Molecular classification and precision therapy in gastric cancer: Current advances and future perspectives (Review)

SHUJING XIA[1,2], XIUMEI ZHANG[3], LIZHONG TANG[4,5], ANQI LI[1,2], JIANHAI CHEN[1,2] and ZHANG TAO[6,7]

[1]Department of Gastroenterology, Yancheng TCM Hospital Affiliated to Nanjing University of Chinese Medicine, Yancheng, Jiangsu 224001, P.R. China; [2]Department of Gastroenterology, Yancheng TCM Hospital, Yancheng, Jiangsu 224001, P.R. China; [3]Department of Pathology, Affiliated Xinghua People's Hospital of Yangzhou University Medical College, Xinghua, Jiangsu 225700, P.R. China; [4]Department of Pharmacy, Yancheng TCM Hospital Affiliated to Nanjing University of Chinese Medicine, Yancheng, Jiangsu 224001, P.R. China; [5]Department of Pharmacy, Yancheng TCM Hospital, Yancheng, Jiangsu 224001, P.R. China; [6]Department of Respiratory Medicine, Yancheng TCM Hospital Affiliated to Nanjing University of Chinese Medicine, Yancheng, Jiangsu 224001, P.R. China; [7]Department of Respiratory Medicine, Yancheng TCM Hospital, Yancheng, Jiangsu 224001, P.R. China

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Abstract. The emergence of molecular classifications for gastric cancer (GC), The Cancer Genome Atlas (TCGA) and Asian Cancer Research Group (ACRG), has advanced targeted and immunotherapies, but their clinical translation faces real-world obstacles including high cost, tissue availability, standardization, and intratumoral heterogeneity. The present review critically compares the two classification systems regarding prognostic utility across geographic populations and boundary conflicts, noting that ACRG is more operable in East Asian populations whereas TCGA is better suited for mechanistic exploration. Focusing on acquired resistance as a core bottleneck in precision therapy, mechanisms underlying anti-Human Epidermal Growth Factor Receptor 2 (HER2) resistance and primary/secondary resistance to immune checkpoint inhibitors (ICIs) were systematically dissected, while also addressing immune-related adverse events and pseudo-/hyperprogression. Moreover, non-immune elements of the tumor microenvironment deserve attention: Cancer-associated fibroblasts limit drug penetration and promote epithelial-mesenchymal transition through physical barriers and paracrine signaling; metabolic reprogramming (high glycolysis and glutamine addiction) impairs chemotherapy and ICI efficacy via an acidic microenvironment and metabolic competition. Finally, multi-target combination strategies are envisioned based on pathway redundancy, along with liquid biopsy-driven dynamic adaptive therapy and single-cell/spatial multi-omics integration for precise microenvironment intervention. The present review aims to offer a systematic reference for moving GC precision therapy from static subtyping toward dynamic, multi-dimensional integration.

Correspondence to: Professor Zhang Tao, Department of Respiratory Medicine, Yancheng TCM Hospital Affiliated to Nanjing University of Chinese Medicine, 53 Renmin Road, Yancheng, Jiangsu 224001, P.R. China
E-mail: taozhang1978@163.com

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Contents

1. Introduction

Gastric cancer (GC) continues to pose a significant global health challenge, with GLOBOCAN 2022 data indicating ~1.09 million new cases and 768,000 annual deaths worldwide (1-3). It remains the fifth most commonly diagnosed cancer across populations and ranks third in cancer-related mortality, following only lung and colorectal cancers (4,5). The prognosis for patients remains largely unfavorable, as age-standardized 5-year survival rates generally remain below 30% in most regions, dropping further to 10-20% among those diagnosed with advanced or metastatic disease (6-8). These dismal outcomes reflect both the aggressive nature of GC and the shortcomings of existing treatment modalities.

The clinical approach to managing GC has historically been complicated by its extensive molecular diversity and variation between tumors (9). While histopathological classification systems have provided some clinical utility, they are insufficient in capturing the full range of molecular profiles that influence treatment response and disease progression (10-13). Conventional chemotherapy regimens, designed

under a one-size-fits-all model, often result in limited efficacy, with response rates typically ranging from 30-40% for first-line combinations and short-lived benefits (14,15). This stagnation in therapeutic progress highlights the urgent need for more refined, genomically informed strategies.

The present review offers an in-depth analysis of the progression of molecular subtyping in GC and its application in precision oncology. The transition from traditional histological categorizations to modern molecular frameworks was examined, emphasizing how these developments have facilitated biomarker-guided treatment strategies. Special attention was given to the emergence and integration of targeted therapies tailored to specific genetic alterations, including HER2-targeted agents, anti-angiogenic drugs and immune checkpoint inhibitors (ICIs). Additionally, ongoing challenges such as tumor heterogeneity, dynamic genomic changes over time and space, and the necessity for improved biomarker validation and standardization, were assessed. The article concludes with a discussion on innovative tools including single-cell sequencing, liquid biopsy techniques, and artificial intelligence (AI)-assisted decision-making that hold promise for advancing personalized treatment approaches. By consolidating current knowledge and addressing both advancements and unresolved issues, the present review seeks to equip clinicians and researchers with a thorough understanding of the current status and future trajectory of precision medicine in GC. Incorporating molecular profiling into everyday clinical practice marks a transformative shift in the management of GC, offering renewed optimism for improved patient outcomes in this complex disease.

2. Molecular classification of GC

Advancements in genomic research, driven by high-throughput sequencing technologies, have significantly reshaped understanding of GC biology (16). Major projects such as The Cancer Genome Atlas (TCGA) and Asian Cancer Research Group (ACRG) have systematically mapped the molecular landscape of GC, identifying distinct subtypes characterized by unique genetic mutations, pathway dependencies and potential therapeutic targets (17-20). The TCGA classification, introduced in 2014, delineated four primary subtypes: Epstein-Barr virus (EBV)-positive, microsatellite instability-high (MSI), genomically stable (GS) and chromosomal instability (CIN); while the ACRG later proposed an alternative system particularly relevant to Asian patient populations (21,22). These molecular classifications have moved beyond theoretical interest and now play a direct role in guiding clinical decisions and drug development (23) (Fig. 1 and Table I).

TCGA classification. The TCGA project has played a pivotal role in transforming the understanding of GC by introducing a comprehensive and biologically meaningful molecular classification system (24). This groundbreaking initiative categorizes the disease into four distinct molecular subtypes. Each subtype is characterized by unique genetic mutations, epigenetic modifications and activation of specific signaling pathways, offering critical insights into the diverse mechanisms underlying gastric tumorigenesis (25). This molecular heterogeneity directly translates into divergent immunotherapeutic responses across subtypes-most notably, robust clinical benefit in EBV^+ and MSI-H tumors, modest or inconsistent activity in CIN, and minimal response in GS tumors (Table II).

This classification not only reflects the underlying genetic and epigenetic alterations driving tumor initiation and progression but also provides a crucial framework for guiding clinical decision-making and developing targeted therapeutic strategies (26). By moving beyond traditional histopathological classifications, the TCGA model allows for a more nuanced understanding of GC as a biologically heterogeneous disease with distinct subtype-specific features and treatment implications (27). This shift toward molecular stratification has significant translational relevance, enabling oncologists to improve prediction of prognosis, select appropriate therapies, and design biomarker-driven clinical trials that match patients with the most effective treatment options based on their tumor's molecular profile (26,27).

ACRG classification. The ACRG classification system has significantly advanced the molecular stratification of GC by delineating four distinct molecular subtypes: Microsatellite instability-high (MSI-H), microsatellite stable/epithelial-mesenchymal transition (MSS/EMT), MSS/TP53-active and MSS/TP53-inactive (20,28-30). This classification represents a paradigm shift from traditional histopathology-based systems, which often failed to capture the biological heterogeneity of GC and provide actionable insights for treatment (31).

Unlike earlier classifications that primarily relied on histopathological features such as tumor morphology and Lauren classification, the ACRG model integrates comprehensive gene expression profiling and functional pathway analysis to better reflect the underlying tumor biology and clinical behavior (32). By leveraging high-throughput transcriptomic data, this molecular framework identifies key signaling pathways and cellular processes that are dysregulated in each subtype, thereby offering a more precise understanding of disease mechanisms (33). For instance, the GS subtype is characterized by low CIN and frequent mutations in the CDH1 gene, often presenting in younger patients with a family history of GC (34). By contrast, the MSI subtype exhibits high mutational burden and is associated with improved prognosis and potential responsiveness to ICIs (19). The immune-like subtype shows prominent infiltration of immune cells and may benefit from immunotherapy, while the MSS subtype typically displays CIN and activation of EMT pathways, suggesting a more aggressive clinical course and limited response to conventional therapies (35-37).

This molecular framework enables oncologists to predict disease progression more accurately and tailor treatment strategies based on subtype-specific characteristics. It also facilitates the design of clinical trials by selecting patient populations most likely to benefit from targeted therapies, ultimately moving GC management toward a more personalized and precision medicine approach.

A critical comparative analysis of TCGA and ACRG molecular classifications: Clinical utility, geographic applicability and boundary discordance

Geographically stratified prognostic and predictive performance. The TCGA classification derives primarily from Western (North American and European) cohorts, while ACRG was developed from a Korean multi-institutional

Table I. Molecular classification of gastric cancer: TCGA vs. ACRG.

