

World Journal of *Gastroenterology*

World J Gastroenterol 2023 May 7; 29(17): 2515-2703



REVIEW

- 2515 Novel biomarkers for early detection of gastric cancer
Matsuoka T, Yashiro M
- 2534 Non-invasive evaluation of liver steatosis with imaging modalities: New techniques and applications
Zeng KY, Bao WYG, Wang YH, Liao M, Yang J, Huang JY, Lu Q
- 2551 Alcohol-related hepatitis: A review article
Chaudhry H, Sohal A, Iqbal H, Roytman M
- 2571 Current and novel approaches in the pharmacological treatment of hepatocellular carcinoma
Villarruel-Melquiades F, Mendoza-Garrido ME, García-Cuellar CM, Sánchez-Pérez Y, Pérez-Carreón JI, Camacho J

MINIREVIEWS

- 2600 Difficult colorectal polypectomy: Technical tips and recent advances
Pattarajierapan S, Takamaru H, Khomvilai S

ORIGINAL ARTICLE

Basic Study

- 2616 Cryptotanshinone induces apoptosis of activated hepatic stellate cells *via* modulating endoplasmic reticulum stress
Hou XX, Li YW, Song JL, Zhang W, Liu R, Yuan H, Feng TT, Jiang ZY, Li WT, Zhu CL
- 2628 *Lafoensia pacari* alleviates intestinal damage by modulating cyclooxygenase-2: *In silico* and *in vivo* evaluation in a colitis model
Peiter GC, Moesch Queiroz TK, Michalkiewicz Jr EL, Chappuis RH, Luz JS, Casagrande Piovezani LH, Ferreira Silva C, Nozomi Tsutumi M, Fernandes Chaves A, Luiz RM, Façanha Wendel C, Zarpelon-Schutz AC, Teixeira KN
- 2642 Establishment and characterization of a new human ampullary carcinoma cell line, DPC-X1
Xu H, Chai CP, Miao X, Tang H, Hu JJ, Zhang H, Zhou WC

Retrospective Study

- 2657 Mucosal patterns change after *Helicobacter pylori* eradication: Evaluation using blue laser imaging in patients with atrophic gastritis
Nishikawa Y, Ikeda Y, Murakami H, Hori SI, Yoshimatsu M, Nishikawa N

Randomized Controlled Trial

- 2666 Fecal microbiota transplantation for the maintenance of remission in patients with ulcerative colitis: A randomized controlled trial
Lahtinen P, Jalanka J, Mattila E, Tillonen J, Bergman P, Satokari R, Arkkila P

SYSTEMATIC REVIEWS

- 2679** Different types of fruit intake and colorectal cancer risk: A meta-analysis of observational studies
Wu ZY, Chen JL, Li H, Su K, Han YW

LETTER TO THE EDITOR

- 2701** T cells in pancreatic cancer stroma: Tryptophan metabolism plays an important role in immunoregulation
Yang T, Li QQ, Liu YM, Yang B

ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Mohamad Amin Pourhoseingholi, PhD, Associate Professor, Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran 19835, Iran. aminphg@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (WJG, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The WJG is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports, Index Medicus, MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 impact factor (IF) for WJG as 5.374; IF without journal self cites: 5.187; 5-year IF: 5.715; Journal Citation Indicator: 0.84; Ranking: 31 among 93 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG's CiteScore for 2021 is 8.1 and Scopus CiteScore rank 2021: Gastroenterology is 18/149.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; Production Department Director: *Xu Guo*; Editorial Office Director: *Jia-Ru Fan*.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

May 7, 2023

COPYRIGHT

© 2023 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Novel biomarkers for early detection of gastric cancer

Tasuku Matsuoka, Masakazu Yashiro

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Chen X, China; Li DH, China; Zhang Y, China; Zhao Q, China

Received: November 19, 2022

Peer-review started: November 19, 2022

First decision: January 2, 2023

Revised: January 31, 2023

Accepted: April 13, 2023

Article in press: April 13, 2023

Published online: May 7, 2023



Tasuku Matsuoka, Masakazu Yashiro, Molecular Oncology and Therapeutics, Osaka Metropolitan University Graduate School of Medicine, Osaka 5458585, Japan

Corresponding author: Masakazu Yashiro, MD, PhD, Assistant Professor, Molecular Oncology and Therapeutics, Osaka Metropolitan University Graduate School of Medicine, 1-4-3 Asahimachi, Abeno-ku, Osaka 5458585, Japan. i21496f@omu.ac.jp

Abstract

Gastric cancer (GC) remains a leading cause of cancer-related death worldwide. Less than half of GC cases are diagnosed at an advanced stage due to its lack of early symptoms. GC is a heterogeneous disease associated with a number of genetic and somatic mutations. Early detection and effective monitoring of tumor progression are essential for reducing GC disease burden and mortality. The current widespread use of semi-invasive endoscopic methods and radiologic approaches has increased the number of treatable cancers. However, these approaches are invasive, costly, and time-consuming. Thus, novel molecular noninvasive tests that detect GC alterations seem to be more sensitive and specific compared to the current methods. Recent technological advances have enabled the detection of blood-based biomarkers that could be used as diagnostic indicators and for monitoring postsurgical minimal residual disease. These biomarkers include circulating DNA, RNA, extracellular vesicles, and proteins, and their clinical applications are currently being investigated. The identification of ideal diagnostic markers for GC that have high sensitivity and specificity would improve survival rates and contribute to the advancement of precision medicine. This review provides an overview of current topics regarding the novel, recently developed diagnostic markers for GC.

Key Words: Gastric cancer; Diagnostic biomarkers; Early detection; Liquid biopsy

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Gastric cancer (GC) is a major unsolved clinical problem. It is the fifth most diagnosed cancer in the world, and the fourth most frequent cause of cancer-related deaths worldwide. The outcome of advanced GC remains tremendously poor despite the use of surgery and adjuvant therapy. Therefore, the detection new biomarkers for early diagnosis will be potential therapeutic strategies for improving survival of GC patients. The aim of this review is to summarize the current status and approaches for novel biomarkers, which could be useful for early diagnosis.

Citation: Matsuoka T, Yashiro M. Novel biomarkers for early detection of gastric cancer. *World J Gastroenterol* 2023; 29(17): 2515-2533

URL: <https://www.wjgnet.com/1007-9327/full/v29/i17/2515.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v29.i17.2515>

INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer and the fourth most common cause of cancer-related death worldwide[1]. The overall survival rate of individuals with GC remains poor, because it is often diagnosed at an advanced stage or even as metastasis. One strategy for lowering the burden of GC is early screening and diagnosis. Even though upper gastrointestinal endoscopy has been well established as the standard for GC screening, capturing a concealed tumor in the stomach requires higher sensitivity and specificity. Upper gastrointestinal endoscopies also involve high costs with regard to cost and human resources, requiring experienced endoscopists and patient understanding.

To achieve large-scale GC screening among healthy individuals in the future, a more general and cost-effective approach is needed. Cancer biomarkers (tumor markers) are molecules indicative of the presence and progression of cancer; as such, they play a crucial role in cancer diagnoses and treatment selection[2]. Their applications are rapidly expanding owing to advances in genetic analysis technology and molecular targeting. There are at present no biomarkers with sufficient sensitivity and specificity for the diagnosis of GC that could be applied in clinical settings. Biomarkers are needed for every stage of GC to improve its clinical course. The emergence of liquid biopsy technology, which enables the detection of specific molecular information of solid tumors from body fluids, has provided major changes in cancer diagnosis and treatment[3]. There are many studies on biomarkers for GC screening. However, many of these candidate biomarkers identified thus far are preferentially expressed at advanced stages, and thus unsuitable for early detection. Moreover, a comprehensive review focusing on early detection of GC is still lacking. Herein, we review novel candidates of biomarkers focusing on early detection of GC comprehensively, from the laboratory to the clinical prevalence and the future prospects. This information will contribute to further research on GC biomarkers and their clinical applications.

METHODS

A non-systematic review was performed based on an electronic search through the medical literature using PubMed and Google Scholar. The keywords “biomarker”, “gastric cancer”, “early detection”, “diagnostics”, “liquid biopsy” were used. Review articles and guidelines investigating the values of biomarker for early detection of GC from gastroenterology, oncology and genetics were included in this review. When more than one guideline concerning the same subject was available, the most up-to-date one was selected. Only full articles in the English language published in the last ten years were considered for further review. Great importance was also given to “Clinical study” and “Review” articles dealing with the topic. The exclusion criteria comprised duplicated articles, studies absent of diagnostic outcomes. Case reports, correspondences, letters, and non-human research were not included.

LIQUID BIOPSY

Various diverse molecules in blood (serum/plasma) have been said to be correlated with GC carcinogenesis. Among them, DNA, proteins, and noncoding RNA (ncRNA) molecules have been focused. These molecules allow the dependable finding of new noninvasive biomarkers for GC in plasma/serum. Liquid biopsy has shown good potential in detecting circulating tumor cells (CTCs) from any bodily fluid, including peripheral blood, urine and cerebrospinal fluid, ascites, pleural effusion, *etc.*, and includes a genomic, proteomic and metabolite assessment. It is a quick, easy and inexpensive method

with minimal invasiveness, making it widely accepted by patients, without major side effects[4]. Liquid biopsy (using mainly peripheral blood) can be used as a screening method to detect early GC (EGC) and minimal residual disease (MRD) after surgery and can create an appropriate treatment plan in GC patients.

CTCs/circulating tumor DNA

CTCs defined as tumor cells that have been detached from the primary tumor or metastases and shed in patient's bloodstream, characterize an easily attainable sample of cancer specimens. As a liquid biopsy, emerging technologies for CTC isolation have enabled the research on the pathology of CTCs and have prompted the clinical uses of CTCs in the diagnosis of malignancies[5]. Although many researchers have come to the same conclusion that CTCs positivity was associated with prognosis, few researches were found for the early diagnosis, especially in the last several years.

Circulating cell-free DNA (cfDNA) consists of fragments of extracellular DNA that can be found in the blood[6]. cfDNA changes across different pathological states have been successfully exploited as noninvasive biomarkers for liquid biopsies. Particularly, the cfDNA that is identified from tumors and shows tumor-specific mutations is named circulating tumor DNA (ctDNA)[7]. The analysis of ctDNA has been predominantly of interest over a decade as its remarkable stability in body fluids. Besides, accumulating evidences showed that ctDNA is useful for early incidence during disease progress after surgical procedure. Further improvement of the ctDNA detection system is progressing. The cfDNA-based liquid biopsy for early diagnosis is mostly restrained by the low signals shed from early-stage cancer, which directly influence the sensitivity of sequencing analyses.

Recent paper has described that the circulating biomarkers, such as cfDNA was highly expressed in stage I GC patients compared with those in benign gastric disease patients and health controls, suggesting the potential for their use for the early detection of GC[8,9]. The human epidermal growth factor receptor 2 (HER2) gene copy number detected in ctDNA was higher in GC patients compared to healthy control. Elucidation of HER2 copy number variation could distinguish healthy individuals and patients with GCs with 58% sensitivity and 98% specificity [area under curve (AUC) = 0.707, 95% confidence interval (CI): 0.593-0.821][10]. ctDNA sequencing identifies fibroblast growth factor receptor 2 (FGFR2) amplification missed by tissue testing in patients with advanced GC, and these patients may respond to FGFR inhibition. ctDNA can detect plasma *FGFR2* alterations, occasionally at a higher frequency than tissue testing, identify patients and these patients may respond to FGFR inhibition[11].

Current cancer biomarkers can be categorized into two groups: (1) Biomarkers generally used for the detection of specific cancer types; and (2) Biomarkers to be aimed to decide personalized medicine, such as companion diagnostics. Even when surgical procedure is successfully carried out, detecting MRD after surgery is still challenging for doctors, and it is difficult to detect MRD in time using radiologic imaging or tissue biopsy. Recent studies presented that ctDNA-based testing were able to detect MRD several weeks earlier than imaging[12]. Another study monitoring ctDNA in postoperative blood has verified that, the median duration from positive ctDNA detection to relapse was 4.05 mo[13]. Moreover, the postoperative positive ctDNA was significantly correlated with tumor recurrence within 12 mo after surgery, suggesting that postoperative ctDNA monitoring possess clinical application value in the prediction of postoperative GC recurrence[13]. In a similar, ctDNA positivity preceded radiographic recurrence by a median of 6 mo, suggesting that, ctDNA is a sensitive and specific biomarker for finding patients at high risk for relapse after curative treatment[14]. ctDNA-positive patients were at higher risk of relapse and exhibited worse outcome compared to the ctDNA-negative group, implying that ctDNA monitoring in the post-treatment setting is predicted to offer knowledge about necessity for further therapy[15]. The clinical usefulness of ctDNA as biomarker for longitudinal disease monitoring and identification of MRD in GC was assessed by ultra-deep sequencing methods. The occurrence of relapse was 100% (7 of 7), 100% (5 of 5), and 94% (16 of 17), respectively in patients with measurable ctDNA at the post-operative, post-adjuvant chemotherapy, and consequent longitudinal time spots. To date, novel high throughput sequencing techniques such as next-generation sequencing (NGS) or whole exome sequence can identify mutations in multiple genetic regions[16]. Recent study conducted surveillance for recurrent disease after curative surgical resection analyzed by whole genome sequence. For 1630 patients with GC and esophageal adenocarcinomas, detection of MRD after successful surgical procedure is intensely correlated with an enhanced risk of relapse by utilizing a Guardant 360, ctDNA-NGS assay[17]. These studies elucidate that risk stratification of patients for adjuvant chemotherapy escalation/de-escalation could be predicted by incorporation of ctDNA. ctDNA-guided treatment strategy in post-surgery surveillance for patients with GC is a novel emerging strategy that will likely replace the current treatment decision, as outlined in Figure 1.

