Genomic Profiling for Precision Cancer Therapies

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Abstract

The transformative power of genetic profiling on the field of precision cancer medicines is examined in this review, which also clarifies the methodological nuances and broad ramifications of incorporating genomic data into clinical oncology. A novel method called "genomic profiling" examines cancer DNA thoroughly to identify particular genetic changes, mutations, and biomarkers that influence tumor activity. Next-generation sequencing (NGS) is a cutting-edge technique for genomic profiling that makes whole-genome sequencing quick and affordable. Thanks to NGS, doctors may now better understand the molecular causes of cancer and develop individualized treatment plans by identifying exact genetic fingerprints. The paper explores the clinical uses of genomic profiling and shows how it can help inform treatment choices by detecting genetic abnormalities that can be targeted, allowing for a deviation from the standard homogeneous therapy paradigms.Genomic profiling-based customized cancer care has far-reaching ramifications. Through the alignment of therapies with the unique genetic composition of each patient's cancer, medical professionals maximize therapy effectiveness while reducing side effects. Beyond clinical applications, the influence on healthcare systems is discussed, emphasizing the need for worldwide standardization, interdisciplinary collaboration, and the construction of a strong infrastructure in order to fully realize the promise of precision cancer therapy.Finally, genetic profiling becomes clear as a keystone in the development of oncology, changing patient outcomes and therapeutic approaches. In order to bring in a new era of precision cancer care, the paper emphasizes the vital significance of continued research, technology developments, and calculated partnerships in establishing genetic profiling as a fundamental part of regular clinical practice.

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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Introduction

Patients' cancer treatments are currently being revolutionized by precision oncology. Understanding the underlying molecular changes that cause the onset and spread of cancer has enhanced our ability to comprehend pro-oncogenic pathophysiologic pathways and may even allow us to interfere with them (Malone et al,2020).This progress has been made possible by numerous important causes. First, next-generation sequencing (NGS) techniques have advanced the technical analysis of genetic data in recent years, making quick and affordable molecular diagnostics possible in everyday clinical practice (Brown & Elenitoba, 2020). Decades of experimental study have also resulted in the accurate characterization of several oncogenic pathways, such as mechanisms of the cancer-host interaction, pro-oncogenic driver

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mutations, and tumor-suppressive mechanisms of compromised immunity against cancer (Mateo et al,2022). Third, developments in drug development have made it possible to directly disrupt these unique molecular pathways (e.g., by using monoclonal antibodies or tyrosine kinase inhibitors), which enables the creation of customized treatment plans predicated on unique patterns of genetic alterations (Dugger et al,2018). Our goals in this study are to clarify the meaning of individualized cancer treatment, particularly in relation to molecular diagnostics, and to go over the use of molecular profiling in tumor-agnostic therapeutic making decisions, as well as highlighting present issues and prospective future paths for the precision oncology strategy from the perspective of oncologists. The present review centers on novel and contemporary methodologies, emphasizes achievements and obstacles, and suggests possible remedies for integrating precision medicine into clinical research and practice (Figure. 1).

