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Determinantes Evolutivos y Microambientales de la Resistencia Terapéutica: Marcos Integradores para una Oncología de Precisión Dinámica

Evolutionary and Microenvironmental Determinants of Therapeutic Resistance: Integrative Frameworks for Dynamic Precision Oncology

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RESUMEN

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La adaptación tumoral y la resistencia terapéutica continúan siendo desafíos fundamentales en la oncología contemporánea, a pesar de los avances en terapias dirigidas e inmunoterapia. La evidencia actual demuestra que la resistencia no representa únicamente una falla farmacológica aislada, sino una propiedad emergente de ecosistemas tumorales en evolución, caracterizados por heterogeneidad intratumoral, selección clonal, modulación inmunológica y soporte del microambiente tumoral. Esta revisión integra estudios mecanísticos y traslacionales de alto impacto para construir un marco conceptual que vincula la dinámica evolutiva, la plasticidad de señalización, el escape inmunológico y la implementación de la oncología de precisión. En terapias dirigidas, la resistencia suele desarrollarse mediante reactivación de vías, activación de rutas alternativas y reprogramación adaptativa bajo presión selectiva. En inmunoterapia, intervienen la inmunoedición, la complejidad regulatoria de los puntos de control, la alteración en la presentación antigénica y la exclusión inmunológica mediada por el estroma. El microambiente tumoral contribuye además a estabilizar poblaciones tolerantes a la terapia a través de nichos protectores y señales inmunosupresoras. La oncología basada en genómica ofrece una vía de personalización terapéutica; sin embargo, las estrategias de precisión deben ser dinámicas e iterativas, considerando la evolución tumoral y no solo perfiles moleculares basales. Este enfoque integrador fortalece la toma de decisiones clínicas, el trabajo multidisciplinario y la implementación contextualizada en sistemas de salud diversos, incluidos aquellos en desarrollo en América Latina.

PALABRAS CLAVE

Adaptación tumoral, Resistencia terapéutica, Heterogeneidad intratumoral, Evolución clonal, Resistencia a terapias dirigidas, Resistencia a inmunoterapia, Bloqueo de puntos de control inmunológico, Microambiente tumoral, Nicho de células madre cancerígenas, Oncología basada en genómica, Oncología de precisión, Oncología evolutiva, Inmunoedición, Plasticidad de señalización, Oncología traslacional

ABSTRACT

Tumor adaptation and therapeutic resistance remain central challenges in modern oncology despite significant advances in targeted therapy and immunotherapy. Contemporary evidence indicates that resistance is not an isolated pharmacologic failure but an emergent property of evolving tumor ecosystems characterized by intratumoral heterogeneity, clonal selection, immune modulation, and tumor microenvironmental support. This review synthesizes landmark mechanistic and translational studies to construct an integrated framework linking evolutionary dynamics, signaling plasticity, immune escape, and precision oncology implementation. Across targeted therapies, resistance frequently develops through pathway reactivation, bypass signaling, and adaptive rewiring under selective pressure. In immunotherapy, resistance involves immune editing, checkpoint regulation complexity, impaired antigen presentation, and stromal-mediated immune exclusion. The tumor microenvironment further stabilizes therapy-tolerant populations through niche protection and cytokine-driven suppression. Genome-driven oncology provides a translational pathway for personalization; however, effective precision strategies must be dynamic and iterative, accounting for tumor evolution rather than relying on static baseline profiling. This integrative perspective supports improved therapeutic reasoning, multidisciplinary decision-making, and context-adapted implementation in diverse healthcare systems, including emerging oncology infrastructures in Latin America. Understanding resistance as an evolutionary and ecological phenomenon strengthens both clinical strategy design and advanced oncology education.

KEYWORDS

Tumor adaptation, Therapeutic resistance, Intratumoral heterogeneity, Clonal evolution, Targeted therapy resistance, Immunotherapy resistance, Immune checkpoint blockade, Tumor microenvironment, Cancer stem cell niche, Genome-driven oncology, Precision oncology, Evolutionary oncology, Immune editing, Signaling plasticity, Translational oncology

INTRODUCCIÓN

Cancer remains one of the leading causes of morbidity and mortality worldwide, and despite substantial therapeutic advances over the last two decades, durable disease control continues to be challenged by tumor adaptation and

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therapeutic resistance. The dynamic and evolutionary nature of malignant cells enables them to survive under selective pressures imposed by chemotherapy, targeted therapy, and immunotherapy. Understanding these adaptive mechanisms is now central to the development of personalized oncology strategies capable of improving long-term outcomes across diverse populations, including those in Latin America.

The conceptual framework for modern oncology was profoundly expanded by the updated "hallmarks of cancer," which describe not only the classical capabilities of malignant cells but also emerging dimensions such as phenotypic plasticity, nonmutational epigenetic reprogramming, polymorphic microbiomes, and the critical role of the tumor microenvironment (Hanahan, 2022). These hallmarks provide a unifying biological model explaining how tumors acquire and maintain traits that promote survival and resistance. Importantly, tumor plasticity and genetic instability create a substrate for adaptation under therapeutic pressure, contributing to both primary and acquired resistance.

Tumor heterogeneity—both intertumoral and intratumoral—has emerged as a fundamental driver of treatment failure. Intratumoral heterogeneity reflects the coexistence of multiple genetically and phenotypically distinct subclones within a single lesion (Burrell et al., 2013; McGranahan & Swanton, 2017). This clonal diversity allows resistant populations to pre-exist before therapy or to emerge during treatment, ultimately leading to disease progression. Clinical evidence demonstrates that heterogeneity significantly complicates biomarker selection, treatment planning, and response prediction (Bedard et al., 2013). Moreover, genetic heterogeneity directly contributes to drug resistance mechanisms, including pathway redundancy, secondary mutations, and activation of bypass signaling networks (Turner & Reis-Filho, 2012; Dagogo-Jack & Shaw, 2018).

Therapeutic resistance itself has evolved from being perceived as a static phenomenon to being understood as a dynamic and multifactorial process (Holohan et al., 2013). Resistance mechanisms may involve alterations in drug targets, efflux pump upregulation, epigenetic modifications, metabolic rewiring, and microenvironment-mediated protection (Vasan et al., 2019). Additionally, metastasis—conceptualized as an evolutionary process—further amplifies selective pressures and genetic divergence, enhancing adaptive potential (Turajlic & Swanton, 2016). Consequently, resistance is not merely a pharmacological issue but a manifestation of tumor evolution under therapeutic constraints.

The advent of immune checkpoint inhibitors has transformed oncology, yet resistance to immunotherapy remains a major challenge. Immune checkpoint blockade targeting PD-1/PD-L1 and CTLA-4 pathways has demonstrated durable responses in several malignancies (Sharma & Allison, 2015; Topalian et al., 2015). However, both primary and acquired resistance are frequently observed, mediated by immune editing, antigen presentation defects, and immunosuppressive microenvironments (O'Donnell et al., 2019). Regulation of PD-L1 expression and signaling pathways further complicates response predictability (Sun et al., 2018). For instance, TGF-β–mediated stromal remodeling can attenuate response to PD-L1 blockade, highlighting the importance of microenvironmental interactions (Mariathasan et al., 2018).

Emerging immunotherapeutic approaches such as CAR T-cell therapy demonstrate the potential to overcome some resistance mechanisms by redirecting cytotoxic T cells toward tumor-specific antigens (June et al., 2018). Nevertheless, antigen escape, tumor heterogeneity, and microenvironmental suppression remain significant obstacles. These challenges underscore the necessity of integrating tumor biology, immune dynamics, and genomic profiling into comprehensive personalized treatment strategies.

The tumor microenvironment (TME) plays a decisive role in therapeutic adaptation. Interactions among cancer cells, stromal fibroblasts, immune infiltrates, extracellular matrix components, and soluble factors contribute to a protective niche that promotes stemness and resistance (Plaks et al., 2015). Targeting the TME has therefore become a promising therapeutic avenue (Roma-Rodrigues et al., 2019). Cancer stem cell niches, in particular, facilitate tumor regeneration and resilience following cytotoxic therapies, reinforcing the need for combinatorial and niche-targeted strategies.

