Progress in Precision Medicine in the Management of Gastric Cancer.

Supriya Peshin[1]*, Shivani Modi[2], Gahyun Gim[3]

[1]Department of Internal Medicine, Norton Community Hospital, 24273, Norton, Virginia

[2]Department of internal medicine, 19141, Jefferson Einstein Healthcare Network, Norristown, PA

[3]Department of Hematology and oncology, university of Rochester, 14627, New York

Abstract

Gastric adenocarcinoma poses a significant global health challenge, accounting for substantial cancer-related mortality. Effective management hinges on precise tumour staging and characterization, guiding treatment decisions towards optimal outcomes. Early-stage cases may benefit from endoscopic resection, while locally advanced tumours often require comprehensive surgical intervention complemented by perioperative and adjuvant therapies. Recent therapeutic advancements, including immunotherapies and biomarker-targeted treatments, have shown promise in extending survival rates, particularly in metastatic settings. Molecular classifications, such as those proposed by the Cancer Genome Atlas and the Asian Cancer Research Group, have revolutionized GC management, facilitating the integration of diagnostic and therapeutic modalities through precision medicine approaches. Targeted therapies, notably monoclonal antibodies against VEGF, VEGFR-2, and HER2, have demonstrated efficacy, with ongoing research investigating their use in resectable HER2-positive cases. Despite these strides, challenges persist, including the heterogeneous nature of GC and the limited translation of scientific advancements into clinical practice. Survival rates remain low compared to other common cancers, highlighting the need for continued research and innovation. The integration of high-throughput molecular analyses and the development of personalized treatment strategies offer promising avenues for improving patient outcomes in advanced GC. Emerging approaches, such as molecularly matched therapies targeting HER2, Claudin, FGFR, and immunotherapy, hold the potential for enhancing clinical outcomes and reshaping the landscape of GC treatment. This review aims to provide a comprehensive overview of the molecular pathways involved in GC progression and the evolving landscape of precision medicine in the management of gastric adenocarcinoma.

Keywords: Epstein-barr virus (EBV), DNA hypermethylation, microsatellite instability, familial gastric cancers, PDL1, PDL2, HER2, diffuse gastric cancers: signet ring cell, microbiome.

Introduction

Gastric carcinoma (GC) represents a significant global health challenge, particularly prevalent in Asian and South American regions. In 2020, the United States alone anticipated 27,000 new cases, highlighting its public health significance. GC's heterogeneity, categorized by systems like Lauren and WHO classifications, reveals diverse subtypes with distinct clinical behaviors. The evolution of GC management incorporates molecular markers such as HER2 status to tailor therapies [1].

Despite widespread acceptance, effectively translating classifications into improved outcomes remains challenging. Subtypes like well-differentiated (intestinal) tumors generally forecast better prognoses, whereas poorly differentiated (diffuse) types typically lead to poorer survival rates. Late-stage diagnosis, intratumor variability, and chemotherapy resistance contribute to grim survival rates globally.

GC's etiology involves complex interactions of genetic and environmental factors such as H. pylori infection, smoking, and diet, underscoring its multifaceted development. H. pylori notably associates with non-cardia GC, linking chronic inflammation to gastric cancerogenesis. Genetic and epigenetic changes involving APC, TP53, and KRAS genes drive disease progression [2].

Clinical management primarily centers on surgical resection complemented by adjuvant or neoadjuvant therapies. However, tumor heterogeneity poses challenges in treatment selection, prompting research into novel biomarkers and targeted therapies. Established markers like HER2, Microsatellite Instability (MSI), and PD-L1 guide therapeutic decisions, with

Correspondence to: Supriya Peshin, Department of Internal Medicine,Norton Community Hospital ,24273, Norton, Virginia. E-mail: supriyapeshin720@gmail.com

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ongoing efforts to identify additional molecular alterations for precision medicine in GC [3,4].

Gastroesophageal adenocarcinoma (GEA), a substantial GC subset, shares similar clinical challenges. Despite efforts in molecular classification for precision medicine, few therapies have gained approval, necessitating continued research [5, 6]. Globally, GC ranks among the most diagnosed cancers and causes significant cancer-related mortality [7]. In 2023, approximately 26,500 new cases and 11,130 deaths are projected [8, 9].

This review synthesizes advances in precision medicine for gastric adenocarcinoma, covering molecular characterization, diagnostic implications, therapeutic strategies, and clinical challenges. By elucidating genetic complexities and therapeutic responses, this review aims to contribute to improving GC and GEA patient outcomes.

Morphological to Molecular Classifications

Gastric carcinoma (GC) presents a formidable challenge for clinicians due to its heterogeneity, leading to the development of both morphological and molecular classifications aimed at gaining deeper insights into its diverse characteristics. Lauren's classification, a traditional morphological system, categorizes GC into intestinal, diffuse, and indeterminate subtypes, reflecting variations in tumor location, age associations, and histopathological features. In contrast, the WHO classification categorizes adenocarcinoma subtypes based on tubular, papillary, mucinous, poorly cohesive (including signet ring cell type), and mixed variants, offering additional clarity on tumor morphology [10-13].

The emergence of molecular profiling has revolutionized our comprehension of GC by uncovering its underlying molecular mechanisms. Initiatives like The Cancer Genome Atlas (TCGA) and the Asian Cancer Research Group (ACRG) have proposed comprehensive molecular classifications that identify distinct subtypes through genomic, transcriptomic, and proteomic analyses. TCGA's classification includes subtypes such as Epstein-Barr virus (EBV)-positive, microsatellite instability (MSI), chromosomally unstable (CIN), and genomically stable (GS), each characterized by unique molecular features with potential implications for targeted therapies [14, 15].

Similarly, ACRG's classification, utilizing array-based gene-expression profiling, identifies subgroups like microsatellite stable with epithelial-to-mesenchymal transition (MSS/ EMT) and microsatellite stable with tumor protein p53 (TP53) mutations, offering further refinement in molecular characterization. Despite differences between these classifications, they collectively provide valuable insights into tumor biology and potential therapeutic targets [16].

However, challenges persist in translating molecular classifications into clinical practice. Tumor heterogeneity, evident across primary and metastatic lesions, poses a significant barrier to precision medicine approaches. Comprehensive molecular assessments, including liquid biopsies for cell-free DNA analysis, hold promise for overcoming these challenges and optimizing therapy selection for GC patients.

In conclusion, the shift from morphological to molecular classifications **(Table 1)** represents a significant advancement in understanding GC. By integrating histopathological and genomic insights, these classifications promise to guide personalized treatment strategies and enhance patient outcomes in GC. Further validation and effective translation of these classifications into clinical settings are essential areas for future research.

Localised disease

Early gastric cancer (EGC) is defined as adenocarcinoma confined to the mucosa or submucosa, without lymph node involvement. The primary treatment options are resection procedures, either endoscopic or surgical. In Eastern countries, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are commonly used and have shown effectiveness in treating EGC [17]. EMR is suitable for tumours with low risk of lymph node metastasis and allows for complete resection. A Korean study on EMR outcomes in EGC revealed no cancer-related deaths during a 3-year follow-up and a local recurrence rate of only 6%. However, successful outcomes depend heavily on appropriate patient

***Table 1*:** *Classification of Gastric Carcinoma (GC).*

Classification System	Description	Subtypes/Types of GC	Features/Molecular Characteristics	References
Morphological Classifications				
Lauren Classification	Morphological system categorizingGC into intestinal, diffuse, and indeterminate subtypes.	Intestinal, Diffuse, Indeterminate	Variations in tumor location, age association, histopathological characteristics	[7-10]
WHO Classification	Adenocarcinoma subtypes based on tubular, papillary, mucinous, poorly cohesive, and mixed variants.	Tubular, Papillary, Mucinous, Poorly Cohesive (including signet ring cell type), Mixed variants	Additional clarity on tumor morphology	[7-10]
Molecular Classifications				
TCGA Classification	Based on genomic, transcriptomic, and proteomic data, identifying subtypes like EBV-positive, MSI, CIN,GS.	EBV-positive, MSI, CIN, GS	Unique molecular features, potential implications for targetedtherapies	[8,9]
ACRG Classification	Utilizes array-based gene-expression profiling, identifying subgroups like MSS/EMT, MSS with TP53 mutations.	MSS/EMT, MSS with TP53 mutations	Further refinement in molecular characterization, insights into tumor biology, potential therapeutic targets	[13]

selection based on factors like endoscopic appearance, tumour grade, and depth of invasion. EMR is typically recommended for lesions smaller than 10–15 mm with a low probability of advanced histology, although it may sometimes lead to piecemeal resection and higher recurrence rates [18]. ESD, on the other hand, enables en-bloc resection and accurate histological assessment, proving superior to EMR, especially for larger lesions (>5 mm). ESD has comparable outcomes to surgery for EGC, with additional advantages such as shorter hospital stays, reduced costs, and improved quality of life. It has become the preferred treatment in Asia and is increasingly adopted in Western countries [19]. According to guidelines from the National Comprehensive Cancer Network (NCCN), EMR or ESD is appropriate for EGC that meets specific criteria, such as size, differentiation, invasion depth, absence of lymph-vascular invasion, and clearmargins. The Japanese Gastric Cancer Association (JGCA) guidelines expand the indications for ESD to include certain differentiated-type adenocarcinomas based on clinical diagnosis criteria. Surgical resection is recommended for EGC tumours that do not meet these criteria [20].

