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

MCED & PATHFINDER: Challenging the Status Quo in Cancer Screening

Announcer:
Welcome to ReachMD. This medical industry feature, titled “MCED & PATHFINDER: Challenging the Status Quo in Cancer Screening” is sponsored by GRAIL.

Disclaimer: The values in this episode are based on an early version of Galleri.

Here’s your host, Dr. Charles Turck.

Dr. Turck:
The state of cancer screening in the United States hasn't changed much over the years, which may be one reason why we lose 600,000 patients to cancer every year.[1] But what if we had a way to detect cancers in earlier stages when treatment with curative intent is possible?

This is ReachMD, and I'm Dr. Charles Turck. Joining me to discuss multi-cancer early detection is Dr. Eric Klein, Professor of Surgery at the Cleveland Clinic Lerner College of Medicine, and Emeritus Chairman of the Glickman Urological and Kidney Institute in Ohio. Dr. Klein, welcome to the program.

Dr. Klein:
Thanks. Pleased to be here.

Dr. Turck:
To start us off, Dr. Klein, what can you tell us about the current state of cancer screening in the United States?

Dr. Klein:
Our current cancer screening in this country isn't nearly good enough. And that's evident by the fact that even though we screen for five common cancers, we're still losing about 600,000 patients a year to cancer in the United States.[1] The reason for that is that most cancers that result in death are diagnosed after patients become symptomatic. And by that time, we're certainly less likely to find a cure,[2] and the burden of cure is a lot higher.

We currently screen for five cancers breast, cervical, colon, lung, and prostate cancer, all these single cancer screening tests. We only screen for one cancer at a time and they all reduce mortality for those specific cancers.[2]

The challenge is though, that about 70% of cancer deaths are caused by cancers that unfortunately have no standard screening methods at all.[2] So with all of that being said, in order to make progress and reduce the death rate due to cancer, which is a major public health goal, we need some disruptive technology and new tests that can screen for multiple cancers at once.[2]

Dr. Turck:
And do any tests like this already exist?

Dr. Klein:
Yes. A company called GRAIL has a test called Galleri. It's a multi-cancer early detection test, or MCED for short, that uses a single blood test based on next generation was used to detect more cancers and a broader array of cancers before symptoms appear.[2]

This test uses a targeted methylation-based assay to detect and analyze cell-free DNA, which is released from cancer cells as they die

into the bloodstream.[3] And it's a form of liquid biopsy. So blood plasma containing the cell-free DNA is isolated and analyzed. And a machine-learning algorithm is then used to detect a cancer signal and help predict the cancer signal of origin, or CSO as we call it, where the cancer might be arising in the body.[3]

Dr. Turck:
Thanks, Dr. Klein. Now, are there any studies on Galleri that demonstrate these results?

Dr. Klein:
So I'd like to focus on a study for which I helped enroll participants called PATHFINDER, which was a prospective single-arm interventional return of results study to evaluate the use of MCED in a clinical setting. The study enrolled a little over 6,600 volunteers aged 50 and older, as this age group is naturally at an elevated risk for cancer.[4]

These volunteers came from seven different U.S. sites, and were divided into two cohorts; those with additional risks such as a history of cancer, a smoking history, or those with a familial predisposition or known genetic risk, and those without additional risk, meaning those who were just over age 50.[4]

The primary endpoint of the study was to assess the amount of time and extent of procedures needed to reach a diagnostic resolution in those who had a positive "signal detected" MCED test result.[2] The secondary endpoint was to evaluate MCED test performance in terms of specificity, positive predictive value, and the accuracy of the signal origin.[2] Keep in mind that the test was not designed to determine the number of cancers that Galleri can detect. That would need many more study participants for that. And it was also not meant to determine Galleri's sensitivity, because at the time the blood was drawn, the cancer status was not known for all of these participants.[2]

And finally, a refined version of the Galleri test was introduced during the study to reduce premalignant hematologic signals, which are fairly common, and to reduce the number of CSO calls down to a maximum of two to simplify physician decision-making and diagnostic planning.[4]

Dr. Turck:
You're listening to ReachMD, and I'm Dr. Charles Turck. Joining me today to talk about multi-cancer early detection and the PATHFINDER study is Dr. Eric Klein.

So Dr. Klein, now that we've reviewed the PATHFINDER study design and endpoints, can you tell us about the results?