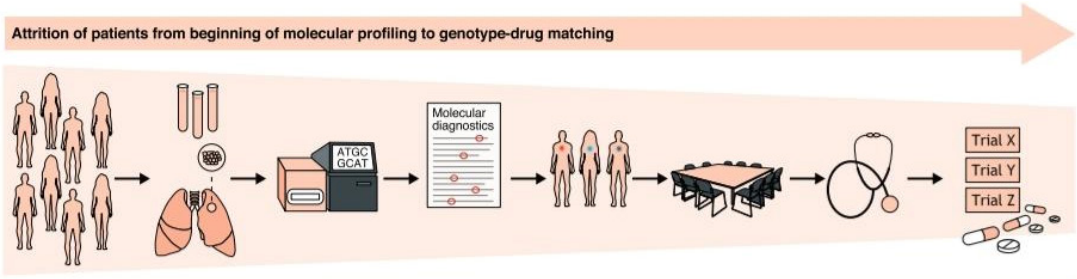
The precision oncology paradigm

The goal of the precision medicine method is to effectively guide illness prevention, diagnosis, and tailored treatment selection by using extensive information at the level of each individual patient (Collins & Varmus, 2015). The field of oncology has taken the lead in the precision medicine paradigm since it has long been understood that cancer is a disease caused by a build-up of genetic abnormalities (Tsimberidou et al,2020). In the past, cytotoxic chemotherapy treatments were limited in number and were chosen based on the location and histology of the individual tumors. The first molecular targeted pharmacological therapies were created in the late 1990s, spurred by a continually improving understanding of carcinogenesis and genetics, which was primarily made possible by the advent of innovative DNA research tools like polymerase chain reactions. Early achievements in precision oncology were the successful clinical introduction of the BCR-ABL tyrosine kinase inhibitor imatinib and the monoclonal HER2-antibody trastuzumab, which ushered in a new age of molecularly stratified cancer therapy (Druker et al,2001) Simultaneously, the introduction of NGS has revolutionized molecular profling by drastically reducing analytic costs and turnaround time due to fundamental technological breakthroughs. Unlike traditional sequencing methods, next-generation sequencing (NGS) allows for the accurate simultaneous investigation of many genes (Berger & Mardis, 2018).. The development of NGS, with its high efficiency, thus made large-scale sequencing efforts possible, such as the cancer genome atlas projects, which allowed for a thorough genomic characterization of different tumors and further changed our knowledge of oncogenesis and cancer evolution (Weinstein et al,2013).Crucially, a number of recurrent genetic changes were found to exist in many cancer types and were later identified as possible targets for therapy. As a result, in recent times, a vast and swiftly expanding range of medication treatments aimed at various genetic modifications such as gene mutations, rearrangements, and amplifications have been created and successfully applied in medical settings (Waarts et al,2022). This was accompanied by an increasing number of standard clinical practices using NGS technology to tailor molecularly stratified cancer treatment decisions for a variety of tumor types, including biliary tract cancer (Lamarca et al,2022), colorectal cancer (Gutierrez, et al,2019) and non-small cell lung cancer (Planchard et al,2018). With the recent approval of the first tumor-agnostic therapies, which are administered based only on the discovery of a specific molecular mutation regardless of cancer histology and tissue of origin, a significant step towards a personalized cancer treatment strategy has finally been taken (Looney et al,2020).

Integration of precision oncology in patient care

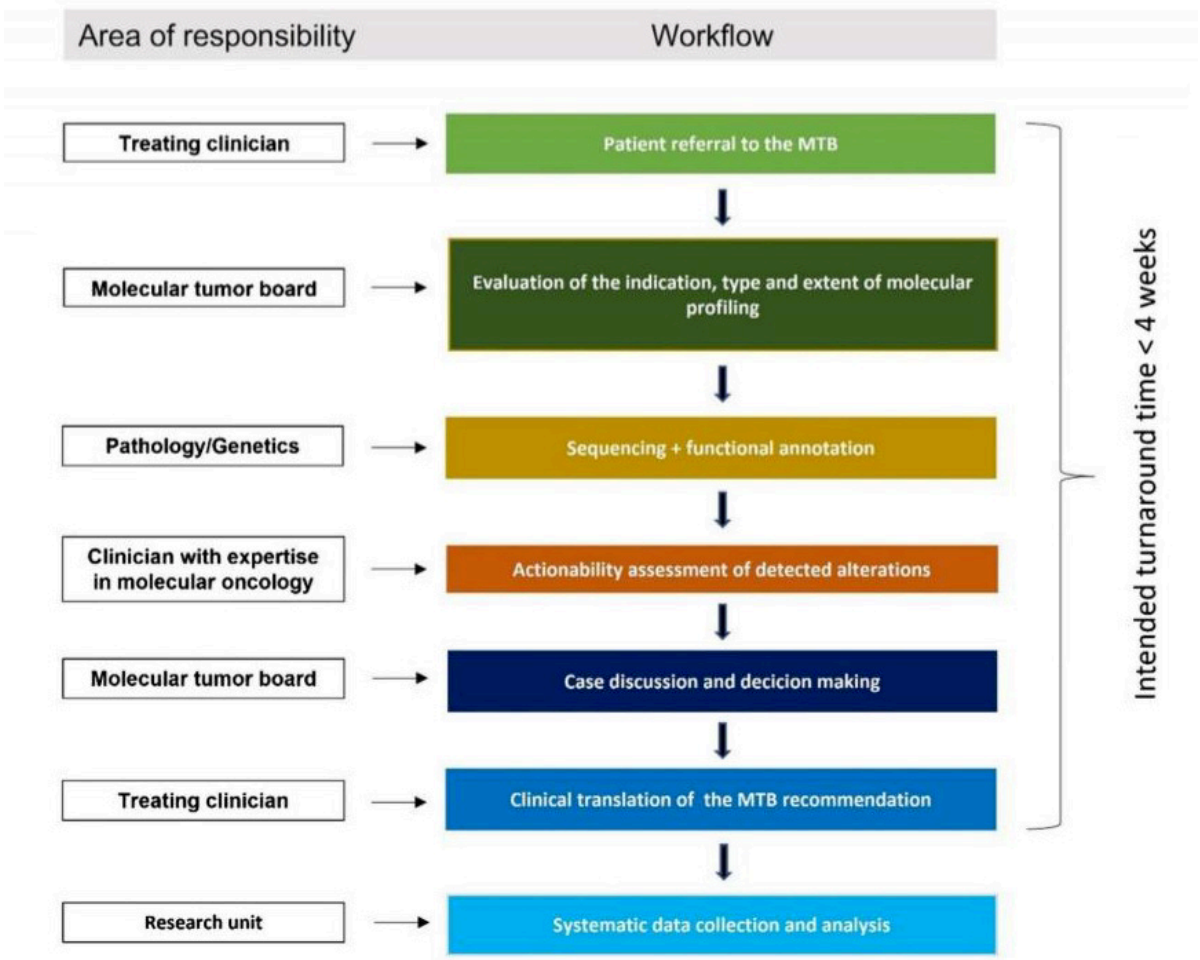
The idea of a tailored treatment that is cancer-agnostic and guided by molecular profiling is quite attractive, but putting it into practice successfully in the clinic comes with some significant hurdles that need to be carefully considered. The difficult and multistep process of linking identified molecular changes to targeted medicines is a significant practical obstacle (Horak et al,2022). The first step in this process is defining the following issues: should molecular probing be implemented based on the patient's overall health status; when should molecular probing be started during the patient's journey; is a liquid biopsy or re-biopsy of the tumor lesion necessary; and, last but not least, which diagnostic genetic analysis should be performed. Pathologists and geneticists collaborate to manage the following stages, which include variant calling, NGS analysis and bioinformatic data processing, and the functional evaluation of identified genetic changes (Li et al,2017).Specific difficulties and dangers are presented by each stage of this multilayered process and are covered in greater detail in subsequent reviews in this series.However, from the perspective of an oncologist, the most crucial and least defined phase in the application of precision oncology is the final step of the workflow: the clinical annotation and clinical actionability assessment of discovered genetic alterations.

