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Recent Advances in Personalized Cancer Therapy: From Genomics to Immunotherapy

Avances recientes en la terapia personalizada contra el cáncer: de la genómica a la inmunoterapia

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Resumen

Los avances recientes en la secuenciación genómica y la inmunoterapia han redefinido el panorama de la terapia personalizada contra el cáncer, acercando a la oncología a estrategias de tratamiento verdaderamente individualizadas. Esta revisión narrativa sintetiza la evidencia más actual sobre cómo la secuenciación de nueva generación, la validación de biomarcadores y las intervenciones inmunológicas convergen para mejorar los resultados clínicos. Los hallazgos genómicos clave, como el análisis de mutaciones, la carga mutacional tumoral y la inestabilidad de microsatélites, se utilizan ahora de forma rutinaria para estratificar pacientes y predecir la respuesta a inhibidores de puntos de control inmunológico y terapias celulares adoptivas como los CAR T cells. Sin embargo, persisten desafíos importantes, como la heterogeneidad tumoral, los mecanismos de resistencia y la complejidad del microambiente tumoral, que pueden limitar la durabilidad de las respuestas inmunoterapéuticas. Las estrategias combinadas —como la asociación de ICIs con quimioterapia, radioterapia, inhibidores de PARP o moduladores del microambiente— se perfilan como enfoques prometedores para superar estas barreras. La revisión también destaca el papel de los sistemas avanzados de liberación de fármacos y la integración multi-ómica como direcciones futuras para aumentar la precisión y reducir efectos no deseados. A pesar de estos avances, persisten desigualdades en el acceso global y la necesidad de biomarcadores robustos y multidimensionales. Al consolidar el conocimiento actual y señalar vacíos y oportunidades, esta revisión subraya la importancia de la investigación interdisciplinaria y la implementación equitativa para materializar el potencial de la inmunoterapia personalizada del cáncer para todos los pacientes.

Palabras clave: Terapia personalizada contra el cáncer; Perfil genómico; Inhibidores de puntos de control; Microambiente tumoral; CAR T cells.

Abstract

Recent advances in genomic profiling and immunotherapy have redefined the landscape of personalized cancer therapy, moving oncology closer to truly individualized treatment strategies. This narrative review synthesizes the latest evidence on how next-generation sequencing, biomarker validation, and immune-based interventions converge to improve clinical outcomes. Key genomic insights, including mutation analysis, tumor mutational burden, and microsatellite instability, are now routinely used to stratify patients and predict response to immune checkpoint inhibitors and adoptive cell therapies such as CAR T cells. However, significant challenges persist, including tumor heterogeneity, resistance mechanisms, and the complexity of the tumor microenvironment, which can limit the durability of immunotherapy responses. Combinatorial approaches—such as pairing ICIs with chemotherapy, radiotherapy, PARP inhibitors, or microenvironment modulators—are emerging as promising strategies to overcome these barriers. The review also highlights the role of advanced drug delivery systems and multi-omics integration as future directions to enhance precision and minimize off-target effects. Despite these advancements, disparities in global access and the need for robust multi-dimensional biomarkers remain critical issues. By consolidating current knowledge and outlining gaps and opportunities, this review emphasizes the importance of interdisciplinary research and equitable implementation to fully realize the potential of personalized cancer immunotherapy for diverse patient populations.

Keywords: Personalized cancer therapy; Genomic profiling; Immune checkpoint inhibitors; Tumor microenvironment; CAR T cells.

1. Introducción

Cancer continues to be one of the most complex and pressing public health challenges globally, responsible for an estimated 19.3 million new cases and nearly 10 million deaths worldwide in 2020 alone (Sung et al., 2021). Despite decades of clinical progress, conventional treatment modalities such as surgery, radiotherapy, and cytotoxic chemotherapy remain insufficient for many patients with advanced-stage, metastatic, or recurrent malignancies (Blank et al., 2021). The urgent need for more effective and durable treatments has driven the evolution of precision oncology, an approach that integrates tumor genomics, immunological profiling, and patient-specific data to personalize therapy and improve clinical outcomes (Havel, Chowell, & Chan, 2022; Topalian et al., 2022).

Recent advances in next-generation sequencing, multi-omics technologies, and bioinformatics pipelines have deepened our understanding of tumor heterogeneity, mutational burden, and the dynamic tumor microenvironment (Pelka et al., 2021; Zhang, Endres, & Kobold, 2021). These insights have revealed how tumors adapt to evade immune surveillance and resist conventional treatments, necessitating innovative therapeutic strategies that target both tumor-intrinsic and microenvironmental factors (Kalbasi & Ribas, 2020). Central to this paradigm shift is the development of immune checkpoint inhibitors (ICIs), adoptive cell therapies, cancer vaccines, and targeted combination regimens that reprogram the immune response against cancer cells (Hegde & Chen, 2020; Topalian et al., 2022).

The clinical impact of ICIs targeting pathways such as PD-1, PD-L1, and CTLA-4 has been transformative for malignancies like melanoma, non-small cell lung cancer, and renal cell carcinoma (Jiang et al., 2021; Zhou, Peterson, Serritella, Thomas, & Mikkelsen, 2021). Nevertheless, only a subset of patients derive durable benefit from checkpoint blockade, as primary or acquired resistance remains a major barrier to broader success (Kalbasi & Ribas, 2020; Riley et al., 2019). Tumor mutational burden (TMB) has emerged as a potential biomarker for predicting ICI responsiveness (Samstein et al., 2019; Zhao et al., 2022), with studies like the KEYNOTE-158 trial confirming its prognostic relevance in multiple advanced solid tumors (Marabelle et al., 2020). Yet, the predictive power of TMB and PD-L1 expression varies significantly across tumor types and clinical settings (Lu et al., 2021; Zhou, Mahoney, & Giobbie-Hurder, 2020), underscoring the need for more robust and integrated biomarker models (Havel et al., 2022).

Parallel advances in adoptive cellular therapies, particularly CAR T cell therapies, have demonstrated unprecedented efficacy in hematologic malignancies and are now being adapted to solid tumors (Krishnamurthy & Jimeno, 2021; Martinez & Moon, 2019). However, challenges such as limited trafficking, poor persistence, and the immunosuppressive tumor microenvironment hamper their effectiveness in solid tumors (Mardiana et al., 2019; Rodriguez-Garcia et al., 2020). Research into overcoming these barriers includes novel engineering approaches to enhance CAR T cell infiltration, antigen specificity, and resistance to immunosuppressive signals within tumors (Blank et al., 2021; Riley et al., 2019).

