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Novel Insights into Preclinical Oncology: Can Blood-Based Genomics Predict Cancer Years in Advance?

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Abstract

Cancer diagnosis at an early stage is essential to enhance prognosis since traditional diagnostic techniques usually detect the tumor at a late stage. The blood-based genomics such as circulating tumor DNA (ctDNA), cell-free DNA (cfDNA), and DNA methylation provide a less invasive solution to identify preclinically occurring malignancies. With ultra-sensitive sequencing and methylation-based assay, it is possible to detect cancer-specific molecular signatures in plasma, which can be used to detect multi-cancer early detection (MCED) with high specificity and moderate sensitivity. Fragmentomic profiling is also more predictive by considering the length of the fragments of the DNA and the pattern on the genomic structure, enabling accurate identification of the tissue-of-origin. Despite all issues still persisting, such as small ctDNA content in early tumors, technical and bioinformatics, cost and ethical issues on the detection of malignancy in non-symptomatic individuals. Genomic approaches targeting blood-based biomarkers would be a game changer in the oncology by presenting a golden opportunity of treating patients and saving their lives by providing early intervention.

Keywords: Blood-based genomics, circulating tumor DNA, Cell-free DNA, DNA methylation, Multi cancer early detection, Fragmentomics

Cancer has ranked as one of the leading causes of morbidity and mortality in most parts of the world, and is mostly diagnosed at the late stages when the tumors are already developed and symptomatic [1]. Conventional methods like imaging and tissue biopsy are usually not able to detect malignancies at the preclinical stages. Blood-based genomic approaches, especially cell-free DNA (cfDNA), circulating tumor DNA (ctDNA), epigenetic methylation and fragmentomic patterns, provide valuable platforms in preventing cancer many years prior to its clinical expression [2]. DNA fragments are released into the blood by tumors as a result of apoptosis and necrosis. A portion of total cfDNA known as ctDNA contains some cancer-specific somatic mutations that can be detected by new next-generation sequencing (NGS) [3]. Mutation allele fractions (MAFs) of ctDNA can now be detected at fractions small enough to be orders of magnitude less than those observed during clinical diagnosis, largely due to the inherent characteristics of modern error.-suppressed digital sequencing platforms, including degrees of penetration of vasculature and rate of DNA shedding in patients [4].

In addition to mutations, DNA methylation and fragments pattern in cfDNA are very strong indicators of neoplastic processes. Alterations in methylation frequently occur in the early stages of tumorigenesis and, in some cases, precede the emergence of mutations or clinical symptoms [5]. Fragmentomics, is a fragment level and genomic location of fragment length has also contributed to the process of early detection, as it has shown unique trends in the fragment of tumor and normal DNA [6]. Prospective longitudinal studies represent one of the strongest pieces of evidence of early genomic prediction. The analysis of archived plasma samples of participants in large cohorts showed that ctDNA signatures could be identified 3-4 years before clinical diagnosis of multiple types of cancer even at very low MAFs. The findings indicate genomic alterations that can precede the clinical manifestation of overt disease by several years, thereby establishing a critical window for early detection and timely therapeutic intervention. Methylation-based detection approaches have demonstrated that epigenomic alterations can be identified in peripheral blood several years prior to the clinical diagnosis of a wide range of solid tumors [7]. Methylome profiling has better resolution of tissue of origin than the mutation base detection methods that did not consider mutation alone [8].

MCED tests combine several building blocks of a cfDNA mutation, methylation, and fragmentation with the help of state-of-the-art machine learning algorithms to reveal cancer signals in a single blood sample [9]. Calibration of these platforms, and hence ability to stratify risks more accurately, has been facilitated by Bayesian modeling and ensemble statistics, which have shown high specificity (>95%), with moderate sensitivity in various cancers, in the absence of symptoms. Early diagnosis of neoplastic processes, with subsequent treatment may lead to better survival and less treatment morbidity [10]. In some cancers such as breast and colorectal, the prognosis and mortality rates are closely linked to the