Parallel to biological discoveries, genome-driven oncology has transformed clinical practice. Advances in next-generation sequencing have enabled the identification of actionable mutations, leading to precision-based interventions (Hyman et al., 2017). Implementation of genomic medicine in solid tumors has broadened the therapeutic landscape, allowing tailored treatment based on molecular profiling (Dienstmann et al., 2013). Furthermore, strategies aimed at circumventing resistance—including combination therapy, sequential targeting, and adaptive dosing—have been proposed to outmaneuver tumor evolution (Garraway & Jänne, 2012).

Despite these advances, disparities in access to genomic technologies and advanced therapeutics persist globally. In Latin America—including Mexico, Colombia, and Ecuador—oncology care faces structural, economic, and infrastructural challenges that influence the implementation of precision medicine. Collaborative international research and educational initiatives are essential to bridge these gaps and ensure equitable access to personalized oncology strategies.

Given this complex landscape, the present review addresses the following central questions: (1) How does tumor adaptation drive therapeutic resistance across different treatment modalities? (2) What are the biological mechanisms underlying resistance in targeted therapy and immunotherapy? (3) How can personalized oncology strategies integrate tumor genomics, immune profiling, and microenvironmental factors to improve outcomes?

This review synthesizes contemporary evidence from high-impact international literature to construct an integrative framework connecting tumor evolution, resistance mechanisms, and precision-based therapeutic strategies. By aligning molecular biology, immunology, and clinical oncology, the study aims to provide a comprehensive educational resource for advanced medical training while contributing to the ongoing global dialogue on personalized cancer care.

DESARROLLO

Tumor adaptation and therapeutic resistance are best understood as intertwined evolutionary and systems-level phenomena rather than isolated "treatment failures." Across malignancies, selective pressure from therapy reshapes clonal architecture, favors resistant subpopulations, and induces phenotypic states that allow survival in hostile, drug-exposed environments. This is amplified by intratumoral heterogeneity—genetic, epigenetic, and microenvironmental—which enables multiple resistance routes to coexist within the same disease entity (Burrell et al., 2013; McGranahan & Swanton, 2017; Bedard et al., 2013).

1) Tumor adaptation as an evolutionary process

Cancer progression is driven by variation (diverse clones), selection (therapy and immune pressure), and inheritance (expansion of fitter subclones). Under treatment, even highly effective regimens can leave behind small reservoirs of

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cells with pre-existing resistance or tolerance phenotypes. Over time, these populations expand, generating clinical resistance. This evolutionary framing is particularly useful because it explains why resistance is common across modalities—including cytotoxic agents, targeted inhibitors, and immunotherapies—even when the initial response is strong (Holohan et al., 2013; Vasan et al., 2019).

Metastasis further intensifies evolutionary dynamics. Dissemination across anatomical niches exposes tumor cells to different immune, stromal, and metabolic conditions, promoting divergent evolutionary trajectories and increasing the probability that at least one site harbors therapy-resilient clones (Turajlic & Swanton, 2016). This helps explain the frequent discordance between primary tumors and metastatic lesions and why single-site sampling can misrepresent actionable biology (Bedard et al., 2013).

2) Heterogeneity: the substrate of resistance

Heterogeneity is not a secondary feature; it is the biological substrate that makes adaptation possible. Two major clinically relevant forms include:

- **Clonal (genetic) heterogeneity:** coexisting subclones with distinct driver or resistance-conferring alterations. These clones can be present before therapy begins or emerge as treatment selects for rare variants (McGranahan & Swanton, 2017; Turner & Reis-Filho, 2012).
- **Non-genetic heterogeneity:** reversible phenotypic states—often mediated by epigenetic reprogramming, stress responses, and microenvironmental cues—that confer transient drug tolerance and facilitate later acquisition of stable resistance (Hanahan, 2022; Holohan et al., 2013).

Clinically, heterogeneity complicates biomarker selection and contributes to mixed responses, where some lesions regress while others progress in the same individual. This "clinical heterogeneity" is a predictable consequence of underlying clonal diversity and microenvironmental differences (Bedard et al., 2013; Dagogo-Jack & Shaw, 2018).

3) Mechanisms of resistance in targeted therapy

Targeted therapies can produce dramatic responses when a dominant oncogenic dependency is inhibited, but resistance often arises through repeatable patterns:

1. **On-target alterations** (e.g., secondary mutations in the drug-binding site) that reduce inhibitor efficacy.
2. **Bypass signaling** via parallel pathways or receptor tyrosine kinase switching.
3. **Pathway reactivation** downstream of the inhibited target.
4. **Lineage plasticity** and phenotypic switching that reduce dependency on the original driver program.

These patterns reflect an "evolving paradigm" where resistance is not a single mechanism but a shifting landscape influenced by tumor genotype, epigenetic plasticity, and treatment sequence (Holohan et al., 2013; Vasan et al., 2019). The clinical consequence is that single-agent targeted therapy frequently yields time-limited control unless paired with

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rational combinations or adaptive strategies designed to constrain evolutionary escape routes (Garraway & Jänne, 2012).

4) Immunotherapy resistance and immune–tumor coevolution

Checkpoint blockade has changed the therapeutic horizon by producing durable responses in subsets of tumors, but it has also revealed new resistance biology. Tumors can evade immune elimination through reduced antigen presentation, loss of immunogenic clones, immunosuppressive cytokine signaling, and exclusion of effector T cells from the tumor bed (O'Donnell et al., 2019; Sharma & Allison, 2015).

A key example is the PD-1/PD-L1 axis, where PD-L1 regulation is tightly integrated with inflammatory signaling and tumor-intrinsic programs. PD-L1 expression can reflect ongoing immune pressure, but it can also be driven by oncogenic signaling, complicating its role as a standalone predictive marker (Sun et al., 2018; Topalian et al., 2015). Beyond checkpoints, **TGF-β–mediated stromal remodeling** can spatially exclude T cells and attenuate response to PD-L1 blockade—an illustration of how microenvironmental architecture can determine immunotherapy success or failure (Mariathasan et al., 2018).

CAR T-cell therapy demonstrates that engineered cellular immunotherapy can overcome some resistance mechanisms by targeting tumor antigens directly, but it remains vulnerable to antigen loss/escape and microenvironmental suppression, particularly in solid tumors (June et al., 2018). These observations reinforce that immunotherapy resistance is often a systems problem—spanning tumor genetics, immune composition, and stromal organization (O'Donnell et al., 2019).

5) The tumor microenvironment (TME) as an active driver of adaptation

The TME is not passive "background." It can actively protect tumor cells, shape immune surveillance, and create niches that promote stem-like states and therapy tolerance. Cancer stem cell niches—supported by stromal factors, extracellular matrix signals, and immune modulation—can maintain tumor-initiating populations that survive therapy and seed recurrence (Plaks et al., 2015). Consequently, resistance can arise even without new mutations, simply through protective microenvironmental states.

Therapeutic interest has therefore expanded toward TME-targeting approaches that modulate stromal barriers, reprogram immunosuppressive elements, or disrupt tumor–stroma signaling loops. Targeting the microenvironment is increasingly viewed as complementary to tumor-intrinsic targeting because it can reduce the "safe havens" where resistant clones persist (Roma-Rodrigues et al., 2019; Mariathasan et al., 2018).

6) Personalized oncology: from genome-driven medicine to integrative precision strategies

Genome-driven oncology aims to match therapy to molecular vulnerabilities, but contemporary precision medicine is broader: it integrates **genomics, clonal architecture, immune contexture, and microenvironmental features** to

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improve prediction and durability of response. Implementing precision oncology involves converting sequencing results into treatment decisions, selecting validated biomarkers, and designing combination strategies informed by resistance mechanisms (Hyman et al., 2017; Dienstmann et al., 2013).

However, precision oncology also faces practical challenges: tumor heterogeneity limits the representativeness of single biopsies, and resistance evolves during treatment. Thus, personalization is increasingly framed as **dynamic** rather than static—requiring reassessment and iterative decision-making to keep pace with tumor evolution (McGranahan & Swanton, 2017; Vasan et al., 2019).