The clinical applications of tailoring cancer treatments to each patient’s unique genetic makeup will be the main topic of this review. We will highlight important elements such as the deliberate selection of patients who are suitable for longer term patient care, the diagnostic selection criteria, and the actionability assessment and biomarker-guided therapeutic decision-making processes. The workflow of a highly standardized and outcome-centered molecular tumor board (MTB) at a significant academic center in Austria is shown in Figureure 2. This MTB could be used as



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

a model for incorporating genomic cancer sequencing into clinical care, among other things.

Who shall we test, when shall we test, How shall we test?

As of right now, molecular profiling in unselected cancer patients does not consistently indicate targets that can be taken further (Haslam et al,2021) As a result, the European Society for Medical Oncology (ESMO) limits the advanced non-small-cell lung cancer, prostate cancer, ovarian cancer, and cholangiocarcinoma for which it recommends the routine clinical use of multigene NGS testing. If extra expenses are acceptable, multigene testing may be regarded as an alternative to single gene polymerase chain reaction testing in advanced colorectal cancer (Mosele et al,2020).In addition, it is not generally advised to use multigene sequencing to customize genome-guided, individualized therapies; rather, this procedure should only be carried out within the parameters of an academic program and should only be applied to patients for whom the results of the testing may directly affect the clinical management (Colomer et al,2020). On the other hand, leading academic institutions in the USA and other countries choose to analyze germline genetics and tumors early and thoroughly in almost all cancer patients (Subbiah et al,2023), a position that is still debatable (Sorscher,2023). The meticulous clinical assessment of whether molecular profiling is even warranted is still the first crucial stage in the genomic cancer sequencing process. In general, it is unrealistic and ineffective to do thorough genomic profiling in every case of early-stage cancer with the current level of understanding of tumor biology and available targeted medicines, as extremely effective established treatments may be available in this situation (Colomer et al,2020).However, in order to be eligible for molecular profling, patients with advanced malignancies must meet certain requirements related to organ function, comorbidities, performance status, and patient desire. They also need to be candidates for further antineoplastic treatment. Patients with significant comorbidities or a decreased performance status are less likely to benefit from tailored medicines according to genomic profiling. As a result, using precision oncology techniques with these patients may possibly be harmful because they could give rise to unfounded expectations and even postpone necessary palliative care measures (Colomer et al,2023). When considering molecular profiling, it is important to properly protect the patient's autonomy. As a result, prior molecular profiling is started. The patient must be fully and accurately informed about the likelihood of finding a potential target as well as the possible consequences of somatic mutational tumor profiling, like the identification of molecular changes that are highly suggestive of inherited cancer syndromes. For patients who have tried every known and clinically effective treatment option and are still in acceptable performance status, the most comprehensive clinical data are available for the application of extended molecular profiling to customize targeted therapy. In this context, a number of precision oncology trials have shown encouraging outcomes (Massard et al,2017). when assessing several NGS test ideas to direct targeted cancer treatment.Additionally, patients with remarkable therapy response patterns and those with uncommon malignancies for which there are few evidence-based treatment alternatives may be good candidates for extended genetic profiling(Horak et al,2021). Still up for debate, though, is whether cancer patients might benefit more from early precision oncology (Wahida et al,2023) This is predicated on the idea that cancer cells respond better to targeted drugs before they undergo multiple rounds of chemotherapy, radiation therapy, or other forms of alternative medicine.

