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The Role of Personalized Medicine in Oncology and Targeted Therapy

Mina Ekrami Noghabi[1,*], **Maryam Abbasi Saeidi**[2]

[1]Department of Pediatrics, Bohlool Hospital, Gonabad University of Medical Sciences, Gonabad, Iran.
[2]Department of Biology, Faculty of Basic Sciences, Science & Research Branch, Islamic Azad University, Tehran, Iran.

**Corresponding author: Mina Ekrami Noghabi, Department of Pediatrics, Bohlool Hospital, Gonabad University of Medical Sciences, Gonabad, Iran, Email:Minaekrami69@gmail.com.*

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Abstract:
Cancer, the second foremost worldwide cause of mortality, affects individuals both physically and emotionally. Traditional therapies, including surgery, chemotherapy, and radiation, have detrimental consequences, necessitating the pursuit of more targeted methods. Precision medicine facilitates more tailored therapies. The introduction of next-generation sequencing technology, as well as the growing frequency of large-scale tumor molecular profiling programs throughout the world, have changed cancer diagnosis and treatment. With the increasing availability of comprehensive genetic tests in medical and scientific settings, healthcare practitioners face complex hurdles in understanding and translating data. The article encapsulates the existing and forthcoming strategies for the implementation of precision cancer therapy, emphasizing the obstacles and potential ways to enhance the understanding and optimize the therapeutic value of molecular profiling outcomes.

Background

Cancer is a collection of illnesses characterized by various aetiologies and prognoses. Consequently, cancer therapy, whether therapeutic or palliative, utilizes a wide array of approaches. In recent years, the molecular comprehension of cancer has significantly advanced (1). The clarification of the arrangement of DNA as its genetic makeup sparked progress in biomedical research, leading to personalized medicine (PM), whereby the newfound comprehension of the relationships between genes and diseases may be used for diagnosis and treatment (2). The new paradigm in oncology has justified mechanism-based strategies that may enhance or supplant non-specific techniques, including cytostatic chemotherapy, radiation, and surgery, with approaches expected to yield better cure rates, cost-effectiveness, and diminished toxicity (3). Cancer is the second foremost reason for mortality globally, impacting not only the person's physical condition but also their mental well-being, psychologically undermining their whole support network. One of the primary exacerbating elements in this procedure is that standard therapies, including surgeries, chemotherapy, and radiation, although effective, are intrusive procedures that induce several negative consequences, even when accounting for the kind of malignancy and the patient's particular characteristics (4, 5).

In the last two decades, there has been a notable rise in scientific papers using "personalized medicine" in their titles, amounting to 115,464 papers generated by March 2024, with more than 103,198 produced post-2010. Nonetheless, the heightened use of the moniker does not align with a widespread comprehension of the notion (6). Numerous efforts have been undertaken to provide a complete description of precision and PM. The notion of PM suggests a less broad approach that emphasizes enhanced accuracy in diagnostic categorization and therapy alignment (7). PM aims to actualise the medical idea of delivering the appropriate medication to the suitable patient at the optimal moment and is notably linked to the genetic

categorization of individuals into more precise disease categories. The notion has emerged as a vital element within the burgeoning life science sector (8). PM emerges as a novel strategy in this complex situation. It tailors medical therapy to each individual's specific genetic composition, circumstances, and habits, to achieve the best possible results. Precision medicine is a significant success in oncology since it provides focused solutions to chronic difficulties like cancer stem cells and treatment resistance (9). The Prime Minister aims to enhance effectiveness and mitigate adverse effects by tailoring medicines to the distinct genetic and molecular characteristics of each individual's malignancy (10). This PM strategy is particularly efficacious in overseeing the complexities of malignant cells' communications with their environment, hence enhancing therapeutic effects. Furthermore, PM possesses the ability to change detection approaches, particularly for malignancies that often go untreated in the early stages. The use of personalized biomarkers may allow for earlier detection and a more detailed evaluation of medication success. Because cancer has a propensity to metastasize, requiring a multi-targeted approach, PM is an important component of cancer therapy (11, 12). This article aims to evaluate the present and prospective possibilities of precision medicine in oncology. This approach may transform cancer therapy by enhancing its effectiveness and safety.

