# Genomic Profiling for Precision Cancer Therapies

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## Abstract

This review explores the transformative impact of genetic profiling on precision cancer medicine, shedding light on its methodological intricacies and implications for clinical oncology. Genetic profiling involves a comprehensive analysis of cancer DNA to identify specific genetic alterations, mutations, and biomarkers that drive tumor behavior. Among the advanced methodologies, next-generation sequencing (NGS) has revolutionized genomic profiling by enabling rapid and cost-effective whole-genome sequencing. NGS provides clinicians with detailed molecular insights into cancer, allowing the identification of unique genetic fingerprints and the formulation of personalized treatment strategies. The review highlights the clinical applications of genomic profiling, emphasizing its role in detecting actionable genetic abnormalities that support tailored therapeutic decisions, moving away from conventional, uniform treatment approaches. Personalized cancer care based on genomic profiling offers profound benefits, including enhanced therapeutic efficacy and reduced side effects through alignment of treatments with the individual genetic landscape of a patient's cancer. Additionally, the broader implications for healthcare systems are discussed, focusing on the necessity for global standardization, interdisciplinary collaboration, and the development of robust infrastructure to optimize precision cancer therapy. The paper underscores the importance of ongoing research, technological advancements, and strategic partnerships in establishing genetic profiling as an integral component of routine clinical practice. In conclusion, genetic profiling is positioned as a cornerstone in modern oncology, fundamentally transforming patient outcomes and therapeutic paradigms. This review advocates for its continued integration into clinical practice to usher in a new era of precision cancer care.

**Keywords:** Genomic Profiling, Precision Cancer Therapies,. Next-Generation Sequencing (NGS), Personalized Medicines

***Significance*** | Genetic profiling revolutionizing precision cancer therapies, offering personalized treatments and reshaping oncology's development for enhanced patient outcomes.

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## 1. Introduction

Precision oncology is revolutionizing the treatment of cancer by leveraging molecular insights to better understand and target the mechanisms underlying tumorigenesis and progression. Advances in this field have significantly enhanced our comprehension of pro-oncogenic pathophysiologic pathways, enabling interventions that may disrupt these processes (Malone et al., 2020). Several key developments have contributed to this paradigm shift.

First, next-generation sequencing (NGS) has transformed molecular diagnostics by making the analysis of genetic data both rapid and cost-effective, facilitating its integration into routine clinical practice (Brown & Elenitoba, 2020). Second, decades of experimental research have elucidated critical oncogenic pathways, including cancer-host interactions, driver mutations, and tumor-suppressive mechanisms that fail in the immune response to cancer (Mateo et al., 2022). Third, innovations in drug development—such as monoclonal antibodies and tyrosine kinase inhibitors—have enabled the targeted disruption of specific

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molecular pathways, allowing for the design of personalized treatment strategies based on a patient's unique genetic alterations (Dugger et al., 2018).

This review aims to provide a comprehensive overview of personalized cancer treatment, with a focus on molecular diagnostics and their application in tumor-agnostic therapeutic decision-making. It explores the role of genomic profiling in identifying actionable mutations and tailoring therapies, while highlighting the challenges and future directions for precision oncology. By addressing the integration of precision medicine into clinical research and practice, the review emphasizes both achievements and obstacles, proposing strategies for overcoming barriers to its widespread adoption.

Through this analysis, we aim to underline the transformative potential of molecular profiling in clinical oncology and its pivotal role in advancing individualized cancer care. The findings of this review underscore the necessity for continued innovation, interdisciplinary collaboration, and infrastructure development to fully realize the promise of precision oncology.

## 2. The Precision Oncology Paradigm

The precision medicine approach seeks to revolutionize healthcare by utilizing detailed patient-specific information to guide disease prevention, diagnosis, and tailored treatment (Collins & Varmus, 2015). Oncology has emerged as a leader in this paradigm, as cancer is fundamentally a disease of accumulated genetic abnormalities (Tsimberidou et al., 2020). Historically, cancer treatments relied on cytotoxic chemotherapies, with therapeutic choices dictated primarily by tumor location and histology. However, the late 1990s marked a turning point with the development of the first molecularly targeted therapies, driven by advancements in genetic research techniques such as polymerase chain reactions.

The successful introduction of targeted therapies like the BCR-ABL tyrosine kinase inhibitor imatinib and the monoclonal HER2-antibody trastuzumab heralded a new era of molecularly stratified cancer treatment (Druker et al., 2001). These breakthroughs were complemented by the advent of next-generation sequencing (NGS), which transformed molecular profiling by drastically reducing costs and turnaround times while enabling the simultaneous analysis of numerous genes with high accuracy (Berger & Mardis, 2018). Unlike traditional sequencing methods, NGS paved the way for large-scale projects such as The Cancer Genome Atlas, which provided comprehensive genomic characterizations of various tumors, deepening our understanding of oncogenesis and cancer evolution (Weinstein et al., 2013).

