

Original Article



Precision Interception of Tumor Evolution: From Genomic Landscape to Clinical Intervention

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Citation of this article: Wang D.D., Chen Y., Zhou P., Precision Interception of Tumor Evolution: From Genomic Landscape to Clinical Intervention. Nat Cell Sci 2027;5(1):e00021. doi: 10.61474/ncs.2027.00021.

Abstract

The development of therapeutic resistance in solid tumors is not merely an incidental response, but a relentless recapitulation of Darwinian evolution under profound pharmacological pressure. Consequently, traditional reactive clinical paradigms are increasingly demonstrating insurmountable limitations. This review highlights the critical paradigm shift from late-stage containment towards "evolutionary interception", a proactive approach that predicts and pre-emptively blockades resistance trajectories during therapeutic windows of minimal clonal complexity. We delineate how the germline genetic background imposes hard constraints on somatic adaptation and creates targetable genomic topologies, exemplified by the baseline hemizygous loss of RB1 in BRCA2-mutated breast cancer. Furthermore, we explore the propulsion of drug-independent evolution by endogenous mutational engines, including homologous recombination deficiency and APO-BEC3, alongside non-genetic adaptations such as transcriptional rewiring and lineage plasticity. Translating these evolutionary concepts requires high-resolution monitoring through circulating tumor DNA, graph genome algorithms, and single-cell multi-omics. Finally, we critically evaluate frontier clinical strategies, such as upfront synthetic lethality and neoantigen vaccines, while addressing the profound challenges of cumulative toxicity and therapy-induced regressive evolution.

Keywords

Evolutionary Interception, Genomic Topology, Germline-Somatic Interactions, Minimal Residual Disease (MRD), Synthetic Lethality

1. Introduction

In the complex molecular ecology of modern oncology, the widespread application of targeted therapies and immunotherapies has substantially prolonged the survival of patients with advanced malignancies; however, almost all solid tumours inevitably progress to clinical resistance and treatment failure.¹⁻³ The emergence of such resistance is not an isolated biochemical response or an incidental stochastic mutational event, but rather a direct and unrelenting recapitulation of Darwinian evolution at the somatic cell level.^{4,5} Under profound and sustained pharmacological selection pressures, tumour cells exhibit remarkable population-level survival fitness, driven by the rapid accumulation of genetic alterations, profound epigenetic reprogramming, and the adaptive remodelling of the tumour microenvironment.⁶ Historically, the standard-of-care paradigms in clinical oncology have been largely reactive. Within current clinical path-

ways, physicians typically pivot to second- or third-line therapeutic regimens only retroactively, following macroscopic radiographic progression or the marked deterioration of clinical symptoms.⁷ However, principles of evolutionary biology and population dynamics have repeatedly demonstrated that once tumour clonal evolution surpasses an irreversible threshold of complexity, its inherent spatiotemporal heterogeneity increases exponentially.⁸⁻¹⁰ Once the tumour ecosystem is saturated with myriad subclones harbouring diverse resistance mechanisms, the probability of achieving complete disease eradication becomes vanishingly small.¹¹

1.1 The Darwinian evolutionary nature of cancer drug resistance

Elucidating the underlying logic of this evolutionary crisis necessitates the integration of the classic Goldie–Coldman hypothesis and Gompertzian growth kinetics models.¹²⁻¹⁴ According to the Goldie–Coldman hypothesis, the absolute

Received: August 2, 2026 | Revised: August 11, 2026 | Accepted: August 30, 2026 | Published online: September 1, 2026



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probability of a tumour harbouring intrinsically resistant mutant clones is directly correlated with its overall volume and total cell number; its mathematical logic can be simplified as the cumulative product of the number of cell divisions and the spontaneous mutation rate.¹⁵ As the tumour burden increases, the probability of the cell population accumulating spontaneous oncogenic mutations over successive divisions becomes exceedingly high. Concurrently, Gompertzian growth kinetics dictates that tumours exhibit a remarkably high growth fraction when the disease burden is minimal. However, as tumour volume expands, spatial and nutritional constraints drive the overall growth rate into an exponentially decaying plateau phase.¹⁶

During the initial phase of clinical intervention, intensive targeted therapies or cytotoxic chemotherapy typically eradicate the vast majority of drug-sensitive dominant clones rapidly, leading to substantial tumour regression on radiographic imaging. However, this process inevitably imposes a severe "evolutionary bottleneck" upon the entire tumour population.¹⁷ In the setting of minimal residual disease (MRD), drug-resistant subclones—initially existing as an ecological minority—experience highly advantageous "competitive release" following the elimination of spatial competition and resource suppression previously exerted by sensitive clones.¹⁸ Within this micro-evolutionary window, these resistant clones undergo rapid "clonal rebound" and repopulation.¹⁹ This rapid resurgence, robustly selected and exponentially amplified by the evolutionary bottleneck, constitutes the core macroscopic and microscopic kinetic foundation of clinically acquired resistance.

1.2 From "passive rescue" to "evolutionary interception"

Confronted with this formidable evolutionary dilemma, conventional "whack-a-mole" approaches to targeted therapy and immunotherapy have increasingly demonstrated insurmountable limitations due to their inherent temporal lag.²⁰ The revolutionary concept of "cancer interception" has emerged against this backdrop, rapidly establishing itself as a central paradigm in global translational oncology research.²¹

The essence of evolutionary interception lies in significantly shifting the frontline of cancer treatment from "late-stage containment" to "early evolutionary blockade".²² The central thesis of this concept is that future curative strategies must not be restricted to targeting the pre-existing, static mutations of a tumour. Instead, they must rely on the precise prediction of the tumour's future evolutionary trajectories to map an "evolutionary probability landscape".²³ Once the most probable evolutionary trajectory toward specific resistance mechanisms has been identified, clinical interventions should be deployed preemptively to establish a physical or biological blockade. This must occur during the therapeutic window characterized by minimal tumour burden and lowest clonal

complexity (e.g., during the post-operative adjuvant setting or the very early stages of neoadjuvant therapy). By front-loading specific synthetic lethal agents or immunotherapies, these resistant clones can be thoroughly eradicated before they attain absolute ecological dominance. Consequently, this approach deprives cancer cells of the opportunity to undergo selection toward fatal therapeutic resistance (Figure 1).²³⁻²⁶

2. Germline-Somatic Interactions and the Shaping of Evolutionary Landscapes

Historically, somatic mutations have been regarded as the primary driving force behind cancer progression. However, recent advances in whole-genomics have revealed that the somatic mutational landscapes of tumors do not emerge randomly in an evolutionary vacuum; rather, they are profoundly guided and subject to the "hard constraints" of the patient's germline genetic background.²⁷ Pathogenic germline variants are not merely static epidemiological indicators for assessing individual cancer risk; they are core intrinsic drivers that dictate the evolutionary trajectories tumors will pursue under specific therapeutic pressures.^{28,29}

2.1 Hard Constraints of the Germline Background on Evolutionary Trajectories

The conceptual prototype of intercepting cancer evolution can be traced back to the historic discovery of Li-Fraumeni syndrome (LFS) by Frederick P. Li and Joseph F. Fraumeni in 1969.³⁰ Through in-depth epidemiological and pedigree analyses of specific families, they discovered that foundational defects in the germline *TP53* gene led to an abnormally high incidence of multiple primary tumors (such as sarcomas, breast cancers, and brain tumors) within the same family, accompanied by a significantly earlier age of onset.³¹ This marked the scientific community's first establishment of the absolute control exerted by innate genetic backgrounds over acquired malignant evolution, laying the conceptual foundation for ultra-early surveillance and clinical "interception" in high-risk populations.

In the modern era of precision medicine, elucidating the germline background holds irreplaceable value for implementing evolutionary interception. A large-scale prospective study utilizing tumor-normal paired whole-genome/targeted sequencing in 1,040 advanced cancer patients demonstrated that up to 17.5% of patients harbored hereditary cancer-predisposing mutations with actionable clinical significance.³² Strikingly, over 55.5% of these mutation carriers would have been entirely missed had they been evaluated solely according to traditional clinical guidelines based on family history or early-onset age. Universal paired germline and somatic sequencing not only directly redirected approximately 3.7% of advanced-stage patients to more tailored targeted therapies, but also prompted predictive genetic testing for their family

members, thereby achieving source interception of potential cancer evolution at the subclinical level.³²

2.2 Subtype-Specific Comparisons: The Divergence Between TNBC and Luminal Subtypes

Supported by large-scale clinical genomics, research has revealed how specific germline variants preferentially direct the somatic adaptive landscapes of distinct molecular breast cancer subtypes. Triple-negative breast cancer (TNBC) and hormone receptor-positive/HER2-negative (Luminal) breast cancer exhibit starkly divergent evolutionary bifurcation points when confronted with similar endogenous instability or exogenous therapeutic pressures (Table 1).³³