Understanding PM in Oncology

The notion of cancer-agnostic individualized therapy informed by molecular profile is attractive; yet, its effective practical application presents significant hurdles that need careful study. A significant practical obstacle is the intricate, multistep process of aligning specific medicines with identified molecular changes (13). The procedure begins by determining whether the patient's overall health permits the use of molecular profiling, the appropriate time to initiate molecular profiling throughout the patient's treatment, the necessity of a re-biopsy of the tumor lesion or a liquid biopsy, and finally, that diagnostic genetic analyses should be performed (14). Subsequent actions involve NGS analysis, bioinformatic analysis of information, variant calling, and the practical evaluation of discovered genetic changes, tasks managed by physicians and geneticists. Every distinct phase in this complex procedure has particular obstacles and hazards, which are elaborated upon in other articles within this series (15).

The conclusion of the Human Genome Project (HGP) enabled scientists to decipher and analyze an individual's genetic code and determine genetic susceptibilities to certain illnesses (16). This pivotal event transformed the viewpoint on health from responsive to preventive. Currently, researchers are striving to get a full comprehension of bodily functions across several omics levels and to delineate how genetic predispositions are influenced by exposure to environmental factors (17). Collectively, this knowledge will enable researchers and physicians to more accurately anticipate patient responses to certain treatments. CDx assays serve as invaluable instruments in tailored therapeutics by evaluating genetic features that determine a patient's responsiveness to certain treatments (18). This method may significantly influence patient treatment. The revolution consists of the transition from a doctor choosing a general medicine, which is mostly exploratory for the patient, to one that precisely addresses the illness using PM (18, 19).

This review discusses the domains of personalized medicine and precision medicine, together referred to as PM. While the phrases are often used interchangeably nowadays, both denote the use of distinct patient features to choose the optimal therapy; the discipline was once termed customized medicine. As it gained popularity and grew prevalent in science, media, and culture, the phrase started to embody a misperception. Numerous individuals erroneously believed that the "personalized" approach included the creation of distinct remedies for each person (20). The scientific community, particularly the National Research Council, advocates for the application of precision medicine to supersede the ambiguous term personalized medicine, therefore elucidating the true objective of the discipline (21). Nonetheless, individualized medicine is becoming acknowledged by all people. Historically, stage II and III tumor clinical studies have assessed

results through histology; however, the histological examination may not sufficiently represent the impacts of gene-targeted medicines or immunotherapy (22). PM methods evaluate patients' circulating DNA (liquid biopsy), immunological indicators, and other biological characteristics to determine effectiveness and guide therapy options. Genomic indicators have shown to be the most successful thus far; however, new biomarkers, such as protein analysis and transcriptomics, are presently being developed and evaluated (23). Numerous molecular abnormalities have been detected by sequencing and high-throughput innovations, resulting in the authorization of targeted medications by the FDA. The precision medicine paradigm has recently been dominated by immunology and its association with genome research, since genetic features, including mismatch repair gene deficiencies, are major drivers of checkpoint inhibition efficacy (24).

Current and upcoming molecular techniques for PM

Integrating PM with other diagnostic procedures in clinical settings

Initially, it is essential to acknowledge the vital connections between research and routine diagnostic procedures in precision oncology (25). Extensive research studies may reveal new clinically relevant indicators, which might then be used as a groundbreaking standard diagnostic tool to enhance patient outcomes. Numerous tumor-specific molecular abnormalities, such as protein amplification, mutations in driver genes, or modifications, have been established as reliable predictors of response to targeted therapy, and novel markers are constantly developing (26). As a result, clinical molecular pathology assessment has become a key lab tool for understanding tumor behavior and directing therapy choices. Standard tests like as immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) are critical tools in precise medicine, with various markers discovered utilizing these procedures (27). IHC may detect modifications at the protein level due to genetic abnormalities, primarily gene amplifications, with specific DNA rearrangements or point mutations, such as EML4-ALK rearrangement in non-small cell lung cancer (NSCLC) (28).

Since the occurrence of druggable gene abnormalities and indicators that predict cancer growth, NGS technologies have increasingly replaced traditional methods, like single-gene testing and focused mutational systems, in regular biological pathology studies (29). Traditional methods have improved their accuracy and sensitivity in detecting actionable alterations that benefit from related targeted medicines, as well as mutations that cause resistance to particular drugs. Nonetheless, these systems demand that each marker be pre-defined for detection, requiring a personalized test for each analyte (30). NGS allows for the simultaneous investigation of several genome modifications, such as genetic mutations, copy number variations (CNV), modifications, and gene combinations (31, 32).

