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Review Article

Multi-omics Biomarkers in Early Gastric Cancer Screening: Translating Discovery Evidence to Routine Screening Implementation

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Abstract

Early detection of gastric cancer is critical for reducing incidence and mortality, as well as for improving survival outcomes. Although gastroscopy remains the gold standard for gastric cancer screening and diagnosis, its invasiveness, discomfort during the procedure, and limited acceptability restrict population participation and screening coverage. Recently, rapid advances in liquid biopsy technologies have led to the discovery of numerous multi-omics biomarkers spanning genomics, transcriptomics, proteomics, and metabolomics, with promising diagnostic performance. However, their translational value for population-based gastric cancer screening and control remains insufficiently characterized. This review aims to provide a comprehensive overview of multi-omics biomarkers for gastric cancer screening and to evaluate their potential role in advancing population-level gastric cancer control. First, we synthesize multi-omics biomarkers with diagnostic and screening relevance across the continuum of gastric carcinogenesis, from chronic inflammation and atrophy to intestinal metaplasia, dysplasia, and early gastric cancer. Furthermore, we highlight the integrative value of multi-omics biomarkers, current limitations, translational challenges, and future opportunities for moving biomarkers from discovery to implementation in organized screening programs. In conclusion, multi-omics biomarkers have the potential to complement existing screening strategies by providing scalable, non-invasive, and risk-adapted approaches for early gastric cancer detection. Bridging the gap between biomarker discovery and real-world implementation will be essential for realizing their value in future gastric cancer screening programs.

Introduction

Gastric cancer is among the five most commonly diagnosed cancers and one of the leading causes of cancer-related deaths worldwide,[1] and remains a critical global health concern, especially in East Asia.[2,3] Early detection is essential for improving clinical outcomes and reducing mortality.[4] While the 5-year relative survival rate for early-stage gastric cancer can exceed 70%, it plummets to less than 10% in patients with advanced-stage disease.[5] Additionally, gastric carcinogenesis is a multistep process, and the identification of precancerous lesions can provide an important opportunity for cancer prevention within screening programs.[6]

Endoscopic examination is the gold standard for diagnosing gastric cancer.[7] However, endoscopy is an invasive procedure that demands significant resources and operator skill, constraining its

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scalability.[8] Importantly, the uptake of and adherence to screening among asymptomatic individuals remain low.[9] Therefore, endoscopy is not an ideal tool for population screening in the real world. In response, there is growing interest in developing minimally invasive or non-invasive approaches that can serve either as prescreening tools to triage high-risk individuals for endoscopy or as standalone methods to improve screening compliance and efficiency.[10]

Recent advances in fields such as genomics, epigenomics, and proteomics now allow scientists to analyze tumor biology using circulating biospecimens such as blood, urine, or saliva, which are commonly referred to as "liquid biopsies".[11] Circulating tumor DNA (ctDNA), microRNA (miRNA), cell-free RNA (cfRNA), methylation signatures, circulating proteins, exosomal cargo, metabolite panels, and cell-free DNA (cfDNA) fragmentation patterns each provide complementary perspectives on tumor presence and biology.[12] Moreover, researchers are now studying these biomarkers not only for detecting early cancer but also for identifying molecular changes associated with precancerous gastric lesions. Integrative multi-omics technologies present an unprecedented opportunity to discover biomarkers with high sensitivity and specificity for early-stage gastric cancer.[13] Despite this promising potential, the majority of multi-omics biomarker research remains in the discovery and preliminary validation phases.[14] Their translation into routine screening programs remains limited, primarily because of the lack of large-scale, prospective, multicenter, real-world studies to validate their clinical utility and cost-effectiveness.[15] This review aims to summarize the current evidence on multi-omics approaches for detecting precancerous lesions and early gastric cancer (EGC) and to outline the path from laboratory discovery to screening implementation, focusing on the need for validation, standardization, and practical integration into existing screening programs.

Specific biomarkers of each stage in gastric carcinogenesis

The development of gastric cancer is a multistep biological process, and the classic Correa cascade model provides a dynamic morphological progression from normal mucosa to non-atrophic gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, and eventually invasive carcinoma.[16] Currently, increasing evidence suggests that distinct genomic, epigenomic, transcriptomic, proteomic, and metabolomic biomarkers exist at each stage.[17,18] These dynamic molecular changes form the biological basis for developing stage-specific biomarkers and risk stratification strategies in gastric cancer screening.

Helicobacter pylori infection and the chronic inflammatory stage

Persistent *H. pylori* infection causes chronic immune activation in the stomach lining.[19] This activation not only triggers localized gastric inflammation but also results in systemic molecular changes that can be detected in peripheral blood.[20] Recent advances in multi-omics technologies have facilitated the identification of circulating biomarkers that reflect these early inflammatory processes. Compared with healthy individuals, patients positive for *H. pylori* show significantly decreased relative levels of miRNA-223 in neutrophils.[21] Earlier work by Zhu *et al*.[22] provided evidence that the cytotoxin-associated gene A toxin of *H. pylori* upregulates miRNA-584 and miRNA-1290, suggesting their potential utility as peripheral blood biomarkers for *H. pylori*-related gastric lesions. Beyond single markers, large-scale miRNA profiling studies have further identified panels of circulating miRNAs, including miRNA-124-3p, miRNA-125a-3p, and miRNA-29b-3p, that are associated with *H. pylori* infection status and subsequent gastric cancer risk.[23] Collectively, miRNA signatures in blood may improve the sensitivity of early detection strategies during the chronic inflammatory stage of gastric carcinogenesis.

Atrophy and intestinal metaplasia stage

Atrophic gastritis and intestinal metaplasia are pivotal precancerous stages in gastric carcinogenesis. Profound molecular reprogramming occurs during these stages, and such changes are increasingly detectable in the peripheral circulation. Circulating exosomal miRNAs, including miRNA-122-5p, miRNA-3591-3p, and miRNA-122-3p, are differentially expressed in atrophic gastritis compared with non-atrophic gastritis,[24] suggesting their potential utility for early lesion detection. Early studies on intestinal metaplasia reported downregulated miRNAs, such as miRNA-490-3p and miRNA-30a.[25–27] Beyond non-coding RNAs, mass spectrometry-based plasma proteomics has identified protein panels that distinguish preneoplastic states from non-atrophic gastritis. Combinations of proteins including arginase 1 (ARG1), carbonic anhydrase II (CA2), haptoglobin (HPT), mannosidase alpha class 2A member 1 (MAN2A1), and lipopolysaccharide-binding protein (LBP) have achieved high discrimination for atrophy and intestinal metaplasia.[28] Currently, relatively few reports have been published on cfDNA biomarkers specifically targeting the atrophic gastritis and intestinal metaplasia stages. However, some studies have found that the positivity rate of *methylated Reprimo, Cell Cycle Regulator* (*RPRM*) cfDNA gradually increases from normal mucosa to atrophic gastritis, intestinal metaplasia, and higher-grade lesions, suggesting that cfDNA methylation can be used for non-invasive detection of intestinal metaplasia in gastric cancer.[29]

Dysplasia and EGC

The transition from dysplasia to EGC is accompanied by increasing genomic instability and epigenetic aberrations. These changes are reflected in the circulation and can be detected using liquid biopsy approaches.[30]

