

Review Article



OPEN ACCESS

Received: Oct 30, 2025

Revised: Dec 9, 2025

Accepted: Dec 9, 2025

Published online: Jan 5, 2026

Correspondence to

Ju-Seog Lee

Department of Systems Biology, The University
of Texas MD Anderson Cancer Center, 6565
MD Anderson Blvd, Houston, TX 77030, USA.

Email: jlee@mdanderson.org

Copyright © 2026. Korean Gastric Cancer
Association

This is an Open Access article distributed
under the terms of the Creative Commons
Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0>)
which permits unrestricted noncommercial
use, distribution, and reproduction in any
medium, provided the original work is properly
cited.

ORCID iDs

Ju-Seog Lee

<https://orcid.org/0000-0002-5666-9753>

Funding

This study was supported by the Cancer
Prevention and Research Institute of Texas
Individual Investigator Research Award
(RP170307), Congressionally Directed Medical
Research Programs Peer-Reviewed Cancer
Research Program Award (CA160616), and the
National Cancer Institute (R01-CA237327 and
P50-CA217674).

Conflict of Interest

No potential conflict of interest relevant to this
article was reported.

Evolving Molecular Subtypes of Gastric Cancer: From Past Classifications to Present Consensus and Future Directions for Precision Therapy

Ju-Seog Lee

Department of Systems Biology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

ABSTRACT

Gastric cancer is a biologically heterogeneous disease. The advent of high-throughput multi-omic technologies has revolutionized our understanding of gastric cancer by deconstructing this heterogeneous entity into distinct and more homogeneous molecular subtypes.

Early classifications based on gene expression, methylation, and histology have laid the groundwork for multi-omic frameworks proposed by The Cancer Genome Atlas and Asian Cancer Research Group, which established the foundation of modern molecular taxonomy. Subsequent integrative efforts, particularly the Consensus Genomic Subtypes (Super 6) model, have unified this collected information into clinically relevant subtypes that bridge prognostic stratification with treatment strategies. Established biomarkers such as human epidermal growth factor receptor 2 amplification, microsatellite instability, and programmed death-ligand 1 expression are now used clinically to guide treatment with targeted agents and immune checkpoint inhibitors. Emerging single-cell and spatial transcriptomic analyses have further refined this landscape by deconstructing tumor microenvironments and potential evolutionary trajectories associated with disease progression. This review examines the evolution of molecular classification systems for gastric cancer, highlights current consensus frameworks, and discusses how subtype-based stratification will transform clinical trial design and enable biomarker-driven precision therapy.

Keywords: Genomics; Classification; Diagnosis; Biomarkers

INTRODUCTION

Gastric cancer remains one of the most prevalent and lethal malignancies worldwide. Despite declining incidence in some Western countries, gastric cancer continues to be the fifth most common cancer and the fourth leading cause of cancer-related mortality globally, accounting for over one million new cases and nearly 660,000 deaths annually [1,2]. This disease burden is disproportionately concentrated in East Asia, particularly Korea, Japan, and China, where standardized screening programs and endoscopic detection have enabled earlier diagnosis and improved survival compared with Western populations [3,4]. However, in several low- and middle-income regions, including Latin America, Eastern Europe, and parts of the Middle East, most patients are still diagnosed at advanced stages, resulting in poor outcomes [5].

Gastric cancer is a biologically diverse disease influenced by environmental exposures, infection, and host genetics [6-8]. Chronic infection with *Helicobacter pylori* remains the primary etiological factor, initiating a multistep cascade from chronic gastritis to atrophy, intestinal metaplasia, dysplasia, and carcinoma [9,10]. In a subset of cases, Epstein-Barr virus (EBV) infection contributes to gastric carcinogenesis through epigenetic silencing and immune evasion mediated by programmed death-ligand 1/2 (PD-L1/2) activation [11,12]. Lifestyle factors such as high salt intake, smoking, alcohol consumption, and diets low in fruits and vegetables further increase gastric cancer risk, whereas hereditary syndromes (e.g., *CDH1* germline mutations and Lynch syndrome) account for a minority of cases [13,14]. Collectively, these diverse etiological backgrounds generate substantial interpatient variability in tumor site, morphology, molecular alterations, and clinical outcomes.

Historically, the classification of gastric cancer has relied on histopathological frameworks, such as Lauren's classification (intestinal and diffuse subtypes) and the World Health Organization scheme [15,16]. The intestinal type often arises in the background of chronic *H. pylori* infection and intestinal metaplasia, whereas the diffuse type frequently exhibits a loss of E-cadherin-mediated adhesion and manifests as scattered signet-ring cells [6-8]. Although these morphological systems remain diagnostic cornerstones, they fail to predict the prognosis or therapeutic response [17].

It is increasingly evident that gastric cancer represents not just a single disease but rather a constellation of biologically distinct entities that differ in molecular pathways, tumor-microenvironment interactions, and treatment sensitivity. Such biological heterogeneity explains the broad variability in clinical behavior observed among patients with similar tumor, node, metastasis (TNM) stages [18]. Some tumors exhibit rapid progression and chemoresistance, whereas others show durable responses to chemotherapy or immune checkpoint inhibitors (ICIs). This diversity stems from distinct genomic alterations, signaling pathways, and stromal or immune contexts that shape tumor evolution and therapeutic responsiveness. Over the past two decades, high-throughput multi-omic technologies have revolutionized our understanding of gastric cancer by delineating its molecular architecture and revealing that distinct oncogenic trajectories underlie molecular subtypes with unique biological and clinical profiles [19,20]. These efforts have collectively underscored the supposition that gastric cancer evolves through distinct molecular pathways, rather than a single linear progression. Thus, the biological heterogeneity of gastric cancer directly translates into differences in disease trajectory and treatment sensitivity.

This review summarizes the current landscape of molecular subtyping in gastric cancer, from early gene expression-based systems to multi-omic consensus frameworks and discusses how these classifications inform therapeutic stratification and development of precision treatment strategies.

TREATMENTS OF GASTRIC CANCER

Curative treatment for resectable gastric cancer is based on complete surgical resection with negative margins and adequate lymphadenectomy, with D2 dissection established as the surgical standard [21,22]. However, surgery alone is rarely sufficient, and multimodal therapy has become essential in reducing recurrence and improving long-term survival. Regional variations in clinical practice largely reflect differences in stage distribution and screening.

In Western countries, perioperative chemotherapy is the standard treatment, whereas in East Asia, adjuvant chemotherapy following D2 gastrectomy remains the preferred strategy [23-27]. Postoperative chemoradiation provides no additional survival advantage after optimal D2 dissection and is generally reserved for patients with inadequate lymphadenectomy (D0/D1) or positive margins [28-30]. Nevertheless, selected subgroups—particularly those with high chromosomal instability—may benefit from adjunctive radiation, a hypothesis supported by recent biomarker-driven analyses but requiring prospective validation [31].

Molecular subtypes are increasingly shaping perioperative and postoperative therapeutic decisions. Tumors with deficient mismatch repair or microsatellite instability-high (dMMR/MSI-H) occur more frequently among resectable tumors and exhibit excellent prognoses following surgery yet derive limited benefit from conventional fluoropyrimidine–platinum chemotherapy [32,33]. Given their strong immunogenicity, these tumors respond well to immune checkpoint blockade, and ongoing trials are exploring neoadjuvant or non-operative management strategies using ICIs [34,35].

