REVIEW

Precision medicine for gastrointestinal cancer: Recent progress and future perspective

Tasuku Matsuoka, Masakazu Yashiro

Tasuku Matsuoka, Masakazu Yashiro, Department of Gastroenterological Surgery, Osaka City University Graduate School of Medicine, Osaka 5458585, Japan

Masakazu Yashiro, Oncology Institute of Geriatrics and Medical Science, Osaka City University Graduate School of Medicine, Osaka 5458585, Japan

Corresponding author: Masakazu Yashiro, MD, PhD, Associate Professor, Department of Surgical Oncology, Osaka City University Graduate School of Medicine, 1-4-3 Asahi-machi, Abeno-ku, Osaka 5458585, Japan. m9312510@med.osaka-cu.ac.jp

Abstract

Gastrointestinal (GI) cancer has a high tumor incidence and mortality rate worldwide. Despite significant improvements in radiotherapy, chemotherapy, and targeted therapy for GI cancer over the last decade, GI cancer is characterized by high recurrence rates and a dismal prognosis. There is an urgent need for new diagnostic and therapeutic approaches. Recent technological advances and the accumulation of clinical data are moving toward the use of precision medicine in GI cancer. Here we review the application and status of precision medicine in GI cancer. Analyses of liquid biopsy specimens provide comprehensive real-time data of the tumor-associated changes in an individual GI cancer patient with malignancy. With the introduction of gene panels including next-generation sequencing, it has become possible to identify a variety of mutations and genetic biomarkers in GI cancer. Although the genomic aberration of GI cancer is apparently less actionable compared to other solid tumors, novel informative analyses derived from comprehensive gene profiling may lead to the discovery of precise molecular targeted drugs. These progressions will make it feasible to incorporate clinical, genome-based, and phenotype-based diagnostic and therapeutic approaches and apply them to individual GI cancer patients for precision medicine.

Key words: Gastrointestinal cancer; Esophageal cancer; Gastric cancer; Colorectal cancer; Precision medicine; Liquid biopsy; Gene panel; Precision surgery; Biomarkers

Core tip: Gastrointestinal (GI) cancer is one of the most common leading causes of cancer death worldwide. Hence, any effort in early diagnosis, choice of appropriate therapeutic strategies can have a pivotal role in reducing the disease related mortalities.

Our review purpose to clarify the current advancement for precision medicine in GI cancer by elucidating the benefit of liquid biopsy, multiple gene panel, novel biomarkers and surgery in GI cancer.

INTRODUCTION

Precision medicine is a strategy designed to treat individual patients with the most suitable therapy at the most appropriate time based on the patient's biologic and molecular features, using the analyses of genes of the patient's cancer cells with next-generation sequencing (NGS). Such analyses can detect cancer-specific gene mutations, and molecular targeted drugs can be designed to be effective for one or more specific gene mutations. Precision medicine is thus a type of tailor-made and personalized therapy. The use of inappropriate medicine may not only do not benefit, but lead to cancer progression. As the accessibility to tumor genome sequencing technologies increases, genome-driven cancer treatment has emerged as a favorable approach[1]. The increasing number of patients who undergo multigene sequencing of their cancer can thus expect to be informed of their genomic alterations that could effectively be targeted with corresponding drugs[2].

Gastrointestinal (GI) cancer has a high tumor incidence and mortality rate worldwide[3]. Although colorectal cancer (CRC) could be largely managed, which results in long-term survival by a combination of drugs even in patients with widespread stage and GI lymphoma (*e.g.*, MALT) may also be associated with good response and prolonged survival, the overall prognosis of patients with advanced GI cancer remains poor. Precision medicine approaches are currently being applied with molecular targeted and immune-based therapeutics across a variety of malignancies, such as advanced melanoma and non-small-cell lung cancer (NSCLC)[4,5]. Although GI cancer has been investigated with biomarkers (*e.g.*, Ras and HER2 status), the development of biomarkers as well as targeted therapies for GI cancer has fallen behind compared to those developed for other malignancies. Analyses of liquid biopsies, multiple gene panels, and well-designed prospective trials are necessary to move the treatment of GI cancer forward. In this review, we summarize the progression of precision medicine in GI cancer in terms of specimens, assays, further biomarker information, surgery, and future perspectives.

LITERATURE SEARCH

We first conducted a search of the PubMed database for English articles using the medical subject heading terms in combination with "gastrointestinal cancer", "esophageal cancer", "gastric cancer", "colorectal cancer", "precision medicine", "liquid biopsy", "gene expression profiling", "biomarker", "molecular targeted therapy", and "gene panel". Relevant articles which were chosen from experimental studies and clinical trials since 1989 were involved as well as articles which were related to the disease processes. Articles which did not deal with the precision medicine of GI cancer were excluded from this review. Liver and pancreatic cancer and GI stromal tumor were not covered in this review due to the limited scope of the topic.

LIQUID BIOPSY

Conventionally, tissue biopsies have been used to access the molecular information of tumors, such as the histology and gene mutation[6]. However, the practical use of consecutive tissue biopsies to monitor for mutations is limited due to patient discomfort, pain, and risks associated with repeat tissue biopsies, and difficulty in capturing intra-tumor heterogeneity[6]. These shortcomings highlight the need for more innovative screening. One promising alternative to tissue biopsy is a new

approach that may change the principles of cancer treatment. The term 'liquid biopsy' refers to the analysis of tumor-derived biomarkers identified from biological fluids of patients with malignancies. Even though peripheral blood is the major specimen for the liquid biopsy approach, tumor biomarkers can be isolated from various body fluids including urine, pleural effusions, ascites, and cerebrospinal fluid[7].

The liquid biopsy technique been studied to a great extent and is attracting further attention as it leads to efficient therapeutic interventions, reducing the therapeutic cost and significantly improving patient outcomes and overall survival[8]. Analyses of liquid biopsy specimens can provide comprehensive real-time data of the tumor-associated changes in an individual patient with a malignancy. These data can be used for cancer screening, the detection of minimal residual disease, drug selection (including sensitivity to anticancer agents), monitoring recurrence, and monitoring the patient's response to targeted agents (including drug resistance)[9]. For example, an analysis of NSCLC patients' plasma for epidermal growth factor receptor (EGFR) to determine the existence of a T790M mutation is widely used[10]. Liquid biopsies could become a new tool with a significant impact on cancer therapy.

Studies of liquid biopsy methodology have focused on the analysis of circulating tumor cells (CTCs), circulating tumor free (cf) DNA or RNA, and tumor-derived extracellular vesicles (exosomes)[11]. For the most effective discussion of the details of liquid biopsy methodology, it is essential to understand the different types of cancer-related biomarkers and their respective molecular aspects.

CTCs
CTCs are tumor cells that are mainly detached from primary or metastatic lesions. They circulate through the body fluid to metastatic sites, either as a single cell or in clusters, which lead to the establishment of one or more secondary tumor foci[12]. The United States Food and Drug Administration (FDA)-cleared CellSearch system has enabled the enumeration of CTCs in cancer patients, and this has made it possible to determine disease activity and patients' treatment responses, which rely on the expressions of epithelial cell adhesion molecule and cytokeratin on cancer cells in blood[13]. The authors of a previous study described the establishment of colon CTC cultures and permanent cell lines which provided *in vivo* experimental models. These experiments may provide genetic and epigenetic information on tumor biology, and they may help assess the cells' sensitivity to anticancer drugs[13]. However, the number of CTCs is generally low in patients with GI cancer[14], and this limits the clinical applications of CTC analyses in site of the progression of various methods[14].

Circulating tumor DNA (ctDNA)
ctDNA has emerged as another component of liquid biopsies as a quantitative marker of tumor DNA, reflecting genomic alterations in the blood[15,16]. Compared to the detection of CTCs, the ctDNA-based approach provides more information about a patient-specific disease and treatment. Further benefits of the use of ctDNA as a marker is that ctDNA measurements can provide the real-time pathology of the patient's disease and higher sensitivity for the early detection of cancers[17]. A previous study showed a significantly broad range for ctDNA among patients with CRC (22–3922 ng/mL of blood) compared to healthy subjects (5-16 ng/mL of blood)[18]. Liquid biopsy analyses may take the place of tissue testing for assessing the mutational status of RAS in patients with CRC. The OncoBEAM RAS CRC Assay identifies the cfDNA of the most frequent *KRAS* and *NRAS* mutations by using BEAMing technology[19].

MicroRNAs (miRNAs)
In addition to the quantification of cfDNA, circulating transcriptome is also detectable in the serum of individuals with malignancies. The circulating transcriptome consists of both coding and noncoding RNAs, such as miRNAs or long noncoding RNAs (lncRNAs)[20]. Although RNA is generally unstable in blood, microRNA (miRNA) comprises stable, short, noncoding molecules made of 18-25 nucleotides. This endogenous, single-stranded RNA mediates the expression of nearly 30% of protein-encoding genes in humans[21]. MiRNAs can be analyzed by targeted or RNA sequencing methods, with miRNA signatures observed to be significantly deregulated in cancer patients compared to healthy parsons, and these analyses may become useful in cancer diagnosis and prognosis.

Exosomes
Exosomes are nanosized vesicles (40-150 nm)[22]. These small, membrane-bound vesicles can transport a number of biomolecules which lead to the modification of the activity of recipient cells[22]. Compared to CTCs and ctDNA, exosomes have advantages in several aspects, including their homogeneous size distribution. In

addition, due to the particular form of exosomes, they can be distinguishable by electron microscopy. Previous studies have obtained evidence that the exosome-mediated recruitment and manipulation of the tumor microenvironment is a critical step in the formation process of metastasis[23].

Liquid biopsy in GI cancer: Toward clinical applications

The clinical utility of a liquid biopsy has been studied in different clinical phases of GI cancer, from the screening for this disease to the identification of outcome factors in early GI cancer, the detection of minimal residual tumor, drug selection, and monitoring for recurrence and the patients' response to targeted agents. Current advances of liquid biopsy as diagnostic, monitoring and predictive markers in GI cancer are summarized in Table 1 and Table 2.

Cancer screening: The noninvasive nature of a liquid biopsy makes this approach ideal for the early detection of cancer. The evaluation of molecular biomarkers in early-stage cancer patients is necessary for the development of more personalized monitoring and treatment schedules. However, the possibility of detecting a malignancy at an early stage with a liquid biopsy is somewhat limited by the low concentration of circulating biomarkers associated with the low tumor burden. With respect to CRC, screening has been impacted using colonoscopy as the gold standard, mainly because of its high sensitivity and specificity for detecting cancerous and precancerous lesions. Despite its strengths, colonoscopy has certain disadvantages and limitations (*e.g.*, bowel preparation, sedation, aspiration, perforation, and splenic injury).Therefore, continued progress in novel assays, such as fecal immunochemical test, fecal DNA and other molecular markers, can be expected to further displace screening colonoscopy[24]. The Epi proColon® 2.0 assay (also referred to as the mSEPT9 assay), which was FDA-approved for CRC screening in April 2016, is a qualitative in vitro diagnostic polymerase chain reaction (PCR) test for the detection of mutated methylated septin9 DNA in EDTA plasma derived from patient whole-blood specimens[25].

Detection of minimal residual disease: One of the major fields of the application of liquid biopsy would be the detection of minimal residual disease in patients with surgically treatable tumors. The tumor burden of GI cancer at diagnosis is acknowledged as a pivotal factor of disease assessment before the beginning of treatment. A recent study indicated that somatic *KRAS*- and *BRAF*-mutated DNA in the peripheral blood of CRC patients may be a good estimate of CTCs and of surgical clearance of the disease[26].

Drug selection: Chemotherapy is often administered for patients with metastatic disease (*e.g.*, metastasis of regional lymph nodes) in a resected tumor specimen. Although there are a number of different chemotherapeutic agents that can be combined in a variety of chemotherapeutic regimens, the effect of chemotherapy on a specific patient cannot be predicted. Specific ctDNA identification has also been used as guidance for specific systemic chemotherapy and targeted agents. For instance, emerging RAS mutations during therapy with anti-EGFR antibody revealed resistance in patients with metastatic CRC (mCRC)[27]. Some studies found that undetectable low-frequency KRAS-mutant clones may be selected for anti-EGFR treatment by assessing ctDNA in the blood of mCRC patients during anti-EGFR therapy[28,29]. In similar, resistance to crizotinib has been emerged by using serial ctDNA measurements in gastric cancer (GC)[30].

Monitoring recurrence: One of the most challenging tasks in GI oncology is the identification of patients who will benefit from postoperative adjuvant chemotherapy after curative surgery. The histopathologic and molecular tumor features correlated with greater relapse risk (*e.g.*, the TNM classification) only imply a tendency for metastasis; they do not reveal whether metastatic cells were seeded during surgery. The identification of postoperative ctDNA is a definite sign that occult tumor cells remain in the patient.

The authors of a recent study proposed that in patients with CRC, the postoperative detection of ctDNA can be used to monitor the patients for residual disease and predict their future relapse risk with high probability[31]. Moreover, serial ctDNA serves as a tool for the early detection of recurrence during patient follow-up and for the patient's response to relapse intervention[31]. In CRC, the novel BCAT1/IKZF1 blood test was found to be more sensitive for recurrence compared to carcinoembryonic antigen (CEA) as a marker, and the likelihood of recurrence given a positive BCAT1/IKZF1 result was twice that compared to a positive CEA result[32].