Circulating miRNAs are the most extensively studied biomarker class at this stage. Compared with normal gastric mucosa, gastric dysplasia and EGC show downregulation of miRNA-26a, miRNA-375, miRNA-574-3p, miRNA-145, and miRNA-15b, alongside upregulation of miRNA-601, miRNA-107, miRNA-18a, miRNA-370, miRNA-300, and miRNA-96,[31] suggesting progressive deregulation of miRNAs during early malignant transformation. In addition, circulating miRNAs such as miRNA-22-3p have been associated with the progression from intestinal metaplasia to early adenocarcinoma. Dysplasia acts as a critical transitional stage, and this transition is reflected by miRNA alterations in the blood.[32]

Beyond non-coding RNAs, plasma and serum proteomics have provided strong evidence that protein expression profiles differ significantly across stages. Quantitative proteomics analysis based on data-independent acquisition identified distinct plasma protein signatures among healthy controls, low-grade dysplasia, and high-grade dysplasia, with three candidate markers—glutathione S-transferase Pi 1, cysteine and glycine rich protein 1, and lymphocyte antigen 6 family member G6F—exhibiting good discriminative ability.[33] Consistently, serum proteomic profiling using liquid chromatography–tandem mass spectrometry identified differentially expressed proteins related to metabolism and inflammation, including apolipoprotein A-IV, cartilage oligomeric matrix protein,

Table 1. Representative circulating multi-omics biomarkers across stages of gastric carcinogenesis

Stage	Biological processes	Categorization	Biomarkers	Relevance	Reference
Infection	Immune activation, cytokine signaling	cfRNA	miR-223	Reflects systemic inflammatory response to *H. pylori*	21
		cfRNA	miR-584, miR-1290	CagA-induced miRNAs linked to metaplastic change	22
		cfRNA	miR-124-3p, miR-125a-3p, miR-29b-3p	Associated with *H. pylori* infection and future GC risk	23
AG/IM	Gland loss, lineage reprogramming	Exosomal miRNA	miR-122-5p, miR-3591-3p, miR-122-3p	Discriminates AG from non-atrophic gastritis	24
		cfRNA	miR-490-3p, miR-30a	Early epigenetic deregulation in IM	26,27
		Proteomics	ARG1, CA2, HPT, MAN2A1, LBP	High discrimination for preneoplastic lesions	28
		cfDNA	*mRPRM*	Positivity increases from AG to IM	29
Dysplasia/ EGC	Genomic instability, epigenetic alteration	cfRNA	miR-26a, miR-375; miR-18a, miR-107	Progressive miRNA deregulation	31
		cfRNA	miR-22-3p	Predicts IM to EGC progression	32
		Proteomics	GSTP1, CSRP1, LY6G6F	Distinguishes dysplasia grades	33
		cfDNA	*mRPRM*	Increasing positivity along progression	29
		evDNA (*5hmC*)	9-marker *5hmC* panel	Associated with high risk of precancerous lesions	37

5hmC, *5-hydroxymethylcytosine*; AG, atrophic gastritis; ARG1, arginase 1; CA2, carbonic anhydrase 2; CagA, cytotoxin-associated gene A; cfDNA, cell-free DNA; cfRNA, cell-free RNA; CSRP1, cysteine and glycine-rich protein 1; EGC, early gastric cancer; evDNA, extracellular vesicle-derived DNA; GC, gastric cancer; GSTP1, glutathione S-transferase Pi 1; *H. pylori*, *Helicobacter pylori*; HPT, haptoglobin; IM, intestinal metaplasia; LBP, lipopolysaccharide-binding protein; LY6G6F, lymphocyte antigen 6 family member G6F; MAN2A1, mannosidase alpha class 2A member 1; miR, microRNA; miRNA, microRNA; *mRPRM*, methylated RPRM; *RPRM*, Reprimo, cell cycle regulator.

and complement component 3, which were altered in precancerous lesions and EGC compared with non-atrophic conditions.[34]

At the genomic level, cfDNA features are emerging as complementary biomarkers, although evidence specifically targeting dysplasia remains relatively limited.[35] Aberrant methylation of tumor-associated genes such as *RPRM* has been detected in plasma cfDNA across the spectrum from premalignant lesions to EGC, with positivity rates increasing as the disease progresses.[29] Notably, extracellular vesicle–derived DNA (evDNA) has emerged as a stable biomarker with abundant biological information.[36] A recent study used *genome-wide 5-hydroxymethylcytosine* (*5hmC*) profiling of plasma evDNA to identify epigenetic markers and construct a nine-marker diagnostic model for gastric precancerous lesions. This model achieved an area under the receiver operating characteristic curve (AUC) greater than 0.96, underscoring evDNA *5hmC* signatures as promising non-invasive biomarkers for the detection of early gastric lesions.[37] Because ctDNA represents only a small tumor-derived fraction of total cfDNA, it is often detected at extremely low concentrations in the early phases of malignancy.[38,39] As a result, large-scale validation studies specifically targeting ctDNA as a biomarker for dysplasia remain limited, and further prospective cohort studies are required to confirm its utility.

Early identification of gastric precancerous lesions allows for timely intervention that can halt or even reverse pathological mucosal changes,[40] thereby reducing gastric cancer incidence and substantially improving survival, with important public health implications for primary prevention. Stage-specific multi-omics biomarkers reflect the dynamic molecular changes that occur during gastric carcinogenesis and provide a biological basis for non-invasive detection strategies (Table 1, Fig. 1).[21–24,26–29,31–33,37]

Despite the considerable value of biomarkers for premalignant lesions, their translational potential for population-based screening remains limited. Key challenges include the low abundance and analytical variability of biomarkers in these early stages, technical constraints of current detection assays,[36] and practical issues related to suboptimal compliance and cost-effectiveness when targeting very early detection in asymptomatic populations.[41,42] Consequently, most contemporary multi-omics research focuses on comparing patients with established gastric cancer to healthy controls, aiming to identify biomarkers capable of distinguishing early-stage gastric cancer patients from truly healthy individuals or to develop integrated panels that enable effective risk stratification for precision screening.[43]

Liquid biopsy biomarkers for early detection of gastric cancer: advances

cfDNA

Extracellular DNA fragments known as cfDNA typically range in length from 100 to 200 base pairs. These fragments are released into bodily fluids through cellular processes such as apoptosis, necrosis, or other physiological activities.[44] Advances in cfDNA detection technologies have greatly expanded its utility, supporting the emergence of liquid biopsy as a non-invasive tool for the early detection of multiple cancers,[45] including gastric cancer. Current cfDNA-based detection approaches include mutation analysis, methylation profiling, and fragmentomics; each of these methods provides unique insights into cancer biology and early detection.[46]