For advanced or metastatic gastric cancer, systemic therapy remains the cornerstone of management, aimed at extending survival and maintaining quality of life [8,27,36]. A platinum–fluoropyrimidine doublet constitutes the standard backbone [36,37] to which biomarker-directed agents are increasingly added. Molecular profiling can guide regimen selection by identifying actionable subgroups, most prominently human epidermal growth factor receptor 2 (HER2) amplification, PD-L1 expression, or dMMR/MSI-H status. The integration of ICIs such as nivolumab or pembrolizumab with first-line chemotherapy has significantly improved outcomes, particularly in PD-L1-high or MSI-H tumors, with consistent benefits demonstrated across multiple phase III trials [38-42]. Comparable efficacy has been observed with other programmed cell death protein 1 (PD-1)/PD-L1 antibodies including tislelizumab, sintilimab, and sugemalimab [43-45]. Despite these advances, the variability in PD-L1 testing assays and scoring remains a limitation, underscoring the need for comprehensive upfront biomarker profiling to guide individualized immunochemotherapy combinations aligned with molecular subtypes.

Targeted therapies have further expanded treatment options for biomarker-defined subsets of gastric cancer. HER2-positive tumors benefit from HER2-directed antibodies such as trastuzumab and trastuzumab deruxtecan, often in combination with immunotherapy [46-48]. Similarly, CLDN18.2-positive cancers represent an emerging entity that is responsive to zolbetuximab in combination with chemotherapy [49,50]. These advances illustrate a paradigm shift from stage-based to subtype-based management, wherein therapeutic strategies are tailored to the molecular and immunological contexts of each tumor.

The integration of surgery, systemic therapy, and molecular stratification has redefined gastric cancer treatment. The transition toward biomarker-driven and subtype-specific precision therapy establishes the clinical foundation for the molecular taxonomies discussed in subsequent sections.

MOLECULAR SUBTYPES OF GASTRIC CANCER

The molecular taxonomy of gastric cancer has evolved through successive efforts to dissect its biological heterogeneity using diverse genomic, epigenomic, and transcriptomic

approaches. These studies have progressively refined our understanding of gastric cancer pathogenesis by revealing distinct oncogenic pathways, microenvironmental contexts, and therapeutic vulnerabilities.

In one of the earliest systematic efforts to classify gastric cancer, Kusano et al. applied methylation profiling across methylated-in-tumor loci and tumor-related genes in primary gastric tumors [51]. This analysis delineated three distinct epigenetic categories: CpG island methylator phenotype-high (CIMP-H), CIMP-low, and CIMP-negative. Each subtype exhibited unique genetic, viral, and clinicopathological characteristics. CIMP-H tumors demonstrated extensive promoter hypermethylation, lacked mutations in *TP53* and *KRAS*, were often proximal or diffuse in type, and showed a strong association with EBV infection, whereas CIMP-negative tumors were associated with poorer outcomes. This work provided the first evidence that gastric cancer could arise through distinct epigenetic trajectories, foreshadowing later multi-omic classifications that integrated genomic and transcriptomic data for deeper biological insights.

Tan et al. introduced intrinsic subtypes of gastric cancer through gene expression profiling of gastric cancer cell lines [52]. Two core transcriptomic subtypes were identified, namely genomic intestinal and genomic diffuse, which captured tumor-intrinsic molecular programs beyond histologic boundaries. These molecular classes were shown to predict prognosis and chemotherapeutic response. The intrinsic subtypes correlated with differential sensitivity to standard agents such as 5-fluorouracil, oxaliplatin, and cisplatin, providing early evidence of subtype-specific therapeutic vulnerabilities. Importantly, this transcriptome-based system outperformed Lauren's classification in prognostic relevance and clinical utility. Furthermore, immunohistochemical surrogates (LGALS4 and CDH17) enabled practical subtype identification in clinical samples. However, this approach was limited by its reliance on cell line-derived signatures and the lack of integrated genomic and epigenetic data.

Lei et al. [53] further advanced gastric cancer molecular taxonomy through a comprehensive transcriptome-based analysis, delineating three molecular subtypes with distinct biological and clinical characteristics. Unsupervised clustering of large patient cohorts revealed the proliferative, metabolic, and mesenchymal subtypes. The proliferative subtype was characterized by genomic instability, frequent *TP53* mutations, and activation of cell cycle and receptor tyrosine kinase pathways. The metabolic subtype exhibited stable genomes with enrichment of metabolic gene expression. The mesenchymal subtype demonstrated epithelial-mesenchymal transition (EMT) and stem-like features linked to poor prognosis and therapeutic resistance. These subtypes were associated with differential drug sensitivities, highlighting their potential for patient stratification. This study provided the first transcriptome-based framework for classifying primary gastric tumors, connecting molecular heterogeneity to clinical behavior.

A major advance in gastric cancer classification emerged from The Cancer Genome Atlas (TCGA), which provided the first integrative multi-omic characterization of gastric adenocarcinoma [54]. Through an integrative analysis of 295 treatment-naïve primary tumors across 6 platforms—including exome, RNA, and miRNA sequencing, DNA methylation, copy-number, and proteomic profiling—the study established 4 major molecular subtypes: 1) EBV-positive, characterized by *PIK3CA* mutations, extensive EBV-CIMP, and *JAK2/PD-L1/PD-L2* amplification, suggesting potential sensitivity to PI3K or immune checkpoint blockade; 2) MSI-H, with *MLH1* silencing and hypermutation involving *PIK3CA*, *ERBB3*, *ARID1A*, and *KRAS*;

(3) Genomically stable (GS), enriched for diffuse-type tumors harboring *RHOA* mutations and *CLDN18-ARHGAP* fusions; and (4) Chromosomal instability (CIN), composed predominantly of intestinal-type cancers with *TP53* mutations and RTK–RAS pathway amplifications (*ERBB2*, *EGFR*, *MET*, and *VEGFA*). Notably, the CIN subtype exhibited the highest heterogeneity, indicating its potential for further subclassification. Although the TCGA study primarily focused on molecular characterization rather than therapeutic outcomes, subsequent clinical analyses using TCGA-derived gene signatures demonstrated clear prognostic and predictive relevance [55]. EBV-positive tumors showed the most favorable outcomes, GS tumors demonstrated the poorest outcomes, and MSI/CIN subtypes had intermediate survival. Moreover, CIN tumors derived the greatest benefit from adjuvant chemotherapy, whereas GS tumors were largely chemoresistant. The investigators further developed the TCGA Risk Score (TRS) by integrating the probabilities across all four subtypes to independently predict recurrence risk and overall survival, outperforming conventional clinicopathologic variables. Collectively, the TCGA classification established a foundational framework for biologically grounded gastric cancer stratification and remains the benchmark for subsequent systems.

The Asian Cancer Research Group (ACRG) introduced another clinically relevant molecular classification of gastric cancer through an integrative analysis of gene expression, copy-number variations, and targeted sequencing in 300 primary tumors [56]. This framework defined 4 molecular subtypes with distinct biological and clinical characteristics: 1) EMT, diffuse-type tumors characterized by *CDH1* loss, early onset, high recurrence frequency, and the poorest prognosis, typically relapsing via peritoneal dissemination; 2) MSI, hypermutated, intestinal-type, antral cancers with *MLH1* silencing and frequent *PIK3CA*, *ARID1A*, and *KRAS* mutations, showing the most favorable survival and lowest recurrence; 3) Microsatellite stable (MSS)/*TP53*-positive, enriched for EBV-positive and *ARID1A*/*PIK3CA*-mutated tumors, and associated with relatively favorable outcomes; and 4) MSS/*TP53*-negative, characterized by *TP53* mutations and RTK/RAS amplifications (*ERBB2*, *EGFR*, *CCND1*, and *MYC*), showing intermediate survival and potential therapeutic relevance. These molecular subtypes partially overlapped with TCGA categories such as MSI and EMT, corresponding to the GS subtype.

