Editorial

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Multi-cancer early detection revisited: insights and lessons from the PATHFINDER 2 study

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The concept of detecting multiple forms of human cancer through a single blood test has long captured the attention of both clinicians and the public [1]. Among the platforms currently in development, the Galleri® assay (GRAIL, Menlo Park, CA), which is based on cell-free DNA methylation profiling, has emerged as one of the most advanced and commercially available multi-cancer early detection (MCED) tests [2]. While the theoretical potential of this approach is remarkable, its translation into tangible clinical benefit remains uncertain.

In a previous editorial, we have highlighted some limitations of this test [3]. Specifically, a prospective cohort study including over 6,000 participants (with 6,621 evaluable cases) reported a cumulative cancer detection rate of approximately 1.4 %, with 99.1 % specificity, but only 28.9 % sensitivity and 38.0 % positive predictive value (PPV) across more than 50 cancer types [4].

Recently, new data on the Galleri® assay have been presented at the 2025 European Society for Medical Oncology (ESMO) Annual Meeting, featuring results from the PATHFINDER 2 trial (NCT05155605), which seemingly represents the largest evaluation of an MCED test to date [5]. The trial enrolled nearly 36,000 participants across the US and Canada, all aged 50 years and older and without a recent cancer diagnosis or treatment. In a prespecified analysis of 23,161 participants with 12 months of follow-up, 329 individuals were diagnosed with cancer, while a cancer signal was detected in 216 participants (0.93 %), corresponding to roughly 9 cases per 1,000 screened. Cancer was ultimately confirmed in 133 individuals, yielding a cumulative diagnostic accuracy of 98.8 %, a specificity of 99.6 %, a sensitivity of 40.4 %, a negative predictive value (NPV) of 99.1 %, and a PPV of 61.6 %. Notably, sensitivity increased to 73.7 % for the 12 cancer types responsible for approximately two-thirds of US cancer deaths.

Taken together, these results do not substantially diverge from earlier data. Although the PPV and detection rate for common cancers has improved, likely related to enrolling older participants, the absolute detection rate remained relatively low and the false-negative rate during the first year of follow-up remained high (196 of 329 cases; 59.6 %), thus raising concerns about the reassurance a negative MCED result can genuinely provide to patients. Therefore, the same essential questions raised during our former editorial persist: does early detection through MCED testing translate into significant reduction in cancer-related mortality? what is the true balance between benefits and harms, including unnecessary investigations, anxiety, and risk of overdiagnosis? and, finally, is population-wide MCED screening sustainable from both economic and organizational perspectives? These issues remain highly relevant.

Although the PATHFINDER 2 data demonstrate incremental progress in PPV and detection of major cancers, mortality outcomes remain unreported, cost-effectiveness analyses are incomplete, and access strategies for such testing remain undefined. Importantly, MCED tests are not yet positioned to replace standard evidence-based screening modalities, such as colonoscopy, mammography, human papilloma virus (HPV) detection or prostate specific antigen (PSA) testing, which continue to represent the current standard of care. On the other hand, MCED tests detect cancers that are not identified via mass screening, and more than 50 types were picked up in the PATHFINDER 2 trial.

Looking ahead, the optimal use of MCED technologies may hence be driven by a paradigm shift, involving targeted implementation in high-risk populations, rather than widespread application to the general public. Unfortunately, like mass screening, which uses age as the singular partitioning for recommendation, there is lack of pre-test probability. Such target populations could hence include individuals with a strong family history of cancer, genetic predisposition, exposure to known carcinogens, or biological markers of accelerated aging or immune dysfunction. This precision-

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based screening strategy could enhance PPV and reduce the burden of unnecessary diagnostic procedures. Moreover, future MCED platforms integrating RNA, exosomal, or proteomic signatures alongside cfDNA methylation patterns may achieve higher diagnostic sensitivity and improved tumor-type discrimination [6].

In conclusion, the PATHFINDER 2 trial confirms that MCED is transitioning from a conceptual innovation to a clinical reality. However, the data also underscore that technological feasibility does not still equate to clinical justification, considering also that MCED tests have not yet undergone evaluation of safety and efficacy in randomized controlled trials [7]. Only through robust, long-term randomized clinical trials, demonstrating reductions in cancer-specific mortality and cost-effective utilization of healthcare resources, will MCED testing gain a clear role in preventive oncology.

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