In the evolutionary landscape of TNBC, germline *BRCA1* (*gBRCA1*) mutations play an indispensable foundational role. Whole-exome data indicate an exceptionally high somatic *TP53* mutation rate (up to 81% to 88%) in TNBC patients, with *gBRCA1* mutations exhibiting a profound co-occurrence with *TP53* loss-of-function (LoF) mutations during the very early stages of tumorigenesis.³⁴ Lacking classical targets such as ER, PR, and HER2, TNBC presents with a higher tumor mutational burden (TMB, averaging 1.2 mutations/Mb) and a highly heterogeneous clonal architecture. Its evolutionary strategy leans toward sustaining high aggressiveness by accumulating co-mutation patterns in driver genes like *PIK3CA* and *TTN*, and it achieves rapid evasion under therapeutic pressure by generating extensive chromosomal structural variants.^{35,36}

In stark contrast, within Luminal (HR+/HER2-) breast cancer, *gBRCA2* mutation carriers display a highly specific and directionally defined network of somatic genomic rewiring.³¹ Compared to wild-type (gWT) patients, the incidence of *PIK3CA* mutations in *gBRCA2* tumors is significantly reduced; more crucially, somatic *RB1* gene alterations and deep amplifications of *MYC* and *AURKA* are highly enriched in these tumors. In clinical targeted therapy, *RB1*, *MYC*, and *AURKA* are all universally recognized as core nodes mediating acquired resistance to CDK4/6 inhibitors (CDK4/6i).^{37,38} This specific somatic landscape, rigidly dictated by the germline background, forewarns that latent molecular mechanisms of resistance are already enriched within the tumor ecosystem prior to the initiation of standard first-line targeted therapies in *gBRCA2* patients.³⁹ [table1]

2.3 Genomic Topology and Allelic Configuration

To deeply understand why *gBRCA2* tumors specifically evolve *RB1* loss with such a high probability, one must transcend the theoretical limitations of the classical Knudson "two-hit" hypothesis and introduce the more refined concept of hemizygosity from genomic topology.^{31,40}

The Knudson hypothesis posits that tumor suppressor genes must undergo complete biallelic inactivation to release the brakes on proliferation.⁴¹ However, in real evolutionary dynamics, the initial configuration of alleles largely determines

the threshold for acquired resistance. On the long arm of human chromosome 13 (13q), the *BRCA2* gene and the prominent cell cycle checkpoint tumor suppressor gene *RB1* exhibit highly syntenic physical linkage. During the early stages of *gBRCA2*-driven tumorigenesis, to achieve loss of heterozygosity (LOH) and eliminate the protective wild-type *BRCA2* allele, tumor cells frequently undergo large-scale chromosomal deletions encompassing the entire 13q region.⁴¹

Due to their extreme geographic proximity, these large chromosomal structural events inevitably cause the "collateral" deletion of the adjacent wild-type *RB1* allele. Independent cohort data from whole-exome sequencing led by Safonov et al. confirmed that a staggering 82.6% of *gBRCA2* primary breast cancers are already in a state of concurrent loss of heterozygosity (co-LOH) for both *BRCA2* and *RB1* at baseline, prior to any targeted therapy.³¹

This baseline hemizygous loss of *RB1* dictates that only a single functional *RB1* allele remains within the cell. Macroscopically, these cells can still maintain basic control over the G1/S cell cycle transition, thus retaining initial sensitivity to CDK4/6 inhibitors. However, this population of tumor cells has already surreptitiously traversed the most arduous first step of evolution. When exposed to potent CDK4/6i combined with endocrine therapy, wild-type tumors with intact dual *RB1* copies require two independent mutations—an extremely low-probability event—to develop resistance. Conversely, cells possessing hemizygous vulnerability only need to acquire a single, minute LoF mutation (such as a nonsense mutation or microdeletion) to effortlessly cross the evolutionary threshold and achieve complete *RB1* inactivation. Multivariate Cox models confirm that this baseline allelic configuration is the sole biomarker capable of independently predicting significantly shortened progression-free survival (PFS) upon CDK4/6i treatment, thereby providing a precise physical anchor for "evolutionary interception" based on genomic topology.³¹

3. Endogenous Mutational Engines and Drug-Independent Evolution

The macroscopic emergence of acquired resistance mutations in tumours is not exclusively a passive, stochastic response to the targeted pressure of exogenous therapeutics. To survive stringent therapeutic bottlenecks, tumour cells mobilise and ingeniously co-opt (exaptation) endogenous mutation-generating mechanisms.^{42,43} Functioning as fundamental biological engines, these mechanisms continuously generate the mutational 'ammunition' required for survival at an exceptionally high rate, profoundly shaping evolutionary trajectories characterised by a high degree of 'drug independence'.^{43,44}

3.1 Homologous Recombination Deficiency (HRD) as a Mutational Catalyst

Under normal physiological conditions, the BRCA1 and BRCA2 proteins serve as central hubs in the homologous recombination repair (HRR) pathway, responsible for the error-free repair of lethal DNA double-strand breaks (DSBs) using sister chromatids as precise templates.⁴⁵ Once the function of these genes is compromised by mutation or epigenetic silencing, the cell enters a state of homologous recombination deficiency (HRD), commonly referred to as 'BRCAness'.⁴⁶ Tumour cells exhibiting BRCAness face an acute crisis of catastrophic genomic collapse and apoptosis. To barely maintain the physical integrity of their chromosomes, they are forced to rely on alternative repair networks with exceptionally low fidelity, particularly microhomology-mediated end joining (MMEJ) and non-homologous end joining (NHEJ).^{47,48} These two repair mechanisms do not require a precise template; instead, they repair DNA by forcibly ligating broken ends. This forced degradation of repair fidelity imprints indelible 'mutational scars' across the genome, manifesting as a high burden of large-scale structural variants (SVs) and short insertions or deletions (indels) flanked by microhomologous sequences.⁴⁹

In the aforementioned model of germline *BRCA2* (gBRCA2)-driven evolution of resistance to CDK4/6 inhibitors, in-depth genomic decoding has revealed that acquired loss-of-function mutations in *RB1* are predominantly not caused by simple single-nucleotide point mutations. Rather, they arise from MMEJ-mediated short deletions or structural rearrangements leading to the large-scale loss of multiple *RB1* exons.⁵⁰⁻⁵² This compellingly demonstrates that an active HRD engine is not merely the instigator of oncogenesis, but also acts as a high-frequency 'mutational catalyst' during targeted therapy, executing the fatal 'second hit' on key tumour suppressor genes like *RB1* with extreme efficiency.⁵³

3.2 Parallel Propulsion by the APOBEC3 Enzymatic System

Beyond homologous recombination deficiency, the aberrant activation of the endogenous cellular APOBEC3 (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3) family of enzymes constitutes another formidable driver governing genomic evolution.^{54,55} Originally a crucial component of the host's innate antiviral defence system, APOBEC3 leverages its cytosine deaminase activity to catalyse the conversion of cytosine to uracil during periods of single-stranded DNA exposure (such as during DNA replication or transcription), thereby inducing characteristic C>T or C>G base substitution mutations.^{56,57}

In breast cancer, particularly within the HR+ subtype exhibiting a high tumour mutational burden and in invasive lobular carcinoma (ILC), the APOBEC3 system is aberrantly hijacked by tumour cells, assuming a central and dominant role in shaping mutational signatures.⁵⁸ A large-scale clinical whole-genome cohort analysis demonstrated that APO-

BEC3-mediated mutational landscapes exhibit explosive enrichment in metastatic breast cancer (MBC) tissues following combined endocrine and CDK4/6i therapy, which tightly and directly correlates with a precipitous decline in patient progression-free survival.⁵⁹

Even more critically, foundational validation experiments have shown that the presence of APOBEC3A (A3A) expression in a mere 10% of subclones within a tumour population is sufficient to ignite mutational cascades and paracrine signalling that can entirely remodel the broader tumour ecosystem.⁶⁰ This evolution, orchestrated by the APOBEC3 enzymatic system, possesses an astonishing degree of 'autonomy': even upon the complete withdrawal of targeted agents and in the absolute absence of exogenous pharmacological selection pressure, active APOBEC3 enzymes can spontaneously and continuously drive clonal genomic drift. This provides a relentless supply of complex resistance gene combinations against endocrine therapy, CDK4/6 inhibitors, and even PI3K inhibitors.^{61,62} Consequently, future evolutionary interception strategies must incorporate specific inhibitors targeting APOBEC3 activity, thereby severing the supply line of resistant clones at its very source.

4. Non-genetic adaptation and network rewiring

Beyond direct and irreversible alterations to the underlying DNA sequence, tumour cells are highly capable of establishing impenetrable barriers of drug resistance without altering any genomic sequences. This is achieved through profound epigenetic remodelling, precise manipulation of protein degradation networks, and the activation of compensatory kinase cascades. Such non-genetic adaptation endows tumours with profound plasticity when confronted with pharmacological catastrophe.^{63,64}

4.1 Protein degradation and transcriptional amplification in CDK4/6 inhibitor resistance

For the vast majority of hormone receptor-positive (HR+) breast cancers that are initially sensitive to CDK4/6 inhibitors (CDK4/6i) and lack baseline *RB1* genetic mutations, acquired resistance is frequently mediated by an elegant, "two-step sequence" non-genetic escape mechanism.