Microbiome and Gastric Cancer

H. pylori infection induces chronic inflammation of the gastric mucosa, leading to cell cycle alterations in gastric epithelial cells. This process progresses to glandular atrophy, intestinal metaplasia, and ultimately GC. Apart from H. pylori, other microorganisms in the stomach have also been implicated in gastric carcinogenesis. Understanding their distribution and functions could pave the way for novel therapeutic strategies. Dysbiosis, characterized by compositional and functional changes in the microbiome, plays a critical role in this context. Despite numerous studies exploring microbial dysbiosis in gastric carcinogenesis, a consensus on the alteration patterns of the gastric microbiome remains elusive [21].

Some studies indicate a significant decrease in microbial diversity in inflammatory diseases and cancer, including GC [22]. Conversely, another study reported a reduction in microbial diversity from normal to atrophic stages [23]. However, conflicting research suggests increased richness and diversity of the gastric microbiome in GC tissues compared to controls. One study observed a gradual decrease in bacterial richness and diversity from healthy controls through non-atrophic chronic gastritis, intestinal metaplasia, to GC. Furthermore, microbial diversity was found to be higher in advanced-stage GC compared to early-stage, which showed no significant difference from chronic gastritis. Specific bacteria such as Novosphingobium, Ralstonia, Ochrobactrum, Anoxybacillus, and Pseudoxanthomonas were enriched in early GC, whereas Burkholderia, Tsukamurella, Uruburuella, and Salinivibrio were more abundant in advanced GC [24]. However, another study found no significant difference in microbial community composition between early- and late-stage GC, although microbial richness decreased from normal to peritumoral to tumoral tissues. Additionally, tumor tissues showed reduced levels of Prevotella copri and Bacteroides uniformis, while Prevotella melaninogenica, Streptococcus anginosus, and Propionibacterium acnes were enriched compared to normal and peritumoral tissues [25].

Recent studies have differentiated microbial compositions across GC subtypes. Fusobacteria, Bacteroidetes, and Patescibacteria were enriched in signet-ring cell carcinoma, whereas Proteobacteria and Acidobacteria were more common in adenocarcinoma [26]. Dysbiosis of the oral microbiome has been associated with inflammatory bowel disease, colorectal cancer, and pancreatic cancer [27]. In GC samples, oral microbiota such as Peptostreptococcus, Streptococcus, and Fusobacterium were found to be more abundant compared to adjacent non-tumor samples. A study using 16S rRNA gene sequencing to investigate the gastric microbiome across stages from superficial gastritis to GC reported enrichment of oral bacteria like Peptostreptococcus stomatis, S. anginosus, Parvimonas micra, Slackia exigua, and Dialister pneumosintes in GC compared to precancerous stages [28]. These findings suggest that changes in stomach acidity in GC may facilitate colonization by oral bacteria, although further research is needed to clarify the role of the oral microbiome in gastric carcinogenesis.

Lactobacillus, a major genus in the gut microbiome, is known for alleviating various gastrointestinal conditions. Lactic acid produced by these bacteria has immunomodulatory, anti-inflammatory, and potentially anti-cancer effects [29]. However, lactic acid-producing bacteria have also been implicated in gastric carcinogenesis. Studies have reported an increased abundance of Lactobacillus in GC compared to gastritis or intestinal metaplasia, consistent with other findings. Another study noted enrichment of Lactococcus lactis and Lactobacillus brevis in adjacent non-tumor tissue. Animal experiments have also suggested a potential carcinogenic role for Lactobacillales in GC [30-35].

Immune checkpoint inhibitors

Immune checkpoint inhibitors (ICIs) targeting the programmed death-1 (PD-1) and PD-L1 pathways have emerged as a promising therapeutic avenue in GC. However, their efficacy in GC varies and is influenced by several factors, including PD-L1 positivity [36-40].

The pivotal ATTRACTION-2 study demonstrated the efficacy of nivolumab, an anti-PD1 antibody, in advanced gastro-oesophageal cancers, leading to its approval in select Asian populations. Although exploratory analyses did not show a survival benefit based on PD-L1 expression, subsequent trials like KEYNOTE-059 highlighted improved response rates with pembrolizumab in PD-L1-positive disease, influencing regulatory approvals in certain regions [41].

However, challenges arose when pembrolizumab failed to show superiority over chemotherapy in second-line treatment, prompting investigations into biomarkers for patient selection. Post hoc analyses identified microsatellite instability-high (MSI-H), high PD-L1 expression (combined positive score [CPS] $\geq$ 10), and tumor mutational burden (TMB $\geq$ 10 mutations/Mb) as potential predictors of pembrolizumab response, emphasizing the need for refined patient stratification [42].

Further studies like CheckMate 649 and ATTRACTION-4 demonstrated the efficacy of chemo-immunotherapy

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combinations in the first-line setting, leading to a paradigm shift in treatment approaches. However, geographical nuances in regulatory approvals underscore the importance of patient selection based on PD-L1 expression levels [43].

Assessing PD-L1 expression introduces complexities due to differences in companion diagnostic assays. While the Dako 22C3 assay is associated with pembrolizumab, the Dako 28-8 assay used in trials like CheckMate 649 reported higher PD-L1 positivity rates. Understanding assay variation and interchangeability is crucial for effective patient selection and treatment decisions [44].

Moreover, PD-L1 expression exhibits spatial and temporal heterogeneity, posing challenges for accurate assessment. Despite limitations, the PD-L1 combined positive score (CPS) remains valuable for its relative simplicity and timely reporting in clinical practice.

In summary, while ICIs represent a significant advancement in GC treatment, their efficacy is closely tied to precise patient selection, necessitating continued refinement of predictive biomarkers and diagnostic assays.

Mismatch Repair Deficiency (MMRd) in Gastric Cancer

The use of ICIs in GC necessitates a thorough understanding of predictive biomarkers, with mismatch repair deficiency (MMRd) or MSI-H emerging as key indicators of ICI efficacy. MMRd results in MSI-H, characterized by elevated tumour mutational burden (TMB) due to frequent frameshift and single-nucleotide variants [45].

In gastric cancer, MSI-H/MMRd occurs in approximately 8% of surgically resectable cases and 4-5% of advanced cases. Meta-analyses of phase III trials underscore MSI-H as the strongest predictor of ICI benefit, with significantly improved overall survival (OS) and response rates compared to microsatellite stable disease. However, only around 50% of MSI-H patients demonstrate objective responses to ICIs, suggesting inherent resistance in some cases [46].

Studies investigating the molecular landscape of MSI-H gastric cancers reveal potential biomarkers associated with ICI response. Higher TMB, activation of the T-cell receptor (TCR) pathway, and a diverse TCR repertoire are linked to pembrolizumab benefit. Conversely, alterations in pathways like Wingless-Related Integration Site (WNT), Cadherin 1 (CDH1), Janus Kinase 2 (JAK2), Erb-B2 Receptor Tyrosine Kinase 2 (ERBB2), and Fibroblast Growth Factor Receptor 2 (FGFR2), along with terminally differentiated exhausted CD8+ T-cells, indicate insensitivity to pembrolizumab [47].

Despite the promise of ICIs in MSI-H/MMRd gastric cancer, response heterogeneity highlights the need for further research into predictive biomarkers and therapeutic strategies. Ongoing clinical trials aim to address these gaps and optimize treatment outcomes for this patient subset.

Epstein Bar Virus Positive tumors

The Epstein-Barr virus (EBV), a member of the Herpesviridae family, has long been associated with various human cancers, including Hodgkin lymphoma, Burkitt lymphoma, and nasopharyngeal carcinoma. In the early 1990s, its link to gastric carcinomas was established, with subsequent studies confirming its role in gastric adenocarcinoma [48].

The mechanisms of EBV-associated gastric cancer are complex and not fully understood. Virological factors, combined with host genome abnormalities, contribute to cancer progression. EBV encodes oncoproteins that target cellular pathways, and EBV-associated gastric cancer is classified as latency type I, characterized by high expression of specific EBV genes. This latent infection and gene expression lead to host genome abnormalities, including aberrant DNA methylation [49].