Targeted cancer gene hotspot panels of 20–500 genes are primarily utilized for genomic profiling in modern clinical practice. Various NGS technologies are available in this area, each providing a somewhat different range of DNA and coverage of RNA(Colomer et al,2020). Individual decisions regarding panel sequencing must be made based on a number of variables, including as the disease's nature and stage, treatment history, availability of prior sequencing data, accessibility to targeted medicines, and, of course, financial resources (Dugger et al,2018).. Currently, complete genomic profiling, which includes transcriptome, entire exome, and genome sequencing, is mostly used for scientific research. Comparing large-scale comprehensive genome sequencing efforts to targeted cancer gene panels is likely to enhance patient outcomes, although the evidence supporting a significantly improved identification of clinically important somatic changes is still equivocal. There are now several trials assessing the clinical usefulness of full genetic profiling (Rosenquist et al,2022). Furthermore, a liquid biopsy may even be able to obtain a more complete picture of the molecular makeup of a patient's tumor than a single tissue biopsy because ctDNA is believed to be released into the bloodstream from multiple tumor lesions at the same time (Heitzer et al,2019). Before ctDNA sequencing can be widely used to customize genome-guided treatment decisions in standard clinical practice, however, its accuracy and dependability must be substantially enhanced and clinically verified (Kim et al,2023).

Therapeutic actionability assessment of molecular alterations

The pathologist's molecular report's validity and accuracy are critical components of the actionability assessment workflow. Therefore, an advanced functional annotation and proper reporting of changes found constitute a crucial requirement for all subsequent actionability evaluation processes (Li et al,2017). This emphasizes how important pathologists are to clinical care and how closely clinicians and pathologists must work together multidisciplinary to successfully apply precision oncology. The actionability assessment often only takes into account variations

classified as pathogenic or potentially pathogenic, as the functional role of variants with unknown significance is uncertain. The foundation of the clinical annotation process is the identification of predictive biomarkers for antineoplastic therapy. Thus far, a wide range of consistently expanding molecular predictive biomarkers have been identified and clinically validated in particular forms of cancer. These include gene mutations (e.g., BRAFV600E) (Chapman et al,2011), protein overexpression (e.g., HER2) [10], and gene amplificcations.Gene fusions (such the EML4-ALK rearrangement)(Kwak et al,2010), as well as compound biomarkers like tumor mutational load (Hellmann et al,2018) and microsatellite status (André et al,2020). Numerous genetic factors exhibit variable frequency across different forms of cancer, leading to the concept of genome-guided treatment selection independent of the cancer's etiology and histology. The concept of very promising tumor agnostic NTRK fusion targeting has been reaffirmed recently (Cocco et al,2018). However, it is important to remember that the effectiveness of targeted therapy in one form of cancer cannot be immediately transferred to another.

