Journal of Multidisciplinary Healthcare Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Mapping the Future: A Comprehensive Bibliometric Analysis of Circulating Tumor DNA in Colorectal Cancer

Chengzu Wang

Clinical Laboratory, Affiliated Cixi Hospital, Wenzhou Medical University, Zhejiang, People's Republic of China

Correspondence: Chengzu Wang, Email wczly1988@163.com

Purpose: Colorectal cancer (CRC) is among the most prevalent malignancies worldwide, with rising incidence and mortality rates presenting substantial public health challenges. Traditional detection methods have inherent limitations, which has led to growing interest in liquid biopsy technologies for the identification of circulating tumor DNA (ctDNA). The aim of this study is to explore the developmental trends and future prospects of ctDNA in colorectal cancer through bibliometric analysis.

Methods: This bibliometric analysis examines the literature on ctDNA in CRC from 2004 to 2024, utilizing the Web of Science Core Collection database to identify research trends, key areas of interest, and potential future directions. The R package "bibliometrix" and VOSviewer software were employed for bibliometric analysis and visualization. The analysis encompassed an evaluation of publication volume, contributing authors, influential journals, country and institutional contributions, and citation metrics.

Results: The analysis encompassed a total of 1,054 publications, demonstrating a marked escalation in research activity since 2015. The journal "Cancers" has been identified as the most prolific publisher within this domain. Prominent researchers, including Bardelli A and Sartore-Bianchi A, have made substantial contributions to the field. The United States is the leading country in terms of both publication volume and citation frequency, followed by China and Italy. A keyword analysis identified seven conceptual clusters, with "circulating tumor DNA" and "liquid biopsy" emerging as predominant themes.

Conclusion: This study emphasizes the evolving emphasis on the clinical applications of ctDNA, encompassing early detection, treatment monitoring, and prognostic assessment in CRC, thereby underscoring its potential as a non-invasive biomarker in oncology.

Keywords: colorectal cancer, circulating tumor DNA, bibliometric analysis

Introduction

Colorectal cancer (CRC) is one of the most prevalent malignancies globally, ranking as the third most common cancer and the second leading cause of cancer-related mortality.[1,2] The incidence and mortality rates of CRC are increasing, presenting a substantial threat to public health. While this trend is partially attributed to factors such as an aging population, lifestyle modifications, and suboptimal dietary practices, the relationship between age and CRC outcomes requires careful consideration. Although elderly patients are more prone to severe postoperative complications, current evidence suggests that age alone does not significantly affect survival outcomes. The prognosis of elderly patients is influenced by multiple factors, including stage differences at diagnosis, tumor location, pre-existing comorbidities, and types of treatment received. The complex interactions among these factors necessitate a more detailed approach in evaluating the prognosis of elderly colorectal cancer patients.[3] In recent years, with advances in sequencing technology, researchers have gained deeper insights into colorectal cancer genomics, focusing more on molecular and genetic level characteristic analysis, which brings new opportunities for future treatment. Against this background, a new subtype of Cancer of Unknown Primary (CUP) - colorectal cancer-type CUP (CUP-CCP) - has been identified. CUP-CCP exhibits molecular characteristics similar to known colorectal cancer (CRC), such as KRAS and BRAF gene mutations, making targeted therapy possible. Studies have shown that treating CUP-CCP patients with colorectal cancer-specific

Received: 30 August 2024
Accepted: 19 November 2024
Published: 22 November 2024

chemotherapy regimens significantly improves overall survival rates, extending median survival by 6 months compared to traditional empirical CUP treatment protocols. Treatment with colorectal-specific chemotherapy regimens has shown better outcomes compared to empirical CUP treatment regimens.[4] Current clinical methodologies for CRC detection, including colonoscopy, tissue biopsy, and fecal occult blood tests, possess inherent limitations: some are invasive, while others fail to achieve optimal sensitivity and specificity.[5–8] In contrast, liquid biopsy, an innovative non-invasive detection technology, facilitates the identification of circulating tumor DNA (ctDNA) and shows potential in early screening, monitoring treatment responses, and predicting CRC recurrence.[9]

Circulating tumor DNA consists of DNA fragments that are released into the bloodstream by tumor cells undergoing apoptosis or necrosis, and these fragments carry tumor-specific mutations. The concentration of ctDNA generally correlates with the tumor's size and stage.[10,11] Contemporary detection technologies for ctDNA predominantly utilize polymerase chain reaction (PCR) and next-generation sequencing (NGS) methodologies.[12] Research suggests that ctDNA analysis can improve early screening for CRC, facilitate the monitoring of minimal residual disease (MRD), and aid in evaluating the risk of cancer recurrence.[13–17] Additionally, variations in ctDNA levels can indicate treatment efficacy, thereby supporting the evaluation of patient response to therapy.[18,19]

Bibliometrics constitutes an academic discipline that utilizes quantitative methodologies to scrutinize publications, encompassing books, journal articles, and other scholarly outputs. This field aims to elucidate research trends, knowledge structures, and academic influences within particular domains. Through the systematic analysis of bibliographic data, bibliometrics provides a thorough assessment of diverse facets of academic research activities, including the productivity and impact of individual researchers, institutions, countries, and research topics.[19]

Over the past two decades, research on ctDNA in relation to CRC has advanced significantly. Despite this progress, a comprehensive bibliometric analysis specifically focusing on ctDNA studies within the context of CRC is still lacking. To address this gap, the present study employs bibliometric techniques to analyze relevant literature from the past 20 years, with the aim of identifying research hotspots and projecting future development trajectories in this field.

Materials and Methods

Search Strategies

On August 15, 2024, we conducted a comprehensive literature search using the Web of Science Core Collection (WoSCC) database, covering publications from 2004 to 2024. Our search strategy was defined as follows: TS = ("Colorectal Neoplasms" OR "Colorectal Neoplasm" OR "Neoplasm, Colorectal" OR "Colorectal Tumors" OR "Colorectal Tumor" OR "Tumor, Colorectal" OR "Tumors, Colorectal" OR "Neoplasms, Colorectal" OR "Colorectal Cancer" OR "Cancer, Colorectal" OR "Cancers, Colorectal" OR "Colorectal Cancers" OR "Colorectal Carcinoma" OR "Carcinoma, Colorectal" OR "Carcinomas, Colorectal" OR "Colorectal Carcinomas") and TS = ("Circulating Tumor DNA" OR "DNA, Circulating Tumor" OR "Tumor DNA, Circulating" OR "Cell-Free Tumor DNA" OR "Cell Free Tumor DNA" OR "DNA, Cell-Free Tumor" OR "Tumor DNA, Cell-Free" OR "ctDNA"). We limited our search to articles and reviews published in English. This search resulted in a total of 1,054 publications. To ensure we obtained comprehensive bibliographic data, we exported the results in "plain text" format, selecting "full records and cited references" as the content type. The detailed process used for literature screening is depicted in Figure 1.

Data Analysis and Visualization

This study utilizes the R package "bibliometrix" (version 4.2.0, https://www.bibliometrix.org) alongside VOSviewer software to perform an exhaustive bibliometric analysis. The primary aim is to develop a global distribution network of literature related to "colorectal cancer and ctDNA." Our data mining and analytical efforts concentrate on critical elements such as journals, authors, citations, keywords, institutions, countries, and co-occurrence networks. We employ the "metaTagExtraction" and "Biblionetwork" commands to investigate collaborative networks, and use "Networkplot" for graphical visualization.