NC RNA

Diverse ncRNAs, such as microRNA (miRNA), circular RNA (circRNA), and long ncRNA (lncRNA), are implicated in GC carcinogenesis[18]. MiRNAs are small ncRNA molecules of approximately 18-22 nucleotides that regulate cell differentiation, proliferation, apoptosis and gene regulation[19]. Currently, due to the stability and specificity of expression in circulation, accumulating evidences suggest that miRNAs can serve as novel biomarkers with a prospective clinical significance tool for patient with GC. MiRNAs are very stable in blood and can be identified by various assays such as reverse transcription



ctDNA: Circulating tumor DNA; Op: Operative; Adj: Ajuvant chemotherapy.

LncRNAs are the transcripts of more than 200 nucleotides that have been found to participate widely in various pathological processes of organisms[24]. In colon cancer, LncRNA small nucleolar RNA host gene 11 has been presented as a promising biomarker for early detection of this malignancy[25]. Meanwhile, hepatocellular carcinoma upregulated lncRNA and ZNF1 antisense RNA 1 have been shown to distinguish GC patients from healthy subjects and proposed as novel diagnostic biomarkers of GC[26]. LncRNAs promoter of CDKN1A antisense DNA damage activated RNA, FOXD2 adjacent opposite strand RNA 1, and SWI/SNF related, matrix associated, actin dependent regulator of chromatin subfamily c member 2 in plasma may serve as novel biomarkers for early detection of GC. The combined these three lncRNAs offer a high sufficient diagnostic sensitivity[27]. LncRNA B3GALT5 antisense RNA 1 was shown to be better than carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) and may serve as a diagnostic biomarker of GC[28]. Distinct levels of serum C5orf66 antisense RNA 1 (C5orf66-AS1) were shown between patients with GC and gastritis. A risk of gastric dysplasia and GC negatively associated with serum expression of C5orf66-AS1, implying that C5orf66-AS1 a potential biomarker for predicting EGC[29]. Combined lncRNAs have been displayed to improve biomarker values for early detection of GC. LncRNA HLA Complex P5 (HCP5) is a kind of RNA gene without protein-coding. The AUC of serum lncRNA HCP5 was 0.818 (95%CI: 0.757-0.880, 80% sensitivity, and 70% specificity) in distinguishing between GC and healthy controls. Besides, the highest AUC of 0.870 (95%CI: 0.819-0.921) with 81% sensitivity and 79% specificity were revealed by the combination of three diagnoses, HCP5, CEA, and CA19-9[30]. Thus, the results above indicate that lncRNAs possess the diagnostic potential for early diagnosis of GC.

CircRNAs are also generally categorized as a ncRNA and physically vigorous nucleic acid molecules that construct closed loop RNA and require polyadenylated tails unlike messenger RNAs[31]. CircRNAs are more stable in tissues, have a superior life period and are more resistant to Ribonuclease R compared with linear RNAs[32]. In a recent, the rapid development of high-throughput sequencing has promoted the detection of circRNAs and their roles in physiological and pathological processes, including GC carcinogenesis, have been evaluated. A recent study found circRNA *Has_circ_0000745* was downregulated in GC tissues and in plasma from patients with GC. Therefore, the use of these circRNAs has great potential as a new biomarker for diagnosis of GC[33]. The expression of *hsa_circ_0001789* in 24 paired of cancerous and paracancerous plasma specimens were examined. A down-regulated expression of *hsa_circ_0001789* was detected in GC plasma samples in comparison to the healthy controls, indicating that *hsa_circ_0001789* has the potential to be a novel GC diagnostic biomarker[34]. CircPTPN22 is an outstanding diagnostic marker for GC. Utilizing receiver operator characteristic (ROC) analysis of circPTPN22 expression in GC patients, gastritis patients, and healthy controls, showed that its AUC was higher than that of traditional tumor markers CEA and CA19-9, and the AUC reached 0.892 after combined use[35]. 8-circRNA biomarker panel (*hsa_circ_0001013*, *hsa_circ_0052001*, *hsa_circ_0034398*, *circ_0006089*, *hsa_circ_0002019*, *hsa_circ_0007380*, *hsa_circ_0008768*, *hsa_circ_0045602*) discriminated patients with GC from normal control tissues, with an AUC value of 0.87 (95%CI: 0.82-0.93, sensitivity 78.3%, specificity 78.3%). Interestingly, 7 of 8 circRNA markers significantly lower expressed in serum specimens after surgery. Furthermore, 8-circRNA panel showed a greater specificity for the identification of patients with GC *vs* all other gastrointestinal cancers, such as colorectal cancer, pancreatic cancer, esophageal cancer, and hepatocellular carcinoma[36]. Studies using ncRNAs in screening/diagnostics of GC in the past 5 years are collected in Table 1.

Exosome

Exosomes are lipid bilayer-enclosed extracellular vehicles (EVs) approximately 30-150 nm in size, consist of a lipid bilayer interspersed with various membrane proteins, and which contain a variety of nucleic acids, proteins, and lipids[37]. Exosomes are secreted continuously by all cells and offer distinct prospects for clinically relevant diagnostic content, including DNA, RNA, and proteins[37]. Exosomes have been said to be associated with driving key features of cancer activity, including facilitation of tumor cell proliferation, suppression of the immune response, stimulation of tumor cell migration, initiation of angiogenesis, and formation of metastases[38]. Recently, growing evidences have established the latent diagnostic value of EVs or circulating exosomes for early diagnosis of GC. Due to the easiness to isolate exosomes compared with CTCs and cfDNA in malignant tumors, an growing number of studies will be highlighted on exosomes in the diagnosis of EGC in the next several decades. Exosomal lncUEGC1 exhibited an AUC of 0.8760 and 0.8406 in distinguishing EGC patients from normal subjects and those with atrophic gastritis, respectively, implying that exosomal lncUEGC1 had higher diagnostic reliability compared with CEA[39]. Circulating exosomal lncRNA proprotein convertase subtilisin/kexin type 2-2:1, G protein subunit alpha q-6:1 and GC-associated lncRNA1 (lncRNA-GC1) have been reported as better biomarkers for distinguishing GC patients from healthy people, compared with CEA, CA19-9, and CA72-4[40-42]. Similarly, serum four exosomes, miR-92b-3p, miR-146b-5p, miR-9-5p, and miR-let-7g-5p have been shown to be latent biomarkers for early detection of GC[43]. Likewise, the ROC showed that serum exosomal miR-590-5p showed a good classifier with an AUC of 0.810 (95%CI: 0.751-0.860) with a sensitivity of 63.7% and specificity of 86.0%, suggesting that serum exosomal miR-590-5p expression may be a noninvasive diagnostic biomarker of GC[44]. MiR-195-5p and miR-211-5p in GC patients' plasma exosomes have shown to be upregulated compared to healthy controls. The AUC values of plasma exosomal 2-miRNAs signature was 0.820, which was more meaningful to discriminate the GC patients from the healthy samples, compared to the AUC values obtained for combined CEA, CA19-9[45]. *circ_0065149* levels in plasma exosomes from EGC patients were significantly lower than those from healthy individuals. Thus, *circ_0065149* revealed distinguished diagnostic accuracy, with an AUC of 0.64, sensitivity of 48.7%, and specificity of 90.2%[46]. Piwi-interacting RNAs (piRNAs) are another class of small ncRNAs that are 26-31 nucleotides in length, and quite comparable in size to miRNAs. PiRNAs are distinctly different from miRNA counterparts because they lack the sequence conservation present in miRNAs. As a source for liquid biopsy, piRNAs have similar properties to miRNAs and stable in the blood flow and resistant to ribonuclease mediated degradation. Therefore, piRNAs can be used as effective biomarkers for the early detection of GC. Serum exosomal piR-019308, piR-004918 and piR-018569 can be utilized for the diagnosis of GC with the AUC value of 0.820, 0.754 and 0.732, respectively. Diagnostic value of these piRNAs were much better than that of CEA, CA19-9 and alpha-fetoprotein[47]. Collectively, circulating exosome has clinical potentials in the early diagnosis of GC, which may lead to the identification of cancer subtypes. Exosome investigated as potential diagnostic GC markers are listed in Table 2.

Collectively, this section highlights the developments in the ncRNAs as a source for the development of non-invasive diagnostic biomarkers for GC patients. NcRNAs appear to have a crucial potential to be implemented into biomarker development for early detection of GC. On the other hand, a variety of circulating biomarkers have been reported in different research team. The clinical value of all these factors is not still defined. Some discrepancies among different studies can be caused by the hetero-

Table 1 Overview of non-coding RNAs for early detection of GC in the past 5 years

Circulating biomarkers	Alterations	Patients	Controls (normal)	Sample	Methods	Sensitivity (%)	Specificity (%)	AUC	Ref.
miRNA									
miR-25	Upregulated	65	65	Plasma	qRT-PCR	87.6	76.9	0.817	[102]
miR-214	Downregulated	168	74	Plasma	qRT-PCR	73.2	91.9	0.880	[103]
miR-376c	Upregulated	47	67	Plasma	qRT-PCR	71.0	78.0	0.77	[104]
miR-381	Downregulated	40	40	Serum	qRT-PCR	83.6	97.5	0.931	[105]
miR-200c	Upregulated	200	250	Tissue and blood	Micoarray and qRT-PCR	74.0	66.0	0.75	[106]
miR-551b-5p	Downregulated	40	40	Serum	qRT-PCR	77.5	80.0	0.84	[107]
Combination of miR-21, miR-93, miR-106a, and miR-196b	Upregulated	11	17	Plasma	qRT-PCR	84.8	79.2	0.887	[108]
Combination of miR-16, miR-25, miR-92a, miR-451 and miR-486-5p	Upregulated	40	40	Plasma	qRT-PCR	72.9	89.2	0.812	[109]
Combination of miR-4257, miR-6785-5p, miR-187-5p and miR-5739	Upregulated	1417	1417	Serum	microarray analysis	0.996 (index)	0.953 (index)	0.998	[23]
Combination of miR-18a, miR-181b, and miR-335	Upregulated	176	173	Serum	qRT-PCR	71.6	87.9	0.86	[95]
Combination of miR-425-5p, miR-1180-3p, miR-122-5p, miR-24-3p and miR-4632-5p	Downregulated	30	90	Plasma	qRT-PCR	NA	NA	0.829	[21]
Combination of miRNA-3185, miRNA-6083, miRNA-6792-3p, and miRNA-659-3p	Upregulated	52	30	Plasma	qRT-PCR	NA	NA	0.825	[110]
Combination of miRNA-936, miRNA-1306-3p	Downregulated	52	30	Plasma	qRT-PCR	NA	NA	0.730	[110]
Long non-coding RNAs									
ZNF1-AS1	Upregulated	50	50	Plasma	qRT-PCR	84	68	0.85	[26]
LINC00978	Upregulated	38	31	Serum	qRT-PCR	80	70	0.831	[111]
CTC-501O10.1	Upregulated	100	100	Plasma	qRT-PCR	90	51	0.74	[112]
AC100830.4	Upregulated	100	100	Plasma	qRT-PCR	84	58	0.73	[112]
RP11-210K20.5	Upregulated	100	100	Plasma	qRT-PCR	89	55	0.737	[112]
CTC-497E21.4	Upregulated	110	84	Serum	qRT-PCR	81.8	75.0	0.896	[113]
SNHG17	Upregulated	67	67	Plasma	qRT-PCR	NA	NA	0.748	[114]
ARHGAP27P1	Downregulated	53	53	Plasma	qRT-PCR	75.5	60.4	0.732	[115]
PANDAR	Upregulated	109	106	Plasma	qRT-PCR	NA	NA	0.767	[27]
FOX2-AS1	Upregulated	109	106	Plasma	qRT-PCR	NA	NA	0.700	[27]
SMARCC2	Upregulated	109	106	Plasma	qRT-PCR	NA	NA	0.748	[27]
LINC00086	Downregulated	168	74	Plasma	qRT-PCR	72.6	83.8	0.86	[103]
B3GALT5-AS1	Upregulated	107	87	Serum	qRT-PCR	87.4	74.7	0.816	[28]
C5orf66-AS1	Downregulated	200	278	Serum	qRT-PCR	77.5	53.6	0.668	[29]

HCP5	Upregulated	98	82	Serum	qRT-PCR	80	70	0.818	[30]
Combined of lnc-MB21D1-3:5, lnc-PSCA-4:2 and lnc-ABCC5-2:1	Upregulated	52	30	Plasma	qRT-PCR	NA	NA	0.904	[110]
circular RNAs									
has_circ_0000745	Downregulated	60	60	Plasma	qRT-PCR	85.5	45.0	0.683	[33]
circPTPN22	Upregulated	120	104	Plasma	qRT-PCR	78.0	84.0	0.857	[35]
hsa_circ_0001789	Downregulated	24	24	Plasma	qRT-PCR	84.0	50.0	0.82	[34]
8-circRNA biomarker panel	Upregulated	92	46	Serum	qRT-PCR	78.3	78.3	0.87	[36]

miRNA: Micro RNA; qRT-PCR: Quantitative reverse transcriptase polymerase chain reaction; AUC: Area under curve; HCP5: HLA Complex P5; lncRNA: Long non-coding RNA; circ RNA: Circular RNA; NA: Not applicable; ZNF1-AS1: ZNF1 antisense RNA 1; PANDAR: Promoter of CDKN1A antisense DNA damage activated RNA; FOXD2-AS1: FOXD2 adjacent opposite strand RNA 1; SMARCC2: SWI/SNF related, matrix associated, actin dependent regulator of chromatin subfamily c member 2; B3GALT5-AS1: B3GALT5 antisense RNA 1; C5orf66-AS1: C5orf66 antisense RNA 1.