The BRAF V600E mutant serves as an excellent example of this, as it can be effectively addressed by either a single drug or a combination of BRAF and MEK inhibition in metastatic melanoma (Chapman et al,2011). And NSCLC [(Planchard et al,2016), but not in colorectal cancer because further EGFR inhibition is required in that case because of a feedback increase of the EGFR. Therefore, interpreting the discovered molecular alteration in light of the current cancer histology and the co-mutational tumor profle presents the main issue of the actionability assessment. The European Society for Medical Oncology Translational Research and Precision Medicine Working Group has proposed a framework that will allow a more precise classification and prioritization of molecular targets in order to harmonize the clinical interpretation and actionability assessment of molecular alterations for personalized cancer treatment. The six levels of evidence for molecular targets are defined by the ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT), which takes into account the clinical data that is now available to support a biomarker drug interaction and its ensuing clinical consequences. (Mateo et al,2018) Drug matches for modification that have been demonstrated in prospective clinical studies to produce better clinical outcomes make up Tier I. Further subclassifications of the evidence level in Tier Ia (randomized), Tier Ib (non-randomized), and Tier Ic (basket trial) are possible based on the underlying trial design. The Tier I targets ought to be regarded as the norm for care. Tier II defines medication matches that have been linked to clinical action; the extent of the benefit is still unknown. These are regarded as experimental targets, and the main purpose of matching them should be to conduct a clinical trial or registry study.

Based on prospective trial data on the same target in a different cancer type (Tier IIIa) or the discovery of an alteration functionally closely related to a known Tier I alteration (Tier IIIb), Tier III describes hypothetical alteration drug matches that are suspected to result in a potential clinical benefit. Ideally, Tier III targets ought to be examined in conjunction with novel precision oncology trial models, including N-of-1 studies. Tier IV targets shouldn't be used as targets in clinical practice because they are only supported by preclinical data. It has been demonstrated that Tier V modification medication matching are linked to anticancer activity; however, this association did not result in increased survival. If functionally feasible, combinational therapeutic options may be taken into consideration within the context of a clinical trial. There is no preclinical or clinical evidence that Tier X abnormalities are actionable.

Role of the molecular tumor board in personalized cancer therapy

The number of approved targeted medicines and existing and newly discovered molecular biomarkers is quickly growing, which has made it more difficult and time-consuming to interpret the results of genome sequencing in a relevant therapeutic setting. The previously described genomic knowledge databases and decision support platforms can help with the clinical actionability assessment of detected alterations; however, the majority of clinicians are not aware of these resources, nor do they possess the necessary genetic knowledge or timely resources to accurately interpret the literature. Thus, to maximize the effective clinical application of NGS testing for therapeutic target identification, a professional assessment of sequencing results is essential.Molecular tumor boards, which offer a multidisciplinary platform to facilitate the effective integration of the precision oncology approach in patient care, are being developed in cancer centers more frequently for this reason. There are currently no industry-wide guidelines for the structure and workflow of molecular tumor boards (MTBs). But the majority of MTBs are made up of professionals from a variety of medical fields, including as pathologists, physicians, geneticists, bioinformaticians, and molecular biologists. The MTB's primary responsibilities include initiating the proper genetic testing, evaluating the results of molecular profiling for target identification and customized treatment recommendations, supporting the diagnosis of patients with unclear histology aberrations, and identifying inherited cancer susceptibilities (Luchini et al,2020)

It is necessary to do a thorough study and assessment of each patient's medical history, the length and effectiveness of prior antineoplastic therapy, the availability of archival tumor samples,

and the outcomes of any prior molecular testing in order to make the best possible decisions. Apart from the aforementioned responsibilities, the MTB plays a crucial role in teaching to enhance comprehension of molecular oncology and disseminate knowledge on how to effectively employ cancer genome diagnostics to customize patient care. Moreover, MTBs will provide a setting for creative translational research initiatives with the ultimate objective of discovering new resistance mechanisms and predictive biomarkers, thereby completing the bedside-to-bench and back research idea (Subbiah et al,2018).Only a small fraction of cancer patients have been able to benefit from MTB facilities thus far since the proper implementation of MTBs demands a high degree of knowledge from several medical disciplines that are typically only given by selected academic institutions (Gardner et al,2021). The adoption of centrally coordinated precision oncology initiatives, which offer a virtually accessible platform for patient case discussion, knowledge exchange, and translation research design across multiple cancer institutions, may be able to address this major challenge (Horak et al 2017).

Tumor-agnostic genomic targets as blueprints for the precision oncology Paradigm

The primary objective in precision oncology is to identify unifying molecular components that are tumor-agnostic and allow for tailored therapy. Regardless of the underlying cancer types, several genetic changes have been identified in recent years that can be targeted therapeutically (Table 1). The next part offers a quick summary of two well-known instances of tumor-agnostic genetic targets that serve as excellent illustrations of the great therapeutic potential of personalized oncology techniques.