Monitoring patients' responses to cytotoxic and targeted agents: The most

Table 1 Current progress of circulating tumor cells, circulating tumor DNA and stool DNA as diagnostic, monitoring and predictive markers in gastrointestinal cancer

Liquid biopsy	Patients/ controls	Organs	Source of fluid	Abnormalities	Technology	Target	Clinical setting	Ref.
CTCs	140/0	EC	B		FIHC	CK19, CD45	Prognosis	Li *et al*[82], 2016
CTCs	NA	EC	B		ISET	NA	Prognosis	Han *et al*[83], 2019
CTCs	116/31	GC	B		FAST-disc	EpCAM, CK, CD45-	Diagnostic	Kang *et al*[84], 2017
CTCs	81/31	GC	B		ISET	CK8/18/19, Vimentin, CD45	Prognostic	Zheng *et al*, 2017
CTCs	101/31	GC	B		CellSearch and IF-FISH	EpCAM, CK8, CK18, CK19, CD45-, HER2	Predictive	Mishima *et al*[86], 2017
CTCs	121/0	CRC	B		Cyttel method/imFISH	CD45	Prognostic	Wang *et al*[87], 2019
ctDNA	11/0	EC	P, T, NT	Mutation	WES and NGS panel		Diagnostic /Therapeutic	Luo *et al*[88], 2016
ctDNA	13/0	EC	P, T	Mutation	NGS panel		Predictive	Ueda *et al*[89], 2016
ctDNA	63/0	EC	P	Copy number status	qPCR	*CCND1*	Predictive	Komatsu *et al*[90], 2014
cfDNA	32/0	GC	P	Copy number status	cfDNA NGS testing	*ERBBB2*	Therapeutic	Kim *et al*[91], 2018
ctDNA	277/0	EC/GC	P, T	Mutation	MassARRAY	*TP53, PIK3CA, ERBB2, KRAS*	Diagnostic /Prognostic	Kato *et al*, 2018
ctDNA	70/0	GC	P, T	Mutation	NGS panel	*HER2*	Therapeutic	Gao *et al*[93], 2017
cfDNA	60/30	GC	P	Mutation	Droplet digital PCR	*HER2*	Therapeutic	Shoda *et al*[94], 2017
ctDNA	1/0	GC	P, T	Mutation	NGS panel	*MET*	Therapeutic	Du *et al*[30], 2017
ctDNA	230/0	CRC	B	Mutation	Safe-SeqS assay	NA	Prognostic	Tie *et al*[95], 2016
cfDNA	22/0	CRC	S	Mutation	NGS/dPCR	*TP53, KRAS, APC, PIK3CA, BRAF, FBXW7, NRAS*	Diagnostic /Prognostic	Furuki *et al*[96], 2018
cfDNA	3/0	CRC	P	Mutation	BEAMing	*RAS, BRAF, PIK3CA*	Predictive	Klein-Scory *et al*, 2018
cfDNA	20/0	CRC	P	Mutation	Droplet digital PCR	*APC, TP53, KRAS, PI3CA*	Predictive	Vandeputte *et al*[97], 2018
Stool DNA	71/22	CRC	Stool	Methylation	QIAamp DNA Stool Mini Kit	*SDC2*	Diagnostic	Oh *et al*[98], 2017

EC: Esophageal cancer; GC: Gastric cancer; CRC: Colorectal cancer; NT: Normal tissue; B: Blood; P: Plasma; S: Serum; T: Tumor tissue; PLF: Peritoneal lavage fluid; NGS: Next-generation sequencing; WES: Whole exome sequencing; FIHC: Fluorescent immunohistochemistry; NA: Not avaiable; EpCAM: Epithelial cell adhesion molecule.

potentially beneficial application of the liquid biopsy approach is the possibility of using this approach to monitor patients' therapeutic responses. In general, ctDNA has seemed to be an early biomarker that can be used to deduce the tumor burden of patients with CRC during chemotherapy and to predict the early therapeutic reaction. Molecular alterations that are related to drug resistance can be identified at an early stage by evaluating ctDNA, and this evaluation can be performed easily for the same patient at different time intervals.

A single-arm phase II trial (Erbitux Study of CPT11, Oxaliplatin, UFToral Targeted-therapy) was carried out in patients with previously untreated *KRAS* wild-type advanced CRC, using a regimen of irinotecan, oxaliplatin, and tegafur-uracil with leucovorin and cetuximab. The stratification of patients by the CTC count can identify the patients who might benefit the most from an intensive four-drug regimen, avoiding the use of high-toxicity regimens in low-CTC groups[33].

Table 2 Current progress of microRNAs and exosome as diagnostic, monitoring and predictive markers in gastrointestinal cancer

Liquid biopsy	Patients/ controls	Organs	Source of fluid	Abnormalities	Technology	Target	Clinical setting	Ref.
MiRNAs	231/0	EC	Peripheral blood lymphocytes	Polymorphism	SNPShot	KIAA0423 rs1053667, GEMIN3 rs197412	Prognostic	Faluyi *et al*[99], 2017
MiRNAs	3156/0	EC	S/P	Upregulation/ Downregulation	NA	miR-15a, miR-22, miR-31, miR-451, miR-506, miR-613, miR-1297	Diagnostic /Prognostic	Yao *et al*[100], 2018
MiRNAs	125/0	EC	S/P	Upregulation/ Downregulation	RT-PCR	miR-21, miR-223, miR-100, miR-25, miR-375	Diagnostic /Prognostic	Zhang *et al*[101], 2018
MiRNAs	250/538	GC	Gastric juice	Upregulation	miScript RT kit	miR-421, miR-21, miR-106a, miR-129	Diagnostic	Virgilio *et al*[102], 2018
MiRNAs	20/20	GC	S	Upregulation	TaqMan OpenArray assays	miR-331 and miR-21	Diagnostic	Sierzega *et al*[103], 2017
MiRNAs	The miRNA expression profile (GSE29298)	CRC	NA -	Upregulation	NA	miR-198, miR-765, miR-630, miR-371-5p, miR-575, miR-202, miR-513a-5p	Predictive	Zhu *et al*[104], 2017
MiRNAs	232/0	CRC	S	Upregulation	NA	miR-21, miR-29b, miR-92.	Diagnostic	Carter *et al*[105], 2017
MiRNAs	61/0	CRC	P	Upregulation	miRVANA PARIS kit	miR-20b, miR-29b, miR-155	Prognosis /Predivtive	Ulivi *et al*[106], 2018
Exosome	66/20	EC	P	Upregulation	AChE activity	Exosomes	Prognostic	Matsumoto *et al*[107], 2016
Exosome	30/0	GC	PLF	Upregulation	MiRNA microarray	miR-21, miR-1225-5p	Diagnostic /Therapeutic	Tokuhisa *et al*[108], 2015
Exosome	232/20	GC	P	Downregulation	Taqman microRNA assays	miR-23b	Prediction /Prognostic	Kumata *et al*[109], 2018
Exosome	227/28	CRC	S	Upregulation/ Downregulation	qRT-PCR microarray	miR-17, miR-18a, miR-19a, miR-19b, miR20a, miR-92a, hsa-miR-25-106b, hsa-miR-17-92a	Predictive /Prognosis	Matsumura *et al*[110], 2015
Exosome	108/0	CRC	S	Downregulation	The total exosome isolation kit	miR-548c-5p	Prognosis	Peng *et al*[111], 2018

EC: Esophageal cancer; GC: Gastric cancer; CRC: Colorectal cancer; NT: Normal tissue; B: Blood; P: Plasma; S: Serum; T: Tumor tissue; PLF: Peritoneal lavage fluid; NGS: Next-generation sequencing; WES: Whole exome sequencing; FIHC: Fluorescent immunohistochemistry; NA: Not avaibable.

GENE PANEL SEQUENCING IN GI CANCER

Sequencing is often performed to identify cancer-associated gene mutations in patients with advanced cancer. Sequencing panels allow the targeting of multiple genes simultaneously, quickly and accurately through comprehensive bioinformatics in order to exploit the useful information from a single study. The NGS of tumor sample DNA can lead to the optimal clinical treatment by offering diagnostic and/or prognostic data and by contributing to the selection of potential treatment regimens (*e.g.*, molecular-targeted and immune checkpoint blockade therapies). Recent advances in NGS has enabled the performance of whole-genome sequencing, whole-exome sequencing, whole-transcriptome sequencing and RNA sequencing, as well as the detection of enormous genetic aberrations[34].

Due to the progress in sequencing technologies, tissue comprehensive genome profiling has become more widely available in clinical practice. For example, the

current National Comprehensive Cancer Network guidelines recommend comprehensive genome profiling in patients with advanced non-small-cell lung adenocarcinoma[4]. Currently, NGS provides faster, cheaper, and more accurate whole-genome sequencing. The Cancer Genome Atlas has revealed the genome profiles of many cancers, including GI cancer[35,36]. Current progress of multiplex gene panels in GI cancer is summarized in Table 3.

Gene panaels contains the most commonly mutated genes or candidate actionable genes in many cancers. In CRC, *KRAS, BRAF, PIK3CA, TP53, CTNNB1, APC, SMAD4,* and *PTEN* are among the most commonly altered genes[37,38]. Patients with CRC in Japan were recently studied using an NGS - based comprehensive genomic panel test[39]. Significant differences in *ERBB2, APC, TP53, CDKN2A,* and *NRAS* mutations were identified in the Japanese patients compared to United States patients. Genomic alterations in DNA repair genes (*e.g., ATM, BLM, BRCA2, NBN, NRE11A*), which are observed in a significant proportion of CRC patients, were also detected. A novel, positive correlation between *APC* and *TP53* mutations with tumors that presented on the left side was reported. A study through deep sequencing in patients with mCRC presented that mutations in *TP53, KRAS, APC, KRAS, GNAS,* and *SMAD4* genes were detected in 69.3%, 39.6%, 23.7%, 16.8% and 13.8% patients, respectively. The mutations in *KRAS, GNAS,* and *SMAD4* were significantly associated with lung metastasis[40].

In GC, comprehensive genomic sequencing using a 435-gene panel in Japanese gastric cancers (GCs) showed that the most frequently mutated gene was *TP53* (53.1%), followed by *ARID1A* (15.9%) and *CDH1* (14.0%); *ERBB2* amplification (12.1%) was the most frequently observed somatic copy number alteration, followed by *CCNE1* (7.2%) and *KRAS* (5.8%) amplification[41]. Specific subcategories of GCs harbor characteristic genetic aberrations, such as somatic mutations in *RHOA* and a chimeric gene fusion of *CLDN18-ARHGAP26* in diffuse-type GCs[42,43]. The landscape of esophageal cancer (EC)-related gene mutations that regulate the cell cycle (*TP53, CCND1, CDKN2A, FBXW7*), epigenetic processes (*MLL2, EP300, CREBBP, TET2*), and the signaling pathways involving NOTCH (*NOTCH1, NOTCH3*), WNT (*FAT1, YAP1, AJUBA*) and receptor-tyrosine kinase-phosphoinositide 3-kinase (*PIK3CA, EGFR, ERBB2*) has been described[44].

Current advances in cancer genome analyses using NGS have revealed an increased mutation burden (a high rate of somatic mutation) in some solid tumors. In GI cancers, one of the leading causes of hypermutation-which is closely related to the generation of neo-antigens-is a defect in DNA mismatch repair (MMR), leading to microsatellite instability (MSI). Several research groups have stated that the tumor mutated burden correlates with the clinical response to immunotherapy[45,46]. GI cancer patients with MMR deficiency and a subsequent hypermutated phenotype achieved outstanding outcomes after anti-PD-1 therapy[47]. This highlights the clinical significance of identifying hypermutated tumors for immunotherapy treatment.

In CRC, mutations in transforming growth factor-beta (TGF-β) signaling genes and *BRAF* were markedly increased in hypermutated tumors[35]. Mutations in DNA polymerase D1 (*POLD1*) and DNA polymerase E (*POLE*) genes have also been described as a cause of hypermutated CRC[48]. The mutation rate of MSI-High GCs was significantly higher than that of MSS tumors[41]. *TGFBR2, ACVR2A, SMAD4,* and *ELF3* as well as the TGF-β pathway are frequently mutated, suggesting a pivotal role in GC pathogenesis, including MSI[43,49].

Given the advances in NGS, it may well become possible in the near future to identify the predominant cancer genes and pathways and tumor-specific genes and pathways. Several multigene assays are available to estimate the risk of relapse after definitive surgery, including the MSK-IMPACT, NCC Oncopanel, Todai OncoPanel, Oncomine Dx Target test, Foundation OneCDx, and CANCERPLEX.

A recent study using the Exiqon panel identified miR-20b-5p, miR-28-3p, miR-192-5p, miR-223-3p, and miR-296-5p as significantly upregulated in the serum of patients with EC, suggesting that these 5-miRNA signatures may serve as potential diagnostic biomarkers for ECs[50]. Similarly, the expressions of seven miRNAs (miR-103a-3p, miR-127-3p, miR-151a-5p, miR-17-5p, miR-181a-5p, miR-18a-5p, and miR-18b-5p) were significantly higher in CRC compared to normal controls[51].

BIOMARKERS FOR GI CANCER

Convincing biomarkers are a crucial aspect of precision medicine, used to match appropriate patients with the right treatment at the right time. Clinically relevant biomarkers are genetic, epigenetic, proteinic, or cellular alterations that are intrinsic to cancer cells. These biomarkers can be used to predict patients' responses to

Table 3 Current progress of multiplex gene panels in gastrointestinal cancer

Organs	Panel tested	Number of genes tested	Number of patients	The type of sample	Companion diagnostic indications	Ref.
EC	HiSeq2000	N/A	144	Tumor tissue DNA	*CCND1, CDKN2A, FBXW7, MLL2, EP300, CREBBP, TET2, NOTCH1, NOTCH3, FAT1, YAP1, AJUBA, PIK3CA, EGFR, ERBB2*	Sawada *et al*[44], 2016
EC	Exiqon miRNA qPCR panel	168miRNA	140	Serum miRNA	*miR-20b-5p, miR-28-3p, miR-192-5p, miR-223-3p, and miR-296-5p*	Huang *et al*[50], 2017
EC	Ion AmpliSeq Custom DNA Panel	12	27	Tumor tissue/Serum DNA	*BRAF, DDR2, ERBB2, HRAS, KEAP1, KRAS, NFE2L2, NRAS, PIK3CA, PTEN, RHOA*	Pasternack *et al*[112], 2018
GC	Illumina HiSeq 2000	38	138	Tumor tissue DNA	*RHOA, CDH1, PIK3CA, CTNNB1, APC, ARID1A, KMT2C, KRAS*	Kakiuchi *et al*[42], 2014
GC	Illumina HiSeq 2000	N/A	100	Tumor tissue DNA	*ARID1A, CDH1, MUC6, CTNNA2, GLI3, RNF43, RHOA*	Wang *et al*[43], 2014
GC	CANCERPLEX	435	207	Tumor tissue DNA	*ARID1A, CDH1, ERBB2, CCNE1, KRAS*	Ichikawa *et al*[41], 2017
GC	Ion-Proton sequencer	50	29	Tumor tissue DNA	*APC, CTNNB, KRAS, NPM1, FBXW7 ERBB2, FGFR2, KIT*	Yoshida *et al*[113], 2019
CRC	CANCERPLEX	415	201	Tumor tissue DNA	*ERBB2, APC, CDKN2A, NRAS, ATM, BLM, BRCA2, NBN, NRE11A*	Nagahashi *et al*[39], 2016
CRC	IT-PGM seqencing	22	77	Tumor tissue DNA	*RAS, PIK3CA, FBXW7, BRAF, SMAD4, MET, FGFR1*	Capalbo *et al*[114], 2019
CRC	OncoAim™ DNA panel	39	648	Tumor tissue DNA	*KRAS, APC, PIK3CA, SMAD4, BRAF, FBXW7, NRAS*	Wang *et al*[115], 2018
CRC	MiSeq	207	22	Tumor tissue DNA	*KRAS, PIK3CA, FBXW7, PTEN, SMAD4, BRAF, CTNNB1, NRAS*	Gao *et al*[116], 2019
CRC	cfDNA panel	14	101	Plasma cfDNA	*AKT1, BRAF, CTNNB1, EGFR, ERBB2, FBXW7, GNAS, KRAS, MAP2K1, NRAS, PIK3CA, SMAD4, APC,*	Osumi *et al*, 2018
CRC	TruSight Cancer Sequencing Panel	42	N/A	Blood ctDNA	*MLH1, MSH6, PMS2 APC, SMAD4, TP53, BRIP1, CHEK2, MUTYH, HNF1A, XPC*	Seifert *et al*[117], 2019

TP53 was commonly implicated in all references except 28035762, 30297788 and 30523343 (PMID)[50,112,117]. EC: Esophageal cancer; GC: Gastric cancer; CRC: Colorectal cancer; NGS: Next-generation sequencing; FFPE: Formalin-fixed paraffin-embedded; N/A: Not available; EBV: Epstein-Barr virus; MSI: Microsatellite instability; NGS: Next-generation sequencing.

chemotherapy, targeted therapy, or immune checkpoint inhibitors. To date, the most

reliable molecular marker in clinical practice is the *KRAS* gene for patients receiving EGFR - targeted therapy for CRC metastatic disease and HER2 overexpression for patients with HER2-positive GC[52,53]. Detection of BRAF mutation status was also recommended due to the ineffectiveness of anti-EGFR therapy for CRC patients with BRAF mutations[54]. Although there is a crucial need for novel diagnostic and prognostic biomarkers to improve GI cancer prognosis, these tools are still being investigated. In this section, we summarize the current advances of biomarkers in GI cancer, with a focus on the development of new biomarkers that are of predictive and/or prognostic values.