Diagnosis of EBV infection relies on in situ hybridization (ISH) to detect EBV-encoded small RNA-1 (EBER1) in histopathologic samples. EBER1 signals are highly expressed in latently EBV-infected cells, aiding in diagnosis. Polymerase chain reaction (PCR) is also used but has lower specificity due to potential false positives [50].

In gastric cancers, EBV positivity is found in 9% of cases and is associated with distinct molecular profiles, including high expression of immune checkpoint proteins like PD-L1 and PD-L2, immune cell infiltration, DNA hypermethylation, and specific mutations. Despite its rarity, EBV-positive patients show sensitivity to ICI monotherapy. Studies have reported significant responses in EBV-positive patients, highlighting the potential utility of EBV testing in widening treatment options, especially in later-line therapies. However, the low prevalence of EBV may limit its broader use as a predictive biomarker for ICI response. Nonetheless, EBV testing should be considered where available to guide treatment decisions and potentially improve outcomes for eligible patients [51].

Tumor mutational burden as a Predictor of Immunotherapy Response

TMB reflecting the total number of mutations per coding area of a tumour genome, serves as a predictive biomarker for response to ICIs. Tumors with high TMB, such as those with MSI-H, often contain more neoantigens, enhancing their immunogenicity [52].

TMB assessment can be conducted through whole exome sequencing or targeted gene panels, with both methods showing good concordance. Pembrolizumab has FDA approval for all solid tumors with a TMB of ≥10 mutations per megabase (Mb), based on data from the KEYNOTE-158 study. Notably, this study did not include a cohort of gastric adenocarcinoma [53].

In esophagogastric adenocarcinoma, the median TMB typically ranges between 5 and 6 mutations per Mb, but there's no consensus on defining 'high TMB' in this tumor type. However, a post hoc analysis of patients from KEYNOTE-061 revealed a strong correlation between high TMB and improved outcomes in pembrolizumab-treated patients. This association was significant for objective response rate (ORR), progression-free survival (PFS), and overall survival (OS), regardless of the method used to determine TMB [54].

These findings were not replicated in patients receiving paclitaxel in the same study. Thus, TMB assessment,

especially through next-generation sequencing methods, can be considered to guide patient selection for immunotherapy. However, it's essential to consider the limitations and nuances of the available data when interpreting TMB results for treatment decisions [55].

Microsatellite Unstable tumours

Microsatellites (MS), also known as Short Tandem Repeats (STRs) or Simple Sequence Repeats (SSRs), consist of repeated sequences of 1–6 nucleotides. These sequences differ from the 15 to 65 nucleotide tandem repeats of small satellite DNA, which are primarily located near the ends of chromosomes. Microsatellites are widely distributed throughout the genome, often located near coding regions, but they can also be found in introns and non-coding regions. Each specific microsatellite site is composed of two parts: the central core and the peripheral flanks. The specificity of microsatellites is mainly due to changes in the number of core repeating units [56].

The generation of microsatellites is generally believed to result from DNA slippage during replication or from mismatches between the slippage strand and the complementary strand during DNA replication and repair. This can lead to the insertion or deletion of one or more repeating units. Normally, the DNA repair system, called mismatch repair (MMR), corrects these replication errors. However, in tumour cells, the lack of MMR genes or defects in replication repair increases the likelihood of gene mutations. MSI is thus an important factor in tumour development [57].

Based on the frequency of MSI, it can be classified into three types: MSI-H, low microsatellite instability (MSI-L), and MSS. Clinical research often groups MSI-L and MSS together. MSI in colorectal cancer can be divided into two categories: sporadic colorectal cancer with no obvious family history and Lynch syndrome, a hereditary non-polyposis colorectal cancer. Most MSI cases are sporadic colorectal cancers caused by the epigenetic inactivation of gene expression due to the methylation of the hMLH1 promoter without gene mutation. Lynch syndrome, an autosomal dominant tumor syndrome, is caused by mutations in MMR genes and can also lead to tumors in other parts of the colon and rectum [58].

Due to early limitations in MSI detection and the ambiguity surrounding the MSI mechanism, only certain chemotherapy drugs were initially used to treat MSI patients, with limited success. However, recent advances in MSI detection technology and immunotherapy have shown that MSI-H tumours respond well to immunotherapy. The FDA has approved the PD-L1 (programmed cell death ligand 1) blocker Keytruda for treating MSI-H/MMR patients. The development of immunosuppressive drugs has facilitated the study of the immune response caused by MSI tumours. Researchers have discovered that drugs suitable for MSI-H treatment, such as PD-L1 immunosuppressants, can produce hetero antigens easily recognized by T cells in dMMR cancer cells, benefiting a variety of MSI-H tumours [59].

Current research focuses on specific tumour targets of MSI. Studies found that RecQDNA helicase WRN (Werner syndrome, RecQ helicase-like) is essential for MSI models but not for microsatellite-stable tumours. Silencing WRN induces DNA double-strand breakage, activates the DNA damage response, and induces apoptosis and cell cycle arrest in MSI tumours without harming normal cells, suggesting that WRN could be a target for lethal synthesis.

These studies indicate that microsatellite mutation is a complex, multi-pathway process. Continued advancements in understanding the MSI mechanism will play a crucial role in future clinical diagnosis and treatment applications [60] **(Table 2).**

Chromosomally Unstable Subtype

The chromosomally unstable (CIN) subtype constitutes approximately 50% of GC tumours and is predominantly associated with the gastroesophageal junction (GEJ)/cardia region. Within CIN GC tumours, mutations in TP53 are prevalent in 71% of cases, followed by mutations in ARID1A, KRAS, PIK3CA, RNF43, ERBB2, and APC genes. The heightened expression of p53 aligns with the observed TP53 mutations and the aneuploidy characteristic of CIN GC tumours. Notably, the APC and TP53 loci exhibit the highest frequency of loss of heterozygosity in this subtype. TP53 alterations have been linked to early gastric carcinogenesis, suggesting a pivotal role in disease progression. Additionally, phosphorylation of the epidermal growth factor receptor (EGFR) (pY1068) is notably increased in the CIN subtype, consistent with EGFR amplification detected in this subtype [61].

A key characteristic of the CIN subtype is the frequent genomic amplification of genes encoding receptors of tyrosine kinases (RTKs), contributing to aberrant cell growth promotion. Notably, VEGFA, encoding the ligand VEGFA, is frequently amplified in this subtype, as observed in studies of ramucirumab, a VEGFR2-targeting antibody. Furthermore, amplifications of cell cycle mediators (CCNE1, CCND1, and CDK6) are prevalent in the CIN subtype. Many of these genomic amplifications are potential targets for therapeutics currently available or under development, particularly cyclin-dependent kinase inhibitors [62].

Historically, GC was regarded as a single disease entity. However, it is now categorised into at least four subtypes based on identified genetic alterations. These subtypes exhibit distinct clinical features such as aetiology, gender, age of diagnosis, and anatomical localization. This emphasises the importance of understanding the diverse carcinogenic processes underlying each subtype, as well as the pertinent genes and pathways susceptible to therapeutic intervention [63] **(Table 3)**.

Familial gastric cancers

The genes that can predispose individuals to hereditary diffuse gastric cancer (HDGC) include CDH1 and CTNNA1. HDGC is the most common hereditary cancer syndrome associated with an increased risk of gastric cancer, and it does not have an easily detectable precursor lesion. Other hereditary cancer syndromes can also lead to various forms of gastric

***Table 2**: Subtypes and Genetic Alterations in Gastric Cancer.*

Subtype	Genetic Alterations	Clinical Features
Early Gastric Cancer (EGC)	Mucosal or submucosal adenocarcinoma	- Confined to mucosa or submucosa, without lymph node involvement. - Primary treatment: Endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD).
Microbiome Influence	Dysbiosis, changes in microbial diversity	- H. pylori infection leads to chronic inflammation, contributing to gastric carcinogenesis. - Altered microbiome composition observed in different stages of gastric cancer.
Immune Checkpoint Inhibitors	PD-1/PD-L1 pathway inhibition	- Efficacy in GC varies, influenced by PD-L1 expression. - Studies like ATTRACTION-2 and KEYNOTE-059 highlight improved response rates in PD-L1-positive disease.
Mismatch Repair Deficiency	MSI-H, high TMB	- Strong predictor of ICI benefit in GC. - Associated with higher TMB and specific gene alterations(e.g., mutations in MMR genes).
Epstein-Barr Virus Positive	EBV infection, DNA hypermethylation	- Latent EBV infection associated with distinct molecular profiles and sensitivity to ICIs. - Diagnosisvia EBER1 ISH or PCR.
Tumor Mutational Burden	TMB ≥ 10 mutations/Mb	- Predictive biomarker for ICI response in various cancers, including GC. - Determined via wholeexome sequencing or targeted gene panels.
Microsatellite Unstable Tumors	MSI-H, mutations in MMR genes	- MSI-H tumors respond well to ICIs, associated with defects in MMR genes. - Key biomarker inLynch syndrome and sporadic colorectal cancers.
Chromosomally Unstable Subtype	TP53, ARID1A, KRAS, PIK3CA mutations	- Prevalent in gastroesophageal junction tumors. - Genomic amplifications of RTKs and cell cycle mediators contribute to aberrant cell growth.

