patterns were by far the most powerful way of reading the genomic material and detecting cancer signals from non-cancer signals. And the study that GRAIL did enriched the non-cancer group with a lot of diseases like autoimmune disease and cardiovascular disease to create a lot of biological noise, so that GRAIL taught its machine learning algorithms to be able to discriminate a cancer signal amidst a sea of biological noise.

And so, our test was developed then using these methylation patterns. And the way it works is we draw an individual's blood, there's no special handling or refrigeration required, and we do bisulfite sequencing, which lets us see the methylation patterns. And then we subject that pattern to a machine-learning classifier, which classifies the pattern as either a cancer or a non-cancer signal. And then if there's a cancer signal, it gets subjected to another machine-learning algorithm that predicts where that cancer signal arose in the body. Because these methylation markers also are very sensitive markers of cell type and tissue type. So, that's really how the test works.

Dr. Doghramji:
Very interesting. So now, what are some of the considerations we should be mindful of when considering multicancer early detection technology?

Dr. Ofman:
Well, this is really a breakthrough to shift away from not only screening for single cancers, but also screening individuals for cancer. And the attributes that are required, you know, firstly, as I mentioned, was that there's a very low false positive rate to distinguish clinically significant cancers from those that are not clinically significant because one of the harms of screening is thought to be this idea of overdiagnosis of indolent disease. So, you know, think back to thyroid cancer and prostate cancer and some hormone positive breast cancers, there's a concern that we may be finding a lot of early cancer that's not actually going to kill the individual.

And so given the way that we at GRAIL find cancer by looking into DNA and blood, it turns out that the indolent cancers are not as invasive and are not shedding a lot of DNA into the blood. So, our technology doesn't really find those. So, that's another really important attribute, not only to have a very low false positive rate, but also to have some evidence that you're not contributing to this problem of overdiagnosis.

Then finally, to be able to localize the cancer signal to very specific tissues is another really important attribute. Now, it turns out that we developed our test to meet all three of those criteria. And Galleri, which is GRAIL's multicancer early detection test, does have those attributes.

And the final attribute is to have very robust clinical data and validation. In a clinical study, GRAIL's test, we found the ability to detect cancer signals across 50 different types of cancer, over 45 of which lack a screening test today all through single blood draw, and then accurately localize those cancer signals to the appropriate tissue where the cancer resides with very high accuracy over 90%.[8] And then that was validated in a real-world study of 6,500 individuals aged 50 and over who had no suspicion of cancer.[13] They were screened with an earlier version of Galleri, results were returned to the doctor who returned them to the patient, cancers were worked up, and it was a very robust, real-world study and the results, the interim results, were just reported out at ASCO.

And what we found was that we were able to find many different types of cancer. And of the cancers detected, 40% of them were localized in Stages 1 or 2. And let's just pause there for a moment, because those are highly treatable and potentially curable, solid cancers. And half of them, or more than half, were detected before distant metastases. And the cancer signal origin accuracy was 96% when both predictions were used.[15] So, this study will continue to monitor patients for a full 12 months. And the final result will be reported out, but you know, this is quite important validation.

Dr. Doghramji:
Very, very promising information, indeed, Dr. Ofman, and we certainly look forward to final results in the coming year.

Before we close, what are some of the key takeaways we should keep in mind when using multicancer early detection technology?

Dr. Ofman:
Well, one is that, you know, we need to focus this technology on populations at elevated risk for cancer. So, one example of those populations are adults over the age of 50, who turns out have about a 10 to 13 times higher incidence of cancer than populations below

the age of 50.[16] Other elevated risk groups are, you know, cancer survivors, and smokers, and people with familial cancer syndromes, and people with obesity and diabetes, and there will be more information coming out about exactly the definition of those elevated risk groups. Other elevated risk groups include, you know, people with HIV and AIDS and transplant recipients who get immunosuppressants. So, a lot more to come on what the elevated risk groups are, but that's the place to focus this test right now. Because finding cancer early, when treatment is likely to be most successful, is one of the most significant opportunities we have in all of public health to make a major impact. And pairing multicancer early detection tests as a complement alongside traditional screening just has an enormous opportunity before us to really make a dent in the cancer mortality curve, and really bring a, you know, kind of wage a new front in the war on cancer using multicancer early detection technology.

Dr. Doghramji:
Well, that's a great way to close out today's program as we strive to improve standards of care and ultimately save lives. With that in mind, I want to thank my guest, Dr. Joshua Ofman, for joining us to provide insight in early cancer detection and MCED technology. Dr. Ofman, it was great to have you on the program.

Dr. Ofman:
Thank you so much. It was great to be here.

Dr. Doghramji:
I'm your host, Dr. Paul Doghramji, and thank you for joining us.

Announcer:
This program was sponsored by GRAIL. If you missed any part of this discussion, visit ReachMD.com/Industry-Feature. This is ReachMD. Be Part of the Knowledge.

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