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Advancing Frontiers and Novel Insights in Colorectal Cancer

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Abstract

Colorectal cancer, a known form of cancer poses a global health threat. Ongoing studies are actively investigating perspectives and evolving treatments. This review explores the developments in cancer research covering topics such as profiling, microbiome interactions, immunotherapy, precision medicine, tumor environment analysis, liquid biopsies, metabolic changes, artificial intelligence applications and patient centric care. Molecular subtyping advancements have greatly improved our understanding of the nature of cancer and how different individuals respond to therapies. The significant link between gut microbiome composition, inflammation levels and immune responses underscores the importance of interventions targeting the microbiome and innovative immunotherapy strategies. Precision medicine initiatives are leveraging biomarkers and molecular signals to inform treatment decisions and optimize outcomes. This thorough examination highlights the impact of evolving trends in cancer research and treatment strategies while offering insights into directions for improving patient care and results.

Introduction

Cancer of the colon and rectum (CRC) is a concern causing a high number of deaths and placing a heavy burden, on healthcare systems and societies globally [1]. It is a form of cancer in developed countries leading to numerous cancer related fatalities. The rise in CRC cases in developing nations due to lifestyle changes and aging populations adds to the urgency for research and innovation to reduce its impact on individuals and communities [2].

In light of this situation, this review aims to explore perspectives and emerging trends in CRC research with the goal of addressing gaps in understanding and treatment approaches. By examining the developments in aspects of CRC biology, diagnosis and treatment this study seeks to identify promising pathways for enhancing patient outcomes and lessening the societal burden of CRC. Through an exploration, we explore areas such as genomic analysis, immunotherapy, precision medicine and artificial intelligence applications. By synthesizing the knowledge generated in these fields, our objective is to offer an overview of current CRC research status while highlighting areas with potential, for progress and innovation.

In today's age of precision medicine and personalized oncology having a grasp of the foundations underlying CRC has become crucial.

The detailed analysis of changes that trigger the onset, advancement and reaction, to treatment in CRC has been uncovered through genomic profiling [3]. Additionally progress in classification has made it easier to group CRC into molecular categories each with unique biological traits and medical implications. Utilizing this information offers potential for customizing treatment plans for patients enhancing treatment effectiveness and reducing unnecessary side effects [4]. The field of immunotherapy has brought about a transformation in cancer treatment methods providing a ray of hope for individuals with CRC. By utilizing the systems capabilities to target and eradicate cancer cells immunotherapy strategies like checkpoint inhibitors have shown promising outcomes in specific groups of CRC patients especially those with MSI H (high microsatellite instability) or dMMR (deficient mismatch repair) tumors. Challenges persist in pinpointing markers and overcoming resistance mechanisms to optimize the effectiveness of immunotherapy for CRC. In addition to targeted treatments understanding the interactions within the tumor microenvironment and stromal cells is shaping our comprehension of CRC biology and resistance mechanisms to treatments. The interrelationship among tumor cells, immune cells and stromal elements within the tumor environment plays a role in cancer progression and response to therapy. Grasping the communication between these components is vital for devising treatment approaches that can combat resistance issues and enhance patient outcomes.

The rise of biopsies and the integration of intelligence and computational methods are set to transform the diagnosis, monitoring and treatment decisions, for CRC. Liquid biopsies provide an invasive way to detect tumor biomarkers in the bloodstream allowing for real time tracking of disease progression and response to treatment [5]. At the time AI (Artificial Intelligence) algorithms are being designed to analyze datasets, such as genomic information and medical images in order to identify patterns and predictive indicators that can guide clinical decision making and improve patient care.

Overall, this analysis highlights the need for research and creativity in the realm of CRC. By delving into insights and emerging developments our goal is to pave the path for efficient prevention, diagnosis and treatment approaches that can ultimately lessen the impact of CRC on individuals and society. Through disciplinary cooperation and translating scientific breakthroughs into clinical applications we can work towards a future where CRC is not just treatable but preventable as well – leading to better outcomes and quality of life, for patients grappling with this devastating illness.

Methods

Literature search and selection criteria

Google Scholar, PubMed, SciFinder and Google Web were utilized to gather information, for this review article. Different keywords were employed to access the data from research and review articles. The papers referenced in this review were sourced from the period, between 2018 and 2024.