In conjunction with the Bibliometrix package, we utilize VOSviewer, a sophisticated software tool designed for the construction and visualization of scientific literature networks. VOSviewer's ability to manage extensive datasets makes

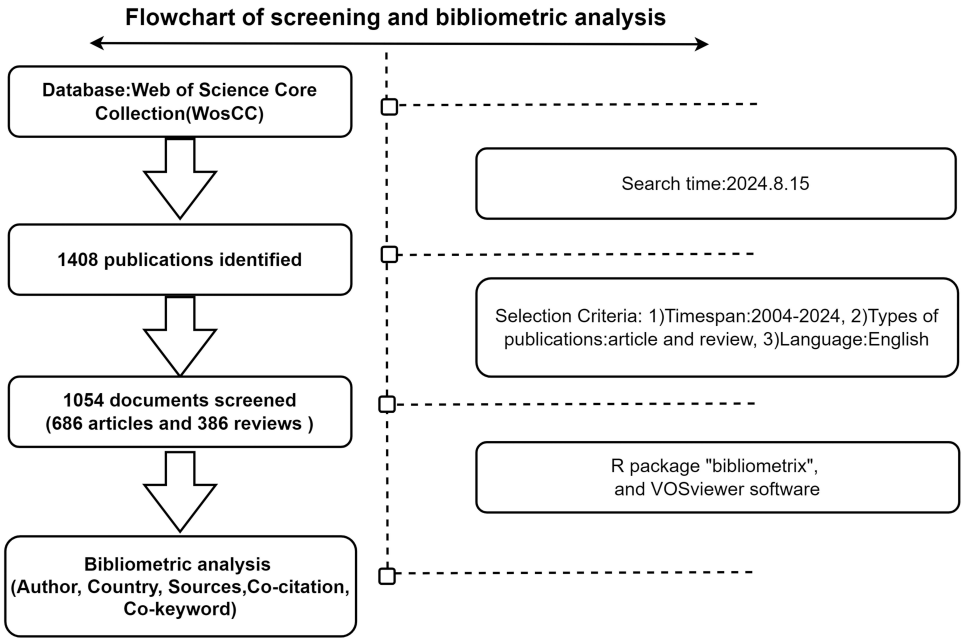

Figure 1 An analysis flowchart for selecting and analyzing studies.
Notes: This figure was drawn by *Figdraw*, www.figdraw.com.

it especially appropriate for the analysis of literature data that includes scientific articles, journals, authors, institutions, and countries. We leverage VOSviewer's capabilities for a range of applications, such as bibliographic coupling analysis of journals, co-citation analysis, and keyword co-occurrence analysis.[20]

The application of integrated analytical approaches provides a thorough examination of the literature landscape concerning colorectal cancer and ctDNA. By leveraging the complementary strengths of Bibliometrix and VOSviewer, this study elucidates research trends, collaboration patterns, and principal focus areas within this field. This multifaceted methodology allows for the visualization of intricate relationships within the scientific literature network, thereby facilitating the identification of influential researchers and high-impact publications. Consequently, it contributes to a more nuanced understanding of the field's evolution and current state.[21]

Results

Publication Trends by Year

This study conducted an analysis of 1,054 pertinent publications, which included 686 (65%) original research articles and 368 (35%) review articles. The temporal distribution of these publications delineates the evolution of the field into two distinct phases: the nascent phase (2004–2014) and the rapid development phase (2015–2024). During the nascent phase, the annual number of publications remained below 10, reflecting the early-stage development of the field. A significant increase in the volume of publications began in 2015, indicating a period of rapid development. Since 2019, the number of annual publications has consistently surpassed 100, highlighting sustained high academic interest. The retrieved literature has accumulated 32,206 citations, with an average citation frequency of 47.39 per document. This significant increase not only reflects the deepening and broadening of research within the field but also indicates potential for continued growth, as showed in Figure 2.

Most Relevant Sources

The study identified 325 journals that published literature in the relevant field. Cancers emerged as the most prolific journal with 85 publications, followed by Frontiers in Oncology (n=42) and Clinical Cancer Research (n=33). Other significant contributors include JCO Precision Oncology (n=23), Scientific Reports (n=21), Annals of Oncology (n=20), Molecular Oncology (n=20), International Journal of Molecular Sciences (n=18), PLoS One (n=18), and British Journal

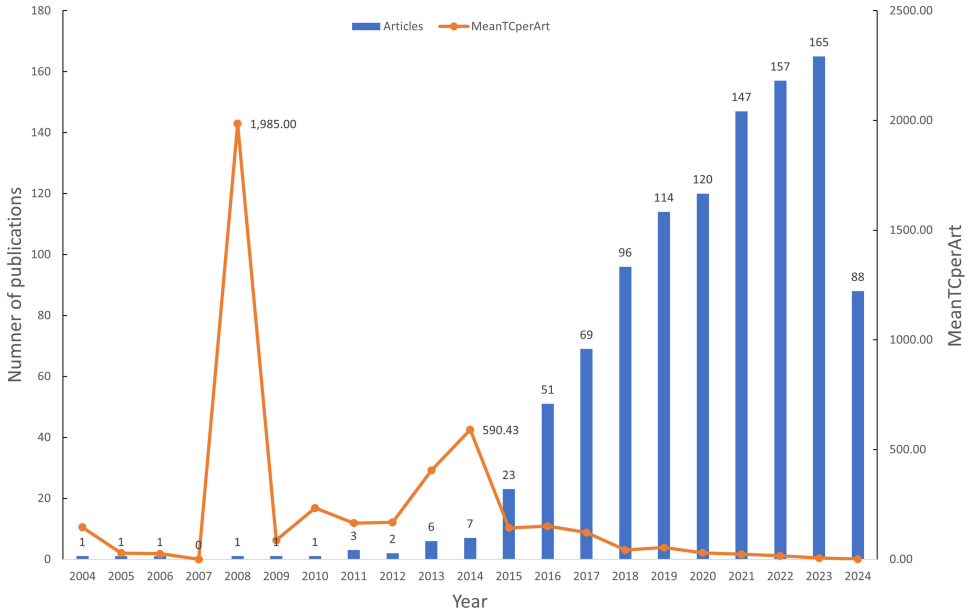

Figure 2 Annual publication trends and average citations.

of Cancer (n=15) (Table 1). This distribution aligns with Bradford's Law, which posits that a small core of journals accounts for a disproportionately large share of publications in a given field.[22] Indeed, further analysis identified 14 journals as core journals in the field of ctDNA research (Figure 3). Consistent with the publication frequency, the top three core journals are Cancers, Frontiers in Oncology, and Clinical Cancer Research, underscoring their pivotal role in disseminating research in this domain.

Most Relevant Authors

Over the past two decades, contributions to the relevant literature have been made by 7,191 authors. Analysis of author productivity identifies Bardelli A as the most prolific author with 33 publications, followed by Sartore-Bianchi A and Siena S, each with 26 publications (Figure 4). This distribution exemplifies Lotka's Law, which posits that a small cohort of prolific authors contributes the majority of literature, while most authors publish infrequently.[23] According to the data, 77.6% of authors published only one article during this period. Notably, between 2014 and 2019, Bardelli A, Sartore-Bianchi A, and Siena S published 25, 15, and 17 articles, respectively, significantly advancing ctDNA research in colorectal cancer. Their sustained contributions have established them as influential figures in this domain (Table 2).

