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Editorial

Genome Sequencing-Based Cancer Diagnostic Methods

Cancer remains a leading cause of morbidity and mortality worldwide, with global incidence and mortality rates steadily increasing despite significant advances in prevention, early detection, and therapeutic strategies. According to GLOBOCAN 2020 estimates, there were approximately 19.3 million new cancer cases and 10 million cancer-related deaths globally, emphasizing the urgent need for more precise, sensitive, and individualized diagnostic approaches.[1] Traditional diagnostic modalities—such as histopathology, immunohistochemistry, imaging, and serum biomarkers—have served as the cornerstone of cancer detection and characterization. However, these methods are often limited by their specificity, sensitivity, and ability to capture the molecular heterogeneity inherent to malignant diseases. In recent years, genome sequencing-based diagnostics have emerged as a transformative frontier in oncology, offering unprecedented insights into the genetic underpinnings of cancer and enabling more accurate, tailored patient care.

The advent of next-generation sequencing (NGS) technologies has revolutionized our understanding of the genetic landscape of cancer. Unlike conventional single-gene assays, NGS allows for the simultaneous interrogation of multiple genes, providing a comprehensive view of the mutational, copy number, and structural variations that drive tumorigenesis.[2,3] Whole-genome sequencing (WGS), whole-exome sequencing (WES), and targeted gene panels have all found clinical utility in different oncological settings. WGS examines the entire genome, offering the broadest coverage and revealing non-coding mutations and complex rearrangements, while WES focuses on the protein-coding regions, which harbor the majority of known pathogenic variants.[4,5] Targeted panels, though limited in scope, provide cost-effective, rapid analyses of clinically actionable genes, making them particularly attractive in routine diagnostic laboratories.[6]

One of the most significant contributions of genome sequencing to cancer diagnostics lies in its ability to detect actionable mutations that can guide personalized therapeutic interventions. Tumor-specific alterations in genes such as EGFR, ALK, BRAF, KRAS, and PIK3CA have become critical biomarkers for selecting targeted therapies in lung, colorectal, melanoma, and breast cancers.[7,8] Comprehensive genomic profiling through NGS has also facilitated the identification of rare or novel mutations, fusion genes, and resistance mechanisms, expanding treatment options and improving outcomes.[9] For instance, the discovery of NTRK gene fusions across multiple tumor types led to the development of tumor-agnostic therapies, marking a paradigm shift in oncology.[10]

Liquid biopsy represents another promising application of genome sequencing in cancer diagnostics. By analyzing circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), or exosomes from peripheral blood, liquid biopsies offer a minimally invasive, real-time snapshot of the tumor's genomic profile.[11,12] This approach has demonstrated clinical utility in early cancer detection, monitoring treatment response, and identifying mechanisms of resistance to targeted therapies.[13] Genome sequencing of ctDNA enables the detection of tumor-specific mutations with high sensitivity and specificity, providing a valuable complement to tissue biopsies, which are often limited by procedural risks, sampling bias, and tumor heterogeneity.[14,15]

Despite its immense potential, the integration of genome sequencing-based diagnostics into routine clinical practice faces several challenges. The complexity of data interpretation, the need for standardized bioinformatics pipelines, and the management of incidental findings pose significant hurdles.[16,17] Moreover, the cost and infrastructure requirements of NGS remain prohibitive in many low- and middle-income countries, limiting access to these advanced diagnostic modalities.[18] However, recent initiatives aimed at democratizing genomic medicine have begun to address these disparities. Notably, icddr,b (International Centre for Diarrhoeal Disease Research, Bangladesh) has recently launched advanced genome sequencing-based cancer diagnostic services, marking a pivotal development in the region's oncology landscape. By establishing state-of-the-art sequencing facilities and expertise, icddr,b aims to enhance precision cancer diagnostics, improve patient outcomes, and contribute to global cancer genomics research.[19]

The clinical impact of genome sequencing extends beyond diagnostics to encompass prognostication and risk stratification. Molecular profiling of tumors can identify biomarkers associated with disease aggressiveness, likelihood of metastasis, and response to specific therapies.[20] For example, mutations in TP53, BRCA1/2, and PTEN have prognostic implications in various cancers, informing clinical decision-making and patient counseling.[21] In hematologic malignancies, genome sequencing has refined disease classification, enabling the identification of distinct

molecular subtypes with different prognoses and therapeutic susceptibilities.[22] The incorporation of genomic data into risk prediction models and clinical algorithms holds promise for more personalized, evidence-based oncology care.

In hereditary cancer syndromes, germline genome sequencing plays a crucial role in identifying individuals at increased risk of developing malignancies, facilitating targeted surveillance and preventive interventions.[23] Multigene panel testing has supplanted single-gene assays in evaluating hereditary cancer predisposition, offering higher diagnostic yields and cost-effectiveness.[24] Genes such as BRCA1/2, MLH1, MSH2, APC, and TP53 are routinely assessed in individuals with personal or family histories suggestive of hereditary cancer syndromes.[25] The identification of pathogenic germline variants not only informs patient management but also enables cascade testing of at-risk family members, promoting early detection and cancer prevention.[26]

Emerging applications of genome sequencing in oncology include the characterization of the tumor microenvironment, epigenomic alterations, and transcriptomic profiles. [27] Integrating multi-omic data through advanced bioinformatics and machine learning algorithms enhances our understanding of tumor biology and facilitates the discovery of novel biomarkers and therapeutic targets.[28] Single-cell sequencing, another cutting-edge technology, offers insights into intratumoral heterogeneity, clonal evolution, and immune evasion mechanisms, informing the development of more effective, individualized treatment strategies.[29]

The growing clinical adoption of genome sequencing-based diagnostics has been supported by evolving regulatory frameworks and clinical guidelines. Regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved several NGS-based companion diagnostics, ensuring their analytical validity and clinical utility.[30] Professional organizations, including the American College of Medical Genetics and Genomics (ACMG) and the National Comprehensive Cancer Network (NCCN), have issued evidence-based recommendations for the use of genomic testing in specific cancer types and clinical scenarios.[31,32] These developments underscore the importance of multidisciplinary collaboration among oncologists, pathologists, geneticists, and bioinformaticians to optimize the implementation and interpretation of genome sequencing results.

Ethical, legal, and social considerations surrounding genome sequencing in oncology warrant careful attention. Issues such as informed consent, data privacy, the management of incidental findings, and equitable access to genomic services must be addressed to maximize the benefits of precision oncology while minimizing potential harms.[33] Public and professional education, transparent communication, and stakeholder engagement are essential components of responsible genomic medicine implementation.[34]

In conclusion, genome sequencing-based cancer diagnostic methods represent a transformative advancement in oncology, offering unparalleled opportunities for precise, individualized patient care. The integration of NGS technologies into clinical practice has improved the detection of actionable mutations, informed prognostic assessments, guided targeted therapies, and facilitated the identification of hereditary cancer syndromes. While challenges related to cost, infrastructure, data interpretation, and ethical considerations persist, ongoing technological innovations, regulatory support, and capacity-building initiatives—such as the recently launched services by icddr,b—are paving the way for more accessible and effective genomic diagnostics. As the field continues to evolve, collaborative efforts among clinicians, researchers, policymakers, and patients will be vital in harnessing the full potential of genome sequencing to reduce the global burden of cancer.

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