Genomic instability, postoperative recurrence and therapeutic vulnerabilities in resectable non-small cell lung cancer (Review)

LINLIN WANG[1*], YONG FENG[1*] and QIANG LIU[2]

[1]Department of Thoracic Surgery, Shenyang Tenth People's Hospital, Shenyang, Liaoning 110044, P.R. China; [2]Oncology Department of Integrated Traditional Chinese and Western Medicine, Shenyang Tenth People's Hospital, Shenyang, Liaoning 110044, P.R. China

Received June 26, 2026; Accepted August 19, 2026

DOI: 10.3892/or.2026.9188

Abstract. Resectable non-small cell lung cancer (NSCLC) is managed largely according to anatomical stage, pathological risk and actionable driver alterations, yet these factors do not fully explain postoperative recurrence. Genomic instability may contribute to recurrence by promoting clonal diversification, intratumoral heterogeneity, occult dissemination, persistence of residual tumor cells, and immune escape. In the present review, chromosomal instability (CIN), copy-number complexity, whole-genome doubling, DNA repair defects, replication stress, and extrachromosomal DNA (ecDNA) were critically evaluated using a three-axis translational framework encompassing biological consequences, potential clinical roles, and strength of evidence. Current evidence suggests that clonal diversity and copy-number complexity have the clearest near-term prognostic rationale. By contrast, CIN and whole-genome doubling are supported more strongly by evolutionary and mechanistic rather than prospective clinical evidence. Defects in DNA repair, replication stress, and ecDNA represent potential therapeutic vulnerabilities, but their clinical relevance remains to be established. To date, no treatment-predictive biomarkers based on genomic instability have been identified for resectable NSCLC. Direct clinical evidence linking any specific genomic instability feature to the presence or longitudinal dynamics of postoperative molecular residual disease (MRD) remains limited. Postoperative circulating tumor DNA-defined MRD provides prognostic information more directly related to residual disease but remains assay-dependent and should not be considered a genomic-instability phenotype. Therefore, features of genomic instability should remain investigational and should not replace established clinical, pathological, or molecular decision-making. Their near-term value lies in refining biological risk models and generating testable hypotheses for biomarker-defined perioperative trials.

Correspondence to: Dr Linlin Wang, Department of Thoracic Surgery, Shenyang Tenth People's Hospital, 11 Beihai Street, Dadong, Shenyang, Liaoning 110044, P.R. China
E-mail: wll514usd@gmail.com

*Contributed equally

Key words: genomic instability, non-small cell lung cancer, postoperative recurrence, molecular residual disease, clonal evolution, chromosomal instability, DNA damage response, perioperative precision oncology

Contents

1. Introduction

The anatomical extent of disease and surgical feasibility usually define the management of resectable non-small cell lung cancer (NSCLC), yet postoperative recurrence is often driven by biological events that precede surgery. Despite advances in neoadjuvant, adjuvant, and perioperative systemic therapies, postoperative relapse remains a major cause of treatment failure following curative-intent therapy (1-5). A tumor that has been completely resected macroscopically may harbour genetically diverse subclones with the capacity for invasion, dissemination, immune escape, and survival under therapeutic pressure. This distinction is important because postoperative recurrence is not simply a failure of local control. In many patients, it may represent the delayed clinical manifestation of tumor populations that have disseminated and evolved before resection.

Evolutionary studies have provided a biological explanation for the disconnect between anatomical resectability and postoperative risk of recurrence. The TRACERx program has shown that intratumoral heterogeneity, subclonal architecture,

copy number instability, and whole-genome doubling are associated with patterns of tumor evolution, progression, and clinical outcomes in lung cancer (6,7). Further analyses of metastatic progression have suggested that metastases may arise from pre-existing or evolving tumor clones subjected to selective pressures, rather than through a simple linear process (8). In parallel, ultrasensitive preoperative circulating tumor DNA (ctDNA) analysis of early-stage lung adenocarcinoma has shown that molecularly detectable disease before surgery can identify patients at increased risk of adverse outcomes, providing evidence that clinically occult tumor burden may persist despite apparently localized disease (9).

Genomic instability provides a conceptual framework that links these observations. Rather than representing a single molecular abnormality, genomic instability encompasses diverse processes and genomic features, including chromosomal instability (CIN), copy number alterations (CNAs), structural variants, aneuploidy, DNA repair defects, replication stress, and genome-wide mutational patterns (10). These processes can increase the genetic diversity available for selection, promote the survival of clinically important subclones, and in some contexts, create candidate therapeutic vulnerabilities. Therefore, genomic instability may contribute to tumor initiation and progression, metastatic dissemination, and persistence of residual disease.

The present review evaluated the genomic instability as a biological framework for interpreting recurrence after NSCLC resection. Rather than treating it as a single, interchangeable construct, each instability process was assessed across three translational dimensions: i) Its principal biological consequence; ii) its potential clinical role as a prognostic marker, treatment-predictive biomarker, or therapeutic vulnerability; and iii) the maturity, directness, and clinical relevance of the supporting evidence in resectable NSCLC. This approach distinguished features with relatively direct evolutionary or prognostic relevance from those supported mainly by mechanistic studies or evidence derived from advanced disease. Notably, the relationship between genomic instability and molecular residual disease (MRD) was treated as a testable evolutionary hypothesis rather than an established biological or causal relationship. Key unresolved controversies were also highlighted and strategies for integrating tumor profiling with longitudinal MRD assessment were outlined. The aim was to define the boundaries of current evidence, identify research priorities, and clarify where genomic instability may complement, but should not replace, established clinical, pathological, or molecular decision-making. The conceptual relationships between genomic instability, clonal evolution, occult residual disease, and postoperative recurrence are summarized in Fig. 1.

2. Forms and sources of genomic instability in NSCLC

Genomic instability in NSCLC is not a single-molecule phenomenon. It arises from several related but biologically distinct processes and genomic alterations. For example, CIN results from ongoing errors in chromosome segregation and maintenance, leading to aneuploidy, chromosome-arm gains or losses, and highly complex karyotypes in some tumors (11). CNAs represent another important component of genomic complexity. These changes may affect oncogenes, tumor suppressor genes, or immune-related loci, and their distribution may vary substantially across different regions of the same tumor. Notably, a recent lung cancer study linked clone-level copy-number diversity to survival, suggesting that copy-number complexity is not simply a descriptive feature but may reflect clinically relevant evolutionary behavior (12).

Whole-genome doubling increases the complexity. Once a tumor cell duplicates its entire chromosomal complement, it may tolerate and accumulate additional chromosomal alterations. TRACERx-based analyses have shown that FAT atypical cadherin 1 (FAT1) loss, Hippo pathway dysregulation, CIN, and whole-genome doubling are associated with NSCLC. Similarly, studies across cancer types have shown that genome-doubled tumors can develop complicated chromosomal histories that may be difficult to reconstruct from a single sampled region (13,14). Structural variants contribute in different ways; they can generate actionable fusions, disrupt tumor suppressor loci, or alter regulatory elements. Genomic changes do not occur in isolation either; during NSCLC evolution, they may interact with epigenetic remodeling, underscoring the close relationship between genome structure and transcriptional state (15). Extrachromosomal DNA (ecDNA) represents a dynamic, non-chromosomal form of amplified DNA that can undergo rapid structural and copy-number evolution. Experimental research suggests that ecDNA-positive cancers may develop dependencies related to transcription-replication conflicts and could be vulnerable to checkpoint kinase 1 (CHK1) inhibition (16).

Instability can also arise from defective DNA repair pathways and persistent replication stress. Deficiencies in homologous recombination, mismatch repair, nucleotide excision repair, base excision repair, or non-homologous end joining can increase the accumulation of mutations, replication-associated lesions, and structural genomic abnormalities (17). When one repair pathway is impaired, tumor cells may become more dependent on alternative repair pathways or cell-cycle checkpoints for survival. This provides a biological rationale for DNA-damaging therapies and DNA damage response (DDR)-targeted strategies in selected settings, although the clinical relevance is likely to vary according to specific molecular defect and cellular context (18). Mutational signatures provide a complementary view of genomic instability and tumor evolution. Rather than identifying a single alteration, they capture patterns of mutations that reflect the processes shaping the tumor genome over time, including carcinogen exposure, enzymatic editing, and repair deficiency. In lung cancer, apolipoprotein B mRNA editing enzyme catalytic polypeptide-like activity has been linked to tumor evolution and treatment resistance, and whole-genome studies have identified distinct mutagenic processes in smoking-associated and never-smoker lung cancers (19-21).