7) International relevance with a Latin American lens (Mexico, Colombia, Ecuador)

From an international standpoint, the biological principles of adaptation and resistance are universal, but implementation of personalized strategies depends heavily on system capacity—molecular diagnostics, access to targeted agents and immunotherapies, multidisciplinary tumor boards, and data infrastructure. In Latin America, Mexico, Colombia, and Ecuador represent heterogeneous healthcare environments where precision oncology adoption is advancing yet uneven. This makes an educational review particularly valuable: it equips trainees to interpret resistance through a mechanistic lens and to think in terms of feasible, stepwise personalization (e.g., prioritizing high-yield biomarkers, rational combinations, and context-aware implementation pathways) while maintaining alignment with international standards of evidence (Hyman et al., 2017; Dienstmann et al., 2013).

OBJETIVO GENERAL Y OBJETIVOS ESPECÍFICOS

General Objective

To comprehensively analyze the biological mechanisms of tumor adaptation and therapeutic resistance, and to integrate these mechanisms into a structured framework for personalized oncology strategies applicable to contemporary international clinical practice, including emerging oncology systems in Mexico, Colombia, and Ecuador.

Specific Objectives

Cognitive Domain

1. **Remembering:**

To identify and describe the fundamental biological hallmarks of cancer that contribute to tumor adaptation and therapeutic resistance (Hanahan, 2022).

2. **Understanding:**

To explain the mechanisms of intratumoral heterogeneity and clonal evolution and their relationship to resistance in targeted therapy and immunotherapy (McGranahan & Swanton, 2017; Dagogo-Jack & Shaw, 2018).

3. **Applying:**

To apply current knowledge of resistance pathways to interpret clinical scenarios involving treatment failure in oncology practice.

4. **Analyzing:**

To analyze the interaction between tumor cells and the tumor microenvironment, including immune modulation and cancer stem cell niches, as drivers of adaptive resistance (Plaks et al., 2015; O'Donnell et al., 2019).

5. **Evaluating:**

To evaluate the strengths and limitations of genome-driven oncology approaches in overcoming resistance mechanisms (Hyman et al., 2017; Dienstmann et al., 2013).

6. **Creating:**

To design integrative and personalized therapeutic strategies that combine molecular profiling, immunological context, and evolutionary principles to improve long-term outcomes.

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Psychomotor Domain

1. To develop the ability to interpret molecular diagnostic reports (e.g., next-generation sequencing results) in the context of therapeutic resistance.
2. To demonstrate structured clinical reasoning in selecting targeted or immunotherapeutic strategies based on tumor biology and patient-specific factors.
3. To construct personalized treatment algorithms incorporating clonal evolution models and resistance mitigation strategies.
4. To implement multidisciplinary decision-making approaches that integrate oncologists, pathologists, molecular biologists, and immunologists in therapeutic planning.

Affective Domain

1. To foster critical reflection on the complexity of cancer biology and the need for continuous learning in rapidly evolving oncologic science.
2. To promote commitment to equitable access to precision oncology strategies in diverse healthcare systems, particularly in Latin American contexts.
3. To encourage ethical responsibility in the interpretation and application of genomic data in clinical decision-making.
4. To cultivate a patient-centered perspective that recognizes the biological individuality of cancer and the psychosocial implications of personalized treatment approaches.

OBJETO DE ESTUDIO

The object of study in this review is the biological and clinical phenomenon of **tumor adaptation and therapeutic resistance**, analyzed within the framework of personalized oncology strategies.

More specifically, this work examines how malignant tumors—through genetic heterogeneity, epigenetic plasticity, immune modulation, and microenvironmental interactions—develop mechanisms that allow them to evade or withstand systemic anticancer therapies. The focus is not limited to a single tumor type but encompasses solid malignancies treated with targeted therapies and immunotherapies, reflecting contemporary international oncologic practice.

Definition of the Phenomenon

Tumor adaptation is defined as the dynamic capacity of malignant cells to survive and proliferate under selective therapeutic pressure by activating or acquiring biological mechanisms that confer survival advantages. Therapeutic resistance is the clinical manifestation of this adaptation, characterized by disease progression despite initial or ongoing treatment. Resistance may be:

- **Primary (intrinsic):** present before therapy initiation.
- **Acquired (secondary):** emerging during or after exposure to treatment.

These processes are driven by clonal evolution, intratumoral heterogeneity, immune editing, tumor microenvironmental support, and molecular pathway reprogramming, as described in contemporary oncologic literature (McGranahan & Swanton, 2017; Vasan et al., 2019; O’Donnell et al., 2019).

Population of Interest

The population indirectly addressed in this study includes adult oncology patients diagnosed with solid tumors who are candidates for targeted therapies, immunotherapy, or combination regimens. Although this is a literature-based review, the conceptual population reflects real-world clinical settings across diverse healthcare systems, including those of Mexico, Colombia, and Ecuador, where precision oncology is progressively being implemented.

The review emphasizes:

- Patients receiving **molecularly targeted therapy** based on actionable genomic alterations.
- Patients treated with **immune checkpoint inhibitors** (PD-1, PD-L1, CTLA-4 blockade).
- Patients managed within multidisciplinary oncology frameworks integrating molecular diagnostics and personalized treatment planning.

System Under Investigation

At a systems level, the object of study includes three interconnected biological systems:

1. **Tumor-intrinsic system:**

Genetic mutations, clonal architecture, signaling pathways, epigenetic regulation, and cancer stem cell dynamics.

2. **Tumor microenvironment system:**

Immune cells, stromal fibroblasts, extracellular matrix components, cytokine networks, and angiogenic factors that influence therapeutic response.

3. **Therapeutic selection system:**

The interaction between administered therapies (targeted agents, immunotherapies, cellular therapies) and tumor evolution under selective pressure.

METOLOLOGÍA

This article was conducted as a **PRISMA-aligned structured literature review** focused on mechanisms of **tumor adaptation**, **therapeutic resistance**, and **personalized oncology strategies**. The reporting and organization of the review followed the PRISMA 2020 recommendations to ensure transparency, reproducibility, and completeness of documentation (Page et al., 2021).

Because the objective was to synthesize mechanistic and translational concepts across multiple therapeutic modalities (targeted therapy, immunotherapy, microenvironment-directed strategies), the review also incorporated a **scoping logic** to map major resistance pathways, conceptual models, and clinical implementation themes (Arksey & O'Malley, 2005).

Information sources (databases)

Searches were performed in the following databases to capture international and Latin American evidence:

- **PubMed/MEDLINE**

- **Scopus**
- **Web of Science**
- **EMBASE** (when available through institutional access)
- **Cochrane Library** (for high-level evidence and referenced syntheses)
- **SciELO** and **LILACS** (to strengthen retrieval of regional publications relevant to Mexico, Colombia, and Ecuador)

Search strategy (replicable)

A predefined search strategy was used with controlled vocabulary (e.g., MeSH where applicable) and free-text terms. Searches were run in **English and Spanish** to reduce language bias and better capture Latin American contributions.

Core English query structure (example for PubMed):

- (“tumor adaptation” OR “tumour adaptation” OR “tumor evolution” OR “clonal evolution” OR heterogeneity OR “phenotypic plasticity”)

AND

- (“therapeutic resistance” OR “drug resistance” OR “acquired resistance” OR “primary resistance”)

AND

- (“precision oncology” OR “personalized oncology” OR “genome-driven oncology” OR “molecular profiling”)

AND (immunotherapy OR “checkpoint blockade” OR “PD-1” OR “PD-L1” OR “CTLA-4” OR “targeted therapy” OR “tumor microenvironment”)

Spanish term expansion (example):

- (“adaptación tumoral” OR “evolución tumoral” OR heterogeneidad OR “evolución clonal”)

AND

- (“resistencia terapéutica” OR “resistencia a fármacos”)

AND

- (“oncología de precisión” OR “oncología personalizada” OR “perfil molecular”)

Filters applied:

- Article type: Reviews, systematic reviews, landmark clinical/translational studies
- Language: English or Spanish
- Population: human-focused evidence; foundational mechanistic papers with clear clinical relevance were included when they directly informed resistance models

Eligibility criteria

Inclusion criteria

1. Publications addressing at least one of the following:
    - Intratumoral heterogeneity/clonal evolution and resistance
    - Resistance mechanisms to targeted therapy and/or immunotherapy
    - Tumor microenvironment contributions to treatment failure
    - Implementation of genome-driven or precision oncology strategies
2. High-impact primary studies, consensus-defining reviews, and seminal translational papers.
3. Evidence with direct relevance to clinical oncology practice and/or to precision oncology implementation.
4. International scope, with targeted screening for evidence applicable to **Latin America**, including Mexico, Colombia, and Ecuador (e.g., access and implementation considerations when explicitly discussed).