Initially, although the intervention of CDK4/6i successfully inhibits kinase complex activity, thereby maintaining the retinoblastoma protein (Rb) in a hypophosphorylated, suppressive state,⁶⁵ prolonged drug exposure inadvertently triggers massive degradation of the Rb protein itself via the ubiquitin-proteasome pathway, driven by intracellular homeostatic feedback mechanisms. Although the mere reduction in the physical concentration of Rb protein is insufficient to fully restore unrestricted cell proliferation, this low-Rb environment drastically lowers the energetic threshold required to release

the critical cell-cycle transcription factor E2F, thereby completing the "first step" of resistance evolution,⁶⁶ Subsequently, as the decisive second step in acquiring resistance, tumour cells achieve profound stabilization and massive transcriptional amplification of the downstream c-Myc protein by rewiring mitogenic or bypass hormonal signalling networks (e.g., through compensatory activation of the PI3K or ERK pathways).⁶⁷ In this context, overexpressed c-Myc functions as a super-enhancer, directly and potently amplifying the transcriptional output of free E2F. This forces the cell to forcibly breach the G1/S physical checkpoint and resume sustained proliferation.^{37,68} The elucidation of this dynamic mechanism provides revolutionary guidance for clinical strategies: front-loading or timely integration of proteasome inhibitors into CDK4/6i treatment regimens to forcibly stabilize the physical concentration of Rb protein holds promise as a potential combinatorial approach to reverse or preemptively intercept this non-genetic evolutionary trajectory.

4.2 Parallel evolutionary trajectories and mutual exclusivity of kinase networks

Within the cohort of patients with endocrine-resistant advanced breast cancer, in-depth profiling based on large-cohort sequencing reveals that the evolutionary trajectory of resistance in the tumour population is by no means restricted solely to the well-characterized mutations in the ligand-binding domain of the *ESR1* gene. Tumours can achieve complete evasion of endocrine deprivation therapy by activating and rewiring the complex MAPK kinase network.⁶⁹

These include activating mutations in the *ERBB2* gene, inactivating deletions of the *NF1* tumour suppressor gene, and profound amplification of *EGFR*.⁷⁰ Crucially, multidimensional statistical analyses have confirmed that these recombinatory variations within the MAPK pathway exhibit a high degree of mutual exclusivity with classical *ESR1* mutations at the individual patient level. This strikingly prominent mutually exclusive evolutionary trait reflects a profound Darwinian logic: when confronted with the identical evolutionary bottleneck of endocrine therapy, the tumour population derives parallel, non-overlapping escape routes to diversify survival risk.^{71,72} Given that these kinase network variations are intrinsically highly actionable in the clinic, this discovery provides a direct translational rationale for adaptive clinical trials: once a tumour is monitored to be skewing towards a specific parallel pathway, targeted kinase inhibitors can be deployed to enact a directed blockade.

4.3 Lineage plasticity and transdifferentiation

The ultimate manifestation of non-genetic tumour evolution is exemplified by lineage plasticity and histological transdifferentiation.⁷³ Taking small cell lung cancer (SCLC)—a highly aggressive neuroendocrine tumour—as an example, it has long been dogmatically maintained within the field that

its pathogenesis fundamentally requires the ubiquitous and obligatory biallelic loss of both the *TP53* and *RB1* genes. However, recent large-scale integrative analyses of molecular pathology have challenged this consensus, identifying a highly distinct lung cancer subtype—"Rb-proficient SCLC"—which accounts for approximately 6% of the overall SCLC population.⁷⁴⁻⁷⁶

Tracing back from a macroscopic perspective of tumour lineage evolution, this SCLC phenotype harbouring functional wild-type Rb protein exhibits a significantly lower degree of neuroendocrine differentiation. Multi-omics data strongly imply that this subpopulation does not originate from the linear evolutionary trajectory of classical SCLC. Instead, it is highly probable that it arises via transdifferentiation from non-small cell lung cancer (NSCLC) progenitor cells harbouring specific driver mutations (e.g., *EGFR* mutations) as an evasion strategy against the profound therapeutic pressure exerted by intensive targeted therapies.⁷⁵

Within the specific microscopic molecular networks, these rare transdifferentiated tumours eschew the time-consuming and energy-intensive strategy of physical *RB1* gene knock-out; rather, they implement a functional "interception" of the Rb pathway via upstream mechanisms. They exhibit exceptionally high frequencies of *CDKN2A* mutations or *CCND1* amplifications.^{77,78} This hyperactivation of upstream signalling drives the Cyclin D-CDK4/6 kinase complex into a state of sustained, high-level phosphorylation, thereby thoroughly inactivating the intact Rb protein. This atypical evolutionary trajectory offers a glimmer of hope for these otherwise untreatable, aggressive transdifferentiated tumours, suggesting that CDK4/6 inhibitors may exert highly selective cytotoxic and suppressive effects against this unique Rb-proficient subpopulation.³¹

5. High-Resolution Monitoring: Locking in on the Interception Window

The successful implementation of evolutionary interception strategies is predicated on the clinician's ability to possess a microscopic, panoramic field of view that outpaces the speed of tumor cell evolution and pierces through the veil of spatio-temporal heterogeneity. Currently, a high-resolution monitoring matrix—centered on the dynamic tracking of circulating tumor DNA (ctDNA), the underlying assembly algorithms of next-generation graph genomes, and single-cell multimodal spatial omics—is radically redefining the temporal anchors and resolution granularity of disease monitoring.⁷⁹⁻⁸¹

5.1 Dynamic Early Warning via ctDNA and Minimal Residual Disease (MRD)

The maturation of liquid biopsy technologies has substantially advanced the timeline for medical intervention. During the evolutionary bottleneck induced by targeted therapies,

the detection of ctDNA in peripheral blood enables physicians to precisely capture minute shifts in clonal abundance (clonal drift) driven by the evolution of resistance, weeks or even months before conventional macroscopic imaging confirms disease progression.⁸²⁻⁸⁴

In large-scale clinical analyses of ER+ advanced breast cancer patients receiving standard endocrine therapy combined with CDK4/6 inhibitors (CDK4/6i), the dynamic characteristics of ctDNA at baseline and early during treatment have demonstrated decisive predictive power. Studies have confirmed that if dynamic monitoring during the initial phase of treatment reveals a failure of the patient's ctDNA variant allele fraction (VAF) to decline significantly, while simultaneously capturing specific genetic alterations conferring immense evolutionary survival advantages (such as pathogenic mutations in *TP53* or structural amplifications of *FGFR1*), this serves as a potent early warning signal for highly dangerous evolution. This subgroup of patients, harboring these specific evolutionary signatures, will suffer a catastrophic truncation of their progression-free survival (PFS). These aberrant genomic fragments circulating in the blood are the absolute "vanguards" of irreversible, consolidated resistance.^{85,86} In future adaptive clinical trials, these MRD-positive patients or those exhibiting clonal drift will be the optimal interception candidates for implementing proactive treatment escalation (e.g., preemptive switching to combinations incorporating specific inhibitors).

5.2 Leap in Underlying Algorithms: Graph Genomes Decipher the Structural Enigma

To unerringly identify highly complex structural variations (SVs) and short insertions/deletions (indels) driven by endogenous motors such as homologous recombination deficiency (HRD) from massive volumes of next-generation sequencing (NGS) short-read data, the foundational algorithms of bioinformatics have undergone a revolutionary paradigm shift.^{87,88} Over the past decade, traditional alignment algorithms based on one-dimensional linear reference sequences (such as standard pipelines utilizing BWA-MEM and SAMtools) have been highly efficient in processing single nucleotide polymorphisms (SNPs).⁸⁹ However, when tumor genomes undergo complex structural aberrations mediated by large-scale rearrangements and repetitive sequences, traditional linear alignment suffers from severe "reference allele bias" and sequence mapping artifacts, leading to substantial false negatives and false positives.⁸⁸

To shatter this technological ceiling, next-generation algorithms like Scalpel have innovatively introduced the mechanism of local microassembly. It entirely abandons the brute-force approach of mapping short reads directly to a reference genome, opting instead to utilize de Bruijn graphs to independently and *de novo* reconstruct genomic sequences

within target regions.^{88,90,91} Through this foundational reconstruction, Scalpel dramatically eliminates PCR and sequencing artifacts, pushing the detection accuracy of complex indels shorter than 100 bp to new heights. Taking this a step further, next-generation structural variant genotyping tools, exemplified by Paragraph, have completely subverted the linear paradigm, propelling analysis into the era of graph genomes.⁹² Paragraph constructs a Directed Acyclic Graph (DAG) for every candidate SV awaiting validation, encompassing the reference path alongside all known variant branch paths.⁹³ Sequencing reads can undergo unbiased local realignment within these three-dimensional sequence graphs spanning breakpoints, thoroughly eradicating the bias detriments inherent to linear alignment at the fundamental level of physical logic. This technology provides the core computational prowess required to precisely reconstruct and track genomic catastrophes under the selective pressure of targeted drugs.⁹⁴

5.3 Microenvironmental Symbiosis and Immune Evasion Networks at the Single-Cell Level

Today, as precision medicine advances into high-dimensional spaces, single-cell multi-omics technologies have successfully and seamlessly stitched together transcriptomics (scRNA-seq), spatial epigenetics, and proteomics, achieving a leap forward in the vectorized tracking of dynamic evolution within the tumor microecosystem 1. At the vanguard of immunotherapy, the emergence of resistance is not merely an accumulation of genetic mutations within isolated cancer cells; rather, it is the product of network-level, coordinated remodeling of the entire tumor microenvironment (TME) under immune pressure.