These differences may have distinct clinical implications. Tumors with extensive CIN may have marked clonal diversity and greater capacity for ongoing genomic evolution; however, CIN itself does not currently define a clinically actionable repair defect. Conversely, a tumor with a specific homologous recombination defect may provide a rationale for a therapeutic

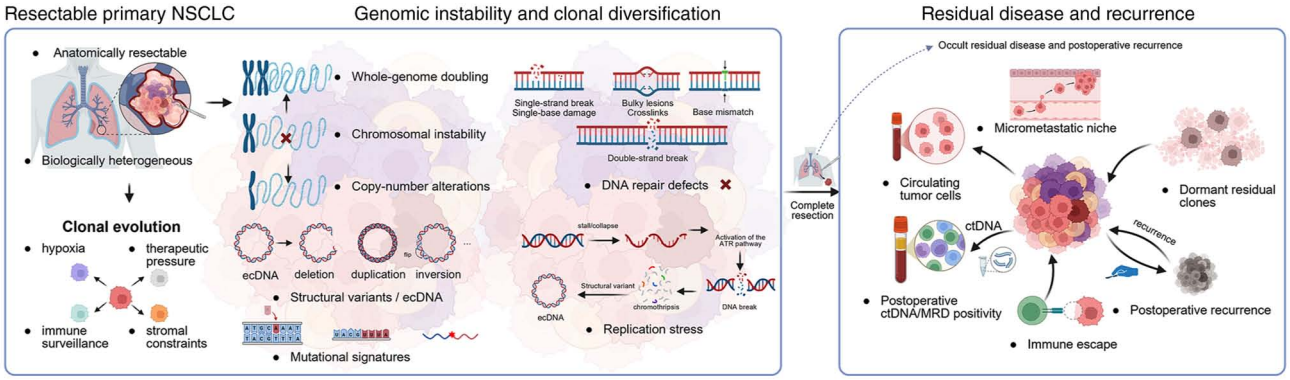

Figure 1. Proposed relationships among genomic instability, clonal evolution, occult residual disease and postoperative recurrence in resectable NSCLC. Genomic instability may generate intratumoral diversity, from which microenvironmental and therapeutic pressures may select subclones with survival or dissemination advantages. These subclones may persist as dormant or micrometastatic residual disease after complete resection and contribute to recurrence. Postoperative ctDNA-defined MRD is an assay-dependent signal rather than a direct measure of viable residual tumor cells or their genomic instability. Direct evidence linking specific instability features to postoperative MRD dynamics remains limited. NSCLC, non-small cell lung cancer; ctDNA, circulating tumor DNA; MRD, molecular residual disease; ATR, ataxia telangiectasia and Rad3-related; DNA, deoxyribonucleic acid; ecDNA, extrachromosomal DNA.

hypothesis, even when broad aneuploidy is not prominent. Collapsing these different processes into a single label such as 'high genomic instability' would therefore risk obscuring the biological and therapeutic differences that may eventually make them useful.

Measurement is equally important. Targeted DNA or RNA sequencing can identify established driver alterations and selected copy-number events but is less suited to comprehensively characterizing global chromosomal complexity, whole-genome doubling, complex structural variation, or mutational signatures (22). Broader genomic profiling is often required to assess these features, while characterization of clonal diversity may additionally require multi-region sampling or phylogeny-informed analysis (23). Repair deficiency presents a particular challenge because alterations in homologous recombination repair genes and genomic-scarring or mutational-signature measures show incomplete concordance in NSCLC and should not be treated as interchangeable readouts (24). This situation is even less mature for ecDNA, which remains a research-stage structural feature for which standardized perioperative assays are not yet available (25). Surgical specimens obtained from patients with resectable NSCLC offer important opportunities for exploratory profiling. However, clinical application requires pre-specified analytical methods, reproducible thresholds, and prospective evidence that these measurements add useful information beyond standard pathology, driver status, and longitudinal MRD assessment. The potential measurement strategies and their current translational relevance for major genomic instability processes in resectable NSCLC are summarized in Table I.

3. Clonal evolution and tumor heterogeneity

Genomic instability can lead to carcinogenesis and tumor progression by continuously generating genetic diversity within the primary tumor. Resectable NSCLC should therefore not be viewed as a single uniform lesion, but as a spatially structured population of genetically related subclones. Single-cell and spatial transcriptomic studies have shown that malignant cells, immune populations, and stromal components in NSCLC form organized spatial communities rather than random cellular mixtures (26,27). This complexity is clinically important because the subclone that ultimately drives recurrence may not be the dominant clone represented in a single resected specimen.

However, sampling limitations further complicate this interpretation. A focal biopsy or a single tissue block may capture only a fraction of the genomic diversity within a lung tumor (28). Longitudinal evolutionary analyses have shown that multiple subclones from a primary tumor may disseminate and contribute to subsequent metastatic disease (29). Therefore, a minor subclone may become clinically important if it acquires or possesses selective advantages in invasion, survival, immune escape, or adaptation to distant microenvironments.

The tumor microenvironment helps determine which subclones persist and expand. Hypoxia, inflammation, stromal pressure, nutrient limitation, vascular invasion, and immune surveillance can act as selective forces during tumor evolution before surgery. Spatial Tumor Atlas studies have shown that malignant cell evolution is closely linked to the surrounding microenvironment, and the spatial organization of immune cells in lung cancer is associated with immune evasion and clinical outcomes (30,31). In this setting, genomic instability should not be viewed as a direct or sufficient cause of recurrence. Rather, it expands the pool of variants, from which microenvironment and environmental and therapeutic selection may favor subclones with greater metastatic potential, immune-evasive capacity, and treatment resistance. This provides a biological link between genomic instability and metastatic progression. Tumor cells capable of leaving the primary lesion before surgery must survive in circulation, adapt to distant tissue environments, and either establish immediate growth or enter a state of disseminated tumor cell dormancy. Dormant disseminated tumor cells may remain clinically invisible for prolonged periods while evading immune surveillance, and their later outgrowth can be supported by stromal, immune, and tissue-niche interactions (32-34). A recent functional study on NSCLC showed that immune-evasive and non-immune-evasive subclones

Table I. Genomic-instability processes, potential measurement approaches and current translational relevance in resectable NSCLC.

Process or consequence	Biological meaning	Potential measurement approach	Implications for resectable NSCLC and recurrence	Evidence status and current interpretation	Representative references
Chromosomal instability	Ongoing chromosome mis-segregation causing aneuploidy and large-scale genomic imbalance	Copy-number burden, aneuploidy metrics or multiregion assessment; no standardized routine clinical assay	May promote subclonal diversification, adaptation and metastatic progression	Emerging evidence; investigational evolutionary and risk marker with context-dependent immune implications	(11,13,14,71)
Copy-number alterations	Gains or losses affecting oncogenes, tumor-suppressor genes or immune-related loci	DNA-based copy-number profiling; clone-level diversity generally requires multiregion or phylogeny-informed analysis	Subclonal copy-number diversity may contribute to heterogeneity and adverse outcome	Investigational for risk modeling and trial stratification; no established perioperative role	(12)
Whole-genome doubling	Duplication of the chromosomal complement, permitting further genomic complexity	Allele-specific copy-number and ploidy inference from whole-exome or whole-genome sequencing	May increase evolutionary capacity and tolerance of subsequent chromosomal alterations	Investigational marker of evolutionary potential; no validated treatment-selection role	(13,14)
Structural variants	Rearrangements that alter genomic architecture	Targeted DNA/RNA sequencing for actionable rearrangements; broader complexity requires comprehensive profiling	Actionable fusions may guide established therapies, whereas global complexity may reflect tumor evolution	Clinically established for selected actionable rearrangements; broader structural-variant complexity remains investigational	(22,92,93)
Extrachromosomal DNA	Circular DNA elements associated with increased gene dosage and rapid adaptation	Research-level genomic or cytogenetic assessment; no routine perioperative assay	May support rapid evolutionary adaptation	Mechanistic evidence; candidate CHK1-related or transcription-replication-conflict vulnerability	(16,25)
DNA repair defects	Impaired repair of DNA lesions or double-strand breaks	Repair-gene profiling and genomic scar/signature assessment; these readouts are non-equivalent	May increase mutation accumulation and create DDR-related vulnerabilities	Candidate biomarker for PARP- or DDR-directed trials; not validated for perioperative selection	(17,18,24, 78,79)
Replication stress	Stalled or collapsed replication forks under oncogenic or cellular stress	No validated routine clinical assay; candidate surrogate markers require prospective evaluation	May support stress-tolerant clones and checkpoint dependence	Investigational ATR/CHK1/WEE1-directed trial concept	(18,78, 80-82,84)
Mutational signatures	Genomic footprints of carcinogen exposure, APOBEC activity or repair deficiency	Whole-exome or whole-genome sequencing, depending on mutation burden and assay resolution	May reconstruct evolutionary history and identify processes associated with adaptation or resistance	Potentially useful for trial stratification, but not validated for routine perioperative selection	(19-22)

Table I. Continued.

Process or consequence	Biological meaning	Potential measurement approach	Implications for resectable NSCLC and recurrence	Evidence status and current interpretation	Representative references
Evolutionary consequence: Intratumoral heterogeneity	Coexisting subclones with distinct genomic or biological features	Multiregion sequencing, spatial profiling or single-cell approaches	Minor subclones may be missed yet later contribute to dissemination, immune escape or recurrence	May inform sampling and risk assessment, but is not a stand-alone treatment marker	(26-30,35)

The listed approaches are intended for translational investigation and have not been validated for routine clinical use. Perioperative treatment decisions for resectable NSCLC are based on anatomical stage, pathological features, actionable driver alterations, and established immunotherapy indications. Genomic instability processes are biologically distinct, and repair gene alterations, genomic scars, replication stress phenotypes, and global chromosomal complexity should not be used interchangeably. Their clinical value requires prospective validation using prespecified assays, sampling strategies, and clinically relevant endpoints. APOBEC, apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like; ATR, ataxia telangiectasia and Rad3-related; CHK1, checkpoint kinase 1; DDR, DNA damage response; NSCLC, non-small cell lung cancer; PARP, poly(ADP-ribose) polymerase; WEE1, WEE1 G2 checkpoint kinase.

can coexist within the same tumor, suggesting that immune escape may emerge during subclonal evolution (35). The clinical relevance of genomic instability therefore lies not in a direct deterministic effect on recurrence, but in its potential to generate diversity that enables adaptation, dissemination, immune evasion, and persistence.