These advancements revealed recurring genetic alterations across different cancer types, many of which were identified as potential therapeutic targets. Consequently, a rapidly expanding arsenal of targeted therapies has been developed to address specific genetic modifications, including mutations, rearrangements, and amplifications. These treatments have been successfully implemented in clinical practice for cancers such as biliary tract cancer (Lamarca et al., 2022), colorectal cancer (Gutierrez et al., 2019), and non-small cell lung cancer (Planchard et al., 2018).

The precision oncology paradigm has reached a new milestone with the approval of tumor-agnostic therapies, which are designed to target specific molecular alterations regardless of cancer histology or tissue of origin. This breakthrough represents a significant step toward fully personalized cancer treatment strategies (Looney et al., 2020).

The integration of NGS technology into standard clinical workflows continues to drive progress in precision oncology, enabling molecularly guided treatment decisions that improve outcomes across diverse tumor types. With ongoing advancements in genomic research and targeted therapy development, precision oncology is reshaping cancer care, offering hope for more effective and individualized interventions.

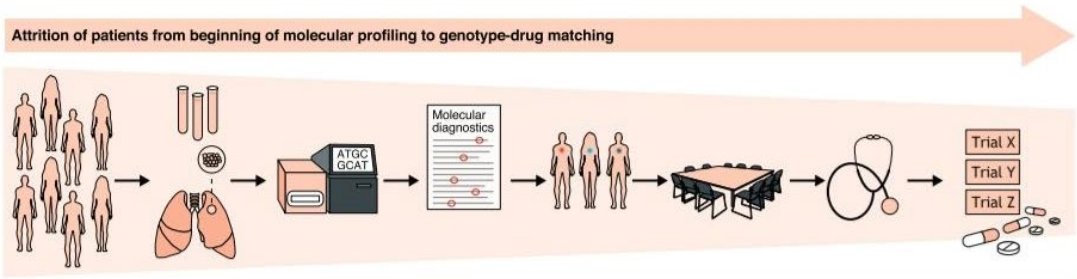
## 3. Integration of Precision Oncology in Patient Care

The concept of cancer-agnostic, molecularly guided treatment is promising, yet its clinical implementation faces several significant challenges. One of the most complex obstacles is the multistep process of linking identified molecular changes to targeted therapies (Horak et al., 2022). This process begins with critical decisions, such as determining whether molecular profiling should depend on the patient's overall health status, when to initiate profiling during the treatment journey, whether liquid biopsy or tumor re-biopsy is necessary, and which diagnostic genetic analyses to perform.

Subsequent steps involve close collaboration between pathologists and geneticists to manage variant calling, next-generation sequencing (NGS) analysis, bioinformatic data processing, and the functional assessment of identified genetic alterations (Li et al., 2017). Each stage of this complex workflow introduces specific challenges and potential risks, which are discussed in more detail in related reviews.

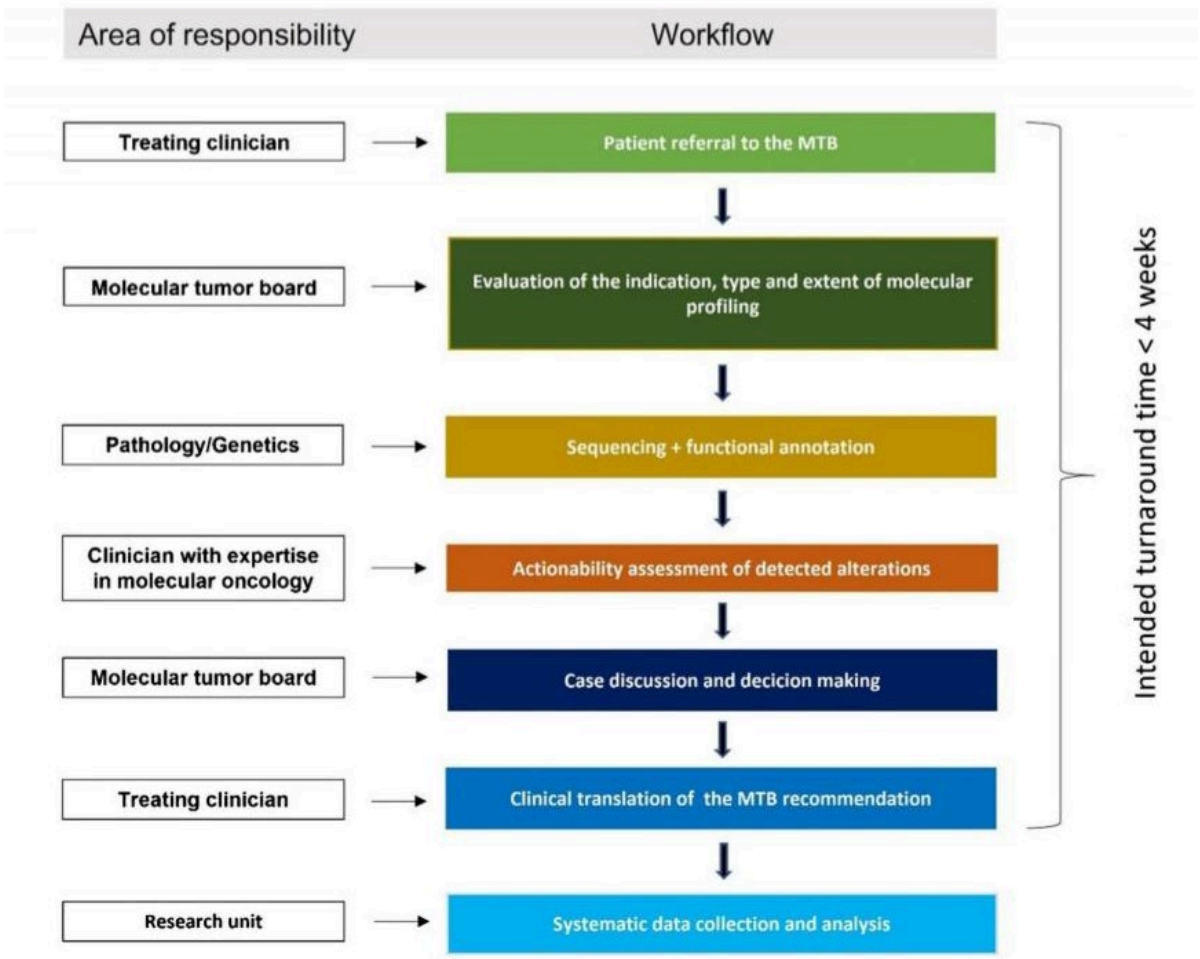
From an oncologist's perspective, however, the most critical and least defined step in precision oncology is the final phase: clinical annotation and the assessment of clinical actionability for discovered genetic alterations. This step determines whether specific genetic findings can guide therapeutic decisions, making it essential for translating molecular data into patient outcomes.