Subsequent transcriptomic studies further refined these molecular paradigms. Lee et al. [57] identified YAP1 activation as a major driver of recurrence in gastric cancer and developed a 6-gene recurrence risk score (RRS) for clinical prognostication [57]. Using transcriptomic data from 267 resected tumors in a training cohort and 317 independent cases for validation, the investigators derived the RRS based on *IGFBP4*, *SFRP4*, *SPOCK1*, *SULF1*, *THBS*, and *GADD45B*, reflecting YAP1-mediated signaling, stress response, and microenvironmental interactions. The RRS stratified patients into low-, intermediate-, and high-risk groups and independently predicted recurrence and overall survival after curative gastrectomy, including in stage II disease. Mechanistically, YAP1 activation was strongly associated with invasive phenotypes, EMT enrichment, and poor prognosis, implicating Hippo pathway dysregulation as a determinant of tumor aggressiveness and recurrence. This study was the first to establish a YAP1-centered prognostic signature in gastric cancer, providing a biologically grounded and clinically practical tool to identify patients who may benefit from intensified adjuvant therapy or novel interventions targeting the YAP1–TEAD axis [58,59]. Recent clinical investigations have further validated this approach, demonstrating the therapeutic potential of small-molecule inhibitors that disrupt YAP–TEAD interactions, such as VT3989 [60,61].

Oh et al. [62] conducted an extensive clinical and multi-omic characterization of gastric cancer with mesenchymal features, a subtype strongly associated with poor prognosis and therapeutic resistance. Using integrated transcriptomic and proteomic analyses across large patient cohorts, they identified two distinct biological classes: mesenchymal phenotype (MP) and epithelial phenotype (EP). MP tumors exhibited hallmark EMT signatures, genomic stability, low mutational burden, microsatellite stability, and pronounced resistance to adjuvant chemotherapy, whereas EP tumors demonstrated higher genomic instability and better treatment responsiveness. Mechanistically, the MP subtype was driven by activation of transforming growth factor- β , Hedgehog, and insulin-like growth factor 1 (IGF1/insulin-like growth factor 1 receptor (IGF1R) signaling pathways, with IGF1 upregulation arising from gene amplification or promoter hypomethylation. Functionally, MP-derived cell lines and xenografts were uniquely sensitive to IGF1R inhibition, indicating a potential therapeutic vulnerability. This study defined a biologically and clinically distinct mesenchymal subtype, refining TCGA and ACRG taxonomies and highlighting IGF1/IGF1R signaling as a promising target in chemoresistant gastric cancer.

Cheong et al. [63] defined 5 transcriptomic subtypes of gastric cancer through a large-scale integrative analysis of transcriptomic data. The following subtypes reflected both biological heterogeneity and differential chemotherapy responsiveness: 1) Inflammatory (INF) subtype, enriched for immune-related signatures and EBV-positive and MSI-H tumors, showing the best prognosis and strong immune activation; 2) Intestinal (INT) subtype, characterized by intestinal epithelial differentiation and proliferative genes, showing moderate chemosensitivity; 3) Gastric (GST) subtype, expressing gastric mucosa-specific genes, with an intermediate prognosis; 4) Mixed-stromal (MXD) subtype, exhibiting proliferative and transit-amplifying features, with an intermediate prognosis; and 5) Stem-like (STL) subtype, defined by EMT and stem-like signatures, demonstrating the worst survival and chemoresistance. These 5 subtypes integrated and expanded on previous classifications, providing a clinically applicable quantitative reverse transcription polymerase chain reaction-based predictive assay (nProfiler I) for stratifying patients by adjuvant chemotherapy benefit and prognosis.

Shin et al. [64] defined 6 long non-coding RNA (lncRNA)-based molecular subtypes (L6A–L6F) of gastric cancer using transcriptomic profiling of over 1,900 cases. These subtypes showed distinct prognostic and therapeutic patterns: L6A and L6F were associated with poor outcomes, L6B and L6D with intermediate outcomes, and L6C and L6E with favorable survival. L6B tumors benefited the most from adjuvant chemotherapy, whereas L6C (MSI-enriched) tumors responded better to ICIs; L6F (mesenchymal-like) tumors exhibited resistance to both chemotherapy and immunotherapy. Mechanistically, the lncRNA ZNF667-AS1 promoted EMT and drug resistance in L6F tumors. This study expanded gastric cancer molecular taxonomy by incorporating lncRNA expression as a predictive layer for prognosis and treatment response.

CONSENSUS AND FUTURE PERSPECTIVE

Despite major advances in genomic studies such as TCGA and ACRG, a unified and clinically actionable consensus for gastric cancer subtyping remains elusive. Divergence among identified subtypes stems from differences in cohort composition, assay platforms, and bioinformatics pipelines. Moreover, most classifications were derived from bulk tumor

transcriptomics data, which inadequately capture non-tumor components, such as immune, stromal, and fibroblast populations. These components substantially shape tumor biology, which inevitably contributes to prognosis therapeutic response. These limitations have hindered cross-cohort reproducibility and clinical translation.

To address this gap, Jeong et al. [31] performed a large-scale meta-integration of 8 independent molecular classification systems encompassing more than 2,500 gastric cancer samples, leading to the identification of 6 consensus genomic subtypes (CGS1–CGS6), referred to as the Super 6 model [31]. CGS1 (Stem-like) tumors were enriched for EMT and YAP1/TAZ activation and aligned with GS, EMT, MP, STL, and L6F subtypes. These tumors exhibited immune exclusion, chemoresistance, and poor prognosis. CGS2 (Canonical epithelial) maintained stable epithelial lineage features, showed intermediate outcomes, and paralleled the GST and metabolic subtypes. CGS3 (CIN-HER2 amplified) displayed marked chromosomal instability, frequent HER2 amplification, and active ferroptosis signaling, corresponding to a subset of TCGA-CIN. CGS3 was validated in the ARTIST clinical trial cohort [28,29], in which patients derived significant benefits from adjuvant chemoradiation, confirming its predictive relevance for therapy response. CGS4 (KRAS/SALL4-driven proliferative) was characterized by strong RTK–RAS pathway activation, enhanced cell-cycle signaling, and poor prognosis. CGS5 (MSI-H) represented mutation-rich, immune-inflamed tumors associated with excellent prognoses and high sensitivity to immunotherapy, whereas CGS6 (EBV-positive) exhibited EBV-CIMP methylation, PD-L1/PD-L2 expression, and pronounced responsiveness to immune checkpoint inhibitors.

Collectively, this consensus framework integrates genomic, transcriptomic, and immunological features, harmonizing previous classification systems into a unified, reproducible model with robust prognostic and therapeutic significance.