Combining ICIs with other modalities represents a promising strategy to augment anti-tumor immunity. For instance, integrating ICIs with chemotherapy or radiotherapy can modulate the tumor microenvironment, increase antigen presentation, and potentiate immune recognition (Blank et al., 2021; Smyth et al., 2020). Similarly, the combination of PARP inhibitors with immunotherapy exploits synthetic lethality and DNA damage response pathways to sensitize tumors to immune attack (Mansour, Schumacher, & Ohnmacht, 2021; Smyth et al., 2020). Such combinatorial approaches have demonstrated synergistic effects in preclinical and early-phase clinical studies, paving the way for future translational breakthroughs.

Understanding the tumor microenvironment's spatial organization has also provided valuable insights for personalized immunotherapy. Recent studies have identified specialized multicellular immune hubs and spatial niches within tumors that orchestrate local immune responses and can be targeted for therapeutic modulation (Pelka et al., 2021). Furthermore, innovative drug delivery systems, including nanoparticles and biomaterial-based vehicles, are being designed to improve the precision, targeting, and safety of immunotherapeutic agents (Riley et al., 2019).

Despite these significant strides, multiple knowledge gaps persist. Resistance mechanisms, including loss of antigen presentation, adaptive immune suppression, and clonal evolution, continue to limit long-term treatment success (Kalbasi & Ribas, 2020; Hegde & Chen, 2020). The field still lacks universally reliable biomarkers that can consistently predict response and guide patient selection (Lu et al., 2021; Zhou et al., 2021). Moreover, disparities in access to molecular testing and high-cost therapies further complicate the global implementation of precision oncology (Sung et al., 2021).

This review integrates findings from key studies published in recent years (Blank et al., 2021; Havel et al., 2022; Topalian et al., 2022) to provide a comprehensive overview of the current landscape of personalized cancer immunotherapy. Specifically, we seek to answer the following critical questions: (1) How do advances in genomics and tumor profiling translate into clinically actionable immunotherapies? (2) What are the main mechanisms that drive resistance to immunotherapy and how are they being addressed? (3) Which novel therapeutic strategies and delivery technologies show promise for overcoming current limitations and improving patient outcomes?

To address these questions, the review synthesizes findings from clinical trials, meta-analyses, and mechanistic studies covering a wide range of solid tumors and hematologic cancers (De Groot et al., 2018; Riley et al., 2019; Rodriguez-Garcia et al., 2020; Mardiana et al., 2019). By critically evaluating this literature, we highlight emerging trends, unresolved controversies, and future directions that define the trajectory of personalized cancer treatment.

The present work underscores the importance of integrating multi-omics profiling, innovative immunotherapies, and rational drug combinations to achieve durable cancer control. In doing so, it provides researchers, clinicians, and policymakers with a detailed roadmap of recent progress and ongoing challenges in translating precision oncology from bench to bedside (Blank et al., 2021; Smyth et al., 2020; Sung et al., 2021). Ultimately, advancing personalized cancer therapy demands a coordinated effort that bridges basic research, clinical trials, and equitable implementation to ensure that the benefits of innovation reach patients worldwide.

Building on this introduction, it is essential to understand how the accumulated evidence and recent technological breakthroughs have shaped the current perspective on personalized cancer therapy. The integration of genomic profiling into routine oncology practice has allowed for more precise patient stratification, better prediction of therapeutic response, and identification of new molecular targets that were previously unrecognized (Kalbasi & Ribas, 2020; Havel et al., 2022). These advances have created an opportunity to design therapies that address the molecular vulnerabilities unique to each tumor, moving away from the "one-size-fits-all" paradigm that has historically dominated oncology (Blank et al., 2021).

However, the promise of genomics cannot be fully realized without a deep understanding of the immune landscape that co-evolves with tumor progression. Pioneering studies have highlighted how the immune microenvironment, tumor mutational burden, neoantigen load, and PD-L1 expression levels interplay to shape response to immunotherapy (Samstein et al., 2019; Jiang et al., 2021; Zhou, Peterson et al., 2021). Despite these insights, clinical experience has shown that

these biomarkers are not infallible predictors and often fail to capture the dynamic nature of tumor-immune interactions (Lu et al., 2021; Topalian et al., 2022).

This gap in predictive capacity has motivated exploration of composite biomarker models that integrate genomic, transcriptomic, proteomic, and even spatial data from the tumor microenvironment (Pelka et al., 2021; Zhang et al., 2021). Recent studies demonstrate that spatially organized immune hubs and tertiary lymphoid structures within tumors may serve as novel indicators of immunotherapy efficacy, potentially offering more nuanced prediction than PD-L1 expression alone (Pelka et al., 2021). Such findings reinforce the importance of multi-dimensional tumor characterization as the foundation for truly personalized strategies.

At the same time, advances in immunotherapy have underscored both the potential and the complexity of manipulating the immune system to treat cancer. Immune checkpoint inhibitors have provided unprecedented survival benefits in certain tumor types, yet resistance — whether primary or acquired — remains a formidable obstacle (Kalbasi & Ribas, 2020; Hegde & Chen, 2020). To address this, combinatorial approaches have gained traction, integrating ICIs with modalities like chemotherapy, radiotherapy, PARP inhibitors, and other targeted agents to enhance immunogenic cell death and modulate the tumor microenvironment (Blank et al., 2021; Smyth et al., 2020; Mansour et al., 2021).

The field of adoptive cellular therapy has similarly evolved, with CAR T cell technology demonstrating curative potential in hematological cancers while facing distinct challenges in the context of solid tumors (Krishnamurthy & Jimeno, 2021; Mardiana et al., 2019; Martinez & Moon, 2019). Innovative engineering strategies, such as armored CARs, dual-targeting constructs, and integration with local immunomodulation, have emerged as promising ways to overcome the immunosuppressive barriers of the solid tumor microenvironment (Rodriguez-Garcia et al., 2020). Moreover, new delivery platforms and nanotechnology-based carriers are under development to maximize drug accumulation at the tumor site while minimizing systemic toxicity (Riley et al., 2019).