This review focuses on the clinical application of tailoring cancer treatments to each patient's unique genetic profile. Key considerations include identifying appropriate patients for long-term precision care, selecting optimal diagnostic strategies, and assessing biomarker actionability to guide therapeutic decisions.




| | Patient accrual | Sample collection | Laboratory operations | Variant interpretation | Clinical utility | Decision | Clinical interpretation | Trial matching |
|---|---|---|---|---|---|---|---|---|
| **Examples of challenges** | Patient factors: medical, logistics | Inadequacy of samples for profiling | Technical issues of NGS and other assays | Challenges with variant interpretation | Low rate of actionable results | Lack of access to MTB | Physician factors: busy clinics, lack of genomic understanding | Lack of access to drugs or clinical trials |
| **Possible solutions** | Appropriate patient selection, navigators, efficient consent and IRB aprocesses | Improvement in sample collection and processing, liquid biopsies | Advances in technology including limits of detection and coverage depth | Integrated knowledge bases, artificial intelligence tools for automation | Expansion of target identification beyond genomics | Increase availability to MTB e.g. virtual MTB | Navigators and tools to help physicians manage profiling results | Increase number and access to precision medicine trials; easier access to approved drugs |

**Figureure 1.** The process from genetic sequencing of patients to enrollment on genotype-matched clinical trials. MTB, molecular tumor board; IRB, Institutional review board; NGS, next-generation sequencing




**Figureure 2.** Precision oncology workfow according to a standardized Molecular Tumor Board at the university hospital of the Medical University of Graz

**Table 1.** Overview of molecular targets with approved biomarker guided therapies in solid cancers. FISH fuorescence in situ hybridization, IHC Immunohistochemistry, NSCLC non-small-cell lung cancer

| Target | Type of alteration | Method of testing | Approved drugs | Clinical indication |
|---|---|---|---|---|
| ALK | Gene fusion | RNA sequencing<br>IHC screening | Alectinib<br>Brigatinib<br>Ceritinib<br>Crizotinib<br>Lorlatinib | NSCLC |
| BRAF | Mutation | DNA sequencing | Dabrafenib<br>Encorafenib<br>Vemurafenib | Anaplastic thyroid carcinoma Colorectal cancer<br>Malignant melanoma<br>NSCLC |
| BRCA | Mutation | DNA sequencing | Niraparib<br>Olaparib<br>Platinum chemotherapy<br>Rucaparib<br>Talazoparib<br>Veliparib | Breast cancer<br>Ovarian cancer<br>Prostate cancer |
| EGFR | Mutation | DNA sequencing | Amivantamab<br>Erlotinib<br>Geftinib<br>Osimertinib | NSCLC |
| ERBB2 | Overexpression<br>Amplifcation<br>Mutation | IHC<br>FISH<br>DNA sequencing | Lapatinib<br>Neratinib<br>Pertuzumab<br>Trastuzumab<br>Trastuzumab-emtansine<br>Trastuzumab-deruxtecan | Breast cancer<br>Colorectal cancer<br>Esophageal cancer<br>Gastric cancer<br>NSCLC |
| FGF(R) | Mutation<br>Gene fusion | DNA sequencing<br>RNA sequencing | Erdaftinib<br>Futibatinib<br>Pemigatinib | Biliary tract cancer<br>Urothelial cancer |
| Homologous recombination defciency | Genomic instability | DNA sequencing | Niraparib<br>Olaparib<br>Platinum chemotherapy<br>Rucaparib<br>Talazoparib<br>Veliparib | Ovarian cancer<br>Prostate cancer |
| KIT | Mutation | DNA sequencing | Imatinib | GIST |
| MET | Amplifcation<br>Mutation | FISH DNA sequencing | Cabmatinib<br>Tepotinib | NSCLC |
| Microsatelitte instability / Mismatch repair defciency | Genomic instability | DNA sequencing<br>IHC | Pembrolizumab | Tumor agnostic |
| NTRK | Gene fusion | RNA sequencing<br>IHC screening | Entrectinib<br>Larotrectinib | Tumor agnostic |
| PDGF(R) A | Mutation | DNA sequencing | Avapritinib | GIST |