Table 1 Journals with the Most Published Articles

Rank	Sources	Articles	IF (2022)	JCR
1	Cancers	85	5.2	Q1
2	Frontiers in oncology	42	4.7	Q2
3	Clinical cancer research	33	11.5	Q1
4	JCO precision oncology	23	4.6	Q1
5	Scientific reports	21	4.6	Q1
6	Annals of oncology	20	50.5	Q1
7	Molecular oncology	20	6.6	Q1
8	International journal of molecular sciences	18	5.6	Q1
9	PLoS one	18	3.7	Q1
10	British journal of cancer	15	8.8	Q1

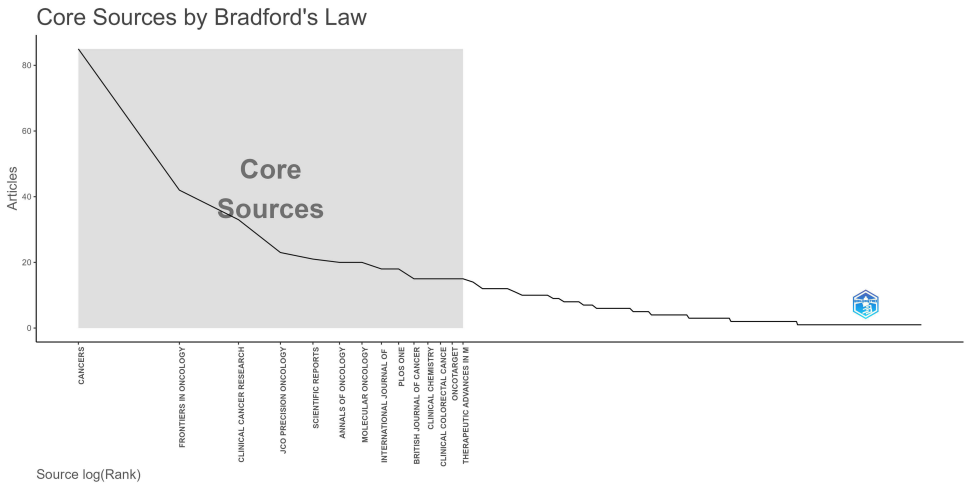

Figure 3 Bradford's Law's core sources.

Figure 4 The analysis of the authors of publications of ctDNA in CRC. (**A**) Top 10 authors in terms of publications. (**B**) Author's production over time.

Analysis of Country and Organizations

Countries are ranked based on publication volume as determined by the location of the corresponding author. The USA leads with 219 publications, comprising 162 Single-Country Publications (SCP) and 57 Multi-Country Publications (MCP). China ranks second with 175 publications (SCP: 155; MCP: 20), followed by Italy with 108 publications (SCP: 81; MCP: 27). Among the top 10 countries, the United Kingdom exhibits the highest SCP ratio at 62.1%, while SCP ratios for the USA and China are 26% and 11.4%, respectively (Figure 5). Beyond publication volume, citation counts provide a critical measure of a country's influence in the field. The USA is the most cited country, with 13,321 citations,

Table 2 Top 10 Research Authors in the Field

Author	h_Index	g_Index	m_Index	TC	NP	PY_Start
Bardelli A	28	33	2.333	11,975	33	2013
Siravegna G	22	24	1.833	8034	24	2013
Siena S	20	26	1.667	7300	26	2013
Sartore-bianchi A	19	26	1.583	6042	26	2013
Di Nicolantonio F	16	20	1.333	3722	20	2013
Taly V	16	21	1.333	1598	21	2013
Gibbs P	13	17	1.182	5775	17	2014
Kopetz S	13	24	1.3	1736	24	2015
Laurent-Puig P	13	21	1.083	3663	21	2013
Nakamura y	13	25	1.625	658	25	2017

Abbreviations: TC, Total citation; NP, Number of the publication; PY_start, The publication year.

followed by Italy (7,368 citations), Australia (3,903 citations), France (3,739 citations), and China (3,552 citations) (Table 3). Notably, Switzerland boasts the highest average citations per article at 288.7, underscoring its prominent role and standing in the field.

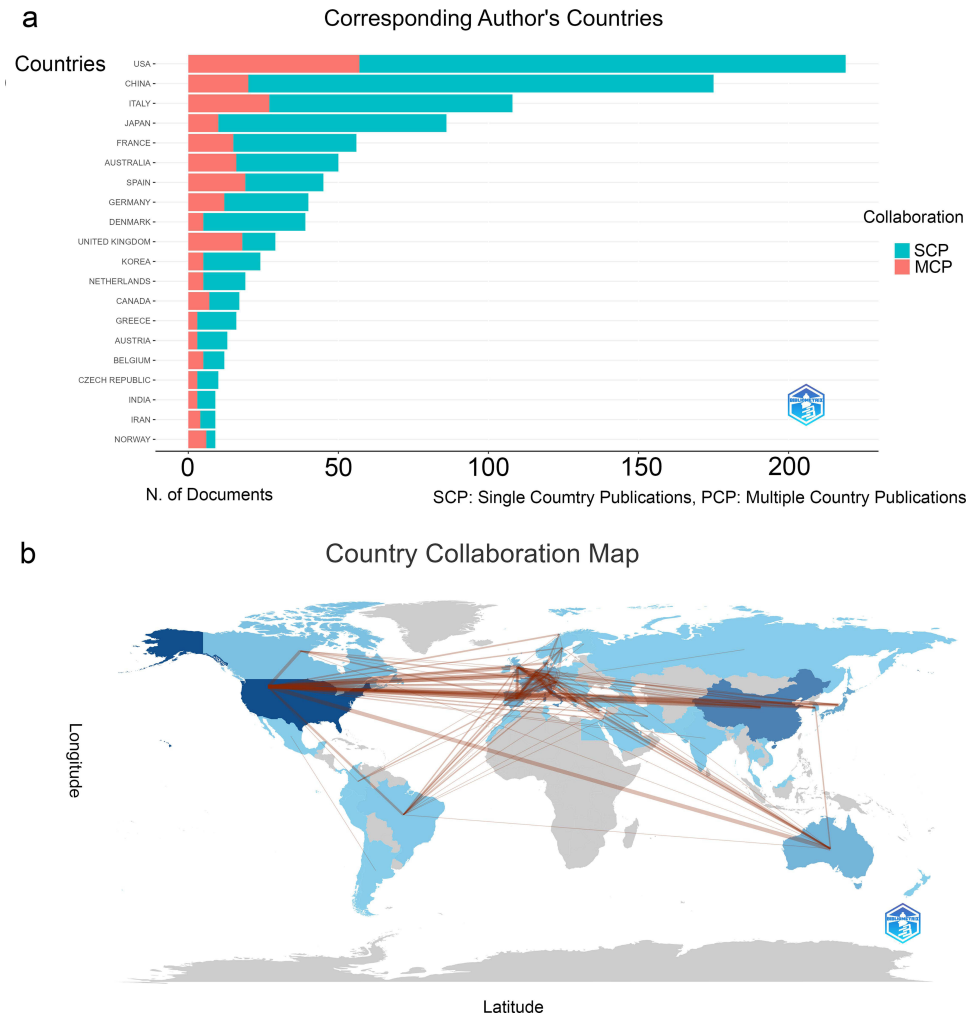

Figure 5 Bibliometric network of country-specific production. (**a**) Publication ranking and international collaboration of the corresponding author's country. (**b**) Country collaboration map.

Table 3 Country with the Highest Number of Citations in the Field

Rank	Country	TC	Average Article Citations
1	USA	13321	60.80
2	Italy	7368	68.20
3	Australia	3903	78.10
4	France	3739	66.80
5	China	3552	20.30
6	Switzerland	2598	288.70
7	United Kingdom	2490	85.90
8	Germany	2190	54.80
9	Spain	2123	47.20
10	Japan	2057	23.90

Abbreviation: TC, total citation.