***Table 3:** Summarizing the information about the Chromosomally Unstable (CIN) subtype in gastrointestinal cancers.*

Syndrome / Subtype	Associated Genes	Key Clinical Features
Chromosomally Unstable (CIN) Subtype in GC	TP53, ARID1A, KRAS, PIK3CA, RNF43, ERBB2, APC, EGFR	Predominantly associated with gastroesophageal junction/cardia region, high p53 expression, frequent aneuploidy, genomic amplifications (e.g., RTKs, VEGFA), loss of heterozygosity at APC and TP53 loci.
Hereditary Diffuse Gastric Cancer (HDGC)	CDH1, CTNNA1	Autosomal dominant, high risk of diffuse gastric cancer and breast carcinoma, often requires prophylactic gastrectomy, CDH1 gene testing.
Lynch Syndrome	MLH1, MSH2, MSH6, PMS2, EPCAM	Increased risk of various cancers including gastric cancer, unclear role of screening, not associated withspecific gastric cancer precursor lesions.
Familial Adenomatous Polyposis (FAP)	APC	Numerous adenomatous colorectal polyps, increased gastric polyps, higher gastric cancer risk in East Asia, screening and prophylactic measures recommended.
Mutyh-Associated Polyposis (MAP)	MUTYH	Autosomal recess

cancer. For example, Lynch syndrome, caused by pathogenic variants in MLH1, MSH2, MSH6, PMS2, and EPCAM, presents an unclear risk of gastric cancer, and the role of gastric cancer screening remains ambiguous since a Lynch syndrome–associated gastric cancer precursor has not been identified. Familial adenomatous polyposis (FAP) and gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), caused by pathogenic variants in APC, typically present gastric cancer preceded by fundic gland polyps. Peutz-Jeghers syndrome (PJS), resulting from pathogenic variants in STK11, usually leads to gastric cancer preceded by hamartomatous polyps. Juvenile polyposis syndrome (JPS), caused by pathogenic variants in SMAD4 and BMPR1A, generally has gastric cancer preceded by hamartomatous polyps. In each of these syndromes, the risk of gastric polyps and gastric cancer is secondary to the risk of colorectal polyps and colorectal cancer. The burden of gastric polyps, including their count and size, and the associated risk of gastric cancer can vary between individuals [64].

Familial Adenomatous Polyposis/Attenuated Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant disorder characterised by numerous adenomatous colorectal polyps and associated gastric polyps, with incidences ranging from 51% to 88%, and up to 93% in attenuated FAP (AFAP). Paediatric cases are notable, with 81% of children with the syndrome developing gastric polyps, 31% of which are dysplastic. The risk of gastric carcinoma in FAP varies geographically, being higher in Japan (4.5%–13.6%) compared to the West (0.6%–4.2%), with Korean and Japanese patients being 7–10 times more likely to develop gastric carcinoma than nonsyndromic patients [65]. Gastric polyps or carcinoma are not defining features of FAP or AFAP in the West, but gastric cancer is considered an extracolonic manifestation of FAP in the East. FAP is established by the presence of over 100 adenomatous colorectal polyps, while AFAP may be diagnosed with fewer polyps and familial patterns of colorectal cancer. FAP and AFAP are caused by heterozygous mutations in the APC gene on chromosome 5q21, with the type and location of mutations influencing clinical severity. Gastric manifestations in FAP vary, with fundic gland polyps (FGPs) detected as early as 8 years and gastric carcinoma as early as 11 years. Benign gastric lesions include FGPs, gastric adenomas, hyperplastic polyps, and pyloric adenomas. Syndromic FGPs are often multiple and have a higher incidence of dysplasia (25% to 44%) compared to sporadic FGPs (~1%). The risk of carcinoma is low, with gastric adenocarcinomas typically being of the World Health Organization tubular type (Lauren intestinal type). Surveillance guidelines suggest starting upper endoscopy at 21–30 years of age at intervals of 3–5 years. Nonsteroidal anti-inflammatory drugs and acid-suppressive therapy can reduce the number and dysplasia incidence of gastric polyps, though their impact on malignancy and survival is unclear. In severe cases, surgical intervention may be necessary [66].

Mutyh-Associated Polyposis

Mutyh-associated polyposis (MAP) is an autosomal recessive polyposis syndrome distinguished by the absence of APC mutations, unlike other polyposis syndromes. The prevalence of MUTYH mutations is estimated to be 1 in 40,000 for

clinical carriers and 1 in 20,000 for subclinical carriers. Gastric involvement is uncommon in MAP, but duodenal involvement, especially duodenal carcinoma, occurs at rates comparable to those in familial adenomatous polyposis (FAP) [67]. Affected individuals are also at increased risk for colorectal, breast, ovarian, skin, sebaceous, and bladder carcinomas. Diagnosis is confirmed through MUTYH mutation testing in individuals with a family history of colorectal cancer with an autosomal recessive inheritance pattern, over 100 colon polyps without an APC mutation, 10-100 colon polyps, 1-10 colon adenomas in individuals under 10 years old, or colorectal cancer with a specific somatic KRAS mutation. MAP is caused by biallelic mutations in the MUTYH gene located on chromosome 1p34.3-p32.1, which is crucial for DNA base-excision repair. Ethnic clustering of mutational hotspots has been observed, particularly biallelic losses at p.Y179C and p.G396D in Caucasians. Clinically, gastric polyps are present in 11% of cases, with a low risk (2%) of gastric cancer, and a significantly increased incidence (17%) of duodenal cancer. Surveillance guidelines recommend starting upper endoscopy at ages 30-35, with intervals of 3-5 years, while colonoscopy should begin earlier, at ages 25-30, and be repeated every 1-2 years. Some suggest beginning upper gastrointestinal screening at 25 years old, with follow-ups at 30 and every two years thereafter if results are normal. Screening minors is not recommended due to the low risk [68].

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder characterised by multiple gastrointestinal hamartomatous polyps, predominantly in the jejunum, and melanotic macules. Its estimated incidence is approximately 1 in 200,000 live births, with patients having a relative lifetime cancer risk of 89%, predisposing them to neoplasms in various organs including the gut, pancreas, breast, uterus, cervix, testis, ovary, and lung [69]. A diagnosis of classic PJS is established if two of the following features are present: small bowel polyposis, hyperpigmentation of lips, buccal mucosa, and digits, and a positive family history, along with histologically confirmed hamartomatous polyps. The syndrome is primarily caused by germline mutations in the STK11 (serine threonine kinase 1) tumour suppressor gene, found in 70% of cases, though additional genetic alterations are present in subsequent adenocarcinomas. The site and type of STK11 mutations may predict the development of gastric polyps and malignancies, with truncating mutations or no mutations associated with earlier onset of gastric polyps [70]. Gastric polyps are detected throughout the gastrointestinal tract and extraintestinal sites, most commonly in the small bowel, colon, and stomach, with a median age of onset of 16 years for gastric polyps. Surveillance guidelines recommend early initiation of endoscopic screening, with baseline endoscopy at age 8 and subsequent screening tailored based on findings. Treatment options include rapamycin, COX2 inhibitors, and metformin to decrease polyp burden. Screening colonoscopy is also recommended starting at age 20-25, with intervals of 2-5 years [71].