Additionally, we showcase the workflow of a standardized molecular tumor board (MTB) at a leading academic center in Austria (Figure 2). This MTB serves as a model for integrating genomic cancer sequencing into clinical care, emphasizing outcome-centered approaches to optimize patient outcomes.

By addressing these challenges, precision oncology continues to advance toward routine clinical application, offering transformative potential in cancer treatment.

## 4. Who Shall We Test, When Shall We Test, and How Shall We Test?

Molecular profiling in unselected cancer patients does not consistently identify actionable targets, limiting its routine clinical applicability (Haslam et al., 2021). Consequently, the European Society for Medical Oncology (ESMO) recommends multigene next-generation sequencing (NGS) testing only for specific cancers, such as advanced non-small-cell lung cancer, prostate cancer, ovarian cancer, and cholangiocarcinoma. For advanced colorectal cancer, multigene NGS testing is considered an alternative to single-gene polymerase chain reaction testing if additional costs are acceptable (Mosele et al., 2020). However, genome-guided individualized therapies are generally not advised outside academic programs and should only be conducted when the results are likely to influence clinical management (Colomer et al., 2020).

Despite these guidelines, leading academic institutions in the USA and elsewhere advocate for early and comprehensive germline and tumor genetic analysis for almost all cancer patients, although this practice remains contentious (Subbiah et al., 2023; Sorscher, 2023). A critical first step in genomic cancer sequencing is the clinical assessment of whether molecular profiling is warranted. It is neither practical nor efficient to conduct comprehensive genomic profiling for all early-stage cancers, given the availability of effective established treatments and limited actionable targets in such cases (Colomer et al., 2020).

For patients with advanced malignancies, eligibility for molecular profiling depends on factors such as organ function, comorbidities, performance status, and willingness to pursue further treatment. Patients with significant comorbidities or reduced performance status are less likely to benefit from tailored therapies and may face harm due to delays in necessary palliative care (Colomer et al., 2023). Importantly, patient autonomy must be respected, requiring full disclosure about the likelihood of identifying actionable targets and potential implications, such as uncovering hereditary cancer syndromes.

The most robust evidence for extended molecular profiling exists for patients with advanced cancers who have exhausted conventional treatments and maintain an acceptable performance status. In such cases, precision oncology trials have demonstrated promising results (Massard et al., 2017). Extended profiling may also benefit patients with rare malignancies lacking evidence-based treatments or those exhibiting exceptional therapeutic responses (Horak et al., 2021). Whether early application of precision oncology provides superior outcomes remains under debate, as it is hypothesized that targeted therapies may be more effective when administered before extensive chemotherapy or radiation therapy (Wahida et al., 2023).

In clinical practice, targeted cancer gene panels covering 20–500 genes are commonly used for genomic profiling. Various NGS platforms offer differing coverage of DNA and RNA, with panel selection guided by factors such as disease stage, treatment history, prior sequencing data, access to targeted therapies, and financial considerations (Dugger et al., 2018). Comprehensive genomic profiling, including whole-genome and transcriptome sequencing, is primarily reserved for research purposes. Although large-scale genome sequencing efforts may improve the identification of clinically relevant somatic alterations, their clinical utility remains uncertain (Rosenquist et al., 2022).

Liquid biopsy using circulating tumor DNA (ctDNA) has emerged as a promising tool, potentially offering a more comprehensive molecular snapshot of a tumor by capturing DNA from multiple lesions simultaneously (Heitzer et al., 2019). However, the accuracy and reliability of ctDNA-based profiling require significant improvement and clinical validation before widespread adoption in standard practice (Kim et al., 2023).

However, the integration of molecular profiling into cancer care must balance clinical utility, patient needs, and resource constraints. Continued research and clinical trials are essential to refine its application and maximize the potential of precision oncology.

## 5. Therapeutic Actionability Assessment of Molecular Alterations

The validity and accuracy of the pathologist's molecular report are vital to the workflow for assessing the therapeutic actionability of molecular alterations. Advanced functional annotation and precise reporting of identified changes are foundational for all subsequent evaluations (Li et al., 2017). This highlights the critical role pathologists play in clinical care and underscores the necessity of close multidisciplinary collaboration between clinicians and pathologists for the successful implementation of precision oncology.