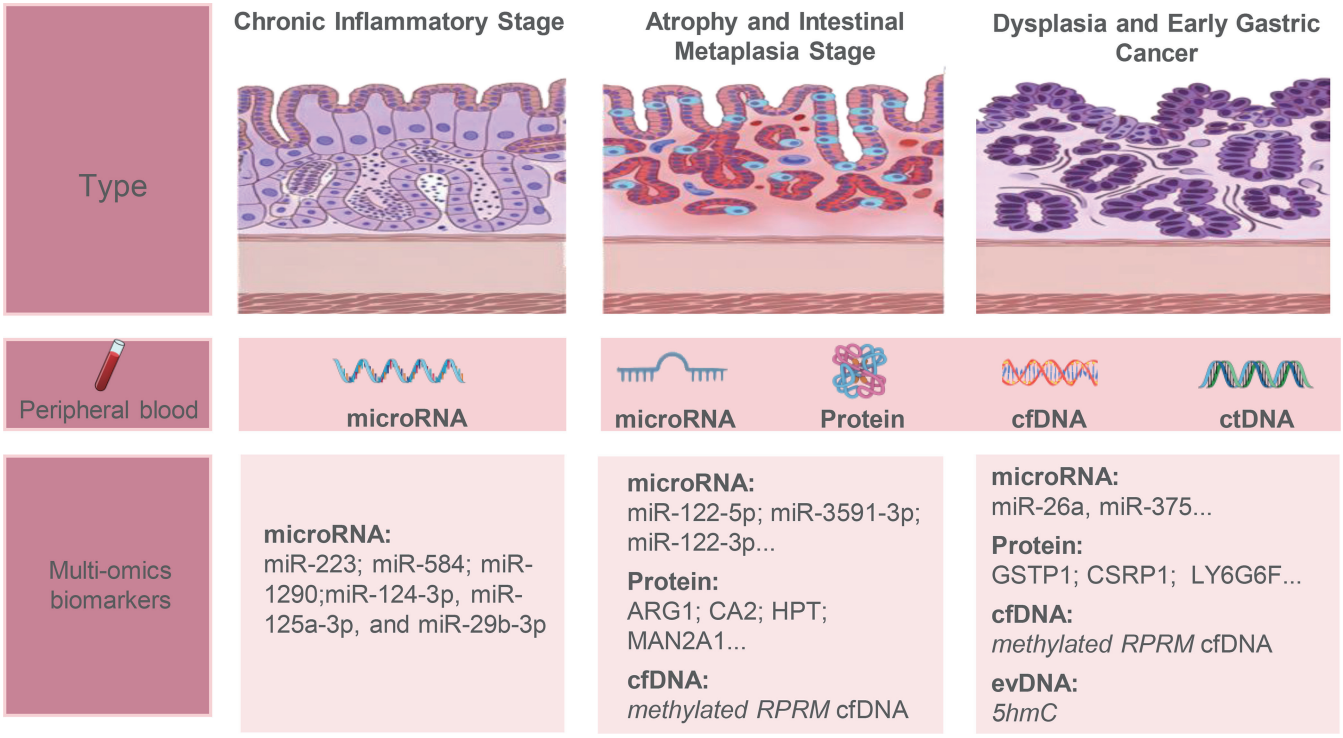

Fig. 1. Gastric precancerous lesions represent a progressive continuum. Specific abnormal molecular signals are released into the peripheral blood, enabling non-invasive detection by multi-omics techniques. *5hmC, 5-hydroxymethylcytosine*; ARG1, arginase 1; CA2, carbonic anhydrase 2; cfDNA, cell-free DNA; CSRP1, cysteine and glycine-rich protein 1; ctDNA, circulating tumor DNA; evDNA, extracellular vesicle–derived DNA; GSTP1, glutathione S-transferase Pi 1; HPT, haptoglobin; LY6G6F, lymphocyte antigen 6 family member G6F; MAN2A1, mannosidase alpha class 2A member 1; miR, microRNA; *mRPRM, methylated RPRM*; *RPRM*, *Reprimo, cell cycle regulator*.

cfDNA mutations

cfDNA, particularly the tumor-derived fraction known as ctDNA, encodes somatic mutations from the primary tumor and can be detected via high-depth sequencing or digital polymerase chain reaction.[47] Earlier studies have uncovered various nucleotide mutations linked to gastric cancer. The most frequently mutated genes include *tumor protein p53* (*TP53*), *titin*, *mucin 16*, *cadherin 1*, *lysine methyltransferase 2C*, and *MutL homolog 1*.[48,49] Furthermore, Cohen *et al*.[50] combined ctDNA mutations, including *TP53*, *Kirsten rat sarcoma viral oncogene homolog*, *phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha*, *catenin beta 1*, and *adenomatous polyposis coli*, with protein markers to develop a blood-based detection method (CancerSEEK) and evaluated its application in the early detection of eight common cancer types, including gastric cancer. However, in EGC, tumor burden and consequent ctDNA shedding are minimal, resulting in very low mutant allele fractions that often fall below the limit of detection (LoD) in plasma cfDNA, thereby reducing sensitivity.[51] At the same time, non-tumor-derived variants, including those from clonal hematopoiesis, can interfere with cfDNA mutation profiles and reduce specificity.[52] Therefore, ctDNA mutation detection is currently more suitable for treatment decision-making and monitoring of advanced disease than for independent early detection.[53]

cfDNA methylation

In contrast to sequence mutations, cfDNA methylation patterns are epigenetic alterations that often occur early in tumorigenesis, making them sensitive biomarkers for early cancer detection.[54] Aberrant DNA methylation signatures specific to gastric tumorigenesis have been detected in plasma cfDNA, enabling discrimination between early-stage gastric cancer patients and non-cancer controls via targeted or genome-wide methylation profiling.[55] For instance, *methylated Septin 9* (*mSEPT9*), a well-established epigenetic marker in colorectal cancer,[56] has also been evaluated in gastric cancer cohorts, where plasma *mSEPT9* showed measurable diagnostic performance. Importantly, *mSEPT9* positivity was detectable in early-stage disease, supporting its potential role in non-invasive screening.[57] Subsequent evaluations of *mSEPT9*'s sensitivity and specificity confirmed its utility as a non-invasive diagnostic biomarker for gastric cancer, outperforming traditional serum markers such as carcinoembryonic antigen and carbohydrate antigen 19-9 (CA19-9) in distinguishing gastric cancer patients from controls.[58] In parallel, *methylated ring finger protein 180* (*mRNF180*), a tumor suppressor gene frequently silenced by promoter hypermethylation in gastric carcinogenesis, has been independently validated as a plasma cfDNA biomarker for gastric cancer diagnosis. In addition, *mRNF180* has exhibited moderate-to-good diagnostic accuracy in differentiating gastric cancer from benign gastric diseases, including chronic gastritis. Notably, combined detection of *mSEPT9* and *mRNF180* further improved diagnostic sensitivity.[57] Beyond such targeted gene-level studies, Qi *et al*.[59] employed genome-wide cfDNA methylome profiling in 250 plasma samples, identifying 21 gastric cancer-specific differentially methylated regions, including *zinc finger protein 74*, *plakophilin 4*, *nuclear pore complex interacting protein family member B3*, *coiled-coil domain containing 144B*, and *RRN3 pseudogene 1*, with the highest AUC values (>0.8).

In addition to incremental improvements in diagnosis, cfDNA methylation technology can address two core limitations of blood-based EGC detection: the detectability of early signals and the determination of the tumor tissue of origin.[60] Aberrant DNA methylation arises early in gastric carcinogenesis and occurs across coordinated CpG regions, providing an intrinsic signal amplification advantage over sparse somatic mutations.[61,62] In addition, methylation profiles retain tissue-specific epigenetic signatures, which enhance the ability to distinguish gastric cancer-derived cfDNA from hematopoietic background signals.[63] Nonetheless, clinical implementation remains constrained by the requirement for high-depth sequencing, complex bioinformatic pipelines, and the current predominance of retrospective case-control evidence rather than prospective screening validation.[52]

cfDNA fragmentomics

cfDNA fragmentomics focuses on analyzing non-sequence features, including fragment size, end motifs, and breakpoint locations, which reflect nucleosomal organization and DNA degradation processes in tumor cells.[64] Unlike random degradation, cfDNA fragmentation presents characteristic profiles that provide valuable clues about tissue and cellular origins, as well as underlying biological mechanisms.[65] These geometric and structural cfDNA characteristics have shown promise as sensitive biomarkers capable of capturing tumor signals even at very low ctDNA fractions, which is a key advantage for early cancer detection.