Genetic hypermutability and microsatellite Instability

Recently, there has been a growing body of research on genomic hypermutability and microsatellite instability as tumor-agnostic prognostic indicators for immune checkpoint inhibitor responsiveness. DNA mismatch repair deficiency leads to an accumulation of genetic changes in short non-coding repeating DNA segments, known as microsatellites, which are dispersed across the genome and induce microsatellite instability. Because the DNA mismatch repair system is essential for preserving genomic stability, its inadequacy is also linked to a rise in somatic tumor mutations.(Li et al,2020). Tumor neoantigen production abundance is significantly correlated with the phenomena of genetic hypermutability, as defined by the tumor mutational burden (TMB), and has been shown to be essential for immunological checkpoint inhibitor (ICI)-mediated T cell response (Schumacher et al,2015). The clinical study of ICI therapy in individuals with high TMB and/or DNA mismatch repair deficiency was spurred by these findings. DNA mismatch repair deficiency, which has an approximate 4% overall frequency across a variety of cancer types, can be evaluated by immunohistochemistry at the protein expression level or indirectly by the genomic detection of microsatellite instability (MSI). The largest disease-specific prevalence of MSI is found in gastric, colorectal, and endometrial adenocarcinomas, among other malignancies linked to Lynch syndrome (Bonneville et al,2017). Crucially, in a groundbreaking research by Le et al., PD-1 blocking with the ICI inhibitor pembrolizumab produced a large percentage of durable remissions and an astounding 52% response rate in severely pretreated patients with various forms of MSI high advanced carcinomas (Li et al,2015). These results led to the FDA approving tumor-agnostic therapy for the first time, and more recently, multiple cancer type-specific trials confirmed the remarkable efficacy of ICI therapy in patients with MSI high tumors (Marabelle et al,2020) The TMB's tumor-agnostic predictive value is less certain. Patients with TMB high tumors defined as ≥10 tumor-specific mutations/megabase found by the targeted FoundationOne CDx assay showed a significantly higher response rate to the PD-1 antibody pembrolizumab in one basket phase II trial that enrolled patients with specific advanced solid tumors (Petrelli et al,2020). Despite the lack of data on key tumor types like colon, prostate, and breast cancer that were not part of this trial, pembrolizumab was approved by the FDA to treat TMB high tumors regardless of the cancer's histology. A thorough retrospective cohort study by McGrail et al. Of over 1500 patients receiving ICI therapy challenged this approval, showing that the TMB is only effective at differentiating ICI response in the subset of tumor types where CD8 cells correlate with the neoantigen load, while it is not associated with ICI response in other cancer types like breast and prostate cancer. Significantly, this study's tumor-specific subgroups were tiny, which lessens the study's overall validity (McGrail et al,2021) Therefore, more investigation is necessary to elucidate the TMB's tumor-agnostic prognostic significance for ICI efficacy.

Ways to expand precision medicine

Mutational signatures

Finding subtle driver mutations that are connected to therapeutic targets or that have diagnostic or prognostic significance is a major emphasis of genomic profiling for cancer precision medicine, as was previously mentioned. One more. Genomic "profiles" that contain common patterns of gene expression or inherited or somatic mutations across a number of genes or genomic areas are used as a genomic tool in cancer research.Patients can be categorized into subgroups based on response, outcomes, or other clinical characteristics with the right analysis. Mutational signatures extend genomics beyond the narrow focus of discrete variant discovery; risk profiles have been described for a variety of cancer types, including diffuse large B cell lymphoma, brain cancer, hepatocellular carcinoma, and breast cancer (Chapuy et

al,2018).These methods have the potential to improve diagnostic yield because traditional panel or single gene testing is unable to fully account for the range of effects of mutations.Nonetheless, a research discovered that while those with a BRCA mutational signature and no germline variant did not react to carboplatin, those with germline mutations in BRCA1 and BRCA2 did (Tutt et al,2018). To comprehend the influence of mutational signatures and response to treatment targets, more clinical assessments are required.

