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REVIEW

Current Approaches, Challenges, and Future Perspectives in Colorectal Cancer Therapeutics and Integrated Care

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Abstract

Colorectal cancer (CRC) is one of the most frequently diagnosed malignancies and a key reason for the increase in the number of cancer-related deaths experienced all over the world, making it a serious global health concern. The approach for CRC is multidimensional managing the factors such as the tumor burden, molecular markers, and factors that are specific to the patient. The primary treatment for early-stage CRC is still the surgical removal of the tumor, and the adjuvant chemotherapy is recommended on the basis of the pathological staging, lymph node involvement, and the features that are high-risk. When it comes to mCRC, the treatment's initial objectives are to extend the patient life and to maintain the quality of life with the help of systemic treatments, localized interventions, and personalized strategies. In this review, we will present the cutting-edge technologies that have emerged and the contention that came up in CRC treatment, including the use of surgical methods, chemotherapy, radiotherapy, targeted therapy (e.g., anti-EGFR, anti-VEGF agents), immunotherapy (particularly for mismatch repair-deficient tumors), and the introduction of gene therapy and novel combinations of drugs which are still at the research stage are also discussed.

Keywords: Colorectal cancer- CRC therapeutics- targeted therapy- immunotherapy- metastatic CRC- precision oncology

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Introduction

Colorectal cancer (CRC) is a prominent health issue being the second most diagnosed and the second cause of death in cancer in the world. The latest projections announced 2 million fresh cases and 612,000 deaths in the United States in 2024 [1]. Of special interest is the fact that the mortality rates have been decreasing continuously since 1991, which has "prevented" over 4 million deaths, mainly due to the introduction of tobacco control policies, screening advancements, and therapeutic breakthroughs. Through the help of newer screening technologies and novel treatments, CRC patient management has improved tremendously. With the diagnosis being the primary guide, the treatment of modern CRC requires a widespread method that combines surgery, systemic therapies (chemotherapy, targeted agents, and immunotherapy), and radiotherapy, along with the addition of molecular characteristics and individualized patient factors [2, 3]. One of the main types of CRC not associated with metastasis is surgical resection, which is also the key type of curative treatment [4]. Following neoadjuvant chemotherapy and/or RT (in rectal cancer) can downstage tumors, improve resectability, and decrease local recurrence. Adjuvant therapy is recommended with reference to pathological findings, such as lymph node involvement, extra-mural vascular invasion, or high-risk features. In metastatic CRC (mCRC), systemic therapy-inclusive chemotherapy, biologics (anti-EGFR or anti-VEGF agents), and immunotherapy (for mismatch repair-deficient tumors)-is the premier approach, while surgery is admitted in select cases with oligometastatic disease or palliative intent [5, 6]. The latest breakthroughs in the targeted therapies (e.g., KRAS/BRAF inhibitors), immunotherapy (e.g., checkpoint inhibitors), and other new modalities like cancer vaccines, adoptive cell therapies (CAR-T), and gene editing have furnished the treatment options for both localized and advanced CRC

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[7, 8]. This publication recaps the prevailing standards, newly developing surgical solutions, and opposing views about cutting-edge surgical techniques in CRC, hence giving clinicians fact-supported recommendations for the best treatment of patients.