Based on publication volume, the top five research institutions in the field are the University of Texas System with 131 publications, UT MD Anderson Cancer Center with 113 publications, Université Paris Cité with 104 publications, Assistance Publique Hôpitaux de Paris (AP-HP) with 101 publications, and Unicancer with 90 publications. Notably, Fudan University in China ranks tenth with 66 publications (Table 4).

Keyword Analysis

Utilizing VOSviewer software, we established a threshold occurrence frequency of greater than five, resulting in the identification of 363 keywords for subsequent analysis. In the generated visualization, the size of the keyword circles denotes their significance, while different colors are used to represent distinct clusters. The analysis identified seven unique keyword clusters. The ten most frequently occurring keywords are: circulating tumor DNA, liquid biopsy, colorectal cancer, cell-free DNA, acquired resistance, ctDNA, plasma, mutations, and therapy (Figure 6).

We performed a trend analysis of the pertinent literature, focusing on the period-specific data to elucidate the principal research themes and evolutionary trajectories of circulating tumor DNA within the domain of colorectal cancer research. Our findings identified several critical research themes that have exhibited notable developmental trends over the past two decades. Since 2017, there has been a notable increase in the frequency of studies on colorectal cancer (frequency: 273) and circulating tumor DNA (frequency: 244), with both topics maintaining high levels of research interest through 2024. This trend underscores their sustained prominence in the scientific community. Initially, research efforts in 2016 were concentrated on tumor heterogeneity and ctDNA hypermethylation. Over time, the focus has progressively shifted towards quantitative detection methodologies for serum/plasma DNA, followed by examinations of acquired resistance,

Table 4 Research Institutions Ranked in the Top 10

Rank	Affiliation	Articles
1	University of texas	131
2	Anderson cancer center	113
3	Universite Paris cite	104
4	Assistance publique hopitaux Paris (APHP)	101
5	Unicancer	90
6	Aarhus University	81
7	Institut national de la sante et de la recherche medicale (inserm)	79
8	Harvard University	76
9	National cancer center - Japan	76
10	Fudan University	66

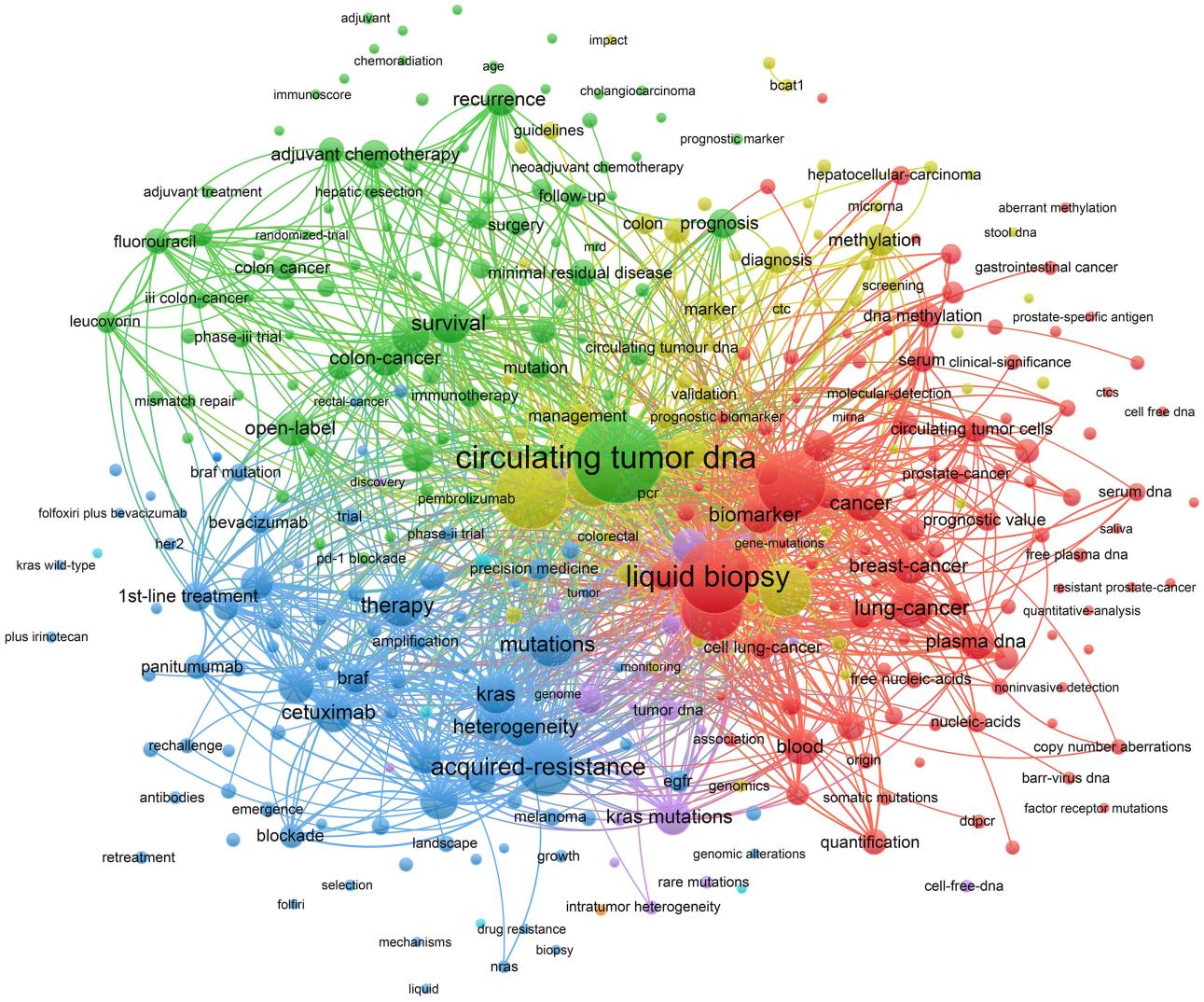

Figure 6 The co-occurrence network between ctDNA and colorectal cancer from 2004 to 2024.

genetic mutations, therapeutic interventions, and patient survival outcomes. Presently, the predominant research interest lies in the application of ctDNA in the context of colorectal cancer chemotherapy (Figure 7).

Co-Citation Network

We initiated our study by employing bibliometric techniques to examine the most frequently cited documents within this field. The preeminent paper, in terms of citation count, is "Detection of Circulating Tumor DNA in Early- and Late-Stage Human Malignancies" authored by Bettegowda, C., and published in 2014, which has garnered 3,311 citations to date. This seminal work investigated the feasibility of detecting ctDNA across different stages of tumor progression, underscoring its potential utility in early tumor screening.[24] The second most frequently cited paper, titled "ESMO Consensus Guidelines for the Management of Patients with Metastatic Colorectal Cancer" by Van Cutsem, published in the Annals of Oncology, has accrued 2,400 citations. This article highlights the potential applications of ctDNA in the management of metastatic colorectal cancer, with particular emphasis on prognostic assessment, monitoring of treatment efficacy, and analysis of resistance mechanisms.[25] Ranked third is the paper by Diehl et al, titled "Circulating Mutant DNA to Assess Tumor Dynamics", with a total of 1,985 citations. The study concludes that circulating mutant DNA can be used to assess tumor dynamics, laying the foundation for future research (Table 5).[26] These three papers illuminate the prospects and