Fig. 1 summarizes how this integrative framework refines the classical TCGA taxonomy. The Sankey plot (**Fig. 1A**) shows that the TCGA-CIN group is subdivided into three consensus subtypes, CGS2, CGS3, and CGS4, demonstrating the enhanced resolution of the CGS classification. The accompanying boxplots (**Fig. 1B**) reveal that HER2 expression and copy-number amplification are the most enriched in the CGS3 subset, defining a distinct CIN-derived population driven by HER2 activation and suggesting that HER2-targeted therapies may be most effective within this molecular context. Building upon this foundation, **Fig. 2** provides an integrative map tracing the evolution of gastric cancer subtypes across major classification systems, from CIMP to CGS, illustrating hierarchical continuity in molecular taxonomy. This diagram highlights how successive studies have converged toward a unified consensus that links genomic instability, immune activation, and stemness programs. The mesenchymal or stem-like subtype (GS/EMT/YAP1-active/STL/L6F/CGS1) has consistently emerged as the most conserved and biologically robust phenotype across independent studies, whereas the MSI-H subtype has remained reliably recognizable. Collectively, these integrated analyses offer a comprehensive perspective on gastric cancer heterogeneity and evolution, demonstrating how earlier frameworks coalesced into a cohesive CGS-based consensus.

Recent single-cell and spatial transcriptomic analyses have refined understanding of the cellular and evolutionary foundations of gastric cancer subtypes. Kumar et al. [65] identified a distinct tumor microenvironment signature in diffuse-type tumors that closely aligned with the GS/CGS1 (Stem-like) subtype. These tumors showed pronounced plasma cell enrichment

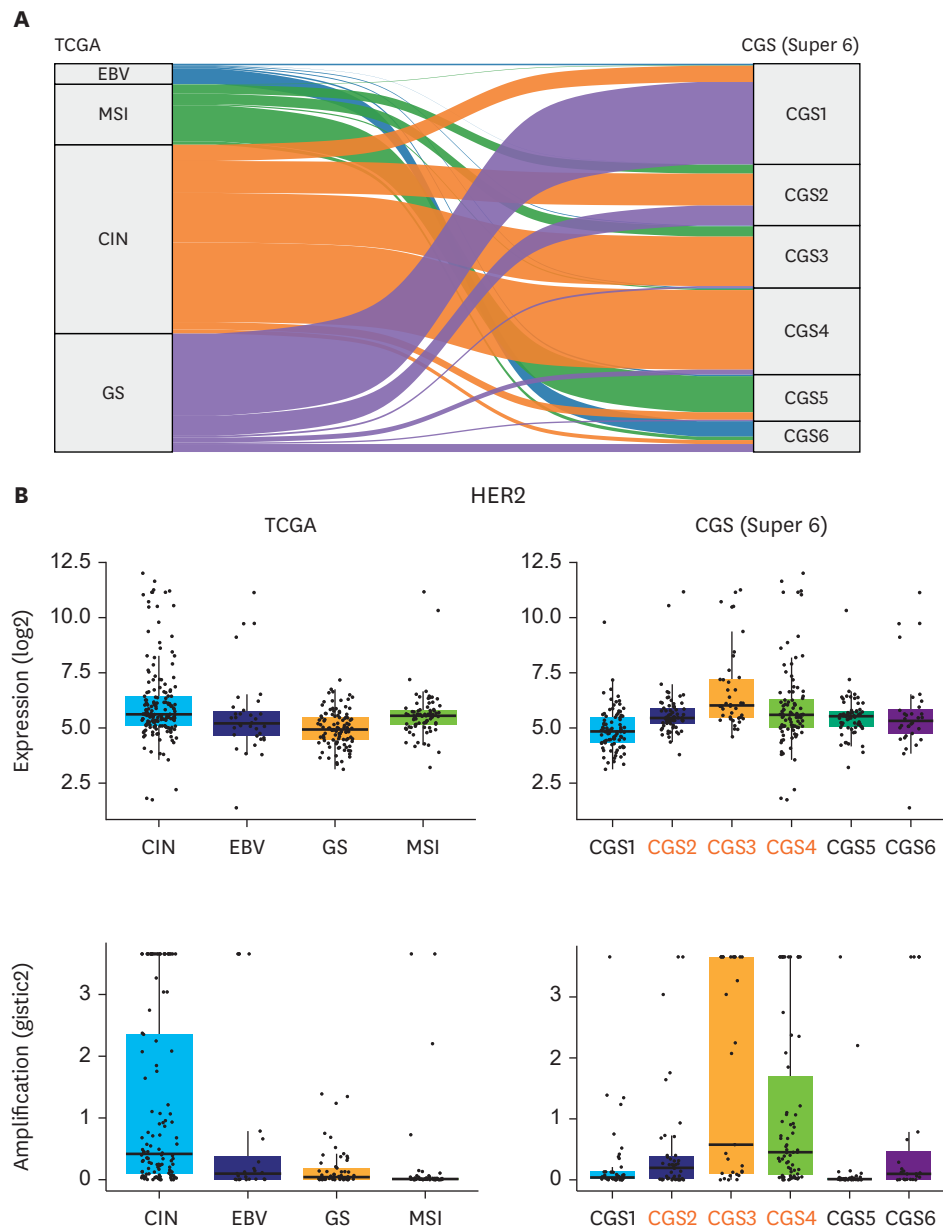


Fig. 1. Relationship between TCGA and CGS (Super 6) molecular subtypes and distribution of HER2 expression and amplification. (A) Sankey diagram depicting the correspondence between TCGA subtypes (EBV, MSI, CIN, and GS) and the CGS (Super 6) subtypes (CGS1–CGS6). The TCGA–CIN group is distributed across 3 Super 6 categories, highlighting its underlying molecular heterogeneity. All gastric cancer cases included in the CGS study (n=2,527) were analyzed for this comparison. (B) Boxplots displaying HER2 expression (top) and HER2 copy number amplification (bottom) across TCGA (left) and Super 6 (right) subtypes. Both HER2 expression and amplification are markedly elevated in the TCGA–CIN subtype, with the CGS3 subgroup showing the highest levels among the CGS classes. These findings suggest that CIN-related tumors can be further resolved into three CGS subsets, with CGS3 representing the most strongly HER2-activated population. Super 6 subtypes derived from the CIN subtype are highlighted in orange. TCGA = The Cancer Genome Atlas; CGS = consensus genomic subtypes (CGS1–CGS6); HER2 = human epidermal growth factor receptor 2; GS = genomically stable; MSI = microsatellite instability; EBV = Epstein–Barr virus; CIN = chromosomal instability.

linked to a tumor-intrinsic program driven by high expression of the transcription factor *KLF2* within the EpiC (chief cell-like) epithelial subcluster. This *KLF2*-driven epithelial-immune crosstalk promoted the recruitment of plasma cells, although the mechanisms by which these infiltrating plasma cells contributed to immune suppression remain unclear. In contrast, intestinal-type tumors, largely corresponding to CIN-related CGS2–CGS4 subtypes, were enriched for malignant intestinal-type epithelial (EpiInt) cells. Within