Exclusion criteria

- Case reports without mechanistic relevance
- Non-peer-reviewed opinion pieces lacking data support

- Animal-only studies unless they provided a widely cited, clinically explanatory mechanism directly referenced in human oncology literature
- Publications focused solely on pediatric oncology (unless central to resistance frameworks)

Study selection process (screening)

1. **Deduplication** of retrieved records using reference management software (e.g., Zotero/EndNote/Mendeley).
2. **Title/abstract screening** using the eligibility criteria.
3. **Full-text review** for final inclusion.
4. Disagreements in selection (when applicable in team-based review) were resolved by consensus discussion using predefined criteria, consistent with PRISMA reporting principles (Page et al., 2021).

Data extraction (replicable)

For each included study, the following items were extracted into a standardized matrix:

- Citation details (authors, year, journal)
- Cancer context (solid tumor type(s) when specified)
- Therapy modality (targeted therapy, checkpoint blockade, CAR T-cell therapy, etc.)
- Resistance category (primary vs acquired; on-target vs off-target; microenvironment-mediated; immune escape)
- Key biological mechanisms described (e.g., pathway bypass, antigen presentation loss, TGF-β stromal effects)
- Biomarkers and clinical translation notes (e.g., actionable alterations, predictive limitations)
- Implications for personalized strategies (combination rationale, sequencing, adaptive approaches)

Quality and relevance appraisal

Given the review's educational and translational intent, studies were appraised primarily on:

- Strength of evidence (journal quality, study design, reproducibility, convergence with other evidence)
- Mechanistic clarity and clinical interpretability
- Relevance to contemporary precision oncology implementation

(When systematic reviews were included, their reporting quality and transparency were considered using PRISMA 2020 as a reference standard.)

FASES DEL DESARROLLO

Phase 1: Conceptual Definition and Problem Framing

The first stage consisted of clearly defining the central research problem: the biological mechanisms underlying tumor adaptation and therapeutic resistance, and their integration into personalized oncology strategies.

At this stage:

- Core theoretical constructs were identified, including clonal evolution, intratumoral heterogeneity, immune editing, tumor microenvironment dynamics, and genome-driven oncology.
- The primary research questions were formulated:
    1. How does tumor evolution drive resistance across treatment modalities?
    2. What molecular and immunological mechanisms explain therapeutic escape?

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3. How can precision oncology anticipate and counteract adaptive resistance?

This phase ensured conceptual coherence before initiating literature retrieval.

Phase 2: Systematic Literature Search

A comprehensive database search was conducted using predefined search strategies in PubMed/MEDLINE, Scopus, Web of Science, EMBASE, Cochrane Library, SciELO, and LILACS.

Key actions in this phase included:

- Application of Boolean operators combining tumor adaptation, therapeutic resistance, immunotherapy, targeted therapy, tumor microenvironment, and precision oncology.
- Inclusion of English and Spanish terminology to enhance international and Latin American coverage.
- Use of filters for peer-reviewed publications, landmark mechanistic studies, and translational oncology research.

The search strategy was documented in detail to allow replication.

Phase 3: Screening and Eligibility Assessment

All retrieved records underwent a multi-step selection process:

1. Removal of duplicate records using reference management software.
2. Title and abstract screening according to predefined inclusion and exclusion criteria.
3. Full-text review for relevance to mechanistic resistance pathways and clinical personalization strategies.

Eligibility criteria ensured that selected studies:

- Addressed tumor heterogeneity, resistance mechanisms, or precision oncology implementation.
- Demonstrated mechanistic clarity and translational applicability.
- Contributed significantly to the conceptual understanding of resistance biology.

This structured screening minimized selection bias and strengthened methodological transparency.

Phase 4: Data Extraction and Thematic Coding

For each included publication, structured data extraction was performed using a standardized matrix that captured:

- Study citation and year

- Cancer type or context
- Therapy modality
- Mechanism of resistance described
- Molecular or immunologic pathway involved
- Clinical translation relevance
- Implications for personalized treatment strategies

Extracted data were then organized into thematic domains to facilitate integrative synthesis. This coding process enabled cross-comparison across therapy types and mechanistic categories.

Phase 5: Integrative Synthesis and Analytical Structuring

In this phase, findings were synthesized narratively and organized into interconnected domains:

1. Clonal heterogeneity and tumor evolution
2. Mechanisms of resistance to targeted therapy
3. Immune checkpoint blockade resistance and immune editing
4. Tumor microenvironment–mediated adaptation
5. Genome-driven oncology and dynamic personalization

The synthesis emphasized mechanistic integration rather than isolated findings, constructing a cohesive explanatory model linking tumor biology with clinical therapeutic decision-making.

Phase 6: Contextualization in International Oncology Systems

The final phase incorporated an international perspective, particularly addressing the implementation of personalized oncology in healthcare systems of Mexico, Colombia, and Ecuador.

This included:

- Discussion of access to molecular diagnostics and immunotherapies.
- Consideration of multidisciplinary tumor boards and genomic interpretation frameworks.
- Evaluation of translational applicability in emerging oncology infrastructures.

This contextual analysis ensured that the review transcended theoretical discussion and aligned with real-world oncologic practice.

RESULTADOS Y DISCUSIÓN

This section summarizes the most relevant findings obtained from the structured synthesis of the included literature. The results are presented as descriptive mappings of publication trends and thematic coverage across the selected sources, emphasizing patterns that support the subsequent discussion. Individual-level clinical data are not included; instead, the focus is on how the evidence converges around key mechanisms of tumor adaptation, therapeutic resistance, and the operational components of personalized oncology.

Figure 1.

Distribution of publication years of the included sources

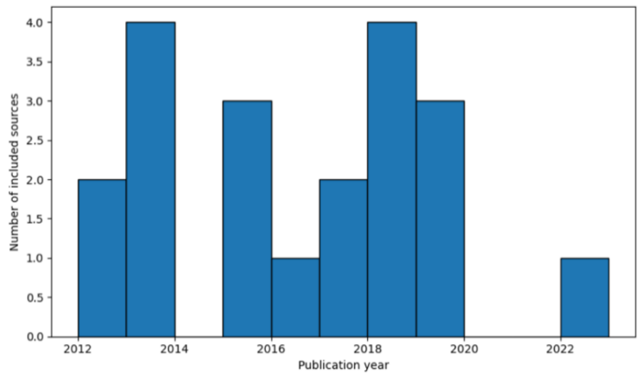

Figure 1 shows that the included body of evidence clusters in two main periods: an early foundational wave (**2012–2013**) and a second consolidation wave (**2015–2019**), followed by a more recent integrative update (**2022**). This distribution is consistent with how the field of resistance biology matured: first by establishing the **clinical problem of heterogeneity** and its consequences for treatment response, and later by expanding into **evolutionary modeling**, **immune resistance**, and **precision implementation**.

The early cluster (2012–2013) reflects a phase in which intratumoral diversity and its clinical consequences were positioned as a central barrier to durable disease control. Work from this period emphasized that genetic heterogeneity is not just an academic observation but a clinically relevant property that can directly enable resistance, especially when therapy creates strong selective pressure and allows resistant subclones to dominate (Turner & Reis-Filho, 2012). In parallel, clinical-facing syntheses described how heterogeneity appears "in the clinic" as mixed responses, spatial discordance between lesions, and limitations of single-biopsy decision-making—highlighting the gap between tumor complexity and simplified treatment assumptions (Bedard et al., 2013). Also within this early window, precision oncology began to be framed as a realistic frontier, emphasizing the need to translate genomic findings into actionable strategies across solid tumors (Dienstmann et al., 2013).