In recent years, research on the application of cfDNA fragmentomics to EGC screening has expanded rapidly. A prospective study conducted by Yu *et al*.[66] integrated four orthogonal features, including size, copy number, nucleosome positioning, and substitutions, into an ensemble model, achieving an AUC > 0.93 across multiple cohorts for stage I–II gastric cancer detection. In addition, Song *et al*.[67] performed low-pass whole-genome sequencing on 733 participants, including 131 gastric cancer patients, and systematically extracted multidimensional cfDNA features such as fragmentation profiles, end motifs, and genome-wide copy number variations. These features were then used to construct a machine learning-based classification model, which demonstrated outstanding performance in distinguishing gastric cancer patients from healthy controls (AUC = 0.998, sensitivity 94.87%, specificity 99.35%). Notably, the study included patients with benign gastric diseases as controls, directly addressing the core challenge in early screening of differentiating malignant from benign conditions.[67] Moreover, the study by Lu *et al*.[12] advances cfDNA fragmentomic analysis through a two-stage neural network ensemble learning stagewise model (ELSM) that integrates 13 distinct fragmentomic feature spaces. This framework effectively addresses challenges of high-dimensional multimodal fusion, achieving an AUC of 0.972 for pan-cancer detection and 0.922 in an independent gastric cancer cohort.[12] Importantly, ELSM not only improves detection accuracy but also retains interpretability by linking the identified genomic regions to known oncogenic pathways, representing a significant methodological step toward clinically applicable multi-omics liquid biopsies.

These studies show that multidimensional analysis of cfDNA's physical and genetic properties is more sensitive and robust than single-feature analyses. Furthermore, fragmentomic signals originate from epigenetically regulated chromatin structures, enabling indirect inference of tissue of origin through nucleosome positioning patterns. Additionally, fragmentomic features can be extracted from standard whole-genome sequencing data without prior knowledge of tumor-specific variants, making it easier to integrate with other cfDNA methods such as copy number variation and methylation profiling.[68] However, some researchers have also pointed out that the definition of fragmentation varies, ranging from the entire genome to specific genomic regions, and these patterns have not been systematically compared, impeding broader research and practical implementation.[69]

Integrated cfDNA biomarkers

Recently, the GUIDE prospective cohort study developed GutSeer, a targeted cfDNA test that combines DNA methylation and fragmentomics to detect early gastrointestinal (GI) cancers. Using tissue-specific methylation markers and fragmentomic signals, GutSeer achieved high accuracy across multiple GI cancers and maintained strong sensitivity for early-stage disease and advanced precancerous lesions.[70] This study shows that integrating multiple cfDNA modalities can improve clinical scalability and real-world screening utility compared with single-marker approaches.

cfRNA

cfRNA refers to fragmented RNA molecules, including messenger RNA, miRNA, and long non-coding RNA, that enter extracellular bodily fluids such as blood through apoptosis, necrosis, or active cellular secretion.[71] Changes in cellular RNA expression are a dynamic biological process and can serve as functional indicators of pathological conditions.[72] Increased expression of specific tumor-associated transcripts can enhance the intensity of tumor-derived cfRNA signals in peripheral blood.[73]

Circulating miRNAs

miRNAs are among the earliest and most extensively studied cfRNA biomarkers for gastric cancer detection.[74] Functionally, miRNAs act as key post-transcriptional regulators and are involved in major oncogenic pathways, such as cell proliferation, apoptosis, and immune modulation.[75] Their relative stability in blood has enabled reliable detection in plasma and serum.[76]

As early as 2014, Zhu *et al*.[77] pioneered a four-phase study to identify plasma miRNA biomarkers for EGC. The study distinguished between gastric non-cardia and cardia adenocarcinoma subtypes and identified a five-miRNA panel (miRNA-16, miRNA-25, miRNA-92a, miRNA-451, and miRNA-486-5p) that achieved an AUC of 0.925.[77] Subsequently, Zhu *et al*.[78] conducted a systematic screening of plasma miRNA biomarkers by comparing patients with EGC, advanced gastric cancer, and benign gastritis. The researchers identified a panel comprising miRNA-7641, miRNA-425-5p, miRNA-1180-3p, and miRNA-122-5p that could distinguish gastric cancer from benign conditions. For the specific detection of EGC, a combination of miRNA-425-5p, miRNA-24-3p, miRNA-1180-3p, and miRNA-122-5p demonstrated diagnostic value (AUC = 0.829). Furthermore, the expression patterns of miRNA-24-3p and miRNA-4632-5p were useful in differentiating EGC from advanced gastric cancer.[78] In a small-sample study, Saliminejad *et al*.[79] also concluded that the circulating miRNA-18a/21/125b combination is a potential biomarker for EGC detection. Recently, many studies have focused on using artificial intelligence (AI) and machine learning as core analytical methods. Using serum miRNA expression profiles from 972 samples, one study constructed a circulating miRNA panel for gastric cancer classification via network biology and machine learning. A specific set of miRNAs, including miRNA-1228-5p, miRNA-1343-3p, miRNA-6765-5p, and miRNA-6787-5p, demonstrated performance of approximately 87% accuracy, 90% specificity, and 89% sensitivity in distinguishing gastric cancer from healthy controls.[80] Lu *et al*.[81]

developed an AI-driven framework, ESGCmiRD, which identified a five-miRNA signature (miRNA-320b, miRNA-222-3p, miRNA-181a-5p, miRNA-103a-3p, miRNA-107) for early-stage gastric cancer detection, achieving high diagnostic accuracy (AUC up to 0.986) across multiple cohorts.

Exosomal miRNAs

Exosomal miRNA is a more refined subset of cfRNA with greater biological relevance. Exosomes are nano-sized extracellular vesicles actively secreted by living cells and act as mediators of intercellular communication.[82] Importantly, their lipid bilayer membrane protects enclosed RNA molecules from enzymatic degradation, making them more stable than freely circulating RNA.[83] For example, a study by Lu *et al*.[84] showed that serum exosomal miR-92a-3p is significantly downregulated in gastric cancer patients compared with healthy controls and correlates with disease progression. With an AUC of 0.829, it performs better than conventional protein markers for diagnosis.[84] Notably, exosomal miRNA can be integrated with other circulating miRNAs to improve diagnostic accuracy. The DESTINEX study illustrates a sophisticated multi-source integration strategy, which combines exosomal and cell-free miRNA signals using machine learning. This approach produced a high-performance 10-miRNA signature (DESTINEX) with an AUC of 96.8% for early-stage gastric cancer detection.[85]

Overall, cfRNA research shows that RNA-based liquid biopsy markers are effective and feasible for EGC detection. Research has evolved from early single-miRNA studies to multi-miRNA panels, and more recently to AI-integrated multi-source signatures. This trajectory reflects efforts to improve diagnostic accuracy through combinatorial and computational methods. However, extracting and stabilizing cfRNA remains challenging. Due to its low abundance and high susceptibility to degradation, cfRNA requires strict operational procedures and sensitive analytical techniques.[86]