The actionability assessment primarily focuses on pathogenic or likely pathogenic variants, as the functional role of variants of uncertain significance remains ambiguous. Central to this process is the identification of predictive biomarkers for antineoplastic therapy. A growing array of molecular predictive biomarkers has been identified and clinically validated in specific cancers.

Examples include gene mutations (e.g., BRAF V600E) (Chapman et al., 2011), protein overexpression (e.g., HER2), gene amplifications, gene fusions (e.g., EML4-ALK rearrangement) (Kwak et al., 2010), tumor mutational burden (Hellmann et al., 2018), and microsatellite instability (André et al., 2020).

These genetic factors vary in frequency across cancer types, supporting the concept of genome-guided treatment selection independent of cancer etiology and histology. A notable example is the tumor-agnostic targeting of NTRK fusions, which has shown promising results (Cocco et al., 2018). However, it is crucial to recognize that the efficacy of targeted therapies in one cancer type may not directly translate to others. For instance, while BRAF V600E mutations can be addressed with BRAF or combined BRAF/MEK inhibition in metastatic melanoma (Chapman et al., 2011) and non-small-cell lung cancer (Planchard et al., 2016), colorectal cancer requires additional EGFR inhibition due to feedback activation of the EGFR pathway. This illustrates the challenge of interpreting molecular alterations within the context of specific cancer histology and co-mutational tumor profiles.

To standardize the clinical interpretation and actionability assessment of molecular alterations, the European Society for Medical Oncology Translational Research and Precision Medicine Working Group proposed the ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT). This framework classifies and prioritizes molecular targets into six evidence tiers based on clinical data supporting biomarker-drug interactions and their clinical implications (Mateo et al., 2018):

- Tier I: Drug-matching alterations with proven clinical benefit in prospective studies. Subcategories include randomized trials (Tier Ia), non-randomized trials (Tier Ib), and basket trials (Tier Ic). Tier I targets are considered the standard of care.
- Tier II: Drug-matching alterations linked to clinical action, though the extent of benefit remains uncertain. These are experimental targets intended primarily for clinical trials or registry studies.
- Tier III: Hypothetical drug matches with potential clinical benefits. Tier IIIa targets are based on prospective trial data in a different cancer type, while Tier IIIb targets involve alterations closely related to known Tier I alterations. These targets are best explored through precision oncology trials, such as N-of-1 studies.
- Tier IV: Preclinical evidence only; these targets are not recommended for clinical use.
- Tier V: Alterations with known anticancer activity that did not improve survival. Combinational therapeutic options may be considered in clinical trials.
- Tier X: Alterations with no evidence of clinical or preclinical actionability.

This tiered framework ensures a systematic and evidence-based approach to therapeutic actionability assessments, promoting the rational integration of precision oncology into clinical care. It also emphasizes the importance of tailoring treatment strategies to the specific biological context of each cancer case, supported by robust clinical and translational research.

## 6. Role of the Molecular Tumor Board in Personalized Cancer Therapy

The rapid increase in approved targeted therapies and the discovery of new molecular biomarkers have made interpreting genome sequencing results in a therapeutic context increasingly complex and time-consuming. While genomic knowledge databases and decision-support platforms are available to assist with clinical actionability assessments, many clinicians are unaware of these resources, lack sufficient genetic expertise, or do not have the time to interpret the literature accurately. To optimize the clinical utility of next-generation sequencing (NGS) for identifying therapeutic targets, a professional evaluation of sequencing results is essential.

To address this need, molecular tumor boards (MTBs) are being established more frequently in cancer centers. MTBs serve as multidisciplinary platforms to integrate precision oncology into patient care effectively. While no universal guidelines exist for the structure and workflow of MTBs, most are composed of experts from various medical fields, including pathologists, oncologists, geneticists, bioinformaticians, and molecular biologists. The primary responsibilities of MTBs include initiating appropriate genetic testing, interpreting molecular profiling results to identify therapeutic targets and provide personalized treatment recommendations, supporting the diagnosis of patients with ambiguous histological findings, and identifying inherited cancer predispositions (Luchini et al., 2020).

Effective decision-making by MTBs requires a thorough review of each patient's medical history, prior antineoplastic treatments, the availability of archival tumor samples, and results from previous molecular testing. Beyond these responsibilities, MTBs play a critical role in education by improving understanding of molecular oncology and disseminating knowledge about the effective use of cancer genome diagnostics to personalize patient care. Additionally, MTBs foster innovative translational research initiatives aimed at identifying new resistance mechanisms and predictive biomarkers, bridging the gap between bedside and bench research (Subbiah et al., 2018).

Despite their potential, only a small proportion of cancer patients have benefited from MTBs, as their proper implementation demands a high level of expertise across multiple disciplines, often available only at select academic institutions (Gardner et al., 2021). To overcome this challenge, the adoption of centrally coordinated

precision oncology initiatives could be a solution. These initiatives would offer a virtual platform for patient case discussions, knowledge exchange, and translational research collaboration across cancer centers (Horak et al., 2017).