4. Postoperative recurrence biology

Postoperative recurrence is the clinical endpoint of a biological process that may begin well before recurrence becomes clinically detectable. Although recurrence is typically recognized by imaging, pathology, or clinical symptoms, the underlying events may include preoperative clonal diversification, occult dissemination, persistence of residual tumor cells, and subsequent metastatic outgrowth. Multiomics profiling of recurrent stage I NSCLC has shown that tumors that subsequently relapse may differ in their genomic, epigenomic, transcriptomic, and microenvironmental features (36). This biological heterogeneity may help explain why patients with similar anatomical stages and apparently complete resection can experience markedly different postoperative outcomes.

Genomic instability may contribute to this process on several levels. First, it increases the diversity from which invasive or stress-tolerant subclones emerge within the primary tumor. Second, it may support metastatic competence by generating alterations that favor cellular motility, vascular invasion, immune escape, or adaptation to distant microenvironments. Third, it may facilitate the persistence of residual tumor cells under postoperative and therapeutic stress. Pulmonary venous circulating tumor cell research has shown that tumor cells may enter the circulation before resection, and that such early dissemination is associated with subsequent relapse and metastatic disease (37). Tumor dormancy research further suggests that disseminated residual tumor cells can persist for prolonged periods before undergoing clinical outgrowth (38).

This provides an important context for understanding the role of MRD. Presurgical ctDNA detection and postoperative ctDNA-defined MRD both have demonstrated prognostic value in early-stage NSCLC (39,40). Imaging-based features, including radiological tumor volume and positron emission tomography/computed tomography-derived parameters, may add another layer of relapse risk assessment when interpreted in conjunction with ctDNA (41,42). In resected epidermal growth factor receptor-mutated NSCLC, exploratory analyses from the ADAURA trial further suggested that MRD signals can remain informative, even in patients receiving effective adjuvant epidermal growth factor receptor (EGFR)-targeted therapy (43).

However, MRD should not be interpreted as a complete or infallible measure of residual disease. The recurrence risk remains heterogeneous, and MRD assays require further analytical and clinical standardization before they can routinely guide treatment decisions (44,45). A positive postoperative ctDNA result may indicate that one or more tumor populations have survived resection and remain detectable in the circulation. Conversely, a negative result is reassuring but does not exclude residual disease, particularly in tumors with low shedding, limited representation of the primary tumor in the sampled tissue, or marked spatial heterogeneity.

Complete resection remains essential, but it cannot reverse evolutionary events that have already occurred. Resected tumors with extensive clonal diversity may harbor subclones that have disseminated, entered dormancy, or acquired immune-evasive properties before surgery. Another tumor at the same stage may not have undergone the same extent of evolutionary diversification. What later appears as postoperative recurrence may, therefore, be the delayed manifestation of carcinogenic and metastatic processes that were established before surgery in some patients.

5. Genomic instability and MRD

Following surgery, ctDNA-defined MRD may provide one of the earliest indications that tumor-derived molecular material remains detectable after resection of the primary lesion. A positive result is consistent with the presence of residual tumor-derived DNA and may reflect clones that disseminated before surgery and persist during the early postoperative period. However, ctDNA-defined MRD is an assay-dependent molecular signal and is not a direct measure of viable residual tumor cells, residual tumor burden, or genomic instability. Therefore, it is best understood as an imperfect but potentially informative biomarker of molecular residual disease and early recurrence risk, rather than a direct measure of residual clonal burden or evolution (46,47).

The relationship between genomic instability and MRD should be regarded as a biologically plausible, testable hypothesis rather than an established causal pathway. Experimental and evolutionary studies have suggested that genomic instability expands clonal diversity and increases the probability that invasive, stress-tolerant, or immune-evasive populations emerge and persist (48-50). However, direct clinical evidence linking specific instability features, such as CIN, copy number complexity, whole-genome doubling, or repair deficiency, to the presence or longitudinal dynamics of postoperative MRD in resectable NSCLC remains limited. Studies characterizing genomic instability patterns and their clinical associations (51) and those linking postoperative MRD with subsequent relapse in resectable NSCLC (52) currently represent related but largely distinct evidence streams.

An MRD result reflects both the biological presence of residual disease and its detectability in the sampled blood compartment. Detectability is influenced by the residual tumor burden, biological shedding, access to the circulation, blood collection timing, and assay sensitivity (53,54). Spatial and temporal intratumoral heterogeneity introduce additional uncertainty, particularly in tissue-informed assays. A tissue block selected for sequencing may represent the dominant primary tumor clone while failing to capture a minor clone that subsequently persists or disseminates. Tumor-derived sequence variants can be used as tracking markers in tumor-informed or targeted sequencing assays (55-58), whereas fragmentomic (59-61) and methylation-based approaches (62) may capture broader signals; however, none eliminate the effects of low shedding, limited vascular access, or very small residual burden. Consequently, a negative result does not establish the biological absence of residual disease (63). Conversely, an association between a genomic instability feature and MRD positivity could partly reflect differences in tumor burden, proliferation, necrosis, or ctDNA shedding rather than a direct effect of genomic instability on the persistence of residual tumor cells.

Therefore, three levels of evidence should be distinguished. First, mechanistic evidence may explain how an unstable process facilitates genomic diversification, dissemination, and survival under therapeutic pressure. Second, prognostic evidence may indicate that a genomic instability feature or postoperative MRD status is associated with recurrence or survival. Third, predictive evidence must demonstrate that a biomarker identifies differential treatment benefit, ideally through a biomarker-by-treatment interaction. Mechanistic plausibility and prognostic associations do not establish predictive utility. At present, no genomic instability feature has demonstrated treatment-predictive value in resectable NSCLC, and no validated perioperative model has established that genomic instability profiling provides prognostic or predictive information beyond standard clinicopathological assessment and longitudinal MRD.

Tissue profiling and serial blood monitoring can provide complementary but distinct information. Analysis of resected tumors can characterize their evolutionary architecture, including chromosomal complexity, repair defects, and other instability-related features. Serial ctDNA testing can determine whether tumor-derived molecular signals persist, clear, or re-emerge after surgery or perioperative treatment (64). Persistent MRD after the resection of a genomically complex tumor may represent a different biological context from a transient low-level signal arising from a tumor with limited pathological risk; however, whether such combined profiling provides clinically actionable information remains unproven and should not yet be considered a validated basis for treatment intensification or surveillance planning.

Prospective studies should pair prespecified, analytically validated tissue-based measures of genomic instability with standardized postoperative and longitudinal blood sampling. Such studies should account for residual tumor burden, DNA shedding, vascular accessibility, spatial and temporal heterogeneity, sampling time, and assay sensitivity while using clinically relevant endpoints such as recurrence-free survival and MRD clearance or conversion. They should also assess whether integrating instability profiling with MRD improves risk stratification beyond established clinicopathological factors and driver status, and whether any instability phenotype identifies differential benefit from a matched intervention through a biomarker-by-treatment interaction. Until these questions are resolved, the genomic instability-MRD relationship should remain a research framework rather than a basis for routine perioperative treatment decisions.

6. Immune microenvironment and perioperative immunotherapy

The immune consequences of genomic instability cannot easily be reduced to simple rules. An unstable genome may generate mutations, structural changes, and novel peptides that can serve as potential tumor antigens. However, a greater number of mutations does not automatically make a tumor more susceptible to immune recognition or control. What matters is whether the relevant neoantigens are expressed

and clonally represented, whether T cells can recognize and reach the tumor, and whether the surrounding microenvironment permits an immune response (65,66). This explains why tumors with a high mutational burden may still evade immunity when antigen presentation is impaired, effector T cells are excluded, or immunosuppressive programs predominate. In NSCLC, acquired resistance to immunotherapy has been linked to defects in antigen processing, interferon signaling, and immune cell function (67). The genomic background also matters: Alterations in serine/threonine kinase 11 and Kelch-like ECH-associated protein 1 have been associated with distinct immune profiles and poorer outcomes after programmed cell death protein 1/programmed death-ligand 1 (PD-L1) blockade, particularly in KRAS-mutated lung adenocarcinoma (68,69).

CIN introduces an additional layer of complexity. Chromosome missegregation can generate micronuclei and activate the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway. In experimental settings, this response may induce type I interferon signaling and enhance antitumor immune responses (70). In other contexts, particularly when signaling becomes chronic or dysregulated, it may promote a pro-metastatic and immunosuppressive environment (71). CIN is therefore not simply 'beneficial' or 'detrimental' for antitumor immunity. Its effects are likely to depend on the magnitude and duration of cGAS-STING signaling, as well as on the local cellular and molecular context of the tumor.

This uncertainty is clinically relevant now that perioperative immunotherapy has become an established component of treatment for selected patients with resectable NSCLC. Phase III studies evaluating perioperative durvalumab and nivolumab-based strategies have demonstrated improvements in event-free survival, supporting the efficacy of perioperative chemoimmunotherapy in appropriately selected patients (72,73). Meta-analytic evidence similarly supports neoadjuvant chemoimmunotherapy across pathological response, surgical, and efficacy outcomes, although the magnitude and interpretation vary according to disease stage, PD-L1 expression, treatment regimen, and clinical setting (74). Genomic instability features may help explain some of this heterogeneity; however, they are not yet sufficiently validated to serve as independent biomarkers for perioperative immunotherapy selection. Their potential relevance should instead be interpreted alongside established clinical, molecular, and immune biomarkers (75). Postoperative ctDNA-defined MRD may provide a complementary, dynamic measure of residual disease risk within this broader assessment (76).

7. Candidate therapeutic vulnerabilities of unstable genomes

Genomic instability can accelerate tumor evolution. In some biological settings, it also creates dependencies on pathways that enable tumor cells to tolerate ongoing DNA damage, including residual repair capacity, cell-cycle checkpoints, and stress-response mechanisms. These dependencies provide a rationale for investigating DDR-directed strategies and agents targeting replication stress or checkpoint pathways. However, in resectable NSCLC, this remains a research hypothesis rather than an established treatment-selection strategy. Platinum-based chemotherapy is an established perioperative systemic treatment, and radiotherapy is used in selected locoregional settings. Neither approach is currently routinely selected on the basis of CIN, whole-genome doubling, homologous recombination deficiency, replication stress, or other genomic instability biomarkers (77,78).

