

## REVIEW

# Precision oncology: A narrative review of recent developments and challenges

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The mainstay generic therapies of cancer including chemotherapy, are partly effective in a subset of the patient population due to the complexity and heterogenous nature of the disease. Nevertheless, the inherent variability of cancer has steered cancer therapy towards the concept of precision medicine. The approach focuses on matching effective and accurate treatment on the genetic profile of a patient and different unique characteristics that distinguishes one patient from another. Currently, precision oncology has been driven by various innovations including liquid biopsy, next generation sequencing (NGS) and multi-omics integration. Recent advances in next generation-based sequences have enabled the analysis of analytes including circulating DNA and genomic DNA. Liquid biopsy has enabled minimal invasion alternative and real-time monitoring of tumour dynamics and analysis of treatment responses. Moreover, emerging technologies including artificial intelligence and nanotechnology has enhanced the sensitivity of liquid biopsy. Similarly, multi-omics integration offers insights into the interactions between transcriptomic, proteomic, epigenomic and genomic enabling the unravelling the complex molecular mechanism driving carcinogenesis. These advances have resulted in the discovery of novel biomarkers and diverse therapeutic targets for different types of cancers. However, despite the promising advancements, challenges remain, such as concerns on data privacy, need for clinical validation and computational limitations. Ongoing research is, therefore, critical to embrace precision oncology in routine clinical care.

**Keywords:** precision oncology, liquid biopsy, next-generation sequencing, multi-omics

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## Introduction

The advancements of precision oncology, a paradigm shift that tailors therapeutic approaches based on the distinct molecular features of a tumour, has significantly transformed cancer treatment and management. The concept of precision medicine in oncology can be traced back to the application of hormonal therapy for breast cancer whereby the efficacy of the treatments was determined by the prediction value of certain hormone receptor expression patterns [1]. As a result, the introduction of targeted medication, such as trastuzumab for breast cancer validated the molecularly targeted approach and fuelled the advancement of cancer therapy driven by specific targets [1,2].

Unlike traditional approaches that primarily rely on the tumour's tissue of origin, precision oncology integrates molecular profiling to identify specific genomic aberrations and match them with targeted therapies. This approach has been made possible by advances in large-scale DNA and RNA sequencing technologies, enabling researchers to uncover actionable mutations and optimize personalized treatment strategies [3].

The molecular alterations driving tumorigenesis are highly diverse, necessitating a deeper understanding of cancer pathophysiology. Emerging molecular analysis techniques including multi-omics have fuelled extensive research aimed at refining and expanding the application of precision oncology. By identifying tumour-specific pathways and therapeutic targets, precision medicine has

rapidly gained acceptance in clinical practice, offering patients more effective and individualized treatment options [3]. However, while this approach is often regarded as a breakthrough in cancer management, it also demands a thoughtful and critical evaluation to assess its broader implications and challenges within the clinical and scientific communities.

## Recent Developments

### Next-Generation Sequencing

Next-generation sequencing, a high throughput DNA sequencing methodology, analyses DNA regions of interest to accurately determine the nucleotide sequence. Various types of analyses apply NGS including Whole Exome Sequencing (WES), multigene panel testing, and Whole Genome Sequencing (WGS) (Georget and Pisan). Building on a foundation laid by Sanger sequencing in the early 2000s, the first generation of NGS sequencer was based on pyrosequencing, a sequencing-by-synthesis approach that quantitatively detects the real time incorporation of nucleotide by monitoring light signal emitted when a nucleotide is added to the growing DNA strand [4].

The NGS workflow begins with sample and library preparation, where DNA or RNA is extracted, purified, and amplified using PCR to create an amplicon sequencing library. Through multiplexing, numerous samples are combined by labelling each with a unique barcode thereby allowing efficient processing. A sequencing of template is formed by attaching the library attached to a solid substrate and amplifying it. The chip is thereafter inserted into the sequencer, which reads the sequence of each amplicon and

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sends the data digitally. The integrated analysis software finally assembles the sequences, identifies variations, and matches them to known biomarkers, therapies clinical trials, and guidelines to help interpret the results [5]. Figure 1 shows a simplified workflow chart of the NGS process.