Feature	TCGA classification	ACRG classification
Population-specific basis	Western populations	East Asian populations
Detection methodology	Multi-omics profiling (whole-exome sequencing, RNA sequencing, DNA methylation array)	Immunohistochemical and *in situ* hybridization assays (Epstein-Barr virus-encoded RNA, MSI, p53, E-cadherin)
Subtype distribution	EBV, MSI, GS, CIN	MSI, MSS/EMT, MSS/TP53+, MSS/TP53-
Subtype with the poorest prognosis	GS (but CIN has high heterogeneity)	MSS/EMT (well-defined)
Immunotherapy eligibility criteria	EBV and MSI status are predictive of favorable therapeutic response	MSI-H status predicts favorable therapeutic response, whereas MSS/EMT status is associated with limited treatment efficacy

TCGA, The Cancer Genome Atlas; ACRG, Asian Cancer Research Group; MSI, microsatellite instability; MSS, microsatellite stable; EMT, epithelial-mesenchymal transition; EBV, Epstein-Barr virus; CIN, chromosomal instability; GS, genomically stable.

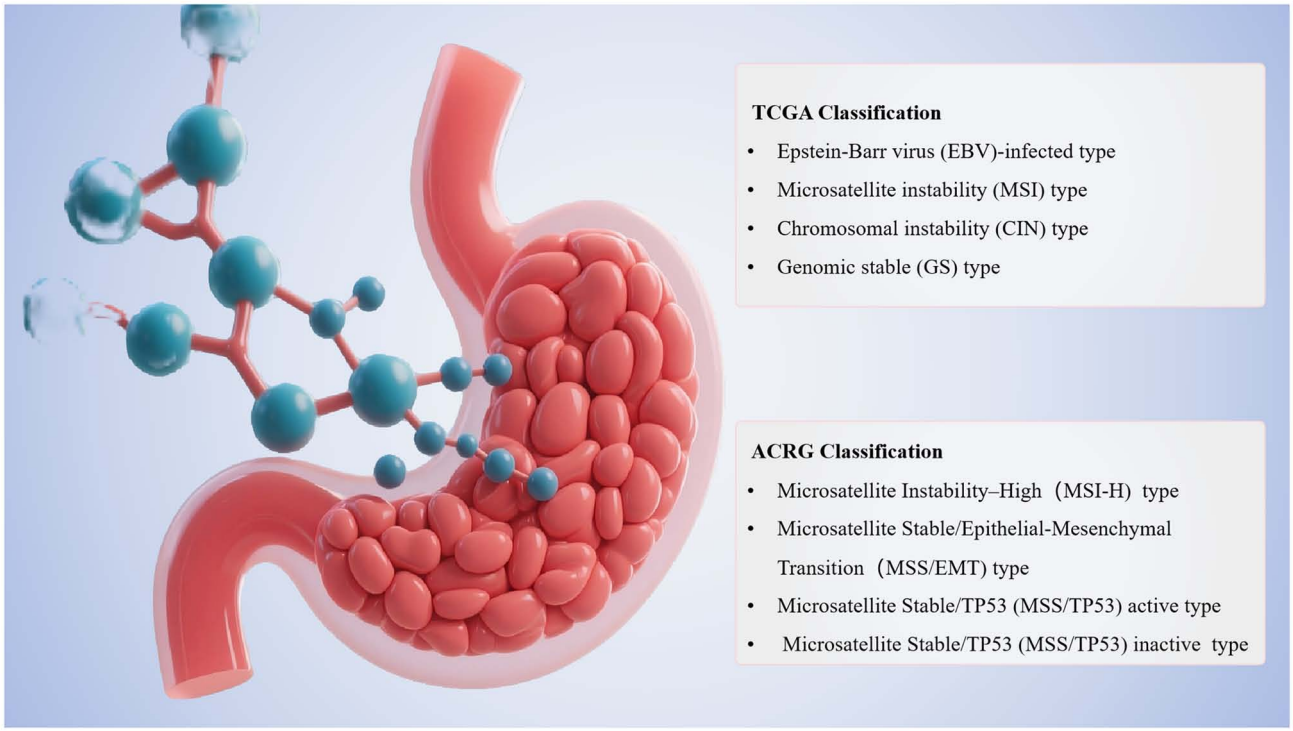

Figure 1. Classification of gastric cancer has transitioned from traditional pathological morphology to molecular profiling. Among the most influential frameworks are the molecular classification systems proposed by TCGA and the ACRG, which represent landmark advancements in the field. TCGA, The Cancer Genome Atlas; ACRG, Asian Cancer Research Group.

cohort, reflecting distinct epidemiological, histopathological and molecular profiles (30). This geographic divergence is corroborated by Korea's K-MASTER program, which confirmed substantial intercontinental differences in genomic events and pathway alterations, underscoring the need for region-specific molecular classifications (38). Consequently, neither system is universally transferable; clinical utility is context-dependent.

In East Asian populations, ACRG offers superior prognostic stratification: The MSS/EMT subtype is strongly linked to aggressive features-including early lymph node metastasis, high peritoneal dissemination rate, shortened overall survival (OS) and elevated postoperative recurrence-making it a clinically actionable marker for adjuvant intensification or trial enrollment (38,39). Among ACRG's four subtypes, EMT carries the worst prognosis and is associated with younger age at diagnosis and Lauren diffuse-type histology (40). By contrast, the TCGA CIN subtype is more prevalent in East Asia, but shows marked heterogeneity across cohorts in genomic instability metrics (for example, allelic deletion fraction and aneuploidy score) and stromal composition (41).

Table II. Response rates to immunotherapy across molecular subtypes of tumors in The Cancer Genome Atlas.

Molecular subtype	ICI response rate	Key data notes
MSI Subtype	ORR was ~30-50% with pembrolizumab treatment. In the KEYNOTE-061 and KEYNOTE-062 trials, patients with MSI-high tumors exhibited significantly improved survival outcomes compared with those with microsatellite stable tumors. Furthermore, a higher IO score was significantly associated with objective response to ICIs (P=0.01) (111)	High tumor mutational burden and an activated immune microenvironment exhibit heightened sensitivity to ICIs
EBV Subtype	ORR to anti-PD-1 therapy was ~-25-35% in EBV-positive GC. All EBV-positive GCs exhibited PD-L1 CPS ≥10, and 57% achieved CPS >50. Moreover, the Consensus Molecular Subtype classification demonstrated predictive value for response to anti-PD-1 treatment (46)	Tumors characterized by abundant lymphocyte infiltration and high expression of PD-L1 and other ICIs
Chromosomal instability subtype	Low ORR: <10% (182)	Tumors with a relatively 'cold' immune microenvironment-characterized by sparse lymphocyte infiltration, low PD-L1 expression, and minimal immune cell activation-demonstrate limited efficacy of ICIs
Genomically stable subtype	Unfavorable ICI response rate (worst prognosis)	Suboptimal ICI response rate, associated with the poorest prognosis

ORR, objective response rate; CPS, combined positive score; ICI, immune checkpoint inhibitor; MSI, microsatellite instability; EBV, Epstein-Barr virus; GC, gastric cancer.

In western populations, TCGA-defined EBV$^+$ and MSI-H GCs consistently predict superior OS and high objective response rates (ORRs) to PD-1 inhibitors. A meta-analysis of 1,247 EBV-associated gastric carcinomas reported Programmed Cell Death Ligand 1 (PD-L1) combined positive score (CPS) >1 in 84.5% and CPS >5 in 52.1% of cases (42). In a dedicated cohort of molecularly confirmed EBV$^+$ GCs, all cases exhibited a PD-L1 CPS of 10 or higher. Furthermore, in surgically resected gastric carcinomas with lymphoid stroma (GCLS), PD-L1 CPS ≥10 was observed in 55.3% of EBV$^+$ GCLS cases (43,44).

These data providing direct histopathological evidence of exceptionally strong, homogeneous PD-L1 upregulation driven by latent EBV infection and associated epigenetic reprogramming. Mechanistically, these subtypes are defined by three interlinked features: Elevated tumor mutational burden (TMB), constitutive PD-L1 overexpression and dense infiltration of cytotoxic CD8$^+$ T cells-collectively establishing a highly immunoreactive tumor microenvironment (TME) that explains their enhanced immunotherapy responsiveness (45-47). By contrast, ACRG has undergone minimal prospective validation outside Asia.

Key drivers of this geographic divergence include: i) lower EBV$^+$ prevalence (<5% vs. 8-10%) and lower MSI-H frequency (10-15% vs. 20-25%) in East Asia-consistent with TCGA's reported rates of 8-9% EBV$^+$ and 21-22% MSI-H GCs (48); ii) higher proportions of Lauren diffuse-type and genomically stable tumors in East Asia-features directly captured by ACRG's EMT-centric framework (28); and iii) greater enrichment of CIN and receptor tyrosine kinase (RTK) alterations in western tumors-aligning with TCGA's classification, where CIN accounts for ~50% of GCs (49).

Taxonomic discordance at classification boundaries. Substantial disagreement arises beyond the well-defined MSI-H and EBV$^+$ categories, particularly in biologically ambiguous 'intermediate' groups.

MSI-EBV co-positivity: Though rare (1-2%), dual-positive tumors constitute a distinct immunobiological entity driven by synergistic EBV antigen presentation (for example, LMP1-mediated NF-κB activation) and hypermutation-induced neoantigen load (50). TCGA assigns them to either EBV$^+$ or MSI-H based on dominant signal; ACRG defaults to MSI-excluding EBV-specific immune features from analysis. This yields divergent prognostic interpretation: TCGA links dual positivity with best survival; ACRG merges these cases with conventional MSI-H, blunting risk discrimination (31,39).