## 7. Tumor-Agnostic Genomic Targets as Blueprints for the Precision Oncology Paradigm

The cornerstone of precision oncology lies in identifying unifying molecular targets that are tumor-agnostic and can guide tailored therapies. Several genetic alterations, regardless of the underlying cancer type, have been identified as viable therapeutic targets in recent years. Below, two examples of tumor-agnostic targets highlight the promise of personalized oncology.

### 7.1 Genetic Hypermutability and Microsatellite Instability

Research into genomic hypermutability and microsatellite instability (MSI) has revealed their value as tumor-agnostic prognostic markers for immune checkpoint inhibitor (ICI) responsiveness. DNA mismatch repair (MMR) deficiency leads to the accumulation of mutations in short, non-coding DNA repeats (microsatellites), causing MSI. Since the MMR system is essential for maintaining genomic stability, its deficiency is also associated with increased tumor mutational burden (TMB) (Li et al., 2020).

TMB, a measure of tumor neoantigen abundance, is strongly correlated with the efficacy of ICI therapies, which enhance T-cell responses (Schumacher et al., 2015). These insights drove clinical investigations of ICI therapy in patients with high TMB and/or MMR deficiency. MMR deficiency, found in approximately 4% of cancers, can be evaluated through immunohistochemistry or by genomic detection of MSI. MSI prevalence is highest in Lynch syndrome-associated cancers, including gastric, colorectal, and endometrial adenocarcinomas (Bonneville et al., 2017).

A landmark study by Le et al. demonstrated that PD-1 blockade using pembrolizumab resulted in durable responses and a 52% overall response rate in heavily pretreated patients with MSI-high advanced cancers (Li et al., 2015). These findings led to the FDA's first tumor-agnostic therapy approval for pembrolizumab. Subsequent cancer type-specific studies further confirmed the efficacy of ICIs in MSI-high tumors (Marabelle et al., 2020).

The tumor-agnostic predictive value of TMB, however, remains uncertain. In a Phase II basket trial, patients with TMB-high tumors (≥10 mutations/megabase) identified by the FoundationOne CDx assay showed improved responses to pembrolizumab in certain advanced cancers (Petrelli et al., 2020). Despite this, the FDA approved pembrolizumab for TMB-high tumors across all histologies, even though data for key cancers like colon, prostate, and breast were lacking.

A retrospective cohort study by McGrail et al. involving over 1,500 patients treated with ICIs challenged this approval. The study found that TMB was predictive of ICI response only in cancers where CD8+ T-cell infiltration correlated with neoantigen load. In other cancers, such as breast and prostate, no such association was observed. However, small sample sizes in tumor-specific subgroups limit the generalizability of these findings (McGrail et al., 2021). Further research is needed to clarify TMB's tumor-agnostic role in predicting ICI efficacy.

MTBs represent a vital component of precision oncology, offering a multidisciplinary framework to navigate the complexities of genomic profiling and personalized treatment. By bringing together diverse expertise, MTBs ensure that molecular profiling results are interpreted accurately and used effectively to inform therapeutic decisions. Additionally, tumor-agnostic targets, such as MSI and TMB, exemplify the potential of precision oncology to transcend traditional cancer classifications. While significant progress has been made, challenges such as access to MTBs, varying levels of clinical expertise, and the need for robust tumor-agnostic biomarkers underscore the ongoing need for collaboration, research, and innovation in this field.

## 8. Expanding Precision Medicine: Genomic and Epigenetic Approaches

The field of precision medicine aims to refine cancer diagnosis and treatment by leveraging genomic and epigenetic insights. Recent advances in mutational signatures, gene expression profiles, and epigenetic modifications provide new avenues for tailoring therapeutic interventions. Below, we explore how these methods contribute to expanding precision medicine.

### 8.1 Mutational Signatures

Genomic profiling in cancer precision medicine focuses on identifying driver mutations that are associated with therapeutic targets or possess diagnostic and prognostic significance. Beyond identifying individual mutations, genomic "profiles" capture patterns of gene expression or recurrent mutations across multiple genes or genomic regions. These profiles can stratify patients into subgroups based on clinical outcomes, therapeutic responses, or other characteristics.

Mutational signatures expand the scope of genomic profiling, enabling risk stratification across various cancer types, including diffuse large B-cell lymphoma, brain cancer, hepatocellular carcinoma, and breast cancer (Chapuy et al., 2018). Unlike traditional panel or single-gene testing, mutational signatures account for the broader effects of mutations. For instance, research has shown that patients with germline mutations in BRCA1 and BRCA2 respond to carboplatin, whereas those with a BRCA mutational signature but no germline variant do not (Tutt et al., 2018).

While mutational signatures hold promise for improving diagnostic and therapeutic precision, further clinical studies are needed to better understand their impact on treatment responses and outcomes.

### 8.2 Gene Expression Signatures

Gene expression profiling, using RNA sequencing (RNA-seq), gene expression microarrays, or single-molecule enumeration techniques, allows for the subclassification of tumors based on gene expression signatures. For example, consensus molecular subtyping of colorectal cancer is achieved through gene expression arrays (Guinney et al., 2015). Similarly, "BRCAness" gene expression signatures predict responses to PARP inhibitors in breast, ovarian, and prostate cancers (Robinson et al., 2015).