Circulating proteins

Compared with nucleic acid markers, circulating proteins and peptides are downstream functional executors of tumor biology; therefore, they provide complementary information for EGC detection.[87] Conventional serum protein markers, including carcinoembryonic antigen and CA19-9, have long been used in clinical practice. However, their sensitivity and specificity in early-stage disease are limited, restricting their utility as standalone screening tools.[88] Still, when added to multi-marker panels or combined with emerging omics-based biomarkers, these traditional proteins can improve diagnostic value.[89]

Du *et al*.[90] used serum proteomics and extensive machine learning model evaluation to identify protein biomarkers for EGC. The generalized linear model boosting and extreme gradient boosting models, incorporating beta-2-microglobulin, cofilin 1, cathepsin D, and heat shock protein 90 alpha family class B member 1, achieved a mean AUC of 0.792. Furthermore, candidate proteins were linked to immune cell infiltration via single-cell sequencing, providing both diagnostic signatures and insights into the tumor microenvironment.[90] Additionally, a prospective proteomic study identified high-performance plasma protein panels for detecting gastric carcinogenesis at all stages. Notably, a five-protein panel (ARG1, CA2, HPT, MAN2A1, and LBP) achieved an AUC of 97.3–99.5% in distinguishing both cancer and preneoplastic lesions from benign conditions.[28]

Traditional mass spectrometry-based proteomics can profile blood protein biomarkers on a large scale, but poor sensitivity for low-abundance proteins limits their use in early cancer diagnosis.[91] Emerging proteomic platforms such as Olink and single-molecule array (Simoa) have improved detection sensitivity, enabling accurate quantification of low-abundance proteins.[15] A recent study employed the high-sensitivity Olink PEA platform to profile 369 plasma proteins, identifying a 13-protein signature, including growth differentiation factor 15 and inter-alpha-trypsin inhibitor heavy chain 3, which achieved exceptional diagnostic accuracy for early-stage gastric cancer with an AUC up to 0.998.[92]

Circulating metabolome

Gastric cancer development involves significant changes in energy metabolism, amino acid utilization, and lipid synthesis,[93] resulting in distinct circulating metabolic "fingerprints" that can be detected in serum or plasma.

Using high-resolution mass spectrometry combined with machine learning algorithms, several studies have identified metabolite panels that distinguish EGC from benign gastric diseases and healthy controls. Chen *et al*.[94] identified a 10-metabolite diagnostic panel from targeted plasma analysis, achieving a sensitivity of 0.905, which significantly outperforms traditional protein markers. Cai *et al*.[8] focused on lipid metabolism, constructing a serum lipid metabolic signature with high efficacy for early-stage detection. They also derived prognostic subtypes using unsupervised clustering.[8] Together, these findings demonstrate that metabolomic and lipidomic approaches using machine learning offer a highly sensitive and functionally informative method for non-invasive gastric cancer screening and risk stratification. Importantly, metabolites are the final products of genomic and proteomic changes,[95] so they often respond rapidly to pathological changes, offering potential advantages for early detection. From a translational perspective, metabolomic assays benefit from relatively fast analytical workflows and lower per-sample costs. However, their clinical use is limited by large inter-individual variability influenced by diet, microbiota, circadian rhythms, and physiological states.[96] Thus, strict standardization of pre-analytical conditions and robust model validation across populations are essential for routine screening (Table 2, Fig. 2).[8,12,28,50,57-59,66,67,70,77,78,81,84,85,90,92,94]

Comparative performance and translational characteristics of multi-omics biomarkers

Among current liquid biopsy strategies for EGC detection, substantial differences in performance have been observed. Generally, cfDNA fragmentomics shows the highest overall accuracy, achieving sensitivities of 79% to 95%, specificities of 90% to 99%, and AUCs of 0.94 to 0.98 in major studies.[66,67,97] cfRNA biomarkers exhibit overall pooled sensitivity and specificity of around 80%.[98] For cfDNA mutations, current studies generally demonstrate relatively high specificity but limited and heterogeneous sensitivity, with reported sensitivities ranging from approximately 16% to 85% and specificities ranging from 74% to 96%.[98–100] In contrast, cfDNA methylation assays demonstrate more balanced performance, with sensitivities of 65% to 94%, specificities of 84% to 96%, and AUCs of 0.79 to 0.96.[98,101–103]

However, simply comparing sensitivity and specificity across different biomarkers is not sufficiently comprehensive due to heterogeneity in analytical platforms and study populations. Technically, ultra-deep sequencing and complex bioinformatic analyses are usually required for cfDNA mutation and methylation assays, resulting in relatively high costs.[104] Circulating protein biomarkers rely on mature immunoassay platforms such as enzyme-linked immunosorbent assay and chemiluminescence immunoassay, which are inexpensive, automated, and widely accessible, whereas

Table 2. Multi-omics biomarkers for early gastric cancer detection

Categorization	Biomarker type	Biomarker name/panel	Study design	Evidence level	Reference
cfDNA	Mutation	*TP53*, *KRAS*, *PIK3CA*, *APC* (CancerSEEK)	Case–control	Discovery	50
cfDNA	Methylation	*mSEPT9*	Case–control	Validation	57,58
cfDNA	Methylation	*mSEPT9* + *mRNF180*	Case–control	Validation	57
cfDNA	Methylation	21 methylated regions (e.g. *ZNF74*, *PKP4*)	Case–control	Validation	59
cfDNA	Fragmentomics	Multi-feature ensemble (size, end motifs, etc.)	Prospective	Prospective evidence	66
cfDNA	Fragmentomics	Multi-omics ML model	Case–control	Validation	67
cfDNA	Fragmentomics	ELSM	Multi-cohort	Validation	12
cfDNA	Integrated	GutSeer (methylation and fragmentomics)	Prospective	Prospective evidence	70
cfRNA	miRNA panel	miR-16/25/92a/451/486-5p	Multi-phase	Validation	77
cfRNA	miRNA panel	miR-425-5p/24-3p/1180-3p/122-5p	Case–control	Discovery	78
cfRNA	miRNA	5-miRNA	Multi-cohort	Validation	81
Exosomal RNA	Exosomal miRNA	miR-92a-3p	Case–control	Discovery	84
Exosomal RNA	Integrated miRNA	DESTINEX (10-miRNA signature)	Multicenter	Validation	85
Proteomics	Protein panel	B2M, CFL1, CTSD, HSP90AB1	Case–control	Validation	90
Proteomics	Protein panel	ARG1, CA2, HPT, MAN2A1, LBP	Prospective	Prospective evidence	28
Proteomics	Protein panel	13-protein Olink panel	Case–control	Validation	92
Metabolomics	Metabolite panel	10-metabolite signature	Case–control	Validation	94
Metabolomics	Lipidomics	SLMS (serum lipid signature)	Case–control	Validation	8

Evidence level was categorized according to study design and validation status. Discovery refers to exploratory studies proposing novel biomarkers without independent validation cohorts. Validation includes studies evaluating biomarkers in independent cohorts, multi-phase case-control studies, or multicenter datasets. Prospective evidence denotes biomarkers assessed in prospective or population-based cohorts that approximate real-world screening settings. *APC*, *adenomatous polyposis coli*; ARG1, arginase 1; B2M, beta-2-microglobulin; CA2, carbonic anhydrase II; cfDNA, cell-free DNA; CFL1, cofilin 1; cfRNA, cell-free RNA; CTSD, cathepsin D; ELSM, ensemble learning stagewise model; HPT, haptoglobin; HSP90AB1, heat shock protein 90 alpha family class B member 1; *KRAS*, *Kirsten rat sarcoma viral oncogene homolog*; LBP, lipopolysaccharide-binding protein; MAN2A1, mannosidase alpha class 2A member 1; miR, microRNA; miRNA, microRNA; ML, machine learning; *mRNF180*, *methylated ring finger protein 180*; *mSEPT9*, *methylated septin 9*; *PIK3CA*, *phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha*; *PKP4*, *plakophilin 4*; SLMS, serum lipid metabolic signature; *TP53*, *tumor protein p53*; *ZNF74*, *zinc finger protein 74*.