Surgery in Colorectal Cancer

Surgical Management of CRC has undergone major changes and is now treated with individually tailored strategies that are based on tumor location, stage, and molecular characteristics and incorporate oncologic treatment effectiveness with preservation of quality of life. In the case of localized disease, total surgical resection, which is still the main method for treating them, is completed by segmental colectomy and good lymphadenectomy (harvesting ≥12 nodes) as the standard for colon cancer and by total mesorectal excision (TME) in the case of rectal tumor to get the best possible oncological outcomes and avoid local recurrence [9-11]. The introduction of minimally invasive surgical methods (laparoscopic and robotic ones) due to the rearrangement of the area, in turn, brought similar oncological results apart from the advantages concerning postoperative morbidity and recovery but their strong application in the fight with advanced rectal cancers is still under discussion [12, 13]. Neoadjuvant therapy is one of the major players in the process, especially in the case of rectal cancer, in which chemoradiation is able to downstage tumors, promote resectability, and also increase the rate of sphincter preservation, the new found "watch-and-wait" strategy that provides organ preservation for a group of selected patients obtaining clinical complete response, the age long data of which though are not yet completely developed [6]. Management of lymph nodes still pertains to the classical lymphadenectomy concurrent with resection, sentinel node mapping is still in trial, and according to some studies, lateral pelvic lymph node dissection could be performed on certain rectal carcinoma patients [14]. In cases with metastatic settings, surgery still remains important in the case of oligometastatic disease where the combination of resection or ablation of metastases in the liver/lung, followed by perioperative chemotherapy treatment could provide patients with long-term results. Peritoneal metastases have been studied with controversial approaches like cytoreductive surgery with HIPEC although these ideas are still in the process of being officially declared [15]. The locoregional recurrences can be checked by radical re-resection which is possible in some cases that is required for R0 resection but decision-making will also be influenced by functional aspects such as sphincter preservation and nerve-sparing approaches that are now being more and more included [11, 16]. As a progressive step, the interconnection of liquid biopsies (especially ctDNA for recurrence risk stratification) and advanced technologies like augmented reality and AI-assisted surgery should further sharpen the precision of lymph node dissection and margin assessment, which may change the whole surgery [17]. With this area developing and expanding, the multidisciplinary team still remains the key to achieving a fine line between eliminating cancer to the max degree and function and quality of life of the patient, with the research still going on in the context of the rules and the types of surgery associated with the entire sector of CRC management which get better with each passing modification of the patient selection process.

Chemotherapy in Colorectal Cancer

CRC has a prominent area in the area of chemotherapy and chemotherapy stands in front in the multidisciplinary efforts for dealing with CRC where it finds applications in preoperative, postoperative, and palliative cases [18, 19]. In the case of locally advanced rectal cancer, use of neoadjuvant chemoradiation (usually 5-FU or capecitabine-based regimens along with radiotherapy) has turned out to be the standard situation and it has now been established as such, it is the standard procedure for significant tumor downstaging, improvement in sphincter preservation rates, and the reduction of the local recurrence compared to surgery alone. In the case of colon cancer, the adjuvant regimen with FOLFOX (5-FU, leucovorin plus oxaliplatin) or CAPOX (capecitabine plus oxaliplatin) will be recommended for a stage III or a high-risk stage II disease, as it will reduce the potential recurrence by about 30-40% [20, 21]. The initiation of adjuvant chemotherapy is the most important factor in time, where it begins within 6-8 weeks after surgery associated with the best possible outcome, but newly released data results of circulating tumor DNA (ctDNA) could help to determine the decision of patient selection [22-25]. Chemotherapy is the main form of treatment in the metastatic state, including the possibility of using FOLFOX, FOLFIRI (5-FU, leucovorin, and irinotecan), or the combinations with targeted agents (anti-EGFR or anti-VEGF therapies) as first-line options [26]. In the latest breakthroughs, molecular profiling takes centre stage in chemotherapy decision-making, where deficient mismatch repair (dMMR)/microsatellite instability-high (MSI-H) tumors, which rarely benefit the use of conventional 5-FU-based adjuvant therapy but heal remarkably well to immunotherapy [27, 28]. In cases with proficient MMR (pMMR) tumors, studies propose the combinación of irinoteça in adjuvant regimens and temporary strategies maintenance (like 5-FU/bevacizumab after the starting induction therapy) in the case of the evolving disease. The ideal length of adjuvant therapy keeps circling the table, with debates arising whether three months are as effective as six for some low-risk patients, particularly in preventing oxaliplatin-related neurotoxicity. New biomarkers such as the concept of conversion therapy have gained traction, where aggressive chemotherapy regimens (usually FOLFOXIRI - 5-FU, leucovorin, oxaliplatin, and irinotecan) together with biologics make it possible, in a limited number of patients, to make surgically unresectable liver metastases operable. The thymidylate synthase expression and dihydropyrimidine dehydrogenase activity levels may be used to further tailor chemotherapy programs and the dosing of the drugs, while innovations in drug forms and transit systems will always boost treatment quality and convenience.