Discussion

Genomics and molecular subtyping of CRC

The recent progress in studying the profiles and subcategories of tumors represents a major step forward in our understanding of colorectal cancer and its clinical impact. These advancements have been made possible by the introduction of sequencing technologies allowing for an examination of CRCs genetic makeup [6]. Through initiatives like The Cancer Genome Atlas (TCGA) and collaborative research efforts scientists have identified subcategories of CRC distinguished by unique genetic changes gene activity patterns and biological pathways [7]. One notable classification system that has emerged from these studies is the Consensus Molecular Subtypes (CMS) which divides CRC into four categories; CMS1 (immune, CMS2 (standard) CMS3 (metabolic) and CMS4 (connective tissue) [8]. Each subtype displays

characteristics, environmental attributes and medical outcomes. For example, CMS1 tumors are marked by immune system activation with increased levels of cell presence and heightened activity in immune related pathways [9]. On the other hand, CMS4 tumors show tissue activation with noticeable signs of cellular transformation and blood vessel formation. Recognizing how molecular subtypes impact prognosis treatment response and targeted therapy selection is vital, for tailoring approaches in CRC [10].

Many research studies have shown the importance of categorizing tumors based on their characteristics with CMS4 tumors linked to poorer outcomes compared to other types. Molecular subtyping also helps predict how well certain treatments will work and identifies targets for therapy [11, 12]. For instance, CMS1 tumors, those with high microsatellite instability (MSI H) are more likely to respond to checkpoint inhibitors because of their immune system triggering features. On the other hand, CMS2 tumors, known for signaling pathways like WNT and MYC, may benefit from treatments targeting these pathways. Understanding subtypes gives us insights into how colorectal cancer progresses and becomes resistant to treatment. For example, CMS4 tumors are rich in processes related to interactions between the tumor and its surrounding tissue changes in the matrix and resistance to chemotherapy drugs [13]. In contrast, CMS1 tumors show signs of avoiding detection by the system and activating checkpoints suggesting that immunotherapy could be effective [14]. Despite advances in subtyping research there are still challenges such as tumor differences within and between patients and the need, for classification systems. It's crucial to refine our approach to subtyping by combining data from sources and confirming our findings in different groups of patients so we can apply these discoveries effectively in medical practice.

Furthermore, exploring the characteristics of cancer not only helps in understanding the diversity within tumors but also guides the creation of new treatment approaches and the identification of indicators that can predict outcomes. By investigating the makeup of CRC scientists have pinpointed targets and pathways that can be targeted for therapy. For instance, CMS4 tumors, known for their content and mesenchymal traits might respond well to treatments that focus on modifying the tumor environment or anti angiogenic therapies [15]. A study aimed to refine how CRCs are categorized by recognizing five subgroups, including those that posed challenges using existing classifications [16]. This method uncovered a population, with genetic mutations and expression patterns separate from established classifications. Notably patients grouped under the CMS4 category in stage III CRCs showed signs of disease indicated by levels of carcinoembryonic antigen (CEA) in their blood. Interestingly analyzing gene expressions and pathways in both tumor and tumor tissues revealed a specific immune profile in this subgroup with high CEA levels. The findings suggested that combining profiling techniques with traditional tumor markers like CEA could improve clinical decision making and potentially enhance treatment choices for colorectal cancer patients. Furthermore, molecular subtyping plays a role, in shaping drug development strategies and designing trials [17]. By categorizing patients based on subtypes scientists can enhance the groups participating in clinical trials with individuals who are more likely to respond well to specific treatments. This approach helps in making clinical trials more effective and increasing the chances of achieving results. Additionally, identifying subtypes enables the discovery of biomarkers that can act as indicators, for how a treatment is working simplifying the evaluation of treatment effectiveness in clinical trials.

In general, recent progress in analyzing profiles and molecular subtypes has provided insights into the genetic makeup of colorectal cancer. By distinguishing subtypes with unique biological traits and clinical behaviours molecular subtyping presents opportunities for tailoring treatment plans to predict outcomes and fostering innovation in treatments. Looking ahead, ongoing research efforts aimed at refining subtyping methods understanding biological processes better and applying discoveries in real world healthcare settings will be crucial, for enhancing outcomes and promoting precision medicine in managing colorectal cancer.

Role of microbiome and gut health in colorectal cancer development and progression

The community of microorganisms living in the gut known as the gut microbiome plays a role in the development and advancement of CRC. Research indicates that changes in the structure and function of the gut microbiome, called dysbiosis are linked to the beginning, growth and spread of CRC [18] (Table 1). Dysbiosis involves alterations in variety, quantity and metabolic processes that can result in the creation of substances, chronic inflammation and disruption of the intestinal barrier [19]. The relationship between microbiota, inflammation and immune response is a factor in how CRC develops. Changes in the gut microbiome due to dysbiosis can trigger reactions by activating toll receptors (TLRs) and producing inflammatory molecules like interleukin 6 (IL 6) and tumor necrosis factor alpha (TNF α) [20]. Persistent inflammation sets up an environment that promotes tumor growth characterized by stress, DNA harm and tissue restructuring which helps benign adenomas

progress into carcinomas. Moreover, inflammation caused by dysbiosis can influence how immune cells interact with tumors within the intestines such, as macrophages, dendritic cells. T lymphocytes affecting surveillance and tolerance [21].