Another biomarker for therapeutic target in GI cancer may be *MET*. A multicenter phase II study demonstrated antitumor activity of small-molecule MET inhibitor was shown in MRT-amplifier gastric/gastroesophageal/esophageal adenocarcinoma[55]. A recent study using whole-exome sequencing characterized KDR/VEGFR2 somatic mutations as potential genetic biomarkers of patients' responses to antiangiogenic cancer therapies[56]. Interestingly, a recent cohort study presented that ALK, ROS1, and NTRK rearrangements classified a new subtype of mCRC with particularly poor outcome[57]. Rearrangements of ALK, ROS1, and NTRK were more frequently observed in elderly patients with right-sided tumors and node-spreading, RAS wild-type, and MSI-high cancers. As noted above, ctDNA and RNA-based biomarkers provide high specificity and are ideal as predictive markers for monitoring patients' responses to chemotherapy as well as tumor progression[52]. MMR-deficiency deficiency has emerged as another meaningful biomarker. MMR deficiency has been shown to be positively prognostic for outcome in patients with GC and CRC[58,59]. Notably, MMR deficiency is a variety of cancer predictor for response to anti-PD-1/PD-L1 blockade therapies[60]. Tumor-infiltrating lymphocytes (TILs) are the major type of infiltrating immune cells[36]. The density of TILs is considered to be an indication of the host immune response against tumor cells. To date, the density of TILs have been investigated as a useful prognostic factor in GI cancer[61]. Collectively, research has moved towards the identification of mutations in key genes involved in the progression of GI cancer. In the meanwhile, large-scale prospective clinical studies for evaluating the sensitivity and specificity of these biomarkers are required before their application in clinical practice, due to their low mutational burden and insufficient specificity. The approved biomarkers and candidate biomarkers of GI cancer are summarized in Table 4.

Future research may identify biomarkers that enable cost-effective and noninvasiveness treatments for GI cancer. It is also necessary to determine the best prognostic panel of biomarkers and to find predictive biomarkers to help in the selection of the most suitable therapy.

PRECISION SURGERY IN GI CANCER

Precision medicine is a general concept and is thus not limited to genetic detection. Although surgery is the most effective treatment for localized GI cancer and is often curative, an insufficient removal of a tumor results in secondary tumor foci for which the existing chemotherapeutics and/or radiation would be ineffective. In this finally section, we would like to discuss the progress of the precision treatment of GI cancers through surgery.

Fluorescence-guided surgery for GI cancer

Surgery has been said to provide the most benefit for patients with GI cancer. When R0 resection was carried out in a series of GI cancer patients, the local 5-year relapse rate was significantly improved[62]. The reported rates of local recurrence and distant metastasis were high at 2.6% and 30% of patients who underwent an R0 resection[63,64]. Real-time imaging to find positive surgical margins during a surgical procedure may be useful to diminish the rates of recurrence. Intraoperative fluorescence imaging, or fluorescence-guided surgery (FGS), can offer highly reliable tumor visualization for localization and margin identification[65]. The targeted fluorescent labeling of cancer cells may therefore alter the ways we detect and treat cancer.

Indocyanine green (ICG) is applied clinically to define liver tumor margins and biliary anatomy. The authors of a recent meta-analysis stated that intraoperative ICG fluorescence angiography has been demonstrated to reduce anastomotic leakage rates after colorectal resection[66]. In CRC, ICG fluorescence lymphangiography can be used to detect the primary tumor, its lymphatic drainage, and potentially malignant nodes, which may change the operative plan[67]. FGS can thus serve as a surgical guide with the potential to provide benefits for patients with GI cancer.

Sentinel node navigation surgery

Table 4 Current progress of biomarkers associated with diagnosis, prognosis, prediction of therapeutic response in gastrointestinal cancer (excluding liquid biopsy)

Market	Tumor type	Alteration	Clinical setting	Ref.
HER2	GC, CRC	Amplification, Overexpression	Predictive	Bang *et al*[118], 2010; Sartore-Bianchi *et al*[119], 2016
KRAS	CRC	Activating mutation within catalytic RAS domain	Predictive	Wormald *et al*, 2013; Febbo *et al*, 2011; Schmoll *et al*[122], 2012; Locker *et al*[123], 2006
NRAS,	CRC	Overexpression	Prognostic/Predictive	Hu *et al*[124], 2018
BRAF	CRC	Mutation	Prognostic/Therapeutic	Tie *et al*[54], 2011
KDR	CRC	Mutation	Predictive	Loaiza-Bonilla *et al*[125], 2016
VEGF-D	CRC	Overexpression	Predictive	Tabernero *et al*[126], 2018
AKT	GC	Activation	Predictive	Ito *et al*[127], 2017
PTEN	GC	Downregulation	Predictive	Kim *et al*, 2017
NTRK fusion	CRC	Overexpression	Predictive	Drilon *et al*[129], 2018
ALK	CRC	Rearrangement	Prognostic	Pietrantonio *et al*[57], 2017
POLE	CRC	Mutation	Predictive	Domingo *et al*[130], 2016
MMR	GC, CRC		Predictive	Llosa *et al*[131], 2015
PD-L1	CRC	Mutatoin	Prognostic	Eriksen *et al*[132], 2019
Tumor infiltrating lymphocyte	GC, CRC	Overexpression	Prognostic	Iseki *et al*[133], 2018
CagA	GC	Upregulated	Diagnostic	Saju *et al*[134], 2016
Gastrokine 1	GC	Downregulated	Diagnostic	Altieri *et al*[135], 2017
MEK	CRC	Activation	Predictive	Martinelli *et al*[136], 2017
PIK3CA	CRC	Mutation	Prognostic/ Therapeutic	Jehan *et al*[137], 2019; Schmoll *et al*[122], 2012
TP53	EC, GC, CRC	Mutation	Prognostic	Schmoll *et al*[122], Guo *et al*[138], 2017
CTNNB1	CRC EC, GC	Mutation Overexpression	Prognostic Prognostic	Gao *et al*[116], 2019; Szász *et al*[139], 2016; Ishiguro *et al*[140], 2016
APC	CRC	Mutation	Prognostic	Liang *et al*[141], 2017; Chen *et al*[142], 2013
IGFR-!R	CRC	Upregulation	Prognostic	Codony-Servat *et al*[143], 2017
SFRP2	CRC	Hypermethylation	Diagnostic/Prognostic	Tang *et al*, 2011
UGT1A1	CRC	Hypermethylation	Predictive	Crea *et al*[145], 2011
SMAD4,	EC, GC, CRC	Downregulation	Prognostic/Predictive	Salem *et al*[146], 2018; Wasserman *et al*[147], 2019
MET	EC, GC	Amplificatoin	Predictive	Van Cutsem *et al*[55], 2018
CDKN2A	EC,	Methylation	Diagnostic	Zhou *et al*, 2017
ATM	GC, CRC	Mutaion/Downregulation	Prognostic	Randon *et al*[149], 2019; Han *et al*[83], 2017
BLM,	CRC	Mutaion/Polymorphisms	Diagnostic	de Voer *et al*[150], 2015; Frank *et al*[151], 2010
BRCA1/2,	CRC	Mutaion	Diagnostic	Oh *et al*[152], 2018
ARID1A	GC	Mutation	Predictive	Wei *et al*[153], 2014
	CRC	Overexpresion	Prognostic	Ronchetti *et al*[154], 2017
CDH1	GC	Mutation	Diagnostic	Hansford *et al*[155], 2015
	CRC	Polymorphism	Diagnostic	Grünhage *et al*[156], 2008
CCNE1	GC	Amplification	Therapeutic	Ooi *et al*[157], 2017
RHOA	GC, CRC	Overexpression	Prognostic	Chang *et al*[158], 2016
CCND1	EC	Amplification/Overexpression	Diagnostic	Hu *et al*[159], 2016
	CRC	Polymorphism	Diagnostic	Grünhage *et al*[156], 2008
FBXW7	CRC	Mutation	Prognostic	Korphaisarn *et al*[160], 2017
NOTCH1	EC	Mutation	Prognostic	Song *et al*[161], 2016
	CRC	Gene copy number	Prognostic	Arcaroli *et al*[162], 2016
NOTCH3	CRC	Overexpression	Predictive	Ozawa *et al*[163], 2014

| YAP1 | EC, GC, CRC | Overexpression | Prognostic | Zhang *et al*[164], 2018 |

EC: Esophageal cancer; GC: Gastric cancer; CRC: Colorectal cancer; MMR: mismatch repair; PD-L1: programmed death ligand 1; PD-1: programmed death-1; POLE: DNA polymerase 1; HER2: human epidermal growth factor receptor type2; EGFR: epidermal growth factor receptor.

Many investigators have described the potential usage of sentinel node (SN) navigation surgery in patients with early-stage EC and GC who have no lymph node metastasis preoperatively[68,69]. In early stage upper GI cancer, SN mapping provides significant information about an individual patient's metastatic situation and enables the modification of the patient's surgery. Several single-institution investigations have noted pivotal benefits of SN mapping for early EC, especially when using the radio-guided method[70]. Clinically T1 esophageal cancers were suitable targets for SN mapping, because in T3 or T4 tumors as well as those with lymph node metastasis, the original lymphatic routes can be obstructed, which leads to a high rate of false-negative outcomes. SNs were detected in 95% of patients, and the accuracy was as high as 94%[71]. Moreover, SNs were identified widely from the cervical area to the abdominal area, which allows the partial resection of the distal esophagus *via* the laparoscopic trans-hiatal approach without extensive mediastinal lymph node dissection when the SNs are identified only in the abdominal region and are pathologically negative in cT1N0 cases of the distal esophagus[71]. The precise indications for laparoscopic surgeries (*e.g.*, partial resection and segmental gastrectomy for cT1N0 GC) based on the SN status could be individually determined. SN navigation surgery could be a strategy to ensure a better prognosis than conventional operative strategies.

FUTURE PERSPECTIVES

Precision medicine is the application of the latest biological technology that takes into account the patient's living environment along with the patient's clinical data (as well as molecular imaging techniques and bioinformatics technology) to achieve accurate diagnoses and treatments. It is difficult to determine the precise clinical and biological significance for each individual patient because of the inconsistency in biological features on the human genome[71]. Moreover, the complexity of the NGS data-analysis process makes it impractical for oncologists to understand the meanings and uncertainties of the results easily. A systematic and easily interpreted system with an accessible database is immediately necessary for detecting specific genomic alterations and genotype-matched therapeutic options with clinical practice. Although it would be impossible to completely prepare a treatment plan for each individual case, more suitable treatment based on the unique genomic changes of each patient's tumor could be adapted.

The recent progress in the use of precision medicine in GI cancer was summarized in this review. Regarding treatment, we expect that the narrowing down of the number of eligible patients in accord with dose setting, schedule setting, and the selection of concomitant drugs based on the mechanism of molecular targeted agents will lead to effective therapy customized to each individual. For GI cancers, there is an urgent need for preclinical models to identify and select suitable target for therapy. Recent developments in stem cell biology have enabled the in vitro generation of complex three-dimensional (3D) multicellular stem cell-derived constructs that mimic their corresponding organ *in vivo*[72]. These organ-like structures denoted as organoids. Patient-derived organoids (PDOs) may be an attractive candidate for an appropriate cancer model that is able to identify the most effective therapy for individual patients with currently available drugs in a timely manner, but also the future of regenerative medicine. therapies, 3D organoids have been advanced for several cancer types and been shown to effectively recapitulate tumor specific characteristics, which may lead to facilitate the development of precision medicine[73]. A recent study demonstrated that the feasibility of GC PODs from endoscopic biopsies and also suggest that endoscopic-derived PDOs may serve as an precise surrogates of the primary lesion of tumor, which may lead to possess the superiority to drug sensitivity screening and precision therapies[74]. Other study using patient-derived CRC organoids presented that of all RASGTPases activating proteins, only neurofibromin (NF1) deficiency facilitate cell survival and prompted EGF-independent tumor cell growth in human CRC samples, suggesting that NF1 protein levels should be measured in CRCs prior to initiate of targeted therapy against the MAPK pathway[75].

Our understanding of the fundamental biology of GI cancer is continually advancing. GI cancer is a heterogeneous disease with significant differences between

patients in prognosis and therapeutic response. Part of these differences can be explained by the molecular diversity detected in GI cancer. So as to provide a more overall insight into this complexity, biologically distinct molecular subtypes of GI cancer based on gene expression analyses were defined and validated. EC is classified into three distinct molecular subgroups based on gene analysis findings[76]. The first subgroup (ESCC1) includes tumors that respond poorly to chemoradiotherapy, leading to poor prognoses. The principal gene alteration identified is NRF2 pathway disruption. The second subgroup is ESCC2, characterized by the mutation of *NOTCH1*, *ZNF750*, *KDM6A*, *KDM2D*, *PTEN*, *PIK3R1*, and *CDK6* amplification. This subgroup is also associated with white blood cell infiltration. The last molecular subgroup (ESCC3) is characterized by PI3K pathway disruption. Similarly, GC is sub-classified into four major subtypes based on the molecular pattern; the EBV group, MSI group, chromosomal instability group, and genomically stable group[36]. In CRC, four consensus molecular subtypes (CMS) were shown. CMS1 is enriched for MSI tumors that reveal marked immune activation. CMS2 reflects the classical subtype encompassing higher CIN and strong WNT/MYC-driven tumors with epithelial characteristics, whereas CMS3 is enriched for *KRAS*-mutated tumors with activation of metabolic pathways. CMS4 has mesenchymal features, shows a high stromal content and activation of TGF-β and VEGFR pathways[77]. Apparent clinical distinctions are distinct with poor prognosis for CMS4 and a relatively good prognosis for CMS1. A study classifying CRC by both tumor side and location using NGS panel presented that RAS mutations are seen in 70% of cecal tumors but only 57% of ascending colon and 43% of hepatic flexure tumors. BRAFV600 mutations occur in 10% of cecal, 16% of ascending colon, and 22% of hepatic flexure tumors. PIK3CA mutations are seen in 26% of descending colon but only 14% of sigmoid and 9% of rectosigmoid tumors. CTNNB1 mutations are almost absent in the sigmoid (1%), rectosigmoid junction (0%), and rectum (1%), but are still present in the descending colon (6%). This study also revealed increasing rates of CMS2 moving from right to left, accompanied by a fall in CMS1, while CMS3 and CMS4 were relatively stable when we compared CMS by tumor side[78]. In summary, the region from the sigmoid colon to the rectum appears unique and the transverse colon appears distinct from other right sided locations.