Table 2 Overview of exosome associated with early detection of gastric cancer

Marker	Alterations	Patients	Controls (normal)	Sample	Methods	Sensitivity (%)	Specificity (%)	AUC	Ref.
miRNA									
miR-590-5p	Downregulated	168	50	Serum	qRT-PCR	63.7	86.0	0.810	[44]
miR-92a-3p	Downregulated	131	122	Serum	qRT-PCR	NA	NA	0.829	[116]
Combination of miR-92b-3p, let-7g-5p, miR-146b-5p, and miR-9-5p	Upregulated	36	12	Serum	qRT-PCR	60	84	0.773	[43]
lncRNA									
HOTTIP	Upregulated	126	120	Serum	qRT-PCR	69.8	85.0	0.827	[117]
UEGC1	Upregulated	51	60	Plasma	qRT-PCR	NA	NA	0.876	[39]
Pcsk2-2:1	Upregulated	63	29	Serum	qRT-PCR	84	86.5	0.896	[40]
GNAQ-6:1	Downregulated	43	27	Serum	qRT-PCR	83.7	55.6	0.736	[41]
RNA-GC1	Upregulated	522	219	Serum	qRT-PCR	88.2	82.3	0.90	[42]
piRNAs									
piR-019308	Upregulated	70	60	Serum	qRT-PCR	57.14	91.67	0.820	[47]
piR-004918	Upregulated	70	60	Serum	qRT-PCR	42.86	95.0	0.754	
piR-018569	Upregulated	70	60	Serum	qRT-PCR	44.29	96.67	0.732	

miRNA: MicroRNA; lncRNA: Long non-coding RNA; circRNA: Circular RNA; piRNA: Piwi-interacting RNAs; qRT-PCR: Quantitative reverse transcriptase polymerase chain reaction; NA: Not applicable; GNAQ-6:1: G protein subunit alpha q-6:1.

geneity of GC. Thus, a more precise patient inclusion criteria or enlarging of the cohort size could overcome the differences in ncRNAs expression caused by the intrinsic heterogeneity of the disease. More multicenter, greater, longer-term studies are warranted to apply liquid biopsies in clinical settings, in terms of early diagnosis of GC. We systematically summarized the ncRNAs as biomarker for early detection of GC in Figure 2.

DNA METHYLATION

DNA methylation is an epigenetic mechanism which lead to oncogenesis in GC through activation of oncogenes and silencing of tumor-suppressor genes[48]. In a recent, a variety of studies demonstrated that aberrant epigenetic regulations, such as DNA methylation, histone posttranslational modifications,

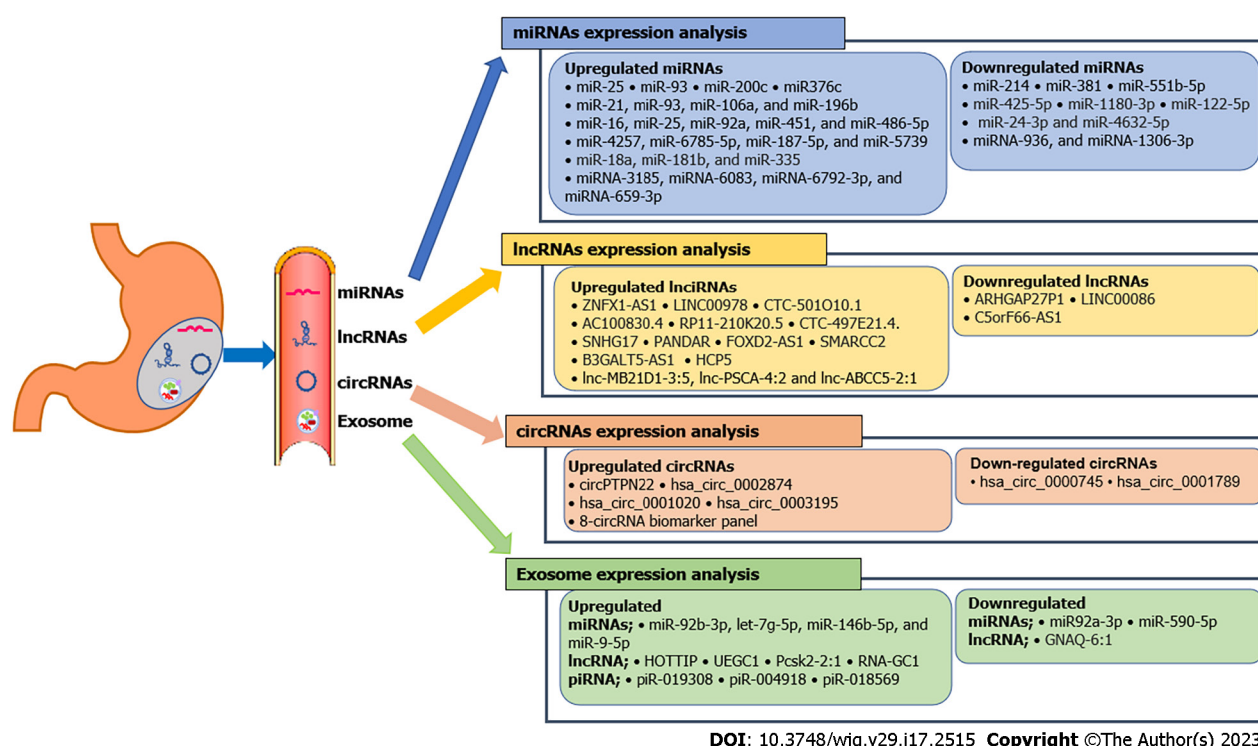


Figure 2 The summary of non-coding RNAs as biomarker for early detection of gastric cancer. Schematic of the non-coding RNAs composition. Liquid biopsy obtained from peripheral blood is composed of different tumoral components such as micro-RNA, long non-coding RNAs, and circular RNAs. miRNA: MicroRNA; lncRNA: Long non-coding RNA; circRNA: Circular RNA; piRNA: Piwi-interacting RNAs.

ncRNAs and chromatin remodeling, have a pivotal influence on the pathogenesis of GC. DNA methylation is well-investigated epigenetic change among the epigenetic modifications[49]. Nowadays, the importance of aberrant DNA methylation is identified by liquid biopsy, including plasma/serum and gastric juice. Tumor suppressor genes methylation in peripheral blood has been examined most broadly. Aberrant gene methylation identified in body fluids could be a useful biomarker for the early detection of GC, likewise SEPT9 in CRC. Numerous methylated gene promoters detected in ctDNA have been proposed for GC detection as a latent diagnostic marker[50]. Among them, aberrant methylation of Reprimo, RUNX3, RASSF1A, SFRP2, PCDH10, H19, and MALAT1 show high sensitivity and specificity, suggesting that they have superiority in the early detection of GC[51-55]. A recent study elucidated the association of aberrant DNA methylation with the risk of GC. Hypermethylation of SOCS3 promoter in blood extensively facilitated GC risk[56]. Genome-wide hypomethylation commonly occurs in repeated components that are normally hypermethylated to keep genomic stability. Long interspersed nucleotide element 1, Alu repetitive elements and human endogenous retroviruses are the main components of scattered repeated sequences[57]. Although a number of studies examined the perspective of DNA methylation as a biomarker in GC, the methylation levels in those studies were mainly shown from the tissues. Thus, novel aberrantly methylated genes whose roles in GC should be investigated, especially those detected by non-invasive methods.

DNA methylation is major epigenetic changes when pathogens invade to gastric mucosa, which allows the infection to persist and promotes the development of GC[58]. *Helicobacter pylori* (*H. pylori*) is one of the most important pathogens for GC. Previous studies have demonstrated that Alu and Sata hypomethylation was significantly correlated with *H. pylori* infection in patients with GC[59]. Although numerous studies were examined to elucidate the mechanism of epigenetic changes induced by *H. pylori* infection, useful biomarker for early detection in GC is still not applied in clinical setting. Most recent report demonstrated that FGFR4 activation was interacted with signal transducer and activator of transcription 3 thorough steroid receptor coactivator in response to *H. pylori* infection, suggesting that FGFR4 could be a candidate of biomarker for early detection of GC[60].

NOVEL BIOMAKER IDENTIFIED FROM MULTI-OMICS DATA

Previous classifications of GC have quite restricted achievement in advocating the advancement of subtype-specific treatment applies due to the heterogeneity of GC and their incapacity to detect latent molecular targets. With NGS, omics technologies have offered beneficial tools to examine the molecular basis of GC. Multiple omics-based studies have been used to evaluate the biofluids of GC patients,

which resulted in numerous novel biomarkers due to rapid progress in machine learning approaches [61]. A number of mutations, gene alteration, protein abundance differences, epigenetic mutations, and metabolite concentrations which is linked to GC heterogeneity and staging, leading to improve our understanding of GC, have been successfully identified. NGS has high throughput and can screen unknown variants. A variety of methods are applying NGS to target panel, namely Tagged-Amplicon deep sequencing, Safe-Sequencing System, and Cancer Personalized Profiling by deep sequencing. The developments of NGS enable many applications in both DNA and RNA sequencing (RNA-seq), such as whole-genome, whole-exome, and targeted sequencing of DNA, and total RNA, mRNA, and small RNA [62].

Proteins contribute to determine the identity of a cell [63]. Cell function can be affected by aberrant protein expression, or altered post-translational arrangements. Proteomic signatures can afford complementary information for patient stratification to genetic signature. Besides, proteins can be a useful tool as a biomarker for malignances [63]. The development of proteomics technologies, such as mass-spectrometry (MS), has made it easier to identify protein biomarkers applied to tumor diagnosis. Liquid chromatography-MS (LC-MS) of digested proteins conducted with high-resolution instruments enable to quantitate thousands of proteins from complex biological specimens. Study using LC-MS/MS combined with TMT labeling, found that 11 proteins differentially expressed in plasma from EGC patients and healthy controls identified from the total of 2040 proteins. This model presented that the altered proteins found by plasma proteomics could provide a resource of potential biomarkers for diagnosis of EGC [64]. Isobaric tags for relative and absolute quantification (iTRAQ) are said to be the most widely used method for high-throughput protein quantification. The study using iTRAQ-labeled quantitative proteomics revealed that NAD(P)-dependent steroid dehydrogenase-like (NSDHL) and neutral cholesterol ester hydrolase 1 (NCEH1), key enzymes in cholesterol metabolism, were aberrantly expressed in patients with GC. Moreover, the combined analysis of NSDHL and NCEH1 showed high sensitivity compared with a single marker in detecting GC, indicating that NSDHL and NCEH1 may be adequate for novel biomarkers in the screening [65]. Identically, thioredoxin reductase 1 was aberrantly expressed in GC by using Itraq-labelling and/or LC-MS, supporting that these proteins are an important target for early determining and follow-up monitoring for GC [66]. Integration of phosphoproteome data with other types of omics data from young diffuse-type GC patients provided links of somatic mutations to phosphorylation changes in signaling pathways, association of mRNA-protein abundance correlations with survivals, and four subtypes of young diffuse-type GC patients characterized by genomic and proteomic signatures, which may contribute to have a deep insight into diffuse-type GCs [67]. More recent study using proteomics methods of serum based on high-resolution MS with ion mobility separation followed by multivariate statistics and network analysis presented that a 29-protein marker panel containing, integrin $\beta 6$ and glutathione peroxidase, and ten serum markers specific for GC (ITIH1, FZD6, DPP10, SERPINA4, AKAP12, S100A9, POTEF, CACNB1, CRP KIAA1328), which were independent of *H. pylori* infection [68]. Multi-omic analysis characterizing the intricate relationships between the intragastric microbiome and gastric mucosal gene expression revealed higher abundances in several bacterial taxa (*Pasteurellaceae*, *Enterococcaceae*, *Helicobacteraceae*, *Gemellales* and *Neisseriaceae*) and genes (*SOCS3* and *ITM2A*) were shown in GC patients. In turn, *Lachnospiraceae* was closely associated with the expression of *Ubiquitin D*, which regulates mitosis and cell cycle time in GC [69]. Besides, lower abundances of B cell signatures in GC compared to gastritis may suggest a previously unidentified immune evasion process in gastric carcinogenesis. These results suggest that a combined analysis of microbiome and gene expression may help to devise a diagnostic kit that screens for high-risk patients of GC who require surveillance endoscopy.