Homologous recombination deficiency provides one potential example. In early-stage resectable NSCLC, a genomic scarring score has been explored as a candidate marker of poly(ADP-ribose) polymerase (PARP) inhibitor sensitivity, although the supporting therapeutic evidence remains largely preclinical, and PARP inhibitors are not part of standard perioperative treatment (79). Replication stress raises additional therapeutic possibilities. Tumors with oncogenic activation, tumor protein p53 dysfunction, or impaired checkpoint control may become increasingly reliant on ataxia telangiectasia and Rad3-related (ATR), CHK1, or WEE1 G2 checkpoint kinase (WEE1) to tolerate persistent DNA damage. ATR inhibitors have shown early clinical activity in biomarker-selected advanced solid tumors (80,81). WEE1 inhibition has preclinical support for KRAS/tumor protein p53-mutant NSCLC (82), whereas DNA-dependent protein kinase (DNA-PK) inhibition has entered early-phase clinical evaluation in advanced cancers (83). These findings provide a rationale for developing and prospectively validating predictive biomarkers, but they do not support treatment selection for resectable NSCLC.

The broader experience with targeting genomic instability-related dependencies also underscores the need for caution. Therapeutic strategies directed at replication stress and DDR dependencies are biologically plausible (84), but most clinical evidence comes from advanced solid tumors or metastatic NSCLC rather than from patients treated with curative intent. In the HUDSON study, biomarker-directed treatment incorporating ATR inhibition and PD-L1 blockade showed clinical activity in advanced NSCLC. By contrast, phase III trials evaluating PARP inhibitor-immunotherapy maintenance approaches have not established a broadly applicable treatment strategy for metastatic disease (85-87). Therefore, it is premature to extend these approaches to routine perioperative care. Homologous recombination deficiency, replication stress phenotypes, and checkpoint dependence are better viewed as candidate biomarkers for prospective, biomarker-defined clinical trials (88). ecDNA represents a distinct candidate biomarker, and the bromodomain and extraterminal domain-containing protein 4-dependent organization of ecDNA hubs may represent a therapeutic vulnerability that requires prospective validation (89,90).

Notably, these candidate vulnerabilities are unlikely to be interchangeable. Repair-deficient tumors may be suitable for prospective evaluation of DDR-directed therapies, whereas tumors with prominent replication stress may be more relevant for studies on ATR, CHK1, or WEE1 dependence. ecDNA-positive cancers may represent another biological setting in which transcription-replication conflicts or CHK1-related dependencies warrant investigation. CIN is less directly actionable, but it may influence the tumor immune microenvironment through context-dependent

inflammatory signaling. Its therapeutic implications remain uncertain and should not be used to guide treatment selection without prospective validation. The practical aim, then, is not to assign existing perioperative therapies based on genomic instability, but to identify well-defined instability phenotypes that can be prospectively and rigorously evaluated in future clinical trials.

8. Translational prioritization and perioperative interpretation

The perioperative management of resectable NSCLC remains grounded in anatomical stage, pathological risk features, actionable driver alterations, and treatment strategies supported by prospective clinical trials. The ninth edition of the tumor-node-metastasis classification provides the current anatomical framework (91), whereas established molecular alterations identify patients eligible for specific targeted therapies (92-94). Postoperative ctDNA-defined MRD is emerging as a longitudinal indicator of residual disease risk, although its utility for treatment selection remains under investigation. Genomic instability features are less clinically mature and should be evaluated on a case-by-case basis, according to the specific clinical claim under consideration, rather than treated as a single, interchangeable biomarker category.

Therefore, a three-axis translational framework is proposed. The first axis defines the principal biological consequence of each feature: The generation of clonal diversity, tolerance to genomic disruption, defective DNA repair, dependence on replication-stress pathways, or dynamic adaptation mediated by ecDNA. The second axis defines its potential clinical role as a prognostic marker, treatment-predictive biomarker, or therapeutic vulnerability. The third axis considers evidence maturity, ranging from mechanistic and preclinical observations to retrospective clinical associations, prospective prognostic validation, and prospective treatment-specific predictive evidence. These levels are not interchangeable. A biologically plausible dependency is not necessarily a predictive biomarker, and an association with recurrence does not establish that treatment decisions based on the feature will improve clinical outcomes.

Among the current candidates, clonal diversity and copy-number complexity have the clearest near-term prognostic rationale. By contrast, CIN and whole-genome doubling have stronger evolutionary and retrospective clinical support than prospective clinical validation. Pan-cancer copy-number signature analyses have linked distinct CNA patterns to whole-genome doubling, aneuploidy, CIN-associated processes, and disease-specific survival (95). In lung adenocarcinoma, multi-region TRACERx validation of ORACLE showed that clonal expression patterns capture prognostic information associated with genetic evolutionary features, including CIN, and are associated with survival (96). However, ORACLE is a clonal expression-based biomarker, rather than a genomic instability phenotype. For genomic instability features, assay definitions, analytical thresholds, and incremental prognostic value beyond established clinicopathological factors remain insufficiently validated, and none have demonstrated treatment-predictive utility in resectable NSCLC. Accordingly, their appropriate near-term role is prospective validation within risk-stratification models, rather than routine treatment assignment.

Repair deficiency, replication stress, and ecDNA represent different translational categories. Their principal promise lies in identifying candidate therapeutic dependencies rather than established prognostic markers of recurrence. Repair-deficient tumors may warrant evaluation in DDR-directed trials, whereas tumors with prominent replication stress may be candidates for ATR-, CHK1-, or WEE1-directed strategies (97). ecDNA-positive cancers may represent another setting in which transcription-replication conflict or checkpoint dependencies can be therapeutically explored (98). However, alterations in repair genes, genomic scars, and functional measures of repair deficiency are not interchangeable, and most therapeutic evidence has been derived from preclinical studies, early phase trials, or advanced cancers. Therefore, these features should be regarded as priorities for biomarker development and prospective clinical testing, rather than validated predictive biomarkers for resectable NSCLC.

The immune effects of genomic instability are highly context-dependent. Mutational or structural complexity may increase the pool of potential tumor antigens; however, immune recognition also depends on antigen clonality and presentation, T-cell access and function, and the surrounding tumor microenvironment. CIN-associated inflammatory signaling may enhance immune recognition in some settings, while promoting immune suppression or metastatic behavior in others (99). Therefore, genomic instability features should not currently supersede established clinical, pathological, molecular, or immune factors in the selection of perioperative immunotherapy. Their immediate role is to generate testable hypotheses regarding heterogeneous treatment responses that can be evaluated prospectively.

Tissue profiling, longitudinal MRD assessment, and immune characterization may provide complementary but non-equivalent information. Tissue analysis describes the evolutionary architecture and candidate therapeutic dependencies of the resected tumors. Postoperative ctDNA-defined MRD provides a dynamic, assay-dependent signal of residual disease rather than a direct measurement of genomic instability. Immune biomarkers characterize the tumor-immune context in which residual clones may persist or respond to treatment. Among these layers, ctDNA-defined MRD currently has the most direct prognostic evidence for postoperative recurrence, although it is not itself a genomic instability phenotype and should not be used as a standalone basis for treatment escalation or de-escalation (100).

This translational prioritization must also be interpreted in the context of histological subtype, driver status, and treatment setting. Evidence derived from lung adenocarcinoma or molecularly selected cohorts should not be assumed to apply uniformly to all patients with resectable NSCLC. EGFR-mutated, anaplastic lymphoma kinase-positive, driver-negative non-squamous and squamous tumors may differ in their patterns of genomic instability, immune context, and therapeutic dependencies. Therefore, the proposed framework is neither a composite score nor a treatment algorithm. Its purpose is to identify which clinical claims are supported for each feature, where the evidence remains indirect or immature,