Another study define the colorectal cancer intrinsic subtypes (CRIS) distinguished by specific molecular, functional and pathogenic features; (1) CRIS-A: Mucinous subtype, glycolytic metabolism, with marked MSI, mutated *BRAF* or *KRAS*; (2) CRIS-B: Active TGF-β signaling, epithelial–mesenchymal transition, bad prognosis; (3) CRIS-C: High EGFR signaling, and to EGFR inhibitors (*i.e.*, cetuximab); (4) CRIS-D: High WNT signaling, *IGF2* gene amplification/ overexpression; and (5) CRIS-E: Paneth-like phenotype and *TP53*-mutated genotype[79]. Recent work revealed that subtype-specific analysis can be used to predict therapy response, which provides a great opportunity to improve patients' management regarding precision medicine[80,81].

Although subclassification systems proposed for each GI cancer type have also possessed major challenges and caused important questions that need to be further investigated still it is applied for patient care timely, there is the possibility that these subgroup analyses revolutionize our approach towards precision medicine. Advances in tumor genomics and the immunologic landscape based on "big data" will allow the identification of expanding indications for molecular target drugs and chemotherapy in GI cancer and its predictive biomarkers. Clinical trials for targeted therapies, coupled with genomic profiling for optimum patient selection, are required to demonstrate clinical utility, including treatment outcomes and cost-effectiveness. Investigations of the safety and efficacy of clinical cancer therapies may reveal novel research directions for treating GI cancer. Increasing our knowledge of the signaling that mediates the driver mutations in GI cancer will improved our understanding of GI cancer and serve to guide future precision medicine applications for this disease. At present, we are in the very early phases of this transition towards precision and personalized medicine. We hope that this review can be a guideline for clinical and bench investigators to further develop precision medicine.

REFERENCES

1   **Hyman DM**, Taylor BS, Baselga J. Implementing Genome-Driven Oncology. *Cell* 2017; **168**: 584-599 [PMID: 28187282 DOI: 10.1016/j.cell.2016.12.015]
2   **Zehir A**, Benayed R, Shah RH, Syed A, Middha S, Kim HR, Srinivasan P, Gao J, Chakravarty D, Devlin SM, Hellmann MD, Barron DA, Schram AM, Hameed M, Dogan S, Ross DS, Hechtman JF. DeLair DF, Yao J, Mandelker DL, Cheng DT, Chandramohan R, Mohanty AS, Ptashkin RN, Jayakumaran G, Prasad M, Syed MH, Rema AB, Liu ZY, Nafa K, Borsu L, Sadowska J, Casanova J, Bacares R, Kiecka IJ,

Razumova A, Son JB, Stewart L, Baldi T, Mullaney KA, Al-Ahmadie H, Vakiani E, Abeshouse AA, Penson AV, Jonsson P, Camacho N, Chang MT, Won HH, Gross BE, Kundra R, Heins ZJ, Chen HW, Phillips S, Zhang H, Wang J, Ochoa A, Wills J, Eubank M, Thomas SB, Gardos SM, Reales DN, Galle J, Durany R, Cambria R, Abida W, Cercek A, Feldman DR, Gounder MM, Hakimi AA, Harding JJ, Iyer G, Janjigian YY, Jordan EJ, Kelly CM, Lowery MA, Morris LGT, Omuro AM, Raj N, Razavi P, Shoushtari AN, Shukla N, Soumerai TE, Varghese AM, Yaeger R, Coleman J, Bochner B, Riely GJ, Saltz LB, Scher HI, Sabbatini PJ, Robson ME, Klimstra DS, Taylor BS, Baselga J, Schultz N, Hyman DM, Arcila ME, Solit DB, Ladanyi M, Berger MF. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. *Nat Med* 2017; **23**: 703-713 [PMID: 28481359 DOI: 10.1038/nm.4333]

3   **Parkin DM**, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74-108 [PMID: 15761078 DOI: 10.3322/canjclin.55.2.74]

4   **Ettinger DS**, Wood DE, Aisner DL, Akerley W, Bauman J, Chirieac LR, D'Amico TA, DeCamp MM, Dilling TJ, Dobelbower M, Doebele RC, Govindan R, Gubens MA, Hennon M, Horn L, Komaki R, Lackner RP, Lanuti M, Leal TA, Leisch LJ, Lilenbaum R, Lin J, Loo BW, Martins R, Otterson GA, Reckamp K, Riely GJ, Schild SE, Shapiro TA, Stevenson J, Swanson SJ, Tauer K, Yang SC, Gregory K, Hughes M. Non-Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2017; **15**: 504-535 [PMID: 28404761 DOI: 10.6004/jnccn.2017.0050]

5   **Gladfelter P**, Darwish NHE, Mousa SA. Current status and future direction in the management of malignant melanoma. *Melanoma Res* 2017; **27**: 403-410 [PMID: 28800028 DOI: 10.1097/CMR.0000000000000379]

6   **Crowley E**, Di Nicolantonio F, Loupakis F, Bardelli A. Liquid biopsy: monitoring cancer-genetics in the blood. *Nat Rev Clin Oncol* 2013; **10**: 472-484 [PMID: 23836314 DOI: 10.1038/nrclinonc.2013.110]

7   **Mader S**, Pantel K. Liquid Biopsy: Current Status and Future Perspectives. *Oncol Res Treat* 2017; **40**: 404-408 [PMID: 28693023 DOI: 10.1159/000478018]

8   **Gao Y**, Zhang K, Xi H, Cai A, Wu X, Cui J, Li J, Qiao Z, Wei B, Chen L. Diagnostic and prognostic value of circulating tumor DNA in gastric cancer: a meta-analysis. *Oncotarget* 2017; **8**: 6330-6340 [PMID: 28009985 DOI: 10.18632/oncotarget.14064]

9   **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, Dobbyn 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, Bettegowda C, Diaz LA, 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]

10   **Díaz-Serrano A**, Gella P, Jiménez E, Zugazagoitia J, Paz-Ares Rodríguez L. Targeting EGFR in Lung Cancer: Current Standards and Developments. *Drugs* 2018; **78**: 893-911 [PMID: 29915896 DOI: 10.1007/s40265-018-0916-4]

11   **Zhang W**, Xia W, Lv Z, Ni C, Xin Y, Yang L. Liquid Biopsy for Cancer: Circulating Tumor Cells, Circulating Free DNA or Exosomes? *Cell Physiol Biochem* 2017; **41**: 755-768 [PMID: 28214887 DOI: 10.1159/000458736]

12   **Ferreira MM**, Ramani VC, Jeffrey SS. Circulating tumor cell technologies. *Mol Oncol* 2016; **10**: 374-394 [PMID: 26897752 DOI: 10.1016/j.molonc.2016.01.007]

13   **Riethdorf S**, Fritsche H, Müller V, Rau T, Schindlbeck C, Rack B, Janni W, Coith C, Beck K, Jänicke F, Jackson S, Gornet T, Cristofanilli M, Pantel K. Detection of circulating tumor cells in peripheral blood of patients with metastatic breast cancer: a validation study of the CellSearch system. *Clin Cancer Res* 2007; **13**: 920-928 [PMID: 17289886 DOI: 10.1158/1078-0432.CCR-06-1695]

14   **Sumanasuriya S**, Lambros MB, de Bono JS. Application of Liquid Biopsies in Cancer Targeted Therapy. *Clin Pharmacol Ther* 2017; **102**: 745-747 [PMID: 28755443 DOI: 10.1002/cpt.764]

15   **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]

16   **Diaz LA**, Bardelli A. Liquid biopsies: genotyping circulating tumor DNA. *J Clin Oncol* 2014; **32**: 579-586 [PMID: 24449238 DOI: 10.1200/JCO.2012.45.2011]

17   **Bettegowda C**, Sausen M, Leary RJ, Kinde I, Wang Y, Agrawal N, Bartlett BR, Wang H, Luber B, Alani RM, Antonarakis ES, Azad NS, Bardelli A, Brem H, Cameron JL, Lee CC, Fecher LA, Gallia GL, Gibbs P, Le D, Giuntoli RL, Goggins M, Hogarty MD, Holdhoff M, Hong SM, Jiao Y, Juhl HH, Kim JJ, Siravegna G, Laheru DA, Lauricella C, Lim M, Lipson EJ, Marie SK, Netto GJ, Oliner KS, Olivi A, Olsson L, Riggins GJ, Sartore-Bianchi A, Schmidt K, Shih lM, Oba-Shinjo SM, Siena S, Theodorescu D, Tie J, Harkins TT, Veronese S, Wang TL, Weingart JD, Wolfgang CL, Wood LD, Xing D, Hruban RH, Wu J, Allen PJ, Schmidt CM, Choti MA, Velculescu VE, Kinzler KW, Vogelstein B, Papadopoulos N, Diaz LA JrDetection of circulating tumor DNA in early- and late-stage human malignancies. *Sci Transl Med* 2014; **6**: 224ra24 [PMID: 24553385 DOI: 10.1126/scitranslmed.3007094]

18   **Schwarzenbach H**, Stoehlmacher J, Pantel K, Goekkurt E. Detection and monitoring of cell-free DNA in blood of patients with colorectal cancer. *Ann N Y Acad Sci* 2008; **1137**: 190-196 [PMID: 18837946 DOI: 10.1196/annals.1448.025]

19   **García-Foncillas J**, Alba E, Aranda E, Díaz-Rubio E, López-López R, Tabernero J, Vivancos A. Incorporating BEAMing technology as a liquid biopsy into clinical practice for the management of colorectal cancer patients: an expert taskforce review. *Ann Oncol* 2017; **28**: 2943-2949 [PMID: 28945877 DOI: 10.1093/annonc/mdx501]

20   **Tóth K**, Barták BK, Tulassay Z, Molnár B. Circulating cell-free nucleic acids as biomarkers in colorectal cancer screening and diagnosis. *Expert Rev Mol Diagn* 2016; **16**: 239-252 [PMID: 26652067 DOI: 10.1586/14737159.2016.1132164]

21   **Bartel DP**. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 2004; **116**: 281-297 [PMID: 14744438 DOI: 10.1016/S0092-8674(04)00045-5]

22   **Munson P**, Shukla A. Exosomes: Potential in Cancer Diagnosis and Therapy. *Medicines (Basel)* 2015; **2**: 310-327 [PMID: 27088079 DOI: 10.3390/medicines2040310]

23   **Rahbari M**, Rahbari N, Reissfelder C, Weitz J, Kahlert C. Exosomes: novel implications in diagnosis and treatment of gastrointestinal cancer. *Langenbecks Arch Surg* 2016; **401**: 1097-1110 [PMID: 27342853 DOI: 10.1007/s00423-016-1468-2]

24   **van Lanschot MC**, Carvalho B, Coupé VM, van Engeland M, Dekker E, Meijer GA. Molecular stool

testing as an alternative for surveillance colonoscopy: a cross-sectional cohort study. *BMC Cancer* 2017; **17**: 116 [PMID: 28173852 DOI: 10.1186/s12885-017-3078-y]

25   **Issa IA**, Noureddine M. Colorectal cancer screening: An updated review of the available options. *World J Gastroenterol* 2017; **23**: 5086-5096 [PMID: 28811705 DOI: 10.3748/wjg.v23.i28.5086]

26   **Norcic G**, Jelenc F, Cerkovnik P, Stegel V, Novakovic S. Role of specific DNA mutations in the peripheral blood of colorectal cancer patients for the assessment of tumor stage and residual disease following tumor resection. *Oncol Lett* 2016; **12**: 3356-3362 [PMID: 27900004 DOI: 10.3892/ol.2016.5078]

27   **Klein-Scory S**, Maslova M, Pohl M, Eilert-Micus C, Schroers R, Schmiegel W, Baraniskin A. Significance of Liquid Biopsy for Monitoring and Therapy Decision of Colorectal Cancer. *Transl Oncol* 2018; **11**: 213-220 [PMID: 29367069 DOI: 10.1016/j.tranon.2017.12.010]

28   **Morelli MP**, Overman MJ, Dasari A, Kazmi SM, Mazard T, Vilar E, Morris VK, Lee MS, Herron D, Eng C, Morris J, Kee BK, Janku F, Deaton FL, Garrett C, Maru D, Diehl F, Angenendt P, Kopetz S. Characterizing the patterns of clonal selection in circulating tumor DNA from patients with colorectal cancer refractory to anti-EGFR treatment. *Ann Oncol* 2015; **26**: 731-736 [PMID: 25628445 DOI: 10.1093/annonc/mdv005]

29   **Diaz LA**, Williams RT, Wu J, Kinde I, Hecht JR, Berlin J, Allen B, Bozic I, Reiter JG, Nowak MA, Kinzler KW, Oliner KS, Vogelstein B. The molecular evolution of acquired resistance to targeted EGFR blockade in colorectal cancers. *Nature* 2012; **486**: 537-540 [PMID: 22722843 DOI: 10.1038/nature11219]

30   **Du J**, Wu X, Tong X, Wang X, Wei J, Yang Y, Chang Z, Mao Y, Shao YW, Liu B. Circulating tumor DNA profiling by next generation sequencing reveals heterogeneity of crizotinib resistance mechanisms in a gastric cancer patient with MET amplification. *Oncotarget* 2017; **8**: 26281-26287 [PMID: 28460431 DOI: 10.18632/oncotarget.15457]

31   **Scholer LV**, Reinert T, Ørntoft MW, Kassentoft CG, Árnadóttir SS, Vang S, Nordentoft I, Knudsen M, Lamy P, Andreasen D, Mortensen FV, Knudsen AR, Stribolt K, Sivesgaard K, Mouritzen P, Nielsen HJ, Laurberg S, Ørntoft TF, Andersen CL. Clinical Implications of Monitoring Circulating Tumor DNA in Patients with Colorectal Cancer. *Clin Cancer Res* 2017; **23**: 5437-5445 [PMID: 28600478 DOI: 10.1158/1078-0432.CCR-17-0510]

32   **Young GP**, Pedersen SK, Mansfield S, Murray DH, Baker RT, Rabbitt P, Byrne S, Bambacas L, Hollington P, Symonds EL. A cross-sectional study comparing a blood test for methylated BCAT1 and IKZF1 tumor-derived DNA with CEA for detection of recurrent colorectal cancer. *Cancer Med* 2016; **5**: 2763-2772 [PMID: 27726312 DOI: 10.1002/cam4.868]

33   **Krebs MG**, Renehan AG, Backen A, Gollins S, Chau I, Hasan J, Valle JW, Morris K, Beech J, Ashcroft L, Saunders MP, Dive C. Circulating Tumor Cell Enumeration in a Phase II Trial of a Four-Drug Regimen in Advanced Colorectal Cancer. *Clin Colorectal Cancer* 2015; **14**: 115-22.e1-2 [PMID: 25680623 DOI: 10.1016/j.clcc.2014.12.006]