The imbalance, in gut bacteria can disrupt the system affecting the body's ability to fight tumors and enabling cancer cells to evade detection. Certain types of bacteria play a role in either promoting or protecting against CRC development. For instance, bacteria like *Fusobacterium nucleatum* and *Enterococcus faecalis* are linked to CRC progression by releasing substances and triggering inflammation [22]. On the other hand, friendly bacteria like *Bifidobacterium* and *Lactobacillus* can help combat tumors by influencing responses strengthening the gut barrier and producing anti-inflammatory compounds [23].

Progress, in sequencing and the analysis of 16S rRNA have enhanced our knowledge of how the gut microbiome influences cancer. These methods aid in pinpointing the types of communities in the gut and their functions. By using probiotics and prebiotics to adjust the composition of the gut microbiome there is a potential to lower the risk of CRC or improve responses to treatment. For example, certain strains of bacteria such as *Faecalibacterium prausnitzii* have been researched for their inflammatory properties and possible protective effects against CRC. [24]. This underscores the significance of integrating microbiome focused approaches, into precision oncology practices.

Immunotherapy and Immunogenomics concept

The recent advancements in immunotherapy for CRC have led to progress in treatment options through the use of immune checkpoint inhibitors and adoptive cell therapies. Immune checkpoint inhibitors like pembrolizumab and nivolumab target pathways that inhibit the immune response, such as PD 1 and CTLA 4. By blocking these checkpoints immune checkpoint inhibitors enable the system to identify and combat cancer cells resulting in lasting anti tumor effects in some CRC patients [25, 26]. Additionally, adoptive cell therapies such as CAR T cell therapy and TIL therapy offer promising strategies to mobilize the system against CRC [27, 28]. CAR T cell therapy involves modifying patient derived T cells to express receptors that target tumor antigens while TIL therapy entails isolating and expanding tumor infiltrating lymphocytes with strong anti tumor capabilities before reintroducing them into the patient. These approaches provide targeted treatments for CRC offering long term remission outcomes even, in challenging cases.

The idea of immunogenomics, which combines genetic and immune profiling information shows a lot of potential for customizing immunotherapy treatments in CRC [29]. Immunogenomics aims to understand the relationship between tumor genetics, tumor immunity and the body's immune response to identify markers and treatment targets for immunotherapy. By studying the tumors environment and decoding immune related changes like tumor mutational burden (TMB) and microsatellite instability (MSI) immunogenomics can classify patients based on their chances of responding to immunotherapy and help in making treatment choices.

Type of Microbiome /Gut Health	Role in CRC Development & Progression	Examples
Composition of Gut Microbiota	Altered composition of gut microbiota characterized by dysbiosis is associated with CRC development.	• Increased abundance of *Fusobacterium nucleatum* • Presence of *Bacteroides fragilis* • Reduction in beneficial bacteria (e.g., *Bifidobacterium, lactobacillus*)
Microbial Metabolites Microbial Dysbiosis	• Production of metabolites by gut microbiota, such as short-chain fatty acids (SCFAs) and secondary bile acids, can influence CRC risk and progression. • Dysbiosis, characterized by imbalance in microbial community structure, promotes inflammation, epithelial barrier dysfunction, and tumor development.	• SCFAs (e.g., acetate, propionate, butyrate). • Secondary bile acids (e.g., deoxycholic acid). • Reduced microbial diversity. • Shift towards pro-inflammatory bacteria.
Mucosal Barrier Integrity	Intestinal epithelial barrier integrity is crucial for preventing microbial translocation and chronic inflammation, which are implicated in CRC development.	• Disruption of tight junctions • Impaired mucin production
Immune Modulation	Gut microbiota influence local and systemic immune responses, playing a key role in immune surveillance and anti-tumor immunity.	• Modulation of regulatory T cells (Tregs) • Activation of toll-like receptors (TLRs)
Microbiome-Mediated Inflammation	Microbiome-derived products, such as lipopolysaccharides (LPS) and peptidoglycans, trigger inflammation, which contributes to CRC initiation and progression.	• Release of inflammatory cytokines (e.g., IL-6, TNF-α). • Activation of NF-κB signaling pathway
Impact of Diet and Lifestyle	Diet and lifestyle factors modulate gut microbiota composition and function, influencing CRC risk and progression.	• High-fat diets • Low-fiber diets • Sedentary lifestyle

Table 1: Types and roles of microbiome and gut health in colorectal cancer development and progression.

In a study at one center, involving 60 diagnosed patients with colorectal cancer researchers looked at how common MSI was the number of mutations present and actionable changes in genes [30]. The study revealed a range in tumor mutational burden TMB levels varying from 5.08 to 2391 mutations per megabase. Interestingly 60% of patients had TMB levels with sided cancers showing higher rates

compared to left sided ones (100%, vs. 47%). Furthermore, most patients showed changes with APC, TP53 and BRCA2 gene mutations being the frequent ones observed.

