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A Changing Paradigm for Cancer Screening: Exploring Surrogate Endpoints for an Urgent Public Health Concern

Announcer:
You're listening to *Project Oncology* on ReachMD. This medical industry feature, titled "A Changing Paradigm for Cancer Screening: Exploring Surrogate Endpoints for an Urgent Public Health Concern" is sponsored by GRAIL.

Here's your host, Dr. Charles Turck.

Dr. Turck:
Cancer remains the second leading cause of death in the U.S., creating an urgent need to detect cancer at earlier stages when outcomes are better. With the emergence of novel multi-cancer screening technologies, the potential public health impact may be substantial. Given these advances, is it time to rethink the way clinical trials are designed to assess the effectiveness of these screening technologies?

This is *Project Oncology* on ReachMD. I'm Dr. Charles Turck. Joining me today is Dr. Eric Klein. Dr. Klein is a distinguished scientist at GRAIL, a healthcare company that has developed a multi-cancer early detection, or MCED, test to detect cancer early when it can be cured. Dr. Klein was formerly the Chair of the Glickman Urological and Kidney Institute, and a professor of surgery in the Lerner College of Medicine of the Cleveland Clinic. He was also one of the lead investigators on the Circulating Cell-free Genome Atlas study, and the PATHFINDER clinical studies conducted by GRAIL that led to the development of the MCED test. Dr. Klein, thanks for being here today.

Dr. Klein:
Thanks for having me.

Dr. Turck:
To get us started, Dr. Klein, would you tell us about the endpoints that are typically used for clinical trials focusing on screening modalities?

Dr. Klein:
Yeah. Mortality has been the gold standard endpoint by which screening programs have been evaluated, and this is based on a framework that was established a few decades ago by a government agency called the United States Preventive Services Task Force. The challenge with using mortality as an endpoint is that it takes many years to accrue patients to a clinical trial, many years of follow-up, and it takes a long time generally for people to die of their cancer. So, of the published trials that we use to justify the screening tests that are in current use, many of them take two decades or more to actually publish their results.[1,2]

And I think it's important to point out what the unmet medical need here is when using mortality as an endpoint. Despite the fact that we currently screen for five different cancers, more than 600,000 people a year still die of cancer in the United States.[3]

Dr. Turck:
So given the urgent public health threat of cancer, how can we measure the effectiveness of multi-cancer early detection tests without waiting decades?

Dr. Klein:
I think the way to do that is to consider using alternative endpoints to mortality. And they could be used in two different ways.

One would be to power clinical trials just on the alternative endpoints alone—something short of a mortality endpoint that takes a long

time—and make a decision then about whether or not these new technologies like MCEDs actually add value to screening the population.

A second way to use them would be to use them as signposts along the way of a longer mortality trial with the idea being that, for example, one alternative endpoint that's being looked at carefully is the reduction in the incidence of late-stage cancer. So, if you built a mortality trial, and built in the signpost or an intermediate endpoint of reduction in late-stage disease, and you didn't see a reduction of late-stage disease using this new technology within a few years, one might say, 'Well, maybe this screening technology isn't as powerful as we thought, and we should go back to the drawing board and rethink things.' On the other hand, if after a few years, you did see a substantial reduction in the incidence of late-stage cancer, like you know, eliminate the presentation of stage IV cancer, for example, one would say, 'Yeah, it looks like this screening paradigm is working, and we should continue the trial and still focus on proving a mortality endpoint.' And you know, both of those approaches have validity.

As far as what alternative endpoints ought to be considered in those circumstances, the field of prevention has really been invested in this and thinking about this. So there are a number to consider. One I've mentioned already, is reducing the number of patients who are newly diagnosed with stage III or IV cancer, which is likely to result in a mortality reduction. Another would be the percentage of patients who are candidates for curative intervention at the time of diagnosis. Another would be reduced treatment-related side effects for the early-stage cancers that are caught. In the current paradigm, for example, we catch ovarian and pancreatic cancers generally in late stages; they're often treated very aggressively, but, we don't know what would be the appropriate way to treat those if we lived in a world where we had a test that detected them at early stage. And we can't and shouldn't assume that the treatments that we use for late-stage disease are necessarily going to be appropriate for treating earlier-stage disease. And there are some others: increased treatment response rates, improved quality of life, utilization, adherence, access… all of those.

Dr. Turck:
For those just joining us, this is *Project Oncology* on ReachMD. I'm Dr. Charles Turck. And today I'm speaking with Dr. Eric Klein about how we can better assess the efficacy of cancer screening modalities.

Now, Dr. Klein, in a recent commentary, Raoof and colleagues suggested an adaptive approach to regulation and assessment of novel cancer screening technologies, the crux of which is conditional approval using surrogate endpoints. What can you tell us about that?

