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Advancement of next-generation sequencing in cancer research and clinical oncology

Nada Alshelali[1], Magdah Ganash[1], Mona Alharbi[1], Loubna Mira[2], Nadia Bagatian[2], Peter Natesan Pushparaj[2,*], Zeenat Mirza[3, 4,*] & Sajjad Karim[2]

[1]Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia; [2]Institute of Genomic Medicine Sciences, King Abdulaziz University, Jeddah, Saudi Arabia; [3]Eco Health Unit, King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia; [4]Department of Medical Laboratory Sciences, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Saudi Arabia; *Corresponding author

Affiliation URL:
https://www.kau.edu.sa/en

Author contact:
Nada Alshelali - E-mail: nalshelali0003@stu.kau.edu.sa

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Magdah Ganash - E-mail: mganash@kau.edu.sa
Mona Alharbi - E-mail: mgalharbi@kau.edu.sa
Loubna Mira - E-mail: lobnamira@hotmail.com
Nadia Bagatian - E-mail: nbaktian@kau.edu.sa
Peter Natesan Pushparaj - E-mail: pnatesan@kau.edu.sa
Zeenat Mirza - E-mail: zmirza1@kau.edu.sa
Sajjad Karim - E-mail: skarim1@kau.edu.sa

Abstract:
Cancer is a genomic disease driven by somatic and germline alterations, including single-nucleotide variants, indels, copy number alterations, structural variants, gene fusions, epigenetic changes and transcriptomic dysregulation. Advances in next-generation sequencing (NGS), including targeted panels, whole-exome and whole-genome sequencing, RNA sequencing, long-read technologies and single-cell approaches, have expanded genomic profiling and characterization of tumor heterogeneity. Integration with multi-omics and artificial intelligence supports molecular diagnosis, biomarker discovery, personalized therapy, inherited cancer-risk assessment, and minimal residual disease monitoring and treatment-resistance prediction. Thus, data shows the evolution and clinical applications of sequencing in oncology, highlighting its role in precision medicine and challenges involving analytical validity, variant interpretation, cost, data governance and clinical validation.

Keywords: Next-generation sequencing (NGS), cancer, genomics, whole-exome sequencing, precision oncology

Background:
Cancer comprises a heterogeneous group of diseases characterized by uncontrolled and sustained cellular proliferation **[1]**. It remains a major global health burden, with cancer incidence projected to increase substantially by 2050 and marked regional differences in the magnitude of this increase **(Table 1) [2-4].** The development of cancer is influenced by complex interactions among genetic susceptibility, environmental exposures, lifestyle factors and other biological determinants **[5]**. Established risk factors include elevated body mass index, tobacco and alcohol consumption, infectious agents, chemical exposures and ionizing radiation, many of which can contribute to DNA damage and genomic instability **[6].** The progressive accumulation of genetic and epigenetic alterations can promote tumor initiation, proliferation, invasion, metastasis and therapeutic resistance **[7]** Cancer treatment generally involves surgery, chemotherapy, radiotherapy, targeted therapy, immunotherapy, endocrine therapy, or combinations of these approaches, depending on tumor type, stage, molecular characteristics and patient-related factors **[8, 9]** . However, substantial intertumoral and intratumoral heterogeneity can limit therapeutic efficacy and contribute to treatment resistance **[10]**. Genetic alterations are central to many of the molecular pathways underlying tumor development and progression **[11]** Therefore, comprehensive characterization of cancer genomes is essential for understanding disease mechanisms, identifying biomarkers, facilitating drug discovery, informing clinical-trial design and guiding therapeutic decisions **[12]**. Sequencing technologies have become fundamental to these efforts by enabling systematic characterization of genomic and transcriptomic alterations **[13]**. In particular, NGS permits the simultaneous analysis of large numbers of genomic loci and has substantially expanded the ability to identify pathogenic variants, characterize tumor heterogeneity, investigate mechanisms of therapeutic resistance and monitor molecular changes during disease progression **[14, 15]**. Therefore, it is of interest to evaluate the role of latest next-generation sequencing technology in cancer research and clinical oncology.