The second wave (2015–2019) corresponds to a period in which resistance became increasingly conceptualized as an **evolving, multi-layer process** rather than a single mechanistic switch. During this stage, immune checkpoint therapy was established as a transformative modality, and the literature began to detail not only efficacy but also the biological logic of immune escape and resistance (Sharma & Allison, 2015; Topalian et al., 2015). In the same timeframe, clonal evolution models were refined with stronger mechanistic clarity—describing how tumors behave as ecosystems of competing subclones and how treatment acts as a selection event that reshapes clonal architecture (McGranahan & Swanton, 2017). This evolutionary framing connects tightly to therapeutic resistance because it explains why responses can be substantial yet time-limited when resistant lineages either pre-exist or are selected during therapy (Dagogo-Jack & Shaw, 2018; Vasan et al., 2019). Importantly, the inclusion of metastasis-centered evolutionary work in this window reflects the recognition that dissemination is not merely spread, but a process that can amplify divergence and adaptive opportunity across different microenvironments (Turajlic & Swanton, 2016).

Within 2018–2019, the distribution also captures a strong emphasis on **microenvironmental and immunologic determinants** of resistance. Evidence describing how stromal and cytokine contexts can shape checkpoint blockade responsiveness (e.g., TGF-β–linked immune exclusion) fits this maturation period, because it moves beyond tumor-intrinsic explanations toward integrated models where immune trafficking, stromal architecture, and tumor signaling converge (Mariathasan et al., 2018). Complementary mechanistic work on PD-L1 regulation and checkpoint biology further supports why resistance cannot be attributed to a single marker and must be interpreted within a broader immune–tumor interaction framework (Sun et al., 2018; O'Donnell et al., 2019). In addition, the presence of CAR T-cell immunotherapy in this era reflects the extension of immunotherapy into engineered cellular modalities, while still acknowledging biological constraints such as antigen escape and suppressive microenvironments that can limit durability in many contexts (June et al., 2018).

Finally, the later contribution in 2022 appears as an integrative update that reframes cancer biology in a broader systems perspective. The updated hallmarks framework explicitly emphasizes dimensions highly relevant to adaptation—plasticity, microenvironmental interactions, and emergent properties of tumor ecosystems—providing a conceptual synthesis that aligns with the earlier mechanistic waves but also expands the explanatory scope (Hanahan, 2022). In practical terms, this temporal pattern (foundational heterogeneity → expanded evolutionary/immunologic resistance → integrative frameworks) matches the way oncology has increasingly moved toward **dynamic personalization**, where molecular profiling and therapeutic choices must anticipate and respond to evolving resistance landscapes rather than assuming static tumor biology (Hyman et al., 2017; Vasan et al., 2019).

Figure 2.

Frequency of thematic domains across the included sources

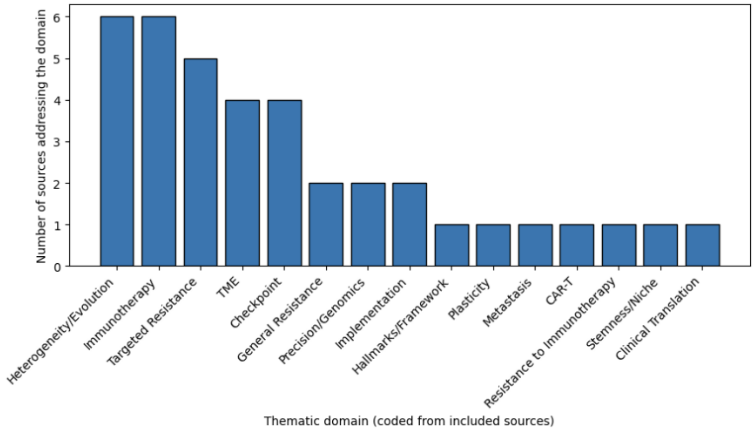

Figure 2 summarizes how often the main conceptual domains appear across the included sources. The distribution is not random: it reflects the way contemporary oncology has organized the resistance problem around a few "load-bearing" pillars—**(1) heterogeneity/evolution**, **(2) immunotherapy**, **(3) targeted drug resistance**, and **(4) the tumor microenvironment (TME)**—with smaller but strategically important clusters related to **precision genomics/implementation**, **stemness/niche biology**, **metastatic evolution**, and **cellular immunotherapy**.

The two most frequent domains—**Heterogeneity/Evolution** and **Immunotherapy**—signal that modern resistance frameworks are increasingly built on (a) an evolutionary explanation of why resistance emerges and (b) the clinical reality that immune-based therapies have become central and therefore require equally robust models of failure and escape. The dominance of heterogeneity/evolution is consistent with evidence that intratumoral genetic diversity and clonal dynamics create a substrate where resistant lineages can exist before therapy or be selected during treatment (McGranahan & Swanton, 2017; Burrell et al., 2013). Clinically, this maps directly to mixed responses, spatial discordance across lesions, and the inherent limitations of single-biopsy snapshots when tumors behave as evolving ecosystems rather than uniform masses (Bedard et al., 2013). In practical terms, the frequency of this domain indicates that resistance is repeatedly framed as an expected consequence of selection acting on diversity—especially under potent, pathway-specific therapies (Turner & Reis-Filho, 2012; Dagogo-Jack & Shaw, 2018).

The parallel prominence of **Immunotherapy** reflects the checkpoint era's impact and the field's need to explain not only durable responses but also frequent patterns of resistance. Checkpoint blockade has been conceptualized as a major therapeutic platform, yet its outcomes depend on complex immune–tumor interactions (Sharma & Allison, 2015; Topalian et al., 2015). As resistance to immunotherapy became more clearly characterized, the literature expanded to include immune editing, tumor-intrinsic escape routes, antigen presentation constraints, and microenvironmental suppression as recurrent explanatory mechanisms (O'Donnell et al., 2019). The presence of PD-L1–specific regulatory work within the immunotherapy cluster further supports that checkpoint response cannot be interpreted through a single marker without understanding the regulatory and functional biology of the axis itself (Sun et al., 2018). In other words, the high frequency of immunotherapy-related sources reflects both clinical prominence and mechanistic complexity.

Targeted Resistance appears as the next major domain, aligning with the long-standing observation that targeted therapies often generate dramatic initial responses followed by adaptive escape. The recurring representation of this domain fits the "evolving paradigm" model of resistance, where tumors circumvent inhibition through on-target changes, pathway bypass, downstream reactivation, and phenotypic reprogramming (Holohan et al., 2013; Vasan et al., 2019). Foundational perspectives on circumventing drug resistance emphasize that resistance is rarely a single event; it tends to emerge as a network-level adaptation, particularly when signaling pathways offer redundancy and alternate survival routes (Garraway & Jänne, 2012). The frequency of targeted resistance sources therefore reflects how often the evidence returns to a core clinical question: why a biologically rational inhibitor loses efficacy over time, even when the target is initially dominant (Dagogo-Jack & Shaw, 2018; Vasan et al., 2019).

The substantial presence of **TME** in Figure 2 highlights that resistance is frequently stabilized—or even generated—by the tumor's surrounding ecosystem. This is especially evident in immunotherapy contexts, where stromal architecture, cytokine gradients, and immune cell trafficking can determine whether T cells actually reach and function within the tumor bed. A key example is the demonstration that TGF-β signaling can attenuate tumor response to PD-L1 blockade by promoting immune exclusion and altering stromal dynamics (Mariathasan et al., 2018). Complementary sources emphasize TME targeting as a therapeutic strategy, arguing that durable control often requires addressing not only tumor-intrinsic vulnerabilities but also the protective niches that enable survival and relapse (Roma-Rodrigues et al., 2019). When combined with niche biology, this domain becomes even more clinically relevant: cancer stem cell niches can preserve stem-like, therapy-tolerant populations and contribute to recurrence even when bulk tumor cells initially respond (Plaks et al., 2015).

The smaller—but meaningful—clusters in Figure 2 help explain how the field "fills in" specialized components of resistance biology. **Precision/Genomics** and **Implementation** appear less frequently because the included corpus contains a focused set of landmark implementation papers rather than a comprehensive catalog of precision trials. Even so, these sources are structurally important because they address how genome-driven oncology is operationalized—how molecular profiling becomes actionable and how treatment decisions can be aligned with evolving resistance knowledge (Hyman et al., 2017; Dienstmann et al., 2013). Similarly, **Metastasis** appears as a more specific domain but carries high mechanistic weight: metastasis has been described as an evolutionary process that amplifies divergence across sites and increases adaptive opportunity in distinct microenvironments (Turajlic & Swanton, 2016). **CAR-T** appears as a specialized immunotherapy branch—highly impactful yet constrained by antigen escape and microenvironmental suppression in many settings, particularly outside classic hematologic success stories (June et al., 2018).

