

Letter

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Early cancer detection by a targeted methylation assay of circulating tumor DNA in plasma

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In a recent issue of your journal, Klein et al. present a large validation study of a targeted methylation-based multi-cancer early detection test using an independent validation set [1]. This is the third and final part of the series of articles by the same authors/company that incorporates their best analytics so far. As presented, the data seem very encouraging, prompting the authors to conclude that “these results support the feasibility of the blood-based multi-cancer early detection test as a complement to existing single-cancer screening tests.” I disagree with this assertion.

In our previous communications, we examined the feasibility of an early cancer diagnostic test by using circulating tumor DNA [2–4]. Although this new cancer biomarker has exciting potential for many clinical applications, its use for early detection and population screening should be approached with caution.

Based on published empirical data, we recently examined tumor size, amount of ctDNA in a 10 mL blood sample, fraction of ctDNA in overall cell-free DNA, and number of retrieved genomes and likelihood of tumor detection with ctDNA analysis. We concluded that, in general, this type of technology is unlikely to detect tumors that are smaller than 10 mm in diameter [2], primarily due to no retrieval of ctDNA from the circulation in patients with early disease, which will lead to sampling error. Our calculations are supported by recent experimental data from the same group, showing poor sensitivity (10%) of

ctDNA analysis in detecting breast cancer in asymptomatic persons in whom breast cancer has been detected by screening mammography [5]. In their latest article, these authors did not cite our concerns with their method, likely for two reasons: (a) Our conclusions do not support their conclusions. (b) This proprietary test is owned by a multi-billion dollar company whose valuation may suffer, if the major findings are questioned.

In their new article, the authors cite an outstanding test specificity of 99.5% and we have no reason to question this strong finding. However, the overall test sensitivity for cancer detection is around 50% and for stage 1 tumors it is only 18%. The sensitivity is higher than 50% in stage 3–4 tumors, but this is irrelevant for the intended application since these tumors are asymptomatic and their detection with the test will not affect significantly their clinical course. Based on the way patients were enrolled (clinically symptomatic disease) it can be safely predicted that about nine out of ten small, asymptomatic tumors, which are amenable to curative therapies, will likely be missed (10% sensitivity as described in ref. [5]).

The authors extrapolated what will be the positive predictive value (PPV) of such tests (PPV = the chances that the disease is present if the test is positive). If the sensitivity is 10%, at 99.5% specificity, and the prevalence of cancer in the general screening population of either 1% (for a fairly common cancer) or 0.1% (for a fairly rare cancer), the PPV will be 17% in the first case and 1.7% in the second case. I seriously doubt that a successful screening program for cancer can be sustained with such low PPVs. The false positivity rates will lead to a rather large number of non-cancer patients who will undergo additional, unnecessary, and probably harmful testing [6].

I conclude that current data, including those reported herein [1], do not warrant population screening based on the analysis of methylation patterns, even if such tests are highly specific. The problem lies in the low (unfortunately currently dismal) sensitivity for detecting early, asymptomatic tumors, as we explained in detail elsewhere [3].

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