Juvenile Polyposis Syndrome/Hereditary Hemorrhagic Telangiectasia

Juvenile polyposis syndrome (JPS) is an autosomal dominant disorder characterised by the development of multiple polyps throughout the gastrointestinal tract. Its estimated incidence ranges from 1 in 16,000 to 1 in 100,000. The inclusion criteria for diagnosis include having more than five juvenile polyps in the colon or rectum, juvenile polyps throughout the gastrointestinal tract, or more than one juvenile polyp with a family history of juvenile polyps. Notably, individuals with mutations in SMAD4 or BMPR1A may exhibit a mixed polyposis phenotype similar to those with hereditary mixed polyposis syndrome (HMPS), suggesting an allelic relationship between JPS and HMPS. Molecularly, JPS is caused by mutations in several genes, most commonly SMAD4 on Chr 18q21.1 and BMPR1A on Chr 10q22.23, with severe gastric polyposis associated with SMAD4 mutations. Additionally, germline mutations in PTEN and possibly ENG genes have been described, with ENG mutations linked to hereditary hemorrhagic telangiectasia (HHT). Clinically, gastric polyps are typically diagnosed in adults at a median age of 41 years, while colorectal polyps are detected earlier, at a median age of 16 years. These polyps may lead to obstructive symptoms and hypergastrinemia, resembling Ménétrier disease in presentation. JPS polyps, which are pedunculated with a smooth surface, may exhibit morphological heterogeneity, including hyperplastic, fundic gland, or inflammatory pseudopolyp phenotypes. Gastric adenocarcinoma has been reported in up to 21% of gastric polyps, with both intestinal and diffuse types observed. Surveillance and clinical management involve initiating upper and lower endoscopy in the midteens or when symptoms arise, with subsequent screening recommendations based on polyp findings. Gastrectomy is recommended for symptomatic patients with extensive polyps or gastric polyposis [72].

Familial Gastric Polyposis

Familial gastric polyposis is a rare autosomal dominant syndrome primarily reported in Portuguese families, characterised by the development of gastric hyperplastic polyposis, a heightened incidence of gastric carcinoma, and concomitant cutaneous psoriasis. Whether the association with cutaneous psoriasis signifies two distinct disorders or pleiotropic manifestations of one syndrome remains uncertain due to its rarity, and thus, definitive inclusion criteria have not been established. Clinical and pathological features manifest predominantly in young patients, with polyposis affecting the entire gastric wall, displaying a prominent villous configuration and globoid features. The epithelium exhibits prominent foveolar hyperplasia or hyperplastic polyps, sometimes with cytologic atypia, while adenomas or fundic gland polyps are notably absent. Gastric adenocarcinoma, typically poorly cohesive, may arise from dysplastic foveolar epithelium. Inheritance follows an autosomal dominant pattern with incomplete penetrance, as evidenced by reported healthy carriers. Presently, no established guidelines exist for surveillance, management, or prevention strategies specific to this syndrome [73].

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Gastric Adenocarcinoma and Proximal Polyposis Syndrome

Gastric adenocarcinoma and proximal polyposis syndrome (GAPPS) is a recently identified syndrome associated with an elevated risk of gastric carcinoma, characterised by multiple fundic gland polyps (FGPs) harbouring areas of multifocal dysplasia and subsequent carcinoma development. Diagnosis requires the exclusion of other polyposis syndromes, and specific diagnostic criteria include the presence of over 100 gastric polyps in the index case or over 30 polyps in a first-degree relative, polyps restricted to the body and fundus of the stomach, absence of colorectal or duodenal polyposis, confirmation of FGPs with dysplasia or carcinoma, and autosomal dominant inheritance [74].

The molecular genetics underlying this disorder remain elusive, as mutations in APC, MUTYH, CDH1, SMAD4, BMPR1A, STK11, and PTEN have been ruled out. Clinically, gastric manifestations have been observed as early as 10 years of age, with gastric carcinoma detected at 33 years, showing a predilection for females. Polyposis predominantly affects the body and fundus with sparing of the lesser curvature, comprising small polyps (<10 mm) resembling sporadic FGPs, often accompanied by areas of dysplasia and mixed morphological features. Gastric carcinomas, primarily gland-forming, have been identified in 12.7% of patients [75].

While some patients presented with a few colorectal adenomas, none exhibited colonic polyposis or colorectal carcinoma. Notably, an inverse association has been observed between H. pylori infection and gastric manifestations of GAPPS. Management strategies should be tailored on a case-by-case basis, considering the individual's familial risk of gastric cancer. The presence of gastric polyposis poses challenges for endoscopic surveillance, and some patients may opt for total gastrectomy, particularly in cases where young relatives have succumbed to metastatic gastric carcinoma despite surveillance and biopsies [76].

Hereditary Diffuse Gastric Cancer

Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant cancer predisposition syndrome characterised by an elevated risk of diffuse gastric cancer and breast carcinoma. The prevalence of HDGC in the general population is less than 0.1 per 100,000 and less than 1% among individuals with gastric cancer. Lifetime risk estimates for gastric carcinoma in male carriers are 70%, with a slightly lower risk of 56% in female carriers. Initially, diagnostic criteria proposed in 1999 included the presence of ≥2 documented cases of diffuse gastric cancer in first and second-degree relatives with at least one diagnosed <50 years of age or ≥3 documented cases of diffuse gastric cancer in first and second-degree relatives regardless of the age of onset. Subsequent updates in 2010 expanded criteria to encompass pathologic confirmation of diffuse type gastric carcinoma, individuals diagnosed with diffuse type gastric cancer <40 years of age, addition of lobular breast carcinoma to the guidelines, and detection of specific cellular features adjacent to diffuse type gastric cancer. The latest guidelines merge previous criteria into a new one requiring ≥2 documented cases of gastric carcinoma (with at least one confirmed diffuse gastric cancer) in first and second-degree relatives, irrespective of age [45]. Mutations in the CDH1 gene are the primary cause of HDGC, inherited as an autosomal dominant disorder with incomplete penetrance. CDH1 gene testing should cover the entire open reading frame, including intron-exon boundaries and copy number analysis. Surveillance biopsies and prophylactic gastrectomies have been essential in identifying early stages of diffuse type gastric carcinoma, with close to 100% histologic penetrance observed in gastrectomy specimens. Prophylactic gastrectomy is the preferred treatment for carriers of pathogenic CDH1 mutations, while endoscopic surveillance is an option for those who decline surgery or carry mutations of uncertain significance. Additionally, annual mammography and breast magnetic resonance imaging are recommended for women over 35 years of age, although data regarding prophylactic mastectomy are insufficient [77]. The prognosis following prophylactic gastrectomy is excellent, typically involving total gastrectomy with end-to-side Roux-en-Y esophagojejunostomy **(Table 4)**.

Table 4: *Hereditary Syndromes Associated with Gastric Cancer Risk.*

Hereditary Diffuse Gastric Cancer (HDGC)	CDH1, CTNNA1	Increased risk of diffuse gastric cancer without detectable precursor lesion. Lifetime risk: 70% (male), 56% (female). Prophylactic gastrectomy recommended.
Lynch Syndrome	MLH1, MSH2, MSH6, PMS2, EPCAM	Unclear gastric cancer risk; no specific precursor lesion identified.
Familial Adenomatous Polyposis (FAP)	APC	Gastric cancer risk variable by region (4.5%-13.6% in Japan, 0.6%-4.2% in the West). Fundic glandpolyps common precursor. Surveillance starts at 21-30 years.
Attenuated FAP (AFAP)	APC	Similar to FAP but with fewer polyps.
Mutyh-Associated Polyposis (MAP)	MUTYH	Gastric polyps in 11%, low gastric cancer risk (2%). Surveillance starts at 30-35 years.
Peutz-Jeghers Syndrome (PJS)	STK11	Hamartomatous polyps throughout GI tract. Gastric polyps detected from age 8 onwards. Earlyscreening recommended.
Juvenile Polyposis Syndrome (JPS)	SMAD4, BMPR1A	Mixed polyposis phenotype. Gastric polyps detected in adults (~41 years). Surveillance from midteens or symptom onset.
Hereditary Hemorrhagic Telangiectasia (HHT)	ENG, ACVRL1	Increased risk for GI neoplasms including gastric cancer.
Familial Gastric Polyposis	Unknown	Rare syndrome with gastric hyperplastic polyposis, association with cutaneous psoriasis. Incomplete penetrance. No established surveillance guidelines.
Gastric Adenocarcinoma and Proximal Polyposis Syndrome (GAPPS)	Unknown	Multiple fundic gland polyps, elevated risk of gastric carcinoma. Diagnosis based on polyp count and family history. Management varies; some opt for prophylactic gastrectomy.

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Signet Ring Cell Carcinoma

GC encompasses various adenocarcinoma types with marked heterogeneity in growth patterns, cell differentiation, histogenesis, and molecular pathogenesis. Despite advances in understanding its aetiology and pathogenesis, clinical utilisation of molecular pathology, particularly concerning relevant molecular markers for diagnosis and treatment, remains limited. Common classifications include those by the Japanese Gastric Cancer Association (JGCA), WHO, Nakamura, and Laurén, dividing GC into five subtypes: tubular, papillary, poorly cohesive, mucinous, and mixed adenocarcinomas. Poorly cohesive carcinomas (PCC) consist mainly or exclusively of signet ring cells, defined by WHO as cells with an optically clear, globoid droplet or cytoplasmic mucin centre and an eccentrically placed nucleus. Signet ring cell carcinoma (SRCC) can pose diagnostic challenges, particularly in distinguishing between gastric and poorly cohesive carcinoma types. Disputes arise regarding the specific proportion of signet ring cells qualifying as GSRC and the optimal treatment strategy, including the suitability of endoscopic submucosal dissection (ESD) [50]. ESD is considered for early-stage GSRC based on stringent criteria, with conflicting data on lymph node metastasis rates influencing treatment decisions.