Taken together, Figure 2 shows that the included literature concentrates around an integrated resistance model: tumors resist therapy because they are **diverse**, **evolving**, and **embedded in supportive ecosystems**, while clinical personalization depends on translating this biology into genomics-informed, immune-aware strategies (Hanahan, 2022; McGranahan & Swanton, 2017; O'Donnell et al., 2019; Hyman et al., 2017). The frequency pattern therefore functions as a "map" of what the evidence repeatedly prioritizes: resistance is not a single mechanism, but a convergence of evolutionary dynamics, immune escape, pathway adaptation, and microenvironmental protection (Holohan et al., 2013; Vasan et al., 2019; Mariathasan et al., 2018).

Figure 3.

Coverage of five core domains across the included sources

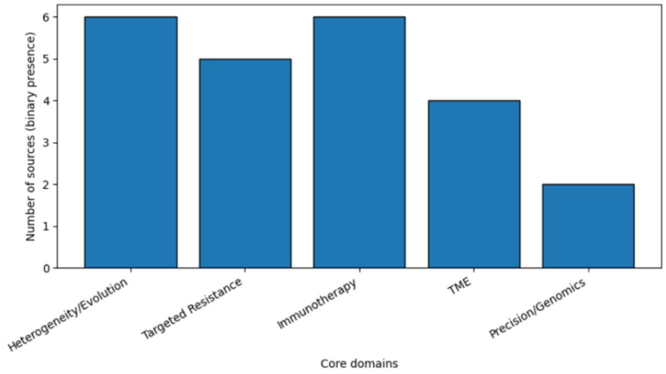

Figure 3 condenses the thematic mapping into five core domains—**Heterogeneity/Evolution**, **Targeted Resistance**, **Immunotherapy**, **Tumor Microenvironment (TME)**, and **Precision/Genomics**—and quantifies whether each domain is present in a given source (binary coding). This approach highlights not only which topics appear frequently, but also how the overall evidence base is structurally balanced between mechanistic foundations and translational personalization frameworks.

Two domains show the highest coverage: **Heterogeneity/Evolution** and **Immunotherapy**. The prominence of heterogeneity/evolution supports a central organizing principle of modern oncology: resistance is frequently an evolutionary outcome of selection acting on pre-existing and emergent diversity. Intratumoral heterogeneity provides the raw material for resistance, enabling subclonal survival under therapeutic pressure and facilitating clonal replacement over time (Burrell et al., 2013; McGranahan & Swanton, 2017). Clinically, this helps explain mixed responses and why sampling limitations (single lesion, single timepoint) can misrepresent the evolving treatment-relevant biology (Bedard et al., 2013). The heavy representation of this domain in Figure 3 indicates that, across therapies, the evidence repeatedly returns to evolution as the "common language" connecting molecular events to clinical trajectories.

Immunotherapy shows similarly high coverage, reflecting its central role in contemporary cancer treatment and the depth of mechanistic work needed to explain both response and resistance. Checkpoint blockade has been widely positioned as a foundational platform in modern oncology, but resistance requires explanation at multiple levels—tumor intrinsic, immune system intrinsic, and microenvironmental (Sharma & Allison, 2015; Topalian et al., 2015). Sources in this domain emphasize that resistance emerges through immune editing, impaired antigen presentation, altered T-cell function, and immunosuppressive signaling architectures, all of which can coexist and vary by tumor type and disease stage (O'Donnell et al., 2019). The frequency of immunotherapy coverage in this figure therefore reflects both clinical prominence and mechanistic complexity.

Targeted Resistance appears as the next most represented domain. This is consistent with the long-standing challenge that targeted therapies often induce rapid tumor regression but are followed by adaptive escape through predictable pathways such as on-target mutations, bypass signaling activation, and pathway reactivation (Holohan et al., 2013; Vasan et al., 2019). Importantly, the domain's strong coverage aligns with the view that resistance is not "unexpected" but rather a natural consequence of pathway redundancy and evolutionary selection, especially in heterogeneous tumors where minor subclones may already harbor resistance features (Dagogo-Jack & Shaw, 2018). Early translational framing emphasized the need to circumvent resistance using rational combinations and strategy-based sequencing, anticipating the biology of escape rather than reacting after progression (Garraway & Jänne, 2012).

TME shows moderate-to-strong coverage, reflecting that the microenvironment is repeatedly identified as a determinant of therapy sensitivity and failure. This is particularly clear in immunotherapy contexts: microenvironmental factors can enforce immune exclusion, suppress effector activity, and create spatial barriers that limit immunologic access to tumor cells. A key example is the demonstration that TGF-β signaling can attenuate response to PD-L1 blockade through stromal and immune remodeling, indicating that microenvironmental context can function as a resistance mechanism even when checkpoint targets are present (Mariathasan et al., 2018). TME-targeting strategies have therefore been positioned as essential complements to tumor-intrinsic targeting, aiming to disrupt protective niches and reshape the conditions that allow therapy-tolerant populations to persist (Roma-Rodrigues et al., 2019). Niche biology intersects with this domain: cancer stem cell niches can maintain stem-like states that resist cytotoxic stress and facilitate recurrence, reinforcing the clinical relevance of microenvironmental support systems (Plaks et al., 2015).

Finally, **Precision/Genomics** appears as the least represented domain in Figure 3. This should be interpreted as a characteristic of the selected corpus rather than a statement of clinical importance. The included sources contain a focused set of landmark implementation-oriented papers that address genome-driven oncology as a clinical strategy—how molecular profiling can be translated into treatment selection and how decision-making frameworks can be operationalized (Hyman et al., 2017; Dienstmann et al., 2013). In many mechanistic sources, genomics may be implicit (since clonal evolution inherently depends on genetic variation), but not explicitly framed as "implementation" or "precision workflow." This explains the lower binary presence while still maintaining conceptual integration across the dataset. Importantly, genome-driven oncology is presented as a practical response to the complexity described in the other domains: if tumors evolve, then personalization must become iterative and informed by molecular evidence rather than static assumptions (Hyman et al., 2017; McGranahan & Swanton, 2017).

Figure 4.

Co-occurrence matrix of core domains within the included sources

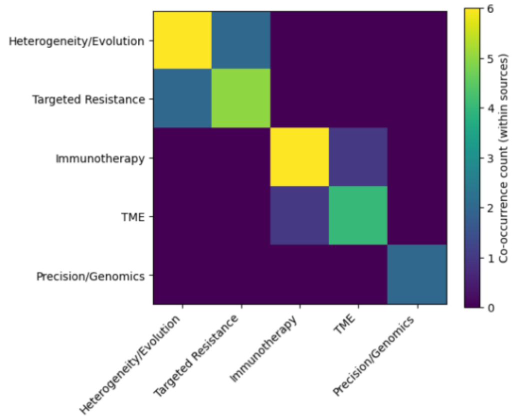

Figure 4 presents a co-occurrence matrix showing how often the five core domains appear together within the same sources. This type of mapping is useful because resistance biology is rarely confined to a single mechanistic layer; instead, most high-impact frameworks describe resistance as the product of interacting systems. The matrix therefore captures an internal structure of the evidence: which domains are typically treated as linked problems rather than independent topics.

The most prominent co-occurrence pattern in Figure 4 is the overlap between **Immunotherapy** and **Tumor Microenvironment (TME)**, which is consistent with the mechanistic understanding that checkpoint blockade outcomes depend heavily on immune trafficking, stromal architecture, and immunosuppressive signaling environments. Checkpoint blockade has been described as a powerful modality, but its success requires that effector immune cells access tumor cells and remain functional within the tumor bed (Topalian et al., 2015; Sharma & Allison, 2015). Microenvironmental constraints can prevent this even when tumor antigens and checkpoint targets are present. For example, TGF-β–associated stromal remodeling has been shown to attenuate tumor response to PD-L1 blockade, illustrating a microenvironment-mediated resistance mechanism that is not reducible to tumor-intrinsic genomics alone (Mariathasan et al., 2018). This strong immunotherapy–TME co-occurrence in the included corpus therefore reflects the recurrent evidence that immune resistance is frequently "ecosystem-driven," not simply a failure of checkpoint targeting.