MSI-like vs. MSS/EMT: ACRG's MSS/EMT group includes MSS tumors with elevated TMB or immune gene signatures-increasingly termed MSI-like or immune-hot MSS (51). In TCGA, such cases are inconsistently classified as CIN or GS, obscuring shared therapeutic vulnerabilities (for example, oxaliplatin sensitivity, responsiveness to emerging

Table III. A critical assessment of clinical utility and translational limitations: TCGA vs. ACRG.

Dimension	TCGA classification	ACRG classification
Operability	Requires multi-omics profiling-including whole-exome sequencing, RNA sequencing and DNA methylation array analysis-which imposes substantial cost, technical complexity, and infrastructure demands that exceed the capabilities of most routine pathology laboratories.	Based on widely available, clinically validated assays-including EBER in situ hybridization, MSI testing, and IHC for p53 and E-cadherin-this classification is readily implementable in most hospitals.
Prognostic discriminative ability	The four molecular subtypes exhibit distinct prognostic gradients-EBV and MSI subtypes confer the most favorable outcomes, the CIN subtype shows intermediate prognosis, and the GS subtype is associated with the poorest survival-though substantial interpatient heterogeneity persists within the CIN group.	The MSS/EMT subtype is associated with the poorest prognosis, whereas the MSI subtype exhibits the most favorable outcomes-yielding asimplified, clinically actionable stratification.
Predictive value for treatment response	It offers well-established biomarkers to guide immunotherapy (for example, MSI-H and EBV positivity) and identifies recurrently altered driver genes with direct implications for targeted therapy.	It is supported by more direct experimental evidence regarding chemotherapy sensitivity (for example, oxaliplatin resistance in MSS/EMT tumors),whereas its predictive value for immunotherapy response remains less established.
Limitations in translational applicability	It requires fresh-frozen tissue specimens and is therefore not applicable to the vast majority of formalin-fixed paraffin-embedded archival samples.	Interpretation ofcertain IHC markers-particularly those exhibiting hetero-geneousexpression, such as E-cadherin-suffers from limited inter-observer reproducibility; moreover, conventional IHC panels fail to capture molecularly defined rare subtypes, including tumors harboring pathogenic POLE mutations.

MSI, microsatellite instability; EMT, epithelial-mesenchymal transition; MSS, microsatellite stable; IHC, immunohistochemistry; TCGA, The Cancer Genome Atlas; ACRG, Asian Cancer Research Group; EBV, Epstein-Barr virus; CIN, chromosomal instability.

immunomodulators) (52). This misalignment impedes cross-study comparison and biomarker harmonization.

Unresolved gray zones: No consensus defines 'true' MSI-H (requiring both PCR/NGS confirmation and MMR protein loss) vs. 'MSI-like' states (POLE-mutant, MSH6-low, epigenetically silenced MMR). Similarly, EBV-negative GCs with PD-L1$^+$/CD8$^+$ rich microenvironments, biologically primed for immunotherapy due to CD8$^+$ T-cell-driven antitumor immunity, lack formal classification in TCGA subtypes (53). This creates direct clinical uncertainty, if an MSS/EMT patient with high CD8$^+$ tumor-infiltrating lymphocytes (TIL) density and PD-L1 CPS ≥10 should receive first-line immunotherapy despite negative MSI/EBV status. While single-agent PD-1 blockade shows <5% response in MSS solid tumors, chemo-immunotherapy combinations demonstrate clinically meaningful benefit. Critically, the strong immunotherapy responses observed in EBV$^+$ and MSI-H GCs-both associated with high PD-L1-further complicate treatment decisions for borderline phenotypes.

In summary, TCGA and ACRG are complementary-not competing-frameworks. TCGA offers a discovery-oriented, mechanism-rich ontology ideal for target identification, pathway modeling and biomarker development. ACRG provides a pathology-integrated, treatment-responsive schema optimized for real-world prognostication and chemotherapy guidance-especially in East Asia and resource-limited settings (Table III).

Real-world barriers to clinical implementation of GC molecular subtyping. Despite their well-established biological and prognostic relevance, the TCGA and ACRG molecular subtyping frameworks remain underutilized in routine clinical practice-primarily owing to systemic implementation barriers that vary substantially across high-, middle-, and low-resource healthcare settings.

Cost and accessibility. TCGA subtyping necessitates multimodal molecular profiling-including whole-exome sequencing (WES), RNA sequencing (RNA-seq) and DNA methylation arrays-entailing per-sample costs of ~3,000-5,000 $ and requiring robust, high-throughput bioinformatics infrastructure (54,55). Even in high-income countries, adoption is constrained by limited reimbursement coverage and institutional budgetary restrictions; in middle- and low-income countries, its application remains largely restricted to academic research centers. By contrast, ACRG subtyping

leverages routinely available clinical assays-EBER *in situ* hybridization, MSI testing via PCR or immunohistochemistry (IHC), and IHC for p53 and E-cadherin-with estimated per-patient costs of 200-500 $ (20). While technically feasible in most tertiary hospitals, its clinical utility is compromised by substantial inter-observer variability in IHC interpretation and the frequent absence of analytically validated antibodies, both of which directly impair assay analytical validity and interlaboratory reproducibility.

Tissue limitations and preanalytical variability. Both frameworks were developed using surgical resection specimens, abundant and spatially representative. Yet >80% of patients with advanced GC undergo endoscopic biopsy, yielding scant tissue (<5 mm^2), often contaminated or insufficient for WES/RNA-seq (>100 ng high-quality DNA/RNA) (56). For ACRG, E-cadherin IHC is especially prone to false negatives in biopsies due to superficial sampling, suboptimal fixation (<6 h in 10% neutral-buffered formalin), or processing delays (57). Preanalytical practices vary widely, fixation time, decalcification, embedding, section thickness, storage, all directly affecting antigen preservation, RNA integrity (RIN >7) and DNA quality (58). This variability erodes cross-center comparability.

Analytical standardization and reproducibility. No FDA- or CE-IVD-certified kits exist for GC-specific TCGA subtyping; validated reference standards are unavailable. For ACRG, consensus criteria for p53 (≥80% nuclear vs. complete loss vs. cytoplasmic) and E-cadherin (≥10% membranous continuity vs. fragmented/absent) are lacking, leading to inconsistent classification even among experts (κ=0.4-0.68 for p53 IHC) (59). Few labs participate in external quality assurance (EQA) programs (for example, CAP, UK NEQAS). Without routine EQA, undetected assay drift, batch effects, or interpretive bias may silently enter clinical reporting.

Intratumoral heterogeneity and sampling bias. Spatial heterogeneity is common: MSI status varies across tumor quadrants; EBV^+ tumors favor fundus/body over antrum; HER2 amplification is often focal; p53 aberrations are patchy (60,61). A single biopsy, for example from ulcer margin or antrum, may misrepresent the dominant subtype and guide incorrect therapy.

Subtypes evolve under treatment: Chemotherapy or immune checkpoint inhibition can drive clonal shifts; for example, mismatch repair (MMR) protein loss or Janus kinases 1 and 2 (JAK1/2) and beta2-microglobulin (B2M) mutations converting MSI-H to 'immune-resistant' MSS-like states (62). Relying solely on archival biopsies misses such dynamics and delays therapeutic adaptation. Therapeutically relevant genomic alterations-including MET amplification, PIK3CA mutations, and fibroblast growth factor receptor 2 (FGFR2) fusions-are frequently subclonal and exhibit spatial heterogeneity (63). Detecting them requires multi-region sequencing or circulating tumor DNA (ctDNA) assays-not captured by standard single-biopsy subtyping.

In summary, clinical utility depends not on biological granularity, but on operational robustness across real-world constraints. Sustainable implementation requires a tiered strategy: Deploying comprehensive TCGA-integrated models where resources allow, while optimizing streamlined ACRG-based algorithms for broader use-both anchored to dynamic, biopsy-informed molecular monitoring. Without addressing cost, tissue logistics, analytical rigor and tumor evolution, even the most elegant subtyping framework will stay in the lab.

3. Precision therapy based on molecular subtypes

The treatment of GC has undergone a major transformation with the integration of molecular profiling into clinical practice (64). As our understanding of the disease's biological complexity deepens, precision therapy-tailored to the specific molecular characteristics of each tumor-has emerged as a powerful strategy for improving patient outcomes (65,66). This approach allows oncologists to select therapies that are more likely to be effective based on the presence of defined biomarkers, thereby avoiding unnecessary treatments and reducing toxicity. An overview of key molecular subtypes in GC and their corresponding targeted and immune-based therapeutic strategies is presented below.

HER2-positive GC. HER2 overexpression or gene amplification is observed in ~15-20% of GCs and is associated with more aggressive tumor behavior, including increased proliferation, invasion, and reduced OS when left untreated (67). HER2-positive GCs often exhibit a distinct molecular profile that differentiates them from other subtypes, making this biomarker not only prognostic but also predictive for targeted therapy (68). The identification of HER2 as a druggable target has significantly transformed the treatment paradigm for this subgroup of patients, introducing a new era of precision oncology in GC management (69).