Next-generation sequencing (NGS) has transformed genomic-driven personalized oncology by enhancing identification of somatic driver mutations, germline mutations, mutational burden quantification, and associated resistance mechanisms [6]. As such the approach enables rapid and accurate identification of multiple genetic aberrations within neoplasms facilitating accurate diagnosis and treatment selection [7].

Previous studies have reported the efficacy of NGS in detecting clinically actionable mutations in patients with cancer [7]. The Genomics Evidence Neoplasia Information Exchange (GENIE) consortium demonstrated that more than 30% of sequenced tumours had mutations that could be targeted by the current therapies [8]. Moreover, sequencing-guided therapy has been associated with improved patient outcomes, including enhanced progression-free survival (PFS) and overall response rates. To demonstrated this, Tsimberidou et al. reported that targeted therapies significantly improved outcomes [9]. Patients who received guided sequencing therapy, exhibited a higher overall response rate (27% vs. 5%), longer median time to treatment failure (5.2 vs. 2.2 months), and improved median survival (13.4 vs. 9 months) compared to those whose treatment did not match their tumour mutations. Similarly, Radovich et al. reported significant improvements in PFS ratio and median PFS for genomically guided patients with refractory metastatic cancer [3].

NGS plays a pivotal role in drug development by identifying tumour-associated mutations. For example, the effectiveness of PD-1 blockade therapy was demonstrated in diverse tumours characterized by mismatch repair deficien-

cy. The findings led to FDA approval of pembrolizumab as the first cancer drug approved solely based on genetic mutation rather than tumour histology [10]. Additionally, LOXO-195 has shown promising efficacy in overcoming acquired resistance outcomes that are mediated by recurrent kinase domain mutations across multiple tumour types [11].

Moreover, approvals have been awarded for various NGS test (Table 1). The NGS test include MSK-IMPACT, which offers information on microsatellite instability and somatic mutations. The FoundationOne CDx test can be used to classify a patient to 15 various targeted therapies for 5 tumour types. The Oncomine Dx Target Test can identify mutations in 23 genes in neoplastic cells from patients with non-small cell lung cancer [12].

Next-generation sequencing has revolutionized precision oncology, however, it is limited by various significant challenges. Privacy and ethical concerns arise from the massive amounts of data generated, necessitating careful management of data protection, informed consent, and result communication [31].

First, NGS may not wholly replace the well standardised and evidenced-based histopathological diagnoses. Tumour histology is the premise upon which the current predictive, diagnostic and prognostic tools are rooted. Though NGS can help with identification and subtyping of different tumours, its clinical applications should be done in tandem with other clinical procedures to achieve a precise pathological assessment [1]. Second, NGS provides a low spatial and temoral resolution of the whole tumour as it can only assess RNA and DNA changes in a small tumour cell subset at any given timepoint. Better spatial resolutions can be achieved through novel techniques [35], single-cell sequencing, serial analysis of circulating cell-free nucleic acids or tumour cells [36,37] or by focusing on actionability of individual targets via functional studies.