Radiotherapy in Colorectal Cancer

Radiotherapy (RT) remains a paramount fixture in the interdisciplinary management of CRC (CRC), especially in rectal cancer cases where the neoadjuvant chemoradiation (nCRT) is currently the therapy of choice for the stage locally advanced disease (T3-4 or N+) [29, 30]. Multiple large randomized trials have identified consistently the effect of the preoperative RT in reducing effectively the local recurrence rates with respect to surgery alone, with two proven approaches being long-course chemoradiation (45-50 Gy over 5 weeks with concurrent 5-FU or capecitabine) and short-course RT (25 Gy in 5 fractions). Short-course RT, on the other hand, not only demonstrates practical advantages but also has similar oncological outcomes for most patients, while long-course chemoradiation still remains the favored treatment for cases, in which the downstaging of the tumor may assist in the sphincter preservation operation [31, 32]. The concept of total neoadjuvant therapy (TNT), which includes administering systemic chemotherapy prior to or after the nCRT, has been examined in recent studies and the results are quite promising showing improved rates of the pathologic complete response and distant control of the disease [6, 33]. Compared to the role of RT in colon cancer where it is not that extensive, it can be taken into consideration in particular cases, which possess high-risk features (T4 disease, positive margins, or resectable recurrence). Intraoperative radiotherapy (IORT) is the boost that can be used in cases where the close or positive margins are concerned particularly in the local recurrent rectal cancer. The advent of such new technology as intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) has led to the advancement in precision and dose escalation to target volumes while toxicity to adjacent organs (e.g., small bowel, bladder, and sexual function structures) could be minimized. The topic of nodal irradiation in rectal cancer is still a frontier area of research. While typically the fields will include the mesorectum and internal iliac nodes, it is ambiguous whether the use of additional proximal nodal coverage (common iliac or para-aortic) would actually benefit high-risk patients. The best way to deal with pelvic lateral lymph nodes in rectal cancer is also changing with time, and some institutions favour the approach of unstabilizing the nodes with a selective nodal irradiation followed by a surgical excision in node-positive cases. Postoperative RT is in the main experimental with patients with positive margins or other high-risk features not treated preoperatively, although the benefit it produces has to be offset by the increased toxicity risks to the previously irradiated tissues [34, 35]. Novel strategies embody the concept of organ preservation for those who respond very well clinically after nCRT ("watch-and-wait"), however, a proper selection of patients and following exact guidelines are imperative [36, 37]. Progressions in the field of radiomics and functional imaging bring about the better assessment of response and planning of RT, notwithstanding the novelty of techniques such as proton therapy being applied to lessen toxicity of treatment even further. Ongoing clinical trials are still making progress in fine-tuning the combination of RT with systemic therapies as well as optimizing the application of the entire spectrum of CRC management [38-41].

Endocrine therapy in Colorectal Cancer

Endocrine therapy, of course, is an essential treatment in hormone receptor-positive breast cancer (42, 43], but at present, it has no defined role in CRC (CRC) management, even though many hormonal pathways have been studied as possible influencers in CRC pathogenesis and progression [44]. Observations from epidemiology imply the potential protective effects of Strogen in CRC, mainly the emphasis on the diminished number of cases that occur in postmenopausal women under the hormone replacement therapy, whereas preclinical studies showed different patches of Strogen receptors (ER-α and ER-β) in CRC tissues, of which ER-β was suggested to inhibit the growth of the tumor via anti-proliferative and pro-differentiation pathways, yet these results have not been reflected in the clinical application of anti-Strogen therapies [45]. The vitamin D endocrine system has also been investigated as an area of interest with extensive preclinical supporting data for the vitamin D receptor (VDR) signaling's proposition of CRC progression modulation through cell differentiation, apoptosis, and Wnt/β-catenin pathway regulation leading to ongoing clinical trials of high-dose vitamin D supplementation as adjuvant therapy; moreover, the VDR expression may also be the prognostic biomarker for some CRC subtypes [46-49]. The insulin-like growth factor (IGF) pathway has also been carried into the conversation when it comes to CRC progression, where the IGF-1/IGF-1R axis was found to play a major role in tumor growth and metastasis, but the early clinical trials testing IGF-1R inhibitors on their own did not show any successful results leading to todayHw exploration of combination with cytotoxic or targeted agents, particularly in the context of metabolic comorbidities like diabetes and obesity that affect CRC risk and treatment outcomes through hormonal mechanisms [50, 51]. The recently emerging studies have distinguished the bile acid metabolism and the Farnesoid X receptor (FXR) signaling as the most likely therapeutic targets since they take part in the inflow and the intestine's homeostasis, while gut hormone receptors like GLP-1 and GIP are being studied for their physiological role in CRC biology through metabolic influences on the tumor microenvironment [52-56]. Future directions in the field of research need to cover development of selective ER-β agonists, the full realization of vitamin D/VDR-targeted strategies, exploration of hormonal-metabolic combination therapies, and investigation of endocrine-immune system crosstalk in CRC, thereby, these progressive changes signal the slowly developing but growing acknowledgment that subclinical endocrine therapy in CRC care is the stepping stone for far-reaching implications.