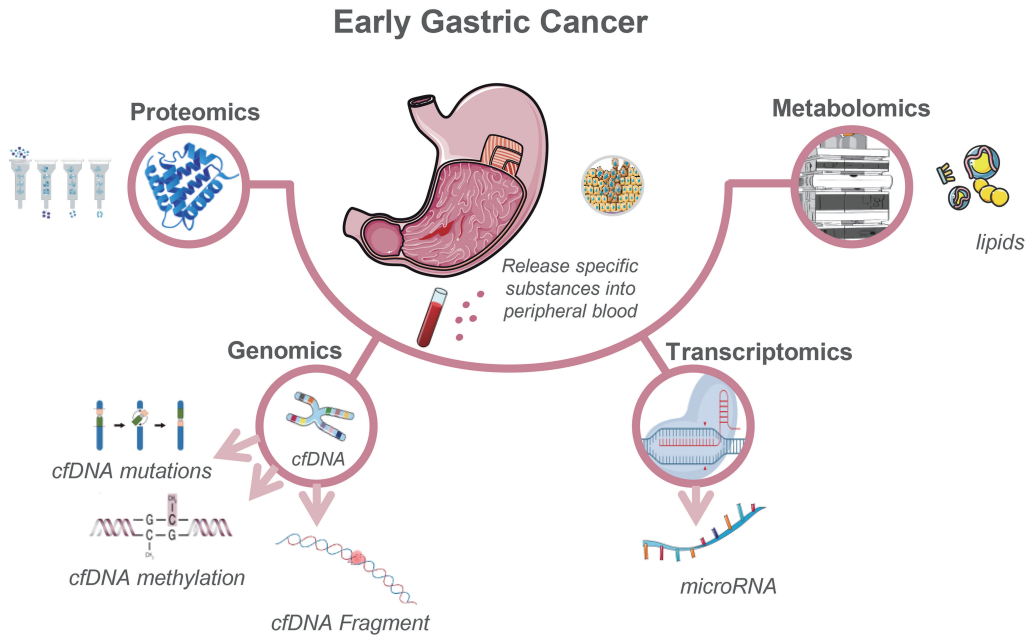

Fig. 2. Early gastric cancer releases specific molecular signals across genomic, transcriptomic, proteomic, and metabolomic spectra into the peripheral blood, which can be captured by multi-omics technologies for non-invasive detection. cfDNA, cell-free DNA.

metabolomic profiling depends on costly mass spectrometry platforms. cfRNA detection is additionally limited by poor RNA stability and strict sample-processing requirements.[105]

From a real-world screening perspective, cfDNA fragmentomics currently provides the best balance between diagnostic performance, scalability, and cost-effectiveness. cfDNA methylation assays also show strong performance but remain technically complex, whereas cfRNA and metabolomic approaches are still limited by stability and standardization challenges. Overall, integrated multi-omics strategies may represent the most feasible future direction for EGC screening.

The integrative value of multi-omics biomarkers in gastric cancer control

Although gastric cancer remains one of the most common and fatal malignancies worldwide, population-based screening programs are currently limited and uneven across regions.[106] Countries with high incidence, such as China, Japan, and the Republic of Korea, have long implemented nationwide organized endoscopic screening for gastric cancer, which has contributed to a measurable decline in mortality over time, particularly in South Korea, where standardized screening has been associated with up to a 41% reduction in gastric cancer deaths.[107] However, coverage rates even within these programs vary depending on participation and access to endoscopic services. For example, in China, large-scale screening is mainly targeted at selected high-risk areas rather than the entire country, and participation rates remain low.[108] Currently, about 38 million gastroscopy examinations are performed annually in China, while the number of eligible high-risk individuals for gastric cancer is as high as 660 million.[109] In other parts of the world, formal gastric cancer screening programs are mostly absent or are not recommended outside high-risk groups.

Multi-omics biomarkers integrate molecular information at different levels, which can comprehensively improve the effectiveness of early gastric cancer screening. They provide new solutions to overcome the limitations of traditional screening, expand coverage, enhance compliance, and optimize resource allocation and health economics. Multi-omics strategies can complement existing screening systems, shifting screening toward a more precise, less invasive, and scalable approach.

Expanding the breadth and precision of screening coverage

Traditional population-based gastric cancer screening relies heavily on upper GI endoscopy, an effective but invasive and resource-intensive modality that limits broad reach, especially outside major urban centers.[110] Endoscopic screening utilization was reported as 8.3% in rural western China and 32.5% in resource-rich eastern regions in a recent community healthcare survey, highlighting the severely restricted access in under-resourced rural areas.[111]

A fundamentally different approach is offered by blood-based multi-omics biomarker tests: samples can be collected in decentralized settings without specialized equipment or clinicians, shipped to central laboratories, and analyzed at scale.[112] Circulating biomolecules, including cfDNA methylation signatures, fragmentomics, proteins, and metabolites, are harnessed by such approaches to detect early tumor signals with high sensitivity and specificity. These screening programs can be extended beyond tertiary care centers into rural and underserved regions. Through these features, the gap between urban and rural regions is narrowed, and equitable access to high-quality gastric cancer screening is supported.[113]

Significantly improving population screening compliance and acceptability

Overcoming psychological and physiological barriers

Endoscopy uptake among asymptomatic populations is significantly deterred by fear of invasive procedures, anticipated discomfort, perceived risk of complications, and logistical challenges.[114] Importantly, the public health impact of endoscopic screening is directly undermined by low compliance, and early detection is hindered as a result.[115] Even with government-funded programs for the early detection and treatment of gastric cancer, compliance with endoscopic examinations reaches only 33.5%.[116] Consequently, the development of simple and non-invasive primary screening approaches is a critical prerequisite for improving participant acceptability and expanding screening coverage.

This need is further supported by population preference studies, where 60.2% of participants favored blood-based testing, and only 29.8% preferred endoscopic examination when asked to identify the most acceptable screening modality for gastric cancer.[116] Notably, individuals' willingness to undergo gastroscopy has been shown to increase with awareness of an elevated personal risk of gastric cancer.[117] Therefore, incorporating blood-based biomarkers as a risk stratification tool prior to endoscopic screening represents a pragmatic and potentially effective strategy. By enabling the non-invasive identification of high-risk individuals, participation in community-based initial screening may be increased, adherence to subsequent endoscopic examination among targeted populations may be improved, and broader population coverage may ultimately be facilitated.