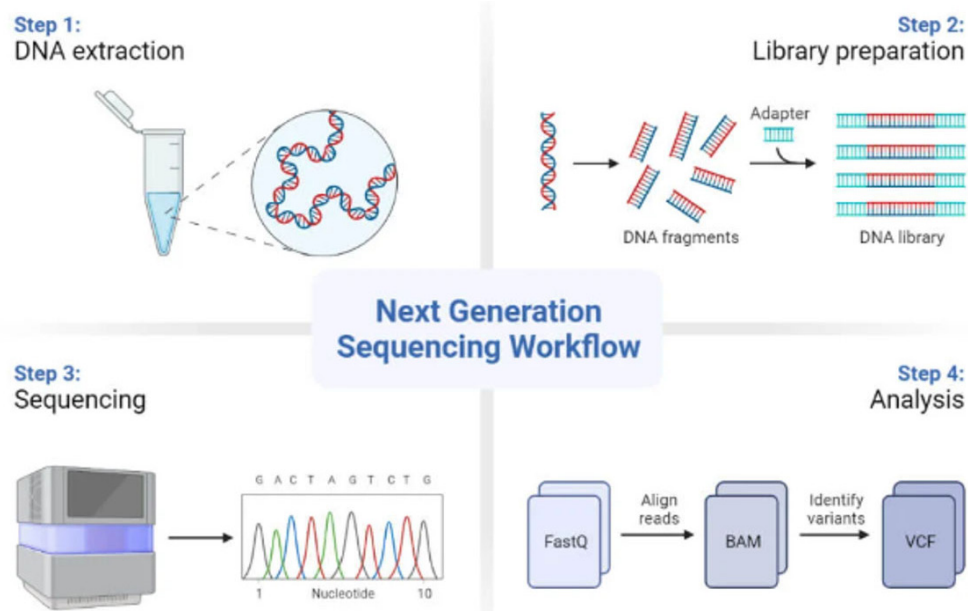


Fig. 1. A simplified workflow chart of the NGS process. It has 4 steps: sample extraction, library preparation, sequencing, and analysis

Table 1. FDA approved NGS tests

| Test                      | Developer                 | No. of targeted genes/target genes   | Description/Outcome                                                                                                                                                                                            |
|---------------------------|---------------------------|--------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Oncomine Dx Target Test   | Thermo Fischer Scientific | 23                                   | Detects mutations in BRAF, EGFR, ERBB2 and IDH 1 genes and chromosomal abnormalities caused by translocation in RET and ROS1 gene from patients with cholangiocarcinoma and non-small cell lung cancer (NSCLC) |
| MSK-IMPACT                | Zehir                     | 468                                  | Identifies somatic mutations, mutation signatures and microsatellite instability                                                                                                                               |
| FoundationOne CDx         | Foundation medicine       | 324                                  | Analysis of tumour mutational burden and microsatellite instability to inform immunotherapy decisions                                                                                                          |
| FoundationFocus CDxBRCA   | Foundation Medicine       | 2                                    | Detects BRCA1/2 mutations in ovarian cancer                                                                                                                                                                    |
| ClonoSEQ                  | Adaptive biotechnologies  | Targets T-cell receptor genes        | Detecting and quantifying minimal residue disease from patients with acute lymphoblastic leukemia, multiple myeloma, relapse free survival, and event free survival.                                           |
| Praxis Extended RAS Panel | Illumina                  | Detects mutations in RAS gene family | Detects 56 specific mutations in RAS genes in patients with metastatic colorectal cancer<br>A companion analytical for panitumumab                                                                             |

Liquid Biopsy

Liquid biopsy has transformed precision oncology by providing a non-invasive alternative to traditional tissue biopsy. By analysing biofluids such as blood, saliva, urine, and cerebrospinal fluid, this technique enables the detection of circulating biomarkers, including miRNAs, extracellular vesicles, circulating tumour cells, and circulating tumour DNA (ctDNA). This approach minimizes patient discomfort, and the risks associated with invasive biopsies, while offering real-time tumour profiling [13].

Although tissue biopsy remains the gold standard for molecular evaluation of solid tumours, liquid biopsy serves as a valuable complementary tool. It is increasingly used for treatment selection, monitoring treatment responses, tracking cancer evolution and prognostication. Moreover, it has been utilized in the identification of targetable genetic variants in cancer thereby guiding treatment in the absence of tissue samples [14].

Recent advancements have significantly improved liquid biopsy technology, particularly in detecting EGFR mutations in plasma cell-free DNA (cfDNA) from patients with advanced non-small cell lung cancer (NSCLC). This breakthrough has led to the development of several ctDNA-based companion diagnostic (CDx) tests including early PCR-based tests, such as Cobas EGFR Mutation Test v2, detect EGFR exon 21 L858R mutations and exon 19 deletions, enabling targeted treatment with tyrosine kinase inhibitors [15]. Similarly, the *therascreen PIK3CA* RGQPCR Kit detects *PIK3CA* mutations in ctDNA, guiding breast cancer treatment with alpelisib. More advanced NGS-based liquid biopsy panels, such as FoundationOne Liquid CDx and Guardant360 CDx, now allow comprehensive genomic profiling, further advancing precision oncology.