Mechanisms of acquired resistance to trastuzumab. The landmark ToGA (Trastuzumab for GC) trial was the first to demonstrate a clinically meaningful improvement in OS by adding trastuzumab, a recombinant humanized monoclonal antibody targeting the extracellular domain of HER2, to standard first-line platinum-based chemotherapy in patients with HER2-positive advanced gastric or gastroesophageal junction (GEJ) cancer (70). This pivotal study led to the global approval of trastuzumab in combination with chemotherapy as the first-line treatment for eligible patients whose tumors test positive for HER2 overexpression or gene amplification (71). The trial established a benchmark for integrating targeted agents into the systemic treatment of GC (72).

Although trastuzumab plus chemotherapy is established as the first-line standard of care for HER2-positive advanced GC, the majority of patients develop acquired resistance within 6-12 months (73,74). Key molecular mechanisms underpinning this resistance include.

Hyperactivation of the phosphatidyl inositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway: Activating mutations in PIK3CA (gain-of-function) or inactivating alterations in phosphatase and tensin homolog (PTEN) (loss-of-function) occur in 30-50% of trastuzumab-resistant gastric tumors. Such aberrations sustain downstream pro-survival and proliferative signaling via AKT and mTOR independent of upstream HER2 activity. Preclinical evidence demonstrates that co-targeting mTOR can resensitize resistant models to trastuzumab.

Intratumoral HER2 heterogeneity: HER2 gene amplification is frequently heterogeneous across GC lesions, with coexisting HER2-amplified and non-amplified subclones observed in 20-40% of cases (75). Trastuzumab exerts selective pressure against HER2-high subpopulations, thereby enabling outgrowth of pre-existing or emergent HER2-low/negative clones-leading to clinically detectable resistance (76). This clonal evolution accounts for the frequent loss of HER2 positivity upon post-progression re-biopsy.

Activation of compensatory RTK pathways: Upregulation or ligand-driven activation of alternative RTKs, including epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 3 (HER3) and mesenchymal to epithelial transition (MET), can reactivate downstream effectors (notably PI3K/AKT) despite effective HER2 blockade (77,78). Critically, HER3 serves as a potent dimerization partner and direct recruiter of PI3K; thus, persistent HER3 expression or phosphorylation can maintain pathway flux even after disruption of the HER2-HER3 heterodimer by trastuzumab (79).

Strategies of novel anti-HER2 agents to overcome classical resistance mechanisms. Dual HER2 blockade: Pertuzumab and trastuzumab act synergistically, trastuzumab primarily inhibits HER2 homodimerization and induces antibody-dependent cellular cytotoxicity (ADCC), whereas pertuzumab sterically blocks HER2 heterodimerization (especially with HER3) (80). Together, they enhance receptor internalization, ubiquitination and lysosomal degradation, thereby delaying the emergence of resistant subclones driven by HER2 heterogeneity (81). While dual blockade shows limited efficacy against resistance mediated by strong bypass RTK activation (for example, MET amplification), it remains mechanistically rational for suppressing HER2-dependent escape.

Antibody-drug conjugates (ADCs): ADCs such as trastuzumab deruxtecan (T-DXd and DS-8201) and disitamab vedotin (RC48) operate independently of intact HER2 signaling transduction (82). Upon binding to surface HER2, these agents undergo efficient internalization and lysosomal trafficking, releasing membrane-permeable cytotoxic payloads (83). Crucially, their antitumor activity is preserved in settings of PI3K/AKT/mTOR hyperactivation, partial HER2 downregulation (provided minimal target expression remains), and intratumoral heterogeneity-features that commonly undermine conventional HER2-targeted antibodies (84). Consistent with this, the DESTINY-Gastric01 and DESTINY-Gastric02 trials demonstrated ORRs of 40.5 and 46.4%, respectively, in heavily pretreated, trastuzumab-refractory HER2-positive GC, robustly validating the ability of T-DXd to circumvent canonical resistance mechanisms (85,86).

There is also increasing interest in combining HER2-targeted agents with ICIs, aiming to harness both adaptive immunity and targeted signaling inhibition to achieve deeper and more durable responses (87). These developments reflect a broader shift toward personalized, mechanism-driven treatment approaches aimed at improving long-term outcomes for patients with HER2-positive GC.

Claudin 18.2-targeted approaches. Claudin 18.2 is a transmembrane tight junction protein that plays a crucial role in maintaining the structural integrity and polarity of epithelial cells in the gastric mucosa under normal physiological conditions (88). Importantly, Claudin 18.2 is largely absent from most normal tissues outside the gastric epithelium but frequently present in gastric tumors, which makes it a viable therapeutic target (89). Clinically, CLDN18.2 loss or downregulation correlates with increased invasiveness and metastasis, possibly via EMT activation (90). The recurrent CLDN18, ARHGAP26/6 fusion, found in 3-15% of GCs, especially diffuse-type and early-onset cases, impairs adhesion and anoikis, promoting aggressive behavior (91). CLDN18.2's therapeutic value lies in three features: i) Highly restricted expression-low baseline in normal gastric epithelium, but strong, uniform overexpression in 70-80% of gastric adenocarcinomas and ~50% of pancreatic ductal adenocarcinomas; ii) minimal overlap with HER2 or PD-L1, enabling treatment for patients resistant to or ineligible for existing immunotherapies or HER2-targeted agents; and iii) structural suitability, its two extracellular domains offer distinct epitopes for monoclonal antibodies, ADCs, bispecific T-cell engagers, and chimeric antigen receptor T-Cell immunotherapy (CAR-T) cells (92-94).

Two pivotal Phase III trials-SPOTLIGHT and GLOW-established zolbetuximab, a chimeric immunoglobulin G1 (IgG1) anti-CLDN18.2 monoclonal antibody, as the first approved targeted therapy for CLDN18.2-positive, HER2-negative advanced gastric or gastroesophageal junction adenocarcinoma (GC/GEJAC) (95,96). In SPOTLIGHT, zolbetuximab + mFOLFOX6 improved median progression-free survival (PFS) [8.7→10.6 months; Hazard Ratio (HR)=0.75] and OS (15.5→18.2 months; HR=0.75) vs. placebo + mFOLFOX6 (95). In GLOW, zolbetuximab + CAPOX improved median PFS (6.8→8.2 months; HR=0.69) and OS (12.2→14.4 months; HR=0.77) (96). Both trials confirmed clinically meaningful survival benefits in biomarker-selected patients. Higher CLDN18.2 expression (by IHC) correlated with greater benefit, validating target biology and underscoring the need for standardized companion diagnostics (95,96). Based on these results, the FDA granted full approval on October 18, 2024, and China's NMPA followed in January 2025-making zolbetuximab the world's first regulatory-approved CLDN18.2-targeted therapy (97).

Beyond antibodies, CLDN18.2-directed ADCs deliver cytotoxic payloads [for example, exatecan or monomethyl auristatin E (MMAE)] directly into tumor cells via receptor internalization-bypassing immune-effector mechanisms and retaining activity despite low/heterogeneous CLDN18.2 expression or prior immunotherapy resistance (98). IBI343 (arcotatug tavatecan), an Fc-silenced exatecan-conjugated ADC, is being evaluated in a global Phase III trial (G-HOPE-001; NCT06233127) enrolling 450 previously treated patients with GC/GEJAC with CLDN18.2 IHC ≥2+ in ≥40% of tumor cells; co-primary endpoints are BICR-assessed PFS and OS (99). LM-302 (tecotabart vedotin), an MMAE-conjugated ADC, achieved a 32.7% ORR and 4.9-month median PFS in a Phase I/II study (n=52), and is the first CLDN18.2 ADC to complete Phase III enrollment (100).

Claudin 18.2-specific CAR-T therapy represents another promising frontier in adoptive cellular immunotherapy

for GC (101). CT041, one of the leading investigational CAR-T candidates targeting Claudin 18.2, has demonstrated encouraging antitumor activity in early-phase clinical trials, particularly in heavily pretreated patients with metastatic disease who have limited therapeutic options (102). Phase II results (CT041-ST-01) revealed that satri-cel significantly improved median PFS (1.77→3.25 months; HR=0.37; P<0.0001) and OS (7.92 vs. 5.49 months; HR=0.69; P=0.0416) (102). CRS occurred in 95% of patients, mostly Grade 1-2 and fully reversible with standard care (102). Nevertheless, several challenges remain before CAR-T therapy can be widely adopted in the treatment of GC. Further research is needed to refine patient selection criteria, optimize lymphodepletion regimens, determine ideal dosing schedules, and assess long-term safety and durability of responses.

Additionally, emerging resistance mechanisms warrant careful consideration: i) CLDN18.2 heterogeneity: Intratumoral variability-such as heterogeneous membranous staining or focal loss-enables zolbetuximab to eliminate CLDN18.2-high subclones while sparing CLDN18.2-low/negative populations, which then expand and drive progression (103); ii) antigen downregulation: Prolonged zolbetuximab binding induces CLDN18.2 internalization, lysosomal degradation, or transcriptional suppression-reducing surface antigen density and impairing antibody binding and effector function (104); iii) impaired complement-dependent cytotoxicity (CDC)/ADCC: Tumor cells often overexpress CD55 and CD59, complement inhibitors that block early activation and membrane attack complex formation, attenuating CDC. ADCC efficacy depends on FcγRIIIa (CD16a) affinity; the common V158F polymorphism in Fc Gamma Receptor IIIa reduces IgG1 binding and natural killer cell cytotoxicity, potentially limiting response (105); iv) distinct ADC mechanism: CLDN18.2-directed ADCs (for example, CMG901) use the target primarily for internalization-not immune activation. After binding and internalization, they release membrane-permeable payloads [(for example, MMAE) into the cytosol, triggering irreversible mitotic arrest and apoptosis independent of immune cells or high antigen expression (106). This preserves activity against heterogeneous, low-antigen, or complement/FcγR-defective tumors-supporting their use after zolbetuximab failure.