Thus, it provides a more accurate, economical, and tissue-conserving approach to tumor analysis compared to sequential single-biomarker evaluations, particularly considering the genetic complexity associated with malignancies (33). Several studies comparing the usefulness of NGS to reverse transcriptase based-(RT-PCR) focused mutation systems, single-gene testing, and various other traditional approaches indicate equivalent precision and selectivity in finding frequent druggable chromosomal aberrations in current practice (34). The declining prices and faster processing times of NGS, enhancements in computational biology assessments, and the standardization of databases to improve the clinical assessment of genomic results make the shift to extensive genome-wide analysis through NGS in patient trials compelling in the context of personalized oncology (35).

Contemporary utilization of next-generation sequencing methodologies

NGS may be confined to a small collection of genes, focus on the coding sections of the genome, or conduct a thorough analysis of the complete tumor genome, including intronic regions. The selection between these approaches is based on many parameters, including the intended use of tumor testing (clinical appointments versus research), required outputs, technical effectiveness, and cost (31). To yet, WES and WGS remain primarily within the investigation sphere,

focused on gathering comprehensive genetic data for translational studies that may improve our knowledge of cancer biology over the years (36). The practical relevance of assessing all genes within large sections is questionable; yet, the benefits of concurrent multi-gene screening by NGS and the minimal additional costs related to adding more genes stimulate the adoption of more broad genomic assessment in clinical scenarios (37). A key issue is that, despite extensive tumor sequencing and genotype-matched studies identifying curable mutations in driver genes in up to 40% of persons, only a much lower number (10-15%) are treated with genotype-matched medicines (38).

Several variables are at play, but the main difficulty is the absence of licensed or experimental medicines that correspond to particular driver changes. Recruiting individuals with unusual molecular disorders for research studies creates challenges and slows the discovery of novel treatments. In addition, intratumoral variety (e.g., trunk versus extended alterations) and the evaluation to identify whether a certain genetic change acts as a "true" driver in a particular tumor may significantly affect the success of the related treatment (39). Hess et al. have shown that numerous somatic hotspot modifications, formerly considered "drivers" in cancer, may actually be recurring passenger mutations occurring in highly changeable parts of the genome (40).

Improvements in sequencing technology, including whole genome sequencing, enabled concurrent detection of single nucleotide modifications, changes in copy number, and changes in a structure such as gene fusions, hence enhancing the diagnostic effectiveness of relevant discoveries in tumor samples (41). The new research analyzed 2,520 examples of metastatic cancers and their matched healthy tissue to underscore the necessity for complete genetic profiling. Whole genome sequencing (WGS) was used to record the genetic alterations observed in each cancer metastasis, thereby elucidating the genomic anomalies in the metastasis of 22 solid tumors, with 62 percent expressing at least one identifiable mutation (41, 42).

Recent sequencing methods have expanded the length of reading sections beyond several kilobases, thereby boosting the ability to find complex structural differences in the genome (43). Research using genomic DNA from individuals with various brain malignancies successfully identified SNV, CNV, and methylation patterns concurrently by a low-pass whole genome sequencing method employing long-read sequencing. In oncology, the bulk of long-read sequencing efforts has focused on RNA sequencing, which has revealed novel combining and splicing variants related to tumor development or resistance to therapy. At present, the incidence of mistakes of long-read techniques is excessive for somatic variation detection; nevertheless, the transition to these approaches for tumor evaluation might give an integrated approach for genomic tumor characterization and better-personalized therapy management (44, 45).

Biomarkers

The quality, amount, and accessibility of tissue specimens from individuals with cancer pose hurdles to the successful application of customized treatment. The chemical treatment of formalin-fixed, paraffin-embedded tissues may modify genetic material, and reduced cancer levels in specimens may impair the accuracy of assays or lead to incorrect alteration identifications (31). Furthermore, using preserved samples or lesions from a particular time point shouldn't effectively depict intratumoral variability across geographic or temporal dimensions. The collecting of many tumor specimens is hampered by the requirement for intrusive procedures that risk patient safety and cost large resources (46-48).

The evaluation of circulatory tumor-specific biomarkers is a growing area that might address several difficulties with tumor specimens. This comprises circulating tumor cells (CTC), circulating tumor DNA (ctDNA), and other RNAs, proteins, or chemicals found in bodily fluids like as plasma, urine, and intraperitoneal or cerebral spinal fluid. Liquid biopsies are readily accessible utilizing less-invasive technologies that provide a continual and dynamic evaluation of tumor-specific assessment, and predictive or diagnostic signs (49, 50). Next-generation sequencing can be used to analyze plasma CTCs and ctDNA, supplying a greater understanding of the tumor's genetic architecture than traditional tumor tissue evaluation, because it spans several areas of the

tumor (including both original and spread locations) and resolves intratumoral variability (51).