Targeted therapy in colorectal cancer

The field of targeted therapy in CRC has begun a new era with the introduction of molecularly targeted therapies that have completely changed the way treatments for CRC

(CRC) are offered, particularly through agents directed against the pathways of epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) [57-60]. Anti-EGFR monoclonal antibodies cetuximab and panitumumab have become significant therapies for RAS/BRAF wild-type mCRC; their introduction, as a result, has shown a significant increase in the overall survival (OS) and progression-free survival (PFS) when they are combined with chemotherapy in first-line settings [61]. The CRYSTAL trial set the point for treating RAS wild-type mCRC with FOLFIRI plus cetuximab as a standard regimen, achieving it with a median OS increase from 20.0 to 23.5 months, while the PRIME trial demonstrated similar benefits for FOLFOX plus panitumumab. The mentioned agents have decreased the number of deaths from metastatic left-sided tumors by more than 60% of patients in the initial treatment phase. The inhibition of VEGF, the first anti-angiogenic therapy with a survival benefit in mCRC, was the result of the combination of bevacizumab with chemotherapy (FOLFOX or FOLFIRI). The AVF2107 trial announced the incorporation of this strategy along with the 20.3 months median OS of bevacizumab plus chemotherapy, compared to 15.6 months median OS achieved by IFL chemotherapy alone. The attempt to treat patients with mCRC through a combination of different drugs has got initial success with this. Subsequent studies confirmed the effectiveness of bevancizumab in various treatment lines, including the option to continue after disease progression. The increment of resistance mechanisms with respect to EGFR inhibitors has prompted the study of RAS (KRAS/NRAS) mutations as adverse predictive biomarkers. Thus, the fundamental switch in treatment algorithms allows anti-EGFR therapy only for RAS wild-type tumors. In the case of BRAF V600E-mutant mCRC (8-10% of disease cases), encorafenib in conjunction with cetuximab was the scheme approved through the BEACON trial, whose result was the median OS of 9.3 months as opposed to 5.9 months in the case of standard chemotherapy. One of the recent milestones achieved is the dual EGFR inhibition technique; according to the PARADIGM trial where the phase III study was conducted, panitumumab plus mFOLFOX6 improved OS significantly in the left-sided RAS wild-type mCRC as compared to the use of bevacizumab (p=0.007, 37.9 vs 34.3 months). The discovery of new agents with HE2 amplifications (2-3% of CRC), still at the experimental stage, has been praiseworthy, as per the MyPathway trial that demonstrated 52% response rates for pertuzumab/trastuzumab in HER2-amplified mCRC, leading to the FDA approval of trastuzumab deruxtecan for HER2-positive mCRC based on the DESTINY-CRC01 trial results. The newly discovered objectives also include NTRK fusions (entrectinib/larotrectinib), RET fusions (selpercatinib), and KRAS G12C mutations (sotorasib/adagrasib); however, their prevalence in CRC is negligible. Even though these improvements have been made, acquired resistance is still a major obstacle, where the focus of ongoing research is on the combination treatment of (EGFR/MET or EGFR/BRAF inhibition) antibody-drug conjugates, and newer mechanisms like Claudin 18.2 targeting. Studies that are taking place also look into the possible sequencing of targeted the therapies apart from RAS/RAF status, which would further personalize CRC treatment with the implementation of rechallenge strategies and the development of sophisticated biomarkers. These strategies, on the other hand, will bring radical changes in the approach to therapy, leading to the higher number of remissions among CRC patients with specific molecular characteristics [61] (Table 1).