It's interesting to note that gene fusion was not observed in any of the patients and mutations, in the type KRAS/NRAS genes were detected in all cases of cancer at the stage. However, there wasn't a link found between mutations and demographic or histological factors like age, gender, tumor type or tumor grade. The study emphasized the importance of identification of mutations and how tailoring targeted treatment based on these mutations could be beneficial. Specifically focusing on changes such as APC, TP53 and RAS mutations could potentially enhance outcomes for individuals with colorectal cancer. These results underscore the significance of genomic profiling in shaping treatment plans and exploring innovative therapeutic strategies for managing colorectal cancer.

Moreover, immunogenomics plays a role in developing combinations of therapies that work together with immunotherapy to boost immune responses against tumors and combat resistance mechanisms. For instance, targeting pathways that suppress the system like the adenosine pathway or myeloid derived suppressor cells (MDSCs) along with immune checkpoint inhibitors might enhance treatment effectiveness. Extend the benefits of immunotherapy to a wider range of patients [31, 32]. Overall advancements in immunotherapy, for CRC including checkpoint inhibitors and adoptive cell therapies show promise in enhancing patient outcomes. Immunogenomics is about tailoring immunotherapy to individuals making it possible to uncover biomarkers that can predict outcomes and develop combination treatments. By leveraging the body's system in the fight against CRC immunotherapy has the capacity to transform how we treat cancer and introduce a more precise approach, to oncology.

Precision Medicine and Biomarkers

The field of medicine in the treatment of cancer is rapidly progressing, thanks to advancements in genetics, molecular biology and targeted treatments. Personalized medicine aims to customize treatment plans for each patient based on their makeup in order to maximize treatment effectiveness and reduce side effects. One important aspect of medicine in cancer treatment is the growing use of techniques to analyze tumors at a molecular level through genome profiling. Technologies like next generation sequencing (NGS) and whole exome sequencing (WES) allow for an examination of tumor genomes helping identify specific genetic changes that promote tumor growth and progression. For instance, memorial sloan kettering-integrated mutation profiling of actionable cancer targets assay (MSK-IMPACT assay) is a targeted NGS panel that is used to identify the actionable mutations in cancer patients [33]. This molecular analysis offers insights into the biology of cancer and helps doctors choose targeted therapies that are likely to work best based on the tumors genetic profile.

Apart from profiling new biomarkers are being discovered for categorizing patients predicting treatment responses and detecting cancer early. For instance, markers like MSI and dMMR have been identified as indicators of how a patient might respond to immunotherapy in cancer [34]. Patients with MSI dMMR tumors have active immune responses against tumors and are more likely to benefit from drugs like pembrolizumab and nivolumab that enhance immune responses. These biomarkers have transformed the way we treat cancer by offering novel treatment options, for patients with stages of the disease.

In a study, researchers examined forty-two patients, with cancer and dMMR who were treated with neoadjuvant programmed cell death protein 1 (PD 1) blockade [35]. Their goal was to find markers that could predict how well patients would respond to this treatment. The study took an approach by analyzing transcriptomic profiles using next generation sequencing, as well as looking at immune cell density through multiplex immunofluorescence (mIF) staining. They also delved into single cell RNA sequencing data from studies and public datasets to better understand the tumor microenvironments impact on treatment response. The findings showed that the number of mutations in tumor tissue and plasma samples was similar in both groups of patients – those who responded completely to treatment and those who did not. However, the levels of HLA DQA1 and HLA DQB1 expression were notably higher in the group that responded well to treatment. Analysis of gene signatures revealed that pathways related to T cell receptors and antigen presentation were more active in the group. Additionally, a higher presence of CD8+ T cells before treatment was linked to a response. Further examination indicated that CD8+ T cells, with levels of programmed cell death protein 1Expressing (PD 1lo CD8+ T cells) with levels of TRGC2, CD160 and KLRB1, along with low levels of genes related to proliferation and exhaustion showed a strong connection to achieving a pathologic complete response (pCR). The research illustrated that immune related characteristics in CD8+ T cells played a key role in the pCR response to immune checkpoint inhibitor (ICI) treatment in colorectal cancer with dMMR. The diversity in the tumor microenvironment among dMMR cancer patients could help distinguish those to respond completely to neoadjuvant ICI therapy. These findings

underscore the importance of immune related markers in predicting treatment outcomes and guiding decisions for cancer. Moreover, various molecular markers like mutations in RAS and BRAF genes have been recognized as indicators for targeted treatments in cancer [36, 37]. Patients with RAS wild type tumors are candidates for EGFR therapy while individuals carrying BRAF V600E mutations might benefit from BRAF inhibitors combined with other targeted medications [38]. Additionally circulating biomarkers such as circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) show potential, for monitoring treatment responses anticipating disease relapse and early detection of cancer [39, 40].