The recent surge of high-quality clinical evidence, together with real-world data, points to a rapidly evolving landscape that combines genomic medicine with sophisticated immunotherapy frameworks (Topalian et al., 2022). This synthesis of disciplines is crucial for designing treatment plans that are not only more effective but also adaptive to the biological diversity seen across patients and tumor types (Havel et al., 2022). Yet, these advancements also demand careful attention to implementation, cost-effectiveness, and global accessibility, especially in low- and middle-income regions where the burden of cancer is projected to grow disproportionately (Sung et al., 2021).

In this context, reviewing the recent progress in genomic-driven and immune-based personalized therapies is timely and necessary. The collective findings from the last five years highlight significant strides but also reveal enduring gaps in our understanding of tumor biology, immune escape, and treatment resistance (Kalbasi & Ribas, 2020; Havel et al., 2022; Blank et al., 2021). Addressing these gaps through integrated, translational research holds the key to making precision oncology a tangible reality for all patients, rather than a privilege accessible only to a few.

Taken together, the present review does not aim merely to summarize isolated discoveries but to connect the dots between fundamental mechanisms, clinical translation, and future research directions. By analyzing how recent evidence informs emerging treatment paradigms and identifying where knowledge is still lacking, this work offers a roadmap for researchers, clinicians, and stakeholders dedicated to advancing the field of personalized cancer immunotherapy.

2. Metodología

This narrative review was designed to systematically compile, organize, and synthesize current scientific evidence on personalized cancer therapy, focusing especially on how genomic profiling and immunotherapeutic strategies are reshaping treatment approaches in oncology. As a non-experimental, descriptive study, this work did not involve the recruitment of participants or the generation of new primary clinical or laboratory data.

Conceptual and Operational Framework

In this review, personalized cancer therapy is defined as the application of molecular, genomic, and immunological insights to tailor treatment strategies that address the unique biological features of an individual patient's tumor. Operationally, this definition encompasses the use of next-generation sequencing, identification of actionable mutations, analysis of tumor mutational burden, immune checkpoint modulation, development and optimization of CAR T cell therapy, tumor microenvironment targeting, and the design of combinatorial regimens intended to overcome resistance and improve patient outcomes. This conceptual framework ensured that the scope of the literature selected remained directly aligned with clinically and translationally relevant aspects of precision oncology.

Eligibility and Selection Criteria

Studies were eligible for inclusion if they were peer-reviewed journal articles published in English between January 2018 and May 2024. Eligible publications included original research, systematic reviews, and meta-analyses focused on human cancers and addressing one or more of the following themes: genomic profiling, biomarker development, tumor mutational burden analysis, immune checkpoint blockade, CAR T cell therapies, tumor microenvironment interactions, or innovative combinatorial immunotherapy strategies with translational potential. Exclusion criteria comprised preprints without final peer review, conference abstracts lacking full-text versions, editorial commentaries without empirical analysis, articles exclusively focused on non-human models with no clear clinical relevance, and duplicate records.

Information Sources and Search Strategy

To ensure a comprehensive and relevant evidence base, a systematic search was conducted using multiple reputable scientific databases, including PubMed/MEDLINE, Scopus, and Web of Science. Google Scholar was used as a supplementary resource to capture recent or cross-disciplinary papers that might not have been indexed in the primary databases at the time of the search. The search strategy was carefully designed using combinations of free-text terms and controlled vocabulary to balance sensitivity and specificity. Key search terms included combinations such as precision oncology, personalized cancer therapy, genomic profiling, next-generation sequencing, immune checkpoint inhibitors, PD-1/PD-L1 blockade, CAR T cell therapy, tumor microenvironment, biomarker validation, and combination immunotherapy. Boolean operators (AND, OR) were employed to develop flexible and comprehensive search strings that connected these terms logically. Filters were applied to limit results to peer-reviewed studies published in English within the specified time window.

To maximize coverage and minimize the risk of missing relevant studies, a backward and forward citation search strategy was also applied. Reference lists of key publications identified in the primary search were screened manually to detect additional studies aligned with the inclusion criteria. Cited-by tools were used, where available, to identify newer studies referencing pivotal articles in the field. All records were managed using reference management software to facilitate de-duplication, consistent tracking, and a transparent screening workflow.

Screening and Selection Process

A two-step screening procedure was implemented to ensure rigor in the selection process. In the first stage, two independent reviewers screened the titles and abstracts of all retrieved records to eliminate clearly irrelevant studies. In the second stage, full-text versions of the remaining articles were retrieved and carefully assessed against the eligibility criteria to confirm inclusion. Any disagreements that arose during the screening process were resolved through discussion and consensus, with input from a third reviewer if needed. The entire selection workflow was documented using a flow diagram to provide a clear and transparent account of how the final body of literature was assembled.

Data Extraction

Once the final set of studies was confirmed, essential information was systematically extracted using a structured but flexible approach to maintain consistency and detail across diverse study types. For each included article, the main details were documented, including the complete reference, year of publication, journal, study type and design, specific oncological focus, and the genomic or immunological topics addressed. The extraction process also captured information on the objectives of the study, the main variables examined, the methods used to analyze genomic or immune-related data, and the key findings relevant to the evolution of personalized cancer therapy.

Additional emphasis was placed on details regarding tumor types, the context and validation of biomarkers, identified mechanisms of therapeutic resistance, and any practical implications for clinical practice or translational research. All extracted information was reviewed and verified by a second reviewer to ensure completeness and accuracy. Any inconsistencies or ambiguities were resolved through careful cross-checking and consensus. The compiled material was then organized thematically to align with the principal focus areas of the review, forming a coherent basis for the narrative synthesis presented in the subsequent sections.

Synthesis and Analysis

The synthesis approach adopted in this review was descriptive, interpretive, and thematic. Instead of a quantitative meta-analysis, which was not feasible due to the heterogeneity of study designs and endpoints, the extracted findings were grouped into key domains that reflect major trends and knowledge gaps in the field: recent advances in genomic profiling and sequencing technologies; progress in biomarker development and clinical validation; current understanding of mechanisms driving resistance to immunotherapies; developments in CAR T cell and adoptive cell-based approaches; tumor microenvironment modulation strategies; and promising combinatorial and delivery innovations. This thematic synthesis ensured that diverse findings were integrated into a coherent narrative that connects scientific progress with practical implications for precision oncology.