ICIs: A deep dive beyond MSI/dMMR. MSI-H/dMMR GC is a distinct molecular subtype-accounting for 5-10% of cases-defined by defective DNA MMR, leading to genome-wide microsatellite errors, high TMB and abundant neoantigens (107). This biology confers exceptional sensitivity to ICIs, which restore antitumor T-cell activity by blocking PD-1/PD-L1 or cytotoxic T lymphocyte-associated antigen-4 (108,109). As a result, ICIs yield markedly higher response rates in MSI-H/dMMR vs. MSS GC, where monotherapy efficacy is limited (110). Pembrolizumab demonstrates durable responses (>50% ORR in KEYNOTE-059; sustained benefit in KEYNOTE-061's MSI-H cohort) and is FDA-approved for all MSI-H/dMMR solid tumors (111). Nivolumab also shows clinical benefit, alone or combined, with nivolumab + ipilimumab + chemotherapy significantly improving PFS and OS specifically in MSI-H/dMMR patients in CheckMate-649 (112).

Despite these promising results, not all patients with MSI-H/dMMR GC respond to ICIs. Some exhibit primary resistance, meaning they do not respond to treatment from the outset, while others develop acquired resistance after initially benefiting from therapy (113,114).

The primary resistance mechanism mainly include: i) Immune-excluded tumors: $CD8^+$ T cells are absent from tumor epithelium and restricted to stroma. Drivers include tumor-derived transforming growth factor beta (TGF-β) (activates fibroblasts, deposits collagen), low C-X-C motif chemokine ligand 9/10 (CXCL9/CXCL10) (impairs T-cell trafficking), and hyperactive Focal Adhesion Kinase (FAK) signaling (remodels stroma immuno-suppressively) (115); ii) immune-desert tumors: Global lack of T-cell priming, recruitment and infiltration. Linked to intrinsic defects, for example downregulated MHC-I-and impaired dendritic cell function or recruitment (116); ii) Gut microbiota: Responders consistently show enrichment of *Akkermansia muciniphila*, *Bifidobacterium spp*. and *Ruminococcus spp*. Their metabolites (for example, short-chain fatty acids) enhance dendritic cell maturation, Th1 polarization and intratumoral $CD8^+$ T-cell accumulation (117). By contrast, *Helicobacter pylori* infection, prolonged antibiotics (for example, during eradication), or chronic proton pump inhibitors use drive gastric dysbiosis-reducing diversity and impairing ICI response (118).

Despite initial responses, durable benefit from ICIs remains rare in GC; most patients progress after an early response. Validated acquired resistance mechanisms include: i) B2M loss-of-function mutations: Truncating or frameshift mutations in B2M-enriched in MSI-H tumors due to DNA repair deficiency, abolish surface Major Histocompatibility Complex Class I (MHC-I) expression, making tumor cells invisible to $CD8^+$ T cells (119); ii) interferon gamma (IFN-γ) pathway disruption. JAK1/JAK2 inactivating mutations block downstream IFN-γ signaling, preventing upregulation of MHC-I, PD-L1 and antiproliferative genes-enabling immune escape (120). Signal Transducer and Activator of Transcription 1 (STAT1) or upstream regulator loss-of-function similarly abrogates IFN-γ responsiveness. Longitudinal sequencing confirms clonal expansion of JAK1/2-mutant cells in progressing lesions (121); ii) Alternative checkpoint upregulation: After PD-1/PD-L1 blockade, tumors or TILs frequently overexpress Lymphocyte Activation Gene 3, T cell Immunoglobulin and ITIM domain, V-domain Immunoglobulin-containing Suppressor of T cell Activation, or T cell Immunoglobulin and Mucin domain-containing protein 3, re-establishing suppression via parallel inhibitory pathways (115).

Clinical implications: Toward multidimensional biomarker integration. These mechanistic insights clarify why MSI-H status or PD-L1 expression alone lacks sufficient predictive power: i) MSI-H-refractory cases: While high TMB generates abundant neoantigens, co-occurring B2M or JAK1/2 mutations, frequently arising *de novo* under ICI selection pressure, functionally uncouple antigen presentation from T-cell recognition or abolish IFN-γ-mediated immune amplification (119); ii) $PD\text{-}L1^+$ but T-cell-excluded/desert tumors: PD-L1 expression may reflect constitutive oncogenic signaling (for example, MYC or EGFR pathway activation) rather than adaptive, IFN-γ-driven upregulation. In such contexts,

PD-1/PD-L1 blockade removes an inhibitory signal ('brake') without providing the requisite effector T-cell infiltration ('accelerator'), resulting in therapeutic futility (122).

Collectively, these findings underscore that precision immuno-oncology requires integration of spatial immune contexture (for example, $CD8^+$ T-cell localization), functional antigen presentation integrity (for example, B2M/JAK1/2 genotyping), and host-microbiome interactions, not merely static biomarkers such as MSI or PD-L1 (120,123). Future predictive models must therefore be multidimensional, dynamic, and biologically grounded.

Clinical phenomena unique to immune checkpoint inhibition in MSI-H GC: immune-related adverse events (irAEs), pseudoprogression and hyperprogression. Although MSI-H GC exhibits markedly higher ORRs to ICIs compared with MSS disease, its clinical management is complicated by three distinct, biologically grounded phenomena, irAEs, pseudoprogression and hyperprogression, that demand vigilant recognition and evidence-informed intervention.

High TMB and abundant neoantigens in MSI-H tumors drive robust T-cell activation, explaining both strong antitumor responses and increased risk of systemic irAEs, including colitis, hepatitis, pneumonitis, thyroiditis, dermatitis, and rarely myocarditis or hypophysitis (124). Grade ≥3 immune-mediated colitis occurs in 15-20% of patients and may be delayed-appearing >6 months after ICI initiation (125). Early patient education, proactive monitoring (for example, stool calprotectin, liver function tests, thyroid stimulating hormone), and rapid multidisciplinary input are critical. Management follows American Society of Clinical Oncology/European Society for Medical Oncology guidelines: Corticosteroids for moderate-to-severe irAEs; permanent ICI discontinuation for recurrent or steroid-refractory grade ≥3 events (126).

Pseudoprogression, transient lesion enlargement or new lesions followed by regression, is observed in 5-10% of ICI-treated solid tumors, including MSI-H GC (127). It reflects inflammation, necrosis, or edema, not true progression. Misdiagnosis risks stopping effective therapy prematurely. Diagnosis requires integrated assessment: i) Confirmatory imaging at 4-8 weeks; ii) ^{18}F-FDG PET-CT (declining SUVmax precedes shrinkage); iii) dynamic ctDNA (sustained drop in variant allele frequency predicts durable response). Per iRECIST, asymptomatic patients with ECOG 0-1 should continue ICI for two more cycles before reassessment (128).

Hyperprogression, ≥2-fold increase in tumor growth rate (TGR) after ICI initiation vs. pre-treatment kinetics, is rare but catastrophic, reported in 5-10% of ICI recipients (129). Proposed mechanisms include aberrant Treg expansion, FcγR-driven pro-tumor macrophage polarization, and paradoxical PD-L1 upregulation post-PD-1 blockade (130). While case reports exist in MSI-H GC, population-level incidence and predictive biomarkers remain undefined (131). Risk factors include age >65 years, ≥3 metastatic sites, and MDM2/MDM4 amplification (rare in GC) (132). Confirmation requires quantitative TGR calculation using volumetric or RECIST-based longitudinal measurements (133). Upon diagnosis, ICI should be discontinued immediately and salvage therapy should be initiated, for example platinum-based chemotherapy or ADCs-without delay (134).

To optimize outcomes, ICI initiation in MSI-H GC should be preceded by baseline contrast-enhanced CT/MRI and quantitative tumor growth kinetics modeling. Surveillance imaging should occur every 6-8 weeks. When radiographic progression is suspected, particularly in the absence of symptoms or clinical deterioration, integrated evaluation incorporating ctDNA dynamics, metabolic imaging, and clinical context is mandatory. This approach prevents erroneous discontinuation due to pseudoprogression while enabling early detection and mitigation of hyperprogression, thereby preserving therapeutic opportunity and patient safety (127,135).

Emerging targets. Beyond well-established therapeutic targets in GC, such as HER2 and Claudin 18.2, researchers are actively investigating novel molecular alterations that may provide new opportunities for targeted therapy (136). These advancements have been driven by innovations in genomic profiling technologies and a more refined understanding of the signaling pathways involved in gastric tumorigenesis (137). Among these emerging targets, FGFR2b has attracted considerable attention due to its role in promoting tumor cell proliferation and survival in specific subtypes of GC (138). In GC, FGFR2b overexpression can result from gene amplification or aberrant splicing, leading to constitutive activation of key downstream signaling pathways such as mitogen-activated protein kinase (MAPK) and PI3K/AKT (139). Bemarituzumab, a first-in-class glycoengineered monoclonal antibody targeting FGFR2b, has demonstrated encouraging antitumor activity in early-phase clinical trials (139). The FIGHT trial, a randomized phase II/III study, is currently evaluating bemarituzumab in combination with standard first-line chemotherapy (fluoropyrimidine and oxaliplatin) in patients with FGFR2b-positive advanced gastric or GEJ cancer (140). Preliminary results from the phase II component indicate statistically significant improvements in both progression-free and OS compared with chemotherapy alone (141).