Furthermore, advancements in imaging technologies like positron emission tomography (PET) with radiotracers that target specific molecular pathways provide chances for a non-invasive evaluation of tumor biology and treatment response in colorectal cancer [41, 42]. The use of c-Met targeting PET probes in cancer diagnosis and therapy monitoring is a subject of discussion in literature. Although there is data on these probes, they offer benefits such as combining anatomical and functional imaging for tumor removal and guided biopsies. However, there are disadvantages like radiation exposure and limited sensitivity for early-stage breast cancer diagnosis. PET imaging, PET/CT and PET/MRI improves the detection of metastases and assists in predicting how well treatments will work [43]. Yet challenges still exist including restrictions related to excretion lived radioactive elements and dependence on specific targets. Despite these challenges integrating imaging radiotracers with PET holds the promise of providing invasive real time diagnosis, personalized medicine and enhanced therapy monitoring which can usher in the era of radiotheranostics. Another research looked into the potential of immune PET is an invasive method for characterizing immune responses, to cancer while guiding anti-cancer treatments [44]. Immune PET has the potential to identify characteristics that can help with treatment choices tailored to individual patients.

The importance of markers, in the field of immunotherapy has been underscored. Immune PET shows potential in predicting how patients will respond to treatments like checkpoint inhibitors and CAR T cell therapy. Moreover, Immune PET could help monitor treatment progress leading to discontinuation of therapies and reducing financial burdens and health risks. The research highlighted the impact Immune PET could have on advancing our understanding of cancer immunobiology and streamlining trial design and regulatory processes. In general, the changing landscape of precision medicine, in cancer treatment involves incorporating profiling technologies and identifying key biomarkers for patient grouping predicting treatment responses and detecting cancer early. These advancements are reshaping how we manage cancer by allowing for treatment plans based on each patient's tumor characteristics.

Tumor Microenvironment and Stromal Interactions

Tumor cells, stromal components and the microenvironment play a role, in CRC development and treatment response. The CRC microenvironment consists of cells like cancer associated fibroblasts (CAFs) immune cells, endothelial cells and ECM elements [45]. These interactions impact aspects of tumor biology.

The communication between tumor cells and stromal components involves signaling pathways through factors, cell interactions and ECM changes. Tumor cells release growth factors and cytokines to attract cells that then produce proteins affecting tumor behaviour such as growth, invasion and spread. Immune cells present in the tumor environment can inhibit tumorigenesis based on their interactions with tumors and stroma. This interplay between tumors and surrounding tissues greatly influences resistance to therapy in CRC. Stromal elements like CAFs and ECM proteins can create obstacles that hinder drug effectiveness by limiting penetration [46]. Moreover, these stromal cells release substances that help tumors survive form blood vessels and evade the system – all contributing to resistance, against chemotherapy, targeted treatments and immunotherapy.

The surrounding environment, on a scale may trigger changes in the characteristics of cancer cells, such as transitioning from epithelial to mesenchymal forms and acquiring stem cell properties. These changes are linked to resistance to treatment and recurrence of the disease.

A potential approach in cancer treatment involves targeting cells around the tumor, such as cancer associated fibroblasts (CAFs) mesenchymal stem cells (MSCs) cancer related fat cells (CAAs) tumor blood vessel cells (TECs) and pericytes (PCs) [47]. These cells impact tumor behaviour through signaling between neighbouring cells or direct interactions. While some initially hinder tumor growth they can eventually adopt traits that promote tumor growth under the influence of cells. Targeting these cells aims to prevent their recruitment reprogram them or disrupt their communication with tumor cells. Despite promising findings in studies, efforts to target cells in clinical trials have been constrained by a lack of specific identifying characteristics. Recent advancements in analyzing individual cell RNA sequences provide insights into subtypes of cells which can guide treatments tailored to specific subtypes. New

therapeutic approaches focusing on disrupting communication between tumors and surrounding stroma in cancer are being investigated as ways to combat resistance to therapy and enhance treatment outcomes. Research is delving into interactions among the immune system tissues within the gut and colorectal cancer using advanced 'omics techniques to pinpoint targets, for therapies [48]. Understanding the cellular mechanisms, such, as changes in the Wnt signaling pathway, tumor budding and oncogenic characteristics within the tissue structure could pave the way for treatments and targeted therapies.