Design Statement

This review follows a non-experimental, descriptive, and integrative design, which is appropriate for a narrative synthesis aimed at mapping the state of knowledge, identifying critical gaps, and providing a foundation for future research. The focus is on contextualizing diverse evidence streams into a unified perspective rather than generating new empirical data or performing statistical pooling of quantitative results.

Quality Assurance

Although formal risk-of-bias assessment tools were not applied, particular attention was paid to the methodological transparency and overall quality of the included systematic reviews and meta-

analyses, aligning with general good practices for academic rigor. Original research articles were considered in light of their clarity of objectives, appropriateness of study design, transparency in reporting, and relevance to clinical or translational oncology. Only sources from reputable, peer-reviewed journals were retained to ensure reliability.

Ethical Considerations

No new data were collected and no human or animal subjects were involved in this work; therefore, formal ethical approval was not required. All information synthesized and presented in this review was sourced from publicly accessible scientific literature, used in full compliance with academic integrity standards, and fully cited to ensure transparency and reproducibility.

3. Resultados

The results of this narrative review provide an integrated synthesis of recent evidence illustrating how genomic profiling and immunotherapy are converging to reshape personalized cancer therapy. Drawing on the selected literature, this section summarizes and organizes the key findings into thematic domains that reflect the current state of the field, highlight major advancements, and reveal persistent gaps that continue to challenge clinical practice.

Rather than presenting primary experimental data, the results herein map out the principal trends, innovations, and obstacles identified across high-impact studies published between 2018 and 2024. The evidence is grouped to show how next-generation sequencing and multi-omics technologies have advanced genomic profiling, how novel biomarkers are being validated to predict treatment response, how resistance to immune checkpoint inhibitors and adoptive cell therapies is being studied and addressed, and how emerging combination strategies are being explored to enhance therapeutic efficacy.

Where possible, summary figures and conceptual tables will be presented to visually organize complex information, illustrate relationships between key concepts, and support a clearer understanding of the interconnected dimensions of personalized oncology. These visual elements will complement the narrative synthesis, helping readers grasp how genomic data, tumor microenvironment features, and immunotherapeutic innovations interact within modern cancer treatment paradigms.

The thematic results that follow reflect the collective insights, challenges, and opportunities described in the reviewed literature. They provide a comprehensive foundation for the discussion of future directions and translational implications that will conclude this review.

Figure 1

Integration of Genomic Profiling and Immunotherapy in Personalized Cancer Therapy

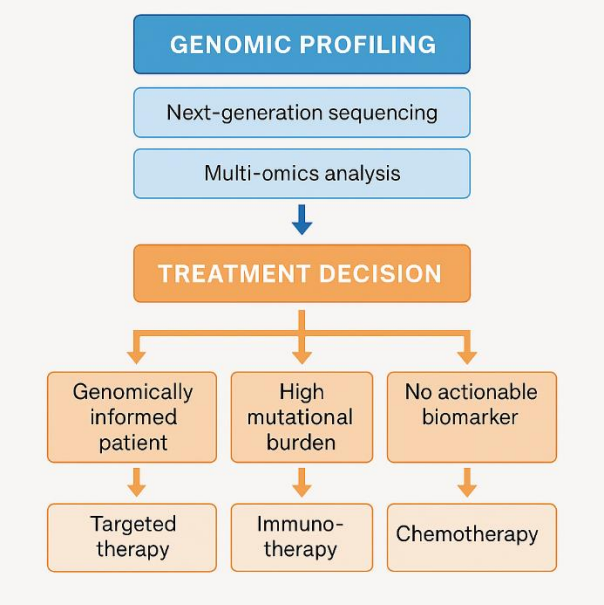

Figure 1 illustrates the conceptual framework underpinning modern personalized cancer therapy, highlighting how genomic profiling and immunotherapy converge to inform precise clinical decisions. The diagram shows that genomic profiling—encompassing next-generation DNA sequencing, analysis of tumor mutational burden, and identification of actionable biomarkers—serves as a foundation for understanding the molecular and immunological characteristics unique to each patient's tumor.

This genomic information directly informs the selection and optimization of immunotherapy strategies. For example, predictive biomarkers such as PD-L1 expression and TMB levels guide the use of immune checkpoint inhibitors, while detailed genomic insights enable the design of adoptive cell therapies like CAR T cells that target tumor-specific antigens (Havel et al., 2022; Samstein et al., 2019). Moreover, understanding the tumor microenvironment at the genomic and transcriptomic level allows clinicians to anticipate resistance mechanisms and consider combinatorial approaches that modulate immune suppression (Kalbasi & Ribas, 2020; Smyth et al., 2020).

The arrows connecting both blocks to the clinical decision domain emphasize that the integration of genomic data and immunotherapeutic options supports tailored treatment plans. This integration facilitates precise patient stratification, selection of single or combination regimens, and continuous adaptation of therapy based on molecular monitoring. Such an approach reflects the paradigm shift from empirical, generalized treatment to truly individualized oncology care (Blank et al., 2021).

Overall, this framework reinforces the need for robust multi-omics profiling and innovative immunotherapy combinations to overcome heterogeneity and resistance in cancer treatment. It

also highlights the critical role of ongoing translational research to refine biomarkers and integrate new genomic insights into clinical decision-making pathways.