Another actionable molecular alteration under investigation is MET amplification, which occurs in ~2-5% of GCs (142). MET encodes the hepatocyte growth factor (HGF) receptor, a tyrosine kinase receptor implicated in tumor cell motility, invasion and resistance to apoptosis (143). MET signaling also contributes to resistance mechanisms against other targeted therapies, particularly HER2 inhibitors, highlighting its role in disease progression and therapeutic failure (144). Selective MET inhibitors such as capmatinib and tepotinib are being evaluated in phase II clinical trials, primarily in patients whose tumors have progressed after standard therapies (145). Early data demonstrate notable antitumor activity, including objective responses in heavily pretreated populations (146). These results underscore the potential of MET inhibition as part of a precision medicine strategy for a small but clinically relevant subgroup of patients with GC (Fig. 2).

Impact of non-immune factors in the TME on precision therapy

Cancer-associated fibroblasts and metabolic reprogramming. The TME not only contains immune cells but is also rich in non-immune components such as cancer-associated fibroblasts (CAFs), extracellular matrix (ECM) and metabolic products (147). These factors play a crucial role in the precise

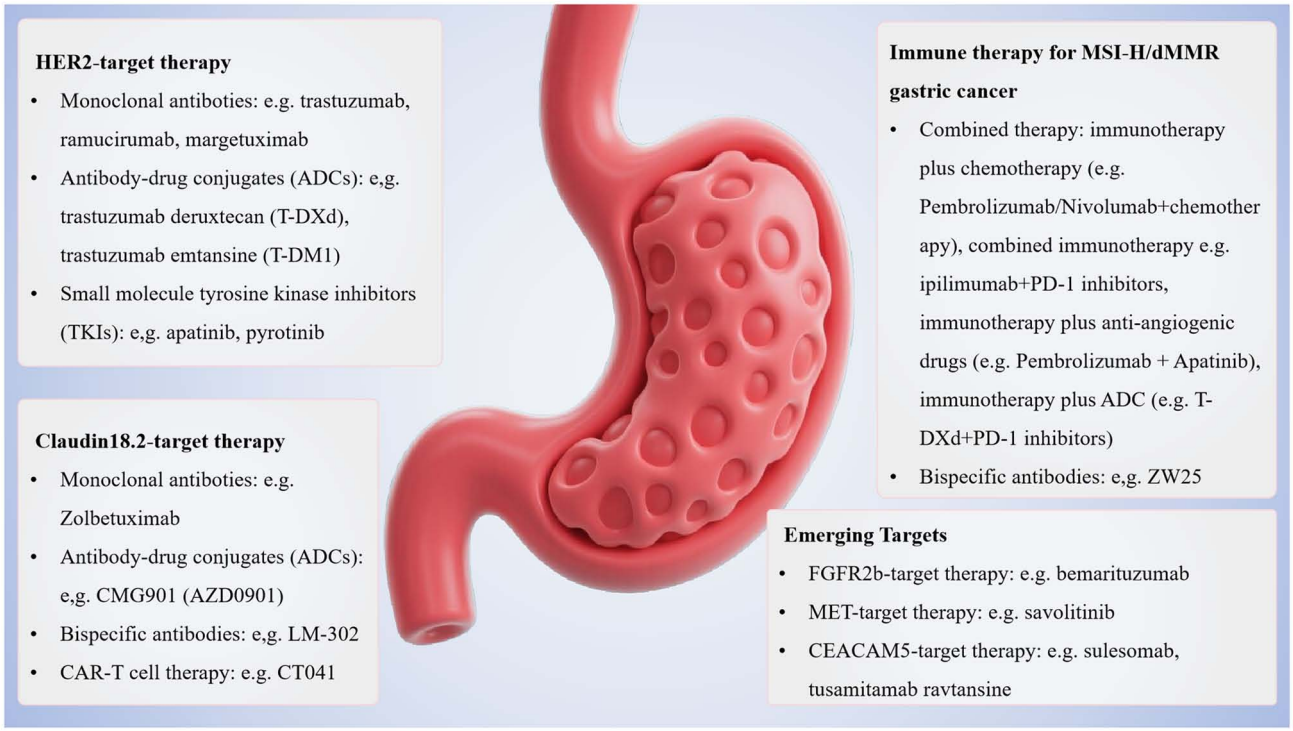

Figure 2. Precision medicine for gastric cancer is expected to advance toward a strategy of multi-target co-targeting and multimodal therapeutic integration. Established molecular targets such as HER2, CLDN18.2 and MSI/dMMR, along with emerging targets including MET, FGFR2, and KRAS G12C, will collectively contribute to the development of a diversified targeted therapy landscape, enabling more personalized and precise treatment approaches for a broader population of gastric cancer patients. MSI, microsatellite instability; MMR, mismatch repair.

treatment of GC, influencing drug penetration, treatment response and the occurrence of drug resistance (148).

Mechanism of action of CAFs. CAFs are the most abundant stromal cells in the TME of GC. They significantly interfere with the efficacy of targeted therapy and chemotherapy through physical barriers, paracrine signals and ECM remodeling (114).

Physical and biochemical barriers restricting drug permeation. ECM remodeling forms a physical barrier: Activated CAFs secrete large amounts of type I collagen, fibronectin and hyaluronic acid, and increase ECM density through LOXL2-mediated collagen cross-linking, raising the interstitial pressure of the tumor (113). This dense matrix significantly hinders the deep penetration of monoclonal antibodies (such as trastuzumab and Zolbetuximab) and ADCs into the tumor (149). Preclinical studies have shown that in GC xenograft models, high-density CAFs reduce the intratumoral distribution of trastuzumab by >50% (150).

Promoting drug efflux. HGF secreted by CAFs can activate the c-Met receptor on tumor cells, thereby upregulating ATP-binding cassette (ABC) transporters (such as ABCB1 and ABCG2), enhancing the efflux capacity of chemotherapy drugs such as paclitaxel and oxaliplatin, and reducing the intracellular effective concentration (150,151).

Promoting EMT and drug resistance

TGF-β-mediated EMT. CAFs are the main source of TGF-β in the TME (152). TGF-β induces EMT in tumor cells through Smad-dependent or -independent pathways, characterized by downregulation of E-cadherin and upregulation of vimentin and zinc finger E-Box binding homeobox 1 (ZEB1) (153). EMT not only drives invasion and metastasis but also confers broad resistance to trastuzumab, chemotherapy and immunotherapy (154). In clinical samples of GC, the subpopulation of CAFs with high TGF-β expression is significantly associated with poor prognosis and resistance to anti-HER2 therapy in patients (155).

HGF/c-Met bypass activation. HGF secreted by CAFs not only affects drug efflux but also directly activates the RAS/MAPK and PI3K/AKT signaling pathways in tumor cells, bypassing HER2 blockade and serving as an important bypass mechanism for acquired resistance to trastuzumab (156).

Interleukin-6/signal transducer and activator of transcription 3 (IL-6/STAT3) axis. IL-6 secreted by CAFs activates STAT3 in tumor cells, upregulating anti-apoptotic proteins such as Bcl-xL and Survivin, leading to broad resistance to chemotherapy and targeted therapy (157). In GC PDX models, inhibition of the IL-6 signal can restore sensitivity to oxaliplatin (158).

Impact of tumor metabolic status on the efficacy of targeted therapy. GC cells often undergo metabolic reprogramming, including the Warburg effect (enhanced aerobic glycolysis), glutamine addiction and abnormal lipid metabolism (159). These metabolic characteristics not only maintain tumor growth but also directly affect drug responses (160).

High glucose consumption and treatment resistance

Altered acidic microenvironment affects drug uptake. GC cells highly express Glucose Transporter Type 1 glucose transporters and lactate dehydrogenase A, generating large amounts of lactic acid and creating an extracellular acidic environment

(pH 6.5-6.9) (161). The acidic pH can ionize weakly basic chemotherapeutic drugs (such as doxorubicin and paclitaxel), reducing their ability to cross the membrane and enter cells, thereby decreasing their efficacy (161).

Metabolic competition inhibits immunotherapy. The high glucose consumption of tumor cells leads to glucose scarcity in the TME, inhibiting the effector function of $CD8^+$ T cells (T cells rely on glycolysis for proliferation and cytotoxicity), thereby weakening the efficacy of ICI (162). Clinical studies have found that even in PD-L1 positive GC, high glycolytic activity can predict ICI resistance (163).

Glutamine addiction and signal pathway interactions

Glutamine metabolism supports drug resistance. GC cells often exhibit glutamine addiction, relying on exogenous glutamine as an alternative energy source and biosynthetic precursor (164). Glutamine is converted to glutamate by glutaminase (GLS), entering the TCA cycle and providing substrates for glutathione synthesis, thereby enhancing antioxidant capacity (165). In trastuzumab-resistant HER2-positive GC models, glutamine metabolism is significantly upregulated, and inhibition of GLS can restore trastuzumab sensitivity (166).

Positive feedback with the mTOR pathway. Glutamate, a product of glutamine metabolism, can activate Mammalian Target of Rapamycin Complex 1 signaling (via the amino acid sensing pathway), and mTOR activation itself enhances glutamine uptake, forming a positive feedback loop (167). This explains the phenomenon that glutamine dependence often increases after resistance to PI3K/mTOR inhibitors.