34   **Mäbert K**, Cojoc M, Peitzsch C, Kurth I, Souchelnytskyi S, Dubrovska A. Cancer biomarker discovery: current status and future perspectives. *Int J Radiat Biol* 2014; **90**: 659-677 [PMID: 24524284 DOI: 10.3109/09553002.2014.892229]

35   **Cancer Genome Atlas Network**. Comprehensive molecular characterization of human colon and rectal cancer. *Nature* 2012; **487**: 330-337 [PMID: 22810696 DOI: 10.1038/nature11252]

36   **Cancer Genome Atlas Research Network**. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014; **513**: 202-209 [PMID: 25079317 DOI: 10.1038/nature13480]

37   **Pino MS**, Chung DC. The chromosomal instability pathway in colon cancer. *Gastroenterology* 2010; **138**: 2059-2072 [PMID: 20420946 DOI: 10.1053/j.gastro.2009.12.065]

38   **Ciombor KK**, Wu C, Goldberg RM. Recent therapeutic advances in the treatment of colorectal cancer. *Annu Rev Med* 2015; **66**: 83-95 [PMID: 25341011 DOI: 10.1146/annurev-med-051513-102539]

39   **Nagahashi M**, Wakai T, Shimada Y, Ichikawa H, Kameyama H, Kobayashi T, Sakata J, Yagi R, Sato N, Kitagawa Y, Uetake H, Yoshida K, Oki E, Kudo SE, Izutsu H, Kodama K, Nakada M, Tse J, Russell M, Heyer J, Powers W, Sun R, Ring JE, Takabe K, Protopopov A, Ling Y, Okuda S, Lyle S. Genomic landscape of colorectal cancer in Japan: clinical implications of comprehensive genomic sequencing for precision medicine. *Genome Med* 2016; **8**: 136 [PMID: 28007036 DOI: 10.1186/s13073-016-0387-8]

40   **Osumi H**, Shinozaki E, Takeda Y, Wakatsuki T, Ichimura T, Saiura A, Yamaguchi K, Takahashi S, Noda T, Zembutsu H. Clinical relevance of circulating tumor DNA assessed through deep sequencing in patients with metastatic colorectal cancer. *Cancer Med* 2019; **8**: 408-417 [PMID: 30575318 DOI: 10.1002/cam4.1913]

41   **Ichikawa H**, Nagahashi M, Shimada Y, Hanyu T, Ishikawa T, Kameyama H, Kobayashi T, Sakata J, Yabusaki H, Nakagawa S, Sato N, Hirata Y, Kitagawa Y, Tanahashi T, Yoshida K, Nakanishi R, Oki E, Vuzman D, Lyle S, Takabe K, Ling Y, Okuda S, Akazawa K, Wakai T. Actionable gene-based classification toward precision medicine in gastric cancer. *Genome Med* 2017; **9**: 93 [PMID: 29089060 DOI: 10.1186/s13073-017-0484-3]

42   **Kakiuchi M**, Nishizawa T, Ueda H, Gotoh K, Tanaka A, Hayashi A, Yamamoto S, Tatsuno K, Katoh H, Watanabe Y, Ichimura T, Ushiku T, Funahashi S, Tateishi K, Wada I, Shimizu N, Nomura S, Koike K, Seto Y, Fukayama M, Aburatani H, Ishikawa S. Recurrent gain-of-function mutations of RHOA in diffuse-type gastric carcinoma. *Nat Genet* 2014; **46**: 583-587 [PMID: 24816255 DOI: 10.1038/ng.2984]

43   **Wang K**, Yuen ST, Xu J, Lee SP, Yan HH, Shi ST, Siu HC, Deng S, Chu KM, Law S, Chan KH, Chan AS, Tsui WY, Ho SL, Chan AK, Man JL, Foglizzo V, Ng MK, Chan AS, Ching YP, Cheng GH, Xie T, Fernandez J, Li VS, Clevers H, Rejto PA, Mao M, Leung SY. Whole-genome sequencing and comprehensive molecular profiling identify new driver mutations in gastric cancer. *Nat Genet* 2014; **46**: 573-582 [PMID: 24816253 DOI: 10.1038/ng.2983]

44   **Sawada G**, Niida A, Uchi R, Hirata H, Shimamura T, Suzuki Y, Shiraishi Y, Chiba K, Imoto S, Takahashi Y, Iwaya T, Sudo T, Hayashi T, Takai H, Kawasaki Y, Matsukawa T, Eguchi H, Sugimachi K, Tanaka F, Suzuki H, Yamamoto K, Ishii H, Shimizu M, Yamazaki H, Yamazaki M, Tachimori Y, Kajiyama Y, Natsugoe S, Fujita H, Mafune K, Tanaka Y, Kelsell DP, Scott CA, Tsuji S, Yachida S, Shibata T, Sugano S, Doki Y, Akiyama T, Aburatani H, Ogawa S, Miyano S, Mori M, Mimori K. Genomic Landscape of Esophageal Squamous Cell Carcinoma in a Japanese Population. *Gastroenterology* 2016; **150**: 1171-1182 [PMID: 26873401 DOI: 10.1053/j.gastro.2016.01.035]

45   **Rizvi NA**, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, Lee W, Yuan J, Wong P, Ho TS, Miller ML, Rekhtman N, Moreira AL, Ibrahim F, Bruggeman C, Gasmi B, Zappasodi R, Maeda Y, Sander C, Garon EB, Merghoub T, Wolchok JD, Schumacher TN, Chan TA. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* 2015; **348**: 124-

128 [PMID: 25765070 DOI: 10.1126/science.aaa1348]

46   **McGranahan N**, Furness AJ, Rosenthal R, Ramskov S, Lyngaa R, Saini SK, Jamal-Hanjani M, Wilson GA, Birkbak NJ, Hiley CT, Watkins TB, Shafi S, Murugaesu N, Mitter R, Akarca AU, Linares J, Marafioti T, Henry JY, Van Allen EM, Miao D, Schilling B, Schadendorf D, Garraway LA, Makarov V, Rizvi NA, Snyder A, Hellmann MD, Merghoub T, Wolchok JD, Shukla SA, Wu CJ, Peggs KS, Chan TA, Hadrup SR, Quezada SA, Swanton C. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. *Science* 2016; **351**: 1463-1469 [PMID: 26940869 DOI: 10.1126/science.aaf1490]

47   **Le DT**, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Luber BS, Wong F, Azad NS, Rucki AA, Laheru D, Donehower R, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Greten TF, Duffy AG, Ciombor KK, Eyring AD, Lam BH, Joe A, Kang SP, Holdhoff M, Danilova L, Cope L, Meyer C, Zhou S, Goldberg RM, Armstrong DK, Bever KM, Fader AN, Taube J, Housseau F, Spetzler D, Xiao N, Pardoll DM, Papadopoulos N, Kinzler KW, Eshleman JR, Vogelstein B, Anders RA, Diaz LA. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017; **357**: 409-413 [PMID: 28596308 DOI: 10.1126/science.aan6733]

48   **Bourdais R**, Rousseau B, Pujals A, Boussion H, Joly C, Guillemin A, Baumgaertner I, Neuzillet C, Tournigand C. Polymerase proofreading domain mutations: New opportunities for immunotherapy in hypermutated colorectal cancer beyond MMR deficiency. *Crit Rev Oncol Hematol* 2017; **113**: 242-248 [PMID: 28427513 DOI: 10.1016/j.critrevonc.2017.03.027]

49   **Nagarajan N**, Bertrand D, Hillmer AM, Zang ZJ, Yao F, Jacques PÉ, Teo AS, Cutcutache I, Zhang Z, Lee WH, Sia YY, Gao S, Ariyaratne PN, Ho A, Woo XY. Veeravali L, Ong CK, Deng N, Desai KV, Khor CC, Hibberd ML, Shahab A, Rao J, Wu M, Teh M, Zhu F, Chin SY, Pang B, So JB, Bourque G, Soong R, Sung WK, Tean Teh B, Rozen S, Ruan X, Yeoh KG, Tan PB, Ruan Y. Whole-genome reconstruction and mutational signatures in gastric cancer. *Genome Biol* 2012; **13**: R115 [PMID: 23237666 DOI: 10.1186/gb-2012-13-12-r115]

50   **Huang Z**, Zhang L, Zhu D, Shan X, Zhou X, Qi LW, Wu L, Zhu J, Cheng W, Zhang H, Chen Y, Zhu W, Wang T, Liu P. A novel serum microRNA signature to screen esophageal squamous cell carcinoma. *Cancer Med* 2017; **6**: 109-119 [PMID: 28035762 DOI: 10.1002/cam4.973]

51   **Zhang H**, Zhu M, Shan X, Zhou X, Wang T, Zhang J, Tao J, Cheng W, Chen G, Li J, Liu P, Wang Q, Zhu W. A panel of seven-miRNA signature in plasma as potential biomarker for colorectal cancer diagnosis. *Gene* 2019; **687**: 246-254 [PMID: 30458288 DOI: 10.1016/j.gene.2018.11.055]

52   **Vacante M**, Borzì AM, Basile F, Biondi A. Biomarkers in colorectal cancer: Current clinical utility and future perspectives. *World J Clin Cases* 2018; **6**: 869-881 [PMID: 30568941 DOI: 10.12998/wjcc.v6.i15.869]

53   **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]

54   **Tie J**, Gibbs P, Lipton L, Christie M, Jorissen RN, Burgess AW, Croxford M, Jones I, Langland R, Kosmider S, McKay D, Bollag G, Nolop K, Sieber OM, Desai J. Optimizing targeted therapeutic development: analysis of a colorectal cancer patient population with the BRAF(V600E) mutation. *Int J Cancer* 2011; **128**: 2075-2084 [PMID: 20635392 DOI: 10.1002/ijc.25555]

55   **Van Cutsem E**, Karaszewska B, Kang YK, Chung HC, Shankaran V, Siena S, Go NF, Yang H, Schupp M, Cunningham D. A Multicenter Phase II Study of AMG 337 in Patients with *MET*-Amplified Gastric/Gastroesophageal Junction/Esophageal Adenocarcinoma and Other *MET*-Amplified Solid Tumors. *Clin Cancer Res* 2019; **25**: 2414-2423 [PMID: 30366938 DOI: 10.1158/1078-0432.CCR-18-1337]

56   **Toledo RA**, Garralda E, Mitsi M, Pons T, Monsech J, Vega E, Otero Á, Albarran MI, Baños N, Durán Y, Bonilla V. Sarno F, Camacho-Artacho M, Sanchez-Perez T, Perea S, Álvarez R, De Martino A, Lietha D, Blanco-Aparicio C, Cubillo A, Domínguez O, Martínez-Torrecuadrada JL, Hidalgo M. Exome Sequencing of Plasma DNA Portrays the Mutation Landscape of Colorectal Cancer and Discovers Mutated VEGFR2 Receptors as Modulators of Antiangiogenic Therapies. *Clin Cancer Res* 2018; **24**: 3550-3559 [PMID: 29588308 DOI: 10.1158/1078-0432.CCR-18-0103]

57   **Pietrantonio F**, Di Nicolantonio F, Schrock AB, Lee J, Tejpar S, Sartore-Bianchi A, Hechtman JF, Christiansen J, Novara L, Tebbutt N, Fucà G, Antoniotti C, Kim ST, Murphy D, Berenato R, Morano F, Sun J, Min B, Stephens PJ, Chen M, Lazzari L, Miller VA, Shoemaker R, Amatu A, Milione M, Ross JS, Siena S, Bardelli A, Ali SM, Falcone A, de Braud F, Cremolini C. ALK, ROS1, and NTRK Rearrangements in Metastatic Colorectal Cancer. *J Natl Cancer Inst* 2017; **109** [PMID: 29370427 DOI: 10.1093/jnci/djx089]

58   **Papadopoulos N**, Nicolaides NC, Wei YF, Ruben SM, Carter KC, Rosen CA, Haseltine WA, Fleischmann RD, Fraser CM, Adams MD. Mutation of a mutL homolog in hereditary colon cancer. *Science* 1994; **263**: 1625-1629 [PMID: 8128251 DOI: 10.1126/science.8128251]

59   **Smyth EC**, Wotherspoon A, Peckitt C, Gonzalez D, Hulkki-Wilson S, Eltahir Z, Fassan M, Rugge M, Valeri N, Okines A, Hewish M, Allum W, Stenning S, Nankivell M, Langley R, Cunningham D. Mismatch Repair Deficiency, Microsatellite Instability, and Survival: An Exploratory Analysis of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial. *JAMA Oncol* 2017; **3**: 1197-1203 [PMID: 28241187 DOI: 10.1001/jamaoncol.2016.6762]

60   **Viale G**, Trapani D, Curigliano G. Mismatch Repair Deficiency as a Predictive Biomarker for Immunotherapy Efficacy. *Biomed Res Int* 2017; **2017**: 4719194 [PMID: 28770222 DOI: 10.1155/2017/4719194]

61   **Yu PC**, Long D, Liao CC, Zhang S. Association between density of tumor-infiltrating lymphocytes and prognoses of patients with gastric cancer. *Medicine (Baltimore)* 2018; **97**: e11387 [PMID: 29979429 DOI: 10.1097/MD.0000000000011387]

62   **Hohenberger W**, Weber K, Matzel K, Papadopoulos T, Merkel S. Standardized surgery for colonic cancer: complete mesocolic excision and central ligation--technical notes and outcome. *Colorectal Dis* 2009; **11**: 354-64; discussion 364-5 [PMID: 19016817 DOI: 10.1111/j.1463-1318.2008.01735.x]

63   **Campos FG**, Calijuri-Hamra MC, Imperiale AR, Kiss DR, Nahas SC, Cecconello I. Locally advanced colorectal cancer: results of surgical treatment and prognostic factors. *Arq Gastroenterol* 2011; **48**: 270-275 [PMID: 22147133 DOI: 10.1590/S0004-28032011000400010]

64   **Shao H**, Ma X, Gao Y, Wang J, Wu J, Wang B, Li J, Tian J. Comparison of the diagnostic efficiency for local recurrence of rectal cancer using CT, MRI, PET and PET-CT: A systematic review protocol. *Medicine (Baltimore)* 2018; **97**: e12900 [PMID: 30508883 DOI: 10.1097/MD.0000000000012900]

65   **Olson MT**, Ly QP, Mohs AM. Fluorescence Guidance in Surgical Oncology: Challenges, Opportunities, and Translation. *Mol Imaging Biol* 2019; **21**: 200-218 [PMID: 29942988 DOI: 10.1007/s11307-018-1239-2]

66 **Shen R**, Zhang Y, Wang T. Indocyanine Green Fluorescence Angiography and the Incidence of Anastomotic Leak After Colorectal Resection for Colorectal Cancer: A Meta-analysis. *Dis Colon Rectum* 2018; **61**: 1228-1234 [PMID: 30192332 DOI: 10.1097/DCR.0000000000001123]

67 **Chand M**, Keller DS, Joshi HM, Devoto L, Rodriguez-Justo M, Cohen R. Feasibility of fluorescence lymph node imaging in colon cancer: FLICC. *Tech Coloproctol* 2018; **22**: 271-277 [PMID: 29551004 DOI: 10.1007/s10151-018-1773-6]