Liquid biopsy has been employed in the detection of EGFR mutation in plasma cell-free from patients with non-small cell lung cancer (NSCLC). As a result, it has led to the development of various ctDNA-based companion diagnostic (CDx) tests which are PCR-based including exon 19 deletion, detect EGFR exon 21 L858R mutations and Cobas EGFR Mutation Test v2 enhancing treatment with tyrosine kinase inhibitors [15]. In addition, identification of *PIK3CA* mutations in ctDNA by the *therascreen*

*PIK3CA* RGQPCR Kit has enabled guided breast cancer therapy with alpelisib. Similarly, liquid biopsy has shown high sensitivity on the identification of oestrogen receptor 1 (*ESR1*) mutations, a driver of endocrine resistance in breast cancer [16]. More advanced techniques including Guardant360 CDx and FoundationOne Liquid CDx has enabled thorough genomic profiling thereby advancing precision oncology.

In addition, single-cell and PCR-based analyses have demonstrated to be effective in understanding the transcriptional, genetic and epigenetic diversity of neoplasm [17]. The single-cell techniques allow the identification of rare tumour populations and diverse molecular changes that might have been undetected in mass sequencing. For example, Fedyuk et al. developed a single molecule multiparametric assay that even at early diseases stages, can profile neoplasm epigenetics with high sensitivity [18].

Continuous discovery of novel of tumour biomarkers such as extracellular vesicles, epigenomes, and proteomes play a significant role in the advancement of liquid biopsy. The profiling of proteomes has been improved with the advent of high sensitivity LC-MS/Ms instruments that have enhanced reproducibility and data accuracy. Similarly, DNA methylation and histone modifications, forms of epigenetic alterations provide significant insights into tumour development and progression [18]. Emerging technologies, particularly nanotechnology have refined the application of liquid biopsy [19]. The nanoparticle-based approach has been reported to improve the stability, sensitivity and detection efficiency of biomarkers enabling detection of the markers even at ultra-low levels.

The integration of artificial intelligence in liquid biopsy has enhance data interpretation, predict disease progression and detection of disease patterns that are critical for personalized oncology. The AI-driven models have assisted in the streamlining of volume of complex data, consequently optimizing clinical decision-making [20, 21].

Liquid biopsy is also facilitating the real-time neoplasm monitoring and individualized treatment selection further refining cancer diagnostics and improvement of therapeutic outcomes thereby enhancing patient survival. Moreover, leveraging NGS through liquid biopsy has been confirmed as a transformative tool for tumour detection, monitoring

and therapy selection. Such broad-spectrum analyses are important for detecting actionable mutations, assisting in selection of targeted treatments [3].

Liquid biopsy holds important promise in detection of minimal residual disease. Minimal residual disease refers to the small number of tumour cells that may remain in the body after treatment. These cells can lead to clinical relapse of the tumour [38, 39]. The suitability of liquid biopsy for monitoring minimal residual disease is attributed to its ability to detect even the smallest amounts of tumour-associated genetic materials in body fluids [40]. However, this technique has some limitations, particularly in areas with a low tumour burden [41]. For these cases, the levels of circulating tumour DNA or circulating tumour cells may not be adequate for precise detection. This holds for tumours such as pancreatic cancer, early-stage lung cancer, colorectal cancer, localized prostate cancer and ovarian cancer, where low tumour burden may limit the effectiveness and sensitivity of liquid biopsy for monitoring tumour progression and detection of minimal residual disease [42,43]. Given these limitations, the low concentrations of circulating tumour DNA in blood raises questions about the specificity and sensitivity of liquid biopsy in clinical applications.

Multi-omics Integration

Multi-omics techniques have advanced precision oncology by offering a deeper understanding of tumour biology by integrating diverse biological datasets. Pathogenesis of tumour is driven by intricate alterations at the transcriptional, genetic, proteomic and metabolic levels, all of which contribute to tumorigenesis [22]. By simultaneously analysing transcriptomics, genomic, proteomic, epigenomic and metabolomic data, it has facilitated the characterization of tumours at unprecedented resolution and scale, offering valuable insights into tumour behaviour, heterogeneity, evolution, and microenvironment interactions thereby enhancing advance of precision cancer management strategies [24]. For example, Dong et al. employed an integrated

approach by combining transcriptomic, phosphoproteomic, genomic, and proteomic datasets to detect underlying molecular mechanisms and subgroups in bile duct cancer that could not be identified using a single-omics method [25] (Figure 2???)