Challenges like oxygen levels (hypoxia) and resistance to drugs call for innovative strategies, such as addressing hypoxia directly and utilizing nanocarriers for delivering medications. The concept of the 'Seed and Soil' theory emphasizes the importance of disrupting both cells and their surrounding environment to impede metastasis. Immunotherapy approaches like checkpoint inhibitors and CAR T cell therapy offer hope especially when combined with immunotherapy to transform the tissue environment from exclusionary to immune infiltrated. Further investigation is essential to maximize these strategies potential explore immunotherapies and comprehend resistance mechanisms for developing combination therapies that boost effectiveness.

Innovative methods are designed to interrupt signaling pathways involved in tumor stroma interactions regulate the surroundings at a microscopic level and improve drug delivery specifically to cancer cells. For example, inhibitors that target the stromal derived factor 1 (SDF 1)/C-X-C chemokine receptor type 4 (CXCR4) pathway have shown results in laboratory models of cancer by hindering communication between tumors and their surrounding tissue while enhancing sensitivity to chemotherapy and immunotherapy [49, 50].

Utilizing nanoparticle-based systems for drug delivery along, with combination treatments that target components of the tumor microenvironment offer hope in overcoming challenges related to resistance [51]. Key obstacles involve enhancing the characteristics of nanocarriers such, as dimensions, morphology, surface charge and composition to target tumors. Tactics like altering surfaces and combining nanostructures can enhance durability and the rate of drug release. It is crucial to address worries about the toxicity of nanocarriers based on oxide (GO) through thorough research for their successful use in clinical settings. Several aspects, such as utilizing nanoscale drug delivery systems, for administering medications targeting tumors and activating drugs for tumors have been investigated [52].

Liquid Biopsies and Circulating Biomarkers

Liquid biopsies and circulating biomarkers show promise as invasive methods, for monitoring colorectal cancer (Table 2). They analyze samples from blood, stool or urine to provide up to date information on tumor behaviour genetic diversity and response to treatment. Circulating tumor DNA (ctDNA) is a biomarker that offers insights into factors like tumor size, residual disease presence after treatment and how well treatments are working. This information can guide treatment plans such as targeted therapies and immunotherapies. Recent research emphasizes that detectable ctDNA after treatment indicates a chance of cancer recurrence. Improvements in ctDNA testing could help identify patients at risk of recurrence potentially sparing them from chemotherapy [53]. In addition to ctDNA, circulating tumor RNA (ctRNA) and exosomes offer details on gene activity patterns and different molecular types of CRC [54]. A particular liquid biopsy assay, Guardant360 test, is used to identify actionable mutations in advanced CRC aiding in treatment decisions [55]. These insights further improve the accuracy of diagnosing the disease predicting its progression and determining how well treatments will work.

Compared to tissue biopsies, liquid biopsies have advantages like being less invasive and providing real time monitoring capabilities. However, they also face challenges related to sensitivity and limitations in detection capabilities. Current methods such as PCR and NGS often fall short in terms of sensitivity levels. Require resources for analysis. New technologies, like CRISPR/Cas based approaches and nanotechnology driven point of care tests show promise in detection of CRC offering comprehensive analysis of its molecular characteristics [56]. However, no single biomarker alone can accurately predict outcomes for cancer. This underscores the importance of using a combination of biopsy techniques to improve effectiveness.

Droplet microfluidics shows promise in addressing the challenges of biopsies by enhancing the detection of biomarkers at the level of cells and supporting studies on tumor variability [57, 58]. It offers benefits such as sample usage and high sensitivity by combining isolation and preparation processes on a chip to minimize contamination. Despite facing obstacles, like background interference and limited encapsulation efficiency droplet-based microfluidics, when coupled with AI for data analysis shows potential in advancing cancer management. The integration of biopsy methods is becoming increasingly crucial for a comprehensive evaluation of cancer leading to enhanced diagnostic capabilities monitoring procedures and personalized treatment approaches.

Application	Description
Early Detection	Detection of circulating tumor DNA (ctDNA), methylated DNA, or exosomal RNA in blood samples for early-stage CRC or precancerous lesions.
Disease Monitoring	Liquid biopsies allow for real-time monitoring of disease progression, recurrence, and response to treatment, providing valuable insights into tumor dynamics.
Prognostic Assessment	Analysis of circulating biomarkers such as ctDNA or CEA levels can predict patient outcomes, such as survival, recurrence, and treatment response.
Predictive Biomarkers	Identification of specific molecular alterations in liquid biopsies such as RAS mutations or MSI status can predict response to targeted therapies, chemotherapy, or immunotherapy targeting immune checkpoints (e.g., PD-1/PD-L1).
Minimal Residual Disease Detection	Detection of minimal residual disease (MRD) using liquid biopsies such as ctDNA can identify residual tumor cells after surgery or treatment, guiding adjuvant therapy decisions.
Surveillance	Liquid biopsies enable regular surveillance of CRC patients' post-treatment, allowing for early detection of recurrence and timely intervention.
Therapeutic Monitoring	Liquid biopsies facilitate monitoring of treatment response and resistance mechanisms, guiding adjustments in therapy to optimize patient outcomes.