Gene therapy in colorectal cancer

Gene therapy has emerged as a new focus area in the treatment of CRC through the use of genetic material conceptually delivered via either viral or non-viral vectors to modulate gene expression, restore, tumor suppressor, functionality, or by introducing these two mechanisms at the same time lead to apoptosis of only the designated cancer cells [62, 63]. They currently remain entirely experimental, and the majority of approaches researched are in the preclinical and early-phase clinical trial periods. CRISPR-Cas9 and other gene-editing technologies are being pursued to create gene abnormalities that CRC (CRC) cells cannot cope with (e.g., KRAS, APC, or TP53 mutations) or to increase T cells' immune response to these changes by lymphocyte editing for adoptive cell therapies, Suicide gene therapy, such as ganciclovir

Table 1. Representative Studies of Targeted Therapies for CRC

Author (Year)	Patients	Intervention	Key Outcomes
Van Cutsem et al. (2009) CRYSTAL Trial	1,198 mCRC (KRAS wild-type)	FOLFIRI + cetuximab vs FOLFIRI	Median OS: 23.5 vs 20.0 mo (HR 0.80; p=0.009)
| Douillard et al. (2010) PRIME Trial	1,183 mCRC (KRAS wild-type)	FOLFOX + panitumumab vs FOLFOX	Median PFS: 9.6 vs 8.0 mo (HR 0.80; p=0.02)
Kopetz et al. (2019) BEACON Trial	665 BRAF V600E-mutant mCRC	Encorafenib + cetuximab vs control	Median OS: 9.3 vs 5.9 mo (HR 0.60; p<0.001)
Yoshino et al. (2022) PARADIGM Trial	823 RAS wild-type mCRC	Panitumumab + mFOLFOX6 vs bevacizumab + mFOLFOX6	Left-sided: Median OS 37.9 vs 34.3 mo (HR 0.82)
Siena et al. (2021) DESTINY-CRC01	86 HER2+ mCRC	Trastuzumab deruxtecan	ORR: 45.3% in HER2 IHC3+ cohort
André et al. (2020) KEYNOTE-177	307 MSI-H/dMMR mCRC	Pembrolizumab vs chemotherapy	Median PFS: 16.5 vs 8.2 mo (HR 0.60; p=0.0002)
Fakih et al. (2022) CodeBreaK 101	40 KRAS G12C-mutant mCRC	Sotorasib + panitumumab	ORR: 30%, median PFS: 5.7 mo

Table 2. Ongoing Trials of Gene Therapy, Vaccines, and CAR-T Therapy in CRC (Highlights the shift toward precision immunotherapies for CRC, with trials focusing on overcoming MSS/pMMR resistance and enhancing antigen-specific responses).