68 **Takeuchi H**, Kitagawa Y. Sentinel lymph node biopsy in gastric cancer. *Cancer J* 2015; **21**: 21-24 [PMID: 25611776 DOI: 10.1097/PPO.0000000000000088]

69 **Yashiro M**, Matsuoka T. Sentinel node navigation surgery for gastric cancer: Overview and perspective. *World J Gastrointest Surg* 2015; **7**: 1-9 [PMID: 25625004 DOI: 10.4240/wjgs.v7.i1.1]

70 **Takeuchi H**, Kawakubo H, Nakamura R, Fukuda K, Takahashi T, Wada N, Kitagawa Y. Clinical Significance of Sentinel Node Positivity in Patients with Superficial Esophageal Cancer. *World J Surg* 2015; **39**: 2941-2947 [PMID: 26296842 DOI: 10.1007/s00268-015-3217-z]

71 **Takeuchi M**, Takeuchi H, Kawakubo H, Kitagawa Y. Update on the indications and results of sentinel node mapping in upper GI cancer. *Clin Exp Metastasis* 2018; **35**: 455-461 [PMID: 30132238 DOI: 10.1007/s10585-018-9934-6]

72 **Roth AD**, Tejpar S, Delorenzi M, Yan P, Fiocca R, Klingbiel D, Dietrich D, Biesmans B, Bodoky G, Barone C, Aranda E, Nordlinger B, Cisar L, Labianca R, Cunningham D, Van Cutsem E, Bosman F. Prognostic role of KRAS and BRAF in stage II and III resected colon cancer: results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial. *J Clin Oncol* 2010; **28**: 466-474 [PMID: 20008640 DOI: 10.1200/JCO.2009.23.3452]

73 **Lin M**, Gao M, Cavnar MJ, Kim J. Utilizing gastric cancer organoids to assess tumor biology and personalize medicine. *World J Gastrointest Oncol* 2019; **11**: 509-517 [PMID: 31367270 DOI: 10.4251/wjgo.v11.i7.509]

74 **Gao M**, Lin M, Rao M, Thompson H, Hirai K, Choi M, Georgakis GV, Sasson AR, Bucobo JC, Tzimas D, D'Souza LS, Buscaglia JM, Davis J, Shroyer KR, Li J, Powers S, Kim J. Development of Patient-Derived Gastric Cancer Organoids from Endoscopic Biopsies and Surgical Tissues. *Ann Surg Oncol* 2018; **25**: 2767-2775 [PMID: 30003451 DOI: 10.1245/s10434-018-6662-8]

75 **Post JB**, Hami N, Mertens AEE, Elfrink S, Bos JL, Snippert HJG. CRISPR-induced RASGAP deficiencies in colorectal cancer organoids reveal that only loss of NF1 promotes resistance to EGFR inhibition. *Oncotarget* 2019; **10**: 1440-1457 [PMID: 30858928 DOI: 10.18632/oncotarget.26677]

76 **Xiong T**, Wang M, Zhao J, Liu Q, Yang C, Luo W, Li X, Yang H, Kristiansen K, Roy B, Zhou Y. An esophageal squamous cell carcinoma classification system that reveals potential targets for therapy. *Oncotarget* 2017; **8**: 49851-49860 [PMID: 28591712 DOI: 10.18632/oncotarget.17989]

77 **Guinney J**, Dienstmann R, Wang X, de Reyniès A, Schlicker A, Soneson C, Marisa L, Roepman P, Nyamundanda G, Angelino P, Bot BM, Morris JS, Simon IM, Gerster S, Fessler E, De Sousa E Melo F, Missiaglia E, Ramay H, Barras D, Homicsko K, Maru D, Manyam GC, Broom B, Boige V, Perez-Villamil B, Laderas T, Salazar R, Gray JW, Hanahan D, Tabernero J, Bernards R, Friend SH, Laurent-Puig P, Medema JP, Sadanandam A, Wessels L, Delorenzi M, Kopetz S, Vermeulen L, Tejpar S. The consensus molecular subtypes of colorectal cancer. *Nat Med* 2015; **21**: 1350-1356 [PMID: 26457759 DOI: 10.1038/nm.3967]

78 **Loree JM**, Pereira AAL, Lam M, Willauer AN, Raghav K, Dasari A, Morris VK, Advani S, Menter DG, Eng C, Shaw K, Broaddus R, Routbort MJ, Liu Y, Morris JS, Luthra R, Meric-Bernstam F, Overman MJ, Maru D, Kopetz S. Classifying Colorectal Cancer by Tumor Location Rather than Sidedness Highlights a Continuum in Mutation Profiles and Consensus Molecular Subtypes. *Clin Cancer Res* 2018; **24**: 1062-1072 [PMID: 29180604 DOI: 10.1158/1078-0432.CCR-17-2484]

79 **Isella C**, Brundu F, Bellomo SE, Galimi F, Zanella E, Porporato R, Petti C, Fiori A, Orzan F, Senetta R, Boccaccio C, Ficarra E, Marchionni L, Trusolino L, Medico E, Bertotti A. Selective analysis of cancer-cell intrinsic transcriptional traits defines novel clinically relevant subtypes of colorectal cancer. *Nat Commun* 2017; **8**: 15107 [PMID: 28561063 DOI: 10.1038/ncomms15107]

80 **Linnekamp JF**, Hooff SRV, Prasetyanti PR, Kandimalla R, Buikhuisen JY, Fessler E, Ramesh P, Lee KAST, Bochove GGW, de Jong JH, Cameron K, Leersum RV, Rodermond HM, Franitza M, Nürnberg P, Mangiapane LR, Wang X, Clevers H, Vermeulen L, Stassi G, Medema JP. Consensus molecular subtypes of colorectal cancer are recapitulated in in vitro and in vivo models. *Cell Death Differ* 2018; **25**: 616-633 [PMID: 29305587 DOI: 10.1038/s41418-017-0011-5]

81 **Okita A**, Takahashi S, Ouchi K, Inoue M, Watanabe M, Endo M, Honda H, Yamada Y, Ishioka C. Consensus molecular subtypes classification of colorectal cancer as a predictive factor for chemotherapeutic efficacy against metastatic colorectal cancer. *Oncotarget* 2018; **9**: 18698-18711 [PMID: 29721154 DOI: 10.18632/oncotarget.24617]

82 **Li SP**, Guan QL, Zhao D, Pei GJ, Su HX, Du LN, He JX, Liu ZC. Detection of Circulating Tumor Cells by Fluorescent Immunohistochemistry in Patients with Esophageal Squamous Cell Carcinoma: Potential Clinical Applications. *Med Sci Monit* 2016; **22**: 1654-1662 [PMID: 27184872 DOI: 10.12659/msm.898335]

83 **Han L**, Li YJ, Zhang WD, Song PP, Li H, Li S. Clinical significance of tumor cells in the peripheral blood of patients with esophageal squamous cell carcinoma. *Medicine (Baltimore)* 2019; **98**: e13921 [PMID: 30732126 DOI: 10.1097/MD.0000000000013921]

84 **Kang HM**, Kim GH, Jeon HK, Kim DH, Jeon TY, Park DY, Jeong H, Chun WJ, Kim MH, Park J, Lim M, Kim TH, Cho YK. Circulating tumor cells detected by lab-on-a-disc: Role in early diagnosis of gastric cancer. *PLoS One* 2017; **12**: e0180251 [PMID: 28662130 DOI: 10.1371/journal.pone.0180251]

85 **Zheng X**, Fan L, Zhou P, Ma H, Huang S, Yu D, Zhao L, Yang S, Liu J, Huang A, Cai C, Dai X, Zhang T. Detection of Circulating Tumor Cells and Circulating Tumor Microemboli in Gastric Cancer. *Transl Oncol* 2017; **10**: 431-441 [PMID: 28448959 DOI: 10.1016/j.tranon.2017.02.007]

86 **Mishima Y**, Matsusaka S, Chin K, Mikuniya M, Minowa S, Takayama T, Shibata H, Kuniyoshi R, Ogura M, Terui Y, Mizunuma N, Hatake K. Detection of HER2 Amplification in Circulating Tumor Cells of HER2-Negative Gastric Cancer Patients. *Target Oncol* 2017; **12**: 341-351 [PMID: 28508152 DOI: 10.1007/s11523-017-0493-6]

87 **Wang L**, Zhou S, Zhang W, Wang J, Wang M, Hu X, Liu F, Zhang Y, Jiang B, Yuan H. Circulating tumor cells as an independent prognostic factor in advanced colorectal cancer: a retrospective study in 121 patients. *Int J Colorectal Dis* 2019; **34**: 589-597 [PMID: 30627849 DOI: 10.1007/s00384-018-03223-9]

88 **Luo H**, Li H, Hu Z, Wu H, Liu C, Li Y, Zhang X, Lin P, Hou Q, Ding G, Wang Y, Li S, Wei D, Qiu F, Li Y, Wu S. Noninvasive diagnosis and monitoring of mutations by deep sequencing of circulating tumor

DNA in esophageal squamous cell carcinoma. *Biochem Biophys Res Commun* 2016; **471**: 596-602 [PMID: 26876573 DOI: 10.1016/j.bbrc.2016.02.011]

89   **Ueda M**, Iguchi T, Masuda T, Nakahara Y, Hirata H, Uchi R, Niida A, Momose K, Sakimura S, Chiba K, Eguchi H, Ito S, Sugimachi K, Yamasaki M, Suzuki Y, Miyano S, Doki Y, Mori M, Mimori K. Somatic mutations in plasma cell-free DNA are diagnostic markers for esophageal squamous cell carcinoma recurrence. *Oncotarget* 2016; **7**: 62280-62291 [PMID: 27556701 DOI: 10.18632/oncotarget.11409]

90   **Komatsu S**, Ichikawa D, Hirajima S, Takeshita H, Shiozaki A, Fujiwara H, Kawaguchi T, Miyamae M, Konishi H, Kubota T, Okamoto K, Yagi N, Otsuji E. Clinical impact of predicting CCND1 amplification using plasma DNA in superficial esophageal squamous cell carcinoma. *Dig Dis Sci* 2014; **59**: 1152-1159 [PMID: 24458211 DOI: 10.1007/s10620-013-3005-2]

91   **Kim ST**, Banks KC, Pectasides E, Kim SY, Kim K, Lanman RB, Talasaz A, An J, Choi MG, Lee JH, Sohn TS, Bae JM, Kim S, Park SH, Park JO, Park YS, Lim HY, Kim NKD, Park W, Lee H, Bass AJ, Kim K, Kang WK, Lee J. Impact of genomic alterations on lapatinib treatment outcome and cell-free genomic landscape during HER2 therapy in HER2+ gastric cancer patients. *Ann Oncol* 2018; **29**: 1037-1048 [PMID: 29409051 DOI: 10.1093/annonc/mdy034]

92   **Kato S**, Okamura R, Baumgartner JM, Patel H, Leichman L, Kelly K, Sicklick JK, Fanta PT, Lippman SM, Kurzrock R. Analysis of Circulating Tumor DNA and Clinical Correlates in Patients with Esophageal, Gastroesophageal Junction, and Gastric Adenocarcinoma. *Clin Cancer Res* 2018; **24**: 6248-6256 [PMID: 30348637 DOI: 10.1158/1078-0432.CCR-18-1128]

93   **Gao J**, Wang H, Zang W, Li B, Rao G, Li L, Yu Y, Li Z, Dong B, Lu Z, Jiang Z, Shen L. Circulating tumor DNA functions as an alternative for tissue to overcome tumor heterogeneity in advanced gastric cancer. *Cancer Sci* 2017; **108**: 1881-1887 [PMID: 28677165 DOI: 10.1111/cas.13314]

94   **Shoda K**, Ichikawa D, Fujita Y, Masuda K, Hiramoto H, Hamada J, Arita T, Konishi H, Komatsu S, Shiozaki A, Kakihara N, Okamoto K, Taniguchi H, Imoto I, Otsuji E. Monitoring the HER2 copy number status in circulating tumor DNA by droplet digital PCR in patients with gastric cancer. *Gastric Cancer* 2017; **20**: 126-135 [PMID: 26874951 DOI: 10.1007/s10120-016-0599-z]

95   **Tie J**, Wang Y, Tomasetti C, Li L, Springer S, Kinde I, Silliman N, Tacey M, Wong HL, Christie M, Kosmider S, Skinner I, Wong R, Steel M, Tran B, Desai J, Jones I, Haydon A, Hayes T, Price TJ, Strausberg RL, Diaz LA, Papadopoulos N, Kinzler KW, Vogelstein B, Gibbs P. Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer. *Sci Transl Med* 2016; **8**: 346ra92 [PMID: 27384348 DOI: 10.1126/scitranslmed.aaf6219]

96   **Furuki H**, Yamada T, Takahashi G, Iwai T, Koizumi M, Shinji S, Yokoyama Y, Takeda K, Taniai N, Uchida E. Evaluation of liquid biopsies for detection of emerging mutated genes in metastatic colorectal cancer. *Eur J Surg Oncol* 2018; **44**: 975-982 [PMID: 29452859 DOI: 10.1016/j.ejso.2018.01.224]

97   **Vandeputte C**, Kehagias P, El Housni H, Ameye L, Laes JF, Desmedt C, Sotiriou C, Deleporte A, Puleo F, Geboes K, Delaunoit T, Demolin G, Peeters M, D'Hondt L, Janssens J, Carrasco J, Marechal R, Galdon MG, Heimann P, Paesmans M, Flamen P, Hendlisz A. Circulating tumor DNA in early response assessment and monitoring of advanced colorectal cancer treated with a multi-kinase inhibitor. *Oncotarget* 2018; **9**: 17756-17769 [PMID: 29707145 DOI: 10.18632/oncotarget.24879]

98   **Oh TJ**, Oh HI, Seo YY, Jeong D, Kim C, Kang HW, Han YD, Chung HC, Kim NK, An S. Feasibility of quantifying *SDC2* methylation in stool DNA for early detection of colorectal cancer. *Clin Epigenetics* 2017; **9**: 126 [PMID: 29225717 DOI: 10.1186/s13148-017-0426-3]

99   **Faluyi OO**, Eng L, Qiu X, Che J, Zhang Q, Cheng D, Ying N, Tse A, Kuang Q, Dodbiba L, Renouf DJ, Marsh S, Savas S, Mackay HJ, Knox JJ, Darling GE, Wong RK, Xu W, Azad AK, Liu G. Validation of microRNA pathway polymorphisms in esophageal adenocarcinoma survival. *Cancer Med* 2017; **6**: 361-373 [PMID: 28074552 DOI: 10.1002/cam4.989]

100   **Yao C**, Liu HN, Wu H, Chen YJ, Li Y, Fang Y, Shen XZ, Liu TT. Diagnostic and Prognostic Value of Circulating MicroRNAs for Esophageal Squamous Cell Carcinoma: a Systematic Review and Meta-analysis. *J Cancer* 2018; **9**: 2876-2884 [PMID: 30123356 DOI: 10.7150/jca.25351]