Table 2: Utility of Liquid Biopsies and Circulating Biomarkers for CRC Monitoring.

Metabolic Reprogramming and Metabolomics

Metabolic changes are crucial, in the advancement of CRC and its resistance to treatment helping tumor cells adapt to their surroundings and withstand therapy related stress [59, 60]. In cancer, cells undergo shifts in metabolic pathways to meet the energy demands for growth, invasion and spread in challenging environments with limited nutrients. These adaptations allow tumor cells to survive in oxygen deprived conditions commonly found within tumors. A key change in CRC metabolism is the transition to glycolysis, known as the Warburg effect [61, 62]. This process enables tumor cells to produce energy and metabolic compounds when oxygen is available. This shift involves increased glucose intake, lactate production and changes in glycolytic enzyme levels like hexokinase and lactate dehydrogenase, CRC cells experience altered lipid metabolism characterized by increased lipid production, fatty acid absorption and lipid storage to support cell membrane formation and signaling important for tumor development [63, 64].

Moreover, modifications in amino acid metabolism—especially involving glutamine—play a role, in CRC advancement and resistance to treatment. Glutamine plays a role, as a provider of carbon and nitrogen for CRC cells supporting essential processes like the TCA cycle, nucleotide production and protection against oxidative stress. The increased use of glutamine is connected to the growth of tumors their spread to parts of the body and their resistance to chemotherapy and targeted treatments in CRC [65]. A study introduced a risk signature made up of five AAMRGs (ENOPH1, ACAT1, ALDH4A1, FAS and ASPG) where higher scores indicate survival outcomes in CRC. The effectiveness of this signature in predicting outcomes was confirmed [66]. Moreover, an analysis related to immunity showed connections between AAMRGs and the immune environment within tumors suggesting that patients with lower risk scores might have responses to immune based therapies. Additionally studying gene functions provided insights into the mechanisms involved and potential avenues for targeting amino acid metabolism therapy specifically for CRC.

The field of metabolomics shows promise in identifying metabolic weaknesses and developing targeted treatments for CRC as an area for exploration in research. Metabolomics involves an examination of molecule metabolites present, in biological samples; it sheds light on the overall metabolic landscape of CRC while pinpointing disrupted metabolic pathways that fuel tumor advancement and resistance to therapies.

By studying the metabolites linked to metabolic processes, like glycolysis, lipid metabolism and amino acid metabolism metabolomics research can pinpoint markers for diagnosing, predicting outcomes and gauging responses to treatment in CRC. Additionally using metabolomics methods shows potential for uncovering treatment targets and creating therapies that take advantage of metabolic weaknesses in CRC [67]. For instance, drugs that target enzymes in glycolysis (such as hexokinase) lipid metabolism (like fatty acid synthase) and glutamine metabolism (such as glutaminase) have demonstrated effectiveness in laboratory models of CRC. Are currently under assessment in clinical trials [68]. Furthermore, combining treatments that target metabolic pathways or pairing metabolic inhibitors with chemotherapy or immunotherapy presents encouraging tactics for overcoming resistance to therapy and enhancing results for individuals, with CRC.

Artificial Intelligence and Computational Approaches

Artificial intelligence (AI) and machine learning (ML) have become tools, in the field of CRC research and clinical practice transforming how diagnoses are made prognoses are determined and treatments are optimized [69, 70]. These computational methods utilize datasets and sophisticated algorithms to uncover insights from complex biological and clinical information leading to more precise and personalized care for patients with CRC. AI and ML algorithms have demonstrated performance in analyzing medical imaging data from CT scans, MRIs and colonoscopies [71]. They help clinicians identify lesions like polyps and tumors with accuracy. Additionally, AI driven systems can automate the analysis of images assisting pathologists in recognizing tissue characteristics and predicting tumor behavior based on visual features.

When it comes to prognosis, AI and ML models can analyze types of data – including genomic,

transcriptomic and proteomic profiles – to classify CRC patients into different molecular categories that carry prognostic importance [72]. These models can forecast outcomes like survival rates. Recurrence risks while pinpointing biomarkers linked to how patients respond to treatment or develop resistance. By integrating both information and molecular data AI powered prognostic tools enable precise risk evaluation and personalized treatment strategies for individuals with CRC. Furthermore, AI techniques play a role in optimizing treatment plans, for CRC patients [73].