Lipid metabolism and ferroptosis sensitivity. Fatty acid synthase and stearoyl-CoA desaturase 1 are often highly expressed in GC, leading to abnormal lipid metabolism, altering the lipid composition of cell membranes and lipid peroxidation levels (168). This directly affects the sensitivity of tumor cells to ferroptosis, a mechanism of action for certain chemotherapy drugs (such as cisplatin and paclitaxel) and targeted drugs (such as sorafenib) (169). Regulating enzymes related to lipid metabolism can change drug efficacy and provide new targets for combination therapy.

4. Future outlook: Pathway redundancy-informed combination therapies and dynamically adaptive treatment strategies in GC

GC is characterized by a deeply entrenched, evolutionarily conserved signaling redundancy, where inhibition of any single core oncogenic driver (for example, HER2, EGFR, or MET) is routinely compensated by rapid rewiring across parallel RTK networks, convergence at shared downstream effectors (for example, RAS/MAPK and PI3K/AKT/mTOR), and robust feedback upregulation of upstream receptors and ligands (167,170,171). This systemic adaptability is not incidental; it is the principal biological determinant of near-universal acquired resistance to monotherapies. Consequently, next-generation clinical development must shift from empiric combination screening to 'mechanism-first' trial design: Prioritizing rationally sequenced or co-administered regimens that preempt defined escape routes, grounded in functional genomics and validated in clinically relevant models. Critically, this paradigm requires seamless integration of longitudinal molecular monitoring (liquid biopsy) and spatially resolved phenotyping (single-cell and spatial multi-omics) to transform treatment from static prescription into real-time, biology-guided adaptation.

Mechanistic framework for rational combination therapy. The accompanying schematic maps the hierarchical architecture of GC signaling-not as isolated linear pathways, but as an interconnected, adaptive network wherein therapeutic pressure at one node predictably propagates to others. It synthesizes three layers of biological insight (Fig. 3).

Membrane receptor layer. Clinically validated targets (HER2); compensatory RTKs with strong preclinical and emerging clinical evidence (EGFR, HER3, FGFR2 and MET); tumor-selective antigens under active clinical evaluation (CLDN18.2); and immunomodulatory targets acting within the TME (PD-1, TGF-β, FAK; purple).

Intracellular signaling layer. The RAS/MAPK and PI3K/AKT/mTOR pathways function not as independent modules, but as reciprocally regulated hubs, exhibiting bidirectional crosstalk, mutual feedback and shared downstream convergence points.

Compensatory dynamics. HER2 blockade induces transcriptional reprogramming that elevates expression and activation of EGFR/HER3 heterodimers and FGFR2; conversely, MAPK inhibition triggers rapid, ligand-dependent rebound activation of multiple RTKs-including MET and EGFR, via relief of ERK-mediated negative feedback.

Evidence-based combination regimens. A total of six non-overlapping, biologically coherent strategies are proposed, each targeting a distinct node of the redundancy network and supported by mechanistic validation in GC models and/or early-phase clinical data.

From static combinations to dynamic adaptive therapy. The efficacy of combination therapy in GC is not determined solely by 'which' agents are combined, but critically by 'when', 'in whom', and 'how precisely' treatment is adapted in response to evolving tumor biology. To move beyond empiric, fixed-dose regimens, two complementary mechanistic technologies must be embedded into clinical development: Liquid biopsy-driven real-time adaptation and single-cell/spatial multi-omics-guided microenvironmental targeting, enabling a shift from static protocols to individualized, biologically informed closed-loop therapy.

Liquid biopsy-driven real-time adaptation therapy. Tumor clonal evolution under therapeutic pressure drives resistance through diverse, often co-occurring alterations-including MET/FGFR2 amplification, PIK3CA mutations and inactivating lesions in B2M, JAK1, or JAK2 (172,173). ctDNA enables non-invasive, quantitative tracking of these dynamics: Longitudinal monitoring detects molecular progression a median of 4-6 months before radiographic evidence of disease progression (174). This temporal advantage creates a critical window for preemptive intervention. Yet key translational questions remain unresolved: What is the optimal sampling frequency? How should clinically meaningful molecular progression thresholds be defined (for example, VAF change magnitude, clonal burden kinetics, multi-marker concordance)? And most importantly, does early molecular intervention improve PFS or OS? Prospective,

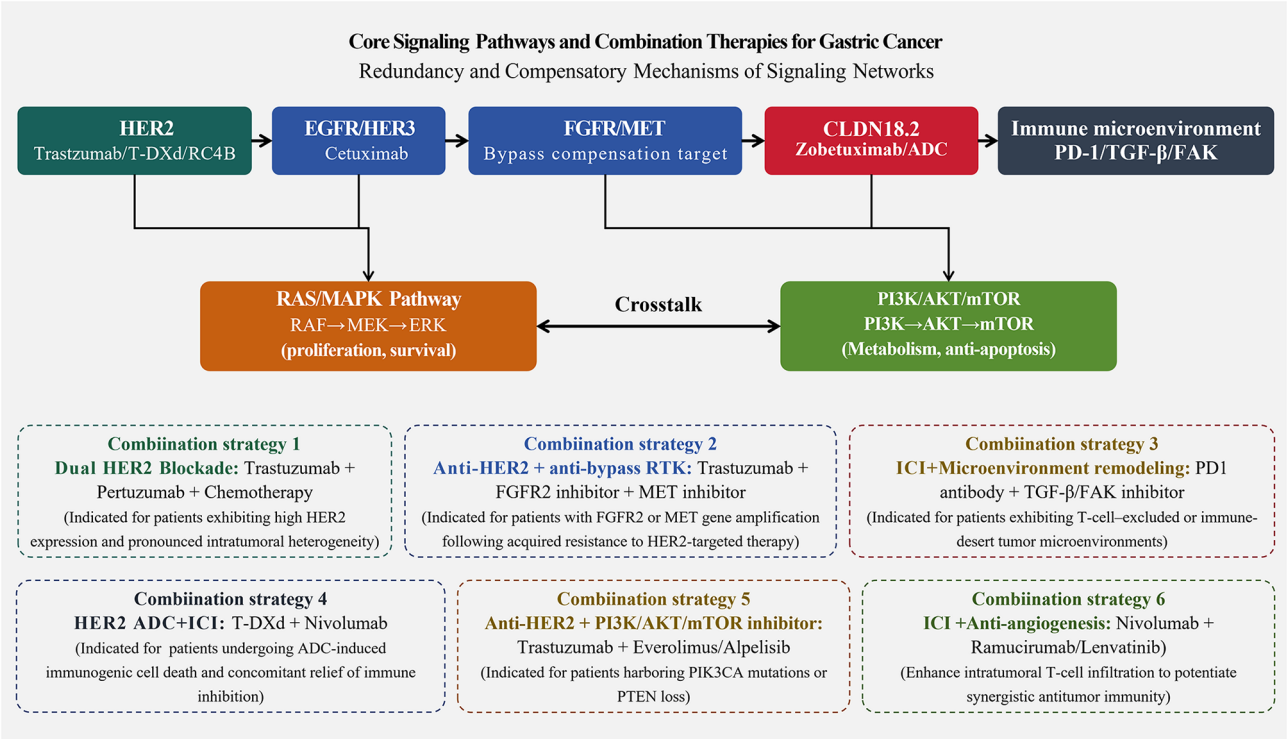

Figure 3. Gastric cancer signaling is depicted as an adaptive, interconnected network, not isolated linear pathways, where inhibiting one node provokes predictable compensatory activation elsewhere. It integrates three layers: Membrane receptors, intracellular signaling, compensatory dynamics, and evidence-based combinations. ICI, immune checkpoint inhibitor; ADC, antigen-drug conjugate; RTK, receptor tyrosine kinase; FGFR, fibroblast growth factor receptor; FAK, focal adhesion kinase.

biomarker-stratified interventional trials, notably adaptive umbrella designs, are essential to answer these questions and establish causal links between molecular adaptation and clinical benefit.

Technical barriers persist, including heterogeneous ctDNA shedding across GC subtypes, confounding signals from clonal hematopoiesis, and lack of harmonized analytical frameworks (for example, standardized panels, bioinformatic pipelines and clinical reporting criteria). Addressing these requires cross-institutional consensus on assay validation, reference standards, and regulatory-grade analytical sensitivity (>95% specificity at ≤0.1% VAF) (Fig. 4).

Microenvironmental combination targeting guided by single-cell and spatial multi-omics. Traditional bulk sequencing masks the heterogeneity of tumors and the microenvironment (175). Single-cell transcriptomics (scRNA-seq), spatial transcriptomics and spatial metabolomics can reveal (176,177): i) CAF functional subtypes: Inflammatory CAF, myofibroblastic CAF, antigen-presenting CAF, which have opposite effects on drug penetration, EMT and immune rejection. Single-cell atlases can guide selective targeting of pathogenic subtypes (such as FAP + TGF-β high-expressing ones); ii) metabolic heterogeneity: Significant differences in glycolysis/oxidative phosphorylation/glutamine dependence in different regions of the same tumor, affecting local drug sensitivity; iii) immune-stromal-tumor interaction networks: Spatial co-localization analysis can identify specific ligand-receptor pairs activated in drug-resistant 'sanctuaries' (such as CAF-derived HGF and tumor cell c-Met), providing new targets for combination therapy; iv) next-generation molecular typing-'cellular ecological typing': Integrating single-cell/spatial markers into the typing system (such as CAF-S1 high-density type, glycolysis-dominant type, immune-rejection type), guiding the allocation of different combination arms in umbrella trials.