STOMACH SPECIFIC BIOMARKER

The measurement of a biomarker in a gastric juice sample should be specific for early-stage GC than the same biomarker measured in plasma/serum because it is obtained directly from the area of the lesion, which would lead to avoid dilution of the biomarkers and their lack of specificity [70]. Because DNA is easily degraded due to gastric juice acidity, the main part of biomarkers identified in gastric juice are ncRNAs and some proteins. A significantly increased miR-135b-3p and miR-199a-3p, and a decreased miR-451a levels in gastric juice-derived EVs from GC patients was shown compared to non-cancer individuals [71]. LncRNAs in gastric juice and urine have also been reported as biomarkers of GC and urinary system cancer, respectively [72]. On the other hand, a recent study revealed that the levels of SNCG in gastric juice detected by enzyme-linked immunosorbent assay were significantly higher in the GC group compared with the control group [73]. Analysis using gastric juice-derived exosomal DNA samples presented that BARHL2 methylation had an area under the curve of 0.923 with 90% sensitivity and 100% specificity which suggested the feasibility of the application of BARHL2 methylation for screening for GC biomarker [74]. Although a number of studies elucidating the value of gastric juice as a biomarker for early detection of GC were carried out, the limitation is the tolerance of the patients as a usual examination due to the discomfort of gastroscopy.

Serological examinations, which are noninvasive and relatively convenient, can offer efficient indicators of gastrointestinal diseases. Markers of gastric function such as pepsinogen (PG)-I, PG-II, PG-I/PG-II ratio, gastrin 17, anti-*H. pylori* antibodies are used to cooperatively diagnose chronic atrophic gastritis (CAG)[75]. A recent meta-analysis has presented the use of serum pepsinogens revealed significant diagnostic accuracy for the early detection of gastric CAG or GC[76]. Among the various cut-off values investigated, PG rate ≤ 3 and PG-I ≤ 70 ng/mL have been proposed for CAG and GC prediction. Although there are numerous studies for evaluating PG as biomarker for early detection of GC, the potential use of pepsinogens in GC prevention is still not well-established.

DISCUSSION AND FUTURE PERSPECTIVE

Biomarkers are biological molecules implicated in the initiation and progression of cancer, and determination of their levels can clarify abnormal molecular changes in patients[77]. Morphological detection of diseased gastric epithelial cells using upper gastrointestinal endoscopy has always been the standard method for diagnosis of GC. However, the false-positive rates for endoscopic screening in the first round are said to be 14.9%. Notably, endoscopy is easily missed during screening, even when it is performed by qualified endoscopists. In this review, we describe the comprehensive and systematic search for and development of blood-based biomarkers for early detection of GC. Identification of highly sensitive biomarkers for GC screening might render upper gastrointestinal endoscopy unnecessary. Biomarker has assisted in the advancement of new DNA, RNA, and protein-based cancer biomarkers that can be detected from noninvasive, sensitive, specific, and cost-effective body fluids. These include the OncoBEAM™ RAS CRC liquid biopsy assay approved by the European Commission as an *in vitro* diagnostic tool for colorectal cancer therapy, and this has led to the early detection of emergent resistance to anti-epidermal growth factor receptor treatment and the assessment of genomic profile during treatment in clinical settings[78]. Such assays may also enable us to abandon approved but useless treatments for patients resistant to molecular targeted agents or immunosuppressants. For instance, with this technology the future patients with stage II or III GC with a low risk of postoperative recurrence may be simply monitored under active surveillance without adjuvant chemotherapy and possibly be started to treat from when MRD is detected (Figure 1). Although ctDNA for detection of MRD can be an emerging clinical biomarker for disease monitoring in GC, applications of ctDNA in clinical practice require more comprehensive examination in prospective trials.

However, several technical factors are hindering the use of liquid biopsy biomarkers in clinical use. A major challenge is the very low levels of peripheral DNA/RNA[79]. In 2022, ESMO published recommendations on the use of ctDNA in genomic testing and clinical practice. Based on its review of the different aspects of ctDNA, the ESMO Precision Medicine Working Group provides some outlook on the future of ctDNA examination. Considering deficient sensitivity in clinical practice for gene fusions and copy number variations and advancing tests to discriminate accurate results for more progressive genotyping are included in their recommendations[80]. To overcome these issues, several upgraded liquid biopsy approaches for cancer diagnosis are under development. It is likely that precancerous and cancerous lesions can be detected by combinations of biomarkers with superior sensitivity and specificity, fulfilling an unmet need in clinical practice. Combining biomarkers, such as ncRNAs, can enhance the sensitivity and specificity for detecting EGC. However, it would be difficult to identify the ideal combination of other biomarkers that can enhance the overall detection performance. Correlations between different types of biomarkers like the association pattern to guide the choice of panels can be effectively identified using biostatistical approaches. For example, a serum biomarker miRNA panel consisting of 12 miRNAs was developed for risk assessment in patients with GC. With the use of a multitarget miRNA assay in more than 5000 individuals in Singapore and Korea, this panel showed an AUC of 0.848 and 87% sensitivity and 68.4% specificity values to distinguish GC patients from healthy controls. Moreover, upgrading of the AUC to 0.884 and specificity to 69.4% for GC detection were achieved by the combination of this 12-miRNA panel with patient age, *H. pylori* serology, and the plasminogen I:II ratio[81]. Combinations of ctDNA mutations with other biomarkers, such as protein or methylation have been examined toward the goal of improving the overall sensitivity. It has been demonstrated that the combination of ctDNA and protein biomarkers can markedly increase the sensitivity[82]. Genome-wide methylation and protein marker profiles have been validated for a combination of *mSEPT9*, *mRNF180* and CA724 for the detection of GC, and the combination of all three markers detected 68.6% of GC cases[83].

Another important strategy for improving the sensitivity and specificity of GC detection is the use of innovative bioinformatic algorithms. Machine learning involves various computational techniques that are used to simplify large numbers of measurements into lower-dimensional outputs that are more explainable[84]. In the case of GC, a combination of artificial intelligence (AI)-based endoscopy and miR148a methylation has been evaluated for the diagnosis of gastric indefinite dysplasia[85]. Interestingly, a recent study using the microbial compositions of the Cancer Genome Atlas (TCGA) of 18116 human blood samples across 33 cancer types and stochastic gradient-boosting machine learning models effectively discriminated cancer-free individuals, patients with cancer, and patients with

multiple types of cancer[86]. A new concept of cfDNA is also expected to be applied to cancer diagnoses in the near future.

Unfortunately, there is a lack of standardized technique for isolation, amplification and detection in the use liquid biopsies for early diagnoses in clinical settings. One of the most meaningful accomplishments regarding biomarkers for early cancer detection is the emergence of high-throughput technological platforms such as NGS, which allows comprehensive quantification of whole genome or transcriptome. The cost of NGS has greatly declined over the past several decades, which has allowed the sequencing of a larger number of clinical biospecimens, as well as the ability to generate datasets with higher depth of coverage. The opportunity to generate higher resolution data for low expressing transcripts improves the ability to detect rare cancer-derived transcripts in circulation. A study aiming to found the latent miRNA for predicting GC by AI in the Gene Expression Omnibus (GEO) datasets, particularly with several states of the machine learning methods and the Boruta algorithm, demonstrated that the use of hsa-miR-1343-3p could predict GC with the AUC of 100% (sensitivity 100%, specificity 100%, ROC 100%)[87]. In a recent study using high-throughput RNA-seq, the expression profiles of circRNAs in serum EV between GC patients and healthy individuals were examined. The results demonstrated that the circRNA, Chr10q11, Chr1p11, and Chr7q11 were upregulated in GC; the AUC of the three combined circRNAs was 0.839 (95%CI: 0.772-0.893) with 73.2% sensitivity and 84.1% specificity. The construction of a circRNA-miRNA-mRNA network predicted that the three identified circRNAs interact with 13 miRNAs and 91 mRNAs. These findings suggest that panels of EV circRNAs may provide new insights into the early diagnosis of GC[88]. With the use of publicly available gene expression profiles from the TCGA and GEO datasets, a recent study explored the circRNA-miRNA-mRNA interaction axis by constructing a competing endogenous (ce)RNA network. On the basis of the hub RNAs included in ceRNA, the screening of the model for predicting the mRNA signature and miRNA signature by LASSO regression analysis found that both five mRNA-based signatures (CTF1, FKBP5, RNF128, GSTM2 and ADAMTS1) and five miRNA-based signatures (miR-145-5p, miR-615-3p, miR-6507-5p, miR-937-3p and miR-99a-3p) had superior capacity to predict the diagnosis of GC patients with the AUC of 0.9975[89]. Similarly, a study using regulatory networks for circRNA-miRNA-immune-related mRNA validated in the new GEO and TCGA datasets identified various ceRNA (circRNA-miRNA-immune-related mRNA) regulatory networks in GC constructed by hsa_circ_0050102-hsa-miR-4537-NRAS-Tgd cells, hsa_circ_0001013-hsa-miR-485-3p-MAP2K1-Tgd cells, hsa_circ_0003763-hsa-miR-145-5p-FGF10-StromaScore, hsa_circ_0001789-hsa-miR-1269b-MET-adipocytes, hsa_circ_0040573-hsa-miR-3686-RAC1-Tgd cells, and hsa_circ_0006089-hsa-miR-5584-3p-LYN-neurons, among which FGF10, MET, NRAS, RAC1, MAP2K1, and LYN showed promising diagnostic significance for GC patients[90]. In a study based solely on bioinformatics models constructed a circRNA-miRNA-mRNA network based on three circRNAs, 43 miRNAs, and 119 mRNAs, and upregulations of hsa_circ_0001013, hsa_circ_0007376, and hsa_circ_0043947 were observed, which may offer a new pathway for mechanical examinations and provide possible biomarkers for early detection of GC[91]. Likewise, in a bioinformatics circRNA-miRNA-gene interaction network analysis, two circRNAs (CircCEACAM5 and CircCOL1A1) cooperated with GC correlated miRNAs and their host genes were suggested as the pivotal diagnostic biomarker for GC[92]. The emergence of single-cell sequencing technologies has markedly improved the resolution of low-input sequencing. The recent introduction of single-cell DNA/RNA-seq provides an opportunity to detect cell types and cell status. For example, a single-cell expression atlas of gastric premalignant gastric lesions and EGC identified the expression signatures of multiple cell types across different lesions, as well as a panel of six high-confidence markers that could serve as specific biomarkers for early diagnosis of GC[93]. A weighted gene co-expression network analysis (WGCNA) aims to: (1) Identify co-expressed modules in multiple biological samples based on correlations between different gene expression profiles; and (2) Explore the relationship between gene networks and phenotypes of interest, as well as the hub genes in the network[94]. Performing a WGCNA can prevent the false-negative and false-positive results of previous biological methods. WGCNA data from the GEO database revealed hub genes involved in GC and identified four functional genes (*ITGAX*, *CCL14*, *ADHFE1*, and *HOXB13*) that were differentially expressed in tumor and normal gastric samples. Another study applying a WGCNA to screen potential biomarkers for EGC using RNA-seq and clinical data from the TCGA database identified five hub genes, *MS4A1*, *THBS2*, *VCAN*, *PDGFRB*, and *KCNA3*[94]. These technological developments will allow more researchers to conduct comprehensive assessment of molecular profiles in the human circulatory system.

Systematic studies applying the molecular profiling of ncRNAs for cancer biomarker have been developed. Several investigations have used tissue profiling data to identify ncRNA as a potential biomarker, leading to the evaluation of these cancer-associated ncRNA signatures in blood cohorts. Multiple tissue sequencing datasets were recently used to identify highly overexpressed miRNAs in GC tissues. Risk probabilities using quantitative reverse transcriptase polymerase chain reaction data for three miRNAs (miR-18a, miR-181b, and miR-335) were validated and showed much better diagnostic performance than the conventional tumor markers CEA and CA19-9 currently in use. Moreover, the three-miRNA signature discriminated between patients with stage I GC and cancer-free individuals. More importantly, using the miRNA signature was significantly more cost-effective relative to the current clinical practice of endoscopic screening, suggesting the robustness of a GC associated miRNA signature in multiple cohorts[95].