A standard gastrectomy with D2 lymph node dissection is the primary curative surgical option for GSRC, aiming for R0 resection. Ensuring an adequate resection margin is crucial, with recommendations for a proximal resection margin distance following guidelines for normal adenocarcinoma types. However, consensus on the optimal margin distance for GSRC is lacking. Adjuvant and neoadjuvant therapies aim to improve survival and reduce recurrence in locally advanced GC post-R0 resection. Preoperative chemotherapy is popular in Europe, while postoperative chemoradiotherapy and chemotherapy are common in the US and Asia, respectively. However, specific regimens for GSRC remain uncertain due to its chemoresistant nature. The efficacy of chemotherapy, both postoperative and preoperative, for GSRC is debated, with conflicting evidence on survival benefits. While some studies suggest potential benefits, others report limited efficacy, highlighting the need for further research to identify effective treatment strategies [78].

Patients with metastatic gastric cancer, including advanced signet ring cell carcinoma (GSRC), often face a grim prognosis, with limited response to conventional chemotherapy compared to other gastric cancer subtypes. Despite the palliative benefits of standard chemotherapy, GSRC patients typically experience shorter overall survival than those with non-GSRC tumours. However, promising outcomes have been observed with triplet chemotherapy using docetaxel-5 FU-oxaliplatin (TEFOX) as a first-line treatment for advanced GSRC, underscoring the urgent need for targeted therapies to enhance survival rates. Hyperthermic intraperitoneal chemotherapy (HIPEC) has emerged as a potential approach for GSRC patients with peritoneal metastasis, a prognostic indicator associated with poor outcomes. Although studies suggest a higher incidence of peritoneal metastasis in GSRC, the efficacy of HIPEC remains uncertain, and challenges persist in achieving complete cytoreduction through cytoreductive surgery (CRS) and HIPEC. Selective application of CRS and HIPEC in carefully chosen GSRC patients with peritoneal metastases is advocated, although its overall efficacy in GSRC warrants further investigation. Despite initial optimism, significant advancements in immunotherapy for GSRC have yet to materialise. Immune checkpoint inhibitors targeting PD-1 and PD-L1 have shown promise in certain tumour types, particularly those with deficient mismatch repair (dMMR) and microsatellite instability (MSI). While GSRC exhibits low MSI frequencies, a subset of GSRC patients with high MSI may derive benefits from immunotherapy, necessitating further research to identify optimal therapeutic strategies and key mutations. Ongoing randomised controlled trials, such as the GASTRICHIP study, hold promise in elucidating the potential efficacy of HIPEC in locally advanced gastric carcinoma, including GSRC, and may guide future treatment paradigms [79].

Human Epidermal Growth Factor Receptor 2 (HER2+)

HER2 is a key receptor involved in the development and prognosis of various cancers, including gastroesophageal adenocarcinomas. As part of the EGFR family, HER2 is assessed mainly via immunohistochemistry (IHC) and fluorescence in situ hybridization (ISH). IHC scores HER2 expression on a scale from 0 to 3+, with 2+ cases requiring ISH confirmation to determine HER2 status. Despite IHC's limitations due to intratumoral heterogeneity and inter-pathologist variability, HER2 expression has been documented in 9% to 23% of gastroesophageal adenocarcinomas, especially in the proximal stomach and esophageal-gastric junction.

HER2 positivity in these tumours generally indicates more aggressive behaviour and higher recurrence rates, underscoring its importance in treatment planning. Trastuzumab, approved in 2010, marked a breakthrough for HER2-positive unresectable or metastatic gastric cancer. HER2 testing is recommended for all patients with advanced disease to guide treatment strategies.

HER2 signalling involves the MAPK and PI3K/Akt pathways, which regulate cell proliferation and survival. Several HER2-directed therapies target various domains of the HER2 receptor, including trastuzumab, margetuximab, T-DM1, T-DXd, pertuzumab, and zanidatamab, providing diverse treatment options.

For resectable, locally advanced HER2-positive tumours, perioperative chemotherapy is preferred. The FLOT regimen (5FU, oxaliplatin, and docetaxel), established by the FLOT4 trial in 2019, is now standard, showing a median overall survival (OS) of 50 months compared to 35 months with the previous ECF/ECX regimen . However, adding anti-HER2 therapy to perioperative chemotherapy has not shown additional benefits in this context.

For unresectable or metastatic disease, the standard first-line treatment combines platinum and fluoropyrimidine chemotherapy with trastuzumab, as established by the ToGa trial, which improved median OS to 13.8 months from 11.1

months with chemotherapy alone. Second-line options include paclitaxel with ramucirumab, demonstrating improved OS over paclitaxel alone in the RAINBOW trial. Additional options are single-agent therapies like taxanes, irinotecan, and ramucirumab.

Despite these treatments, most patients develop resistance within a year, highlighting the need for new therapies. Novel approaches include antibody-drug conjugates (ADCs) like T-DXd, which has shown promise in the DESTINY-Gastric01 trial, and immunotherapy combinations, such as pembrolizumab with trastuzumab and chemotherapy, showing high response rates in the KEYNOTE-811 trial . Other emerging therapies include margetuximab and zanidatamab, which target different HER2 domains and have shown potential in clinical trials.

HER2-targeted therapies continue to evolve, with ongoing trials exploring combinations of HER2 inhibitors with other treatment modalities to overcome resistance and improve outcomes in HER2-positive gastroesophageal cancers.

Phase III trials with targeted therapies based on molecular features other than HER2 have shown disappointing results in gastroesophageal adenocarcinoma (GEA) **(Table 5)**.

Epidermal growth factor receptor (EGFR) is amplified in about 5% of cases, and overexpressed in 30–50% of cases. Anti-EGFR monoclonal antibodies, such as cetuximab and panitumumab, which are approved for advanced colon cancer, have been tested in GEA. However, two randomised Phase III trials revealed no improvement in clinical outcomes when anti-EGFR treatment was added to first-line platinum-based chemotherapy. These antibodies may have reduced the tolerance of the chemotherapy, leading to dose delays and reductions, potentially impacting effectiveness. Furthermore, the anti-EGFR tyrosine kinase inhibitor gefitinib showed no clinical benefit versus placebo beyond the first line of treatment. A key limitation was the lack of proper molecular patient selection. Subset analyses of the COG [53] and EXPAND [51] trials suggested potential benefits in EGFR-amplified patients, but these results need prospective confirmation.

Similarly, results for MET inhibition have been discouraging. MET amplification is detectable in about 6% of cases and overexpressed in 25–60% of GEA cases [10,49]. Adding monoclonal antibodies like onartuzumab [54] and rilotumumab [55] to first-line chemotherapy provided no clinical benefit. Negative outcomes were also seen with tyrosine kinase inhibitors like AMG 337 in heavily treated MET-amplified

Table 5: *Phase III trials with targeted therapies based on molecular features other than HER2 have shown disappointing results in gastroesophageal adenocarcinoma (GEA).*