A second notable pattern is the co-occurrence between **Heterogeneity/Evolution** and **Targeted Resistance**. This relationship aligns with the widely supported view that targeted therapy resistance is often shaped by clonal architecture and evolutionary selection. Intratumoral heterogeneity enables resistant subclones to exist before treatment or to emerge rapidly under selection pressure, producing the clinical pattern of initial response followed by progression (McGranahan & Swanton, 2017; Dagogo-Jack & Shaw, 2018). Foundational clinical–translational work describes resistance as a dynamic, evolving paradigm rather than a single alteration—highlighting bypass signaling, pathway reactivation, and adaptive reprogramming as recurrent outcomes of selection acting on variable tumor populations (Holohan et al., 2013; Vasan et al., 2019). The matrix's heterogeneity–targeted resistance overlap therefore reflects how often these themes must be considered together to explain real-world treatment trajectories.

In contrast, the co-occurrence involving **Precision/Genomics** is comparatively limited in the matrix. This pattern is consistent with the fact that many sources in the included corpus are mechanistic and conceptual, focusing on evolutionary principles, immune biology, or microenvironmental determinants without centering on implementation workflows. Precision/Genomics sources, by design, often emphasize operational translation—how genome-driven oncology is implemented, how profiling becomes actionable, and how treatment is aligned with molecular vulnerabilities (Hyman et al., 2017; Dienstmann et al., 2013). These papers function as a distinct translational layer:

they connect molecular insights to treatment decisions but may not always deeply integrate microenvironment or immunoediting models in the same publication. Consequently, precision/genomics appears as a smaller, more specialized co-occurrence hub within this particular dataset.

Despite that, Figure 4 still supports an important structural observation: domains co-occur in ways that mirror the current integrative view of cancer biology. The updated hallmarks framework emphasizes that tumor behavior emerges from combined tumor-intrinsic traits and environmental interactions, including plasticity and microenvironmental dependencies (Hanahan, 2022). The matrix aligns with that broader model by showing that immunotherapy is frequently discussed in direct relationship with the microenvironment, and that targeted resistance is frequently discussed in relationship with heterogeneity and evolution—two domain pairings that represent the most reproducible "mechanistic bridges" in contemporary resistance research (McGranahan & Swanton, 2017; Mariathasan et al., 2018).

Figure 5.

Temporal distribution of implementation-oriented versus primarily mechanistic sources

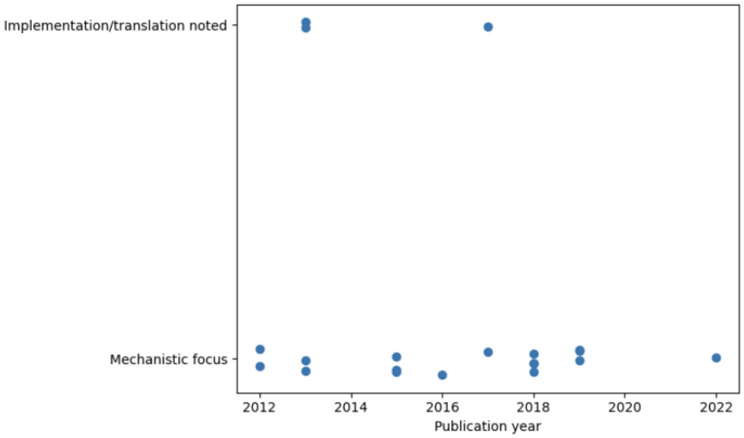

Figure 5 differentiates between sources primarily focused on **mechanistic resistance biology** and those explicitly emphasizing **clinical implementation or translational precision oncology frameworks**, plotted across publication years. The visual distribution shows that most publications in the selected corpus are mechanistically oriented, while a smaller subset centers directly on implementation and translational decision-making.

The predominance of mechanistic sources is consistent with the historical trajectory of oncology research: before large-scale implementation of precision frameworks can occur, resistance pathways must be biologically characterized. Foundational work describing intratumoral heterogeneity, clonal evolution, and genetic instability provided the structural explanation for why targeted therapies and immunotherapies eventually fail in many contexts (Burrell et al., 2013; McGranahan & Swanton, 2017). Similarly, conceptual expansions of resistance paradigms framed therapeutic escape as a dynamic, evolving process rather than a single mutational event (Holohan et al., 2013; Vasan et al., 2019). These contributions are primarily mechanistic, building the biological scaffolding upon which later translational models depend.

In contrast, the smaller number of implementation-focused publications reflects landmark efforts to operationalize genome-driven oncology. These sources emphasize structured integration of molecular profiling into clinical workflows, including tumor sequencing interpretation, treatment matching, and decision-making frameworks in multidisciplinary settings (Hyman et al., 2017; Dienstmann et al., 2013). The temporal positioning of these

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implementation-oriented contributions within the mid-2010s aligns with the maturation of next-generation sequencing technologies and the expansion of actionable molecular targets in solid tumors.

The figure also illustrates that mechanistic and implementation-focused publications coexist rather than occur in strictly sequential waves. For example, while immune checkpoint biology was being deeply characterized (Sharma & Allison, 2015; Topalian et al., 2015), parallel translational discussions were already emerging about how to incorporate molecular stratification and biomarker-guided therapy selection into practice (Hyman et al., 2017). This overlap indicates that the field does not move linearly from biology to practice; instead, biological discovery and clinical integration progress in parallel, often informing each other.

An additional observation from the timeline is that the more recent integrative conceptual update (Hanahan, 2022) appears after both mechanistic and implementation-focused frameworks had already been established. This positioning reflects a consolidation phase in which cancer biology is reframed in systems-level terms—emphasizing plasticity, microenvironmental interaction, and adaptive potential as cross-cutting determinants of therapeutic resistance. In practical terms, this reinforces the notion that implementation strategies must remain dynamic and responsive to evolving biological insights rather than fixed to static biomarker models.

DISCUSIÓN

The results mapped in this review support a coherent interpretation: therapeutic resistance is best explained as an **emergent property of evolving tumor ecosystems**, rather than a single pathway defect. Across the included literature, four elements repeatedly converge—**(1) intratumoral heterogeneity and clonal evolution, (2) therapy-imposed selection pressure, (3) microenvironmental protection, and (4) immune escape dynamics**—and together they define why durable control remains difficult even in the era of precision oncology (McGranahan & Swanton, 2017; Holohan et al., 2013; O'Donnell et al., 2019; Hanahan, 2022).

Tumor evolution as the "common denominator" of resistance

The strong emphasis on heterogeneity/evolution in the dataset aligns with a central concept: resistance often reflects **Darwinian selection acting on pre-existing variation**. Even when a therapy effectively suppresses the dominant clone, minor subclones with reduced sensitivity may persist and expand, generating clinically observable progression (McGranahan & Swanton, 2017; Turner & Reis-Filho, 2012). This is consistent with clinical observations that responses can be heterogeneous across lesions and timepoints, reflecting spatial and temporal divergence within the same patient—an issue highlighted in clinic-oriented discussions of tumor heterogeneity (Bedard et al., 2013).

Importantly, this evolutionary framing also explains why resistance remains common across distinct treatment classes. Targeted therapy, immunotherapy, and even cellular therapies can all impose strong selection. Under these pressures, tumors may escape via genetic changes, transcriptional rewiring, or shifts in cellular state—especially when plasticity is available as an adaptive route (Hanahan, 2022; Vasan et al., 2019). Thus, the dataset's temporal and thematic structure supports a modern view in which resistance is not an exception but an expected outcome unless strategies explicitly anticipate evolutionary escape.