Table 3 Clinical trials of blood-based biofluid biomarkers for gastric cancer detection

Clinical trials	Type of trial	Phase	Results	Participants (estimated)	Assay	Comments
ctDNA						
NCT05027347	Cohort	NA	Recruiting	200	Ultradeep massive parallel sequencing assay	Development of a protocol for detection of ctDNA in plasma of patients with early stages of GC
NCT04511559	Cohort	NA	Not yet recruiting	540	ctDNA methylation sequencing	The correlation between the plasma ctDNA methylation status and the diagnosis of patients with early GC
NCT05208372	Case-control	NA	Recruiting	200	CTC and ctDNA test	Investigation of the value of CTCs and ctDNA in the diagnosis of metastasis of GC in peritoneal flushing fluid and blood
NCT04665687	Cohort	NA	Recruiting	1730	Illumina HiSeq2000/2500-based, MiSeq NGS targeted sequencing	Identification whether tumor's molecular profiling based on blood could be used for diagnosis of EGC and precancerous gastric adenoma
NCT05029869	Cohort	NA	Recruiting	100	NGS technologies	Study aims to evaluate the use of NGS to detect ctDNA in GC patients after gastrectomy
NCT05224596	Case-control	NA	Recruiting	498	Blood draw and blood-based biomarkers analyses	Multi-omics 498 study aimed at detecting GC by combined assays for serum protein markers, deep sequencing of cfDNA, ctDNA mutation and RNA
miRNAs						
NCT04329299	Cohort	NA	Completed	6862	Blood-based biomarkers analyses	Validation of the predictive value of various blood biomarkers, such as miRNA
lncRNAs						
NCT05397548	Cohort	NA	Recruiting	700	RT-PCR	Study to investigate the predictive value of circulating exosomal lncRNA-GC1 for early-detection and monitoring progression of GC
Methylation						
NCT04511559	Cohort	NA	Not yet recruiting	540	ctDNA methylation sequencing	Methylation analysis of ctDNA in early diagnosis in patients with GC
NCT03076567	Observational	NA	Completed	440	NA	Discovery and validation of plasma DNA methylation biomarker for detection of GC
NCT05336058	Cohort	NA	Recruiting	1240	Multi-target PCR	Exploration of the clinical performance of polygene methylation in the adjunctive diagnosis of GC
NCT04253106	Non-randomized	NA	Recruiting	10	NGS	Activating methylation profiles identified by liquid biopsies could identify CDH1 and CTNNA1 pathogenic variants carriers with DGC
Multi-omics						
NCT04947995	Case-control	NA	Recruiting	450	ctDNA multi-omics test	Exploration of a blood-based multi-omics assay and computational model for early detection of GC
NCT05347524	Observational	NA	Recruiting	384	Blood draw and blood-based biomarkers analyses	Detection of peritoneal metastasis of GC by combined assays for methylation of cfDNA and other blood-based biomarkers

GC: Gastric cancer; NGS: Next generation sequencing; PCR: Polymerase chain reaction; DGC: Diffuse gastric cancer; ctDNA: Circulating tumor DNA; cfDNA: Cell-free DNA; miRNA: MicroRNA; lncRNA: Long non-coding RNA; NA: Not applicable; lncRNA-GC1: Gastric cancer-associated lncRNA1.

More multicenter studies and prospective evaluations in large clinical trials are necessary for the integrations of such biomarkers into GC screening platforms supporting the daily clinical treatments of GC patients. Several clinical trials have explored the use of a liquid biopsy for early diagnosis of setting for patients with GC (Table 3). However, all of the trials were either observational, case-control, or cohort trials; no randomized control trial assessing liquid biopsy have been conducted to date. Hence, incorporating liquid biopsies into clinical practice for GC may be difficult.

Regarding the development of a circulating non-invasive biomarkers for early detection of GC, specificity for stomach would provide an additional confidence and suggested robustness of GC biomarkers. Biomarkers that are highly specific to GC will reduce the false positive rates, and thus are helpful in clinical practice. The detection of dysregulated genes that are highly expressed specifically in distinct organ could make it easier to find the locations of cancer. For example, KRAS mutations are rarely identified in healthy individuals, which makes these mutations highly cancer-specific. Nevertheless, detecting KRAS mutations in the circulation does not help identify the location of cancer as KRAS mutations can occur in multiple cancer types. Using candidates for GC specific driver genes, such as CDH1 and RhoA, may be possible to increase the specificity as diagnostic biomarkers of GC [96]. Growing evidences suggest that some EVs released from specific organs retain tissue-specific molecular features. It was recently reported that tumor cell-specific molecules, *i.e.*, circulating exosome-derived lncRNA-GC1 can be used as a biomarker to detect EGC and monitor disease progression[42]. Interestingly, a clinical study (ClinicalTrials.gov identifier NCT05397548) investigated whether circulating exosomal lncRNA-GC1 could support the early-detection and progression monitoring of GC. It is thus possible to measure ncRNA content of cancer-specific exosomes to further increase cancer specificity as biomarkers for GC diagnosis. The status of acquired DNA methylation can be tissue-specific and maintained during carcinogenesis, and examination of this status could allow the discovery of the tumor of origin[97], suggesting that biomarkers based on DNA methylation could have the additional potential to provide key information to guide follow-up clinical decision making. Multiple cancer types have been identified *via* high-depth, targeted bisulfite sequencing analysis of a large panel of methylation sites that have signals specific to certain organs; these panels include DEEPGEN™, CancerSEEK, PanSEER, cfMeDIP-se,q GRAIL, IvyGene®, and stMCEDs. Using these panels, excellent rates of detection in individuals with cancer were obtained[98]. However, the specificity of GC in individuals with early disease have been limited. A cost-effective experimental assay, called cell-free DNA Methylome Sequencing (cfMethyl-Seq) profiles the genome-wide methylation of cfDNA, offering > 12 × enrichment over whole-genome bisulfite sequencing in CpG islands[99]. By integrating four marker types, namely cancer-specific hypermethylation markers, tissue hypermethylation markers, cancer-specific hypomethylation markers types, and tissue hypomethylation markers, a cfMethyl-Seq model showed an AUR of 0.974 (95%CI: 0.926-0.998), yielding a sensitivity of 80.7% (95%CI: 68.6%-90.7%) at 97.9% specificity in multiple organs, including those with GC.

Collectively, the combination of multiple parameters and multiple analytes obtained by emerging machine learning methods will help address the challenges of EGC detection. Overcoming the limitation of cancer biomarker translation into clinical practice will require the development of high throughput, multiplexing techniques that can be easily incorporated into clinical settings as well as large-scale prospective research and interventional clinical trials with standardized specimen processing and data collection procedures.

CONCLUSION

Increased understanding of the molecular genetics and epigenetics of GC has led to the progress of molecular marker assays for GC screening. Liquid biopsy is emerging as a promising future screening technique for clinical testing owing to the use of a single sample and ease of specimen collection. The advancement of new technologies with improved sensitivity, such as methylation sequencing and multi-omics analysis, and rapid, global detection capacities that allowed the identification of novel potential biomarkers for early detection of GC.

FOOTNOTES

Author contributions: Matsuoka T and Yashiro M performed literature research; Matsuoka T wrote the manuscript and performed the revision and approval of the final version; Yashiro M designed research, coordinated and corrected the writing of the paper.

Supported by the National Cancer Center Research and Development Fund, No. 23-A-9.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Japan

ORCID number: Tasuku Matsuoka 0000-0001-5019-8519; Masakazu Yashiro 0000-0001-5743-7228.

S-Editor: Wang JJ

L-Editor: A

P-Editor: Yu HG

REFERENCES

- 1 Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin* 2022; **72**: 7-33 [PMID: 35020204 DOI: 10.3322/caac.21708]
- 2 Matsuoka T, Yashiro M. Biomarkers of gastric cancer: Current topics and future perspective. *World J Gastroenterol* 2018; **24**: 2818-2832 [PMID: 30018477 DOI: 10.3748/wjg.v24.i26.2818]
- 3 Alix-Panabières C, Pantel K. Liquid Biopsy: From Discovery to Clinical Application. *Cancer Discov* 2021; **11**: 858-873 [PMID: 33811121 DOI: 10.1158/2159-8290.CD-20-1311]
- 4 Heitzer E, Haque IS, Roberts CES, Speicher MR. Current and future perspectives of liquid biopsies in genomics-driven oncology. *Nat Rev Genet* 2019; **20**: 71-88 [PMID: 30410101 DOI: 10.1038/s41576-018-0071-5]
- 5 Joosse SA, Gorges TM, Pantel K. Biology, detection, and clinical implications of circulating tumor cells. *EMBO Mol Med* 2015; **7**: 1-11 [PMID: 25398926 DOI: 10.15252/emmm.201303698]
- 6 Wan JCM, Massie C, Garcia-Corbacho J, Mouliere F, Brenton JD, Caldas C, Pacey S, Baird R, Rosenfeld N. Liquid biopsies come of age: towards implementation of circulating tumour DNA. *Nat Rev Cancer* 2017; **17**: 223-238 [PMID: 28233803 DOI: 10.1038/nrc.2017.7]
- 7 Pessoa LS, Heringer M, Ferrer VP. ctDNA as a cancer biomarker: A broad overview. *Crit Rev Oncol Hematol* 2020; **155**: 103109 [PMID: 33049662 DOI: 10.1016/j.critrevonc.2020.103109]
- 8 Qian C, Ju S, Qi J, Zhao J, Shen X, Jing R, Yu J, Li L, Shi Y, Zhang L, Wang Z, Cong H. Alu-based cell-free DNA: a novel biomarker for screening of gastric cancer. *Oncotarget* 2017; **8**: 54037-54045 [PMID: 28903321 DOI: 10.18632/oncotarget.11079]
- 9 Lan YT, Chen MH, Fang WL, Hsieh CC, Lin CH, Jhang FY, Yang SH, Lin JK, Chen WS, Jiang JK, Lin PC, Chang SC. Clinical relevance of cell-free DNA in gastrointestinal tract malignancy. *Oncotarget* 2017; **8**: 3009-3017 [PMID: 27936467 DOI: 10.18632/oncotarget.13821]
- 10 Grenda A, Wojas-Krawczyk K, Skoczylas T, Krawczyk P, Sierocińska-Sawa J, Wallner G, Milanowski J. HER2 gene assessment in liquid biopsy of gastric and esophagogastric junction cancer patients qualified for surgery. *BMC Gastroenterol* 2020; **20**: 382 [PMID: 33198632 DOI: 10.1186/s12876-020-01531-5]
- 11 Jogo T, Nakamura Y, Shitara K, Bando H, Yasui H, Esaki T, Terazawa T, Satoh T, Shinozaki E, Nishina T, Sunakawa Y, Komatsu Y, Hara H, Oki E, Matsuhashi N, Ohta T, Kato T, Ohtsubo K, Kawakami T, Okano N, Yamamoto Y, Yamada T, Tsuji A, Odegaard JJ, Taniguchi H, Doi T, Fujii S, Yoshino T. Circulating Tumor DNA Analysis Detects FGFR2 Amplification and Concurrent Genomic Alterations Associated with FGFR Inhibitor Efficacy in Advanced Gastric Cancer. *Clin Cancer Res* 2021; **27**: 5619-5627 [PMID: 34376535 DOI: 10.1158/1078-0432.CCR-21-1414]
- 12 Reinert T, Schøler LV, Thomsen R, Tobiasen H, Vang S, Nordentoft I, Lamy P, Kannerup AS, Mortensen FV, Stribolt K, Hamilton-Dutoit S, Nielsen HJ, Laurberg S, Pallisgaard N, Pedersen JS, Ørntoft TF, Andersen CL. Analysis of circulating tumour DNA to monitor disease burden following colorectal cancer surgery. *Gut* 2016; **65**: 625-634 [PMID: 25654990 DOI: 10.1136/gutjnl-2014-308859]
- 13 Kim YW, Kim YH, Song Y, Kim HS, Sim HW, Poojan S, Eom BW, Kook MC, Joo J, Hong KM. Monitoring circulating tumor DNA by analyzing personalized cancer-specific rearrangements to detect recurrence in gastric cancer. *Exp Mol Med* 2019; **51**: 1-10 [PMID: 31395853 DOI: 10.1038/s12276-019-0292-5]
- 14 Yang J, Gong Y, Lam VK, Shi Y, Guan Y, Zhang Y, Ji L, Chen Y, Zhao Y, Qian F, Chen J, Li P, Zhang F, Wang J, Zhang X, Yang L, Kopetz S, Futreal PA, Zhang J, Yi X, Xia X, Yu P. Deep sequencing of circulating tumor DNA detects molecular residual disease and predicts recurrence in gastric cancer. *Cell Death Dis* 2020; **11**: 346 [PMID: 32393783 DOI: 10.1038/s41419-020-2531-z]
- 15 Chae YK, Oh MS. Detection of Minimal Residual Disease Using ctDNA in Lung Cancer: Current Evidence and Future Directions. *J Thorac Oncol* 2019; **14**: 16-24 [PMID: 30296486 DOI: 10.1016/j.jtho.2018.09.022]
- 16 Koldby KM, Mortensen MB, Detlefsen S, Pfeiffer P, Thomassen M, Kruse TA. Tumor-specific genetic aberrations in cell-free DNA of gastroesophageal cancer patients. *J Gastroenterol* 2019; **54**: 108-121 [PMID: 30242476 DOI: 10.1007/s00535-018-1508-5]
- 17 Maron SB, Chase LM, Lomnicki S, Kochanny S, Moore KL, Joshi SS, Landron S, Johnson J, Kiedrowski LA, Nagy RJ, Lanman RB, Kim ST, Lee J, Catenacci DVT. Circulating Tumor DNA Sequencing Analysis of Gastroesophageal Adenocarcinoma. *Clin Cancer Res* 2019; **25**: 7098-7112 [PMID: 31427281 DOI: 10.1158/1078-0432.CCR-19-1704]
- 18 Zhang M, Du X. Noncoding RNAs in gastric cancer: Research progress and prospects. *World J Gastroenterol* 2016; **22**: 6610-6618 [PMID: 27547004 DOI: 10.3748/wjg.v22.i29.6610]
- 19 Finnegan EF, Pasquinelli AE. MicroRNA biogenesis: regulating the regulators. *Crit Rev Biochem Mol Biol* 2013; **48**: 51-68 [PMID: 23163351 DOI: 10.3109/10409238.2012.738643]
- 20 ZiaSarabi P, Sorayayi S, Hesari A, Ghasemi F. Circulating microRNA-133, microRNA-17 and microRNA-25 in serum and its potential diagnostic value in gastric cancer. *J Cell Biochem* 2019; **120**: 12376-12381 [PMID: 30861177 DOI: 10.1002/jcb.28503]
- 21 Zhu XL, Ren LF, Wang HP, Bai ZT, Zhang L, Meng WB, Zhu KX, Ding FH, Miao L, Yan J, Wang YP, Liu YQ, Zhou WC, Li X. Plasma microRNAs as potential new biomarkers for early detection of early gastric cancer. *World J Gastroenterol* 2019; **25**: 1580-1591 [PMID: 30983818 DOI: 10.3748/wjg.v25.i13.1580]

