The Impact of a Positive Multi-Cancer Early Detection Test Result and Follow-up Testing on Cancer Risk

Summary of “Modeled residual current cancer risk after clinical investigation of a positive multi-cancer early detection test result”
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Most cancers are found in people after they start to show symptoms.[1] These symptoms can be difficult to connect to a specific type of cancer.[2,3] In an effort to find common cancers earlier, screening is done in certain people even if they don't show symptoms. Because cancer can be deadly, it is important to follow-up a positive screening test with additional testing for diagnosis. The follow-up of symptoms may be important. There are recommendations for physicians about whether to follow-up depending on the patient’s risk for cancer based on symptoms. For example, in the UK, the National Health System (NHS) recommends that nonspecific signs and symptoms that may be related to cancer be investigated even if the patient’s risk of cancer is as low as 3%.[4]

A multi-cancer early detection (MCED) test has been developed by GRAIL that can detect with a single blood draw whether or not a person may have cancer.[5] It does this by looking at small pieces of DNA that cancer cells shed into the blood. The test also uses DNA patterns to predict up to two places where the cancer is located in the body (cancer signal origin [CSO] prediction). This is important to help physicians choose follow-up diagnostic testing.[6]

Ideally, the first predicted place to look in the body for cancer (the top CSO prediction) would lead to just one follow-up test resulting in a specific cancer diagnosis. However, there will be cases where a cancer is not confirmed with a single follow-up test. This may happen because the prediction of where to look was wrong, because the follow-up test missed the cancer even though the place to look was correct, or because the person does not have cancer at all. If the first follow-up test doesn't find cancer, physicians need to make a hard decision. Should they perform additional testing — and at what location? If they stop looking for cancer, a treatable cancer may be missed. If the patient does not have cancer, continuing to test is only

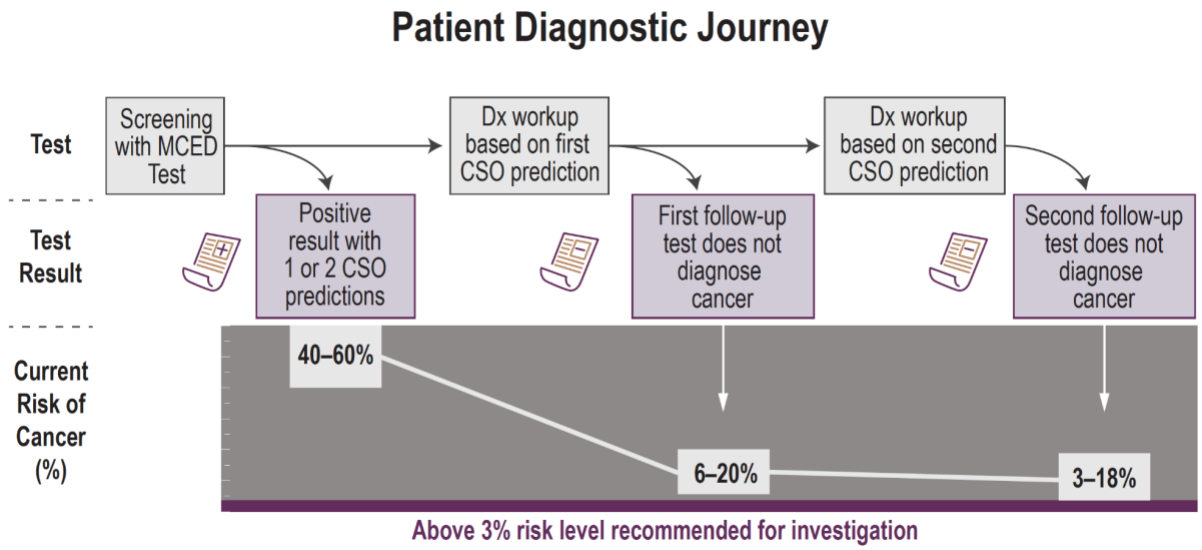
causing harm. To help physicians understand the odds, the researchers of this study calculated the "residual current risk of cancer" — the remaining odds of having cancer after having done a certain set of tests.

When the researchers calculated cancer risk, they assumed a number of decisions and inputs. First, they assumed that a positive MCED test result, that is, a MCED test result that showed a cancer signal was detected, had already led to a transition from screening to diagnosis; any follow-up tests would be used for diagnosis of cancer. Second, they assumed that the first follow-up test would be looking at the location of the body noted by the top CSO prediction. A cancer risk was estimated at this point assuming that follow-up testing did not find cancer. After the first follow-up test, if the estimated cancer risk was still high enough to justify it, it was assumed that a second follow-up test looking at the location of the body noted by the second CSO prediction was done. At this point, another estimate of cancer risk was calculated assuming that this second follow-up test also did not find cancer. Calculation inputs for how well the MCED test worked in terms of ability to detect a cancer signal were based on results from a clinical study that has been previously published.[6,7] Calculation inputs for how well follow-up tests worked were based on the published data for widely used tests such as mammography,[8,9] colonoscopy,[10,11] and whole-body imaging.[12,13]

Although most cancers are expected to be found at the top CSO prediction location, the researchers found that after a failure to diagnose cancer, there is still a noticeable risk that the patient has cancer. At the low end, a 6% risk of cancer could remain, even with highly sensitive follow-up testing; a highly sensitive test is a test that is good at detecting cancer in people who actually have cancer (few false positives). In other words, among all people remaining with no cancer diagnosis after the first follow-up test, one in seventeen could still have cancer. At the high end, a 20% risk of cancer could remain, if the cancer is difficult to diagnose. That would mean 1 in 5 of the remaining people could have cancer. Both of these risks are far higher than 3%, which is the lowest risk level at which the UK NHS recommends physicians look for cancer

in their patients.[4] Even after a second follow-up test, the risk that a patient still has cancer could range from 3% (~1 in 30) to 18% (~1 in 6). Thus, stopping the search for cancer in patients who have some indications of its presence in their bodies could be risky.

In summary, although most cancers will be found at the top CSO prediction location due to the high accuracy of the MCED test in determining the location when cancer is diagnosed, failure to find a cancer at the top CSO prediction location does not mean the physician should abandon testing. Careful weighing of the odds and consideration of each individual patient is needed. This research may help physicians make decisions in interpreting an MCED test report and any further follow-up testing they order.



MCED, multi-cancer early detection; Dx, diagnostic; CSO, cancer signal origin

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