Targeted therapy resistance: pathway plasticity and adaptive rewiring

Targeted agents illustrate the strengths and limitations of precision approaches. When tumors are driven by a dominant oncogenic dependency, inhibition can be highly effective, but the literature consistently shows that escape is enabled by **on-target alterations, bypass activation, and pathway reactivation** (Holohan et al., 2013; Vasan et al., 2019). What becomes especially important in a discussion context is that these resistance routes are often **predictable** at a systems level: signaling networks contain redundancy, and tumors can re-route survival signals through alternate nodes (Garraway & Jänne, 2012).

In that sense, precision oncology should not be interpreted as "one biomarker → one drug → durable control," but rather as a starting point for strategy design, where combinations, sequencing, and adaptive approaches are built around the expectation of evolution (Garraway & Jänne, 2012; Vasan et al., 2019). The implementation literature reinforces that genome-driven oncology is most impactful when it is embedded in decision systems that can adjust over time as resistance emerges (Hyman et al., 2017; Dienstmann et al., 2013).

Immunotherapy resistance: immune editing, exclusion, and checkpoint complexity

The prominent immunotherapy domain in the results reflects the clinical centrality of checkpoint blockade and the need to explain why responses are durable in some tumors but limited in others. Checkpoint inhibitors can unleash effective anti-tumor immunity, but resistance can arise through **immune editing, impaired antigen presentation, and altered T-cell function**, as well as through tumor-intrinsic programs that shape immune interactions (O'Donnell et al., 2019; Topalian et al., 2015).

A key nuance supported by the included sources is that checkpoints like PD-1/PD-L1 are not isolated switches; PD-L1 expression and function are regulated by inflammatory cues and tumor-intrinsic signaling, complicating its use as a standalone predictor (Sun et al., 2018). This aligns with clinical experience in which PD-L1 status alone does not fully account for response heterogeneity, and it suggests that effective personalization requires a broader immune-context interpretation rather than reliance on single-marker stratification (Topalian et al., 2015; O'Donnell et al., 2019).

The tumor microenvironment as a resistance "amplifier"

A major integrative insight from the co-occurrence patterns is the frequent pairing of immunotherapy with TME, supporting the idea that resistance can be created or stabilized by local ecological conditions. The evidence describing TGF-β–associated stromal remodeling as a factor that attenuates response to PD-L1 blockade is particularly illustrative: it shows that even when immune targets are present, the microenvironment can enforce immune exclusion and functional suppression (Mariathasan et al., 2018).

From a broader perspective, this reinforces that resistance is often **multi-compartmental**: tumor cells, immune cells, stromal cells, extracellular matrix, and cytokine networks jointly shape response. The TME-targeting literature supports the concept that disrupting these protective niches can complement tumor-intrinsic targeting (Roma-Rodrigues et al., 2019). In addition, stemness and niche biology deepen this point: cancer stem cell niches can maintain therapy-tolerant populations and facilitate recurrence, even after apparent initial control (Plaks et al., 2015). Thus, personalization is not only about identifying mutations; it also involves characterizing and, when feasible, modulating the ecosystem that enables survival under therapy.

Precision oncology as dynamic personalization rather than static matching

The implementation-focused sources in the dataset are fewer, but they play a structural role in bridging mechanism and practice. Genome-driven oncology emphasizes actionable alterations and the translation of profiling into therapy selection (Dienstmann et al., 2013; Hyman et al., 2017). However, when interpreted alongside the evolution and heterogeneity literature, a key implication emerges: **precision must be iterative**. A tumor's actionable landscape may change under therapy, and sampling limitations can obscure relevant subclones (Bedard et al., 2013; McGranahan & Swanton, 2017).

Therefore, contemporary personalized oncology strategies increasingly require integrating:

- baseline genomic vulnerabilities,
- expected resistance trajectories (based on pathway architecture),
- immune context and microenvironmental constraints, and
- clinical feasibility of combinations/sequencing.

This integrative model aligns closely with the updated hallmarks perspective, which emphasizes plasticity and ecosystem-level dependencies as central dimensions of cancer biology (Hanahan, 2022).

International and Latin American context: Mexico, Colombia, and Ecuador

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While the biological principles of resistance are universal, implementation is context-dependent. In Mexico, Colombia, and Ecuador, precision oncology adoption is expanding but can be limited by access to comprehensive genomic testing, availability of targeted agents and immunotherapies, and the presence of multidisciplinary molecular tumor boards. In this setting, the review's synthesis can support stepwise implementation strategies: prioritizing high-yield biomarkers and clinically validated targets, using rational combination principles where feasible, and integrating immune and microenvironment considerations into clinical reasoning even when advanced testing is not universally accessible (Hyman et al., 2017; Dienstmann et al., 2013).

Educationally, this matters because oncology trainees in these systems must learn to interpret resistance not only as "drug failure," but as a predictable biological outcome shaped by evolution and ecosystems—an approach that remains valuable even when resources vary across institutions.

CONCLUSIÓN

The present review consolidates contemporary evidence demonstrating that tumor adaptation and therapeutic resistance are not isolated events but structured biological processes rooted in **evolution, heterogeneity, immune dynamics, and microenvironmental interaction**. Across targeted therapies, immunotherapies, and genome-driven approaches, resistance consistently emerges as a consequence of selection acting on diverse and plastic tumor ecosystems (McGranahan & Swanton, 2017; Holohan et al., 2013).

A central conclusion supported by the reviewed literature is that **intratumoral heterogeneity provides the biological substrate for resistance**. Genetic diversity, clonal competition, and evolutionary selection under therapeutic pressure allow tumors to adapt through pre-existing or emergent resistant populations (Burrell et al., 2013; Turner & Reis-Filho, 2012). This evolutionary model explains why even highly effective initial responses can be followed by progression and why static treatment strategies often fail to produce durable control (Vasan et al., 2019).

In targeted therapy, resistance frequently arises through pathway reactivation, bypass signaling, and adaptive rewiring of oncogenic networks (Holohan et al., 2013; Dagogo-Jack & Shaw, 2018). These patterns underscore that signaling systems possess redundancy and flexibility, requiring treatment designs that anticipate alternative survival routes rather than relying on single-node inhibition (Garraway & Jänne, 2012).

In immunotherapy, resistance is shaped by immune editing, impaired antigen presentation, checkpoint pathway regulation, and microenvironmental exclusion (O'Donnell et al., 2019; Sun et al., 2018). The interplay between tumor cells and the tumor microenvironment is particularly decisive, as stromal remodeling and immunosuppressive signaling—such as TGF-β–mediated effects—can attenuate response even in the presence of immune checkpoint blockade (Mariathasan et al., 2018). These findings reinforce that immune resistance cannot be fully understood through tumor genomics alone but requires integrated immune-context analysis (Topalian et al., 2015; Sharma & Allison, 2015).

The tumor microenvironment emerges as a recurrent stabilizer of resistant phenotypes. Protective niches, stromal interactions, and stemness-supporting environments allow tumor cells to survive cytotoxic stress and contribute to recurrence (Plaks et al., 2015; Roma-Rodrigues et al., 2019). Consequently, durable therapeutic control may require simultaneous targeting of tumor-intrinsic vulnerabilities and microenvironmental support systems.

Precision oncology represents a critical translational response to this biological complexity. Genome-driven oncology enables alignment between molecular alterations and therapeutic selection (Dienstmann et al., 2013; Hyman et al., 2017). However, the synthesis of evidence indicates that personalization must be **dynamic and iterative**, accounting

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for evolving clonal architecture and immune–microenvironmental interactions rather than relying solely on baseline molecular snapshots (McGranahan & Swanton, 2017; Hanahan, 2022).

From an international perspective, including healthcare systems in Mexico, Colombia, and Ecuador, the conceptual framework outlined in this review supports stepwise implementation of precision strategies adapted to available resources. Even in contexts where comprehensive genomic profiling is not universally accessible, understanding evolutionary resistance principles can improve therapeutic reasoning, sequencing strategies, and multidisciplinary decision-making.

In summary, tumor adaptation and therapeutic resistance should be interpreted as predictable outcomes of evolutionary and ecological dynamics within cancer systems. Effective personalized oncology strategies must therefore integrate molecular profiling, evolutionary modeling, immune-context assessment, and microenvironmental considerations into cohesive and adaptable clinical frameworks. This integrative perspective not only advances scientific understanding but also strengthens oncology education and translational practice in diverse healthcare environments.

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