THE AMERICAN JOURNAL of MEDICINE®

The Promise of Multicancer Early Detection

To the Editor:

We read with interest the articles by Ueberroth et al[1] and Olivier et al[2] about emergence of Multicancer Early Detection (MCED) in primary care. We applaud the effort to outline the salient issues about use of MCED tests with the goal of arming clinicians with factual knowledge about the rationale and performance of the tests, the key questions that patients may ask, and potential downsides of MCED. Both articles raise issues that require further clarification.

While existing single cancer tests generally have good sensitivity for detecting stage I disease for individual cancer types, they have a lower all-cancer sensitivity than an MCED when considering all cancers as the denominator. The Circulating Cell-free Genome Atlas (CCGA) study showed that for 12 common cancers that account for two-thirds of US cancer deaths (anus, bladder, colon/rectum, esophagus, head and neck, liver/bile duct, lung, lymphoma, ovary, pancreas, plasma cell neoplasm, stomach), GRAIL's Galleri test had a sensitivity of 53% for stage I and II disease.[3] For ovarian and pancreatic cancers that effectively have a 0% early detection rate currently due to the lack of existing screening tests, Galleri detected 60% of stage I and II tumors.[3] Ueberroth et al[1] cite a post hoc analysis[4] that suggests that the estimated positive predictive value (PPV) should be based on the prevalence of individual cancers, an assertion that is fundamentally incorrect for an MCED, where test performance is based on the aggregated prevalence of all cancers.[5] Using a prespecified analysis, 2 studies,[3,6] including the interim results of one in an intended-use adult screening population (PATHFINDER),[6] demonstrated that Galleri's PPV exceeds 40%, far higher than current single-cancer tests such as mammography[7] and low-dose computed tomography for lung cancer,[8] which have PPVs <10%.

Olivier et al[2] question whether early detection is better and raise appropriate concerns about over-detection of nonlethal cancers. Chen et al[9] demonstrated in the CCGA study[3,10] that, while cancers detected by Galleri had expected survival outcomes, *those not detected had better than expected outcomes*, clearly suggesting that over-detection of nonlethal cancers is less likely by this MCED. Additional research is needed to better define this area, but it is possible that by relying on circulating tumor DNA as the principal analyte, MCEDs in development will be more sensitive for cancers with lethal potential than for clinically insignificant cancers. While we share concerns about the potential harms that may result from false positive tests, there were several inaccuracies in the commentary related to the analysis of this issue. First, Olivier et al incorrectly imply that 200 million adults would be eligible to be screened by broad use of MCED, resulting in 1 million false positive results. Cancer screening in the United States is generally limited to those aged 50-79 years, defining an eligible population estimated at 107 million.[11] Further, there is a 10-fold error in the calculation of the number of potential false positives based on a hypothetical sample size of 95,174 in a randomized trial: a 0.5% (0.005) rate of false positives would result in 476 false positives (95,174 × 0.005), not the 4758 estimated in the article. Relative to a collective estimated false positive rate of 7.5% for currently recommended screening tests[11] (excluding prostate cancer, which is higher), the addition of an MCED such as Galleri, with a false positive rate of 0.005 (0.5%) and an estimated 26% reduction in cancer mortality,[12] is likely to yield a substantial gain in the efficacy of screening. Finally, in the PATHFINDER study,[6] testing was met with high levels of participant satisfaction regardless of result; most patients with a false positive test had only radiographic evaluation and not an invasive procedure, and there were no clinical adverse events associated with diagnostic evaluation of false positives.

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https://doi.org/10.1016/j.amjmed.2022.05.016

Funding: None.
Conflicts of Interest: EAK is a consultant for GRAIL, Inc. MS is a consultant for GRAIL, Inc.
Authorship: All authors had access to the data and a role in writing the manuscript.

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