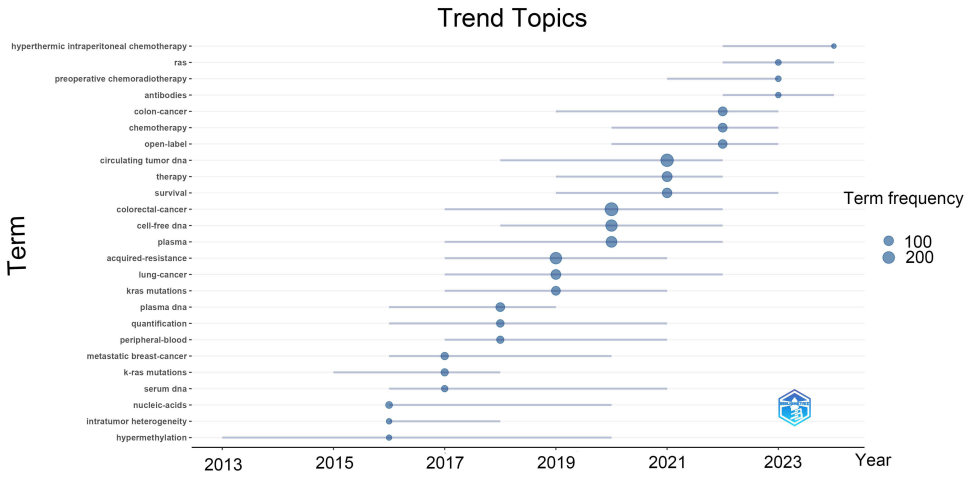

Figure 7 Topic trends related to field research.

potential applications of ctDNA in colorectal cancer research from various perspectives. Collectively, they represent the most influential publications in this domain.

We also performed a co-citation analysis utilizing VOSviewer, establishing a threshold of 50 citations, which yielded a selection of 80 documents. The resultant diagram categorizes the references into three distinct clusters, with larger and redder nodes indicating more frequently cited references. The three most frequently cited authors identified are Bettegowda C (2014, Science Translational Medicine), Diehl F (2008, Nature Medicine), and Tie J (2016, Science Translational Medicine) (Figure 8).

Discussion

This study utilizes bibliometric methods and data visualization techniques to conduct a comprehensive analysis of 1,054 articles related to ctDNA and colorectal cancer, published between 2004 and 2024. It not only describes the development of this field but also forecasts future trends. Since 2004, the literature has grown at an annual rate of 25.09%. The period from 2004 to 2014 marked the initial phase of research, producing 24 papers over that decade. Beginning in 2015, there was a rapid increase in publications, culminating in 1,030 papers by August 2024. Among these, Bettegowda's 2014 paper titled "Detection of Circulating Tumor DNA in Early- and Late-Stage Human Malignancies" garnered the highest number of citations. This landmark study effectively sparked widespread research interest, highlighting the growing significance of ctDNA. The study confirms that ctDNA is detectable in most patients with advanced tumors, including

Table 5 The ten Most Cited Documents Worldwide

Rank	Paper	Year	Total Citations	TC per Year	IF (2022)
1	Detection of circulating tumor DNA in early- and late-stage human malignancies	2014	3311	301.00	15.8
2	ESMO consensus guidelines for the management of patients with metastatic colorectal cancer	2016	2400	266.67	56.7
3	Circulating mutant DNA to assess tumor dynamics	2008	1985	116.76	58.7
4	Liquid biopsies come of age: towards implementation of circulating tumour DNA	2017	1602	200.25	72.5
5	Liquid biopsy: monitoring cancer-genetics in the blood	2013	1300	108.33	81.1
6	Integrating liquid biopsies into the management of cancer	2017	1243	155.38	81.1
7	Clinical Applications of Circulating Tumor Cells and Circulating Tumor DNA as Liquid Biopsy	2016	979	108.78	29.7
8	Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer	2016	964	107.11	15.8
9	Direct detection of early-stage cancers using circulating tumor DNA	2017	739	92.38	15.8
10	Clonal evolution and resistance to EGFR blockade in the blood of colorectal cancer patients	2015	685	68.50	58.7

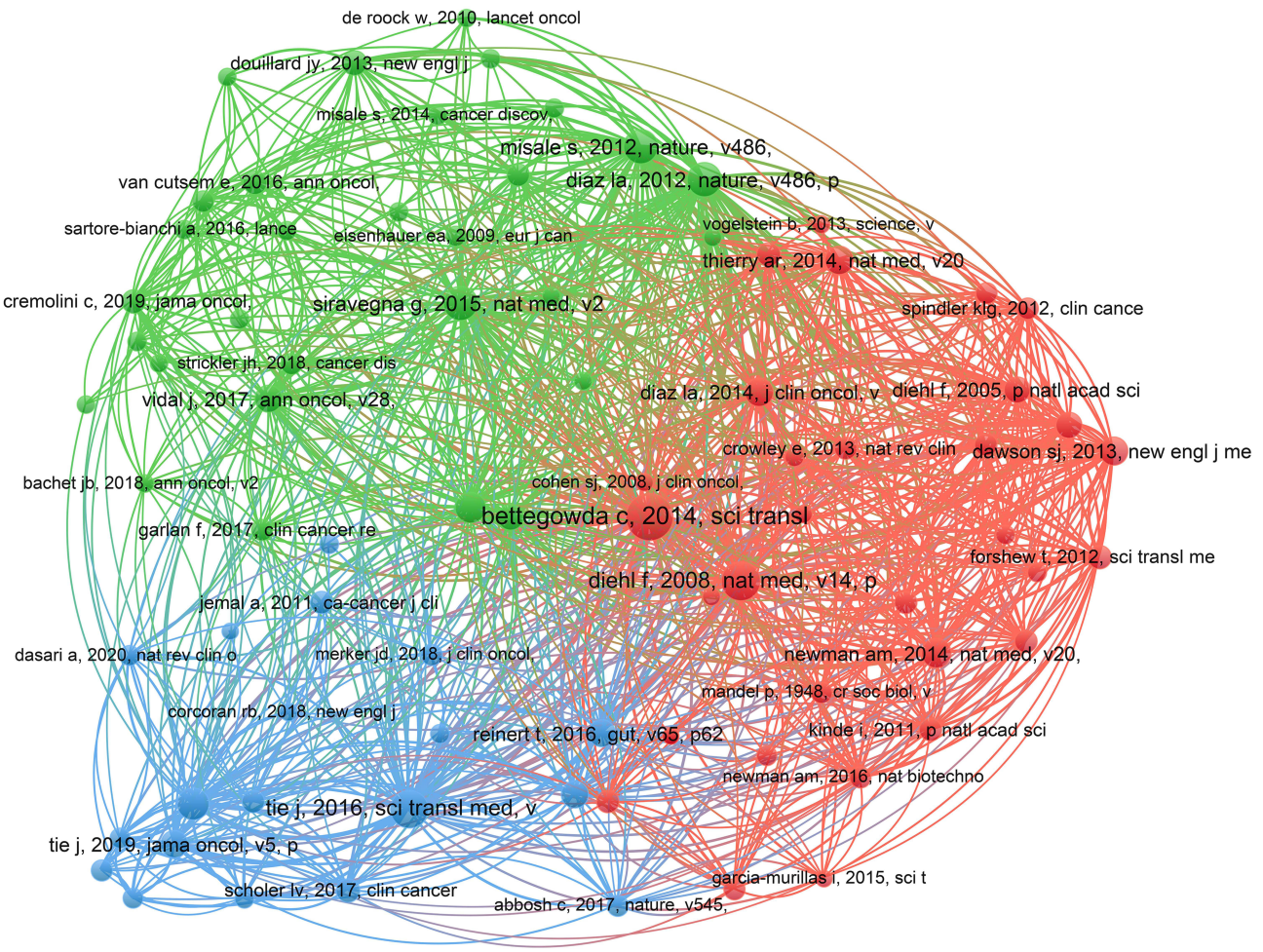

Figure 8 Reference co-citation network between 2004 and 2024.

those with pancreatic, ovarian, colorectal, bladder, and breast cancers. It exhibits high sensitivity and specificity, rendering it suitable for both clinical and research applications in oncology. Additionally, the study underscores ctDNA's potential as a liquid biopsy for detecting resistance mutations in EGFR-targeted therapies.[24] This study laid the foundation for subsequent research in the field.