Gene expression profiling offers higher clinical sensitivity than single-gene mutation testing. Prognostic predictions, such as breast cancer recurrence risk or new subgroups of diffuse large B-cell lymphoma, exemplify the utility of expression signatures in guiding therapeutic decisions (Nielsen et al., 2014; Andre et al., 2019). By analyzing the transcriptome, gene expression networks and oncogenic pathways can be mapped, enabling more functional tumor profiling and expanding therapy options (Senft et al., 2017).

The WINTHER study conducted by the Worldwide Innovative Network (WIN) Consortium highlights the practical application of transcriptome analysis in precision oncology. This study incorporated transcriptome analysis alongside tumor genotyping to guide treatment decisions. Patients were treated based on variations in gene expression between tumor and normal tissue when actionable changes in cancer driver genes were not identified. The study demonstrated that incorporating transcriptome analysis increased actionable treatment options, with 35% of patients receiving targeted therapies. The response rates for transcriptome- and genotype-matched therapies were comparable, ranging from 20% to 30% (Rodon et al., 2015).

### 8.3 The Role of Epigenetics in Precision Medicine

Epigenetic modifications regulate gene expression by altering the genome's architecture, promoting or inhibiting cell division and growth. These modifications include histone acetylation, DNA methylation of CpG islands in promoter regions, and non-coding RNA (e.g., microRNA) interactions with promoter regions (Nebbioso et al., 2018).

Technologies such as methylation microarrays, bisulfite sequencing, and chromatin immunoprecipitation sequencing enable the identification of epigenetic alterations. Global epigenetic mapping initiatives, including the International Human Epigenome Consortium and the NIH Roadmap Epigenomics Mapping Consortium, aim to create comprehensive maps of DNA methylation and histone modifications (Stunnenberg et al., 2016). These maps provide insights into tumor biology and potential therapeutic targets.

Epigenetic modifications are increasingly recognized as critical contributors to carcinogenesis and cancer progression. Differences in DNA methylation profiles, for instance, can distinguish between regressors and progressors in pre-invasive lung cancer lesions (Teixeira et al., 2019). Similarly, concurrent mutations in the IDH2 and SRSF2 genes drive leukemogenesis by affecting RNA splicing and the epigenome (Yoshimi et al., 2019). Genome-scale DNA methylation mapping has revealed spatial and temporal differences between primary and recurrent glioblastomas (Klughammer et al., 2018). In colorectal cancer, BRAF mutations are associated with a high CpG island methylator phenotype, whereas KRAS mutations correlate with a low CpG island methylator phenotype (Hinoue et al., 2012).

The potential for therapeutic intervention through epigenetic targeting is immense. For example, epigenetic therapies could exploit DNA methylation differences in pre-invasive cancers or disrupt the oncogenic effects of epigenetic mutations. As research progresses, early therapeutic interventions and pharmacological targeting of epigenetic pathways are likely to become integral components of precision medicine.

Precision medicine is advancing rapidly through innovations in genomic and epigenetic profiling. Mutational signatures provide valuable risk stratification tools, while gene expression profiling enhances diagnostic sensitivity and expands therapeutic options. Moreover, epigenetics offers a promising avenue for understanding cancer biology and identifying new therapeutic targets. Together, these approaches hold the potential to transform cancer care, enabling more personalized and effective treatments. Ongoing research and clinical studies will be critical to fully realizing the benefits of these cutting-edge methods in precision medicine.

## 9. Integration of Precision Cancer Medicine in the Immuno-Oncology (IO) Era

The integration of precision cancer medicine (PCM) with immuno-oncology (IO) therapies marks a significant advancement in cancer treatment. Genomic analyses play a critical role in predicting responses or resistance to IO drugs, alongside assessing the protein expression of immune checkpoint molecules such as PD-L1 (Conway et al., 2018).

One promising biomarker in this field is tumor mutation burden (TMB), defined as the total number of coding mutations in the tumor genome. TMB has demonstrated potential as a predictor of response to anti-PD-1/PD-L1 drugs in numerous prospective trials across different tumor types (Cristescu et al., 2018). Both blood-derived circulating tumor DNA (ctDNA) and tumor tissue samples can be used to evaluate TMB (Gandara et al., 2018).

However, the standardization of TMB analysis remains a challenge. Efforts such as the Friends of Cancer TMB Quality Assurance Initiative aim to harmonize TMB interpretation for therapeutic applications (Stenzinger et al., 2018). Still, issues like unclear cutoff values and variability in genomic footprint requirements hinder broader adoption (Allgäuer et al., 2018). Interestingly, some tumor types, such as Merkel cell carcinomas, respond well to IO therapies despite low TMB levels, illustrating the complexity of IO responses (Yarchoan et al., 2017).