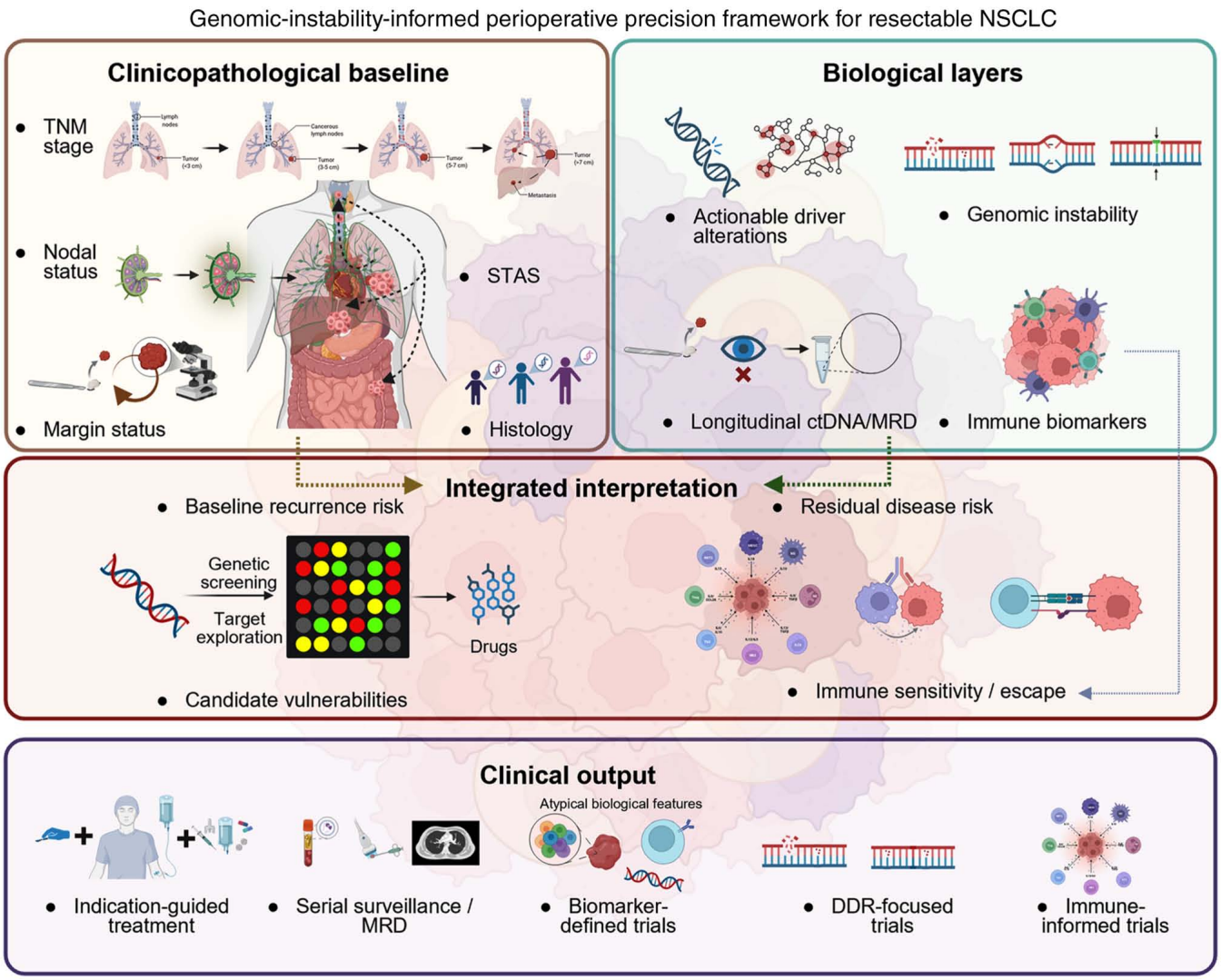

Figure 2. Genomic-instability-informed perioperative precision framework for resectable NSCLC. Established clinicopathological factors and validated molecular tests remain the basis for perioperative management. Tissue-based genomic instability profiling, longitudinal ctDNA-defined MRD assessment, and immune characterization may provide complementary but non-equivalent information on tumor evolution, residual disease risk, and candidate vulnerabilities. These investigational layers may support risk model development and biomarker-defined clinical trials but should not replace validated treatment indications. NSCLC, non-small cell lung cancer; ctDNA, circulating tumor DNA; MRD, molecular residual disease; DDR, DNA damage response; STAS, spread through air spaces; TNM, tumor-node-metastasis.

and which biomarker-defined questions should be prioritized for prospective evaluations. This evidence-based prioritization is summarized in Table II, and Fig. 2 places the framework within the broader perioperative treatment pathway.

9. Challenges and future directions

Clinical translation requires standardized, phenotype-specific, and analytically validated assays rather than a generic designation of 'genomic instability'. Future studies should prospectively define the instability phenotype, assay, analytical thresholds, tissue and blood sampling strategy, and clinically relevant endpoints (101,102). The key questions are whether genomic instability features add prognostic information beyond stage, pathology, driver status, and longitudinal MRD, and whether they identify differential benefit from matched therapies. Prospective biomarker-defined trials will be required to establish clinical utility (103).

10. Conclusions

Genomic instability provides a useful evolutionary framework for understanding postoperative recurrence in resectable NSCLC, but its individual components have distinct and unequally mature clinical implications. Clonal diversity and copy-number complexity have the strongest near-term prognostic rationale, whereas CIN and whole-genome doubling remain primarily evolutionary and prognostic candidates. Repair defects, replication stress, and ecDNA represent candidate therapeutic vulnerabilities rather than validated predictive biomarkers. Postoperative ctDNA-defined MRD provides more direct prognostic information, but its relationship with specific genomic instability features remains unproven. At present, genomic instability profiling should support biomarker development and prospective clinical trials rather than routine perioperative treatment decisions.

Table II. Translational prioritization of genomic-instability-related features for perioperative interpretation in resectable NSCLC.

Component	Evidence relevant to resectable NSCLC	Principal potential clinical role	Evidence maturity and translational priority	Current interpretation	Representative references
Intratumoral heterogeneity and clonal evolution	Multiregion and longitudinal studies link subclonal architecture and selection to lung cancer progression and metastasis	Prognostic and biological-context marker	Relatively mature translational evidence; near-term risk-stratification priority	May help explain recurrence after complete resection, but is not a treatment-selection marker	(6-8,26-31,35)
Copy-number complexity, CIN and whole-genome doubling	Copy-number diversity, CIN and whole-genome doubling are associated with evolutionary capacity and adverse outcomes	Candidate prognostic or evolutionary-context marker	Mixed evidence; strongest prognostic rationale for copy-number complexity, with limited prospective validation for CIN and whole-genome doubling	Promising for risk stratification, but assays, thresholds and incremental value remain unvalidated	(6,7,11-14)
Occult dissemination before surgery	Circulating tumor-cell and ctDNA studies support dissemination before clinically detectable relapse	Mechanistic and prognostic context	Direct evidence of pre-relapse dissemination; contextual priority	Supports the premise that surgery may not eliminate previously disseminated clones	(37,64)
Postoperative ctDNA-defined MRD	Serial ctDNA studies after curative-intent treatment show strong associations with relapse	Dynamic prognostic marker; potential treatment-guiding biomarker	Most mature postoperative risk signal, but treatment-guiding utility remains unproven	Not a genomic-instability phenotype or a stand-alone basis for treatment escalation or de-escalation	(40,43,55, 58,63)
Integration of genomic instability with MRD	No validated perioperative model has integrated instability profiling with postoperative MRD	Composite prognostic and treatment-selection hypothesis	Conceptual framework; high prospective validation priority	Requires paired tissue and serial blood studies accounting for burden, shedding, heterogeneity, timing and assay sensitivity	(6,12,40,51, 52,55)
Repair deficiency and genomic scarring	Genomic scars and repair-gene alterations have been explored as markers of DDR sensitivity, without perioperative validation	Therapeutic vulnerability; treatment-predictive biomarker development priority	Preliminary evidence; biomarker-development priority	These readouts are non-equivalent, and neither is validated for perioperative treatment selection	(17,18,24, 78,79)
Replication stress and checkpoint dependence	ATR-, CHK1-, WEE1- and DNA-PK-directed strategies are supported mainly by preclinical, advanced-disease or early-phase evidence	Therapeutic vulnerability; exploratory biomarker-development priority	Indirect evidence for resectable NSCLC; early-phase clinical trial priority	Appropriate for biomarker-selected trials, but not routine perioperative use	(78,80-85,88)
Extrachromosomal DNA	Experimental studies identify transcription-replication conflict and CHK1-related dependence in ecDNA-positive cancers	Candidate therapeutic vulnerability	Mechanistic evidence; exploratory priority	Biologically compelling, but lacks a validated assay and direct perioperative evidence	(16,25,98)

Table II. Continued.

Component	Evidence relevant to resectable NSCLC	Principal potential clinical role	Evidence maturity and translational priority	Current interpretation	Representative references
CIN-related immune context	CIN may promote inflammatory or immunosuppressive microenvironmental states, but predictive evidence is lacking	Potential immunotherapy-response modifier	Mechanistic and translational evidence; exploratory priority	Cannot currently guide perioperative immunotherapy selection	(11,71,99)

Mechanistic plausibility, prognostic association, and treatment predictive utility represent distinct levels of evidence. MRD is an assay-dependent signal of residual tumor-derived material, not a direct measure of genomic instability or a complete representation of residual disease. Associations with instability features should not be interpreted as causal without accounting for residual tumor burden, DNA shedding, vascular accessibility, spatial and temporal heterogeneity, sampling time, and assay sensitivity. The priorities shown refer to translational validation rather than readiness for routine clinical use or a hierarchy of standard treatments and may vary according to histological subtype, driver status, and treatment context. Findings from lung adenocarcinoma or molecularly selected cohorts should not be generalized to all populations with resectable NSCLC. ATR, ataxia telangiectasia and Rad3-related; CHK1, checkpoint kinase 1; CIN, chromosomal instability; ctDNA, circulating tumor DNA; DDR, DNA damage response; DNA-PK, DNA-dependent protein kinase; ecDNA, extrachromosomal DNA; MRD, molecular residual disease; NSCLC, non-small cell lung cancer; WEE1, WEE1 G2 checkpoint kinase.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

LW and YF wrote the original draft. LW and QL contributed to conceptualization, literature search and selection, interpretation of the literature, and critical revision of the manuscript. LW provided project administration. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, Felip E, Broderick SR, Brahmer JR, Swanson SJ, *et al*: Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. N Engl J Med 386: 1973-1985, 2022.
2. Wakelee H, Liberman M, Kato T, Tsuboi M, Lee SH, Gao S, Chen KN, Dooms C, Majem M, Eigendorff E, *et al*: Perioperative pembrolizumab for Early-stage non-small-cell lung cancer. N Engl J Med 389: 491-503, 2023.
3. Tsuboi M, Herbst RS, John T, Kato T, Majem M, Grohé C, Wang J, Goldman JW, Lu S, Su WC, *et al*: Overall survival with osimertinib in resected EGFR-Mutated NSCLC. N Engl J Med 389: 137-147, 2023.
4. Felip E, Altorki N, Zhou C, Csőszi T, Vynnychenko I, Goloborodko O, Luft A, Akopov A, Martinez-Marti A, Kenmotsu H, *et al*: Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): A randomised, multicentre, open-label, phase 3 trial. Lancet 398: 1344-1357, 2021.
5. Mountzios G, Remon J, Hendriks LEL, Garcia-Campelo R, Rolfo C, Van Schil P, Forde PM, Besse B, Subbiah V, Reck M, *et al*: Immune-checkpoint inhibition for resectable non-small-cell lung cancer-opportunities and challenges. Nat Rev Clin Oncol 20: 664-677, 2023.
6. Frankell AM, Dietzen M, Al Bakir M, Lim EL, Karasaki T, Ward S, Veeriah S, Colliver E, Huebner A, Bunkum A, *et al*: The evolution of lung cancer and impact of subclonal selection in TRACERx. Nature 616: 525-533, 2023.
7. Martínez-Ruiz C, Black JRM, Puttick C, Hill MS, Demeulemeester J, Larose Cadieux E, Thol K, Jones TP, Veeriah S, Naceur-Lombardelli C, *et al*: Genomic-transcriptomic evolution in lung cancer and metastasis. Nature 616: 543-552, 2023.