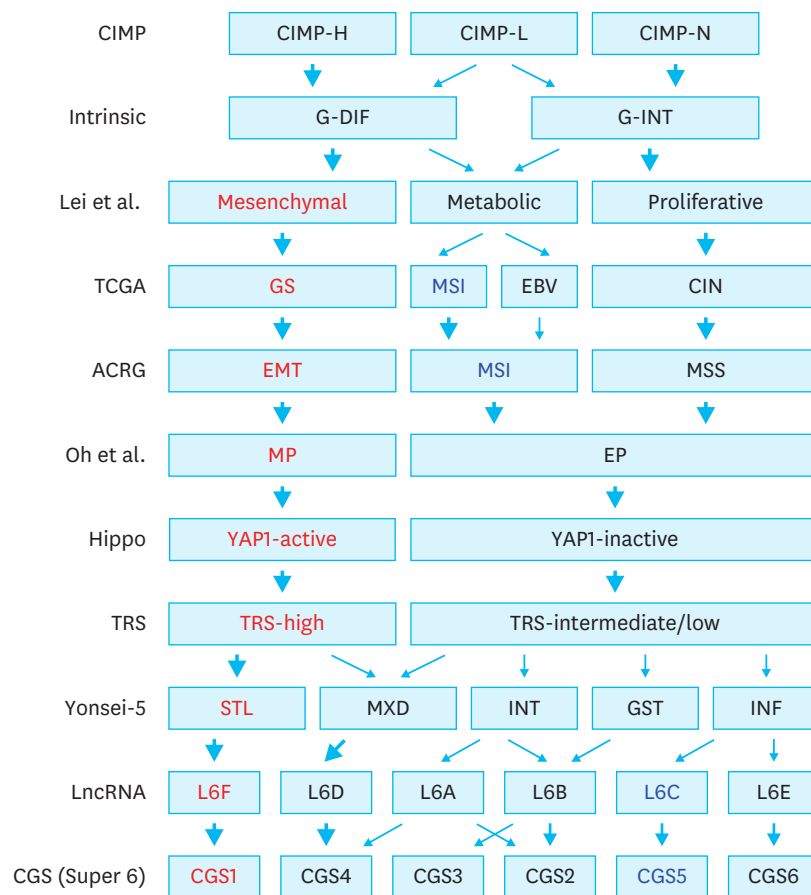


Fig. 2. Integrative landscape of molecular subtype classifications in gastric cancer.

Schematic overview illustrating the concordance and evolution of major molecular subtype frameworks derived from genomic and transcriptomic profiling studies. The TCGA classification (GS, MSI, EBV, and CIN) serves as the genomic foundation upon which subsequent expression-based and functionally defined subtypes were developed. Later cohorts and pathway-oriented classifiers are positioned according to their biological correspondence and hierarchical relationships. Arrows denote predominant molecular or transcriptomic transitions between subtype systems (for example, Mesenchymal → GS/EMT/YAP1-active/STL/L6F/CGS1). Subtypes highlighted in red indicate the most conserved and biologically consistent phenotypes across independent classification systems, whereas subtypes with MSI-related features are highlighted in blue. Each study is labeled according to its representative organization, theme, or author. ACRG = Asian Cancer Research Group; EMT = epithelial-mesenchymal transition; MSI = microsatellite instability; MSS = microsatellite stable; CGS = consensus genomic subtypes (CGS1–CGS6); CIMP = CpG island methylator phenotype; Hippo = Hippo pathway subtype; G-DIF = genomically differentiated; G-INT = genomically intestinal; lncRNA = long non-coding RNA (L6A–L6F); MP = mesenchymal phenotype; EP = epithelial phenotype; TCGA = The Cancer Genome Atlas; GS = genomically stable; EBV = Epstein–Barr virus; CIN = chromosomal instability; TRS = TCGA Risk Score; Yonsei-5 = Yonsei University cohort; STL = stem-like; MXD = mixed; INT = intestinal; GST = gastric; INF = inflammatory.

this lineage, the EpiInt1 subcluster exhibited the highest oncogene expression (e.g., *KRAS* and *MET*) and extensive copy-number alterations, consistent with a malignant population derived from intestinal metaplasia. The study also delineated cancer-associated fibroblast (CAF) heterogeneity, identifying a distinct INHBA–FAP co-expressing CAF population whose accumulation increased with tumor stage and was correlated with poor prognosis, although it was not associated with specific histological or molecular subtypes.

Complementary work by Ma et al. extended these insights by reconstructing tumor phylogenies from single-cell RNA-seq-derived somatic copy-number alterations, revealing 2 principal evolutionary trajectories [66]. The first, a branched evolution pattern, represented gradual clonal diversification from a diploid ancestor and was commonly observed in GS and MSI-H tumors. The second, termed internal diaspora evolution [67], involved rapid and early diversification into multiple subclones with distinct copy-number alteration profiles

typical of the CIN molecular subtype and was associated with aggressive clinical behavior. This dichotomy highlights that evolutionary mode, whether gradual branching or rapid diversification, serves as an additional determinant of tumor biology within established molecular subtypes.

Overall, these studies illustrate how single-cell and spatial analyses deconstruct bulk-defined subtypes, revealing the distinct epithelial, stromal, and immune ecosystems that drive subtype-specific biology. Integrating these high-resolution datasets with the molecular subtype frameworks will enable a next-generation taxonomy that incorporates gene expression, evolutionary trajectory, and microenvironmental architecture, laying the groundwork for precision therapeutic stratification and predictive biomarker development in gastric cancer.

THERAPEUTIC IMPLICATIONS OF MOLECULAR SUBTYPING AND CHALLENGES

Despite major advances in molecular characterization, current genomic classifications still have notable limitations. Most studies were based on surgically resected primary tumors, with limited data from premalignant lesions or metastatic sites, which are often more clinically relevant to treatment response. In addition, bulk sequencing analyses typically selected samples with high tumor purity, thereby underrepresenting stromal and immune cell populations, which are now recognized as central determinants of tumor progression, immune evasion, and therapeutic resistance. Consequently, Lauren's histopathological classification remains the prevailing framework in clinical trials, whereas the prognostic and predictive significance of most molecular subtypes, except for MSI-H and HER2-positive tumors, is yet to be confirmed in prospective studies.

Recognition of gastric cancer as a molecularly heterogeneous disease has reshaped prognostic assessment. Although traditional TNM staging remains indispensable, it lacks biological depth and does not reliably predict therapeutic response. In contrast, molecular subtyping offers biologically informed stratification that correlates closely with patient outcomes. MSI-H (CGS5) and EBV-positive (CGS6) tumors consistently exhibit favorable prognoses owing to their high immunogenicity. CIN/HER2-amplified (CGS3) subtypes have an intermediate prognosis but demonstrate responsiveness to HER2-targeted regimens. EMT or GS/Stem-like (CGS1) tumors show the poorest survival and are characterized by chemoresistance, immune exclusion, and stromal activation. Analysis of TCGA data showed that KLF2, a transcription factor linked to plasma cell infiltration, has elevated expression in the CGS1, CGS2, and CGS5 subtypes, whereas FAP and INHBA (canonical CAF markers) were the most highly expressed in the CGS1 (Stem-like/mesenchymal) subtype (**Fig. 3**). These findings underscore the supposition that molecular subtypes capture distinct biological and microenvironmental programs, providing a more precise framework for prognostic modeling and therapeutic stratification than conventional clinicopathological classifications.