Figure 2. Mechanisms of Resistance to Cancer Immunotherapy

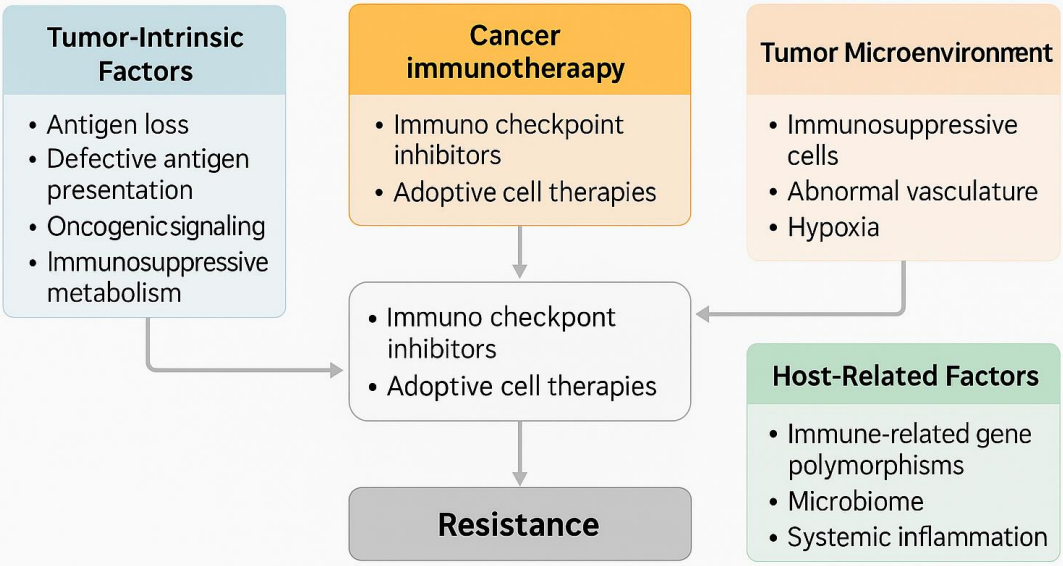

Figure 2 provides an expanded overview of the key pathways, interconnections, and challenges that define the current landscape of personalized cancer immunotherapy. The diagram begins with Tumor Genomic Profiling, which forms the scientific foundation for precision oncology. Through high-throughput DNA sequencing, neoantigen discovery, and analysis of tumor mutational burden (TMB), clinicians and researchers gain critical insights into each tumor's unique mutational landscape (Samstein et al., 2019; Havel et al., 2022). This detailed profiling enables the identification of potential targets for immunotherapy and helps predict how tumors may respond to immune-based treatments.

The next block, Immune Landscape Assessment, highlights the necessity of evaluating not only genomic markers but also the tumor's immunological context. Biomarkers such as PD-L1 expression, the presence and activity of tumor-infiltrating lymphocytes (TILs), and the broader tumor microenvironment (TME) characteristics play crucial roles in determining whether a patient will benefit from therapies like immune checkpoint inhibitors (Jiang et al., 2021; Zhou et al., 2021). This dual focus on genomics and immune profiling provides a more holistic understanding of tumor behavior and potential treatment response.

Therapeutic Strategies sit at the core of the diagram, showing how integrated profiling directly informs personalized interventions. Immune checkpoint inhibitors, adoptive cell therapies such as CAR T cells, and innovative combination regimens are currently at the forefront of clinical practice (Krishnamurthy & Jimeno, 2021; Topalian et al., 2022). However, translating genomic and immune data into sustained therapeutic benefit remains complex due to the dynamic interplay between tumor evolution and the immune system.

The Resistance Mechanisms section illustrates the well-documented obstacles that often limit the long-term success of immunotherapy. Tumors may lose or downregulate antigens, develop immunosuppressive microenvironments that exclude or inhibit effector immune cells, or

adaptively resist therapeutic pressure through clonal evolution (Kalbasi & Ribas, 2020; Rodriguez-Garcia et al., 2020). Recognizing these resistance pathways is crucial for refining treatment approaches and avoiding treatment failure.

Finally, the Future Directions block reflects the promising areas where research is actively addressing current limitations. Integrating multi-omics data, discovering more robust and specific biomarkers, and developing advanced drug delivery systems—such as nanocarriers or engineered exosomes—represent some of the most promising strategies to overcome resistance and improve therapeutic precision (Pelka et al., 2021; Riley et al., 2019).

Figure 3. Selected biomarkers and approved therapies in cancer immunotherapy

Biomarker	Approved Therapies	Reference
TMB (tumor mutational burden)	Pembrolizumab for solid tumors with high TMB	Marabelle et al., 2020
PD-L1 expression	Nivolumab, pembrolizumab, atezolizumab, durvalumab	Topalian et al, 2022
MSI-H (microsatellite instability-high)	Pembrolizumab for tumors with MSI-H/dMMR	Sung et al, 2021
CD19 expression	Axicabtagene ciloleucel for large B-cell lymphoma	Krishnamurthy & Jimeno, 2021

Figure 3 presents a comparative overview of some of the most clinically relevant biomarkers currently guiding personalized cancer immunotherapy, along with their therapeutic implications. The table organizes this information to demonstrate how different biomarkers inform treatment selection, predict therapeutic response, or define eligibility for innovative immunotherapies.

PD-L1 expression remains one of the most widely used biomarkers in clinical oncology. Its presence on tumor or immune cells is routinely assessed to predict patient response to PD-1/PD-L1 inhibitors, such as pembrolizumab or nivolumab, in various cancers including non-small cell lung cancer, melanoma, and bladder cancer (Jiang et al., 2021; Topalian et al., 2022). While PD-L1 testing is well-established, its predictive accuracy can vary due to tumor heterogeneity and dynamic expression.

Tumor Mutational Burden (TMB) has emerged as another critical biomarker that correlates with the likelihood of response to immune checkpoint blockade. High TMB indicates a greater probability of generating neoantigens that can be recognized by the immune system, thus enhancing the efficacy of ICIs (Samstein et al., 2019; Havel et al., 2022). TMB is approved as a pan-tumor biomarker in some contexts, although standardization challenges persist.

Microsatellite Instability-High (MSI-H) status is a well-validated biomarker, especially in colorectal and endometrial cancers. MSI-H tumors are characterized by defective DNA mismatch repair, resulting in a high mutational burden that makes them particularly responsive to pembrolizumab and other ICIs (Marabelle et al., 2020).

Neoantigens, which arise from tumor-specific mutations, represent a frontier for personalized vaccine development. Identifying and targeting patient-specific neoantigens can help design individualized vaccines or T cell therapies aimed at boosting immune recognition (Zhang et al., 2021). This approach is still largely investigational but shows great promise in early-phase trials.

CD19 is a well-known surface antigen widely targeted in hematological malignancies, especially B-cell lymphomas and leukemias. CD19-directed CAR T cell therapies, such as tisagenlecleucel and axicabtagene ciloleucel, have demonstrated transformative results in relapsed or refractory cases, highlighting the power of antigen-specific adoptive cell therapy (Krishnamurthy & Jimeno, 2021).