High-resolution, dynamic single-cell tracking has revealed that minute populations of drug-resistant, stem-like subclones lie dormant at a very early stage within tumor tissues that are otherwise sensitive to immunotherapy. When subjected to sudden surges in immune surveillance pressure, these latent subclones rapidly achieve explosive, selective expansion via the hyperactivation of the Wnt/ β -catenin signaling axis, accompanied by drastic cellular metabolic reprogramming.⁹⁵ A more sophisticated evolutionary strategy, confirmed through the analysis of intercellular ligand-receptor communication networks at single-cell resolution, reveals that these aggressively expanding resistant clones actively secrete specific immunosuppressive metabolites. This systematically and irreversibly induces deep functional exhaustion in the CD8+ cytotoxic T cells infiltrating the tumor margins.^{96,97} By precisely capturing these early metabolic or transcriptional signals during the nascent stage of clonal expansion, clinicians can preemptively deploy specific metabolic pathway inhibitors or Wnt inhibitors to execute a fundamental interception of these adaptive evolutionary pathways, well

before the tumor can fully construct an impregnable immune sanctuary.^{98,99}

6. Clinical Translation: The Endgame Strategy of Implementing Evolutionary Interception

Following the comprehensive deconstruction of the spatio-temporal evolutionary dynamics, genomic topological vulnerabilities, and microenvironmental symbiotic networks of tumours, the ultimate objective of modern clinical oncology trials is undergoing a radical paradigm shift. It is transitioning from a reactive 'salvage' approach against established, large-scale drug resistance to a proactive 'upfront interception' strategy that reconfigures the sequencing of targeted therapies to sever evolutionary trajectories at their very source.^{100,101}

6.1 Evolutionary Sequence Reconfiguration: The Proactive Deployment of Synthetic Lethality

Perhaps the most striking clinical translation of the evolutionary interception concept to date is the subversion and reconfiguration of standard guidelines based on the specific evolutionary logic of luminal breast cancer. As previously discussed, in breast cancers harbouring germline *BRCA2* (*gBRCA2*) mutations, the physical linkage on chromosome 13q renders the *RB1* gene in a highly vulnerable state of baseline monoallelic loss.¹⁰² When these tumours are exposed to first-line CDK4/6 inhibitors (CDK4/6i), the active HRD mutational engine readily catalyses the generation of minute short-fragment deletions. This executes the fatal 'second hit' on *RB1*, thereby rapidly and thoroughly evading cell cycle inhibition.

According to traditional, reactive medical guidelines, patients must endure irreversible biallelic loss and rapid clinical deterioration before the use of PARP inhibitors, which target HRD, is considered in the compromised setting of later-line therapy. However, by this juncture, the clonal landscape of the tumour is already extraordinarily complex. Based on the precise prediction of evolutionary probabilities, international multicentre clinical trials have substantially advanced the lines of therapeutic defence. These trials deploy the next-generation, highly selective PARP1 inhibitor saruparib (AZD5305) in combination with an oral SERD (camizestrant) as the absolute first-line treatment for patients harbouring *BRCA1/2* or *PALB2* mutations, directly competing head-to-head against standard CDK4/6i combination regimens.¹⁰³ The underlying logic of this evolutionary interception relies on the exceptionally efficient 'PARP trapping' mechanism of saruparib, which physically deadlocks the PARP1 protein at the sites of DNA single-strand breaks. This precipitates catastrophic 'synthetic lethality' within this occult population of HRD-deficient tumour cells as their replication forks collapse¹⁰⁴⁻¹⁰⁶. This strategy preemptively and thoroughly eradicates the 'seedbed cell

pool' with the potential to generate *RB1* loss-of-function mutations from a physical standpoint, *before* CDK4/6 inhibitors are introduced to exert selection pressure. By directly dismantling the assembly line of resistance mutations, trials such as EvoPAR-Breast01 truly actualise the ultimate goal of truncating specific molecular evolutionary trajectories.

6.2 Precision Cancer Prevention: Frontier Applications of Neoantigen Vaccines

On a more expansive scale of public health and precision prevention, the highest manifestation of evolutionary interception is the extension of the defensive frontline to a stage prior to macroscopic solid tumourigenesis, achieving ultimate evolutionary blockade during the subclinical phase in high-risk hereditary populations.^{107,108}

Consider Lynch syndrome (LS) as a paradigm. This autosomal dominant disorder, driven by germline mutations in mismatch repair (MMR) genes, predisposes patients to a lifetime risk of up to 80% for developing colorectal, endometrial, and urothelial cancers.¹⁰⁹ Constrained by definitive mismatch repair deficiency, the mucosal precursor cells in these patients inevitably develop microsatellite instability (MSI) during the nascent stages of malignant transformation. This foundational mechanism precipitates a high frequency of extensive frameshift mutations, resulting in the cell-surface presentation of highly immunogenic 'frameshift neoantigen peptides' (FSPs) that are strikingly distinct from the host's native tissues.¹¹⁰

Because the evolutionary emergence of these neoantigens exhibits an exceptionally high degree of deterministic certainty, researchers have successfully developed NOUS-209, an 'off-the-shelf' neoantigen-specific viral vector vaccine tailored for individuals with Lynch syndrome.¹¹¹ This vaccine encodes 209 FSPs that are broadly shared during the early stages of MSI tumour evolution. In follow-up data, NOUS-209 demonstrated excellent prophylactic efficacy: among 45 enrolled Lynch syndrome carriers, the vaccine exhibited an outstanding safety profile and a 100% immunogenic response rate. It successfully elicited a robust, broad, and highly durable response network of CD4+ and CD8+ memory T cells, with peak effector functions reaching approximately 1,100 IFN- γ spot-forming cells (SFCs) per million peripheral blood mononuclear cells (PBMCs).¹¹² Sustained through the continuous remodelling provided by annual boosters, the vaccine essentially deploys a preemptive, highly targeted, and patrolling immunological armed force within the patient. Should cells in any organ begin to express these characteristic MSI neoantigens during the primordial stages of evolution, the patrolling memory T cells can instantly initiate exceptionally precise, targeted clearance at a microscopic node, well before the formation of a macroscopic adenoma or tumour. Clinical data reveal that over a one-year follow-up period, a remarkable 'zero incidence' of new high-grade adenomas was

achieved within this extremely high-risk cohort (compared to a natural expected annual incidence of approximately 4%).¹¹¹ This dynamic, long-lasting defence, relying on the host's potent immunological memory system, perfectly exemplifies the ultimate vision of utilising highly deterministic molecular evolutionary trajectories to achieve absolute 'evolutionary blockade' of the primary lesion at its earliest inception.

7. Conclusions and future challenges

The profound integration of modern genomic topology, underlying sequencing algorithms, and molecular evolutionary biology has irrefutably revealed that cancer is fundamentally far more than a disease of uncontrolled cellular proliferation driven by localized genetic mutations. Rather, it is an exceptionally complex, adaptive evolutionary system that is highly dynamic within the microscopic host ecosystem, driven by the dual pressures of natural selection and intensive pharmacological intervention.^{21,113}

From the baseline allelic vulnerability conferred by the *in cis* linkage of germline *BRCA2* (*gBRCA2*) and *RB1*, to the mutational fuel supplied at an ultra-high frequency by homologous recombination deficiency (HRD) and the endogenous APO-BEC3 mutational motor, through to the compensatory rewiring of epigenetic and metabolic networks at the non-genetic level, tumour populations demonstrate an almost impeccable fault tolerance and survival instinct when confronted with therapeutic pressure. Faced with this system-level biological challenge, the global oncology community is driving a historic paradigm shift from passive defence to proactive "evolutionary interception" with unprecedented resolve. Whether leveraging underlying graph genome algorithms to decipher exceedingly complex structural variations, deploying the NOUS-209 subclinical neoantigen vaccine developed for high-risk hereditary syndromes, or utilizing the elegant sequential drug combination of EvoPAR-Breast01 to preemptively truncate CDK4/6i resistance pathways via profound synthetic lethality mechanisms, these frontier advancements collectively delineate the grand contours of next-generation curative strategies.

However, as the medical defensive frontline is comprehensively and substantially advanced, "evolutionary interception"—as a highly radical interventional paradigm—inevitably confronts formidable, high-order critical challenges and ethical scrutiny.

Foremost among these are the ethical controversies surrounding overtreatment and the risks of cumulative toxicity invariably precipitated by "preemptive interception". The prediction of evolutionary trajectories is fundamentally predicated on probabilistic models. This implies that even if early high-risk clonal drift is captured via circulating tumour DNA (ctDNA) or specific baseline allelic vulnerabilities are identified, not all lesions in the subclinical or minimal residual dis-

ease (MRD) stages will inexorably progress to lethal macroscopic malignancies within a patient's natural lifespan. The widespread, prolonged administration of potent targeted inhibitors or viral vector vaccines to high-risk but asymptomatic individuals will subject a subset of the population—who might not require immediate intervention—to significant long-term physical toxicity and substantial "financial toxicity".^{24,114} When implementing prophylactic evolutionary interception spanning years or even a lifetime, this often-overlooked, low-grade cumulative toxicity could profoundly impact patients' quality of life.