- 22 **Yao Y**, Ding Y, Bai Y, Zhou Q, Lee H, Li X, Teng L. Identification of Serum Circulating MicroRNAs as Novel Diagnostic Biomarkers of Gastric Cancer. *Front Genet* 2020; **11**: 591515 [PMID: [33597967](#) DOI: [10.3389/fgene.2020.591515](#)]
- 23 **Abe S**, Matsuzaki J, Sudo K, Oda I, Katai H, Kato K, Takizawa S, Sakamoto H, Takeshita F, Niida S, Saito Y, Ochiya T. A novel combination of serum microRNAs for the detection of early gastric cancer. *Gastric Cancer* 2021; **24**: 835-843 [PMID: [33743111](#) DOI: [10.1007/s10120-021-01161-0](#)]
- 24 **Fang XY**, Pan HF, Leng RX, Ye DQ. Long noncoding RNAs: novel insights into gastric cancer. *Cancer Lett* 2015; **356**: 357-366 [PMID: [25444905](#) DOI: [10.1016/j.canlet.2014.11.005](#)]
- 25 **Xu W**, Zhou G, Wang H, Liu Y, Chen B, Chen W, Lin C, Wu S, Gong A, Xu M. Circulating lncRNA SNHG11 as a novel biomarker for early diagnosis and prognosis of colorectal cancer. *Int J Cancer* 2020; **146**: 2901-2912 [PMID: [31633800](#) DOI: [10.1002/ijc.32747](#)]
- 26 **Xian HP**, Zhuo ZL, Sun YJ, Liang B, Zhao XT. Circulating long non-coding RNAs HULC and ZNF1-AS1 are potential biomarkers in patients with gastric cancer. *Oncol Lett* 2018; **16**: 4689-4698 [PMID: [30197680](#) DOI: [10.3892/ol.2018.9199](#)]
- 27 **Yang Z**, Sun Y, Liu R, Shi Y, Ding S. Plasma long noncoding RNAs PANDAR, FOXD2-AS1, and SMARCC2 as potential novel diagnostic biomarkers for gastric cancer. *Cancer Manag Res* 2019; **11**: 6175-6184 [PMID: [31308753](#) DOI: [10.2147/CMAR.S201935](#)]
- 28 **Feng W**, Zong W, Li Y, Shen X, Cui X, Ju S. Abnormally expressed long noncoding RNA B3GALT5-AS1 may serve as a biomarker for the diagnostic and prognostic of gastric cancer. *J Cell Biochem* 2020; **121**: 557-565 [PMID: [31338903](#) DOI: [10.1002/jcb.29296](#)]
- 29 **Zhou Q**, Li H, Jing J, Yuan Y, Sun L. Evaluation of C5orf66-AS1 as a Potential Biomarker for Predicting Early Gastric Cancer and Its Role in Gastric Carcinogenesis. *Onco Targets Ther* 2020; **13**: 2795-2805 [PMID: [32308414](#) DOI: [10.2147/OTT.S239965](#)]
- 30 **Qin S**, Yang L, Kong S, Xu Y, Liang B, Ju S. LncRNA HCP5 : A Potential Biomarker for Diagnosing Gastric Cancer. *Front Oncol* 2021; **11**: 684531 [PMID: [34222007](#) DOI: [10.3389/fonc.2021.684531](#)]
- 31 **Li X**, Yang L, Chen LL. The Biogenesis, Functions, and Challenges of Circular RNAs. *Mol Cell* 2018; **71**: 428-442 [PMID: [30057200](#) DOI: [10.1016/j.molcel.2018.06.034](#)]
- 32 **Enuka Y**, Lauriola M, Feldman ME, Sas-Chen A, Ulitsky I, Yarden Y. Circular RNAs are long-lived and display only minimal early alterations in response to a growth factor. *Nucleic Acids Res* 2016; **44**: 1370-1383 [PMID: [26657629](#) DOI: [10.1093/nar/gkv1367](#)]
- 33 **Huang M**, He YR, Liang LC, Huang Q, Zhu ZQ. Circular RNA hsa_circ_0000745 may serve as a diagnostic marker for gastric cancer. *World J Gastroenterol* 2017; **23**: 6330-6338 [PMID: [28974900](#) DOI: [10.3748/wjg.v23.i34.6330](#)]
- 34 **Lu H**, Zhang Z, Yuan X, Song H, Li P. The role of circular RNA hsa_circ_0001789 as a diagnostic biomarker in gastric carcinoma. *Scand J Gastroenterol* 2023; **58**: 248-253 [PMID: [36111683](#) DOI: [10.1080/00365521.2022.2122865](#)]
- 35 **Ma S**, Kong S, Gu X, Xu Y, Tao M, Shen L, Shen X, Ju S. As a biomarker for gastric cancer, circPTPN22 regulates the progression of gastric cancer through the EMT pathway. *Cancer Cell Int* 2021; **21**: 44 [PMID: [33430866](#) DOI: [10.1186/s12935-020-01701-1](#)]
- 36 **Roy S**, Kanda M, Nomura S, Zhu Z, Toiyama Y, Taketomi A, Goldenring J, Baba H, Kadera Y, Goel A. Diagnostic efficacy of circular RNAs as noninvasive, liquid biopsy biomarkers for early detection of gastric cancer. *Mol Cancer* 2022; **21**: 42 [PMID: [35139874](#) DOI: [10.1186/s12943-022-01527-7](#)]
- 37 **Yu W**, Hurley J, Roberts D, Chakraborty SK, Enderle D, Noerholm M, Breakefield XO, Skog JK. Exosome-based liquid biopsies in cancer: opportunities and challenges. *Ann Oncol* 2021; **32**: 466-477 [PMID: [33548389](#) DOI: [10.1016/j.annonc.2021.01.074](#)]
- 38 **Xu R**, Rai A, Chen M, Suwakulsiri W, Greening DW, Simpson RJ. Extracellular vesicles in cancer - implications for future improvements in cancer care. *Nat Rev Clin Oncol* 2018; **15**: 617-638 [PMID: [29795272](#) DOI: [10.1038/s41571-018-0036-9](#)]
- 39 **Lin LY**, Yang L, Zeng Q, Wang L, Chen ML, Zhao ZH, Ye GD, Luo QC, Lv PY, Guo QW, Li BA, Cai JC, Cai WY. Tumor-originated exosomal lncUEGC1 as a circulating biomarker for early-stage gastric cancer. *Mol Cancer* 2018; **17**: 84 [PMID: [29690888](#) DOI: [10.1186/s12943-018-0834-9](#)]
- 40 **Cai C**, Zhang H, Zhu Y, Zheng P, Xu Y, Sun J, Zhang M, Lan T, Gu B, Li S, Ma P. Serum Exosomal Long Noncoding RNA psk2-2:1 As A Potential Novel Diagnostic Biomarker For Gastric Cancer. *Onco Targets Ther* 2019; **12**: 10035-10041 [PMID: [31819499](#) DOI: [10.2147/OTT.S229033](#)]
- 41 **Li S**, Zhang M, Zhang H, Hu K, Cai C, Wang J, Shi L, Ma P, Xu Y, Zheng P. Exosomal long noncoding RNA lnc-GNAQ-6:1 may serve as a diagnostic marker for gastric cancer. *Clin Chim Acta* 2020; **501**: 252-257 [PMID: [31730812](#) DOI: [10.1016/j.cca.2019.10.047](#)]
- 42 **Guo X**, Lv X, Ru Y, Zhou F, Wang N, Xi H, Zhang K, Li J, Chang R, Xie T, Wang X, Li B, Chen Y, Yang Y, Chen L. Circulating Exosomal Gastric Cancer-Associated Long Noncoding RNA1 as a Biomarker for Early Detection and Monitoring Progression of Gastric Cancer: A Multiphase Study. *JAMA Surg* 2020; **155**: 572-579 [PMID: [32520332](#) DOI: [10.1001/jamasurg.2020.1133](#)]
- 43 **Tang S**, Cheng J, Yao Y, Lou C, Wang L, Huang X, Zhang Y. Combination of Four Serum Exosomal MiRNAs as Novel Diagnostic Biomarkers for Early-Stage Gastric Cancer. *Front Genet* 2020; **11**: 237 [PMID: [32256526](#) DOI: [10.3389/fgene.2020.00237](#)]
- 44 **Zheng GD**, Xu ZY, Hu C, Lv H, Xie HX, Huang T, Zhang YQ, Chen GP, Fu YF, Cheng XD. Exosomal miR-590-5p in Serum as a Biomarker for the Diagnosis and Prognosis of Gastric Cancer. *Front Mol Biosci* 2021; **8**: 636566 [PMID: [33681295](#) DOI: [10.3389/fmolb.2021.636566](#)]
- 45 **Yang J**, Li X, Wei S, Peng L, Sang H, Jin D, Chen M, Dang Y, Zhang G. Evaluation of the Diagnostic Potential of a Plasma Exosomal miRNAs Panel for Gastric Cancer. *Front Oncol* 2021; **11**: 683465 [PMID: [34422636](#) DOI: [10.3389/fonc.2021.683465](#)]
- 46 **Ni D**, Zhang Z, Liu X. Benthic ecological quality assessment of the Bohai Sea, China using marine biotic indices. *Mar*