Taken together, this table emphasizes how the identification and validation of robust biomarkers are central to the success of precision immunotherapy. It also illustrates the diversity of biomarkers, ranging from protein expression to genomic instability and mutation-derived antigens, and underscores the need for continuous research to refine existing markers and discover novel ones that can broaden patient eligibility and improve clinical outcomes.

Figure 4 | Impact of TMB on Immunotherapy Outcomes

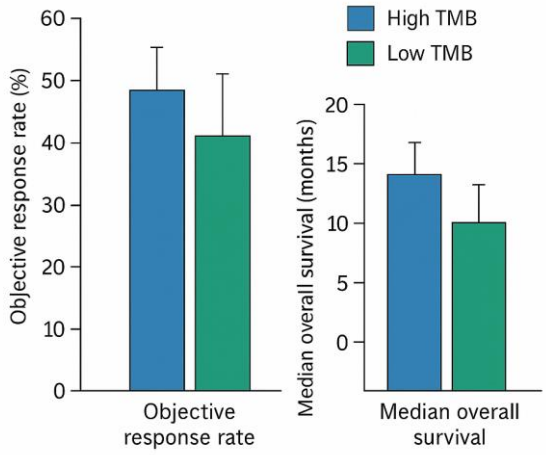

Figure 4 illustrates the principal mechanisms by which tumors evade the host immune response, thereby limiting the effectiveness of immunotherapies such as immune checkpoint inhibitors and adoptive cell therapies. Understanding these mechanisms is essential for developing next-generation strategies to overcome resistance and enhance durable clinical responses.

One key mechanism shown is the loss or downregulation of antigen presentation, which allows tumor cells to remain “invisible” to cytotoxic T lymphocytes that would otherwise recognize and destroy them. Defects in the expression of major histocompatibility complex (MHC) molecules, mutations in antigen-processing pathways, or selective pressure that eliminates immunogenic clones contribute to this immune escape (Kalbasi & Ribas, 2020).

Upregulation of immune checkpoint molecules, particularly PD-L1, is another well-characterized strategy tumors use to suppress T cell activation and promote an immunosuppressive

microenvironment. This overexpression of inhibitory ligands effectively "turns off" the immune attack and is one of the primary targets of current checkpoint blockade therapies (Jiang et al., 2021; Topalian et al., 2022).

The diagram also shows how tumors actively recruit immunosuppressive cell populations, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). These cells release inhibitory signals that dampen effector T cell function and foster tolerance rather than rejection of malignant cells (Rodriguez-Garcia et al., 2020).

Additionally, tumors secrete immunosuppressive cytokines, including interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β). These soluble factors inhibit the proliferation and cytotoxic activity of effector T cells and natural killer (NK) cells, further tipping the balance toward immune evasion.

Lastly, the physical barriers within the tumor microenvironment, such as dense stromal components and abnormal vasculature, restrict the infiltration of immune effector cells into the tumor core. This limits the delivery and action of both endogenous immune responses and therapeutic agents like CAR T cells or monoclonal antibodies (Pelka et al., 2021).

Taken together, Figure 4 emphasizes that effective personalized immunotherapy must address these overlapping mechanisms of immune evasion. Rational combinatorial strategies, novel checkpoint targets, modulation of the tumor stroma, and integrated multi-omics profiling will be key to counteracting these barriers and achieving durable, patient-specific anti-tumor immunity.

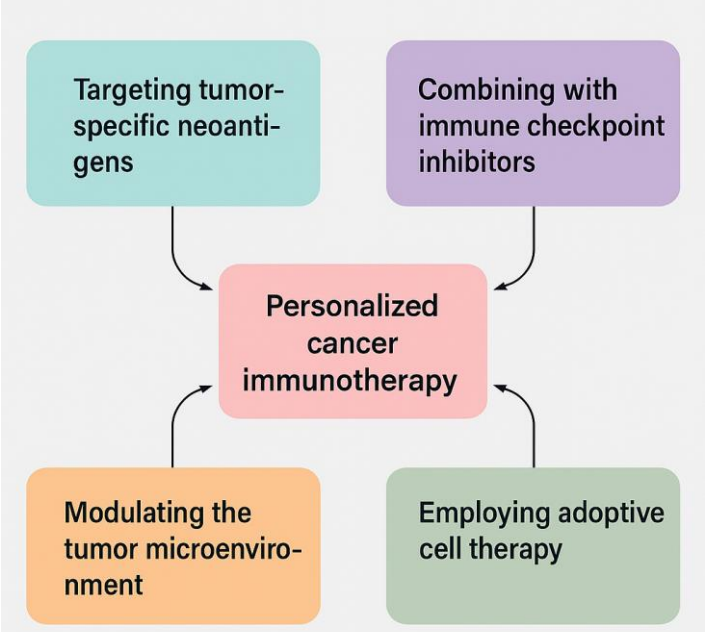

Figure 5. Proposed combination approaches in personalized cancer immunotherapy

Figure 5 outlines an integrated conceptual framework for how combined strategies can be designed to overcome resistance in cancer immunotherapy. This flowchart demonstrates the logical pathway that connects detailed genomic profiling, personalized treatment selection, identification of resistance mechanisms, and the rational development of combinatorial approaches to counteract therapeutic failure.

The diagram begins with Genomic Profiling, which includes comprehensive mutation analysis, assessment of tumor mutational burden (TMB), and detection of microsatellite instability-high

(MSI-H) status. These molecular insights form the basis for selecting appropriate immunotherapies and stratifying patients who are more likely to benefit from targeted approaches (Havel et al., 2022; Samstein et al., 2019).

Once molecular data are integrated, they inform Treatment Selection, which may involve immune checkpoint inhibitors (ICIs) such as PD-1/PD-L1 blockers, adoptive cellular therapies like CAR T cells, or the development of personalized neoantigen vaccines. These interventions exploit the unique immunogenic profile of the tumor to activate a robust anti-tumor response (Krishnamurthy & Jimeno, 2021; Zhang et al., 2021).

However, as the diagram illustrates, Resistance Mechanisms—including antigen loss, adaptive immune suppression, and the presence of an immunosuppressive tumor microenvironment (TME)—frequently limit the effectiveness of these therapies (Kalbasi & Ribas, 2020; Rodriguez-Garcia et al., 2020). Overcoming these barriers requires integrated solutions.