101   **Zhang L**, Dong B, Ren P, Ye H, Shi J, Qin J, Wang K, Wang P, Zhang J. Circulating plasma microRNAs in the detection of esophageal squamous cell carcinoma. *Oncol Lett* 2018; **16**: 3303-3318 [PMID: 30127929 DOI: 10.3892/ol.2018.8995]

102   **Virgilio E**, Giarnieri E, Giovagnoli MR, Montagnini M, Proietti A, D'Urso R, Mercantini P, Balducci G, Cavallini M. Gastric Juice MicroRNAs as Potential Biomarkers for Screening Gastric Cancer: A Systematic Review. *Anticancer Res* 2018; **38**: 613-616 [PMID: 29374683 DOI: 10.21873/anticanres.12265]

103   **Sierzega M**, Kaczor M, Kolodziejczyk P, Kulig J, Sanak M, Richter P. Evaluation of serum microRNA biomarkers for gastric cancer based on blood and tissue pools profiling: the importance of miR-21 and miR-331. *Br J Cancer* 2017; **117**: 266-273 [PMID: 28641313 DOI: 10.1038/bjc.2017.190]

104   **Zhu Y**, Peng Q, Lin Y, Zou L, Shen P, Chen F, Min M, Shen L, Chen J, Shen B. Identification of biomarker microRNAs for predicting the response of colorectal cancer to neoadjuvant chemoradiotherapy based on microRNA regulatory network. *Oncotarget* 2017; **8**: 2233-2248 [PMID: 27903980 DOI: 10.18632/oncotarget.13659]

105   **Carter JV**, Galbraith NJ, Yang D, Burton JF, Walker SP, Galandiuk S. Blood-based microRNAs as biomarkers for the diagnosis of colorectal cancer: a systematic review and meta-analysis. *Br J Cancer* 2017; **116**: 762-774 [PMID: 28152545 DOI: 10.1038/bjc.2017.12]

106   **Ulivi P**, Canale M, Passardi A, Marisi G, Valgiusti M, Frassineti GL, Calistri D, Amadori D, Scarpi E. Circulating Plasma Levels of miR-20b, miR-29b and miR-155 as Predictors of Bevacizumab Efficacy in Patients with Metastatic Colorectal Cancer. *Int J Mol Sci* 2018; 19 [PMID: 29361687 DOI: 10.3390/ijms19010307]

107   **Matsumoto Y**, Kano M, Akutsu Y, Hanari N, Hoshino I, Murakami K, Usui A, Suito H, Takahashi M, Otsuka R, Xin H, Komatsu A, Iida K, Matsubara H. Quantification of plasma exosome is a potential prognostic marker for esophageal squamous cell carcinoma. *Oncol Rep* 2016; **36**: 2535-2543 [PMID: 27599779 DOI: 10.3892/or.2016.5066]

108   **Tokuhisa M**, Ichikawa Y, Kosaka N, Ochiya T, Yashiro M, Hirakawa K, Kosaka T, Makino H, Akiyama H, Kunisaki C, Endo I. Exosomal miRNAs from Peritoneum Lavage Fluid as Potential Prognostic Biomarkers of Peritoneal Metastasis in Gastric Cancer. *PLoS One* 2015; **10**: e0130472 [PMID: 26208314 DOI: 10.1371/journal.pone.0130472]

109   **Kumata Y**, Iinuma H, Suzuki Y, Tsukahara D, Midorikawa H, Igarashi Y, Soeda N, Kiyokawa T, Horikawa M, Fukushima R. Exosomeencapsulated microRNA23b as a minimally invasive liquid biomarker for the prediction of recurrence and prognosis of gastric cancer patients in each tumor stage.

Oncol Rep 2018; **40**: 319-330 [PMID: 29749537 DOI: 10.3892/or.2018.6418]

110 **Matsumura T**, Sugimachi K, Iinuma H, Takahashi Y, Kurashige J, Sawada G, Ueda M, Uchi R, Ueo H, Takano Y, Shinden Y, Eguchi H, Yamamoto H, Doki Y, Mori M, Ochiya T, Mimori K. Exosomal microRNA in serum is a novel biomarker of recurrence in human colorectal cancer. *Br J Cancer* 2015; **113**: 275-281 [PMID: 26057451 DOI: 10.1038/bjc.2015.201]

111 **Peng ZY**, Gu RH, Yan B. Downregulation of exosome-encapsulated miR-548c-5p is associated with poor prognosis in colorectal cancer. *J Cell Biochem* 2018 [PMID: 30171732 DOI: 10.1002/jcb.27291]

112 **Pasternack H**, Fassunke J, Plum PS, Chon SH, Hescheler DA, Gassa A, Merkelbach-Bruse S, Bruns CJ, Perner S, Hallek M, Büttner R, Bollschweiler E, Hölscher AH, Quaas A, Zander T, Weiss J, Alakus H. Somatic alterations in circulating cell-free DNA of oesophageal carcinoma patients during primary staging are indicative for post-surgical tumour recurrence. *Sci Rep* 2018; **8**: 14941 [PMID: 30297788 DOI: 10.1038/s41598-018-33027-4]

113 **Yoshida T**, Yamaguchi T, Maekawa S, Takano S, Kuno T, Tanaka K, Iwamoto F, Tsukui Y, Kobayashi S, Asakawa Y, Shindo H, Fukasawa M, Nakayama Y, Inoue T, Uetake T, Ohtaka M, Sato T, Mochizuki K, Enomoto N. Identification of early genetic changes in well-differentiated intramucosal gastric carcinoma by target deep sequencing. *Gastric Cancer* 2019; **22**: 742-750 [PMID: 30756200 DOI: 10.1007/s10120-019-00926-y]

114 **Capalbo C**, Belardinilli F, Raimondo D, Milanetti E, Malapelle U, Pisapia P, Magri V, Prete A, Pecorari S, Colella M, Coppa A, Bonfiglio C, Nicolussi A, Valentini V, Tessitore A, Cardinali B, Petroni M, Infante P, Santoni M, Filetti M, Colicchia V, Paci P, Mezi S, Longo F, Cortesi E, Marchetti P, Troncone G, Bellavia D, Canettieri G, Giannini G. A Simplified Genomic Profiling Approach Predicts Outcome in Metastatic Colorectal Cancer. *Cancers (Basel)* 2019; 11 [PMID: 30691222 DOI: 10.3390/cancers11020147]

115 **Wang Y**, Liu H, Hou Y, Zhou X, Liang L, Zhang Z, Shi H, Xu S, Hu P, Zheng Z, Liu R, Tang T, Ye F, Liang Z, Bu H. Performance validation of an amplicon-based targeted next-generation sequencing assay and mutation profiling of 648 Chinese colorectal cancer patients. *Virchows Arch* 2018; **472**: 959-968 [PMID: 29705968 DOI: 10.1007/s00428-018-2359-4]

116 **Gao XH**, Yu GY, Hong YG, Lian W, Chouhan H, Xu Y, Liu LJ, Bai CG, Zhang W. Clinical significance of multiple gene detection with a 22-gene panel in formalin-fixed paraffin-embedded specimens of 207 colorectal cancer patients. *Int J Clin Oncol* 2019; **24**: 141-152 [PMID: 30612269 DOI: 10.1007/s10147-018-1377-1]

117 **Seifert BA**, McGlaughon JL, Jackson SA, Ritter DI, Roberts ME, Schmidt RJ, Thompson BA, Jimenez S, Trapp M, Lee K, Plon SE, Offit K, Stadler ZK, Zhang L, Greenblatt MS, Ferber MJ. Determining the clinical validity of hereditary colorectal cancer and polyposis susceptibility genes using the Clinical Genome Resource Clinical Validity Framework. *Genet Med* 2019; **21**: 1507-1516 [PMID: 30523343 DOI: 10.1038/s41436-018-0373-1]

118 **Bang YJ**, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK; ToGA Trial Investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; **376**: 687-697 [PMID: 20728210 DOI: 10.1016/S0140-6736(10)61121-X]

119 **Sartore-Bianchi A**, Trusolino L, Martino C, Bencardino K, Lonardi S, Bergamo F, Zagonel V, Leone F, Depetris I, Martinelli E, Troiani T, Ciardiello F, Racca P, Bertotti A, Siravegna G, Torri V, Amatu A, Ghezzi S, Marrapese G, Palmeri L, Valtorta E, Cassingena A, Lauricella C, Vanzulli A, Regge D, Veronese S, Comoglio PM, Bardelli A, Marsoni S, Siena S. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. *Lancet Oncol* 2016; **17**: 738-746 [PMID: 27108243 DOI: 10.1016/S1470-2045(16)00150-9]

120 **Wormald S**, Milla L, O'Connor L. Association of candidate single nucleotide polymorphisms with somatic mutation of the epidermal growth factor receptor pathway. *BMC Med Genomics* 2013; **6**: 43 [PMID: 24152305 DOI: 10.1186/1755-8794-6-43]

121 **Febbo PG**, Ladanyi M, Aldape KD, De Marzo AM, Hammond ME, Hayes DF, Iafrate AJ, Kelley RK, Marcucci G, Ogino S, Pao W, Sgroi DC, Birkeland ML. NCCN Task Force report: Evaluating the clinical utility of tumor markers in oncology. *J Natl Compr Canc Netw* 2011; **9** Suppl 5: S1-32; quiz S33 [PMID: 22138009 DOI: 10.6004/jnccn.2011.0137]

122 **Schmoll HJ**, Van Cutsem E, Stein A, Valentini V, Glimelius B, Haustermans K, Nordlinger B, van de Velde CJ, Balmana J, Regula J, Nagtegaal ID, Beets-Tan RG, Arnold D, Ciardiello F, Hoff P, Kerr D, Köhne CH, Labianca R, Price T, Scheithauer W, Sobrero A, Tabernero J, Aderka D, Barroso S, Bodoky G, Douillard JY, El Ghazaly H, Gallardo J, Garin A, Glynne-Jones R, Jordan K, Meshcheryakov A, Papamichail D, Pfeiffer P, Souglakos I, Turhal S, Cervantes A. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. *Ann Oncol* 2012; **23**: 2479-2516 [PMID: 23012255 DOI: 10.1093/annonc/mds236]

123 **Locker GY**, Hamilton S, Harris J, Jessup JM, Kemeny N, Macdonald JS, Somerfield MR, Hayes DF, Bast RC; ASCO. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. *J Clin Oncol* 2006; **24**: 5313-5327 [PMID: 17060676 DOI: 10.1200/JCO.2006.08.2644]

124 **Hu Y**, Tao SY, Deng JM, Hou ZK, Liang JQ, Huang QG, Li LH, Li HB, Chen YM, Yi H, Chen XL, Liu H. Prognostic Value of NRAS Gene for Survival of Colorectal Cancer Patients: A Systematic Review and Meta-Analysis. *Asian Pac J Cancer Prev* 2018; **19**: 3001-3008 [PMID: 30484984 DOI: 10.31557/APJCP.2018.19.11.3001]

125 **Loaiza-Bonilla A**, Jensen CE, Shroff S, Furth E, Bonilla-Reyes PA, Deik AF, Morrissette J. KDR Mutation as a Novel Predictive Biomarker of Exceptional Response to Regorafenib in Metastatic Colorectal Cancer. *Cureus* 2016; **8**: e478 [PMID: 27004155 DOI: 10.7759/cureus.478]

126 **Tabernero J**, Hozak RR, Yoshino T, Cohn AL, Obermannova R, Bodoky G, Garcia-Carbonero R, Ciuleanu TE, Portnoy DC, Prausová J, Muro K, Siegel RW, Konrad RJ, Ouyang H, Melemed SA, Ferry D, Nasroulah F, Van Cutsem E. Analysis of angiogenesis biomarkers for ramucirumab efficacy in patients with metastatic colorectal cancer from RAISE, a global, randomized, double-blind, phase III study. *Ann Oncol* 2018; **29**: 602-609 [PMID: 29228087 DOI: 10.1093/annonc/mdx767]

127 **Ito C**, Nishizuka SS, Ishida K, Uesugi N, Sugai T, Tamura G, Koeda K, Sasaki A. Analysis of PIK3CA mutations and PI3K pathway proteins in advanced gastric cancer. *J Surg Res* 2017; **212**: 195-204 [PMID: 28550907 DOI: 10.1016/j.jss.2017.01.018]

128   **Kim C**, Lee CK, Chon HJ, Kim JH, Park HS, Heo SJ, Kim HJ, Kim TS, Kwon WS, Chung HC, Rha SY. PTEN loss and level of HER2 amplification is associated with trastuzumab resistance and prognosis in HER2-positive gastric cancer. *Oncotarget* 2017; **8**: 113494-113501 [PMID: 29371924 DOI: 10.18632/oncotarget.23054]

129   **Drilon A**, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, Nathenson M, Doebele RC, Farago AF, Pappo AS, Turpin B, Dowlati A, Brose MS, Mascarenhas L, Federman N, Berlin J, El-Deiry WS, Baik C, Deeken J, Boni V, Nagasubramanian R, Taylor M, Rudzinski ER, Meric-Bernstam F, Sohal DPS, Ma PC, Raez LE, Hechtman JF, Benayed R, Ladanyi M, Tuch BB, Ebata K, Cruickshank S, Ku NC, Cox MC, Hawkins DS, Hong DS, Hyman DM. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. *N Engl J Med* 2018; **378**: 731-739 [PMID: 29466156 DOI: 10.1056/NEJ-Moa1714448]

130   **Domingo E**, Freeman-Mills L, Rayner E, Glaire M, Briggs S, Vermeulen L, Fessler E, Medema JP, Boot A, Morreau H, van Wezel T, Liefers GJ, Lothe RA, Danielsen SA, Sveen A, Nesbakken A, Zlobec I, Lugli A, Koelzer VH, Berger MD, Castellví-Bel S, Muñoz J; Epicolon consortium, de Bruyn M, Nijman HW, Novelli M, Lawson K, Oukrif D, Frangou E, Dutton P, Tejpar S, Delorenzi M, Kerr R, Kerr D, Tomlinson I, Church DN. Somatic POLE proofreading domain mutation, immune response, and prognosis in colorectal cancer: a retrospective, pooled biomarker study. *Lancet Gastroenterol Hepatol* 2016; **1**: 207-216 [PMID: 28404093 DOI: 10.1016/S2468-1253(16)30014-0]

131   **Llosa NJ**, Cruise M, Tam A, Wicks EC, Hechenbleikner EM, Taube JM, Blosser RL, Fan H, Wang H, Luber BS, Zhang M, Papadopoulos N, Kinzler KW, Vogelstein B, Sears CL, Anders RA, Pardoll DM, Housseau F. The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints. *Cancer Discov* 2015; **5**: 43-51 [PMID: 25358689 DOI: 10.1158/2159-8290.CD-14-0863]

132   **Eriksen AC**, Sørensen FB, Lindebjerg J, Hager H, dePont Christensen R, Kjær-Frifeldt S, Hansen TF. Programmed Death Ligand-1 expression in stage II colon cancer - experiences from a nationwide populationbased cohort. *BMC Cancer* 2019; **19**: 142 [PMID: 30755167 DOI: 10.1186/s12885-019-5345-6]