The top five countries with the highest paper outputs are the USA (219), China (175), Italy (108), Japan (86), and France (56). In terms of citations, the leading countries are the USA (13,321), Italy (7,368), Australia (3,903), France (3,739), and China (3,552). These results highlight that the USA, China, Italy, France, Australia, and Japan are spearheading research in this field, with the USA clearly at the forefront. Despite China having the second-highest number of published articles, its citation count ranks fifth. This disparity suggests a need for China to enhance the quality of its research outputs.

Analyzing keywords can reveal emerging themes in the field and help predict future research directions, as research hotspots evolve over time. The years 2015–2024 represent a decade of rapid research development, which can be roughly divided into three phases based on thematic trends. Initially, there was significant interest in the relationship between ctDNA and intratumor heterogeneity and hypermethylation. Tumor heterogeneity refers to the presence of diverse cell populations within the same tumor, each possibly harboring different genetic mutations, phenotypes, and biological characteristics. ctDNA can reflect this heterogeneity because it contains DNA fragments from various tumor cells, thereby providing insights into the tumor's diversity.[10] Hypermethylation refers to an abnormal increase in DNA methylation levels, often associated with the onset and progression of tumors. In ctDNA, specific gene hypermethylation

patterns can be detected, serving as biomarkers for the early detection and monitoring of tumors.[27] In summary, ctDNA not only reflects tumor heterogeneity but also provides important information about tumor characteristics through hypermethylation markers, making it significant for tumor monitoring and personalized treatment.

The second phase primarily focuses on investigating the role of ctDNA in quantitative detection in serum/plasma, early cancer screening, and molecular mutation analysis including KRAS and microsatellite instability (MSI). ctDNA can be quantitatively detected in serum or plasma, offering a non-invasive method to assess tumor burden. The concentration of ctDNA often correlates with tumor size and stage, allowing for real-time monitoring of disease progression and treatment response.[27] ctDNA serves as a promising biomarker for early cancer detection. Abnormalities in ctDNA, such as specific methylation patterns or mutations, can indicate the presence of tumors even before clinical symptoms emerge or imaging abnormalities are detected. Studies have shown that ctDNA can enhance the sensitivity and specificity of early screening tests, potentially enabling earlier interventions and improving patient outcomes.[28–31] In molecular mutation analysis, both KRAS mutations and MSI status are crucial factors. Particularly, MSI detection has significant implications for colorectal cancer treatment, as MSI-positive colorectal cancer responds well to immune checkpoint inhibitor therapy. Compared to mismatch repair-proficient (MSI-L) colorectal cancer, mismatch repair-deficient (MSI-H) tumors show significantly higher expression levels of PD-L1 in immune cells, though no differences are observed among different MSI-H molecular subtypes. For MSI detection, it is recommended to use immunohistochemistry (IHC) and/or MSI testing to screen for defective DNA mismatch repair. It should be noted that IHC testing for mismatch repair mechanisms on the same germline mutation may yield different results, which could be attributed to somatic mutations.[32]

KRAS mutations are common in various cancers, particularly colorectal cancer, and are associated with poor prognosis and resistance to certain therapies. ctDNA analysis allows for the detection of these mutations in a non-invasive manner. The identification of KRAS mutations in ctDNA can guide treatment decisions, including the selection of targeted therapies and the monitoring of treatment efficacy. It can also help in assessing minimal residual disease (MRD) after surgery, providing insights into the likelihood of recurrence.[33,34] ctDNA is a valuable tool in oncology, offering a non-invasive approach for quantifying tumor DNA in serum/plasma, facilitating early cancer detection, and enabling the identification of critical mutations like KRAS, which can influence treatment strategies and patient management.

The third stage mainly studies the roles of ctDNA in survival, preoperative chemoradiotherapy, and hyperthermic intraperitoneal chemotherapy. The ctDNA level in cancer patients can serve as a prognostic indicator. Studies have shown that higher levels of ctDNA are associated with poorer overall survival (OS) and progression-free survival (PFS). For instance, patients with detectable ctDNA after surgery have a higher risk of recurrence compared to those without detectable ctDNA.[35] In patients with locally advanced cancer, ctDNA analysis can help assess the effectiveness of preoperative chemoradiotherapy. By measuring ctDNA levels before and after treatment, clinicians can evaluate the tumor's response to therapy, which may guide further treatment decisions.[36] It is possible to evaluate the effectiveness of HIPEC in treating peritoneal carcinomatosis using ctDNA. By analyzing ctDNA levels before and after HIPEC, clinicians can determine whether the treatment has successfully reduced the tumor burden.[37] In cancer management, ctDNA provides insight into survival outcomes, treatment efficacy, and disease monitoring. Its non-invasive nature allows for frequent testing, making it an attractive option for personalized cancer care. Further research and standardization of ctDNA testing methods are essential to fully integrate ctDNA into clinical practice for these applications.

Diehl et al first confirmed in 2008 the use of circulating mutant DNA to assess tumor dynamics. In 2014, Bettegowda et al employed digital polymerase chain reaction-based technologies to evaluate ctDNA's capability in detecting tumors among 640 patients with various types of cancer, demonstrating its potential in tumor detection. This pivotal finding ignited significant enthusiasm among researchers, leading to a rapid increase in published studies within this field. The sensitivity of ctDNA in detecting clinically relevant KRAS gene mutations is 87.2%, with a specificity of 99.2%. Moreover, ctDNA can provide insights into resistance mechanisms. In 2016, Van Cutsem et al proposed the application of ctDNA in patients with metastatic colorectal cancer. The ctDNA level can be used for the molecular typing of tumors, non-invasive detection of tumor mutations, and guiding responses to EGFR antibody treatment, showcasing its broad application prospects. Studies have shown that KRAS gene mutations are associated with reduced disease-free survival and overall survival in patients with MSI-L tumors, and can predict patient response to anti-EGFR therapy.[38] Individuals

carrying KRAS mutations typically respond poorly to treatments such as cetuximab and panitumumab, while KRAS wild-type patients are more likely to benefit. Additionally, KRAS mutations may promote tumor progression and drug resistance by activating downstream EGFR pathways.[39]

Beyond genetic mutations detectable in ctDNA, aberrantly expressed microRNAs (miRNAs) in blood and body fluids have emerged as crucial molecular markers in CRC. These small non-coding RNAs function as both tumor suppressors and oncogenes, playing vital roles in tumor initiation, progression, and metastasis. Specifically, high expression of miR-320e is associated with disease progression and poor prognosis, while downregulation of miR-148a correlates with CRC development and progression. Furthermore, a panel of miRNAs including miR-31, miR-141, and miR-16 has demonstrated significant value in monitoring postoperative recurrence of CRC.[40–42]