Molecular subtyping is increasingly shaping the development and clinical application of targeted and immunotherapeutic strategies. HER2-amplified (CIN/CGS3) tumors benefit from the use of anti-HER2 agents, such as trastuzumab, trastuzumab deruxtecan, and emerging antibody-drug conjugates. Emerging evidence suggests a potential benefit of adjuvant chemoradiation in this subgroup, although further validation in independent

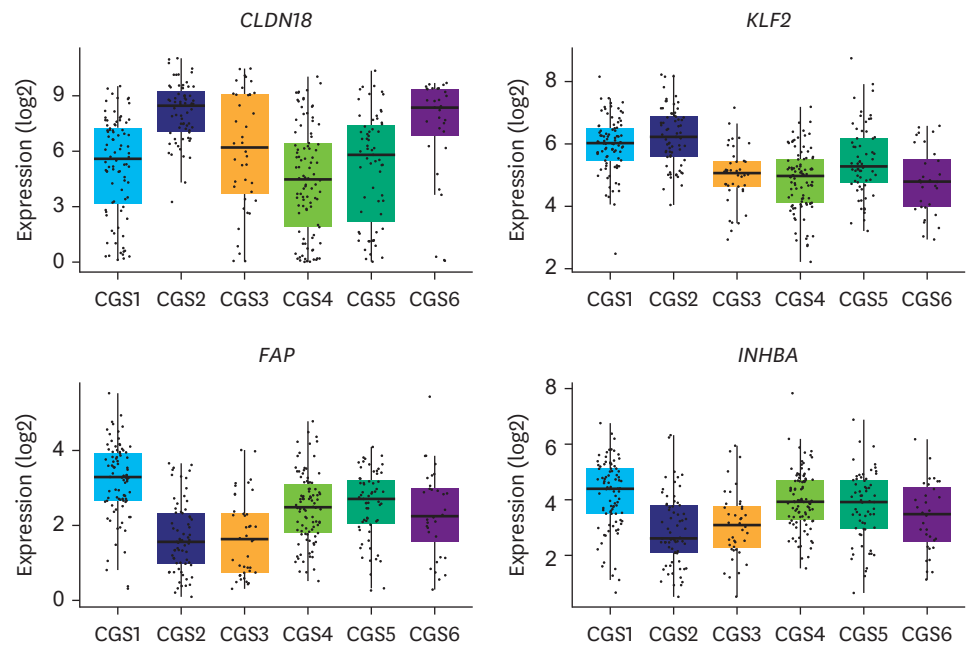


Fig. 3. Association of key molecular markers and therapeutic targets with CGS (Super 6) molecular subtypes in TCGA-STAD. Expression patterns of *CLDN18*, *KLF2*, *FAP*, and *INHBA* are displayed across the CGS (Super 6) subtypes. *CLDN18* shows the highest expression in CGS2 and CGS6, whereas *KLF2* expression is elevated in CGS1, CGS2, and CGS5. Both *FAP* and *INHBA* are most highly expressed in CGS1. *CLDN18* represents the therapeutic target of the CLDN18.2-directed antibody zolbetuximab; *KLF2* serves as a marker of plasma cell infiltration; and *FAP* and *INHBA* are established markers of CAFs. CGS = consensus genomic subtypes (CGS1–CGS6); TCGA = The Cancer Genome Atlas; CAF = cancer-associated fibroblast.

cohorts is required. MSI-H and EBV-positive (CGS5–CGS6) tumors are characterized by high PD-L1 expression, elevated neoantigen load, and dense T-cell infiltration, consistent with their strong response to PD-1 blockade using agents such as nivolumab and pembrolizumab. An analysis of TCGA data demonstrated high expression of *CLDN18*, the target of the CLDN18.2-directed antibody zolbetuximab, in the CGS2 and CGS6 subtypes (**Fig. 3**), providing a molecular basis for patient selection and genomic rationale for the efficacy of CLDN18.2-targeted therapy. In contrast, GS- or EMT-enriched (CGS1) tumors remain largely refractory to existing therapies. Molecular profiling supports the investigation of novel agents targeting YAP/TEAD signaling (e.g., VT3989) [61] and strategies aimed at reprogramming the tumor microenvironment to overcome immune exclusion and therapeutic resistance.

Beyond individual therapies, molecular subtyping provides a framework for biomarker-driven clinical trial design and cross-study harmonization. This framework enables rational patient selection for precision agents, reduces biological heterogeneity in trial cohorts, and enhances the identification of predictive biomarkers. The Super 6 (CGS1–CGS6) consensus taxonomy has unified prior classification systems into a robust, multi-ethnic framework, setting the stage for molecular diagnostics in routine clinical practice. Integration of established biomarkers, such as HER2, PD-1/PD-L1, and MSI, with transcriptome-based tools, such as the Gastric Cancer Predictor of Integrated Consensus Subtype with 120 genes (GPICS120) [31], provides an formalin-fixed paraffin-embedded-compatible platform that translates multi-omic signatures into clinically actionable assays for prognosis and treatment selection.

CONCLUSION

Over the past 2 decades, the molecular dissection of gastric cancer has transformed our understanding of this complex disease from a histological to a genomic and transcriptomic continuum. Multiple studies, including TCGA and ACRG, together with subsequent Super 6 subtyping have established a biologically coherent framework that links molecular alterations, immune contexts, and clinical behaviors. This integrative taxonomy now underpins biomarker-driven therapy, enabling rational use of HER2-targeted agents for CIN-HER2 (CGS3) tumors, ICIs for MSI-H and EBV-positive (CGS5–CGS6) tumors, and emerging pathway inhibitors for EMT/Stem-like (CGS1) tumors.

Despite these advances, translation into routine clinical practice remains incomplete. Most classifications rely on primary resection specimens and bulk data that overlook tumor-stroma-immune dynamics, metastatic evolution, and spatial heterogeneity. Future research will require integration of single-cell, spatial, and liquid biopsy-based profiling to capture tumor plasticity and microenvironmental ecosystems. The convergence of these technologies with consensus subtyping will foster a next-generation clinically deployable taxonomy that aligns molecular identity with therapeutic vulnerability. Ultimately, realization of precision therapy for gastric cancer depends on embedding these molecular insights into clinical decision-making and prospective biomarker-guided trials to improve patient outcomes worldwide.

REFERENCES

1. Filho AM, Laversanne M, Ferlay J, Colombet M, Piñeros M, Znaor A, et al. The GLOBOCAN 2022 cancer estimates: data sources, methods, and a snapshot of the cancer burden worldwide. *Int J Cancer* 2025;156:1336-1346. [PUBMED](#) | [CROSSREF](#)
2. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2024;74:229-263. [PUBMED](#) | [CROSSREF](#)
3. Sun D, Mülder DT, Li Y, Nieboer D, Park JY, Suh M, et al. The effect of nationwide organized cancer screening programs on gastric cancer mortality: a synthetic control study. *Gastroenterology* 2024;166:503-514. [PUBMED](#) | [CROSSREF](#)
4. Abengoza R, Sharma A, Sharma R. Gastric cancer: lessons learned from high-incidence geographic regions. *J Gastrointest Oncol* 2021;12:S350-S360. [PUBMED](#) | [CROSSREF](#)
5. Morgan E, Arnold M, Camargo MC, Gini A, Kunzmann AT, Matsuda T, et al. The current and future incidence and mortality of gastric cancer in 185 countries, 2020–40: a population-based modelling study. *EClinicalMedicine* 2022;47:101404. [PUBMED](#) | [CROSSREF](#)
6. Van Cutsem E, Sagaert X, Topal B, Haustermans K, Prenen H. Gastric cancer. *Lancet* 2016;388:2654-2664. [PUBMED](#) | [CROSSREF](#)
7. Ajani JA, Lee J, Sano T, Janjigian YY, Fan D, Song S. Gastric adenocarcinoma. *Nat Rev Dis Primers* 2017;3:17036. [PUBMED](#) | [CROSSREF](#)
8. Sundar R, Nakayama I, Markar SR, Shitara K, van Laarhoven HWM, Janjigian YY, et al. Gastric cancer. *Lancet* 2025;405:2087-2102. [PUBMED](#) | [CROSSREF](#)
9. Fox JG, Wang TC. Inflammation, atrophy, and gastric cancer. *J Clin Invest* 2007;117:60-69. [PUBMED](#) | [CROSSREF](#)
10. Duan Y, Xu Y, Dou Y, Xu D. *Helicobacter pylori* and gastric cancer: mechanisms and new perspectives. *J Hematol Oncol* 2025;18:10. [PUBMED](#) | [CROSSREF](#)
11. Naseem M, Barzi A, Brezden-Masley C, Puccini A, Berger MD, Tokunaga R, et al. Outlooks on Epstein–Barr virus associated gastric cancer. *Cancer Treat Rev* 2018;66:15-22. [PUBMED](#) | [CROSSREF](#)
12. Ignatova E, Seriak D, Fedyanin M, Tryakin A, Pokataev I, Menshikova S, et al. Epstein–Barr virus-associated gastric cancer: disease that requires special approach. *Gastric Cancer* 2020;23:951-960. [PUBMED](#) | [CROSSREF](#)