Enhancing convenience and integration into routine health checks

Substantial advantages for cancer screening programs are offered by the integration of multi-omics biomarker testing into routine health examination workflows, particularly in terms of convenience, acceptability, and health-economic efficiency. Unlike diagnostic procedures, which require separate appointments, additional travel, and specialized clinical infrastructure, multi-omics assays based on blood samples can be performed alongside common clinical laboratory tests such as lipid profiles, glucose levels, and complete blood counts. This co-testing model may significantly reduce "opportunity costs", such as time off work, travel expenses, and appointment scheduling complexities.[15,118]

Optimizing the health economic benefits of gastric cancer control

More efficient reallocation of limited health resources can be achieved by investing in multi-omics biomarkers. Through the precise stratification of individuals based on molecular risk, these tools can reduce unnecessary endoscopic procedures in low-risk groups and reserve more costly invasive diagnostics for those with high biomarker scores.[119] Early detection through non-invasive biomarkers also enables less invasive and less expensive treatments compared with advanced disease management, which often necessitates surgery, systemic therapy, and intensive supportive care.[18] Indirect economic gains, including reduced work absenteeism, preserved productivity, and lower caregiver burden, further augment societal returns on investment.[120]

Currently, high-risk groups are mainly identified by questionnaires in the national-level early diagnosis and treatment program for gastric cancer. Although this method has limited diagnostic accuracy, it remains irreplaceable due to advantages such as low

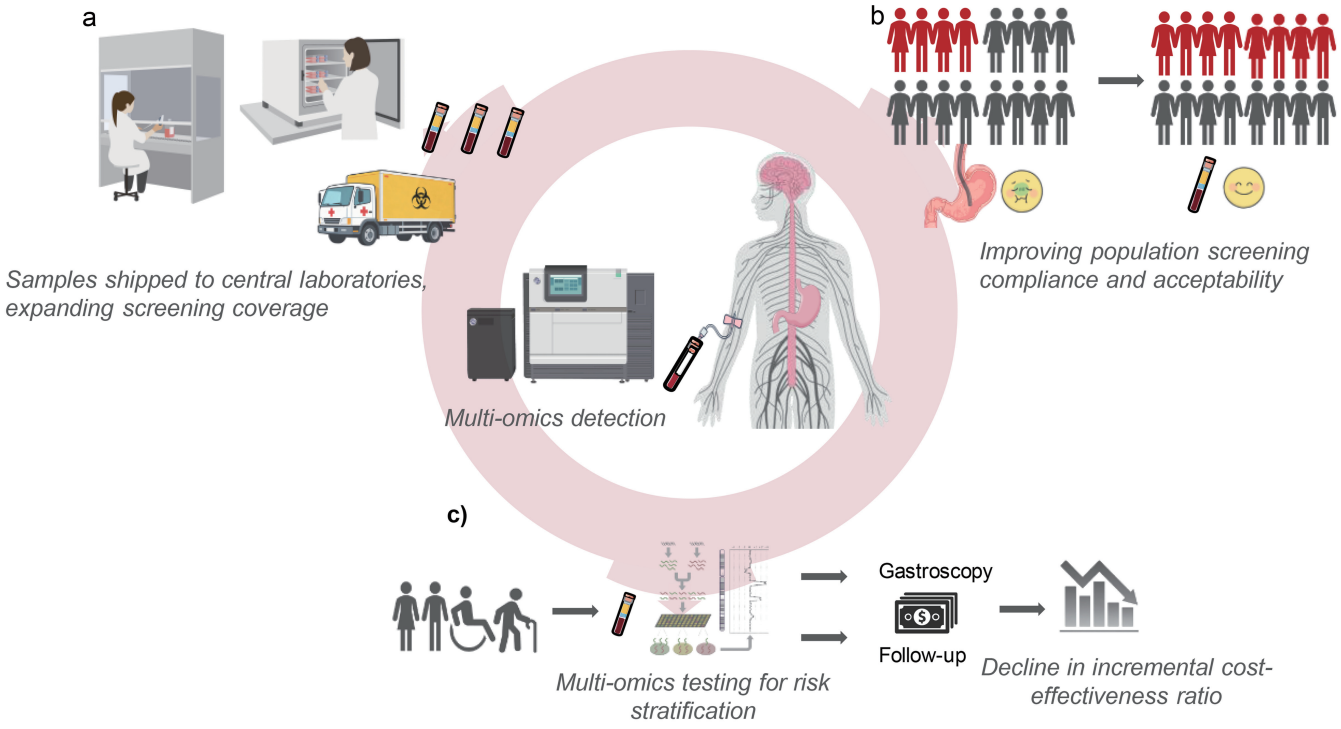

Fig. 3. Applications of multi-omics techniques for gastric cancer screening demonstrate integrative advantages. a) Multi-omics testing enables decentralized sample collection with centralized analysis, thereby expanding screening reach across geographically diverse regions. b) Multi-omics approaches improve acceptability and participation by providing a non-invasive alternative to primary endoscopic screening. c) Multi-omics risk stratification guides targeted use of gastroscopy, achieving efficient resource allocation and improved cost-effectiveness.

cost, non-invasiveness, and the ability to assess acceptance and behavioral propensity in the target population.[121] Undeniably, there is still considerable controversy regarding whether to introduce additional risk stratification indicators such as serological and liquid biopsy methods, as in-depth, rigorous, and specialized health economic research is required to measure the relationship between economic input and health outcomes.[122,123] However, risk stratification models based on serological indicators are often considered the most cost-effective strategy in China.[124] The Markov model developed by Saito *et al*.[125] also demonstrates that serological methods are the most cost-effective, with an incremental cost-effectiveness ratio of $2,964 per quality-adjusted life year and a willingness-to-pay threshold of $50,000 (Fig. 3).

Limitations, challenges, and future opportunities

Key limitations: The translational gap from discovery to validation

Despite considerable progress in the identification of candidate biomarkers for EGC via multi-omics approaches, insufficient sensitivity in real-world screening remains one of the most critical limitations hindering clinical translation.[126] This challenge is attributed to both intrinsic technical constraints of early tumor biology and methodological limitations in current study designs.

From a technical perspective, the analytical sensitivity of many circulating biomarker assays remains inadequate for detecting the extremely low abundance of tumor signals in early-stage gastric cancer and precancerous lesions, such as high-grade gastric intraepithelial neoplasia.[127] Minimal amounts of ctDNA, RNA, proteins, or metabolites are often shed into the bloodstream by early gastric tumors, resulting in signal levels that approach or fall below the LoD of existing platforms.[128] The probability of detecting EGC using single-analyte or single-omics assays is substantially reduced by this biological constraint, even when advanced sequencing or proteomic technologies are employed.