Moreover, multi-omics have played a critical role in establishing potential targets biomarkers associated with the initiation and progression of cancer [26]. For instance, genomic characterization of breast cancer has given critical insights into diverse mutations that drive tumorigenesis [27]. Similarly, Sun et al. analysed proteins that are linked to colorectal cancer risk, offering new perspectives on disease aetiology, development of screening biomarkers and therapeutic targets [28]. Li et al. applied multi-omics profiling to colorectal cancer patients, demonstrating that network analysis, combined with phosphoproteomics and proteomics data, provides accurate information on drug responses [29]. Their findings emphasized the importance of analysing metastatic tissues for effective personalized treatment strategies.

Furthermore, multi-omics integration has enabled the detection of various molecular alterations driving tumorigenesis, further advancing the field of precision oncology. Bertucci et al. identified high mutation frequencies in nine key driver genes, including *GATA3*, *ESR1*, *RB1*, *TP53*, and *AKT1*, in metastatic breast cancer [27]. Knisbacher et al. combined epigenomic, genomic, and transcriptomic data from patients with chronic lymphocytic leukaemia, and discovered 109 new genetic drivers of the tumour [30]. This study allowed for sub-categorization of the tumour, with these genetic factors proving to be independent prognostic markers. Revelation of the heterogeneity found within neoplasms has paved the way for more targeted and personalized therapeutic strategies. As multi-omics research continues to evolve, its role in advancing precision oncology is expected to further refine treatment strategies, informing more effective and targeted cancer management [24] (Table 2???)

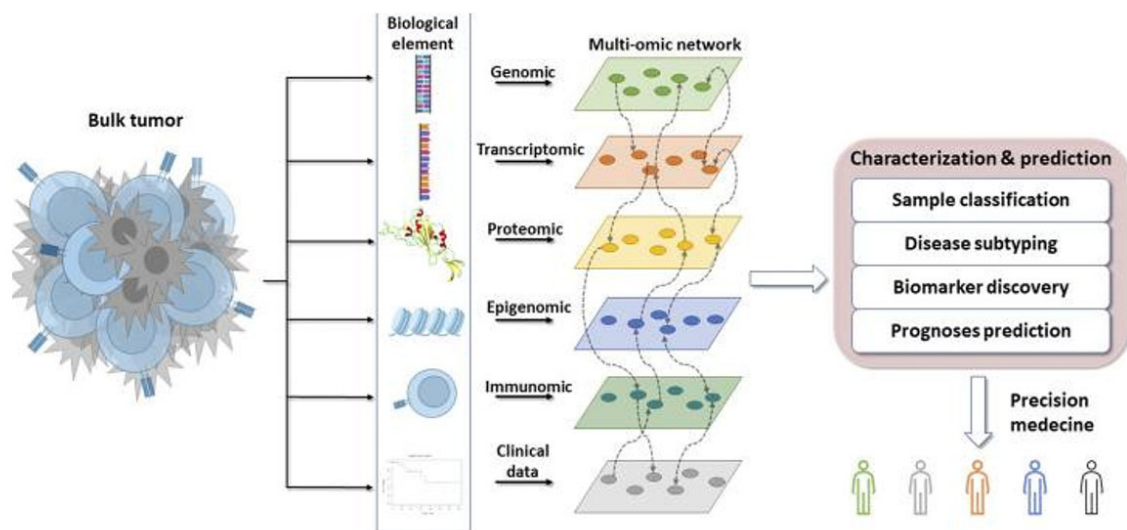


Fig. 2. Overflow of the multi-omics integration for precision oncology [23]



Table 2. Applications of multi-omics in gene detection

| Author/ Year                | Type of cancer                                    | Data type                                                              | Outcome                                                                                                                                                                                                                             |
|-----------------------------|---------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sun et al. 2023 [28]        | Colorectal cancer                                 | Protein quantification trait loci                                      | Elevated levels of two proteins (GREM1 and CHRDL2) and suppressed levels of 11 others were associated with increased risk of colorectal cancer. Four proteins, CD86, MMP2,POLR2F and CSF2RA have been targeted for drug development |
| Dong et al. 2022 [25]       | Bile duct cancer/ intrahepatic cholangiocarcinoma | Integrative proteomics, genomic, phosphoproteomics and transcriptomics | Co-mutation of TP53 and KRAS enhanced tumour metastasis; identified biomarkers (HKDC1 and SLC16A3) that predict clinical outcomes of the disease; identified 4 groups with specific biomarkers with potential therapeutics.         |
| Bertucci et al. 2019 [27]   | Breast cancer                                     | Whole exome sequencing                                                 | Identified genes that are frequently mutated in metastatic breast cancer such as TP53, ESR1, KMT2C and GATA3                                                                                                                        |
| Knisbacher et al. 2022 [30] | Chronic lymphocytic leukemia (CLL)                | Genomic, epigenomic and transcriptomic                                 | Identified 109 new drivers for chronic lymphocytic leukemia.                                                                                                                                                                        |
| Li et al. [29]              | Colorectal cancer                                 | Genomic, proteomics and phosphoproteomics                              | Identified kinase-substrate correlations as accurate indicators of drug response for potential treatment.                                                                                                                           |