13. Bouras E, Tsilidis KK, Triggi M, Siargkas A, Chourdakis M, Haidich AB. Diet and risk of gastric cancer: an Umbrella Review. *Nutrients* 2022;14:1764. [PUBMED](#) | [CROSSREF](#)
14. Guilford P, Hopkins J, Harraway J, McLeod M, McLeod N, Harawira P, et al. E-cadherin germline mutations in familial gastric cancer. *Nature* 1998;392:402-405. [PUBMED](#) | [CROSSREF](#)
15. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand* 1965;64:31-49. [PUBMED](#) | [CROSSREF](#)
16. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. *Histopathology* 2020;76:182-188. [PUBMED](#) | [CROSSREF](#)
17. Biesma HD, Soeratrham TTD, van Essen HF, Egthuijsen JMP, Poell JB, van Dijk E, et al. Chromosomal copy number based stratification of gastric cancer has added prognostic value to Lauren's histological classification. *BJC Rep* 2024;2:58. [PUBMED](#) | [CROSSREF](#)
18. Sexton RE, Hallak MNA, Uddin MH, Diab M, Azmi AS. Gastric cancer heterogeneity and clinical outcomes. *Technol Cancer Res Treat* 2020;19:1533033820935477. [PUBMED](#) | [CROSSREF](#)
19. Shi D, Yang Z, Cai Y, Li H, Lin L, Wu D, et al. Research advances in the molecular classification of gastric cancer. *Cell Oncol (Dordr)* 2024;47:1523-1536. [PUBMED](#) | [CROSSREF](#)
20. Díaz Del Arco C, Fernández Aceñero MJ, Ortega Medina L. Molecular classifications in gastric cancer: a call for interdisciplinary collaboration. *Int J Mol Sci* 2024;25:2649. [PUBMED](#) | [CROSSREF](#)
21. Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V, et al. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. *Lancet* 1996;347:995-999. [PUBMED](#) | [CROSSREF](#)
22. Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol* 2010;11:439-449. [PUBMED](#) | [CROSSREF](#)
23. Al-Batran SE, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet* 2019;393:1948-1957. [PUBMED](#) | [CROSSREF](#)
24. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;355:11-20. [PUBMED](#) | [CROSSREF](#)
25. Lordick F, Mauer ME, Stocker G, Cella CA, Ben-Aharon I, Piessen G, et al. Adjuvant immunotherapy in patients with resected gastric and oesophagogastric junction cancer following preoperative chemotherapy with high risk for recurrence (ypN+ and/or R1): European Organisation of Research and Treatment of Cancer (EORTC) 1707 VESTIGE study. *Ann Oncol* 2025;36:197-207. [PUBMED](#) | [CROSSREF](#)
26. Rahman S, Thomas B, Maynard N, Park MH, Wahedally M, Trudgill N, et al. Impact of postoperative chemotherapy on survival for oesophagogastric adenocarcinoma after preoperative chemotherapy and surgery. *Br J Surg* 2022;109:227-236. [PUBMED](#) | [CROSSREF](#)
27. Shitara K, Fleitas T, Kawakami H, Curigliano G, Narita Y, Wang F, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with gastric cancer. *ESMO Open* 2024;9:102226. [PUBMED](#) | [CROSSREF](#)
28. Lee J, Lim DH, Kim S, Park SH, Park JO, Park YS, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. *J Clin Oncol* 2012;30:268-273. [PUBMED](#) | [CROSSREF](#)
29. Park SH, Sohn TS, Lee J, Lim DH, Hong ME, Kim KM, et al. Phase III trial to compare adjuvant chemotherapy with capecitabine and cisplatin versus concurrent chemoradiotherapy in gastric cancer: final report of the adjuvant chemoradiotherapy in stomach tumors trial, including survival and subset analyses. *J Clin Oncol* 2015;33:3130-3136. [PUBMED](#) | [CROSSREF](#)
30. Cats A, Jansen EPM, van Grieken NCT, Sikorska K, Lind P, Nordsmark M, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. *Lancet Oncol* 2018;19:616-628. [PUBMED](#) | [CROSSREF](#)
31. Jeong YS, Eun YG, Lee SH, Kang SH, Yim SY, Kim EH, et al. Clinically conserved genomic subtypes of gastric adenocarcinoma. *Mol Cancer* 2023;22:147. [PUBMED](#) | [CROSSREF](#)
32. Pietrantonio F, Miceli R, Raimondi A, Kim YW, Kang WK, Langley RE, et al. Individual Patient Data Meta-Analysis of the Value of Microsatellite Instability As a Biomarker in Gastric Cancer. *J Clin Oncol* 2019;37:3392-3400. [PUBMED](#) | [CROSSREF](#)