Dr. Klein:
Well, the concept, which I like, borrows an idea from what the FDA does with oncology drugs. So, the FDA adopted a policy many years ago now that they sometimes will grant accelerated approval to drugs that demonstrate efficacy by making patients live longer—that's called progression-free survival—while waiting to see whether or not those treated with this drug compared to the placebo, for example, actually have better overall survival. And that accelerated approval program was created to allow the approval for drugs for unmet needs for diseases that have no other treatments or diseases that are highly lethal, and so forth. And it's been accepted because of the lack of available therapies and significant disease morbidity for many of these cancers. And so there's no reason that we couldn't apply the same rationale of accelerated approval to MCEDs and other newer screening technologies, while we're waiting for the mortality data to mature.

Dr. Turck:
So with that being said, why do you think it might be difficult for clinicians and regulators to accept surrogate endpoints for cancer screening trials?

Dr. Klein:
You know, new technology is always disruptive and it challenges what I call our status quo bias. And we get used to thinking about how we manage patients based on our everyday practices. And in the absence of being challenged, that's the path of least resistance. So clinicians are accustomed to historical screening data, based on mortality as the primary endpoint. That's what we've been told is necessary.

But data from screening trials for some of the cancers we screen for now—breast, colorectal, and lung cancer, for example—support the use for one of these alternative endpoints that I mentioned, reduction of late-stage cancer incidence as a surrogate for mortality. So that's one way to think about it.

Another interesting aspect of this is that currently we screen for five single cancers. So, we screen for breast, colon, prostate, cervical, and lung cancer. So, one test for each individual cancer. MCEDs have a completely different biological underpinning than these screening tests do. We need to wrap our heads around the fact that because of that, the performance characteristics of these tests are going to be different. We can aggregate the prevalence of the cancers, and come up with a single positive predictive value, which is far superior to single-cancer screening tests, while having a single false-positive rate of under 1%.

And so this is new information, it's a new way of thinking about things. And so again, we have to challenge the status quo here. And that can be challenging for people and communities of practicing physicians and public health individuals who are sort of set in their ways.

Dr. Turck:
And we know that some of these newer screening tests are based on molecular characteristics. Let's talk about how that impacts how we evaluate efficacy.

Dr. Klein:
Yeah, this new technology is based on the fact that cancers secrete cancer-related DNA into the bloodstream. And we can do what's called a liquid biopsy, by taking a sample of blood, we can see the cancer signals when present in the blood and tune out all the noise. And that allows us to screen the entire body at once, instead of focusing on specific organ systems that the current screening tests do. And so again, because that's novel technology, we need to think differently about how it allows us to evaluate how this works.

So in the past, we have decided on approving these screening technologies based on just looking at single cancers. So you know, mammography is approved for screening for breast cancer, but it says nothing about all the other cancers that afflict people and what they might die from and so forth; whereas these liquid biopsies allow us to do it in a way that's far more efficient.

Dr. Turck:
Now, before we close, Dr. Klein, I'd like to take a look at some of the new screening tests, like MCED. In your opinion, what kind of impact can these tests have on this public health threat? And do they demand a different approach when evaluating the efficacy of cancer screening?

Dr. Klein:
Yeah, no question they demand a different approach, again, because it's a fundamentally different way of assessing the presence of cancer. So, existing screening tests are maximized for sensitivity, and therefore, they have a very high false-positive rate. And that can be measured in something called positive predictive value, which means if you have, for example, an abnormality on a lung CT that suggests lung cancer, what's the likelihood that that abnormality actually is a cancer? Well, it turns out that for all our existing screening tests, the positive predictive value is less than 10%.[4-6]

Whereas, MCEDs are calibrated opposite to these screening tests, and they're maximized for specificity to minimize the false-positive rate, rather than sensitivity. So in the aggregate, you have a false-positive rate for all those cancers that's under 1%.[7]

Compare that to individuals who participated in one large and very famous screening trial called PLCO—the men in that trial, who had a total of 10 screens, so you know, add up those four cancers and they were screened repeatedly for them, their likelihood of having a false positive was 50% after 10 screens, and for women, it was about 40%.[8] So compare that to this new technology that has a false-positive rate of under 1%,[7] so that's an increase in efficiency in our ability to detect cancers that really should inform the way we think about these.

Dr. Turck:
Those are all great points for us to think on as we come to the end of today's program. I want to thank my guest, Dr. Eric Klein, for helping us better understand the changing paradigm for cancer screening. Dr. Klein, it was great speaking with you today.

Dr. Klein:
Likewise. Thank you.

Announcer:
This program was sponsored by GRAIL. If you missed any part of this discussion, visit ReachMD.com/ProjectOncology. This is ReachMD. Be part of the knowledge.

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