Furthermore, comprehensive interception strategies must confront the exceedingly complex "whack-a-mole" ecological effects inherent in tumour evolution. To completely abrogate acquired resistance, there is a strong clinical propensity to employ multi-target combinatorial strategies aimed at comprehensively blockading major kinase escape networks, such as MAPK and PI3K. However, when all mainstream mutational escape routes are simultaneously subjected to overwhelming evolutionary suppression, this profound existential bottleneck may paradoxically compel tumour cells to undergo extreme regressive evolution. This can drive them into a "rare dedifferentiated phenotype" or a neural crest stem cell-like (NCSC-like) state of deep dormancy that is entirely independent of specific kinases.^{115,116} This broad-spectrum resistance and immune evasion—achieved through profound transcriptional plasticity and lineage reprogramming—not only obliterates the expression of tumour-specific antigens but also deprives any subsequent precision targeted therapies of their physical targets, thereby precipitating a far more lethal systemic therapeutic recalcitrance.¹¹⁷

Looking ahead to the next decade, the breakthrough to conquering the ultimate enigma of cancer lies in the profound integration of the ultimate variant-resolution capabilities of graph genomes—which eliminate allelic bias—with adaptive microenvironmental evolutionary computational models trained by advanced artificial intelligence. Only by establishing dynamic mathematical constraint models that balance exceedingly high predictive confidence with the minimal cost of cumulative interventional toxicity, thereby accurately delineating the unique "evolutionary probability landscape" for tumours of diverse genetic backgrounds, can we truly reverse our passive stance in this life-or-death Darwinian game. Ultimately, this will elevate our approach from the often-futile "palliative prolongation" in late-stage malignancies to a "curative interception" defined by absolute, proactive dominance.

Declarations

Acknowledgement

None.

Funding

This study was supported by grants from the National Natural Science Foundation of China (82473273), the Wu Jieping Medical Foundation (Grant No. 320.6750.2024-21-32) and the Beijing Public Health Foundation (Grant No. QYJJ-QNXZ-20).

Conflict of interest

The authors have no conflicts of interest related to this publication.

cation.

Authors' contributions

ZQW: Study concept, drafting and editing of the manuscript. YYS and LF: Study concept and editing of the manuscript. All authors revised the manuscript critically and approved the version to be published.

Figure and Figure Legends

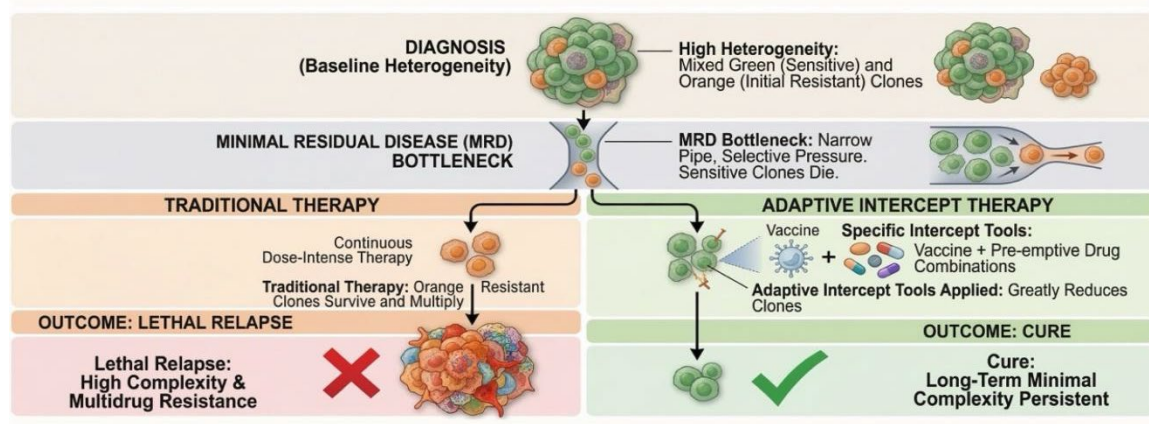


Figure 1. Comparison of tumor evolutionary trajectories under traditional vs. adaptive interception paradigms. Starting from baseline heterogeneity, initial therapy creates an MRD bottleneck that inevitably leads to "competitive release" and lethal relapse in traditional reactive models as resistant clones (orange) multiply. In contrast, Adaptive Intercept Therapy proactively deploys specific tools—such as neoantigen vaccines or preemptive synthetic lethal combinations—during this window of minimal clonal complexity to target predicted resistance mechanisms. By front-loading interventions based on genomic topology and evolutionary probability landscapes, this strategy aims to truncate the "second hit" of resistance, maintaining long-term minimal complexity and shifting the clinical outcome from passive containment toward a definitive cure.

Table 1. Evolutionary Features and Molecular Dimensions of TNBC vs Luminal Breast Cancer

Evolutionary Features and Molecular Dimensions	Triple-Negative Breast Cancer (TNBC) Evolutionary Trajectory	Luminal (HR+/HER2-) Breast Cancer Evolutionary Trajectory
Core germline susceptibility genes	Strongly associated with gBRCA1	Strongly associated with gBRCA2 1
Core somatic co-occurrence events	Exceptionally high TP53 mutation rate (>80%), presenting as foundational co-occurrence	Enrichment of RB1 loss-of-function and MYC/AURKA amplifications 1
Mutational networks and evolutionary strategies	High TMB, widespread co-mutation patterns among driver genes	Relatively low PIK3CA mutation rate, mutations often exhibit mutually exclusive evolutionary features 1
Genomic topological features	Early extensive metastasis to lymph nodes, exhibiting global chromosomal instability	Physical linkage of BRCA2 and RB1 on chromosome 13q leads to baseline Co-LOH 1
Resistance bottlenecks under therapeutic pressure	Lacks a single targetable pathway; relies on complex structural variants and clonal diversity	Highly susceptible to complete RB1 inactivation via a second hit when facing CDK4/6i pressure 1

Reference:

- [1] Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG. Cancer drug resistance: An evolving paradigm. *Nat Rev Cancer*. 2013;13(10):714–26. doi:10.1038/nrc3599
- [2] Vasan N, Baselga J, Hyman DM. A view on drug resistance in cancer. *Nature*. 2019;575(7782):299–309. doi:10.1038/s41586-019-1730-1
- [3] Chen L, Li H, Zhang H, et al. Camrelizumab vs placebo in combination with chemotherapy as neoadjuvant treatment in patients with early or locally advanced triple-negative breast cancer: The camrelief randomized clinical trial. *JAMA*. 2025;333(8):673–681. doi:10.1001/jama.2024.23560
- [4] Vendramin R, Litchfield K, Swanton C. Cancer evolution: Darwin and beyond. *Embo J*. 2021;40(18):e108389. doi:10.15252/embj.2021108389
- [5] Savy T, Flanders L, Karpanasamy T, Sun M, Gerlinger M. Cancer evolution: From darwin to the extended evolutionary synthesis. *Trends Cancer*. 2025;11(3):204–215. doi:10.1016/j.trecan.2025.01.001
- [6] Greaves M, Maley CC. Clonal evolution in cancer. *Nature*. 2012;481(7381):306–13. doi:10.1038/nature10762
- [7] Fennell KA, Vassiliadis D, Lam EYN, et al. Non-genetic determinants of malignant clonal fitness at single-cell resolution. *Nature*. 2022;601(7891):125–131. doi:10.1038/s41586-021-04206-7
- [8] Baumann N, Wagener RJ, Javed A, et al. Regional differences in progenitor metabolism shape brain growth during development. *Cell*. 2025;188(13):3567–3582.e20. doi:10.1016/j.cell.2025.04.003
- [9] Zhao TT, Chiang ZD, Morriss JW, et al. Spatial genomics enables multi-modal study of clonal heterogeneity in tissues. *Nature*. 2022;601(7891):85–91. doi:10.1038/s41586-021-04217-4
- [10] Mathur R, Wang QX, Schupp PG, et al. Glioblastoma evolution and heterogeneity from a 3D whole-tumor perspective. *Cell*. 2024;187(2):446–463.e16. doi:10.1016/j.cell.2023.12.013
- [11] Zhang SS, Xiao XY, Yi YL, et al. Tumor initiation and early tumorigenesis: Molecular mechanisms and interventional targets. *Signal Transduct Target Ther*. 2024;9(1):149. doi:10.1038/s41392-024-01848-7
- [12] Dembo AJ. Spontaneous mutation to chemotherapy resistance: Implications of the Goldie-Coldman model for the management of ovarian cancer. *J Clin Oncol*. 1984;2(12):1311–6. doi:10.1200/jco.1984.2.12.1311
- [13] Wagner A. Evolvability-enhancing mutations in the fitness landscapes of an RNA and a protein. *Nat Commun*. 2023;14(1):3624. doi:10.1038/s41467-023-39321-8
- [14] Vander Velde R, Shaffer S, Marusyk A. Integrating mutational and nonmutational mechanisms of acquired therapy resistance within the Darwinian paradigm. *Trends Cancer*. 2022;8(6):456–466. doi:10.1016/j.trecan.2022.02.004
- [15] Mancini C, Lori G, Pranzini E, Taddei ML. Metabolic challengers selecting tumor-persistent cells. *Trends Endocrinol Metab*. 2024;35(3):263–276. doi:10.1016/j.tem.2023.11.005
- [16] Li JX, Hu JT, Yang YR, et al. Drug resistance in cancer: Molecular mechanisms and emerging treatment strategies. *Mol Bio-med*. 2025;6(1):111. doi:10.1186/s43556-025-00352-w
- [17] Martinez Lopez J, Lopez Muñoz N, Chari A, et al. Measurable residual disease (MRD) dynamics in multiple myeloma and the influence of clonal diversity analyzed by artificial intelligence. *Blood Cancer J*. 2024;14(1):131. doi:10.1038/s41408-024-01102-x
- [18] Parseghian CM, Sun R, Woods M, et al. Resistance mechanisms to anti-epidermal growth factor receptor therapy in RAS/RAF wild-type colorectal cancer vary by regimen and line of therapy. *J Clin Oncol*. 2023;41(3):460–471. doi:10.1200/jco.22.01423
- [19] Zhang JL, Duan YJ, Wu P, et al. Clonal evolution dissection reveals that a high MSI2 level promotes chemoresistance in T-cell acute lymphoblastic leukemia. *Blood*. 2024;143(4):320–335. doi:10.1182/blood.2023020490
- [20] Leighow SM, Reynolds JA, Sokirniy I, et al. Programming tumor evolution with selection gene drives to proactively combat drug resistance. *Nat Biotechnol*. 2025;43(5):737–751. doi:10.1038/s41587-024-02271-7
- [21] Domchek SM, Vonderheide RH. Advancing cancer interception. *Cancer Discov*. 2024;14(4):600–604. doi:10.1158/2159-8290.Cd-24-0015
- [22] Stanton SE, Castle PE, Finn OJ, Sei S, Emens LA. Advances and challenges in cancer immunoprevention and immune interception. *J Immunother Cancer*. 2024;12(3):doi:10.1136/jitc-2023-007815
- [23] Albini A, Cantelmo AR, Mortara L, Noonan DM, Corso G. Cancer prevention and interception with antidiabetic and anti-obesity drugs: Current and future perspectives. *Semin Cancer Biol*. 2025;115:40–52. doi:10.1016/j.semcancer.2025.07.008
- [24] Zhu B, Chen PJ, Aminu M, et al. Spatial and multiomics analysis of human and mouse lung adenocarcinoma precursors reveals TIM-3 as a putative target for precancer interception. *Cancer Cell*. 2025;43(6):1125–1140.e10. doi:10.1016/j.ccell.2025.04.003
- [25] Tonelli C, Deschênes A, Gaeth VA, et al. FGFR2 abrogation intercepts pancreatic ductal adenocarcinoma development. *Cancer Res*. 2025;85(11):1960–1977. doi:10.1158/0008-5472.Can-24-4576
- [26] Janssen EM, Smith IP, Liu XY, et al. Patient preferences for lung cancer interception therapy. *JAMA Netw Open*. 2023;6(11):e2342681. doi:10.1001/jamanetworkopen.2023.42681
- [27] Chen C, Lin CJ, Pei YC, et al. Comprehensive genomic profiling of breast cancers characterizes germline-somatic mutation interactions mediating therapeutic vulnerabilities. *Cell Discov*. 2023;9(1):125. doi:10.1038/s41421-023-00614-3

- [28] Liu YX, Gusev A, Kraft P. Germline cancer gene expression quantitative trait loci are associated with local and global tumor mutations. *Cancer Res.* 2023;83(8):1191–1202. doi:10.1158/0008-5472.Can-22-2624
- [29] Liu J, Tran D, Xue LY, et al. Germline genetic variation impacts clonal hematopoiesis landscape and progression to malignancy. *Nat Genet.* 2025;57(8):1872–1880. doi:10.1038/s41588-025-02250-x
- [30] Kleinerman RA, Tucker MA, Tarone RE, et al. Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: An extended follow-up. *J Clin Oncol.* 2005;23(10):2272–9. doi:10.1200/jco.2005.05.054
- [31] Safonov A, Lee M, Brown DN, et al. Homologous recombination deficiency and hemizyosity drive resistance in breast cancer. *Nature.* Accessed 2026–03–04. <https://pubmed.ncbi.nlm.nih.gov/41781623/>.
- [32] Mandelker D, Zhang LY, Kemel Y, et al. Mutation detection in patients with advanced cancer by universal sequencing of cancer-related genes in tumor and normal DNA vs guideline-based germline testing. *JAMA.* 2017;318(9):825–835. doi:10.1001/jama.2017.11137
- [33] Hua Z, White J, Zhou JJ. Cancer stem cells in TNBC. *Semin Cancer Biol.* 2022;82:26–34. doi:10.1016/j.semcancer.2021.06.015
- [34] Lehmann BD, Colaprico A, Silva TC, et al. Multi-omics analysis identifies therapeutic vulnerabilities in triple-negative breast cancer subtypes. *Nat Commun.* 2021;12(1):6276. doi:10.1038/s41467-021-26502-6
- [35] Liu YQ, He JW, Chen JL, et al. Programmed cell death in triple-negative breast cancer. *Cell Mol Biol Lett.* 2025;30(1):111. doi:10.1186/s11658-025-00789-5
- [36] Verma S, Singh V, Lang JE, Gupta S. Reprogramming the immune microenvironment in triple-negative breast cancer with mRNA therapeutics. *Cancer Lett.* 2026;645:218350. doi:10.1016/j.canlet.2026.218350
- [37] Ma J, Li L, Ma BH, et al. MYC induces CDK4/6 inhibitors resistance by promoting pRB1 degradation. *Nat Commun.* 2024;15(1):1871. doi:10.1038/s41467-024-45796-w
- [38] Palafox M, Monserrat L, Bellet M, et al. High p16 expression and heterozygous RB1 loss are biomarkers for CDK4/6 inhibitor resistance in ER⁺ breast cancer. *Nat Commun.* 2022;13(1):5258. doi:10.1038/s41467-022-32828-6
- [39] Lozano R, Castro E, Lopez Campos F, et al. Impact of concurrent tumour events on the prostate cancer outcomes of germline BRCA2 mutation carriers. *Eur J Cancer.* 2023;185:105–118. doi:10.1016/j.ejca.2023.02.022
- [40] Shih J, Sarmashghi S, Zhakula Kostadinova N, et al. Cancer aneuploidies are shaped primarily by effects on tumour fitness. *Nature.* 2023;619(7971):793–800. doi:10.1038/s41586-023-06266-3
- [41] Brzezinski JJ, Malkin D. Knudson's "Two-Hit" hypothesis and cancer predisposition: A bit more complicated but still going strong. *Cancer Discov.* 2025;15(2):258–260. doi:10.1158/2159-8290.Cd-24-1662
- [42] Pénisson S, Lambert A, Tomasetti C. Evaluating cancer etiology and risk with a mathematical model of tumor evolution. *Nat Commun.* 2022;13(1):7224. doi:10.1038/s41467-022-34760-1
- [43] Butler K, Banday AR. APOBEC3-mediated mutagenesis in cancer: Causes, clinical significance and therapeutic potential. *J Hematol Oncol.* 2023;16(1):31. doi:10.1186/s13045-023-01425-5
- [44] Ottaiano A, Santorsola M, Sabbatino F, et al. Interpreting cancer genetics through a two-step "evolutionary cascade hypothesis": Bridging neutral and selective perspectives. *J Transl Med.* Accessed 2026–02–13. <https://pubmed.ncbi.nlm.nih.gov/41680760/>.
- [45] Li WB, Gao L, Yi X, et al. Patient assessment and therapy planning based on homologous recombination repair deficiency. *Genomics Proteomics Bioinformatics.* 2023;21(5):962–975. doi:10.1016/j.gpb.2023.02.004
- [46] Stewart MD, Merino Vega D, Arend RC, et al. Homologous recombination deficiency: Concepts, definitions, and assays. *Oncologist.* 2022;27(3):167–174. doi:10.1093/oncolo/oyab053
- [47] Pasani J, Lamy C, Lecompte L, et al. Constitutional BRCA1 Methylation is associated with high level of tumoral BRCA1 methylation and homologous recombination deficiency in triple-negative breast cancer. *NPJ Breast Cancer.* Accessed 2026–02–07. <https://pubmed.ncbi.nlm.nih.gov/41654537/>.
- [48] Abbasi A, Steele CD, Bergstrom EN, et al. HRProfiler detects homologous recombination deficiency in breast and ovarian cancers using whole-genome and whole-exome sequencing data. *Cancer Res.* 2025;85(13):2504–2513. doi:10.1158/0008-5472.Can-24-2639
- [49] Kechin A, Koryukov M, Mikheeva R, Filipenko M. Homologous recombination deficiency (HRD) diagnostics: Underlying mechanisms and new perspectives. *Cancer Metastasis Rev.* 2024;44(1):19. doi:10.1007/s10555-024-10238-y
- [50] Ho JJ, Cheng E, Wong CJ, et al. The BLM-TOP3A-RMI1-RMI2 proximity map reveals that RAD54L2 suppresses sister chromatid exchanges. *EMBO Rep.* 2025;26(5):1290–1314. doi:10.1038/s44319-025-00374-z
- [51] Stossel C, Raites Gurevich M, Atias D, et al. Spectrum of response to platinum and PARP inhibitors in germline BRCA-associated pancreatic cancer in the clinical and preclinical setting. *Cancer Discov.* 2023;13(8):1826–1843. doi:10.1158/2159-8290.Cd-22-0412
- [52] Li Y, Yang XH, Cai HY, Wang F. Homologous recombination deficiency among patients with germline or somatic non-BRCA1/2 homologous recombination repair gene variations. *NPJ Precis Oncol.* 2025;9(1):192. doi:10.1038/s41698-025-00999-2
- [53] McGrail DJ, Li Y, Smith RS, et al. Widespread BRCA1/2-independent homologous recombination defects are caused by alterations in RNA-binding proteins. *Cell Rep Med.* 2023;4(11):