33. Smyth EC, Wotherspoon A, Peckitt C, Gonzalez D, Hulkki-Wilson S, Eltahir Z, et al. Mismatch repair deficiency, microsatellite instability, and survival: an exploratory analysis of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial. *JAMA Oncol* 2017;3:1197-1203. [PUBMED](#) | [CROSSREF](#)
34. Raimondi A, Lonardi S, Murgioni S, Cardellino GG, Tamperi S, Strippoli A, et al. Tremelimumab and durvalumab as neoadjuvant or non-operative management strategy of patients with microsatellite instability-high resectable gastric or gastroesophageal junction adenocarcinoma: the INFINITY study by GONO. *Ann Oncol* 2025;36:285-296. [PUBMED](#) | [CROSSREF](#)
35. André T, Tougeron D, Piessen G, de la Fouchardière C, Louvet C, Adenis A, et al. Neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in localized deficient mismatch repair/microsatellite instability-high gastric or esophagogastric junction adenocarcinoma: the GERCOR NEONIPGA phase II study. *J Clin Oncol* 2023;41:255-265. [PUBMED](#) | [CROSSREF](#)
36. Lordick F, Carneiro F, Cascinu S, Fleitas T, Haustermans K, Piessen G, et al. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2022;33:1005-1020. [PUBMED](#) | [CROSSREF](#)
37. Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Cooke D, Corvera C, et al. Gastric cancer, version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2022;20:167-192. [PUBMED](#) | [CROSSREF](#)
38. Shitara K, Ajani JA, Moehler M, Garrido M, Gallardo C, Shen L, et al. Nivolumab plus chemotherapy or ipilimumab in gastro-oesophageal cancer. *Nature* 2022;603:942-948. [PUBMED](#) | [CROSSREF](#)
39. Kang YK, Chen LT, Ryu MH, Oh DY, Oh SC, Chung HC, et al. Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2022;23:234-247. [PUBMED](#) | [CROSSREF](#)
40. Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet* 2021;398:27-40. [PUBMED](#) | [CROSSREF](#)
41. Chao J, Fuchs CS, Shitara K, Tabernero J, Muro K, Van Cutsem E, et al. Assessment of pembrolizumab therapy for the treatment of microsatellite instability-high gastric or gastroesophageal junction cancer among patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 clinical trials. *JAMA Oncol* 2021;7:895-902. [PUBMED](#) | [CROSSREF](#)
42. Rha SY, Oh DY, Yañez P, Bai Y, Ryu MH, Lee J, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol* 2023;24:1181-1195. [PUBMED](#) | [CROSSREF](#)
43. Zhang X, Wang J, Wang G, Zhang Y, Fan Q, Lu C, et al. First-line sugemalimab plus chemotherapy for advanced gastric cancer: the GEMSTONE-303 randomized clinical trial. *JAMA* 2025;333:1305-1314. [PUBMED](#) | [CROSSREF](#)
44. Qiu MZ, Oh DY, Kato K, Arkenau T, Tabernero J, Correa MC, et al. Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first line treatment for advanced gastric or gastro-oesophageal junction adenocarcinoma: RATIONALE-305 randomised, double blind, phase 3 trial. *BMJ* 2024;385:e078876. [PUBMED](#) | [CROSSREF](#)
45. Xu J, Jiang H, Pan Y, Gu K, Cang S, Han L, et al. Sintilimab plus chemotherapy for unresectable gastric or gastroesophageal junction cancer: the ORIENT-16 randomized clinical trial. *JAMA* 2023;330:2064-2074. [PUBMED](#) | [CROSSREF](#)
46. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010;376:687-697. [PUBMED](#) | [CROSSREF](#)
47. Janjigian YY, Kawazoe A, Yañez P, Li N, Lonardi S, Kolesnik O, et al. The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. *Nature* 2021;600:727-730. [PUBMED](#) | [CROSSREF](#)
48. Shitara K, Bang YJ, Iwasa S, Sugimoto N, Ryu MH, Sakai D, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. *N Engl J Med* 2020;382:2419-2430. [PUBMED](#) | [CROSSREF](#)
49. Shitara K, Lordick F, Bang YJ, Enzinger P, Ilson D, Shah MA, et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. *Lancet* 2023;401:1655-1668. [PUBMED](#) | [CROSSREF](#)
50. Shah MA, Shitara K, Ajani JA, Bang YJ, Enzinger P, Ilson D, et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. *Nat Med* 2023;29:2133-2141. [PUBMED](#) | [CROSSREF](#)

51. Kusano M, Toyota M, Suzuki H, Akino K, Aoki F, Fujita M, et al. Genetic, epigenetic, and clinicopathologic features of gastric carcinomas with the CpG island methylator phenotype and an association with Epstein–Barr virus. *Cancer* 2006;106:1467-1479. [PUBMED](#) | [CROSSREF](#)
52. Tan IB, Ivanova T, Lim KH, Ong CW, Deng N, Lee J, et al. Intrinsic subtypes of gastric cancer, based on gene expression pattern, predict survival and respond differently to chemotherapy. *Gastroenterology* 2011;141:476-485. [PUBMED](#) | [CROSSREF](#)
53. Lei Z, Tan IB, Das K, Deng N, Zouridis H, Pattison S, et al. Identification of molecular subtypes of gastric cancer with different responses to PI3-kinase inhibitors and 5-fluorouracil. *Gastroenterology* 2013;145:554-565. [PUBMED](#) | [CROSSREF](#)
54. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014;513:202-209. [PUBMED](#) | [CROSSREF](#)
55. Sohn BH, Hwang JE, Jang HJ, Lee HS, Oh SC, Shim JJ, et al. Clinical significance of four molecular subtypes of gastric cancer identified by The Cancer Genome Atlas project. *Clin Cancer Res* 2017;23:4441-4449. [PUBMED](#) | [CROSSREF](#)
56. Cristescu R, Lee J, Nebozhyn M, Kim KM, Ting JC, Wong SS, et al. Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. *Nat Med* 2015;21:449-456. [PUBMED](#) | [CROSSREF](#)
57. Lee KW, Lee SS, Hwang JE, Jang HJ, Lee HS, Oh SC, et al. Development and validation of a six-gene recurrence risk score assay for gastric cancer. *Clin Cancer Res* 2016;22:6228-6235. [PUBMED](#) | [CROSSREF](#)
58. Zagiel B, Melnyk P, Cotellet P. Progress with YAP/TAZ-TEAD inhibitors: a patent review (2018-present). *Expert Opin Ther Pat* 2022;32:899-912. [PUBMED](#) | [CROSSREF](#)
59. Santucci M, Vignudelli T, Ferrari S, Mor M, Scalvini L, Bolognesi ML, et al. The Hippo pathway and YAP/TAZ-TEAD protein-protein interaction as targets for regenerative medicine and cancer treatment. *J Med Chem* 2015;58:4857-4873. [PUBMED](#) | [CROSSREF](#)
60. Zhang L, Zhang F, Liang H, Qin X, Mo Y, Chen S, et al. Hippo/YAP signaling pathway in colorectal cancer: regulatory mechanisms and potential drug exploration. *Front Oncol* 2025;15:1545952. [PUBMED](#) | [CROSSREF](#)
61. Yap TA, Kwiatkowski DJ, Dagogo-Jack I, Offin M, Zauderer MG, Kratzke R, et al. YAP/TEAD inhibitor VT3989 in solid tumors: a phase 1/2 trial. *Nat Med* 2025;31:4281-4290. [PUBMED](#) | [CROSSREF](#)
62. Oh SC, Sohn BH, Cheong JH, Kim SB, Lee JE, Park KC, et al. Clinical and genomic landscape of gastric cancer with a mesenchymal phenotype. *Nat Commun* 2018;9:1777. [PUBMED](#) | [CROSSREF](#)
63. Cheong JH, Yang HK, Kim H, Kim WH, Kim YW, Kook MC, et al. Predictive test for chemotherapy response in resectable gastric cancer: a multi-cohort, retrospective analysis. *Lancet Oncol* 2018;19:629-638. [PUBMED](#) | [CROSSREF](#)
64. Shin MK, Kim J, Kim D, Lee SH, Shin JH, Jeong YS, et al. Long non-coding RNAs are significantly associated with prognosis and response to therapies in gastric cancer. *Clin Transl Med* 2021;11:e421. [PUBMED](#) | [CROSSREF](#)
65. Kumar V, Ramnarayanan K, Sundar R, Padmanabhan N, Srivastava S, Koiwa M, et al. Single-cell atlas of lineage states, tumor microenvironment, and subtype-specific expression programs in gastric cancer. *Cancer Discov* 2022;12:670-691. [PUBMED](#) | [CROSSREF](#)
66. Ma H, Srivastava S, Ho SWT, Xu C, Lian BSX, Ong X, et al. Spatially resolved tumor ecosystems and cell states in gastric adenocarcinoma progression and evolution. *Cancer Discov* 2025;15:767-792. [PUBMED](#) | [CROSSREF](#)
67. Lee JE, Kim KT, Shin SJ, Cheong JH, Choi YY. Genomic and evolutionary characteristics of metastatic gastric cancer by routes. *Br J Cancer* 2023;129:672-682. [PUBMED](#) | [CROSSREF](#)