The current major challenges include cost and throughput; data standardization across platforms; and the need to reduce dimensionality to accessible techniques such as IHC for clinical translation.

Decision support system integrated with multi-modal AI. By fusing genomic, digital pathology, radiomics and clinical data, an interpretable machine learning model can be constructed (178). Application scenarios include directly inferring EBV/MSI status from routine H&E sections (179); non-invasive assessment of metabolic and microenvironmental features based on radiomics (180); outputting individualized combination therapy recommendations and drug resistance risk scores (180). In the future, when embedded in electronic medical record systems, it can provide real-time clinical decision support.

Toward 4D precision oncology in GC: From static classification to spatiotemporal, mechanism-guided intervention. The convergence of liquid biopsy and single-cell-resolved spatial multi-omics is catalyzing a paradigm shift in GC management, transitioning precision oncology from static, time-limited molecular classification to dynamic, spatiotemporal mapping of tumor evolution and ecosystem remodeling (46,181,182).

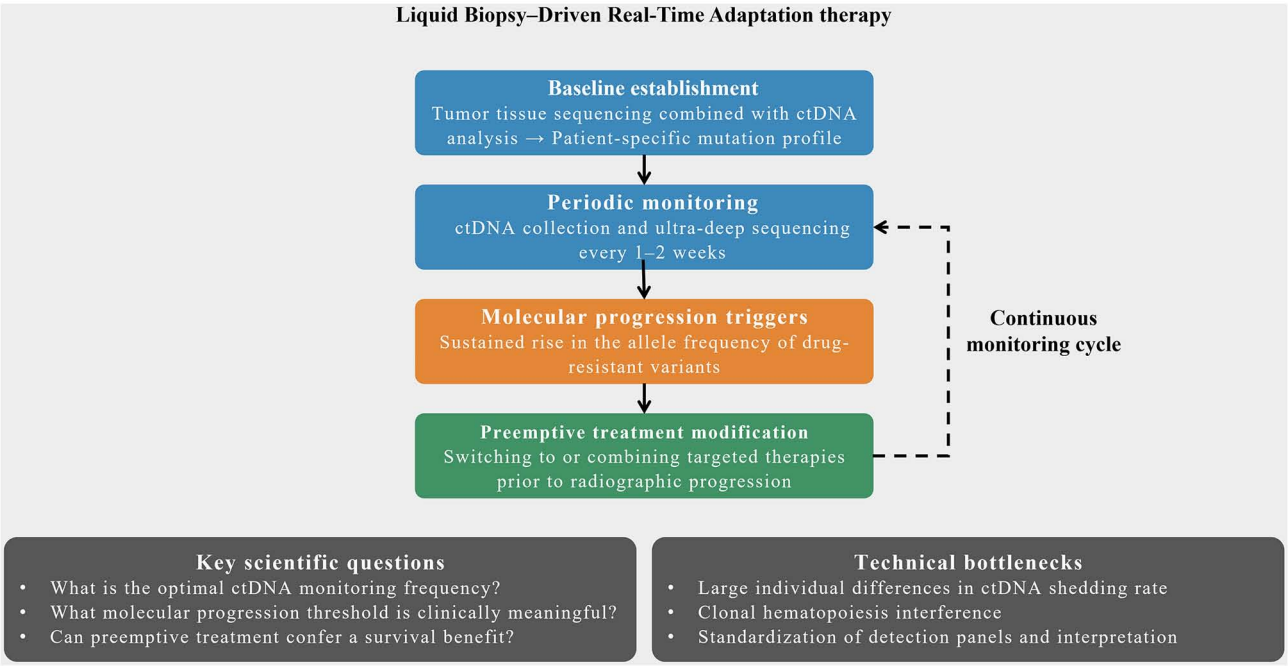

Figure 4. Schematic of liquid biopsy-driven real-time adaptive therapy for gastric cancer. ctDNA, circulating tumor DNA.

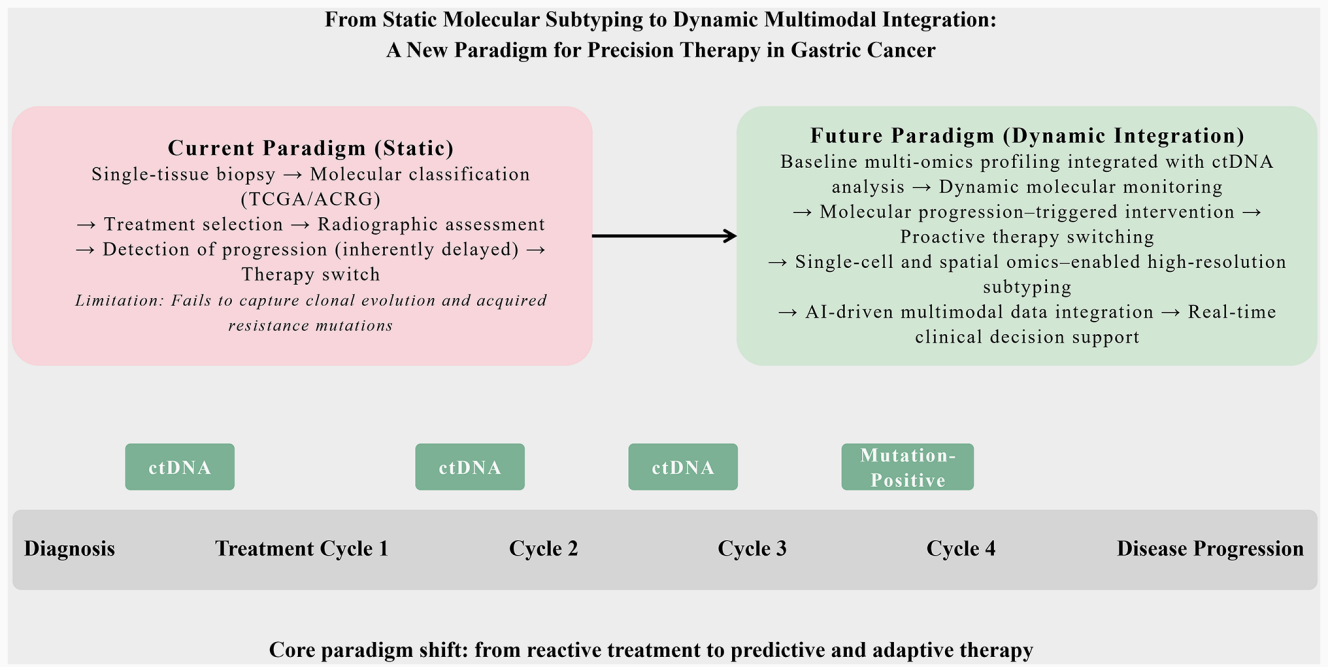

Figure 5. Schematic of the paradigm shift from static molecular subtyping to dynamic multimodal biomarker integration in gastric cancer precision therapy. TCGA, The Cancer Genome Atlas; ACRG, Asian Cancer Research Group; ctDNA, circulating tumor DNA.

This integrative framework enables clinical decision-making to evolve beyond the question of 'which drug is most likely to be effective', toward a precise, actionable triad: i) When should intervention occur; ii) which functionally defined cellular compartment or signaling node is driving resistance or immune evasion; and iii) which rationally combined therapeutic modalities will selectively disrupt that context-specific vulnerability. Such an approach embodies true mechanism-driven, adaptive precision oncology.

In conclusion, the future of GC therapeutics lies not in static genotype-therapy matching tables, but in adaptive, closed-loop systems characterized by continuous molecular surveillance, multi-layered biological interpretation, and iterative, evidence-guided regimen optimization. Realizing this vision demands coordinated advancement across fundamental cancer biology, translational technology development, innovative clinical trial methodology and agile regulatory science (Fig. 5).

5. Conclusion

Integrating molecular classification into GC management has deepened the understanding of this complex disease and improved treatment approaches. By identifying distinct molecular subtypes, clinicians can tailor therapies to match the biology of individual tumors. However, challenges remain, particularly the development of resistance to targeted therapies and immunotherapies. Understanding both primary and acquired resistance mechanisms is essential for designing next-generation strategies, such as combination therapies that target multiple pathways or boost immune responses. Discovering and validating new biomarkers is also a priority. Liquid biopsy tools such as ctDNA analysis and exosome profiling offer non-invasive ways to monitor tumor changes over time. Looking ahead, precision oncology in GC will benefit from integrating multi-omics data, genomics, transcriptomics, proteomics and metabolomics, to gain a full picture of tumor biology and identify new treatment targets. AI and machine learning are increasingly used to analyze large datasets, speeding up the discovery of clinically useful patterns and predictive models. Progress in this field depends on strong collaboration between academic institutions, pharmaceutical companies and regulators. Large multinational clinical trials are needed to confirm the effectiveness of new treatments across diverse populations. Real-world evidence from routine care also plays a role in supporting broader adoption of personalized therapies. In conclusion, molecular insights have transformed GC care, but the path to fully personalized medicine continues. With ongoing research and collaboration, more precise and effective treatments lie ahead for patients with this challenging disease.

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Authors' contributions

SX, XZ and LT take the responsibility for the integrity of the figures and the literature search and the article writing. AL, XZ, JC and ZT completed the final version of the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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