8. Al Bakir M, Huebner A, Martínez-Ruiz C, Grigoriadis K, Watkins TBK, Pich O, Moore DA, Veeriah S, Ward S, Laycock J, *et al*: The evolution of non-small cell lung cancer metastases in TRACERx. Nature 616: 534-542, 2023.
9. Black JRM, Bartha G, Abbott CW, Boyle SM, Karasaki T, Li B, Chen R, Harris J, Veeriah S, Colopi M, *et al*: Ultrasensitive ctDNA detection for preoperative disease stratification in early-stage lung adenocarcinoma. Nat Med 31: 70-76, 2025.
10. Yap TA, Manning HC, Sapra P, Mills GB and O'Connor MJ: Targeting genomic instability in cancer. Cell 189: 2278-2306, 2026.
11. Chen X, Agustinus AS, Li J, DiBona M and Bakhoum SF: Chromosomal instability as a driver of cancer progression. Nat Rev Genet 26: 31-46, 2025.
12. Pawlik P, Grigoriadis K, Bunkum A, Coggan H, Frankell AM, Martínez-Ruiz C, Karasaki T, Huebner A, Rowan A, Fisher J, *et al*: Clone copy number diversity is linked to survival in lung cancer. Nature 646:190-197, 2025.
13. Lu WT, Zalmas LP, Bailey C, Black JRM, Martinez-Ruiz C, Pich O, Gimeno-Valiente F, Usaite I, Magness A, Thol K, *et al*: TRACERx analysis identifies a role for FAT1 in regulating chromosomal instability and whole-genome doubling via Hippo signalling. Nat Cell Biol 27:154-168, 2025.
14. Baker TM, Lai S, Lynch AR, Lesluyes T, Yan H, Ogilvie HA, Verfaillie A, Dentro S, Bowes AL, Pillay N, *et al*: The history of chromosomal instability in Genome-Doubled tumors. Cancer Discov 14: 1810-1822, 2024.
15. Gimeno-Valiente F, Castignani C, Larose Cadieux E, Mensah NE, Liu X, Chen K, Chervova O, Karasaki T, Weeden CE, Richard C, *et al*: DNA methylation cooperates with genomic alterations during non-small cell lung cancer evolution. Nat Genet 57: 2226-2237, 2025.
16. Tang J, Weiser NE, Wang G, Chowdhry S, Curtis EJ, Zhao Y, Wong ITL, Marinov GK, Li R, Hanoian P, *et al*: Enhancing transcription-replication conflict targets ecDNA-positive cancers. Nature 635: 210-218, 2024.
17. Hopkins JL, Lan L and Zou L: DNA repair defects in cancer and therapeutic opportunities. Genes Dev 36: 278-293, 2022.
18. Li Q, Qian W, Zhang Y, Hu L, Chen S and Xia Y: A new wave of innovations within the DNA damage response. Signal Transduct Target Ther 8: 338, 2023.
19. Caswell DR, Gui P, Mayekar MK, Law EK, Pich O, Bailey C, Boumelha J, Kerr DL, Blakely CM, Manabe T, *et al*: The role of APOBEC3B in lung tumor evolution and targeted cancer therapy resistance. Nat Genet 56: 60-73, 2024.
20. Díaz-Gay M, Zhang T, Hoang PH, Leduc C, Baine MK, Travis WD, Sholl LM, Joubert P, Khandekar A, Zhao W, *et al*: The mutagenic forces shaping the genomes of lung cancer in never smokers. Nature 644: 133-144, 2025.
21. Zhang T, Sang J, Hoang PH, Zhao W, Rosenbaum J, Johnson KE, Klimczak LJ, McElderry J, Klein A, Wirth C, *et al*: APOBEC affects tumor evolution and age at onset of lung cancer in smokers. Nat Commun 16: 4711, 2025.
22. Everall A, Tapinos A, Hawari A, Cornish AJ, Sud A, Chubb D, Kinnersley B, Frangou A, Barquin M, Jung J, *et al*: Comprehensive repertoire of the chromosomal alteration and mutational signatures across 16 cancer types. Nat Genet 58: 570-581, 2026.
23. Jamal-Hanjani M, Wilson GA, McGranahan N, Birkbak NJ, Watkins TBK, Veeriah S, Shafi S, Johnson DH, Mitter R, Rosenthal R, *et al*: Tracking the evolution of non-small-cell lung cancer. N Engl J Med 376: 2109-2121, 2017.
24. Diossy M, Sztupinszki Z, Borcsok J, Krzystanek M, Tisza V, Spisak S, Rusz O, Timar J, Csabai I, Fillinger J, *et al*: A subset of lung cancer cases shows robust signs of homologous recombination deficiency associated genomic mutational signatures. NPJ Precis Oncol 5: 55, 2021.
25. Yan X, Mischel P and Chang H: Extrachromosomal DNA in cancer. Nat Rev Cancer 24: 261-273, 2024.
26. De Zuani M, Xue H, Park JS, Dentro SC, Seferbekova Z, Tessier J, Curras-Alonso S, Hadjipanayis A, Athanasiadis EI, Gerstung M, *et al*: Single-cell and spatial transcriptomics analysis of non-small cell lung cancer. Nat Commun 15: 4388, 2024.
27. Lomakin A, Svedlund J, Strell C, Gataric M, Shmatko A, Rukhovich G, Park JS, Ju YS, Dentro S, Kleshchevnikov V, *et al*: Spatial genomics maps the structure, nature and evolution of cancer clones. Nature 611: 594-602, 2022.
28. Hertel A, Streuer A, Diehl S, Boch T, Nörenberg D, Strittmatter A, Zöllner FG, Schoenberg SO, Hofmann WK, Loges S, *et al*: Targeting tumoral heterogeneity in lung cancer: A novel, CT-texture-guided targeted biopsy approach with exome sequencing. NPJ Precis Oncol 9: 342, 2025.
29. Hessey S, Bunkum A, Huebner A, Haase K, Grigoriadis K, Naceur-Lombardelli C, Liu WK, Harrigan CF, Grieco C, Marinelli D, *et al*: Evolutionary characterization of lung cancer metastasis. Nature 653: 911-922, 2026.
30. Enfield KSS, Colliver E, Lee C, Magness A, Moore DA, Sivakumar M, Grigoriadis K, Pich O, Karasaki T, Hobson PS, *et al*: Spatial architecture of myeloid and T cells orchestrates immune evasion and clinical outcome in lung cancer. Cancer Discov 14: 1018-1047, 2024.
31. Mo CK, Liu J, Chen S, Storrs E, Targino da Costa ALN, Houston A, Wendl MC, Jayasinghe RG, Iglesia MD, Ma C, *et al*: Tumour evolution and microenvironment interactions in 2D and 3D space. Nature 634: 1178-1186, 2024.
32. Gerstberger S, Jiang Q and Ganesh K: Metastasis. Cell 186: 1564-1579, 2023.
33. Goddard ET, Linde MH, Srivastava S, Klug G, Shabaneh TB, Iannone S, Grzelak CA, Marsh S, Riggio AI, Shor RE, *et al*: Immune evasion of dormant disseminated tumor cells is due to their scarcity and can be overcome by T cell immunotherapies. Cancer Cell 42: 119-134.e12, 2024.
34. Li Y, Liu F, Cai Q, Deng L, Ouyang Q, Zhang XHF and Zheng J: Invasion and metastasis in cancer: Molecular insights and therapeutic targets. Signal Transduct Target Ther 10: 57, 2025.
35. Dijkstra KK, Vendramin R, Karagianni D, Witsen M, Gálvez-Cancino F, Hill MS, Foster KA, Barbè V, Angelova M, Hynds RE, *et al*: Subclonal immune evasion in non-small cell lung cancer. Cancer Cell 43: 1833-1849.e10, 2025.
36. Wang C, Li J, Chen J, Wang Z, Zhu G, Song L, Wu J, Li C, Qiu R, Chen X, *et al*: Multi-omics analyses reveal biological and clinical insights in recurrent stage I non-small cell lung cancer. Nat Commun 16: 1477, 2025.
37. Chemi F, Rothwell DG, McGranahan N, Gulati S, Abbosh C, Pearce SP, Zhou C, Wilson GA, Jamal-Hanjani M, Birkbak NJ, *et al*: Pulmonary venous circulating tumor cell dissemination before tumor resection and disease relapse. Nat Med 25: 1534-1539, 2019.
38. Liang Y, Chen WM, Zhang Y and Li L: Remodeling the tumor dormancy ecosystem to prevent recurrence and metastasis. Signal Transduct Target Ther 11: 1, 2026.
39. Hong TH, Hwang S, Dasgupta A, Abbosh C, Hung T, Bredno J, Walker J, Shi X, Milenkova T, Horn L, *et al*: Clinical utility of Tumor-Naïve presurgical circulating tumor DNA detection in Early-stage NSCLC. J Thorac Oncol 19: 1512-1524, 2024.
40. Gale D, Heider K, Ruiz-Valdepenas A, Hackinger S, Perry M, Marsico G, Rundell V, Wulff J, Sharma G, Knock H, *et al*: Residual ctDNA after treatment predicts early relapse in patients with early-stage non-small cell lung cancer. Ann Oncol 33: 500-510, 2022.
41. Tran HT, Heeke S, Sujit SJ, Vokes N, Zhang J, Aminu M, Lam VK, Vaporciyan A, Swisher SG, Godoy MCB, *et al*: Circulating tumor DNA and radiological tumor volume identify patients at risk for relapse with resected, early-stage non-small-cell lung cancer. Ann Oncol 35: 183-189, 2024.
42. Sujit SJ, Aminu M, Karpinets TV, Chen P, Saad MB, Salehjahromi M, Boom JD, Qayati M, George JM, Allen H, *et al*: Enhancing NSCLC recurrence prediction with PET/CT habitat imaging, ctDNA, and integrative radiogenomics-blood insights. Nat Commun 15: 3152, 2024.
43. Herbst RS, John T, Grohé C, Goldman JW, Kato T, Laktionov K, Bonanno L, Tiseo M, Majem M, Dómine M, *et al*: Molecular residual disease analysis of adjuvant osimertinib in resected EGFR-mutated stage IB-IIIA non-small-cell lung cancer. Nat Med 31: 1958-1968, 2025.
44. Stetson D, Labrousse P, Russell H, Shera D, Abbosh C, Dougherty B, Barrett JC, Hodgson D and Hadfield J: Next-Generation molecular residual disease assays: Do we have the tools to evaluate them properly? J Clin Oncol 42: 2736-2740, 2024.
45. Boukouris AE, Michaelidou K, Joosse SA, Charpidou A, Mavroudis D, Syrigos KN and Agelaki S: A comprehensive overview of minimal residual disease in the management of early-stage and locally advanced non-small cell lung cancer. NPJ Precis Oncol 9: 178, 2025.
46. Moding EJ, Nabet BY, Alizadeh AA and Diehn M: Detecting liquid remnants of solid tumors: Circulating tumor DNA minimal residual disease. Cancer Discov 11: 2968-2986, 2021.
47. Zheng J, Qin C, Wang Q, Tian D and Chen Z: Circulating tumour DNA-Based molecular residual disease detection in resectable cancers: A systematic review and meta-analysis. EBioMedicine 103: 105109, 2024.