These methods can analyze sets of clinical data to find predictive markers, for how well someone responds to treatment and their resistance to chemotherapy targeted therapy and immunotherapy. By considering patient traits and molecular profiles AI powered treatment plans can suggest personalized therapies based on each person's biology and disease progression. Recent research has shown the value of using computer-based methods in studying CRC from analyzing images to discovering drugs. For instance, advanced algorithms have been created using learning to study colonoscopy images and identify polyps and early-stage tumors with accuracy reducing the chances of missed diagnoses and unnecessary biopsies. A study introduced the idea of automated colonoscopy as an improvement over examination [74]. Manual colonoscopy is time consuming, subject to biases and affected by examiner fatigue. On the hand automated colonoscopy uses technology to aid in the examination process with the goal of improving accuracy and efficiency. The method discussed in the text focuses on achieving precision in both identifying polyps from surrounding tissue (polyp segmentation) and determining their type or nature (polyp classification). This precision is crucial, for enabling colonoscopy where the system can conduct examinations effectively without human involvement. The statement indicates that by showcasing the effectiveness of the proposed system, in an environment it could potentially become a tool in hospitals for colon care. Furthermore, it hints at the possibility of expanding this technology to detect polyps during procedures like gastroscopy thus widening its use and influence, in healthcare settings. Moreover, AI powered models have been leveraged to combine genomic and drug response information to pinpoint targets and repurpose current medications for treating CRC thereby speeding up drug discovery and development endeavours [75].

Patient-Centered Care and Survivorship

Patient focused care and programs, for survivors play a role in managing CRC catering to the needs of patients from diagnosis to survivorship. These programs stress the importance of care taking into account emotional, social and dietary aspects to improve overall wellbeing and quality of life. They prioritize involving patients in decision making processes empowering them to engage in their treatment plans. Survivorship programs offer support to patients after treatment by addressing symptoms, emotional challenges, dietary issues and long-term effects [76]. They provide monitoring, follow up care, encourage healthy lifestyle choices. Research underscores the importance of care from various disciplines and regular monitoring for effectively managing survivorship issues. Approaches include therapy sessions, support networks, nutritional advice, physical exercise recommendations, personalized care strategies and symptom control to enhance quality of life and lower the risk of cancer recurrence, among CRC survivors.

Cancer Vaccines

Several cancer vaccines are currently being studied in trials showing potential, for treating types of cancer. For example, there are mRNA vaccines like Moderna's mRNA 4157 and mRNA 5671 that target neoantigens and KRAS mutations found in cancer [77]. In trials, combining mRNA 4157 with pembrolizumab an immune checkpoint inhibitor has produced promising outcomes in treating solid tumors, including colorectal cancer. Peptide vaccines such as SurVaxM and IMA950 have also shown results in targeting survivin and multiple tumors associated peptides [78]. SurVaxM has exhibited survival benefits in glioblastoma trials while IMA950 has shown immunogenicity and some clinical advantages in studies for glioblastoma and other cancers. Dendritic cell vaccines like DCVAC/OvCa (SOTIO) have demonstrated progression survival when used with chemotherapy, in ovarian cancer phase II trials [79]. Similar strategies are being explored for cancer with trials suggesting potential immune responses and clinical benefits DNA vaccines, such, as VGX 3100 from Inovio Pharmaceuticals were initially created to target HPV related cancers. Are now being explored for applications [80]. Early-stage research is underway to adapt these vaccines for cancer (CRC) with results seen in preclinical studies regarding their ability to trigger immune responses. Personalized neoantigen vaccines like NEO PV 01 by Neon Therapeutics are designed to target neoantigens to each patient identified through genetic sequencing [81]. Another approach involves oncolytic virus vaccines like Talimogene laherparepvec (T VEC, Imlygic) which has been approved for treating melanoma [82]. Clinical trials are investigating its potential when combined with treatments for CRC showing signs of positive synergistic effects.

While many of these vaccines are still in testing phases there is optimism, about their ability to

stimulate immune responses and enhance outcomes for CRC patients. Success rates vary based on the type of vaccine cancer being treated and the characteristics of the population. Ongoing research and efforts to combine these vaccines with immunotherapies aim to improve their effectiveness.

Conclusion

This review summarizes the progress, in research and treatment for CRC emphasizing the complexity of the disease. It discusses profiling, interactions with the microbiome, immunotherapy, personalized medicine, tumor environment, liquid biopsies, metabolic changes, artificial intelligence and patient centered care. Understanding subtypes has enhanced our understanding of CRC diversity. Enabled personalized treatment approaches. The role of the gut microbiome and immune system in CRC development suggests interventions targeting these areas. Precision medicine utilizing biomarkers provides tailored treatments while insights into tumor interactions with surrounding tissue address challenges in treatment resistance. Liquid biopsies offer invasive monitoring and early detection supported by AI for informed decision making in drug development. Prioritizing patient centered care ensures an approach to managing CRC that improves quality of life and survivorship. These advancements present opportunities to translate research findings into practice to enhance prevention, diagnosis and treatment strategies, for CRC.

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Conflict of Interest

The author declare that there is no conflict of interest regarding the publication of this paper.

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