101255. doi:10.1016/j.xcrm.2023.101255
- [54] Jang GM, Annan Sudarsan AK, Shayeganmehr A, et al. Protein interaction map of APOBEC3 enzyme family reveals deamination-independent role in cellular function. *Mol Cell Proteomics*. 2024;23(5):100755. doi:10.1016/j.mcpro.2024.100755
- [55] Grillo MJ, Jones KFM, Carpenter MA, Harris RS, Harki DA. The current toolbox for APOBEC drug discovery. *Trends Pharmacol Sci*. 2022;43(5):362–377. doi:10.1016/j.tips.2022.02.007
- [56] Petljak M, Green AM, Maciejowski J, Weitzman MD. Addressing the benefits of inhibiting APOBEC3-dependent mutagenesis in cancer. *Nat Genet*. 2022;54(11):1599–1608. doi:10.1038/s41588-022-01196-8
- [57] Yang YQ, Liu N, Gong LK. An overview of the functions and mechanisms of APOBEC3A in tumorigenesis. *Acta Pharm Sin B*. 2024;14(11):4637–4648. doi:10.1016/j.apsb.2024.08.020
- [58] Roelofs PA, Martens JWM, Harris RS, Span PN. Clinical implications of APOBEC3-mediated mutagenesis in breast cancer. *Clin Cancer Res*. 2023;29(9):1658–1669. doi:10.1158/1078-0432.Ccr-22-2861
- [59] Gupta A, Gazzo A, Selenica P, et al. APOBEC3 mutagenesis drives therapy resistance in breast cancer. *Nat Genet*. 2025;57(6):1452–1462. doi:10.1038/s41588-025-02187-1
- [60] Maiti A, Hedger AK, Myint W, et al. Structure of the catalytically active APOBEC3G bound to a DNA oligonucleotide inhibitor reveals tetrahedral geometry of the transition state. *Nat Commun*. 2022;13(1):7117. doi:10.1038/s41467-022-34752-1
- [61] Harjes S, Kurup HM, Rieffer AE, et al. Structure-guided inhibition of the cancer DNA-mutating enzyme APOBEC3A. *Nat Commun*. 2023;14(1):6382. doi:10.1038/s41467-023-42174-w
- [62] Schwartz I, Budroni V, Meyenberg M, et al. Guardian ubiquitin E3 ligases target cancer-associated APOBEC3 deaminases for degradation to promote human genome integrity. *Nat Commun*. 2026;17(1):1723. doi:10.1038/s41467-026-68420-5
- [63] Marine JC, Dawson SJ, Dawson MA. Non-genetic mechanisms of therapeutic resistance in cancer. *Nat Rev Cancer*. 2020;20(12):743–756. doi:10.1038/s41568-020-00302-4
- [64] McDonald PC, Dedhar S. Persister cell plasticity in tumour drug resistance. *Semin Cell Dev Biol*. 2024;156:1–10. doi:10.1016/j.semcdb.2023.11.003
- [65] Asciolla JJ, Wu XW, Adamopoulos C, Gavathiotis E, Poulikakos PI. Resistance mechanisms and therapeutic strategies of CDK4 and CDK6 kinase targeting in cancer. *Nat Cancer*. 2025;6(1):24–40. doi:10.1038/s43018-024-00893-z
- [66] Huang JY, Zheng L, Sun ZC, Li J. CDK4/6 inhibitor resistance mechanisms and treatment strategies (Review). *Int J Mol Med*. 2022;50(4):doi:10.3892/ijmm.2022.5184
- [67] Shanabag A, Armand J, Son E, Yang HW. Targeting CDK4/6 in breast cancer. *Exp Mol Med*. 2025;57(2):312–322. doi:10.1038/s12276-025-01395-3
- [68] Kim S, Armand J, Safonov A, et al. Sequential activation of E2F via Rb degradation and c-Myc drives resistance to CDK4/6 inhibitors in breast cancer. *Cell Rep*. 2023;42(11):113198. doi:10.1016/j.celrep.2023.113198
- [69] Nakajima N, Hayashi T, Fujiki K, et al. Codependency and mutual exclusivity for gene community detection from sparse single-cell transcriptome data. *Nucleic Acids Res*. 2021;49(18):e104. doi:10.1093/nar/gkab601
- [70] Angelopoulos N, Chatziplis A, Nangalia J, Maura F, Campbell PJ. Bayesian networks elucidate complex genomic landscapes in cancer. *Commun Biol*. 2022;5(1):306. doi:10.1038/s42003-022-03243-w
- [71] Fu BL, Liang JJ, Hu JY, et al. GPCR-MAPK signaling pathways underpin fitness trade-offs in whitefly. *Proc Natl Acad Sci USA*. 2024;121(28):e2402407121. doi:10.1073/pnas.2402407121
- [72] Gatenby RA, Teer JK, Tsai KY, Brown JS. Parallel and convergent dynamics in the evolution of primary breast and lung adenocarcinomas. *Commun Biol*. 2025;8(1):775. doi:10.1038/s42003-025-08123-7
- [73] Meador CB, Lovly CM. A tale of two histologies: Dissecting the biology of lineage transformation in lung cancer. *Cancer Discov*. 2021;11(12):2962–2964. doi:10.1158/2159-8290.Cd-21-1222
- [74] Febres Aldana CA, Chang JC, Ptashkin R, et al. Rb tumor suppressor in small cell lung cancer: Combined genomic and IHC analysis with a description of a distinct RB-proficient subset. *Clin Cancer Res*. 2022;28(21):4702–4713. doi:10.1158/1078-0432.Ccr-22-1115
- [75] Corbett V, Sen T, Chauhan A. Role of CDK4/6 inhibitors in targeting Rb proficient small cell lung cancer. *Transl Lung Cancer Res*. 2024;13(1):190–194. doi:10.21037/tlcr-23-337
- [76] Jain P, Pillai M, Duddu AS, Somarelli JA, Goyal Y, Jolly MK. Dynamical hallmarks of cancer: Phenotypic switching in melanoma and epithelial-mesenchymal plasticity. *Semin Cancer Biol*. 2023;96:48–63. doi:10.1016/j.semcancer.2023.09.007
- [77] Sun SW, Sun YW, Lan L, et al. Tumor cell plasticity in cancer: Signaling pathways and pharmaceutical interventions. *MedComm* (2020). 2025;6(12):e70541. doi:10.1002/mco2.70541
- [78] Li XL, Gardner EE, Molina Pinelo S, Wilhelm C, Mu P, Quintana-Villalonga Á. Lineage plasticity and histological transformation: Tumor histology as a spectrum. *Cell Res*. 2025;35(11):803–823. doi:10.1038/s41422-025-01180-x
- [79] Knisely A, Dai Y, Barlow GL, et al. Surgical and blood-based minimal residual disease in patients with ovarian cancer after first-line therapy: Clinical outcomes and translational opportunities. *Clin Cancer Res*. 2025;31(19):4122–4135. doi:10.1158/1078-0432.Ccr-25-0512
- [80] Ji FS, Xia HM, Xiao Y, et al. Spatial multi-omics mapping of tumor microanatomy dynamics following radiotherapy combined with targeted-immunotherapy in hepatocellular carcinoma. *Biomark Res*. 2026;14(1):7. doi:10.1186/s40364-025-00876-x
- [81] Miao JS, Li JZ, Xin JX, et al. MultiGATE: integrative analysis