48. Venkatesan S, Angelova M, Puttick C, Zhai H, Caswell DR, Lu WT, Dietzen M, Galanos P, Evangelou K, Bellelli R, *et al*: Induction of APOBEC3 exacerbates DNA replication stress and chromosomal instability in early breast and lung cancer evolution. Cancer Discov 11: 2456-2473, 2021.
49. Isozaki H, Sakhtemani R, Abbasi A, Nikpour N, Stanzione M, Oh S, Langenbucher A, Monroe S, Su W, Cabanos HF, *et al*: Therapy-induced APOBEC3A drives evolution of persistent cancer cells. Nature 620: 393-401, 2023.
50. Wang X, Bai H, Zhang J, Wang Z, Duan J, Cai H, Cao Z, Lin Q, Ding X, Sun Y, *et al*: Genetic intratumor heterogeneity remodels the immune microenvironment and induces immune evasion in brain metastasis of lung cancer. J Thorac Oncol 19: 252-272, 2024.
51. Drews RM, Hernando B, Tarabichi M, Haase K, Lesluyes T, Smith PS, Morrill Gavarró L, Couturier DL, Liu L, Schneider M, *et al*: A pan-cancer compendium of chromosomal instability. Nature 606: 976-983, 2022.
52. Chen K, Yang F, Shen H, Wang C, Li X, Chervova O, Wu S, Qiu F, Peng D, Zhu X, *et al*: Individualized tumor-informed circulating tumor DNA analysis for postoperative monitoring of non-small cell lung cancer. Cancer Cell 41: 1749-1762.e6, 2023.
53. Stejskal P, Goodarzi H, Srovnal J, Hajdúch M, van 't Veer LJ and Magbanua MJM: Circulating tumor nucleic acids: Biology, release mechanisms, and clinical relevance. Mol Cancer 22: 15, 2023.
54. Normanno N, Morabito A, Rachiglio AM, Sforza V, Landi L, Bria E, Delmonte A, Cappuzzo F and De Luca A: Circulating tumour DNA in early stage and locally advanced NSCLC: Ready for clinical implementation? Nat Rev Clin Oncol 22: 215-231, 2025.
55. Black JRM, Karasaki T, Abbott CW, Li B, Veeriah S, Al Bakir M, Liu WK, Huebner A, Martínez-Ruiz C, Pawlik P, *et al*: Longitudinal ultrasensitive ctDNA monitoring for high-resolution lung cancer risk prediction. Cell 188: 7083-7098.e18, 2025.
56. Schuurbiers MMF, Smith CG, Hartemink KJ, Rintoul RC, Gale D, Monkhorst K, Mandos BLR, Paterson AL, van den Broek D, Rosenfeld N, *et al*: Recurrence prediction using circulating tumor DNA in patients with early-stage non-small cell lung cancer after treatment with curative intent: A retrospective validation study. PLoS Med 22: e1004574, 2025.
57. Qiu B, Guo W, Zhang F, Lv F, Ji Y, Peng Y, Chen X, Bao H, Xu Y, Shao Y, *et al*: Dynamic recurrence risk and adjuvant chemotherapy benefit prediction by ctDNA in resected NSCLC. Nat Commun 12: 6770, 2021.
58. Zhang JT, Liu SY, Gao W, Liu SYM, Yan HH, Ji L, Chen Y, Gong Y, Lu HL, Lin JT, *et al*: Longitudinal undetectable molecular residual disease defines potentially cured population in localized Non-Small cell lung cancer. Cancer Discov 12: 1690-1701, 2022.
59. Tsui WHA, Jiang P and Lo YMD: Cell-free DNA fragmentomics in cancer. Cancer Cell 43: 1792-1814, 2025.
60. Mathios D, Johansen JS, Cristiano S, Medina JE, Phallen J, Larsen KR, Bruhm DC, Niknafs N, Ferreira L, Adleff V, *et al*: Detection and characterization of lung cancer using cell-free DNA fragmentomes. Nat Commun 12: 5060, 2021.
61. van 't Erve I, Alipanahi B, Lumbard K, Skidmore ZL, Rinaldi L, Millberg LK, Carey J, Chesnick B, Cristiano S, Portwood C, *et al*: Cancer treatment monitoring using cell-free DNA fragmentomes. Nat Commun 15: 8801, 2024.
62. Lo YMD, Han DSC, Jiang P and Chiu RWK: Epigenetics, fragmentomics, and topology of cell-free DNA in liquid biopsies. Science 372: eaaw3616, 2021.
63. Pascual J, Attard G, Bidard FC, Curigliano G, De Mattos-Arruda L, Diehn M, Italiano A, Lindberg J, Merker JD, Montagut C, *et al*: ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: A report from the ESMO Precision Medicine Working Group. Ann Oncol 33: 750-768, 2022.
64. Abbosh C, Frankell AM, Harrison T, Kisistok J, Garnett A, Johnson L, Veeriah S, Colliver E, Moreau M, Ward S, *et al*: Tracking early lung cancer metastatic dissemination in TRACERx using ctDNA. Nature 616: 553-562, 2023.
65. Peri A, Salomon N, Wolf Y, Kreiter S, Diken M and Samuels Y: The landscape of T cell antigens for cancer immunotherapy. Nat Cancer 4: 937-954, 2023.
66. Litchfield K, Reading JL, Puttick C, Thakkar K, Abbosh C, Bentham R, Watkins TBK, Rosenthal R, Biswas D, Rowan A, *et al*: Meta-analysis of tumor- and T cell-intrinsic mechanisms of sensitization to checkpoint inhibition. Cell 184: 596-614.e14, 2021.
67. Memon D, Schoenfeld AJ, Ye D, Fromm G, Rizvi H, Zhang X, Keddar MR, Mathew D, Yoo KJ, Qiu J, *et al*: Clinical and molecular features of acquired resistance to immunotherapy in non-small cell lung cancer. Cancer Cell 42: 209-224.e9, 2024.
68. Ricciuti B, Arbour KC, Lin JJ, Vajdi A, Vokes N, Hong L, Zhang J, Tolstorukov MY, Li YY, Spurr LF, *et al*: Diminished efficacy of programmed Death-(Ligand)1 inhibition in STK11- and KEAP1-Mutant lung adenocarcinoma is affected by KRAS mutation status. J Thorac Oncol 17: 399-410, 2022.
69. Ricciuti B and Garassino MC: Precision immunotherapy for STK11/KEAP1-mutant NSCLC. J Thorac Oncol 19: 877-882, 2024.
70. Huang Y, Lu C, Wang H, Gu L, Fu YX and Li GM: DNAJA2 deficiency activates cGAS-STING pathway via the induction of aberrant mitosis and chromosome instability. Nat Commun 14: 5246, 2023.
71. Li J, Hubisz MJ, Earlie EM, Duran MA, Hong C, Varela AA, Tsao JL, Petersson EJ, Lok BH, Modrek AS, *et al*: Non-cell-autonomous cancer progression from chromosomal instability. Nature 620: 1080-1088, 2023.
72. Heymach JV, Harpole D, Mitsudomi T, Taube JM, Galffy G, Hochmair M, Winder T, Zukov R, Garbaos G, Gao S, *et al*: Perioperative durvalumab for resectable Non-Small-Cell lung cancer. N Engl J Med 389: 1672-1684, 2023.
73. Cascone T, Awad MM, Spicer JD, He J, Lu S, Sepesi B, Tanaka F, Taube JM, Cornelissen R, Havel L, *et al*: Perioperative nivolumab in resectable lung cancer. N Engl J Med 390: 1756-1769, 2024.
74. Sorin M, Prosty C, Ghaleb L, Nie K, Katergi K, Shahzad MH, Dubé LR, Atallah A, Swaby A, Dankner M, *et al*: Neoadjuvant Chemoimmunotherapy for NSCLC: A systematic review and meta-analysis. JAMA Oncol 10: 621-633, 2024.
75. Vaccaro A, Rahal Z, Kadara H and Cascone T: A roadmap to precision immunotherapy for Early-stage non-small cell lung cancer. Cancer Discov 15: 884-889, 2025.
76. Xia L, Mei J, Kang R, Deng S, Chen Y, Yang Y, Feng G, Deng Y, Gan F, Lin Y, *et al*: Perioperative ctDNA-Based molecular residual disease detection for Non-Small cell lung cancer: A prospective multicenter cohort study (LUNGCA-1). Clin Cancer Res 28: 3308-3317, 2022.
77. Zer A, Ahn MJ, Barlesi F, Bubendorf L, De Ruysscher D, Garrido P, Gautschi O, Hendriks LE, Jänne PA, Kerr KM, *et al*: Early and locally advanced non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 36: 1245-1262, 2025.
78. Drew Y, Zenke FT and Curtin NJ: DNA damage response inhibitors in cancer therapy: Lessons from the past, current status and future implications. Nat Rev Drug Discov 24: 19-39, 2025.
79. Tsilingiri K, Chalari A, Christopoulou G, Voutsina A, Constantoulakis P, Potaris K, Vamvakaris I, Hatzidaki D, Zachou G, Vatsellas G, *et al*: Genomic scarring score predicts the response to PARP inhibitors in non-small cell lung cancer. NPJ Precis Oncol 8: 291, 2024.
80. Yap TA, Fontana E, Lee EK, Spigel DR, Højgaard M, Lheureux S, Mettu NB, Carneiro BA, Carter L, Plummer R, *et al*: Camonsertib in DNA damage response-deficient advanced solid tumors: Phase 1 trial results. Nat Med 29: 1400-1411, 2023.
81. Yap TA, Tan DSP, Terbuch A, Caldwell R, Guo C, Goh BC, Heong V, Noor NR, Bashir S, Drew Y, *et al*: First-in-Human trial of the oral ataxia telangiectasia and RAD3-Related (ATR) inhibitor BAY 1895344 in patients with advanced solid tumors. Cancer Discov 11: 80-91, 2021.
82. Fukuda K, Takeuchi S, Arai S, Nanjo S, Sato S, Kotani H, Kita K, Nishiyama A, Sakaguchi H, Ohtsubo K, *et al*: Targeting WEE1 enhances the antitumor effect of KRAS-mutated non-small cell lung cancer harboring TP53 mutations. Cell Rep Med 5: 101578, 2024.
83. Yap TA, LoRusso P, Miller RE, Kristeleit R, Paulovich AG, McMorn S, Oplustil O'Connor L, Lombardi B, Marco-Casanova P, Gangl ET, *et al*: The DNA-PK inhibitor AZD7648 alone or combined with pegylated liposomal doxorubicin in patients with advanced cancer: Results of a first-in-human Phase I/IIa study. Br J Cancer 133: 168-177, 2025.
84. da Costa AABA, Chowdhury D, Shapiro GI, D'Andrea AD and Konstantinopoulos PA: Targeting replication stress in cancer therapy. Nat Rev Drug Discov 22: 38-58, 2023.
85. Besse B, Pons-Tostivint E, Park K, Hartl S, Forde PM, Hochmair MJ, Awad MM, Thomas M, Goss G, Wheatley-Price P, *et al*: Biomarker-directed targeted therapy plus durvalumab in advanced non-small-cell lung cancer: A phase 2 umbrella trial. Nat Med 30: 716-729, 2024.