- Pollut Bull* 2019; **142**: 457-464 [PMID: 31232324 DOI: 10.1016/j.marpolbul.2019.03.055]
- 47 **Ge L**, Zhang N, Li D, Wu Y, Wang H, Wang J. Circulating exosomal small RNAs are promising non-invasive diagnostic biomarkers for gastric cancer. *J Cell Mol Med* 2020; **24**: 14502-14513 [PMID: 33169519 DOI: 10.1111/jcmm.16077]
- 48 **Puneet**, Kazmi HR, Kumari S, Tiwari S, Khanna A, Narayan G. Epigenetic Mechanisms and Events in Gastric Cancer- Emerging Novel Biomarkers. *Pathol Oncol Res* 2018; **24**: 757-770 [PMID: 29552712 DOI: 10.1007/s12253-018-0410-z]
- 49 **Skvortsova K**, Stirzaker C, Taberlay P. The DNA methylation landscape in cancer. *Essays Biochem* 2019; **63**: 797-811 [PMID: 31845735 DOI: 10.1042/EBC20190037]
- 50 **Zeng Y**, Rong H, Xu J, Cao R, Li S, Gao Y, Cheng B, Zhou T. DNA Methylation: An Important Biomarker and Therapeutic Target for Gastric Cancer. *Front Genet* 2022; **13**: 823905 [PMID: 35309131 DOI: 10.3389/fgene.2022.823905]
- 51 **Alarcón MA**, Olivares W, Córdova-Delgado M, Muñoz-Medel M, de Mayo T, Carrasco-Aviño G, Wichmann I, Landeros N, Amigo J, Norero E, Villarroel-Espindola F, Riquelme A, Garrido M, Owen GI, Corvalán AH. The Reprimo-Like Gene Is an Epigenetic-Mediated Tumor Suppressor and a Candidate Biomarker for the Non-Invasive Detection of Gastric Cancer. *Int J Mol Sci* 2020; **21** [PMID: 33322837 DOI: 10.3390/ijms21249472]
- 52 **Wen J**, Zheng T, Hu K, Zhu C, Guo L, Ye G. Promoter methylation of tumor-related genes as a potential biomarker using blood samples for gastric cancer detection. *Oncotarget* 2017; **8**: 77783-77793 [PMID: 29100425 DOI: 10.18632/oncotarget.20782]
- 53 **Wu S**, Zhang Y, Zhang L, Ma JL, Zhou T, Li ZX, Liu WD, Li WQ, You WC, Pan KF. Methylation and Expression of Nonclustered Protocadherins Encoding Genes and Risk of Precancerous Gastric Lesions in a High-Risk Population. *Cancer Prev Res (Phila)* 2018; **11**: 717-726 [PMID: 30213786 DOI: 10.1158/1940-6207.CAPR-18-0119]
- 54 **Miao J**, Liu Y, Zhao G, Liu X, Ma Y, Li H, Li S, Zhu Y, Xiong S, Zheng M, Fei S. Feasibility of Plasma-Methylated SFRP2 for Early Detection of Gastric Cancer. *Cancer Control* 2020; **27**: 1073274820922559 [PMID: 32379490 DOI: 10.1177/1073274820922559]
- 55 **Hu D**, Lou X, Meng N, Li Z, Teng Y, Zou Y, Wang F. Peripheral Blood-Based DNA Methylation of Long Non-Coding RNA H19 and Metastasis-Associated Lung Adenocarcinoma Transcript 1 Promoters are Potential Non-Invasive Biomarkers for Gastric Cancer Detection. *Cancer Control* 2021; **28**: 10732748211043667 [PMID: 34615385 DOI: 10.1177/10732748211043667]
- 56 **Han Q**, Zhou H, Xie W, Sun T, Wei R, Nie C, Hong J, Zhu L, Tian W. Association between the methylation of the STAT1 and SOCS3 in peripheral blood and gastric cancer. *J Gastroenterol Hepatol* 2020; **35**: 1347-1354 [PMID: 32108380 DOI: 10.1111/jgh.15021]
- 57 **Chansangpetch S**, Prombhul S, Tantisevi V, Sodsai P, Manassakorn A, Hirankarn N, Lin SC. DNA Methylation Status of the Interspersed Repetitive Sequences for LINE-1, Alu, HERV-E, and HERV-K in Trabeculectomy Specimens from Glaucoma Eyes. *J Ophthalmol* 2018; **2018**: 9171536 [PMID: 29651348 DOI: 10.1155/2018/9171536]
- 58 **Fattahi S**, Kosari-Monfared M, Ghadami E, Golpour M, Khodadadi P, Ghasemiyan M, Akhavan-Niaki H. Infection-associated epigenetic alterations in gastric cancer: New insight in cancer therapy. *J Cell Physiol* 2018; **233**: 9261-9270 [PMID: 30076708 DOI: 10.1002/jcp.27030]
- 59 **Yoshida T**, Yamashita S, Takamura-Enya T, Niwa T, Ando T, Enomoto S, Maekita T, Nakazawa K, Tatsumatsu M, Ichinose M, Ushijima T. Alu and Satα hypomethylation in Helicobacter pylori-infected gastric mucosae. *Int J Cancer* 2011; **128**: 33-39 [PMID: 20602342 DOI: 10.1002/ijce.25534]
- 60 **Zhang X**, Soutto M, Chen Z, Bhat N, Zhu S, Eissmann MF, Ernst M, Lu H, Peng D, Xu Z, El-Rifai W. Induction of Fibroblast Growth Factor Receptor 4 by Helicobacter pylori via Signal Transducer and Activator of Transcription 3 With a Feedforward Activation Loop Involving Steroid Receptor Coactivator Signaling in Gastric Cancer. *Gastroenterology* 2022; **163**: 620-636.e9 [PMID: 35588797 DOI: 10.1053/j.gastro.2022.05.016]
- 61 **Shi XJ**, Wei Y, Ji B. Systems Biology of Gastric Cancer: Perspectives on the Omics-Based Diagnosis and Treatment. *Front Mol Biosci* 2020; **7**: 203 [PMID: 33005629 DOI: 10.3389/fmolb.2020.00203]
- 62 **Morganti S**, Tarantino P, Ferraro E, D'Amico P, Viale G, Trapani D, Duso BA, Curigliano G. Complexity of genome sequencing and reporting: Next generation sequencing (NGS) technologies and implementation of precision medicine in real life. *Crit Rev Oncol Hematol* 2019; **133**: 171-182 [PMID: 30661654 DOI: 10.1016/j.critrevonc.2018.11.008]
- 63 **Ren AH**, Diamandis EP, Kulasingam V. Uncovering the Depths of the Human Proteome: Antibody-based Technologies for Ultrasensitive Multiplexed Protein Detection and Quantification. *Mol Cell Proteomics* 2021; **20**: 100155 [PMID: 34597790 DOI: 10.1016/j.mcpro.2021.100155]
- 64 **Zhou B**, Zhou Z, Chen Y, Deng H, Cai Y, Rao X, Yin Y, Rong L. Plasma proteomics-based identification of novel biomarkers in early gastric cancer. *Clin Biochem* 2020; **76**: 5-10 [PMID: 31765635 DOI: 10.1016/j.clinbiochem.2019.11.001]
- 65 **Xiao Y**, Xie J, Liu L, Huang W, Han Q, Qin J, Liu S, Jiang Z. NAD(P)-dependent steroid dehydrogenase-like protein and neutral cholesterol ester hydrolase 1 serve as novel markers for early detection of gastric cancer identified using quantitative proteomics. *J Clin Lab Anal* 2021; **35**: e23652 [PMID: 33219617 DOI: 10.1002/jcla.23652]
- 66 **Zhu Y**, Hu Y, Zhu X, Zhang J, Yuwen D, Wei X, Tang C, Zhang W. Plasma thioredoxin reductase: a potential diagnostic biomarker for gastric cancer. *Carcinogenesis* 2022; **43**: 736-745 [PMID: 35709525 DOI: 10.1093/carcin/bgac052]
- 67 **Mun DG**, Bhin J, Kim S, Kim H, Jung JH, Jung Y, Jang YE, Park JM, Lee H, Bae J, Back S, Kim SJ, Kim J, Park H, Li H, Hwang KB, Park YS, Yook JH, Kim BS, Kwon SY, Ryu SW, Park DY, Jeon TY, Kim DH, Lee JH, Han SU, Song KS, Park D, Park JW, Rodriguez H, Kim KP, Yang EG, Kim HK, Paek E, Lee S, Lee SW, Hwang D. Proteogenomic Characterization of Human Early-Onset Gastric Cancer. *Cancer Cell* 2019; **35**: 111-124.e10 [PMID: 30645970 DOI: 10.1016/j.ccell.2018.12.003]
- 68 **Aziz S**, Rasheed F, Zahra R, König S. Gastric Cancer Pre-Stage Detection and Early Diagnosis of Gastritis Using Serum Protein Signatures. *Molecules* 2022; **27** [PMID: 35566209 DOI: 10.3390/molecules27092857]
- 69 **Park CH**, Hong C, Lee AR, Sung J, Hwang TH. Multi-omics reveals microbiome, host gene expression, and immune landscape in gastric carcinogenesis. *iScience* 2022; **25**: 103956 [PMID: 35265820 DOI: 10.1016/j.isci.2022.103956]
- 70 **Kon OL**, Yip TT, Ho MF, Chan WH, Wong WK, Tan SY, Ng WH, Kam SY, Eng AKh, Ho P, Viner R, Ong HS,

- Kumarasinghe MP. The distinctive gastric fluid proteome in gastric cancer reveals a multi-biomarker diagnostic profile. *BMC Med Genomics* 2008; **1**: 54 [PMID: [18950519](#) DOI: [10.1186/1755-8794-1-54](#)]
- 71 **Skryabin GO**, Vinokurova SV, Galetsky SA, Elkin DS, Senkovenko AM, Denisova DA, Komelkov AV, Stilidi IS, Peregorodiev IN, Malikhova OA, Imaraliev OT, Enikeev AD, Tchevkina EM. Isolation and Characterization of Extracellular Vesicles from Gastric Juice. *Cancers (Basel)* 2022; **14** [PMID: [35884376](#) DOI: [10.3390/cancers14143314](#)]
 - 72 **Shao Y**, Ye M, Li Q, Sun W, Ye G, Zhang X, Yang Y, Xiao B, Guo J. LncRNA-RMRP promotes carcinogenesis by acting as a miR-206 sponge and is used as a novel biomarker for gastric cancer. *Oncotarget* 2016; **7**: 37812-37824 [PMID: [27192121](#) DOI: [10.18632/oncotarget.9336](#)]
 - 73 **Pan Y**, Zheng Y, Yang J, Wei Y, Wu H, Liu S, Yin A, Hu J, Zeng Y. A new biomarker for the early diagnosis of gastric cancer: gastric juice- and serum-derived SNCG. *Future Oncol* 2022; **18**: 3179-3190 [PMID: [35947016](#) DOI: [10.2217/fon-2022-0253](#)]
 - 74 **Yamamoto H**, Watanabe Y, Oikawa R, Morita R, Yoshida Y, Maehata T, Yasuda H, Itoh F. BARHL2 Methylation Using Gastric Wash DNA or Gastric Juice Exosomal DNA is a Useful Marker For Early Detection of Gastric Cancer in an H. pylori-Independent Manner. *Clin Transl Gastroenterol* 2016; **7**: e184 [PMID: [27441821](#) DOI: [10.1038/ctg.2016.40](#)]
 - 75 **Botezatu A**, Bodrug N. Chronic atrophic gastritis: an update on diagnosis. *Med Pharm Rep* 2021; **94**: 7-14 [PMID: [33629042](#) DOI: [10.15386/mpr-1887](#)]
 - 76 **Bang CS**, Lee JJ, Baik GH. Prediction of Chronic Atrophic Gastritis and Gastric Neoplasms by Serum Pepsinogen Assay: A Systematic Review and Meta-Analysis of Diagnostic Test Accuracy. *J Clin Med* 2019; **8** [PMID: [31083485](#) DOI: [10.3390/jcm8050657](#)]
 - 77 **Sarhadi VK**, Armengol G. Molecular Biomarkers in Cancer. *Biomolecules* 2022; **12** [PMID: [35892331](#) DOI: [10.3390/biom12081021](#)]
 - 78 **Nakajima H**, Kotani D, Bando H, Kato T, Oki E, Shinozaki E, Sunakawa Y, Yamazaki K, Yuki S, Nakamura Y, Yamanaka T, Yoshino T, Ohta T, Taniguchi H, Kagawa Y. REMARRY and PURSUIT trials: liquid biopsy-guided rechallenge with anti-epidermal growth factor receptor (EGFR) therapy with panitumumab plus irinotecan for patients with plasma RAS wild-type metastatic colorectal cancer. *BMC Cancer* 2021; **21**: 674 [PMID: [34098908](#) DOI: [10.1186/s12885-021-08395-2](#)]
 - 79 **Ignatiadis M**, Sledge GW, Jeffrey SS. Liquid biopsy enters the clinic - implementation issues and future challenges. *Nat Rev Clin Oncol* 2021; **18**: 297-312 [PMID: [33473219](#) DOI: [10.1038/s41571-020-00457-x](#)]
 - 80 **Pascual J**, Attard G, Bidard FC, Curigliano G, De Mattos-Arruda L, Diehn M, Italiano A, Lindberg J, Merker JD, Montagut C, Normanno N, Pantel K, Pentheroudakis G, Popat S, Reis-Filho JS, Tie J, Seoane J, Tarazona N, Yoshino T, Turner NC. ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO Precision Medicine Working Group. *Ann Oncol* 2022; **33**: 750-768 [PMID: [35809752](#) DOI: [10.1016/j.annonc.2022.05.520](#)]
 - 81 **So JBY**, Kapoor R, Zhu F, Koh C, Zhou L, Zou R, Tang YC, Goo PCK, Rha SY, Chung HC, Yoong J, Yap CT, Rao J, Chia CK, Tsao S, Shabbir A, Lee J, Lam KP, Hartman M, Yong WP, Too HP, Yeoh KG. Development and validation of a serum microRNA biomarker panel for detecting gastric cancer in a high-risk population. *Gut* 2021; **70**: 829-837 [PMID: [33028667](#) DOI: [10.1136/gutjnl-2020-322065](#)]
 - 82 **Cohen JD**, Li L, Wang Y, Thoburn C, Afsari B, Danilova L, Douville C, Javed AA, Wong F, Mattox A, Hruban RH, Wolfgang CL, Goggins MG, Dal Molin M, Wang TL, Roden R, Klein AP, Ptak J, Dobbryn L, Schaefer J, Silliman N, Popoli M, Vogelstein JT, Browne JD, Schoen RE, Brand RE, Tie J, Gibbs P, Wong HL, Mansfield AS, Jen J, Hanash SM, Falconi M, Allen PJ, Zhou S, Bettgowda C, Diaz LA Jr, Tomasetti C, Kinzler KW, Vogelstein B, Lennon AM, Papadopoulos N. Detection and localization of surgically resectable cancers with a multi-analyte blood test. *Science* 2018; **359**: 926-930 [PMID: [29348365](#) DOI: [10.1126/science.aar3247](#)]
 - 83 **Xu J**, Song J, Wang T, Zhu W, Zuo L, Wu J, Guo J, Yang X. A combination of methylation and protein markers is capable of detecting gastric cancer detection by combined markers. *Epigenomics* 2021; **13**: 1557-1570 [PMID: [34632818](#) DOI: [10.2217/epi-2021-0080](#)]
 - 84 **Ko J**, Baldassano SN, Loh PL, Kording K, Litt B, Issadore D. Machine learning to detect signatures of disease in liquid biopsies - a user's guide. *Lab Chip* 2018; **18**: 395-405 [PMID: [29192299](#) DOI: [10.1039/c7lc00955k](#)]
 - 85 **Watanabe Y**, Oikawa R, Agawa S, Matsuo Y, Oda I, Futagami S, Yamamoto H, Tada T, Itoh F. Combination of artificial intelligence-based endoscopy and miR148a methylation for gastric indefinite dysplasia diagnosis. *J Clin Lab Anal* 2022; **36**: e24122 [PMID: [34811809](#) DOI: [10.1002/jcla.24122](#)]
 - 86 **Poore GD**, Kopylova E, Zhu Q, Carpenter C, Fraraccio S, Wandro S, Kosciolk T, Janssen S, Metcalf J, Song SJ, Kanbar J, Miller-Montgomery S, Heaton R, McKay R, Patel SP, Swafford AD, Knight R. Microbiome analyses of blood and tissues suggest cancer diagnostic approach. *Nature* 2020; **579**: 567-574 [PMID: [32214244](#) DOI: [10.1038/s41586-020-2095-1](#)]
 - 87 **Gilani N**, Arabi Belaghi R, Aftabi Y, Faramarzi E, Edgünlü T, Somi MH. Identifying Potential miRNA Biomarkers for Gastric Cancer Diagnosis Using Machine Learning Variable Selection Approach. *Front Genet* 2021; **12**: 779455 [PMID: [35082831](#) DOI: [10.3389/fgene.2021.779455](#)]
 - 88 **Xiao K**, Li S, Ding J, Wang Z, Wang D, Cao X, Zhang Y, Dong Z. Expression and clinical value of circRNAs in serum extracellular vesicles for gastric cancer. *Front Oncol* 2022; **12**: 962831 [PMID: [36059681](#) DOI: [10.3389/fonc.2022.962831](#)]
 - 89 **Ding W**, Wu L, Li X, Chang L, Liu G, Du H. Comprehensive analysis of competitive endogenous RNAs network: Identification and validation of prediction model composed of mRNA signature and miRNA signature in gastric cancer. *Oncol Lett* 2022; **23**: 150 [PMID: [35350591](#) DOI: [10.3892/ol.2022.13270](#)]
 - 90 **Wu Z**, Liu P, Zhang G. Identification of circRNA-miRNA-Immune-Related mRNA Regulatory Network in Gastric Cancer. *Front Oncol* 2022; **12**: 816884 [PMID: [35280778](#) DOI: [10.3389/fonc.2022.816884](#)]
 - 91 **Gong Y**, Jiao Y, Qi X, Fu J, Qian J, Zhu J, Yang H, Tang L. Construction of a circRNA-miRNA-mRNA network based on differentially co-expressed circular RNA in gastric cancer tissue and plasma by bioinformatics analysis. *World J Surg Oncol* 2022; **20**: 34 [PMID: [35164778](#) DOI: [10.1186/s12957-022-02503-7](#)]