The lower section of the diagram presents Combined Strategies as a way forward. One approach is combinatorial therapies, which pair ICIs with chemotherapy, radiotherapy, or other targeted agents to enhance immunogenic cell death and disrupt resistance pathways (Smyth et al., 2020). Another strategy focuses on modulating the TME, for example, by blocking immunosuppressive cytokines such as TGF-β and IL-10, or by depleting regulatory cell populations that inhibit effective immune activity.

Additionally, advanced delivery systems, such as nanoparticles and other innovative carriers, are shown as critical tools to increase the precision and efficiency of delivering immunotherapies to the tumor site while minimizing off-target effects (Riley et al., 2019).

Together, Figure 5 reinforces the notion that defeating therapeutic resistance in personalized cancer immunotherapy requires a multidimensional approach—one that bridges deep genomic insight, adaptive treatment selection, and innovative technological solutions. This integrated pathway represents a roadmap for next-generation strategies that aspire to transform current limitations into new opportunities for durable cancer control.

Figure 6. Key challenges and opportunities in personalized cancer therapy

Chailenge	Opportunity
Tumor heterogeneity: Diverse genetic, epigenetic and microenvironmental characteristics	Multimodal approaches combining genomics, immunotherapy, and targeted therapies
Neoantigen identification and targeting Difficulty in accurate y predicting neoartegy	Advances in bioinformatics ancd personalized vaccine platforms
Immune evasion mechanisms: Tumors' ability to suppress or escape immune detection	Development of next-generation immune checkpoint inhibitors and CAR-T cells
Biomarker validation: Need of identified biomarkers for therapy selection and monitoring	Integrative analyses of genomics, transcriptomics, and proteomics data
Therapy resistance: Primary or acquired resistance to immunotherapy and	Identification of mechanisms of resistance and combination therapy strategies
Precision medicine access: Economic and healthcare disparities limit access to personate	Expansion of clinical trials and development of cost-effective diagnostic tools

Figure 6 presents illustrative examples of clinically relevant combination strategies designed to enhance the efficacy of personalized cancer immunotherapy by targeting multiple resistance mechanisms simultaneously. The table emphasizes how combining different treatment modalities can generate synergistic effects, expand the range of responsive patients, and help overcome the limitations associated with monotherapies.

One widely explored approach is the combination of immune checkpoint inhibitors (ICIs) with chemotherapy. Chemotherapeutic agents can induce immunogenic cell death, thereby increasing tumor antigen presentation and enhancing T cell infiltration into the tumor microenvironment. This mechanism provides a rationale for approved regimens such as pembrolizumab combined with platinum-based chemotherapy in non-small cell lung cancer (Blank et al., 2021).

ICIs combined with radiotherapy represent another synergistic strategy. Localized radiation can trigger the release of neoantigens and promote the recruitment of effector T cells, thereby amplifying the effects of systemic immune checkpoint blockade. For example, combining nivolumab with stereotactic radiotherapy is under investigation in several solid tumor types to test this immunogenic boost (Kalbasi & Ribas, 2020).

The pairing of ICIs with PARP inhibitors exploits the synthetic lethality of impaired DNA damage response pathways in certain tumors. By inducing DNA damage and genomic instability, PARP inhibitors can increase neoantigen load, potentially sensitizing tumors to checkpoint blockade. Durvalumab combined with olaparib is one example being tested in advanced ovarian and breast cancers (Smyth et al., 2020).

Targeting the immunosuppressive tumor microenvironment directly is another promising tactic. Combining ICIs with anti-TGF-beta agents seeks to neutralize the inhibitory signals that restrict effector T cell activity. Agents like atezolizumab co-administered with anti-TGF-beta antibodies

aim to remodel the microenvironment to favor immune cell infiltration and function (Pelka et al., 2021).

Finally, CAR T cells combined with checkpoint blockade illustrate an innovative dual approach to reinforce adoptive cellular therapies. Checkpoint inhibitors can prevent the exhaustion of infused CAR T cells within a hostile tumor microenvironment, improving their persistence and anti-tumor activity. Early-phase trials are exploring the co-administration of CAR T cells with PD-1 inhibitors in solid tumors and hematologic malignancies (Krishnamurthy & Jimeno, 2021).

Taken together, Figure 6 demonstrates that rationally designed combination strategies address multiple dimensions of tumor immune evasion. By leveraging complementary mechanisms of action, these approaches aim to expand the benefits of personalized immunotherapy to a broader patient population and achieve more durable responses.

4. Discusión

The findings synthesized in this review highlight the remarkable advances and persistent challenges in implementing personalized cancer immunotherapy based on genomic and immunological profiling. Over the last decade, the integration of next-generation sequencing, biomarker validation, and innovative immunotherapeutic strategies has profoundly transformed the landscape of oncology, offering new hope for patients who previously faced limited options (Blank et al., 2021; Havel et al., 2022).

The results presented here demonstrate how tumor genomic profiling, including comprehensive mutation analysis, tumor mutational burden (TMB) quantification, and microsatellite instability-high (MSI-H) status, provides essential information for stratifying patients and predicting responses to immune checkpoint inhibitors (Samstein et al., 2019; Marabelle et al., 2020). Studies consistently show that high TMB correlates with improved response rates to ICIs, reflecting an increased likelihood of generating neoantigens that the immune system can recognize (Havel et al., 2022; Lu et al., 2021). However, the predictive power of TMB remains context-dependent, varying by tumor type and influenced by additional factors such as the composition of the tumor microenvironment (Zhou, Mahoney, & Giobbie-Hurder, 2020).

The review also underscores the vital role of immune landscape assessment, including PD-L1 expression and tumor-infiltrating lymphocytes (TILs), which guide ICI use in diverse cancers such as lung, melanoma, and urothelial carcinoma (Jiang et al., 2021; Zhou, Peterson et al., 2021; Topalian et al., 2022). While PD-L1 testing is a routine clinical tool, its variable expression and limited standardization across assays can lead to inconsistent predictions of treatment benefit. This echoes findings from prior studies suggesting that reliance on a single biomarker is insufficient and should be complemented by integrated multi-omics approaches (Pelka et al., 2021; Riley et al., 2019).