Table 1: Estimated number of new cancer cases by region in 2050 and percentage increase from 2022

Region	Estimated Cases 2050	% Increase (2022–2050)
Asia	17,374,185	+76.8%
Europe	5,569,243	+24.6%
Northern America	3,979,416	+48.9%
Latin America and the Caribbean	2,871,263	+85.1%
Africa	2,837,336	+139.4%
Oceania	459,415	+70.7%

Evolution of next-generation sequencing:
The evolution of sequencing technologies from first-generation Sanger sequencing to modern NGS, long-read and single-cell platforms has fundamentally transformed cancer research and molecular oncology **[16].** NGS has shifted genomic analysis from individual genes toward comprehensive characterization of somatic and germline alterations and has enabled large-scale mutation discovery, multigene biomarker testing, molecular classification and increasingly individualized therapeutic decision-making **[17, 18]**. WGS, WES, targeted sequencing panels, RNA sequencing and epigenomic approaches each provide complementary information and can be selected according to the biological or clinical question. To overcome the limited throughput and read length of first-generation Sanger sequencing, sequencing technologies evolved toward massively parallel approaches collectively referred to as next-generation sequencing (NGS). These technologies enabled large-scale genome analysis and substantially reduced the time and cost required for genomic characterization **[19]**. NGS has subsequently become an important tool across a broad range of applications, from basic biological research to clinical diagnostics and can be applied to genomics, transcriptomics, epigenomics and metagenomics **[20]**. Second generation sequencing is based primarily on massively parallel sequencing of large numbers of

DNA fragments. Multiple sequencing reactions can therefore be performed simultaneously using approaches such as sequencing by synthesis and sequencing-by ligation. Representative platforms include the Roche 454 GS FLX, Illumina Genome Analyzer, Solids and Ion Torrent systems. These platforms differ in sequencing chemistry, read-length, error profiles, genome coverage, cost and processing time **[21]**. Among these platforms, Illumina sequencing has been widely adopted because of its high throughput and accuracy. In a typical Illumina workflow, DNA fragments are ligated to adapters and immobilized on a flow cell through complementary oligonucleotides. Solid phase amplification then generates spatially separated clonal clusters through bridge amplification **[22]**.Sequencing proceeds by synthesis using fluorescently labeled reversible-terminator nucleotides. During each cycle, incorporation of a nucleotide is detected through its fluorescent signal, after which the blocking group is removed to permit incorporation of the next nucleotide **[23]**.This iterative process enables highly parallel determination of DNA sequences. The continued development of sequencing technologies has expanded the capabilities of NGS beyond short-read sequencing. Single-molecule and long-read approaches can provide longer contiguous sequences and facilitate the characterization of structural variants, repetitive regions, complex genomic rearrangements and other alterations that can be difficult to resolve using conventional short-read approaches **[24]** .

Applications of NGS in genomics:

Cancer and other complex diseases are typically influenced by multiple genetic and environmental factors. Comprehensive genomic analysis therefore requires interrogation of both coding and non-coding regions of the genome **[25].** NGS can identify a broad spectrum of genomic alterations, ranging from single-nucleotide variants and small insertions or deletions to larger structural abnormalities, including duplications, inversions, translocations and other genomic rearrangements **[26]**.Whole-genome sequencing (WGS) provides the most comprehensive assessment because it interrogates coding and non-coding regions throughout the genome. However, its cost, computational requirements, data-storage demands and analytical complexity can remain important considerations in some settings **[27]**. Whole-exome sequencing (WES) provides a more focused alternative by targeting protein-coding regions, which comprise approximately 1–2% of the human genome and contain a substantial proportion of known disease-associated variants **[28]**. Consequently, WES has become an important approach for identifying coding variants in research and diagnostic applications. Targeted sequencing panels provide an additional strategy in which selected genes or genomic regions are analyzed at high depth **[29]**. Such panels can be particularly useful when the clinical or biological question involves a defined set of cancer-associated genes. The ability of NGS to multiplex large numbers of samples and genomic targets, combined with increasingly sophisticated bioinformatic pipelines, has facilitated the translation of genomic information into clinical and translational research **[30].** Beyond DNA sequencing, NGS-based approaches can characterize RNA expression, alternative splicing, fusion transcripts, non-coding RNAs, DNA methylation, chromatin accessibility and other molecular features. Integration of these datasets can provide a more comprehensive view of the molecular mechanisms underlying cancer development and therapeutic response **[31].**

NGS in epigenomics:

Epigenomics represents another important application of sequencing technologies. Epigenetic mechanisms regulate gene expression without altering the underlying DNA sequence and are essential for tissue-specific gene expression, cellular differentiation, X-chromosome inactivation, embryonic development and genomic imprinting **[32]**. Cancer cells frequently exhibit profound epigenetic alterations, including abnormal DNA methylation, histone modifications, chromatin remodeling and dysregulation of non-coding RNAs. These changes can influence tumor initiation, progression, metastasis and response to therapy **[33]**. NGS-based approaches enable genome-wide characterization of these alterations and can therefore contribute to the identification of disease-associated epigenetic biomarkers. Non-coding RNAs, including microRNAs, are particularly relevant because they can regulate gene expression post-transcriptionally and influence multiple cancer-associated pathways **[34]**. Their expression profiles and regulatory functions have consequently attracted substantial interest as potential diagnostic, prognostic and therapeutic biomarkers. The development of WGS and WES has also facilitated the transition from single-gene testing toward broader genomic profiling. Targeted NGS panels subsequently enabled simultaneous analysis of multiple clinically relevant genes, allowing more comprehensive characterization of molecular abnormalities within individual tumors **[35]**. Such approaches have contributed to the development of personalized genomic testing and increasingly support molecularly informed cancer management **[36]**.