Gene expression signatures

Gene expression profiling from RNA sequencing (RNAseq), gene expression microarrays, or other single-molecule enumeration techniques that are used to subclassify tumors into gene expression signatures is the most sophisticated use of gene signatures. For instance, consensus molecular subtyping of colorectal cancer is achieved by the use of gene expression arrays (Guinney et al,2015). Response to PARP inhibitors is predicted by mutated signatures that imply "BRCAness" in breast, ovarian, and prostate malignancies (Robinson et al,2015)Single-molecule enumeration technologies have been utilized to characterize expression signatures in numerous disease areas and have produced counts of gene expression. Examples include prognostic predictions for disease recurrence in breast cancer and new subgroups of diffuse large B cell lymphoma (Nielsen et al,2014).Clinical practice guidelines have included several different expression signature-based breast cancer recurrence risk testing platforms (Andre et al,2019). Compared to single gene mutation testing, these investigations demonstrate the higher clinical sensitivity of gene expression signatures because many mutated signature profiles lacked a conventional mutation in the corresponding gene. Through transcriptome analysis, gene expression networks and the activity of oncogenic pathways can be found, contributing to a more "functional" tumor profiling that may ultimately lead to more therapy options (Senft et al,2017) The WINTHER study conducted by the Worldwide Innovative Network (WIN) Consortium assessed the therapeutic value and practicability of incorporating transcriptome analysis into tumor genotyping (Rodon et al,2015) Patients in this trial were treated according to variations in gene expression between the patients' tumor and normal tissue after first being assessed for targetable changes in cancer driver genes, if any were found. According to the study, actionability rose when transcriptome analysis was added to genomes, as evidenced by the 35% of patients who received matching targeted medicines.Transcriptome-matched medications' overall efficacies were comparable to genotype-matched medications', with responses falling between 20 and 30% (Rodon et al,2015)

Role of epigenetics in precision medicine

Epigenetic modifications alter the genome to control transcriptional activity, which in turn creates an architecture that either promotes or inhibits cell division and growth (Nebbioso et al,2018). The modifications in epigenetics consist of histone acetylation, the methylation of CpG islands in promoter regions, and the binding of noncoding RNA molecules (such as microRNA) to promoter regions. Numerous technologies, like as methylation microarrays, bisulfite sequencing, and chromatin immunoprecipitation sequencing arrays, can be used to identify these epigenetic alterations. All-encompassing epigenetic maps of DNA methylation and histone modifications are being developed (e.g., International Human Epigenetic Consortium or NIH roadmap Epigenomics Mapping Consortium), even though many oncogenic targets of epigenetic pathways still depend on the identification of traditional mutations found in genes that are involved in epigenetic modifications, such as DNMT and EZH2 (Stunnenberg et al,2016). With the use of epigenetic mapping, it is hoped to better understand tumor biology and the possibilities of therapeutic intervention. New information on the role of epigenetic modifications in carcinogenesis and cancer development opens the door to pharmacological targeting or early therapeutic intervention. For instance, there are differences in DNA methylation profiles between regressors and progressors in pre-invasive lung cancer lesions (Teixeira et al,2019).Leukemogenesis is facilitated by concurrent mutations in the IDH2 and SRSF2 genes, which act in concert to affect RNA splicing and the epigenome (Yoshimi et al,2019). The difference between primary and recurrent glioblastoma in terms of time and space is shown by genome-scale DNA methylation mapping (Klughammer et al,2018)..BRAF mutations or KRAS mutations are linked to high and low CpG island methylator phenotypes in colorectal cancer, respectively (Hinoue et al,2012).

Integration of PCM in the IO era

Genomic analyses are involved in the prediction of response or resistance to IO drugs, in addition to the protein expression of immune checkpoint molecules such PD-L1 (Conway et al,2018) In many prospective trials involving various tumor types, tumor mutation burden (TMB)—defined as the total number of coding mutations in the tumor genome—has shown promise as a predictive biomarker of response to anti-PD-1/PD-L1 drugs (Cristescu et al,2018) TMB can be evaluated using ctDNA from blood samples or tumor tissues (Gandara et al,2018). Harmonization efforts are in place to standardize the method of interpreting tumor mutations for therapeutic uses (e.g., Friends of Cancer TMB initiative Quality Assurance Initiative Pathology) (Stenzingeret al,2018). Nevertheless, the cutoff values and the size and content of the genomic footprint required for TMB analysis remain unclear (Allgäuer et al,2018) Not all malignancies respond to anti-PD-1/PD-L1 drugs in the same way, as some tumor types

like Merkel cell carcinomas respond well to IO medicines while having relatively low TMBs (Yarchoan et al,2017)

Evolving scope of precision cancer medicine

To improve understanding of tumor biology and expand therapeutic options, precision oncology is shifting from single-genomic analysis to a multi-omic approach. The Children's Oncology Group is leading the ACNS02B3 brain tumor biology study across several institutions, is a good illustration of how to use molecular profiling for purposes other than genomics. Based on IHC, genomes, epigenetics, and transcriptome studies, five unique tumor molecular subgroups were found in this work (Brabetz et al,2018). These subgroups were repeatable in patient-derived xenograft models, enabling in vivo drug sensitivity testing.