Subtype	Genetic Alterations	Clinical Features
Chromosomally Unstable (CIN)	TP53 mutations (71%), ARID1A, KRAS, PIK3CA, RNF43, ERBB2, APC	- Predominant in gastroesophageal junction (GEJ)/cardia region - Aneuploidy and heightened p53 expression - High frequency of APC and TP53 loss of heterozygosity - Increased EGFR phosphorylation and amplification
Familial Gastric Cancers	CDH1 (HDGC), MLH1, MSH2, MSH6, PMS2, EPCAM (Lynch syndrome), APC (FAP), STK11 (PJS), SMAD4, BMPR1A (JPS), unknown (GAPPS)	- HDGC: Diffuse gastric cancer risk (CDH1 mutations) - Lynch syndrome: Unclear gastric cancer risk - FAP: Gastric cancer associated with colorectal polyps - PJS: Gastric cancer preceded byhamartomatous polyps - JPS: Gastric cancer preceded by hamartomatous polyps - GAPPS: Multiple FGPs with risk of carcinoma
Familial Adenomatous Polyposis (FAP)	APC gene mutations	- Numerous adenomatous colorectal and gastric polyps - Early onset of gastric carcinoma in some populations
Mutyh-Associated Polyposis (MAP)	MUTYH gene mutations	- Autosomal recessive syndrome with colorectal polyposis - Increased risk of duodenal and other extracolonic cancers
Peutz-Jeghers Syndrome (PJS)	STK11 gene mutations	- Autosomal dominant syndrome with gastrointestinal hamartomatous polyps - Increased risk ofvarious cancers in multiple organs
Juvenile Polyposis Syndrome (JPS)	SMAD4, BMPR1A, PTEN, ENG	- Autosomal dominant syndrome with multiple gastrointestinal polyps - Mixed polyposis phenotype including juvenile and hamartomatous polyps - Increased risk of colorectal and gastric cancers
Familial Gastric Polyposis	Unknown	- Rare autosomal dominant syndrome with gastric hyperplastic polyposis - Potential association with cutaneous psoriasis
Gastric Adenocarcinoma and Proximal Polyposis Syndrome (GAPPS)	Unknown	- Multiple fundic gland polyps with areas of dysplasia - Increased risk of gastric carcinoma
Hereditary Diffuse Gastric Cancer (HDGC)	CDH1 gene mutations	- Autosomal dominant syndrome with diffuse gastric cancer risk - Elevated lifetime risk of gastric and lobular breast carcinoma
Signet Ring Cell Carcinoma (SRCC)	Poorly cohesive carcinomas, signet ring cell morphology	- Predominantly signet ring cell morphology - Aggressive behaviour with poorer prognosis in advanced stages
HER2 Positive (HER2+)	HER2 gene amplification, overexpression	- Higher aggressiveness and recurrence rates - Responds to HER2-targeted therapies like trastuzumab
EGFR Positive (EGFR+)	EGFR gene amplification, overexpression	- Limited efficacy of anti-EGFR therapies in clinical trials
MET Positive (MET+)	MET gene amplification, overexpression	- Discouraging outcomes with MET inhibitors in clinical trials
PI3K-Akt-mTOR Pathway Activation	PIK3CA mutations, AKT amplification	- Everolimus showed no survival benefit in clinical trials

patients. Activation of the PI3K–AKT–mTOR pathway is another common molecular alteration in GEA. However, everolimus, an mTOR inhibitor approved for breast cancer, showed no clinical benefit in overall survival beyond the first line in unselected patients.

Recognizing the complex molecular landscape of GEA, an umbrella platform [57] was designed with preplanned genomic biomarker analyses to assign advanced GEA patients to molecularly matched therapies. Several biomarker groups were identified, including RAS alterations, TP53 and PIK3CA mutations, and MET and PIK3CA amplification. Only 14.7% of the screened population received biomarker-assigned drug treatment. The highest response rate was observed in patients with MET amplification treated with savolitinib, a potent MET kinase inhibitor. This strategy showed encouraging response rates and survival compared to conventional second-line chemotherapy, especially in patients with high MET expression and higher MET copy number. Circulating tumour DNA (ctDNA) analysis showed a good correlation between high MET copy number and response to MET inhibitors, and further results are awaited.

Given the recent identification of NTRK as a relevant molecular driver across solid tumours, molecular evaluation for NTRK fusion, despite its low incidence in GEA, could be considered for patients with good performance status [80].

CLDN

The tight junction molecule claudin-18 isoform 2 (CLDN18.2) is expressed in approximately 40% of gastric cancer patients, making it a promising target for therapies, as it is usually not found in non-malignant tissues outside the gastric mucosa. Zolbetuximab, a monoclonal antibody targeting CLDN18.2, has been investigated in several phase II trials as both monotherapy and in combination with standard chemotherapy [3,71], most recently in the phase III SPOTLIGHT trial.

In the phase II MONO trial, zolbetuximab showed an overall response rate (ORR) of 9% in tumours expressing CLDN18.2, increasing to 14% in those with moderate to strong expression (≥70% of tumour cells). The phase II FAST trial, which combined zolbetuximab with first-line ECX chemotherapy (epirubicin, cisplatin, and capecitabine) in patients with ≥40% CLDN18.2-expressing tumour cells, reported a 39% ORR compared to 25% in the chemotherapy-alone arm. Additionally, the FAST trial showed a significant improvement in overall survival (OS) with 13.0 months in the zolbetuximab arm versus 8.3 months in the control arm. In the subgroup with ≥70% CLDN18.2 expression, OS further increased to 16.5 months versus 8.9 months. However, no significant OS difference was observed in patients with 40–69% CLDN18.2 expression (8.3 vs. 7.4 months, HR 0.78, p = 0.4).

Ongoing phase III trials are investigating zolbetuximab combined with standard first-line chemotherapy [69-71]. The recently presented SPOTLIGHT trial involved 575 patients randomized to zolbetuximab or placebo with mFOLFOX6 (5-FU, leucovorin, and oxaliplatin) chemotherapy. It included patients with moderate to strong CLDN18 staining in ≥75% of tumor cells. Results showed a median progression-free survival (PFS) of 10.61 versus 8.67 months (HR 0.751, p = 0.0066) and a median OS of 18.23 versus 15.54 months (HR 0.750, p = 0.0053) in the zolbetuximab and placebo arms, respectively. Common treatment-related adverse events (TRAEs) in the zolbetuximab arm were nausea, vomiting, and appetite loss, leading to drug discontinuation in 13.6% of patients compared to 2% in the placebo group. The median OS of 18.23 months is the longest reported in a phase III trial for gastric/gastroesophageal junction (G/GOJ) adenocarcinomas. However, it remains to be seen how quickly these results will lead to regulatory approvals and availability for patients globally. Future trials need to address first-line treatment strategies when both CPS and CLDN18.2 are high, though there is currently thought to be minimal overlap between these biomarkers.

In addition to zolbetuximab, other CLDN18.2-targeting agents, including monoclonal and bispecific antibodies, chimeric antigen receptor (CAR) T cells, and antibody-drug conjugates (ADCs), are being investigated in early-phase clinical trials [60]. One interim analysis of CLDN18.2-targeted CAR-T cells (CT041) showed promising results in previously treated gastrointestinal (GI) cancers [71]. This study included 28 patients with G/GOJ cancers, most of whom had received at least two prior lines of treatment. Among these patients, the ORR was 57.1%, the disease control rate (DCR) was 75.0%, and the 6-month OS rate was 81.2%. Approximately half had high CLDN18.2 expression (≥70%), 35% had medium expression (40–69%), and 13% had low expression (≤40%) [81]. These findings suggest that CLDN18.2-targeting agents may benefit a broader range of patients, including those with lower target expression, similar to HER2-targeted therapies [81].

Exploring the Role of Immunotherapy in First-Line HER2-Positive Gastric Cancer Treatment Investigator-Initiated Trials

An investigator-initiated single-arm phase II trial (NCT02954536) [70] led by Janjigian et al. between 2016 and 2019 evaluated pembrolizumab combined with standard first-line chemotherapy in 37 patients. The chemotherapy regimens included cisplatin or oxaliplatin plus capecitabine or 5-FU. The primary endpoint, six-month progression-free survival (PFS), was achieved in 70% of patients. The overall response rate (ORR) was 91% (32/35 patients), with complete responses in 17% (6 patients), partial responses in 74% (26 patients), and stable disease in three patients. The median duration of response (DoR) was 10 months, and the 12-month overall survival (OS) rate was 80%. The combination therapy was safe and showed no dose-limiting toxicities.

Similarly, the phase Ib/II trial (NCT02901301) conducted by Lee et al. assessed pembrolizumab with first-line standard chemotherapy (cisplatin and capecitabine) in 43 patients. This trial reported an ORR of 76.7% (14% complete responses and 62.8% partial responses), with a median PFS of 8.6 months, median OS of 19.3 months, and DoR of 10.8 months. The toxicity profile was acceptable, and no patients discontinued pembrolizumab due to severe toxicities. PD-L1 status was not related to survival.

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Phase III KEYNOTE-811 Study: The KEYNOTE-811 study (NCT03615326) evaluated the addition of pembrolizumab to the standard first-line treatment of trastuzumab and chemotherapy versus placebo. The ORR improved by 22.7% in the pembrolizumab arm compared to the placebo group (77.4% vs. 51.9%, respectively; p = 0.00006). Complete responses were 11.3% in the pembrolizumab group versus 3.1% in the placebo group. The median DoR was 10.6 months for the pembrolizumab group and 9.5 months for the placebo group. Grade 3 or higher adverse events occurred in 57.1% of the pembrolizumab group compared to 57.4% in the placebo group. These interim results led to the FDA's accelerated approval of pembrolizumab combined with trastuzumab and chemotherapy for first-line HER2-positive gastric cancer, with OS and PFS results pending.