Multi-omics holds significant promise in tumour diagnostics, however, to realize its potential, there are various challenges that should be addressed. First, there is a challenge with regards to standardization of data collection and analysis procedures across different research institutions and omics layers [24, 44]. Computational challenges include big data handling and algorithmic problems [32]. Setting up large-scale data analysis workflows requires substantial bioinformatics expertise, involving tool selection, high-performance computing implementation, automation strategies, and data storage solutions [33]. As the new technologies expand into clinical diagnostics, they will enable personalized therapeutic approaches but introduce new technological, legal, and ethical challenges [34]. The reproducibility and reliability of multi-omics studies is dependent on standardized quality control measures and protocols. Second, to handle the high complexity and dimensionality of multi-omics data, there is need for development of robust statistical tools and methods. Sophisticated statistical methods will be essential for accurate interpretation of these data to imform meaningful conclusions [24, 44].

Future advancements in technology and methodologies will address these challenges, enhancing the accessibility and effectiveness of personalized medicine [34]. Successful implementation of multi-omics in precision medicine demands rigorous validation, real-world applications, and seamless integration into existing healthcare infrastructures [24].

Future prospects in precision oncology

Advances in molecular approaches have enabled the precise characterization of human tumours, while the elucidation of novel drug targets, an aspect of precision oncology, has improved drug response rates and alleviated safety concerns for some patients. However, accessing precision medicine is still a challenge for some cancer patients [45]. Standardization of experimental as well as reporting approaches requires global collaborations, while establishment of clinical cutoffs in biomarker analyses will reduce the noise obtained from data in various clinical studies [45,46]. Moreover, there is need for intelligent techniques to molecular profiling. One day, comprehensive multi-omics profiling

for the vast majority of patients may be possible, however, the outcomes are likely to be impractical or irrelevant in real-world settings. Therefore, performing the right tests for the appropriate biomarkers at the right time will be beneficial for some patients.

Efforts should also be aimed at ensuring that all patient populations have representative molecular datasets in designated databases, and that they have easy access to suitable molecular tests. Moreover, novel targeted therapeutic approaches should be denoted for the “hard-to-treat” tumor types [47]. For product developers, pathologists, cell and molecular biologists, oncologists, payers, government bodies and patients, interdisciplinary communication is required. This can be realized through enhanced awareness and literacy about molecular oncologic approaches and their clinical applications [48]. Finally, the evolution of ethical guidelines should match the pace at which technological advances are occurring. This will improve patient privacy and safety [46,47]. Addressing these challenges will inform appropriate development of appropriate disease diagnosis methods, drug discovery, treatment decisions and improve precision oncology for cancer patients.

Conclusion

Precision oncology has revolutionized cancer treatment by shifting focus to personalized therapeutic strategies based on the molecular profile of individual tumours. Technologies including NGS, liquid biopsy, and multi-omics integration have accelerated the clinical application of precision oncology and significantly enhanced the detection of actionable mutations, unveiled tumour heterogeneity, and develop targeted therapies. Such advancements have improved clinical outcomes, as demonstrated by increased progression-free survival and overall response rates in patients receiving genomically guided treatments.

Despite its transformative impact, precision oncology faces notable challenges including ethical concerns, data privacy, computational demands, and the need for integration into healthcare systems. Addressing these hurdles requires a multidisciplinary approach involving robust bioinformatics support, clear ethical frameworks, and continued research.

## Authors' contribution

CM (Conceptualization; review of literature; writing-original draft; writing-review and editing)

JW (Conceptualization; review of literature; Writing-review and editing)

## Conflict of interest

The authors declare no conflict of interest.

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