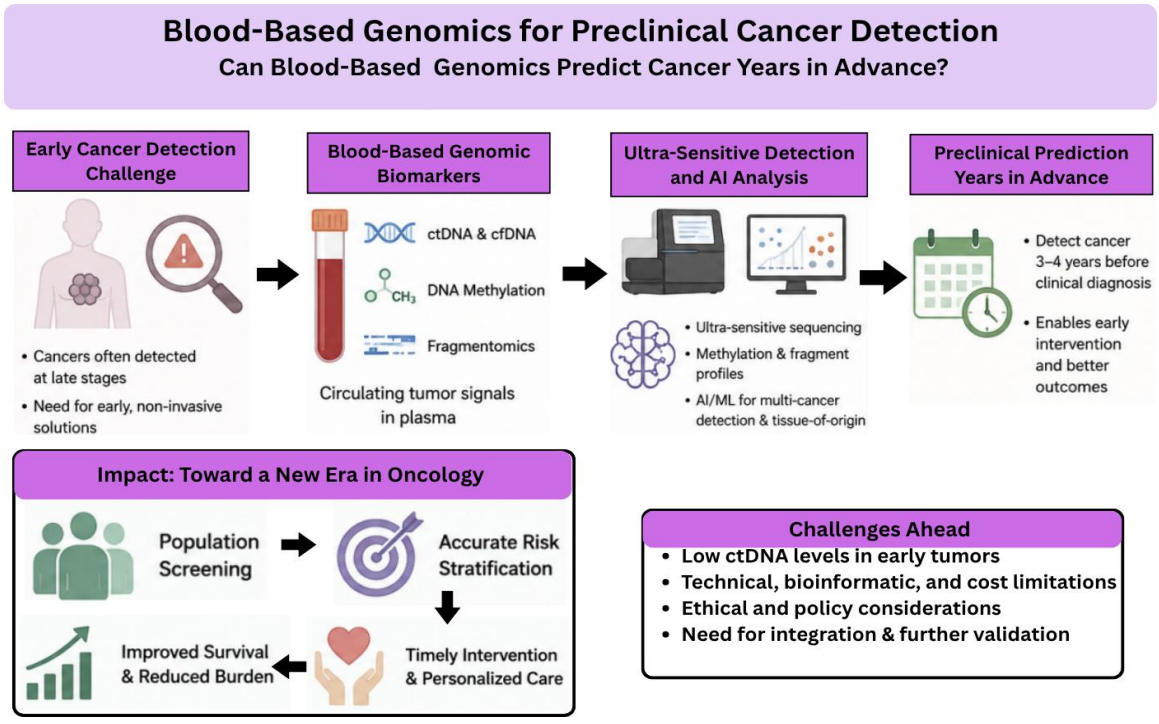
early detection rate of the ailments. Genomic screening of blood might then supplement or indeed surpass other conventional screening procedures such as mammography or colonoscopy [11].

Sensitivity of stage I cancers is still not as high as desired and is limited in cases characterized by lower levels of shedding ctDNA, cancers, or early tumors with limited access to vascularity. Genomic blood tests are, therefore, presently being viewed as complementary to the current screening pathways and not a replacement of them. Other advantages of genomic prediction are the use of genomic prediction to determine tissue of origin signals, which may be used to direct subsequent diagnostics without waste [12]. One major problem of preclinical detection is the attainment of high sensitivity at low ctDNA levels. Preclinical tumors typically do not release much DNA, and therefore require profound sequencing and complex error- suppressing methods to separate the real tumor signal and the noise [13]. Technical advances, i.e., unique molecular identifiers (UMIs) and combined fragmentomic analysis, are enhancing detection limits but are more resource-consuming.

Genomic blood testing for population-level screening has economic and logistical challenges to scale. The high cost of sequencing, the need to have large volumes of blood, and the use of complicated bioinformatics pipelines should be weighed against the expected health gains. Moreover, before mass clinical adoption, it is critical to develop standardized protocols and turnaround time and quality control systems [7]. Genomic prediction at an early stage is associated with complicated ethical concerns. The consequences of the positive genomic signals including how to act in case of a signal without observing a tumor necessitate effective guidelines that would reduce false positive diagnosis, avoid the unnecessary treatment, and maintain the autonomy of patients. Integrating cfDNA genomics with additional biomarkers is promising to enhance the predictive accuracy e.g. circulating tumor cells (CTCs), proteomic panels, metabolomics, and imaging [14].

Multimodal-trained deep learning models can potentially discover composite signatures that are better than single metric assays. Preliminary studies have demonstrated that clinical data when combined with genomic markers and sophisticated algorithms can be used to improve risk prediction models. Genomic technologies utilizing blood-derived biomarkers have undergone rapid development over the past decade. , showing the possibility to identify neoplastic processes earlier than clinical manifestation, ctDNA, methylation patterns, fragmentomic patterns, provide molecular windows into the early biology of tumors and are in line with the idea of preclinical prediction of oncologic diseases. Although there has been an inevitable technical constraint and ethical dilemma, the combination of these applications with the current screening and follow-up plans can revamp the paradigm of cancer detection. Genomic blood testing can become a foundation of cancer prevention and early intervention in the near future with ongoing innovation, validation and careful and well-considered policy frameworks.

Graphical Summary



Conclusion

Genomic technologies, such as ctDNA, methylation profiling, and fragmentomics, are revolutionizing cancer diagnosis through blood-based detection of malignancies before clinical diagnosis even occurs, years prior to diagnosis. While there are challenges of sensitivity, cost, scalability and ethical concerns, advances in technology are improving their clinical usefulness. Combining genomic markers with multimodal diagnostics and AI could further improve the prediction. Blood-based genomics could be a key component of future cancer prevention and early intervention strategies if it continues to be validated and can be regulated appropriately.

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Conflict of Interest

None

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Use of Artificial Intelligence

The corresponding author declared that no artificial intelligence or AI-assisted tools were used in this manuscript except the graphical summary for the better illustration and understandings for scientific readers.

Authors' Contribution

AY and FA contributed equally as per ICMJE. Both authors gave final approval of manuscript to be published.

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