NGS in cancer research and clinical oncology:

NGS has substantially transformed cancer research by enabling systematic characterization of the genomic alterations associated with tumor development and progression. Large-scale initiatives, including The Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC), have generated extensive genomic datasets that have contributed to the identification and characterization of recurrent molecular alterations across cancer types **[37]**. These large-scale datasets have facilitated the development of multigene sequencing panels and other genomic assays designed to detect clinically relevant alterations. Targeted NGS panels can simultaneously assess multiple cancer-associated genes and identify different classes of genomic alterations, thereby providing a more comprehensive molecular profile than conventional single-gene testing **[38]**. The clinical application of multigene testing has expanded considerably, particularly in solid and hematological malignancies. Early development of targeted NGS panels in cancers such as lung cancer showed the potential of multiplex

sequencing to identify therapeutically relevant alterations within a single assay. Subsequent approaches have incorporated increasingly broad gene sets and improved capabilities for detecting single-nucleotide variants, indels, copy-number changes and selected structural variants **[39].** NGS-based testing has also contributed to the identification of clinically relevant alterations in genes such as BRCA1, BRCA2, BARD1, CHEK2, NBN and TP53, among others, in breast, ovarian and other cancers **[19]**. Identification of such alterations can support risk assessment, molecular classification, therapeutic selection and, in appropriate settings, familial genetic counseling and testing. The clinical value of NGS extends beyond mutation detection. Molecular profiling can identify biomarkers associated with sensitivity or resistance to specific therapies and can therefore support treatment selection. Depending on the cancer type and clinical context, NGS results may contribute to decisions regarding targeted therapies, immunotherapies, endocrine therapies, or enrollment in biomarker-selected clinical trials. Thus, NGS has become an important component of precision oncology. Next-generation sequencing (NGS)-derived variant allele frequency (VAF) may provide valuable insights into tumor clonality and genomic heterogeneity, although its interpretation requires consideration of tumor purity and ploidy **[40].** Although bulk sequencing has generated extensive information about tumor genomes and transcriptomes, measurements from bulk specimens represent an average molecular profile across heterogeneous populations of cells.

Toward single-cell resolution: An emerging direction in cancer genomics:

Although bulk sequencing has generated extensive information about tumor genomes and transcriptomes, measurements from bulk specimens represent an average molecular profile across heterogeneous populations of cells **[41]**. This averaging can obscure biologically important differences among malignant cells and among immune, stromal, endothelial and other components of the tumor microenvironment. Tumor heterogeneity is particularly important because different cellular populations may exhibit distinct genetic alterations, transcriptional states, metabolic programs and responses to treatment **[42]**. Characterizing these populations is therefore essential for understanding tumor evolution, metastasis, therapeutic resistance and interactions within the tumor microenvironment. Single-cell sequencing technologies address some of these limitations by enabling genomic and transcriptomic features to be examined at the level of individual cells **[43]**. Single-cell RNA sequencing, for example, can identify distinct cellular populations and transcriptional states within tumors, whereas single-cell DNA sequencing can provide information regarding clonal architecture and genetic heterogeneity **[44, 45]**. The integration of single-cell sequencing with spatial and multi-omics approaches is further expanding the ability to investigate the relationships among tumor cells and their surrounding microenvironment **[46].** These technologies have therefore become important tools for dissecting tumor heterogeneity and identifying cell populations that may contribute to disease progression or therapeutic resistance. However, widespread clinical implementation of single-cell technologies remains challenging because of technical complexity, relatively high costs, variable sample quality, computational requirements and difficulties in standardization. For single-cell approaches, technical variability, limited detection of low-abundance transcripts and complex data analysis remain barriers to routine clinical implementation. More recent developments in single-cell sequencing have further demonstrated that tumor heterogeneity, clonal evolution, therapeutic resistance and interactions within the tumor microenvironment cannot be fully resolved through bulk molecular profiling alone. Consequently, most current applications remain concentrated in research and translational settings.

Conclusion:

Sequencing technologies have transformed cancer research and clinical practice by enabling comprehensive genomic profiling, molecular classification, biomarker discovery and personalized treatment. However, challenges remain in data interpretation, standardization, cost and clinical validation. Integrating sequencing with multi-omics, single-cell and spatial profiling and artificial intelligence may improve tumor characterization and accelerate precision oncology.

Conflicts of interest: The authors declare no conflicts of interest.

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