Challenges and prospect of precision oncology

While precision oncology has made great strides, there are still significant obstacles and problems with genome guided therapy that need to be resolved before it can be used in more clinical settings and benefit patients to the fullest (Wahida et al,2022). First, as tumors proceed via the process of clonal evolution in carcinogenesis, they pick up a range of abnormalities in the pro-oncogenic molecules. Consequently, malignancies progress toward greater levels of heterogeneity and subclonality as the disease progresses (Gerstung et al,2020). Consequently, the significant likelihood that underlying genetic characteristics of malignancies would evade single-target tailored medicines limits the efficacy of therapy in very advanced cancer scenarios. From a conceptual standpoint, a stronger anti-cancer effect may thus be possible if certain cancer driver genes were targeted at early stages of treatment. Consequently, more promising therapeutic outcomes may result from the incorporation of individualized treatment approaches in clinical care.

Second, the ability to assign the level of pathogenicity to identified genetic changes is still limited in precision oncology. In particular, malignancies sometimes acquire several passenger co-mutations that are not essential for the advancement of the malignancy.Moreover, it has been shown that somatic mutations with variable degrees of pathogenic significance can occur in healthy tissues. For instance, somatic mutations in hematopoiesis, which occur more frequently as people age, are commonly found during the diagnostic assessment of circulating tumor DNA, which reduces the specificity of the patterns of mutations that are seen.Furthermore, mutations in a number of traditional prooncogenic driver genes have been found in a variety of benign illnesses (Adashek et al,2020). These restrictions could be removed in the future with the application of tailored modeling of the corresponding therapeutic targeting on RNA, protein, or cellular levels and the functional impact of identified genetic modifications (Letai et al,2022). In addition, pathologic and clinical annotation of molecular diagnostics may be made easier with the development of artificial intelligence-based technologies.

Thirdly, there are now a number of structural and technical limitations that limit precision oncology from a practical standpoint. Currently, it can take several weeks from the time molecular diagnostics are started until tailored therapy are actually put into practice. Therefore, a sizable fraction of patients are lost during the process in a primarily advanced oncologic therapy context. In addition, because of the process of clonal evolution and genetic mechanisms of treatment resistance that may accumulate during prior anti-cancer therapies, the availability of recent tissue samples is often required to enable reliable genetic information on the current molecular makeup of a cancer. Consequently, the effectiveness of novel tissue sample and biopsy techniques is often dependent on customized oncology, which may have an impact on the therapeutic approach's risk-benefit ratio. Nevertheless, future developments in the field of liquid biopsies through the analysis of circulating tumor DNA may eliminate the requirement for extra tissue-based testing (Ignatiadis et al,2021)

Ultimately, a significant obstacle to the broad global implementation of the precision oncology strategy is the financial strain associated with whole genome sequencing and the expense of targeted medicine itself. Regretfully, only a limited number of people can now get individualized cancer therapy and molecular probing. A tiny fraction of cancer patients in developed nations. Long-term cost savings over blindly following conventional treatment guidelines could be achieved by selecting targeted cancer therapies with greater precision and efficacy due to better treatment benefit prediction, which would also prevent hospitalizations brought on by treatment complications (Christofyllakis et al,2022) Therefore, there is an urgent need for studies that specifically include cost-effectiveness evaluations of the precision oncology strategy.

Conclusion

Cancer patient care is presently seeing a significant change as customized therapy with molecular diagnostics becomes the norm. To optimize patient benefit, several obstacles still need to be overcome, such as the degree of genetic heterogeneity specific to cancer, the interpretation and clinical annotation of detected genetic changes, and the existing technological limits in molecular diagnostics. Personalized oncology will fundamentally alter our current understanding of cancer therapy in the future by improving our understanding of the intricate underlying molecular mechanisms through the integration of multiple layers of genetic and functional analyses in a refined process of personalized clinical decision-making. Additionally, liquid biopsies will enable us to more accurately detect and track individual molecular aberrations that drive cancer.

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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