Clinically, a major barrier to sensitivity optimization lies in the heavy reliance on retrospective case-control studies with small sample sizes, frequently derived from single centers or secondary analyses of public repositories such as The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO). While such studies are indispensable for biomarker discovery, selection bias, batch effects, and overfitting are inherently prone to occur.[14,129] As a result, inflated diagnostic performance is often observed in multi-omics models within discovery cohorts, but substantial performance degradation occurs when these models are applied to independent validation sets or prospective populations.[130] Importantly, most current EGC biomarker studies prioritize diagnostic accuracy metrics, such as sensitivity, specificity, and AUC, rather than clinically meaningful screening endpoints, including reductions in advanced-stage incidence or gastric cancer-specific mortality.[131] Real-world screening effectiveness cannot be reliably inferred due to this disconnect. When deployed in asymptomatic, average-risk populations, biomarkers that perform well in controlled case-control settings may fail to maintain sensitivity, as spectrum bias and differences in disease prevalence, stage distribution, and comorbidity profiles are present.[132,133] False-negative results in this context are not merely statistical artifacts but represent a tangible clinical risk. Diagnostic endoscopy may be delayed due to missed early-stage cancers, adherence to standard-of-care sur-

veillance strategies may be reduced, and the preventive potential of screening programs may ultimately be compromised.[134]

To address these challenges, a more balanced and clinically grounded strategy should be adopted in future multi-omics screening research for gastric cancer. Instead of disproportionately prioritizing specificity to minimize false positives, biologically and clinically justified LoD thresholds should be defined by investigators to optimize the trade-off between sensitivity and specificity in screening contexts. Enhancing detection of early-stage and precancerous disease signals is essential, which can be achieved through continued innovation in ultra-sensitive detection technologies combined with advanced integrative algorithms. Moreover, a rational strategy to overcome biological heterogeneity is the integration of multiple classes of biomarkers, such as cfDNA methylation, fragmentomics, circulating RNA, proteomics, and metabolomics. Multi-omics integration can provide complementary biological information, reduce noise through feature redundancy, and expand the effective feature space for risk modeling, all of which contribute to improved sensitivity and robustness. Finally, the adverse impact of spectrum bias can be mitigated through rigorous study designs that better reflect real-world screening populations. Such designs include enrolling participants across a broad range of disease stages and risk profiles, implementing prospective cohort studies, and adopting nested case-control designs within population-based screening programs. These approaches can generate more reliable estimates of sensitivity and ensure the clinical credibility of multi-omics-based EGC screening tools.

Core challenges in translation

Pre-analytical variability and platform harmonization

A major barrier to clinical translation is the lack of standardized pre-analytical and analytical workflows across studies and platforms.[135] Factors including blood collection tubes, plasma versus serum selection, processing time, storage conditions, and freeze–thaw cycles may substantially affect cfDNA or cfRNA integrity, protein stability, and metabolomic profiles.[136,137] In addition, differences in sequencing platforms, library preparation protocols, and bioinformatic pipelines currently limit assay harmonization and inter-study reproducibility.[138] Therefore, establishing standardized operating procedures and unified analytical criteria will be critical for large-scale clinical implementation of multi-omics liquid biopsy screening.

Screening utility and integration pathways

A fundamental challenge in translating multi-omics biomarkers into clinical screening practice is the lack of clearly defined clinical decision thresholds and pathways. While risk scores derived from integrative biomarker analyses show potential for non-invasive detection, no consensus has been reached on actionable cutoffs linked to specific clinical responses.[139] For example, decisions regarding when a positive multi-omics screen should trigger endoscopy, which endoscopic modality should be used, and how follow-up intervals should be stratified based on individual risk remain unsettled. Without these standardized decision rules, implementation in routine clinical workflows is challenging, and variability across institutions is observed.[14]

Future clinical decision thresholds will likely need to be determined through risk-benefit calibration rather than biomarker positivity alone. Threshold selection should consider multiple factors, including gastric cancer prevalence, endoscopic resource availability, acceptable false-positive rates, patient compliance, and cost-effectiveness in population screening settings.

For subsequent risk-stratification strategies, individuals with high-risk molecular profiles could be prioritized for immediate endoscopy, whereas intermediate-risk individuals may undergo repeat liquid biopsy surveillance at shorter intervals. In contrast, low-risk individuals may continue routine population-based screening. Such tiered screening pathways may improve endoscopic resource allocation while reducing unnecessary invasive procedures.

Integration with existing screening systems

New multi-omics assays should demonstrate incremental value over established screening pathways and integrate seamlessly with existing public health frameworks. In high-incidence regions such as East Asia, established strategies include *H. pylori* testing, serum pepsinogen screening, ABC stratification, and population-based endoscopic screening in some areas.[140] Embedding multi-omics risk models into these systems will require rigorous comparative effectiveness studies. Superiority or added value in terms of earlier detection, improved risk stratification, cost-effectiveness, and enhanced clinical outcomes should be demonstrated in these studies.

Future opportunities and strategic directions

From biomarker discovery to an integrated screening system

To bridge the translational gap, emphasis should be placed on well-designed prospective screening studies in future research, with large population-based cohorts enrolled—particularly in high-risk countries such as China, Japan, and South Korea. Multi-omics risk models should be evaluated against clinical endpoints, including reductions in late-stage gastric cancer incidence and gastric cancer mortality. Definitive evidence of clinical utility and public health impact can be generated through such prospective and ideally randomized trials.

An integrated "molecular screening–endoscopy–intervention" strategy

A core strategic direction is positioning multi-omics tests not as replacements for endoscopy but as complementary triage tools. The ultimate role of multi-omics screening should focus on improving the efficiency of endoscopic resources. High-risk individuals can be prioritized for diagnostic endoscopy, unnecessary invasive procedures in low-risk individuals can be reduced, and early detection of asymptomatic disease can be enhanced.

Emerging technologies and future directions

Emerging technologies may further accelerate the translation of multi-omics liquid biopsy screening. Single-cell and spatial multi-omics technologies may improve understanding of tumor heterogeneity and the biological origins of circulating biomarkers, thereby facilitating more precise biomarker discovery. In parallel, AI and machine learning algorithms are increasingly being integrated with multi-omics data to optimize feature selection, risk prediction, and individualized screening strategies. In addition, rapid point-of-care testing platforms and microfluidic devices may enable faster, lower-cost, and more accessible liquid biopsy testing in large-scale population screening settings. Together, these technologies may promote the transition of multi-omics screening from research settings toward real-world clinical implementation.

Limitations of this review

Several limitations of this review should be acknowledged. First,

this is a narrative review rather than a systematic review, and no formal systematic search strategy, study quality assessment, or meta-analysis was performed. Consequently, the selection and interpretation of the included studies may be subject to potential selection bias. Second, the evidence summarized in this review is derived from studies with substantial heterogeneity in study design, patient populations, specimen types, biomarker platforms, and diagnostic thresholds, which limits direct comparison across studies. Third, many multi-omics biomarkers remain at the discovery or early validation stage, and a considerable proportion of the available evidence originates from retrospective or case-control studies rather than prospective population-based screening cohorts. Therefore, although this review highlights the potential value of multi-omics biomarkers for gastric cancer screening and control, the findings should be interpreted within the context of the current evidence base and its inherent limitations.

Conclusions

Early detection remains a key strategy for reducing gastric cancer mortality, and multi-omics biomarkers provide opportunities for non-invasive risk assessment across the gastric carcinogenesis continuum. By integrating complementary molecular information from multiple biological layers, multi-omics approaches have shown improved performance over single-marker strategies and may enhance the effectiveness of population-based screening. Despite growing evidence supporting their potential utility, challenges related to validation, standardization, and clinical implementation remain to be addressed before routine adoption. Overall, multi-omics risk stratification may serve as a complementary approach to endoscopic screening and has the potential to contribute to future precision gastric cancer prevention and control programs.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Study concept and design (YL, JZ, BL, JL), acquisition of data (YB, MY, JyL), analysis and interpretation of data (JY, QW), drafting of the manuscript (YL, YB), critical revision of the manuscript for important intellectual content (JY, QW, JL), administrative, technical, or material support (MY, DH, WM), and study supervision (JL). All authors have made significant contributions to this study and have approved the final manuscript.

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