## 10. The Evolving Scope of Precision Cancer Medicine

Precision oncology is evolving beyond single-genomic analysis to embrace a multi-omic approach, improving our understanding of tumor biology and expanding therapeutic options. A prime example is the ACNS02B3 brain tumor biology study by the Children's Oncology Group, which combined data from immunohistochemistry (IHC), genomic, epigenetic, and transcriptomic analyses to identify five distinct molecular subgroups of brain tumors (Brabetz et al., 2018). These subgroups were validated in patient-derived xenograft models, which enabled in vivo drug sensitivity testing and offered insights into targeted therapy options.

## 11. Challenges and Prospects of Precision Oncology

While precision oncology has achieved remarkable advancements, several challenges must be addressed to maximize its clinical potential.

### *11.1 Tumor Heterogeneity and Clonal Evolution*

Cancer progresses through clonal evolution, accumulating genetic abnormalities that drive malignancy. As tumors evolve, they exhibit increasing heterogeneity and subclonality, complicating the efficacy of single-target therapies, particularly in advanced stages (Gerstung et al., 2020). Targeting cancer driver genes during earlier disease stages could yield better therapeutic outcomes. Incorporating individualized treatment approaches into early clinical care may enhance patient survival rates and reduce treatment resistance.

### *11.2 Interpreting Genetic Variants*

Assigning pathogenic significance to identified genetic changes remains a significant limitation in precision oncology. Many malignancies harbor passenger co-mutations that do not contribute to cancer progression. Moreover, somatic mutations with varying pathogenic potential can occur in healthy tissues. For instance, somatic mutations in hematopoietic cells, which increase with age, are often detected during ctDNA analysis, reducing the specificity of observed mutation patterns. Additionally, mutations in pro-oncogenic driver genes have been identified in benign conditions (Adashek et al., 2020).

Future advances in tailored modeling of therapeutic targets at the RNA, protein, or cellular levels could address these limitations. Artificial intelligence (AI)-driven technologies may also improve the pathologic and clinical annotation of molecular diagnostics, streamlining precision oncology applications (Letai et al., 2022).

### *11.3 Structural and Technical Barriers*

Practical implementation of precision oncology faces several logistical challenges. Currently, it can take weeks to transition from molecular diagnostics to tailored therapy initiation. This delay is particularly detrimental for patients with advanced-stage cancers, where rapid intervention is critical. Additionally, genetic mechanisms of treatment resistance often necessitate the availability of recent tumor samples, which can be challenging to obtain due to prior anti-cancer therapies and clonal evolution.

Advances in liquid biopsy technology, such as ctDNA analysis, hold promise for overcoming these barriers by reducing the dependence on tissue-based testing (Ignatiadis et al., 2021). Liquid biopsies offer a less invasive, faster, and more comprehensive approach to assessing tumor genetics, potentially improving treatment timelines and outcomes.

### *11.4 Financial and Accessibility Challenges*

The high costs associated with whole-genome sequencing, molecular profiling, and targeted therapies pose a significant barrier to the widespread adoption of precision oncology. Access to individualized cancer treatment is currently limited to a small fraction of patients, primarily in developed countries.

However, precision oncology has the potential to reduce long-term healthcare costs by enabling more effective treatments and minimizing complications from suboptimal therapies. For instance, selecting targeted cancer therapies with higher precision could improve treatment efficacy and reduce hospitalizations caused by adverse events, leading to overall cost savings (Christofyllakis et al., 2022). Evaluating the cost-effectiveness of precision oncology strategies through dedicated studies is essential to facilitate broader implementation, especially in resource-limited settings.

The integration of PCM in the IO era represents a transformative shift in cancer care. By leveraging biomarkers like TMB, multi-omic profiling, and advances in liquid biopsy technology, precision oncology is increasingly capable of tailoring treatments to individual patients. Nevertheless, challenges such as tumor heterogeneity, the interpretation of genetic variants, logistical delays, and financial constraints must be addressed to fully realize its potential.

Ongoing research and technological advancements, including AI-driven diagnostics and cost-effectiveness evaluations, are critical to overcoming these barriers. As precision oncology continues to evolve, it holds the promise of providing more effective,

personalized, and accessible cancer treatments, ultimately improving patient outcomes and quality of life.

## 12. Conclusion

In conclusion, the landscape of cancer care is undergoing a profound transformation, with personalized therapy driven by molecular diagnostics taking center stage. While this shift holds immense promise, several challenges remain to be addressed. These include the complexities of cancer's genetic heterogeneity, the need for improved interpretation and clinical annotation of genetic changes, and the current limitations in molecular diagnostic technologies. However, as personalized oncology continues to evolve, it is poised to revolutionize cancer treatment by offering deeper insights into the molecular mechanisms that drive cancer. The integration of multi-omic data and functional analyses will refine clinical decision-making, paving the way for more precise and tailored therapies. Furthermore, the advent of liquid biopsies will significantly enhance our ability to detect and monitor the molecular aberrations driving cancer, enabling real-time, non-invasive tracking of disease progression. As these advancements unfold, personalized oncology will not only improve the efficacy of treatments but also usher in a new era of more individualized, effective, and timely cancer care.

## Author Contribution

M.S.S.K., F.S.R.A.S., M.K.A.B., A.M.S.A.M. wrote and reviewed the manuscript.

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## Competing financial interests

The author has no conflict of interest.

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