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COMMENTARY

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Modeling the impact of a screening blood test on the use of adjunct breast imaging

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With increasing interest in the development of a blood test for the detection of early breast cancer, it is important to consider the exact role such a test would play in different clinical settings. Rather than a stand-alone tool, results would be incorporated into existing algorithms, prompting speculation as to how those pathways might be altered. A blood test might be used to monitor for recurrence or to assist with diagnostic problems, but our focus here is the use of a blood test to guide adjunct imaging for screening purposes.

In the past, it was widely accepted that screening mammography in the general population performed well with a sensitivity of 80%-90%,[1] but this level of sensitivity has not been upheld in multimodality studies. Using breast MRI for average-risk screening, Dr Kuhl et al[2] reported a cancer detection rate (CDR) of 1.5% in 3861 screening MRIs after patients were given clearance through clinical exam, negative mammograms, and in most cases, screening ultrasound. With this CDR well above what is generated by screening mammography, it is apparent that the superior sensitivity of MRI is not limited to high-risk patients.

However, cost-effectiveness for MRI screening is a major challenge, with indicators that disease prevalence should be 3%, allowing a comparable CDR (30 per 1000), in order to justify its use.[3] And while a 3% CDR has been achieved in some of the high-risk MRI screening trials that are heavily weighted with prevalence screens, 3% cannot be maintained long-term in the subsequent annual incidence screens. Even if MRI is restricted to only the highest risk gene-positive patients, annual incidence would be 2%, and for most high-risk patients, annual incidence is 1% or lower.

An idealized way to use adjunct imaging efficiently in the screening setting would be through the use of a low-cost tool, such as a blood test, that signals the likely presence of mammographically occult breast cancer. This would obviate the need for predetermined incidence screens at fixed intervals with attendant low-yield CDRs. Instead, when blood test results prompt adjunct imaging, yields would more closely approximate the higher CDRs found in prevalence screens.

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Different schools of thought prevail when it comes to the most desirable characteristics of the ideal screening blood test, many believing specificity is the most critical requirement, a feature anticipated with circulating tumor DNA fragments, or "liquid biopsy." Given the specificity problems already inherent with screening, this viewpoint holds that we should not make the false-positive situation any worse, even at the expense of sensitivity.

The other view is that sensitivity is the more critical issue, avoiding false-negatives. After all, the purpose of a blood test is to capture those cancers missed by mammography. Lack of adequate sensitivity would result in cancers being missed on both mammography and blood testing, an undesirable outcome for a two-pronged approach.

Rarely, we can have it both ways. Usually, as one adjusts thresholds, the sensitivity and specificity are inversely related. And this brings up the possibility that two different approaches (even using different technologies) might co-exist. High specificity screening with strong PPV could be used to "rule in" adjunct imaging in the general population where a dual-modality approach is not currently recommended. Then, high sensitivity screening with strong NPV could "rule out" adjunct imaging in women with high density or high risk who are currently issued a blanket recommendation for fixed-interval adjunct screening.

Unexpectedly, performance characteristics in the "rule out" scenario can generate beneficial outcomes in spite of what appears to be only modest stand-alone performance.

Consider a blood test that has been validated as having a sensitivity of 75% and specificity of 75%, with these suboptimal performance characteristics having little clinical use at first glance. If such a blood test were applied to 1000 women with Level D breast density where, for illustration, we assume there are eight mammographically occult cancers, then the false-positive "problem" generates 250 ultrasounds, instead of a guideline-generated 1000 ultrasounds. Then,

the 75% sensitivity is able to capture six of the eight cancers, while avoiding 750 ultrasounds.

A similar "rule out" scenario would apply to patients at borderline risk (20%-25% lifetime), who marginally qualify for annual MRI in addition to annual mammography. By relying on a blood test with the same parameters of 75%/75% sensitivity/specificity, the only impact of a false-positive would be an MRI, which is currently recommended by guidelines anyway. So, instead of 1000 MRIs, a 75% specificity would prompt 250 MRIs (plus true positives), a major cost savings.

The difference in this MRI scenario is that, instead of eight occult cancers detectable by ultrasound, there would be an estimated 20 MRI-detectable cancers present, 15 of which (75% sensitivity) would be picked up through the blood test, then confirmed on the MRI. Fifteen cancers identified from 265 MRIs generated a CDR of 5.7%, a higher yield, by far, than any approach to screening MRI that has been used to date, even though our candidates were originally considered borderline for meeting the MRI screening guidelines. And without fixed-interval incidence screens, these high yields would be maintained long-term in a cost-effective fashion.

Of course, the cost of the blood test itself would need to be incorporated in studies of efficiency. Still, the above exercises can be applied using different performance characteristics, where it becomes apparent that cost-effectiveness using adjunct screening modalities can be greatly improved with a blood test having modest accuracy.

A blood test to detect early breast cancer would not stand alone. A high specificity test with strong PPV could be used to "rule in" adjunct screening in normal risk/normal density patients, even if the sensitivity is marginal. And when it comes to those patients in whom adjunct imaging at fixed intervals has already been recommended according to current guidelines, even mid-range performance characteristics can vastly improve cost-effectiveness with very high CDRs. Since these modest performance characteristics in a blood test might be within our reach soon, it is a timely exercise to consider the many variables that would impact utilization.

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