Editorial

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Multi-cancer early detection: searching for evidence

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According to the World Health Organization (WHO), cancer is a leading cause of death worldwide and is responsible for more than 10 million deaths each year [1]. Most deaths are due to lung cancer (about 18.0 % of all cancer deaths), followed by colorectal cancer (9.2 %), liver cancer (8.3 %) and stomach cancer (7.7 %). Two other important aspects of cancer biology are that almost half of all cancer deaths are potentially preventable [2], and that therapeutic opportunities are greater and survival better when cancer is detected at an early stage [3]. These straightforward concepts lead to the obvious conclusion that cost-effective screening is the best strategy in humanity's ongoing battle against cancer.

There are already a number of examples of established population screening programs that have been implemented, such as mammography (for breast cancer), cytology and HPV (for cervical cancer), fecal occult blood testing (for colorectal cancer), while others have been implemented in different countries with varying degrees of success (e.g., PSA for prostate cancer, HCV for liver cancer). The so-called multi-cancer early detection (MCED) test has been recently proposed as an innovative and potentially ground-breaking strategy for screening a wide range of cancers. GRAIL, one of the diagnostics companies that has invested more in this direction, is now marketing a test (called Galleri) that is designed to "detect cancer signals and predict where in the body the cancer signal is located" [4]. As can be read on the company's website, it also states: "The Galleri test has not been cleared or approved by the U.S. Food and Drug Administration". According to the company, the current version of the test can detect a signal of over 50 (51 to be precise) cancers, by evaluating DNA fragments (especially circulating cell-free DNA [cfDNA]) in the bloodstream and complementing these measurements with a machine learning algorithm designed to distinguishing between healthy or cancer cell origin.

The first results of the practical application of MCED by Galleri were recently published in the Lancet [5]. In this prospective cohort study, 6,662 participants were initially recruited, of whom 6,621 were eventually included in the statistical analysis. The cumulative detection rate of cancer was 1.38 % (92/6,662), while no cancer signal was detected in the remaining part of the population. The cumulative performance of the assay, as summarized in Table 1, was derived from the data reported in the article, i.e., 35 true positive cases, 57 false positive cases, 6,235 true negative cases, 86 false negative cases (208 cases did not reach the end of the study). Despite remarkably high accuracy (up to 97.8 %) and specificity (99.1 %), this test has low sensitivity (28.9 %) and a corresponding negative likelihood ratio LR^- of 0.72. This means that this test is neither theoretically able to absolutely rule out the presence of cancer, since then the LR^- should be less than 0.1, nor is it able to always detect cancer (signals) early due to the low sensitivity (28.9 %) [6].

A recent opinion paper published in the journal by Chatanaka and colleagues [7], expresses a series of practical, clinical and economical considerations about the test and the first available results. These comments, which are not necessarily shared by the members of the Editorial Board of the journal, criticize unsatisfactory clinical performance, emphasize the interim review of the British National Health Service (NHS)-Galleri trial which led to postponement of the planned large-scale pilot program in NHS clinical practice until final results of

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Table 1: Clinical performance of multi-cancer early detection (MCED) for early detection of over 50 types of cancer in asymptomatic subjects as calculated from reference [5].

Statistic	Value	95 % CI
Sensitivity	28.93 %	21.05–37.87 %
Specificity	99.09 %	98.83–99.31 %
Positive likelihood ratio	31.93	21.82–46.71
Negative likelihood ratio	0.72	0.64–0.80
Positive predictive value	38.04 %	29.56–47.32 %
Negative predictive value	98.64 %	98.48–98.78 %
Accuracy	97.77 %	97.38–98.12 %

the trial become available, and calculate the balance between cost and effectiveness, concluding that implementation of this test for the entire lifetime of US residents would generate a cost that "is approx. eight times higher than the budget of the US Government".

A paper published in the *British Medical Journal* reported serious concerns raised by some scientists, including Mike Richards, the chair of the independent UK National Screening Committee, who highlighted the current lack of evidence "on whether the benefits of testing outweigh any potential harms and at reasonable cost." [8] In addition, another paper published in *New England Journal of Medicine* reported other concerns on the introduction of this test in clinical practice "without evidence that such tests can reduce cancer-related mortality – preferably evidence derived from trials in which commercial entities don't influence final decisions regarding design or conduct and aren't involved in data management or analysis" [9].

While there is certainly an unmet medical need for a comprehensive MCED test, only further large studies in diverse populations will show whether and to what extent this could be provided by the Galleri test. In particular, potential harms, not only physical, but also psychological and financial, of invasive procedures triggered by false-positive MCED test results should be carefully weighted. Cancer is a lethal disease and a gold standard for every intervention aiming to modify the outcome is demonstrating an overall survival benefit. To achieve this, much larger population trials with longer follow up are needed. It should not be forgotten that in the clinical trials, the Galleri test complemented and not replaced standard screening procedures, so that it should not be presented as an alternative to well established screening methods such as mammography or colonoscopy. Screening oriented at a particular cancer (e.g., lung cancer screening) provides also an opportunity for interventions targeting specific risk factors, in this case counseling on smoking cessation, that may further improve the health outcomes, not limited to cancer-related mortality.

There is a need to stress the dangers associated with the use of MCED tests before the demonstration of a survival benefit in prospective trials. While many anticancer drugs are offered to the patients based on surrogate efficacy endpoints before the demonstration of overall survival benefit, such approach is not justified in the setting of cancer screening. The difference between these two situations should be realized. Patients with active cancer have a disease which is lethal without effective therapy and may not have time to wait. In many instances, the benefits of administering a medication based on efficacy demonstrated using surrogate endpoints outweighs the potential harms. On the other hand, in the setting of cancer with less than 2 % of the individuals expected to have a positive test result, the introduction of a procedure that is costly and may lead to other potentially invasive diagnostic interventions remains questionable before having gathered robust evidence of mortality reduction.

General limitation of an approach aiming at detecting genetic changes in the circulation should also be discussed. Some methods of cancer screening (e.g., colonoscopy) not only detect early cancer, but also eliminate precancerous conditions. With increasing cure rates for many cancers, there is a growing number of cancer survivors who also need to be screened for second or third cancers, and it should be investigated how such test will perform in this rapidly expanding populations. Some tumors (e.g., prostate cancer) often take an indolent course, so that potential therapeutic interventions should be considered in the context of competing causes of mortality, while, on the other end of the spectrum, other tumors (e.g., pancreatic ductal adenocarcinoma) are still rarely cured, even when detected during screening. The greatest benefit of screening is probably for cancer that are between these two extremes of the spectrum, and the risks or benefits of a screening program should be considered more in the context of a given primary tumor. In cancer screening, there is probably not a one-fits-all solution. On the contrary, screening interventions should be tailored individually to reflect, among others, patient history, comorbidities and environmental risk factors, and any MCED testing should be used in the context of this paradigm. In conclusion, the jury is still out on the utility of the Galleri test in clinical practice. Continuous scientific debate has to accompany the ongoing research while more results are awaited. The Editors of *Clinical Chemistry and Laboratory*

Medicine, after receiving some complaints on the paper by Chatanaka and Coll., have invited the Grail scientists to submit a Counterpoint to provide the readership with the full and comprehensive vision of the topic, but they have preferred to decline the invitation. The *Journal,* in fact, is committed to provide a forum for such discussion in the interest of scientific progress, the ultimate goal of which is improving health outcomes at the population as well as at the individual level.

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