133   **Iseki Y**, Shibutani M, Maeda K, Nagahara H, Fukuoka T, Matsutani S, Kashiwagi S, Tanaka H, Hirakawa K, Ohira M. A new method for evaluating tumor-infiltrating lymphocytes (TILs) in colorectal cancer using hematoxylin and eosin (H-E)-stained tumor sections. *PLoS One* 2018; **13**: e0192744 [PMID: 29698402 DOI: 10.1371/journal.pone.0192744]

134   **Saju P**, Murata-Kamiya N, Hayashi T, Senda Y, Nagase L, Noda S, Matsusaka K, Funata S, Kunita A, Urabe M, Seto Y, Fukayama M, Kaneda A, Hatakeyama M. Host SHP1 phosphatase antagonizes Helicobacter pylori CagA and can be downregulated by Epstein-Barr virus. *Nat Microbiol* 2016; **1**: 16026 [PMID: 27572445 DOI: 10.1038/nmicrobiol.2016.26]

135   **Altieri F**, Di Stadio CS, Federico A, Miselli G, De Palma M, Rippa E, Arcari P. Epigenetic alterations of gastrokine 1 gene expression in gastric cancer. *Oncotarget* 2017; **8**: 16899-16911 [PMID: 28129645 DOI: 10.18632/oncotarget.14817]

136   **Martinelli E**, Morgillo F, Troiani T, Ciardiello F. Cancer resistance to therapies against the EGFR-RAS-RAF pathway: The role of MEK. *Cancer Treat Rev* 2017; **53**: 61-69 [PMID: 28073102 DOI: 10.1016/j.ctrv.2016.12.001]

137   **Jehan Z**, Bavi P, Sultana M, Abubaker J, Bu R, Hussain A, Alsbeih G, Al-Sanea N, Abduljabbar A, Ashari LH, Alhomoud S, Al-Dayel F, Uddin S, Al-Kuraya KS. Frequent PIK3CA gene amplification and its clinical significance in colorectal cancer. *J Pathol* 2009; **219**: 337-346 [PMID: 19697359 DOI: 10.1002/path.2601]

138   **Guo J**, Yu W, Su H, Pang X. Genomic landscape of gastric cancer: molecular classification and potential targets. *Sci China Life Sci* 2017; **60**: 126-137 [PMID: 27460193 DOI: 10.1007/s11427-016-0034-1]

139   **Szász AM**, Lánczky A, Nagy Á, Förster S, Hark K, Green JE, Boussioutas A, Busuttil R, Szabó A, Győrffy B. Cross-validation of survival associated biomarkers in gastric cancer using transcriptomic data of 1,065 patients. *Oncotarget* 2016; **7**: 49322-49333 [PMID: 27384994 DOI: 10.18632/oncotarget.10337]

140   **Ishiguro H**, Wakasugi T, Terashita Y, Sakamoto N, Tanaka T, Mizoguchi K, Sagawa H, Okubo T, Takeyama H. Decreased expression of CDH1 or CTNNB1 affects poor prognosis of patients with esophageal cancer. *World J Surg Oncol* 2016; **14**: 240 [PMID: 27600761 DOI: 10.1186/s12957-016-0956-8]

141   **Liang TJ**, Wang HX, Zheng YY, Cao YQ, Wu X, Zhou X, Dong SX. APC hypermethylation for early diagnosis of colorectal cancer: a meta-analysis and literature review. *Oncotarget* 2017; **8**: 46468-46479 [PMID: 28515349 DOI: 10.18632/oncotarget.17576]

142   **Chen TH**, Chang SW, Huang CC, Wang KL, Yeh KT, Liu CN, Lee H, Lin CC, Cheng YW. The prognostic significance of APC gene mutation and miR-21 expression in advanced-stage colorectal cancer. *Colorectal Dis* 2013; **15**: 1367-1374 [PMID: 23773491 DOI: 10.1111/codi.12318]

143   **Codony-Servat J**, Cuatrecasas M, Asensio E, Montironi C, Martínez-Cardús A, Marín-Aguilera M, Horndler C, Martínez-Balibrea E, Rubini M, Jares P, Reig O, Victoria I, Gaba L, Martín-Richard M, Alonso V, Escudero P, Fernández-Martos C, Feliu J, Méndez JC, Méndez M, Gallego J, Salud A, Rojo F, Castells A, Prat A, Rosell R, García-Albéniz X, Camps J, Maurel J. Nuclear IGF-1R predicts chemotherapy and targeted therapy resistance in metastatic colorectal cancer. *Br J Cancer* 2017; **117**: 1777-1786 [PMID: 29123263 DOI: 10.1038/bjc.2017.279]

144   **Tang D**, Liu J, Wang DR, Yu HF, Li YK, Zhang JQ. Diagnostic and prognostic value of the methylation status of secreted frizzled-related protein 2 in colorectal cancer. *Clin Invest Med* 2011; **34**: E88-E95 [PMID: 21463549 DOI: 10.25011/cim.v34i1.15105]

145   **Crea F**, Nobili S, Paolicchi E, Perrone G, Napoli C, Landini I, Danesi R, Mini E. Epigenetics and chemoresistance in colorectal cancer: an opportunity for treatment tailoring and novel therapeutic strategies. *Drug Resist Updat* 2011; **14**: 280-296 [PMID: 21955833 DOI: 10.1016/j.drup.2011.08.001]

146   **Salem ME**, Puccini A, Xiu J, Raghavan D, Lenz HJ, Korn WM, Shields AF, Philip PA, Marshall JL, Goldberg RM. Comparative Molecular Analyses of Esophageal Squamous Cell Carcinoma, Esophageal Adenocarcinoma, and Gastric Adenocarcinoma. *Oncologist* 2018; **23**: 1319-1327 [PMID: 29866946 DOI: 10.1634/theoncologist.2018-0143]

147   **Wasserman I**, Lee LH, Ogino S, Marco MR, Wu C, Chen X, Datta J, Sadot E, Szeglin B, Guillem JG, Paty PB, Weiser MR, Nash GM, Saltz L, Barlas A, Manova-Todorova K, Uppada SPB, Elghouayel AE, Ntiamoah P, Glickman JN, Hamada T, Kosumi K, Inamura K, Chan AT, Nishihara R, Cercek A, Ganesh K, Kemeny NE, Dhawan P, Yaeger R, Sawyers CL, Garcia-Aguilar J, Giannakis M, Shia J, Smith JJ. SMAD4 Loss in Colorectal Cancer Patients Correlates with Recurrence, Loss of Immune Infiltrate, and Chemoresistance. *Clin Cancer Res* 2019; **25**: 1948-1956 [PMID: 30587545 DOI:

10.1158/1078-0432.CCR-18-1726]

148   **Zhou C**, Li J, Li Q. CDKN2A methylation in esophageal cancer: a meta-analysis. *Oncotarget* 2017; **8**: 50071-50083 [PMID: 28637022 DOI: 10.18632/oncotarget.18412]

149   **Randon G**, Fucà G, Rossini D, Raimondi A, Pagani F, Perrone F, Tamborini E, Busico A, Peverelli G, Morano F, Niger M, Antista M, Corallo S, Saggio S, Borelli B, Zucchelli G, Milione M, Pruneri G, Di Bartolomeo M, Falcone A, de Braud F, Cremolini C, Pietrantonio F. Prognostic impact of ATM mutations in patients with metastatic colorectal cancer. *Sci Rep* 2019; **9**: 2858 [PMID: 30814645 DOI: 10.1038/s41598-019-39525-3]

150   **de Voer RM**, Hahn MM, Mensenkamp AR, Hoischen A, Gilissen C, Henkes A, Spruijt L, van Zelst-Stams WA, Kets CM, Verwiel ET, Nagtegaal ID, Schackert HK, van Kessel AG, Hoogerbrugge N, Ligtenberg MJ, Kuiper RP. Deleterious Germline BLM Mutations and the Risk for Early-onset Colorectal Cancer. *Sci Rep* 2015; **5**: 14060 [PMID: 26358404 DOI: 10.1038/srep14060]

151   **Frank B**, Hoffmeister M, Klopp N, Illig T, Chang-Claude J, Brenner H. Colorectal cancer and polymorphisms in DNA repair genes WRN, RMI1 and BLM. *Carcinogenesis* 2010; **31**: 442-445 [PMID: 19945966 DOI: 10.1093/carcin/bgp293]

152   **Oh M**, McBride A, Yun S, Bhattacharjee S, Slack M, Martin JR, Jeter J, Abraham I. BRCA1 and BRCA2 Gene Mutations and Colorectal Cancer Risk: Systematic Review and Meta-analysis. *J Natl Cancer Inst* 2018; **110**: 1178-1189 [PMID: 30380096 DOI: 10.1093/jnci/djy148]

153   **Wei XL**, Wang DS, Xi SY, Wu WJ, Chen DL, Zeng ZL, Wang RY, Huang YX, Jin Y, Wang F, Qiu MZ, Luo HY, Zhang DS, Xu RH. Clinicopathologic and prognostic relevance of ARID1A protein loss in colorectal cancer. *World J Gastroenterol* 2014; **20**: 18404-18412 [PMID: 25561809 DOI: 10.3748/wjg.v20.i48.18404]

154   **Ronchetti L**, Melucci E, De Nicola F, Goeman F, Casini B, Sperati F, Pallocca M, Terrenato I, Pizzuti L, Vici P, Sergi D, Di Lauro L, Amoreo CA, Gallo E, Diodoro MG, Pescarmona E, Vitale I, Barba M, Buglioni S, Mottolese M, Fanciulli M, De Maria R, Maugeri-Saccà M. DNA damage repair and survival outcomes in advanced gastric cancer patients treated with first-line chemotherapy. *Int J Cancer* 2017; **140**: 2587-2595 [PMID: 28233295 DOI: 10.1002/ijc.30668]

155   **Hansford S**, Kaurah P, Li-Chang H, Woo M, Senz J, Pinheiro H, Schrader KA, Schaeffer DF, Shumansky K, Zogopoulos G, Santos TA, Claro I, Carvalho J, Nielsen C, Padilla S, Lum A, Talhouk A, Baker-Lange K, Richardson S, Lewis I, Lindor NM, Pennell E, MacMillan A, Fernandez B, Keller G, Lynch H, Shah SP, Guilford P, Gallinger S, Corso G, Roviello F, Caldas C, Oliveira C, Pharoah PD, Huntsman DG. Hereditary Diffuse Gastric Cancer Syndrome: CDH1 Mutations and Beyond. *JAMA Oncol* 2015; **1**: 23-32 [PMID: 26182300 DOI: 10.1001/jamaoncol.2014.168]

156   **Grünhage F**, Jungck M, Lamberti C, Berg C, Becker U, Schulte-Witte H, Plassmann D, Rahner N, Aretz S, Friedrichs N, Buettner R, Sauerbruch T, Lammert F. Association of familial colorectal cancer with variants in the E-cadherin (CDH1) and cyclin D1 (CCND1) genes. *Int J Colorectal Dis* 2008; **23**: 147-154 [PMID: 17960397 DOI: 10.1007/s00384-007-0388-6]

157   **Ooi A**, Oyama T, Nakamura R, Tajiri R, Ikeda H, Fushida S, Dobashi Y. Gene amplification of CCNE1, CCND1, and CDK6 in gastric cancers detected by multiplex ligation-dependent probe amplification and fluorescence in situ hybridization. *Hum Pathol* 2017; **61**: 58-67 [PMID: 27864121 DOI: 10.1016/j.humpath.2016.10.025]

158   **Chang HR**, Nam S, Lee J, Kim JH, Jung HR, Park HS, Park S, Ahn YZ, Huh I, Balch C, Ku JL, Powis G, Park T, Jeong JH, Kim YH. Systematic approach identifies RHOA as a potential biomarker therapeutic target for Asian gastric cancer. *Oncotarget* 2016; **7**: 81435-81451 [PMID: 27806312 DOI: 10.18632/onco-target.12963]

159   **Hu X**, Moon JW, Li S, Xu W, Wang X, Liu Y, Lee JY. Amplification and overexpression of *CTTN* and *CCND1* at chromosome 11q13 in Esophagus squamous cell carcinoma (ESCC) of North Eastern Chinese Population. *Int J Med Sci* 2016; **13**: 868-874 [PMID: 27877079 DOI: 10.7150/ijms.16845]

160   **Korphaisarn K**, Morris VK, Overman MJ, Fogelman DR, Kee BK, Raghav KPS, Manuel S, Shureiqi I, Wolff RA, Eng C, Menter D, Hamilton SR, Kopetz S, Dasari A. FBXW7 missense mutation: a novel negative prognostic factor in metastatic colorectal adenocarcinoma. *Oncotarget* 2017; **8**: 39268-39279 [PMID: 28424412 DOI: 10.18632/oncotarget.16848]

161   **Song B**, Cui H, Li Y, Cheng C, Yang B, Wang F, Kong P, Li H, Zhang L, Jia Z, Bi Y, Wang J, Zhou Y, Liu J, Wang J, Zhao Z, Zhang Y, Hu X, Shi R, Yang J, Liu H, Yan T, Li Y, Xu E, Qian Y, Xi Y, Guo S, Chen Y, Wang J, Li G, Liang J, Jia J, Chen X, Guo J, Maugeri Y, Zhang Y, Li Q, Wang C, Cheng X, Zhan Q, Cui Y. Mutually exclusive mutations in NOTCH1 and PIK3CA associated with clinical prognosis and chemotherapy responses of esophageal squamous cell carcinoma in China. *Oncotarget* 2016; **7**: 3599-3613 [PMID: 26528858 DOI: 10.18632/oncotarget.6120]

162   **Arcaroli JJ**, Tai WM, McWilliams R, Bagby S, Blatchford PJ, Varella-Garcia M, Purkey A, Quackenbush KS, Song EK, Pitts TM, Gao D, Lieu C, McManus M, Tan AC, Zheng X, Zhang Q, Ozeck M, Olson P, Jiang ZQ, Kopetz S, Jimeno A, Keysar S, Eckhardt G, Messersmith WA. A NOTCH1 gene copy number gain is a prognostic indicator of worse survival and a predictive biomarker to a Notch1 targeting antibody in colorectal cancer. *Int J Cancer* 2016; **138**: 195-205 [PMID: 26152787 DOI: 10.1002/ijc.29676]

163   **Ozawa T**, Kazama S, Akiyoshi T, Murono K, Yoneyama S, Tanaka T, Tanaka J, Kiyomatsu T, Kawai K, Nozawa H, Kanazawa T, Yamaguchi H, Ishihara S, Sunami E, Kitayama J, Morikawa T, Fukayama M, Watanabe T. Nuclear Notch3 expression is associated with tumor recurrence in patients with stage II and III colorectal cancer. *Ann Surg Oncol* 2014; **21**: 2650-2658 [PMID: 24728738 DOI: 10.1245/s10434-014-3659-9]

164   **Zhang L**, Song X, Li X, Wu C, Jiang J. Yes-Associated Protein 1 as a Novel Prognostic Biomarker for Gastrointestinal Cancer: A Meta-Analysis. *Biomed Res Int* 2018; **2018**: 4039173 [PMID: 30539010 DOI: 10.1155/2018/4039173]