The predictive value of miRNAs in treatment response has been particularly noteworthy in metastatic CRC patients receiving targeted therapies. For anti-VEGF therapy, upregulation of miR-126 strongly correlates with bevacizumab resistance, potentially through modulation of VEGF signaling pathways. In the context of anti-EGFR therapy, a distinct miRNA signature has been identified: overexpression of miR-31, miR-100, and miR-125b, along with downregulation of miR-7, is associated with cetuximab resistance.[39,43,44] These miRNAs may influence treatment outcomes by regulating key signaling pathways involved in drug response and resistance mechanisms.[45] Recent studies have also revealed that specific miRNA expression patterns can predict treatment efficacy before therapy initiation, offering potential for treatment stratification and personalized medicine approaches.[46] Moreover, emerging evidence suggests that targeting these dysregulated miRNAs, particularly in KRAS-mutant CRC, may represent a promising therapeutic strategy.[47] This understanding provides new directions for developing innovative treatment approaches, especially for patients with limited therapeutic options.[48] Despite its potential, ctDNA liquid biopsy is not yet standard for guiding treatment decisions in routine clinical practice. The clinical utility of ctDNA continues to be validated through ongoing clinical trials.

Currently, several ctDNA testing products have been approved in the market. For instance, the FDA has approved the plasma SEPT9 gene methylation detection kit for the auxiliary diagnosis of colorectal cancer. These kits not only enhance the accuracy of early cancer screening but also offer more personalized treatment options for patients.

To enable the widespread clinical application of ctDNA, it is essential to improve detection technologies to enhance sensitivity and specificity. Additionally, establishing standardized testing procedures and result evaluation criteria is crucial. These improvements will help integrate ctDNA testing more effectively into routine clinical practice, ensuring reliable and consistent results across different settings.

Limitations

Several limitations of our study should be noted: 1) Database Limitation: The study exclusively utilized articles and reviews indexed in the Web of Science Core Collection database. This methodological choice may have resulted in the exclusion of significant papers available in other databases, such as PubMed and Scopus. 2) Language Limitation: The analysis was confined to literature published in English. Consequently, this restriction may have led to the omission of pertinent research published in other languages, thereby potentially rendering the search results incomplete.

Conclusions

This bibliometric analysis offers an extensive examination of the research landscape pertaining to ctDNA in colorectal cancer over the past two decades. The marked rise in publications since 2015 underscores an escalating academic interest and highlights the potential of ctDNA as a transformative tool in oncology. The analysis of keywords reveals that ctDNA is pivotal not only for early cancer detection and monitoring treatment responses but also for assessing minimal residual disease and predicting recurrence. The United States, China, and Italy are leading contributors to this research domain, with numerous prolific authors driving the advancement of knowledge. As the field progresses, emerging topics such as the role of ctDNA in evaluating survival rates, the efficacy of preoperative chemotherapy, and the application of hyperthermic intraperitoneal chemotherapy in colorectal cancer patients are poised to shape future investigations. Collectively, ctDNA represents a promising avenue for improving clinical outcomes in colorectal cancer, necessitating further exploration and validation within clinical settings.

Data Sharing Statement

The original contributions are included in the article material. For further information, please contact the corresponding author.

Ethics Statement

According to local legislation and institutional requirements, no ethical review or approval was required for the study on human participants.

Acknowledgment

Thank you to all authors who participated in the study.

Funding

This research was not funded by any specific grant from a public, commercial, or not-for-profit funding agency.

Disclosure

The authors reports no conflicts of interest.

References

1. Siegel RL, Miller KD. Colorectal cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(3):145–164. doi:10.3322/caac.21601
2. Siegel RL, Miller KD. Cancer statistics, 2023. *CA Cancer J Clin*. 2023;73(1):17–48. doi:10.3322/caac.21772
3. Osseis M, Nehmeh WA, Rassy N, Derienne J. Surgery for T4 colorectal cancer in older patients: determinants of outcomes. *J Pers Med*. 2022;12(9):1534. doi:10.3390/jpm12091534
4. Rassy E, Parent P, Lefort F, Boussios S, Baciarello G, Pavlidis N. New rising entities in cancer of unknown primary: is there a real therapeutic benefit? Critical reviews in oncology/hematology. *Crit Rev Oncol Hematol*. 2020;147:102882. doi:10.1016/j.critrevonc.2020.102882
5. Shaukat A, Levin TR. Current and future colorectal cancer screening strategies. *Nat Rev Gastroenterol Hepatol*. 2022;19(8):521–531. doi:10.1038/s41575-022-00612-y
6. Hanna M, Dey N, Grady WM. Emerging tests for noninvasive colorectal cancer screening. *Clin Gastroenterol Hepatol*. 2023;21(3):604–616. doi:10.1016/j.cgh.2022.12.008
7. Imperiale TF, Ransohoff DF, Itzkowitz SH. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med*. 2014;371(2):187–188. doi:10.1056/NEJMoa1311194
8. Tao XY, Li QQ, Zeng Y. Clinical application of liquid biopsy in colorectal cancer: detection, prediction, and treatment monitoring. *Mol Cancer*. 2024;23(1):145. doi:10.1186/s12943-024-02063-2
9. Marcuello M, Vymetalkova V, Neves RPL, et al. Circulating biomarkers for early detection and clinical management of colorectal cancer. *Mol Aspects Med*. 2019;69:107–122. doi:10.1016/j.mam.2019.06.002
10. Tivey A, Church M. Circulating tumour DNA - looking beyond the blood. *Nat Rev Clin Oncol*. 2022;19(9):600–612. doi:10.1038/s41571-022-00660-y
11. Abbosh C, Birkbak NJ, Wilson GA, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. *Nature*. 2017;545:7655):446–51. doi:10.1038/nature22364
12. Heitzer E, Haque IS. Current and future perspectives of liquid biopsies in genomics-driven oncology. *Nat Rev Genet*. 2019;20(2):71–88. doi:10.1038/s41576-018-0071-5
13. Luo H, Zhao Q. Circulating tumor DNA methylation profiles enable early diagnosis, prognosis prediction, and screening for colorectal cancer. *Sci Transl Med*. 2020;12(524). doi:10.1126/scitranslmed.aax7533
14. Xu F, Yu S, Han J, et al. Detection of circulating tumor DNA methylation in diagnosis of colorectal cancer. *Clin Transl Gastroenterol*. 2021;12(8):e00386. doi:10.14309/ctg.0000000000000386
15. Tie J, Wang Y, Tomasetti C, et al. Circulating tumor DNA analysis detects minimal residual disease and predicts recurrence in patients with stage II colon cancer. Science translational medicine. *Sci Transl Med*. 2016;8(346):346ra92. doi:10.1126/scitranslmed.aaf6219
16. Boysen AK, Pallisgaard N, Andersen CSA, Spindler KG. Circulating tumor DNA as a marker of minimal residual disease following local treatment of metastases from colorectal cancer. *Acta Oncol*. 2020;59(12):1424–1429. doi:10.1080/0284186x.2020.1806357
17. Chen G, Peng J, Xiao Q, et al. Postoperative circulating tumor DNA as markers of recurrence risk in stages II to III colorectal cancer. *J Hematol Oncol*. 2021;14(1):80. doi:10.1186/s13045-021-01089-z
18. Wang F, Zhao Q, Wang YN, et al. Evaluation of POLE and POLD1 mutations as biomarkers for immunotherapy outcomes across multiple cancer types. *JAMA Oncol*. 2019;5(10):1504–1506. doi:10.1001/jamaoncol.2019.2963
19. Lecomte T, Berger A, Zinzindohoué F, et al. Detection of free-circulating tumor-associated DNA in plasma of colorectal cancer patients and its association with prognosis. *Int J Cancer*. 2002;100(5):542–548. doi:10.1002/ijc.10526
20. van Eck NJ, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. *Scientometrics*. 2010;84(2):523–538. doi:10.1007/s11192-009-0146-3
21. Hirsch JE. An index to quantify an individual's scientific research output. *Proc Natl Acad Sci U S A*. 2005;102(46):16569–16572. doi:10.1073/pnas.0507655102
22. Naranan S. Bradford's law of bibliography of science: an interpretation. *Nature*. 1970;227(5258):631–632. doi:10.1038/227631a0