Our synthesis further highlights how adoptive cell therapies, such as CAR T cells, have achieved transformative outcomes in hematological malignancies but continue to face significant obstacles in solid tumors due to the immunosuppressive tumor microenvironment and barriers to trafficking and persistence (Krishnamurthy & Jimeno, 2021; Mardiana et al., 2019; Martinez & Moon, 2019). Efforts to combine CAR T therapies with checkpoint blockade or microenvironment modulators represent promising avenues to overcome these limitations (Rodriguez-Garcia et al., 2020).

The resistance mechanisms mapped in this review, and visualized in Figure 4, emphasize the multifaceted ways in which tumors adapt to escape immune surveillance. Loss of antigen presentation, upregulation of immune checkpoints, recruitment of suppressive cell populations, secretion of inhibitory cytokines, and physical barriers within the tumor stroma have all been

well-documented as drivers of immunotherapy failure (Kalbasi & Ribas, 2020; Smyth et al., 2020). Consistent with previous findings, this review confirms that rational combinatorial strategies, illustrated in Figure 6, are required to address these barriers and sustain therapeutic responses (Blank et al., 2021; Riley et al., 2019).

One important implication of these findings is the growing evidence that single-agent immunotherapies will not suffice for many patients. Combination regimens, such as ICIs with chemotherapy or radiotherapy, exploit the immunogenic effects of traditional modalities to boost anti-tumor immunity (Smyth et al., 2020; Kalbasi & Ribas, 2020). The emerging pairing of ICIs with PARP inhibitors or anti-TGF-beta agents shows potential to reshape the immunosuppressive microenvironment and augment the effectiveness of checkpoint blockade (Mansour et al., 2021; Pelka et al., 2021). These combinations echo the evolving consensus that tackling multiple resistance pathways simultaneously is critical for meaningful clinical benefit.

The discussion of advanced drug delivery systems, including nanocarriers and other targeted platforms, also aligns with prior work emphasizing the need to increase treatment specificity and minimize off-target effects (Riley et al., 2019). Integrating genomic profiling with innovative delivery technologies may further personalize immunotherapy and address longstanding challenges in achieving sufficient immune cell infiltration in solid tumors (Zhang et al., 2021).

While the collective evidence reviewed here demonstrates significant progress, it also reveals enduring limitations. First, the heterogeneity of tumors and the dynamic evolution of their genomic and immunological features continue to challenge the predictive accuracy of existing biomarkers (Havel et al., 2022). Many current tests, including PD-L1 and TMB, fail to capture the full complexity of tumor-immune interactions. Standardizing assays and validating more robust multi-dimensional biomarker panels remain urgent priorities (Zhou, Mahoney, & Giobbie-Hurder, 2020).

Second, despite promising early-phase results, many combinatorial strategies lack large-scale randomized trial evidence, limiting definitive conclusions about their clinical benefit in diverse patient populations (Kalbasi & Ribas, 2020; Rodriguez-Garcia et al., 2020). The potential for increased toxicity with combination approaches also raises practical concerns that require careful monitoring and optimization.

Third, access to advanced genomic profiling and immunotherapies is uneven globally. High costs, limited infrastructure, and disparities in healthcare delivery pose significant barriers to widespread implementation of precision oncology, especially in low- and middle-income countries (Sung et al., 2021). Without targeted policies and global collaboration, these inequalities risk widening the gap in cancer outcomes.

This review also recognizes its own methodological limitations. Being a narrative synthesis, it is inherently dependent on the quality and heterogeneity of the included studies and may be subject to selection bias. No formal meta-analysis was conducted, and quantitative comparisons were not possible due to the diversity of study designs and endpoints.

Despite these limitations, this work contributes to the field by consolidating key advances, mapping unresolved challenges, and highlighting where future research should focus. Priority areas include developing robust, integrated biomarker panels that combine genomic, transcriptomic, and spatial data (Pelka et al., 2021), refining strategies to modulate the tumor microenvironment, and designing safer, more effective delivery systems (Riley et al., 2019). Furthermore, real-world data and prospective registries will be vital to validate emerging biomarkers and combination regimens beyond controlled trial settings.

In summary, this discussion underscores that personalized cancer immunotherapy is rapidly evolving, driven by technological advances in genomics, deeper understanding of tumor-immune dynamics, and an expanding toolkit of targeted therapies. Continued interdisciplinary research, global collaboration, and equitable implementation strategies are essential to translate these innovations into improved patient survival and quality of life worldwide (Blank et al., 2021; Topalian et al., 2022).

5. Conclusión

This review demonstrates that personalized cancer therapy has entered a transformative era, driven by rapid advances in genomic profiling, biomarker discovery, and innovative immunotherapeutic strategies. The integration of next-generation sequencing and comprehensive tumor immune landscape assessment has made it possible to move beyond traditional one-size-fits-all treatments toward individualized approaches that address the unique molecular and immunological characteristics of each patient's tumor (Blank et al., 2021; Havel et al., 2022).

The evidence synthesized here shows that while immune checkpoint inhibitors, CAR T cell therapies, and combination regimens have redefined what is possible in cancer care, multiple barriers persist. Resistance mechanisms such as antigen loss, tumor heterogeneity, and an immunosuppressive microenvironment continue to limit the long-term efficacy of current immunotherapies (Kalbasi & Ribas, 2020; Rodriguez-Garcia et al., 2020). Robust predictive biomarkers such as PD-L1 expression and tumor mutational burden are useful but imperfect tools, and there remains a critical need to refine and integrate multi-omics approaches to better guide patient selection and monitor therapeutic responses (Samstein et al., 2019; Pelka et al., 2021).

Emerging strategies to overcome these challenges, including rationally designed combinatorial treatments, modulation of the tumor microenvironment, and advanced delivery systems, hold great promise. However, the translation of these innovations into widespread clinical practice requires continued interdisciplinary research, large-scale validation trials, and collaborative efforts to ensure equitable access, especially in underserved regions where the burden of cancer is growing disproportionately (Sung et al., 2021; Topalian et al., 2022).

Ultimately, the future of personalized cancer immunotherapy depends on the ability to integrate deep molecular insights with practical clinical application, while balancing efficacy, safety, and accessibility. By building on recent progress and addressing persistent gaps through coordinated research and global cooperation, precision oncology can fulfill its promise of delivering more effective, durable, and patient-centered cancer care.

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