86. Gray JE, Schenker M, Şendur MAN, Leonova V, Kowalski D, Kato T, Orlova R, Yang JC, Langleben A, Pilz A, *et al*: The Phase 3 KEYLYNK-006 study of pembrolizumab plus olaparib versus pembrolizumab plus pemetrexed as maintenance therapy for metastatic nonsquamous NSCLC. J Thorac Oncol 20: 219-232, 2025.
87. Hochmair M, Schenker M, Cobo Dols M, Kim TM, Ozyilkan O, Smagina M, Leonova V, Kato T, Fedenko A, De Angelis F, *et al*: Pembrolizumab with or without maintenance olaparib for metastatic squamous NSCLC that responded to First-Line pembrolizumab plus chemotherapy. J Thorac Oncol 20: 203-218, 2025.
88. Cleary JM, Aguirre AJ, Shapiro GI and D'Andrea AD: Biomarker-guided development of DNA repair inhibitors. Mol Cell 78: 1070-1085, 2020.
89. Bailey C, Pich O, Thol K, Watkins TBK, Luebeck J, Rowan A, Stavrou G, Weiser NE, Dameracharla B, Bentham R, *et al*: Origins and impact of extrachromosomal DNA. Nature 635: 193-200, 2024.
90. Hung KL, Yost KE, Xie L, Shi Q, Helmsauer K, Luebeck J, Schöpflin R, Lange JT, Chamorro González R, Weiser NE, *et al*: ecDNA hubs drive cooperative intermolecular oncogene expression. Nature 600: 731-736, 2021.
91. Rami-Porta R, Nishimura KK, Giroux DJ, Detterbeck FC, Asamura H, Goldstraw P, Crowley J, Chansky K, Edwards J, Nicholson AG, *et al*: The international association for the study of lung cancer lung cancer staging project: Proposals for revision of the TNM stage groups in the forthcoming (Ninth) edition of the TNM classification for lung cancer. J Thorac Oncol 19: 1007-1027, 2024.
92. Spicer JD, Cascone T, Wynes MW, Ahn MJ, Dacic S, Felip E, Forde PM, Higgins KA, Kris MG, Mitsudomi T, *et al*: Neoadjuvant and adjuvant treatments for early stage resectable NSCLC: Consensus recommendations from the international association for the study of lung cancer. J Thorac Oncol 19: 1373-1414, 2024.
93. Wu YL, Dziadziuszko R, Ahn JS, Barlesi F, Nishio M, Lee DH, Lee JS, Zhong W, Horinouchi H, Mao W, *et al*: Alectinib in resected ALK-Positive Non-Small-Cell lung cancer. N Engl J Med 390: 1265-1276, 2024.
94. Passaro A, Al Bakir M, Hamilton EG, Diehn M, André F, Roy-Chowdhuri S, Mountzios G, Wistuba II, Swanton C and Peters S: Cancer biomarkers: Emerging trends and clinical implications for personalized treatment. Cell 187: 1617-1635, 2024.
95. Steele CD, Abbasi A, Islam SMA, Bowes AL, Khandekar A, Haase K, Hames-Fathi S, Ajayi D, Verfaillie A, Dhami P, *et al*: Signatures of copy number alterations in human cancer. Nature 606: 984-991, 2022.
96. Biswas D, Liu YH, Herrero J, Wu Y, Moore DA, Karasaki T, Grigoriadis K, Lu WT, Veeriah S, Naceur-Lombardelli C, *et al*: Prospective validation of ORACLE, a clonal expression biomarker associated with survival of patients with lung adenocarcinoma. Nat Cancer 6: 86-101, 2025.
97. Groelly FJ, Fawkes M, Dagg RA, Blackford AN and Tarsounas M: Targeting DNA damage response pathways in cancer. Nat Rev Cancer 23: 78-94, 2023.
98. Wong IT, Yi H, Melillo B, Cravatt BF, Chang HY and Mischel PS: Targeting extrachromosomal DNA in human cancers. Nat Rev Drug Discov 25: 374-389, 2026.
99. Al-Rawi DH, Lettera E, Li J, DiBona M and Bakhoum SF: Targeting chromosomal instability in patients with cancer. Nat Rev Clin Oncol 21: 645-659, 2024.
100. Tan AC, Liao BC, Li M, Lee D, Uehara Y, Thamlikitkul L, Zhang JT, Zheng M, Lee CK, Pavlakis N, *et al*: Consensus statement on ctDNA minimal residual disease testing in early stage NSCLC: A Delphi study by the Asian thoracic oncology research group. J Thorac Oncol 21: 103696, 2026.
101. Karasaki T, Moore DA, Veeriah S, Naceur-Lombardelli C, Toncheva A, Magno N, Ward S, Bakir MA, Watkins TBK, Grigoriadis K, *et al*: Evolutionary characterization of lung adenocarcinoma morphology in TRACERx. Nat Med 29: 833-845, 2023.
102. Malki Y, Zhou Q, Jiang P and Lo YMD: The comings and goings of cell-free DNA: Biological and clinical implications. Med 7: 100926, 2026.
103. Hayes DF: Defining clinical utility of tumor biomarker tests: A Clinician's Viewpoint. J Clin Oncol 39: 238-248, 2021.