Currently, there are no FDA-approved diagnostics for identifying and assessing these conditions, and their therapeutic value is uncertain (52). MiRNAs are important because of their longevity and frequency in the bloodstream, and their fingerprints are being studied as markers for diagnosis and prognosis in a variety of kinds of tumors, particularly for the detection of minimum remaining illness. The primary obstacles, nevertheless, continue to be the unpredictability and absence of repeatability in research outcomes caused by unclear data gathering and processing procedures. There is an essential demand for academic consistency to maximize the possibility of liquid samples in clinical situations, and numerous projects are presently in the works to fulfil this requirement (53, 54).

Challenges and prospects of PM in oncology

Although significant progress in precision oncology, critical constraints and obstacles of genome-guided treatment persist, necessitating resolution to facilitate larger and more effective clinical applications and optimize patient outcomes. Initially, during clonal development in carcinogenesis and cancer progression, malignancies acquire several pro-oncogenic genetic abnormalities (55). As a result, tumors vary and become more subclonal as the sickness progresses. As a result, treatment effectiveness in late cancer phases is essentially constrained owing to the considerable likelihood of underlying genetic features that enable malignancies to escape single-target customized therapy (56). Focusing on certain cancer-driver genes during the early stages of treatment may result in a more significant anti-cancer impact. In subsequent decades, the early implementation of tailored treatment strategies in medical care may give better therapeutic effectiveness (57).

Furthermore, our knowledge of how to assess the toxicity of detected genetic changes limits cancer precision. Cancers often obtain multiple passenger co-mutations that aren't necessary for tumor development (58). Furthermore, normal tissues show a buildup of genetic mutations with different clinical implications. Somatic alterations in blood cell production that grows with age are often identified in the clinical examination of circulating tumor DNA, therefore lowering the accuracy of the disclosed mutational patterns (58).

Furthermore, changes in other typical pro-oncogenic driver genes were found in several non-malignant diseases (59). Future improvements may address these constraints by using tailored models to assess the functional ramifications of detected genetic changes and the most relevant therapy targets at the RNA, protein, or physiological stages. Furthermore, the introduction of artificial intelligence-driven technologies may enhance the pathological and therapeutic interpretation of molecular testing (60).

Thirdly, from a pragmatic standpoint, project management in oncology is now hindered by several structural and technical constraints. The interval between the initiation of genetic testing and the implementation of personalized medications may last a few weeks (61). Therefore, in a primarily progressed oncological therapeutic scenario, a considerable percentage of persons are lost throughout the operation. Furthermore, the availability of recent tissue specimens is often critical for gathering accurate genetic data on the present molecular composition of cancer, owing to the modular formation and genetic causes of treatment tolerance that may evolve after past treatments for cancer (62). As a consequence, customized oncology is often dependent on the efficacy of sophisticated tissue collection and biopsy, which could impact the balance between risk and benefit for this therapy strategy. Future improvements in liquid biopsies by examining circulating tumor DNA may obviate the need for additional tissue-based analysis (63).

The primary barrier to global adoption of precision oncology is the financial strain of comprehensive genetic sequencing and, more importantly, the cost of personalized treatments (64). Unfortunately, the availability of genetic testing and personalized cancer therapy is now restricted to a small percentage of cancer patients in wealthy countries. In the long term, improved precision in selecting targeted cancer therapies through improved forecasting of therapeutic advantages may lower expenses in comparison to conventional unguided therapy by enabling patient treatment and averting hospital stays due to disease-

related adverse effects. A significant need exists for research specifically focused on efficiency evaluations of the precision oncology approach (65, 66).

CONCLUSION

The medical care of cancer patients is undergoing a notable shift towards personalized therapy through the application of molecular diagnostic technologies. Substantial restrictions remain that need to be resolved to enhance patient outcomes, notably the degree of cancer-specific variation in genes, the meaning and therapeutic classification of identified genetic anomalies, and current technology limits in molecular testing. A deeper understanding of complex molecular processes, achieved by integrating various genetic and functional investigations within an advanced personalized healthcare decision-making framework, as well as a better capacity to rapidly identify and monitor personal cancer-driving molecular changes via liquid biopsy specimens, will soon profoundly alter the present knowledge of tumor biology and therapies.

Authors' Contribution

Conceptualization and reviewing the manuscript draft: Mina Ekrami Noghabi, Design and Writing of the manuscript draft: Maryam Abbasi Saeidi.

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Ethics approval and consent to participate

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