Other immunotherapy agents have been evaluated in this setting. The phase II INTEGA study (NCT03409848) assessed combinations of nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) with trastuzumab. The median OS was 21.8 months in the FOLFOX arm versus 16.4 months in the chemotherapy-free arm, showing significant improvement compared to historical controls.

Camrelizumab, another anti-PD-1 agent, was evaluated in combination with standard chemotherapy (ChiECRCT20220008). This study involved 41 patients and showed ORRs of 75% versus 46.2% (p = 0.032), favouring the combination arm. The DCR, PFS, and OS were also significantly better in the camrelizumab arm. The treatment was well tolerated, although higher incidences of reactive cutaneous capillary endothelial proliferation and hypothyroidism were observed.

Novel Anti-HER2 and Immunotherapy Combinations: The phase II/III MAHOGANY trial (NCT04082364) is exploring combinations of margetuximab (anti-HER2), retifanlimab (anti-PD-1), tebotelimab (anti-PD-1/anti-LAG3), trastuzumab, and chemotherapy. Initial safety analysis reported significant tumour shrinkage, leading to a randomised study comparing these combinations to standard first-line therapy.

The phase III HERIZON-GEA-01 trial (NCT05152147) is testing chemotherapy and trastuzumab versus chemotherapy with zanidatamab (bispecific anti-HER2) alone or combined with tislelizumab.

The phase Ib/II Destiny-Gastric03 trial (NCT04379596) investigates the antibody–drug conjugate T-DXd in various combinations, including with durvalumab (anti-PD-L1), pembrolizumab, and chemotherapy. Preliminary results indicate promising ORR and tolerability, with ongoing patient recruitment.

T-DXd (trastuzumab deruxtecan) works by blocking HER2-receptor dimerization and delivering a cytotoxic topoisomerase I inhibitor payload inside cancer cells, exerting a bystander effect and enhancing antibody-dependent cellular cytotoxicity against tumors. These studies highlight the ongoing efforts to improve treatment outcomes for HER2-positive gastric cancer through innovative combinations of immunotherapy and targeted therapies [82].

Comparing between classifications

When comparing the classifications proposed by The Cancer Genome Atlas (TCGA) and the Asian Cancer Research Group (ACRG), it's evident that the TCGA subtypes EBV, MSI, GS, and CIN primarily align with the ACRG subtypes MSS/TP53+, MSI, MSS/EMT, and MSS/TP53-, respectively. However, some disparities exist between the two classifications, likely due to variations in patient populations, tumour sampling techniques, and technological platforms.

Noteworthy differences between the classifications include the prevalence of CDH1 mutations, which are more frequently observed in the GS subtype (37%) compared to the MSS/EMT subtype (2.8%). Additionally, RHOA mutations, characteristic of the GS subtype, are detected in the MSS/TP53+ and MSS/TP53- subtypes but are rare in MSS/EMT tumours. Moreover, the CIN and GS subtypes are distributed across all ACRG subtypes.

HER2 gene amplifications are identified in several subtypes, including CIN, GS, and EBV, with a higher prevalence in the CIN molecular subtype. In the ACRG classification, recurrent focal amplifications in HER2 are predominantly found in the MSS/TP53- subgroup . Considering these molecular classifications, HER2-positive gastric cancer is more commonly associated with the CIN and MSS/TP53-molecular subtypes.

Future Directives

Choi et al. [24] suggest that microsatellite instability (MSI) is also present in gastric cancer. Using hMLH1 and hMSH2 in immunohistochemistry (IHC) and MSI analysis systems, patients with MSI-related gastric cancer can be detected. Small intestinal adenocarcinoma is the most common type of gastric cancer in individuals with Lynch syndrome. Imamura et al. [25] found that MSI esophagogastric junction adenocarcinoma (EGJ), a specific type of gastric cancer, is closely associated with genetic instability. Their research indicated that tumours in Siewert type I are not related to MSI, while tumours in Siewert types II and III are associated with MSI. Smyth et al. [26] highlighted that the survival time of patients with MSI-H gastric cancer who undergo surgery is not better than that of patients with MSI-L or MSS. The American Society of Clinical Oncology Gastrointestinal Cancer Symposium suggested that MSI can serve as a good prognostic indicator for resectable primary gastric cancer. Consequently, future clinical trials should consider whether to use immune checkpoint inhibitors (ICI) to treat gastric cancer with high microsatellite instability, using MSI as a stratification factor. The mechanism of ICI treatment may involve the high expression of CD8 positive T cell molecular markers, the PD-L1 gene, and the IFN-γ (interferon-γ) gene in patients with MSI-H. Marrelli et al. noted that MSI-H gastric cancer is more common in women and typically occurs in non-cardiac areas.

Several clinical trials targeting advanced signet ring cell carcinoma (GSRC) are currently underway to explore various treatment strategies. One such trial is PRODIGE-19-FFCD1103-ADCI002, a prospective multicenter controlled randomised phase II/III trial comparing the efficacy of

Table 6: *Summarizing ongoing clinical trials in precision medicine for gastric adenocarcinoma.*

Trial Name	Phase	Interventions	Target Population	Primary Endpoints	Status	Trial Number
KEYNOTE-811	III	Pembrolizumab, Trastuzumab, Chemotherapy	HER2-positive advanced gastric or GEJ cancer	Overall survival (OS), Progression-free survival (PFS)	Ongoing	NCT03615326
EDGE-Gastric	II	Domvanalimab, Zimberelimab, Chemotherapy	Advanced gastric, GEJ, or esophageal cancer	Incidence and severity of AEs, ORR	Ongoing	NCT04400122
Pembrolizumab Combination Study	II	Pembrolizumab, Doublet Chemotherapy	Resectable gastric or GEJ cancer	Complete pathological response, Near-complete response	Ongoing	NCT03745170
RAINBOW-Asia	III	Ramucirumab, Paclitaxel	Advanced gastric or GEJ adenocarcinoma	OS, PFS	Active, not recruiting	NCT02443324
CheckMate 649	III	Nivolumab, Ipilimumab, Chemotherapy	Advanced gastric or GEJ adenocarcinoma	OS, PFS	Ongoing	NCT02872116
FIGHT	III	Bemarituzumab, Chemotherapy	FGFR2b-overexpressing advanced gastric cancer	OS, PFS	Ongoing	NCT03656536

*This table provides a comprehensive overview of the genetic alterations, clinical features, and syndromic associations for each subtype of gastric cancer discussed in the review article.

perioperative chemotherapy versus primary surgery followed by adjuvant chemotherapy in patients with stage IB-III GSRC. Launched in France in 2013 by Guillaume et al, this trial is currently in the recruiting phase (NCT01717924).

Another ongoing study, conducted by Liang et al in China, is a randomised, multicenter, controlled trial comparing XELOX chemotherapy alone versus XELOX combined with apatinib as postoperative chemotherapy for locally advanced GSRC with D2 dissection. This trial, initiated in 2017, has not yet reached the recruitment stage (NCT03355612).

Furthermore, Glehen et al have initiated a phase III trial aimed at comparing the overall 5-year survival rates between patients with advanced GSRC and/or positive peritoneal cytology who undergo curative gastrectomy combined with adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) versus those undergoing curative gastrectomy alone. This trial, currently in progress, is actively recruiting participants (NCT01882933) [83] **(Table 6)**.

Conclusion

Over a decade ago, the first targeted treatments for advanced gastric cancer showed promising results, yet the everyday use of targets to guide treatment options remains limited. Recently discovered druggable targets in specific patient subgroups have begun to shift the treatment paradigm away from the one-size-fits-all approach of combination chemotherapy. Despite this progress, results from multiple platform and umbrella trials are still awaited to determine their impact on survival outcomes. Given the aggressive nature of gastric cancer, combination chemotherapy remains a crucial component of treatment. However, rapid advancements in immunotherapy offer new hope for extending overall survival (OS) beyond the previously static one-year mark and have introduced new predictive biomarkers.

The evolving landscape of molecular alterations in gastric cancer presents significant challenges and opportunities. These include questions about treatment sequencing, overlapping toxicity, necessary technologies for molecular testing, and the resource implications of precision medicine. Gastric and gastroesophageal adenocarcinoma (GEA) is highly heterogeneous, with numerous molecular alterations, particularly in the chromosomal instability (CIN) subtype, complicating a precision medicine approach. Nevertheless, recent advancements in omics have enabled the identification of certain drivers, opening up new treatment opportunities.

For HER2-amplified tumours, more effective molecules are significantly improving patient outcomes. Additionally, the growing interest in the tumour microenvironment and the development of novel immunotherapies and combinations could lead to new treatment approaches. While the journey toward a personalised approach in gastric cancer is long and requires further studies and breakthroughs, these advancements mark significant progress toward individualised treatment strategies.

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