- 92 **Hossain MT**, Li S, Reza MS, Feng S, Zhang X, Jin Z, Wei Y, Peng Y. Identification of circRNA Biomarker for Gastric Cancer through Integrated Analysis. *Front Mol Biosci* 2022; **9**: 857320 [PMID: [35359600](#) DOI: [10.3389/fmolb.2022.857320](#)]
- 93 **Zhang P**, Yang M, Zhang Y, Xiao S, Lai X, Tan A, Du S, Li S. Dissecting the Single-Cell Transcriptome Network Underlying Gastric Premalignant Lesions and Early Gastric Cancer. *Cell Rep* 2019; **27**: 1934-1947.e5 [PMID: [31067475](#) DOI: [10.1016/j.celrep.2019.04.052](#)]
- 94 **Tan R**, Zhang G, Liu R, Hou J, Dong Z, Deng C, Wan S, Lai X, Cui H. Identification of Early Diagnostic and Prognostic Biomarkers via WGCNA in Stomach Adenocarcinoma. *Front Oncol* 2021; **11**: 636461 [PMID: [34221961](#) DOI: [10.3389/fonc.2021.636461](#)]
- 95 **Izumi D**, Zhu Z, Chen Y, Toden S, Huo X, Kanda M, Ishimoto T, Gu D, Tan M, Kadera Y, Baba H, Li W, Chen J, Wang X, Goel A. Assessment of the Diagnostic Efficiency of a Liquid Biopsy Assay for Early Detection of Gastric Cancer. *JAMA Netw Open* 2021; **4**: e2121129 [PMID: [34427680](#) DOI: [10.1001/jamanetworkopen.2021.21129](#)]
- 96 **Dong Y**, Song N, Wang J, Shi L, Zhang Z, Du J. Driver Gene Alterations in Malignant Progression of Gastric Cancer. *Front Oncol* 2022; **12**: 920207 [PMID: [35903675](#) DOI: [10.3389/fonc.2022.920207](#)]
- 97 **Flavahan WA**, Gaskell E, Bernstein BE. Epigenetic plasticity and the hallmarks of cancer. *Science* 2017; **357** [PMID: [28729483](#) DOI: [10.1126/science.aal2380](#)]
- 98 **Liu MC**, Oxnard GR, Klein EA, Swanton C, Seiden MV; CCGA Consortium. Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. *Ann Oncol* 2020; **31**: 745-759 [PMID: [33506766](#) DOI: [10.1016/j.annonc.2020.02.011](#)]
- 99 **Stackpole ML**, Zeng W, Li S, Liu CC, Zhou Y, He S, Yeh A, Wang Z, Sun F, Li Q, Yuan Z, Yildirim A, Chen PJ, Winograd P, Tran B, Lee YT, Li PS, Noor Z, Yokomizo M, Ahuja P, Zhu Y, Tseng HR, Tomlinson JS, Garon E, French S, Magyar CE, Dry S, Lajonchere C, Geschwind D, Choi G, Saab S, Alber F, Wong WH, Dubinett SM, Aberle DR, Agopian V, Han SB, Ni X, Li W, Zhou XJ. Cost-effective methylome sequencing of cell-free DNA for accurately detecting and locating cancer. *Nat Commun* 2022; **13**: 5566 [PMID: [36175411](#) DOI: [10.1038/s41467-022-32995-6](#)]
- 100 **Chakrabarti S**, Kasi AK, Parikh AR, Mahipal A. Finding Waldo: The Evolving Paradigm of Circulating Tumor DNA (ctDNA)-Guided Minimal Residual Disease (MRD) Assessment in Colorectal Cancer (CRC). *Cancers (Basel)* 2022; **14** [PMID: [35804850](#) DOI: [10.3390/cancers14133078](#)]
- 101 **Kasi PM**, Fehringer G, Taniguchi H, Starling N, Nakamura Y, Kotani D, Powles T, Li BT, Pusztai L, Aushev VN, Kalashnikova E, Sharma S, Malhotra M, Demko ZP, Aleshin A, Rodriguez A, Billings PR, Grothey A, Taieb J, Cunningham D, Yoshino T, Kopetz S. Impact of Circulating Tumor DNA-Based Detection of Molecular Residual Disease on the Conduct and Design of Clinical Trials for Solid Tumors. *JCO Precis Oncol* 2022; **6**: e2100181 [PMID: [35263168](#) DOI: [10.1200/PO.21.00181](#)]
- 102 **Kong Y**, Ning L, Qiu F, Yu Q, Cao B. Clinical significance of serum miR-25 as a diagnostic and prognostic biomarker in human gastric cancer. *Cancer Biomark* 2019; **24**: 477-483 [PMID: [30909187](#) DOI: [10.3233/CBM-182213](#)]
- 103 **Ji B**, Huang Y, Gu T, Zhang L, Li G, Zhang C. Potential diagnostic and prognostic value of plasma long noncoding RNA LINC00086 and miR-214 expression in gastric cancer. *Cancer Biomark* 2019; **24**: 249-255 [PMID: [30689553](#) DOI: [10.3233/CBM-181486](#)]
- 104 **Hung PS**, Chen CY, Chen WT, Kuo CY, Fang WL, Huang KH, Chiu PC, Lo SS. miR-376c promotes carcinogenesis and serves as a plasma marker for gastric carcinoma. *PLoS One* 2017; **12**: e0177346 [PMID: [28486502](#) DOI: [10.1371/journal.pone.0177346](#)]
- 105 **Li Y**, Sun H, Guan J, Ji T, Wang X. Serum microRNA-381: A Potential Marker for Early Diagnosis of Gastric Cancer. *Yonsei Med J* 2019; **60**: 720-726 [PMID: [31347326](#) DOI: [10.3349/ymj.2019.60.8.720](#)]
- 106 **Huang ZS**, Guo XW, Zhang G, Liang LX, Nong B. The Diagnostic and Prognostic Value of miR-200c in Gastric Cancer: A Meta-Analysis. *Dis Markers* 2019; **2019**: 8949618 [PMID: [31089400](#) DOI: [10.1155/2019/8949618](#)]
- 107 **Jiang X**, Jiang M, Xu M, Xu J, Li Y. Identification of diagnostic utility and molecular mechanisms of circulating miR-551b-5p in gastric cancer. *Pathol Res Pract* 2019; **215**: 900-904 [PMID: [30732916](#) DOI: [10.1016/j.prp.2019.01.035](#)]
- 108 **Zhao G**, Jiang T, Liu Y, Huai G, Lan C, Li G, Jia G, Wang K, Yang M. Droplet digital PCR-based circulating microRNA detection serve as a promising diagnostic method for gastric cancer. *BMC Cancer* 2018; **18**: 676 [PMID: [29929476](#) DOI: [10.1186/s12885-018-4601-5](#)]
- 109 **Herrera-Pariente C**, Montori S, Llach J, Bofill A, Albeniz E, Moreira L. Biomarkers for Gastric Cancer Screening and Early Diagnosis. *Biomedicines* 2021; **9** [PMID: [34680565](#) DOI: [10.3390/biomedicines9101448](#)]
- 110 **Yu Z**, Rong Z, Sheng J, Luo Z, Zhang J, Li T, Zhu Z, Fu Z, Qiu Z, Huang C. Aberrant Non-Coding RNA Expressed in Gastric Cancer and Its Diagnostic Value. *Front Oncol* 2021; **11**: 606764 [PMID: [34295803](#) DOI: [10.3389/fonc.2021.606764](#)]
- 111 **Fu M**, Huang Z, Zang X, Pan L, Liang W, Chen J, Qian H, Xu W, Jiang P, Zhang X. Long noncoding RNA LINC00978 promotes cancer growth and acts as a diagnostic biomarker in gastric cancer. *Cell Prolif* 2018; **51** [PMID: [29271006](#) DOI: [10.1111/cpr.12425](#)]
- 112 **Liu J**, Wang J, Song Y, Ma B, Luo J, Ni Z, Gao P, Sun J, Zhao J, Chen X, Wang Z. A panel consisting of three novel circulating lncRNAs, is it a predictive tool for gastric cancer? *J Cell Mol Med* 2018; **22**: 3605-3613 [PMID: [29700972](#) DOI: [10.1111/jcmm.13640](#)]
- 113 **Zong W**, Feng W, Jiang Y, Ju S, Cui M, Jing R. Evaluating the diagnostic and prognostic value of serum long non-coding RNA CTC-497E21.4 in gastric cancer. *Clin Chem Lab Med* 2019; **57**: 1063-1072 [PMID: [30763257](#) DOI: [10.1515/ccbm-2018-0929](#)]
- 114 **Zhang G**, Xu Y, Wang S, Gong Z, Zou C, Zhang H, Ma G, Zhang W, Jiang P. LncRNA SNHG17 promotes gastric cancer progression by epigenetically silencing of p15 and p57. *J Cell Physiol* 2019; **234**: 5163-5174 [PMID: [30256413](#) DOI: [10.1002/jcp.27320](#)]
- 115 **Zhang G**, Xu Y, Zou C, Tang Y, Lu J, Gong Z, Ma G, Zhang W, Jiang P. Long noncoding RNA ARHGAP27P1 inhibits gastric cancer cell proliferation and cell cycle progression through epigenetically regulating p15 and p16. *Aging (Albany NY)* 2019; **11**: 9090-9110 [PMID: [31665700](#) DOI: [10.18632/aging.102377](#)]

- 116 **Lu X**, Lu J, Wang S, Zhang Y, Ding Y, Shen X, Jing R, Ju S, Chen H, Cong H. Circulating serum exosomal miR-92a-3p as a novel biomarker for early diagnosis of gastric cancer. *Future Oncol* 2021; **17**: 907-919 [PMID: [33533649](#) DOI: [10.2217/fon-2020-0792](#)]
- 117 **Zhao R**, Zhang Y, Zhang X, Yang Y, Zheng X, Li X, Liu Y. Exosomal long noncoding RNA HOTTIP as potential novel diagnostic and prognostic biomarker test for gastric cancer. *Mol Cancer* 2018; **17**: 68 [PMID: [29486794](#) DOI: [10.1186/s12943-018-0817-x](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