- and regulatory inference in spatial multi-omics data via graph representation learning. *Nat Commun.* 2025;16(1):9403. doi:10.1038/s41467-025-63418-x
- [82] Semenkovich NP, Szymanski JJ, Earland N, Chauhan PS, Pellini B, Chaudhuri AA. Genomic approaches to cancer and minimal residual disease detection using circulating tumor DNA. *J Immunother Cancer.* 2023;11(6):e006284. doi:10.1136/jitc-2022-006284
- [83] Wan JCM, Mughal TI, Razavi P, et al. Liquid biopsies for residual disease and recurrence. *Med.* 2021;2(12):1292–1313. doi:10.1016/j.medj.2021.11.001
- [84] Tan HN, Elliott MJ, Silverman IM, Siu LL, Yap TA. Circulating tumor DNA as a biomarker in early phase clinical trials. *Cancer Cell.* 2026;44(2):240–247. doi:10.1016/j.ccell.2025.11.011
- [85] Li LY, Sun YL. Circulating tumor DNA methylation detection as biomarker and its application in tumor liquid biopsy: Advances and challenges. *MedComm.* 2024;5(11):e766. doi:10.1002/mco2.766
- [86] Hitchen N, Shahnam A, Tie J. Circulating tumor DNA: A pan-cancer biomarker in solid tumors with prognostic and predictive value. *Annu Rev Med.* 2025;76(1):207–223. doi:10.1146/annurev-med-100223-090016
- [87] Liu Y, Huang Y, Wang G, Wang Y. A deep learning approach for filtering structural variants in short read sequencing data. *Brief Bioinform.* 2021;22(4):doi:10.1093/bib/bbaa370
- [88] Chandra G, Gibney D, Jain C. Haplotype-aware sequence alignment to pangenome graphs. *Genome Res.* 2024;34(9):1265–1275. doi:10.1101/gr.279143.124
- [89] Geoffroy V, Lamouche JB, Guignard T, et al. The AnnotSV webserver in 2023: Updated visualization and ranking. *Nucleic Acids Res.* 2023;51(W1):W39–W45. doi:10.1093/nar/gkad426
- [90] Tetikol HS, Turgut D, Narci K, et al. Pan-African genome demonstrates how population-specific genome graphs improve high-throughput sequencing data analysis. *Nat Commun.* 2022;13(1):4384. doi:10.1038/s41467-022-31724-3
- [91] Chandra G, Hossen MH, Scholz S, Dilthey AT, Gibney D, Jain C. Pangenome-based genome inference using integer programming. *Genome Res.* 2025;35(12):2661–2670. doi:10.1101/gr.280567.125
- [92] Groza C, Schwendinger-Schreck C, Cheung WA, et al. Pangenome graphs improve the analysis of structural variants in rare genetic diseases. *Nat Commun.* 2024;15(1):657. doi:10.1038/s41467-024-44980-2
- [93] Tennant PWG, Murray EJ, Arnold KF, et al. Use of directed acyclic graphs (DAGs) to identify confounders in applied health research: Review and recommendations. *Int J Epidemiol.* 2021;50(2):620–632. doi:10.1093/ije/dyaa213
- [94] Setton J, Hadi K, Choo ZN, et al. Long-molecule scars of backup DNA repair in BRCA1- and BRCA2-deficient cancers. *Nature.* 2023;621(7977):129–137. doi:10.1038/s41586-023-06461-2
- [95] Chaabane SB, Alenzi FQ, Abedalqader Qannas AM, et al. Deciphering immune evasion mechanisms in precision oncology: Insights from single-cell multiomics approaches. *Int J Surg.* 2026;112(2):4563–4574. doi:10.1097/js9.0000000000003911
- [96] Yang GW, Cheng JT, Xu JY, et al. Metabolic heterogeneity in clear cell renal cell carcinoma revealed by single-cell RNA sequencing and spatial transcriptomics. *J Transl Med.* 2024;22(1):210. doi:10.1186/s12967-024-04848-x
- [97] Cheng JH, Li JY, Jiang XJ, et al. CD74 facilitates immunotherapy response by shaping the tumor microenvironment of hepatocellular carcinoma. *Mol Med.* 2024;30(1):116. doi:10.1186/s10020-024-00884-x
- [98] Nemati M, Hsu CY, Nathiya D, et al. Gemcitabine: Immunomodulatory or immunosuppressive role in the tumor microenvironment. *Front Immunol.* 2025;16:1536428. doi:10.3389/fimmu.2025.1536428
- [99] Kim J, Kim M, Han H, Kim S, Lahiji SF, Kim YH. Dual-delivery of exosome inhibitor and immune-activating gene via lipid nano-assemblies for tumor immune evasion inhibition. *J Control Release.* 2025;381:113569. doi:10.1016/j.jconrel.2025.02.065
- [100] Wang X, Wang P, Liao Y, et al. Expand available targets for CAR-T therapy to overcome tumor drug resistance based on the "Evolutionary Traps". *Pharmacol Res.* 2024;204:107221. doi:10.1016/j.phrs.2024.107221
- [101] Ingesson T, Gisselsson D. Wargaming cancer: A strategy for future precision oncology? *Trends Cancer.* 2023;9(9):697–699. doi:10.1016/j.trecan.2023.06.006
- [102] Ghosh M, Kang MS, Katuwal NB, et al. SOX5 inhibition overcomes PARP inhibitor resistance in BRCA-mutated breast and ovarian cancer. *Cell Death Dis.* 2025;16(1):333. doi:10.1038/s41419-025-07660-7
- [103] Cai SX, Ma N, Wang X, Guo M, Jiang Y, Tian YE. The discovery of a potent PARP1 inhibitor senaparib. *Mol Cancer Ther.* 2025;24(1):47–55. doi:10.1158/1535-7163.Mct-23-0625
- [104] Loap P, Loirat D, Stern MH, et al. Safety and potential radiosensitizing effect of olaparib in combination with breast radiation therapy for patients with triple-negative breast cancer with residual disease: Long-term results from the RADIOPARP phase 1 trial. *Int J Radiat Oncol Biol Phys.* 2025;123(3):726–731. doi:10.1016/j.ijrobp.2025.05.013
- [105] Herencia Ropero A, Llop Guevara A, Staniszevska AD, et al. The PARP1 selective inhibitor saruparib (AZD5305) elicits potent and durable antitumor activity in patient-derived BRCA1/2-associated cancer models. *Genome Med.* 2024;16(1):107. doi:10.1186/s13073-024-01370-z
- [106] Fugger K, Hewitt G, West SC, Boulton SJ. Tackling PARP inhibitor resistance. *Trends Cancer.* 2021;7(12):1102–1118. doi:10.1016/j.trecan.2021.08.007
- [107] Katsikis PD, Ishii KJ, Schliehe C. Challenges in developing personalized neoantigen cancer vaccines. *Nat Rev Immunol.* 2024;24(3):213–227. doi:10.1038/s41577-023-00937-y
- [108] Sultan H, Schreiber RD. Cancer neoantigen vaccines emerge

- efficacious. *Annu Rev Med*. 2026;77(1):297–314. doi:10.1146/annurev-med-071723-045853
- [109] Peltomäki P, Nyström M, Mecklin JP, Seppälä TT. Lynch syndrome genetics and clinical implications. *Gastroenterology*. 2023;164(5):783–799. doi:10.1053/j.gastro.2022.08.058
- [110] Gebert J, Gelincik O, Oezcan Wahlbrink M, et al. Recurrent frameshift neoantigen vaccine elicits protective immunity with reduced tumor burden and improved overall survival in a lynch syndrome mouse model. *Gastroenterology*. 2021;161(4):1288–1302.e13. doi:10.1053/j.gastro.2021.06.073
- [111] D'Alise AM, Willis J, Duzagac F, et al. Nous-209 neoantigen vaccine for cancer prevention in Lynch syndrome carriers: A phase 1b/2 trial. *Nat Med*. 2026;doi:10.1038/s41591-025-04182-9
- [112] Perrinjaquet M, Richard Schlegel C. Personalized neoantigen cancer vaccines: An analysis of the clinical and commercial potential of ongoing development programs. *Drug Discov Today*. 2023;28(11):103773. doi:10.1016/j.drudis.2023.103773
- [113] Thol K, Pawlik P, McGranahan N. Therapy sculpts the complex interplay between cancer and the immune system during tumour evolution. *Genome Med*. 2022;14(1):137. doi:10.1186/s13073-022-01138-3
- [114] Lustberg MB, Kuderer NM, Desai A, Bergerot C, Lyman GH. Mitigating long-term and delayed adverse events associated with cancer treatment: Implications for survivorship. *Nat Rev Clin Oncol*. 2023;20(8):527–542. doi:10.1038/s41571-023-00776-9
- [115] Liu I, Hack OA, Filbin MG. The imitation game: How glioblastoma outmaneuvers immune attack. *Cell*. 2021;184(9):2278–2281. doi:10.1016/j.cell.2021.04.008
- [116] Benboubker V, Boivin F, Dalle S, Caramel J. Cancer cell phenotype plasticity as a driver of immune escape in melanoma. *Front Immunol*. 2022;13:873116. doi:10.3389/fimmu.2022.873116
- [117] Sævarsson T, de Lomana ALG, Sánchez Ó, et al. Differentiation status determines the effects of IFN γ on the expression of PD-L1 and immunomodulatory genes in melanoma. *Cell Commun Signal*. 2024;22(1):618. doi:10.1186/s12964-024-01963-6