Dr. Klein:
At this time, we have some positive seminal PATHFINDER results. First by adding MCED testing to other screening detection methods, we were able to increase the number of cancers detected compared with standard screening alone by more than double.[4] In fact, 72% of the cancers found in the PATHFINDER study would not have been found by standard screening tests.[4]

Second, even though PATHFINDER wasn't designed to determine the number of cancer types, Galleri detected more cancers than all United States Preventive Services Task Force recommendations for single cancer screenings combined.[4] Galleri also helped detect and diagnose cancers with no routine screening, including 48% of cancers at early stages.[4] For example, it found stage 1 cancers of the liver, small intestine, and uterus, as well as two stage II pancreatic, bone, and head and neck cancers.[4] So overall Galleri detected cancer signals in 1.4% of the participants.[4] Of those with true positive results, 73% had diagnostic resolution accomplished in less than 3 months. This was the primary endpoint of the study.[4] And I'll remind everyone that this study was performed at the height of COVID, when access to diagnostic tests was really restricted, and in my view, it's likely that the time to arrive at a final diagnosis in an MCED screen patients is likely to be shorter when things return to normal.

Also, CSO prediction was highly accurate at 97% for the first or second CSO, which was the secondary endpoint of the study, and this helped clinicians direct their diagnostic workups more accurately.[4]

Dr. Turck:
So let's break this all down, Dr. Klein, what can we infer from these study results?

Dr. Klein:
These results show that Galleri has high specificity at 99.5%, meaning a very low false positive rate of about 0.50%, and a high likelihood that a positive test is actually cancer, which is known as the positive predictive value, which reached 43.1%, as a secondary endpoint in this study.[4] As I mentioned, the false positive rate was less than 1%, and that's consistent with GRAIL's previous case-

controlled study called CCGA.[5] If we put this into context, mammography has a false positive rate of around 11%.[6] We didn't see any serious study-related adverse events as a result of MCED testing or from the diagnostic workup or from a positive "signal detected" result.[4]

And finally, MCED testing was associated with high satisfaction, low negative psychosocial impact, and a high likelihood of screening adherence.[4]

Dr. Turck:
Now we're almost out of time for today. But before we close, what key takeaways would you like to leave with our audience?

Dr. Klein:
I would say that we need to do a better job detecting more cancers earlier as the burden of cancer continues to grow, not only in the United States, but worldwide. While we have some ongoing work to do with future studies, the results of the PATHFINDER study show us that it's possible to detect cancers in early stages with a blood test in patients who are asymptomatic, and detect cancers that don't have standard screening tests currently. By combining MCED testing and the standard screening protocols, we can detect more cancers and treat more patients earlier, which is likely to improve mortality rates in the future.

Dr. Turck:
Thank you. Those are great practical takeaways to consider as we end today's program. I want to thank my guest, Dr. Eric Klein, for helping us better understand the potential of multi-cancer early detection.

Dr. Klein, it was great speaking with you today.

Dr. Klein:
Thanks for having me.

Dr. Turck:
Before we go, let's take a moment to review some important safety information.

Announcer:
Important Safety Information
The Galleri test is recommended for use in adults with an elevated risk for cancer, such as those aged 50 or older. The Galleri test does not detect all cancers and should be used in addition to routine cancer screening tests recommended by a healthcare provider. Galleri is intended to detect cancer signals and predict where in the body the cancer signal is located. Use of Galleri is not recommended in individuals who are pregnant, 21 years old or younger, or undergoing active cancer treatment.

Results should be interpreted by a healthcare provider in the context of medical history, clinical signs and symptoms. A test result of "No Cancer Signal Detected" does not rule out cancer. A test result of "Cancer Signal Detected" requires confirmatory diagnostic evaluation by medically established procedures (e.g. imaging) to confirm cancer.

If cancer is not confirmed with further testing, it could mean that cancer is not present or testing was insufficient to detect cancer, including due to the cancer being located in a different part of the body. False-positive (a cancer signal detected when cancer is not present) and false-negative (a cancer signal not detected when cancer is present) test results do occur. Rx only.

Laboratory/test information
GRAIL's clinical laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and accredited by the College of American Pathologists. The Galleri test was developed, and its performance characteristics were determined by GRAIL. The Galleri test has not been cleared or approved by the Food and Drug Administration. GRAIL's clinical laboratory is regulated under CLIA to perform high-complexity testing. The Galleri test is intended for clinical purposes.

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

References

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3. Liu MC, Oxnard GR, Klein EA, Swanton C, Seiden MV; CCGA Consortium. Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. *Ann Oncol.* 2020;31(6):745-759. doi:10.1016/j.annonc.2020.02.011