23. Sa R, Xu Y, Pan X, et al. A bibliometric analysis of research progress on pharmacovigilance and cancer from 2002 to 2021. *Front Oncol*. 2023;13:1078254. doi:10.3389/fonc.2023.1078254
24. Bettegowda C, Sausen M, Leary RJ, et al. Detection of circulating tumor DNA in early- and late-stage human malignancies. Science translational medicine. *Sci Transl Med*. 2014;6(224):224ra24. doi:10.1126/scitranslmed.3007094
25. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol*. 2016;27(8):1386–1422. doi:10.1093/annonc/mdw235
26. Diehl F, Schmidt K, Choti MA, et al. Circulating mutant DNA to assess tumor dynamics. *Nat Med*. 2008;14(9):985–990. doi:10.1038/nm.1789
27. Schøler LV, Reinert T, Ørntoft MW, et al. Clinical implications of monitoring circulating tumor DNA in patients with colorectal cancer. *Clin Cancer Res*. 2017;23(18):5437–5445. doi:10.1158/1078-0432.ccr-17-0510
28. Ryu H, Kim JH, Kim YJ, et al. Quantification method of ctDNA using cell-free DNA methylation profile for noninvasive screening and monitoring of colon cancer. *Clin Clin Epigenet*. 2024;16(1):95. doi:10.1186/s13148-024-01708-9
29. Wang F, Li X, Li M, et al. Ultra-short cell-free DNA fragments enhance cancer early detection in a multi-analyte blood test combining mutation, protein and fragmentomics. *Clin Chem Lab Med*. 2024;62(1):168–177. doi:10.1515/cclm-2023-0541
30. Bessa X, Vidal J, Balboa JC, et al. High accuracy of a blood ctDNA-based multimodal test to detect colorectal cancer. *Ann Oncol*. 2023;34 (12):1187–1193. doi:10.1016/j.annonc.2023.09.3113
31. Nguyen VTC, Nguyen TH, Doan NNT, Pham TMQ, Nguyen GTH. Multimodal analysis of methylomics and fragmentomics in plasma cell-free DNA for multi-cancer early detection and localization. *Elife*. 2023;12. doi:10.7554/eLife.89083
32. Adeleke S, Haslam A, Choy A, Diaz-Cano S, Galante JR. Microsatellite instability testing in colorectal patients with Lynch syndrome: lessons learned from a case report and how to avoid such pitfalls. *Per Med*. 2022;19(4):277–286. doi:10.2217/pme-2021-0128
33. Wang JY, Hsieh JS, Chang MY, et al. Molecular detection of APC, K- ras, and p53 mutations in the serum of colorectal cancer patients as circulating biomarkers. *World J Surg*. 2004;28(7):721–726. doi:10.1007/s00268-004-7366-8
34. Sefrioui D, Sarafan-Vasseur N, Beaussire L, et al. Clinical value of chip-based digital-PCR platform for the detection of circulating DNA in metastatic colorectal cancer. *Dig Liver Dis*. 2015;47(10):884–890. doi:10.1016/j.dld.2015.05.023
35. Schraa SJ, van Rooijen KL, van der Kruijssen DEW, et al. Circulating tumor DNA guided adjuvant chemotherapy in stage II colon cancer (MEDOCC-CrEATE): study protocol for a trial within a cohort study. *BMC Cancer*. 2020;20(1):790. doi:10.1186/s12885-020-07252-y
36. Emiloju OE, Storandt M, Zemla T, Tran N. Tumor-informed circulating tumor DNA for minimal residual disease detection in the management of colorectal cancer. *JCO Precis Oncol*. 2024;8:e2300127. doi:10.1200/PO.23.00127
37. Dhiman A, Kothary V, Witmer HDD, et al. Role of tumor-informed personalized circulating tumor DNA assay in informing recurrence in patients with peritoneal metastases from colorectal and high-grade appendix cancer undergoing curative-intent surgery. *Ann Surg*. 2023;278(6):925–931. doi:10.1097/sla.0000000000005856
38. Phipps AI, Buchanan DD, Makar KW, et al. KRAS-mutation status in relation to colorectal cancer survival: the joint impact of correlated tumour markers. *Br J Cancer*. 2013;108(8):1757–1764. doi:10.1038/bjc.2013.118
39. Boussios S, Ozturk MA. The developing story of predictive biomarkers in colorectal cancer. *J Pers Med*. 2019;9(1):12. doi:10.3390/jpm9010012
40. Perez-Carbonell L, Sinicrope FA, Alberts SR, et al. MiR-320e is a novel prognostic biomarker in colorectal cancer. *Br J Cancer*. 2015;113 (1):83–90. doi:10.1038/bjc.2015
41. Hibino Y, Sakamoto N, Naito Y, et al. Significance of miR-148a in colorectal neoplasia: downregulation of miR-148a contributes to the carcinogenesis and cell invasion of colorectal cancer. *Pathobiology*. 2015;82(5):233–241. doi:10.1159/000438826
42. Yuan Z, Baker K, Redman MW, et al. Dynamic plasma microRNAs are biomarkers for prognosis and early detection of recurrence in colorectal cancer. *Br J Cancer*. 2017;117(8):1202–1210. doi:10.1038/bjc.2017.266
43. Suto T, Yokobori T, Yajima R, et al. MicroRNA-7 expression in colorectal cancer is associated with poor prognosis and regulates cetuximab sensitivity via EGFR regulation. *Carcinogenesis*. 2015;36(3):338–345. doi:10.1093/carcin/bgu242
44. Lu Y, Zhao X. lncRNA MIR100HG-derived miR-100 and miR-125b mediate cetuximab resistance via Wnt/β-catenin signaling. *Nat Med*. 2017;23 (11):1331–1341. doi:10.1038/nm.4424
45. Xiong B, Huang Q, Zheng H, Lin S, Xu J. Recent advances microRNAs and metabolic reprogramming in colorectal cancer research. *Front Oncol*. 2023;13:1165862. doi:10.3389/fonc.2023.1165862
46. Jassi C, Kuo WW, Chang YC, et al. MicroRNA-376a-3p sensitizes CPT-11-resistant colorectal cancer by enhancing apoptosis and reversing the epithelial-to-mesenchymal transition (EMT) through the IGF1R/PI3K/AKT pathway. *Transl Oncol*. 2024;50:102125. doi:10.1016/j.tranon.2024.102125
47. Tang YL, Li DD, Duan JY, Sheng LM, Wang X. Resistance to targeted therapy in metastatic colorectal cancer: current status and new developments. *World J Gastroenterol*. 2023;29(6):926–948. doi:10.3748/wjg.v29.i6.926
48. Bortoletto AS, Parchem RJ. KRAS hijacks the miRNA regulatory pathway in cancer. *Cancer Res*. 2023;83(10):1563–1572. doi:10.1158/0008-5472.CAN-23-0296