Identifier	Patient Population	Phase	Intervention	Primary Endpoints	Target/Mechanism
NCT05381454	KRAS-mutant mCRC	I/II	CRISPR-edited KRAS T cells	Safety, MTD	KRAS G12D/V-specific CAR-T
NCT05341492	CEACAM5+ mCRC	I	CEACAM5-directed CAR-T	Dose-limiting toxicity (DLT), ORR	CEACAM5 antigen
NCT05241331	MSS/pMMR mCRC	II	GUCY2C-targeted CAR-T + PD-1 inhibitor	PFS, immune response	GUCY2C tumor antigen
NCT05076682	MSI-H/dMMR mCRC	I/II	Personalized neoantigen DNA vaccine + pembrolizumab	Safety, immunogenicity	Tumor-specific neoantigens
NCT05141721	Refractory mCRC	I	Oncolytic vaccinia virus (Pexa-Vec) + nivolumab	Safety, viral shedding	Oncolytic immunotherapy
NCT03563326	Metastatic CRC	I/II	HER2-targeted CAR-NK cells	MTD, ORR	HER2 amplification
NCT05433181	Advanced GI cancers (CRC)	I	Claudin 18.2 CAR-T (CT041)	Safety, DLTs	Claudin 18.2 overexpression
NCT04853017	MSS mCRC	II	| Tumor RNA-loaded dendritic cell vaccine + regorafenib	Immune response, PFS	Autologous DC vaccination
NCT04503278	TP53-mutant CRC	I	TP53 mRNA-loaded lipid nanoparticles	Safety, TP53 restoration	TP53 tumor suppressor
NCT05137275	Locally advanced rectal cancer	I	CRISPR-Cas9 PD-1 knockout TILs	Feasibility, pCR rate	PD-1 disruption in TILs

which is given with herpes simplex virus thymidine kinase (HSV-TK) is showing tumor-specific cytotoxicity in CRC models. Early trials were done to see if it could be safely administered via adenoviral vectors. The second strategy is about the deployment of the oncolytic viruses types, which are especially designed to reproduce CRC cells that are already under the attack of immune system like modified adenoviruses (e.g., ONCOS-102) and vaccinia viruses (e.g. Pexa-Vec), both of them are in the test phase, being performed with the immune checkpoint inhibitors [64, 65]. MicroRNA interference (RNAi) and microRNA therapies deal primarily with oncogenes being silent or the inclining tissue miRNAs (e.g., miR-143/145, which target KRAS and ERK5). Liabilities of systemic delivery notwithstanding, nanoparticle-encapsulated siRNAs and miRNA mimics are finding their applications in preclinical CRC models [66]. DNA vaccines concentrated on CRC-related antigens (e.g., CEACAM5, GUCY2C, or neoantigens) are also being developed with pilot trials that investigate their capacity of strengthening antitumor immunity. Furthermore, CAR-T cell therapy that is being predominantly used for blood cancers, is also in preparation for colon cancer adaptation based on new targets like GUCY2C or TAG-72. Nonetheless, the protection from tumor microenvironment immunosuppression remains the major obstacle to such development [67-69]. Besides the aforementioned breakthroughs, clinical translation runs into problems like the safety of delivery, the possibility of unintended consequences, and immune vector eviction. Yet the forward movement may very well be embodied by the latest experiments those that involve KRAS-targeted CRISPR editing (NCT05381454) or CEACAM5-directed CAR-T cells (NCT05341492) for example which are testimonials of the state of the field, fast progress. It is plausible that the field of CRC diathesis through genetic therapy will be fragmented and include various other combinations like with immunotherapy or chemotherapy, as the accuracy of gene-editing is upgraded. Organic endeavors will be spotlighted not just on the establishment of better transmission systems, recognition of superior molecular targets, inclusion of gene therapy in the “multimodal treatment regimens” as well [70-73] (Table 2).

In conclusion, as the treatment landscape for CRC has experienced radical changes [31], it is now common to use combined multimodal techniques, which include surgery, chemotherapy, radiotherapy, and targeted therapies. In the case of localized CRC, curative surgery is the mainstay of treatment, which is transformed into a neoadjuvant and adjuvant precision method designed according to tumor biology and anatomical factors. The total neoadjuvant therapy (TNT) has revolutionized treatment pathways in rectal cancer by elevating the rates of pathologic complete response and giving the opportunity to organ preservation to rightly chosen patients. For mCRC, the growth of median survival in the case of the population with the wild-type RAS gene beyond 30 months is a result of the combining of cytotoxic regimens (FOLFOX/FOLFIRI) with biological agents (anti-EGFR, anti-VEGF). Nevertheless, with these achievements, the problem remains unresolved since the effectiveness of traditional treatments has ceased to increase, which indicates the strong necessity for new therapeutic measures.

Future Frontiers in CRC Therapeutics

Frontiers of the CRC in Therapy is indeed innovative. CRC crisscrossing the intravenous management will be mainly on finding ways to break the intrinsic and acquired resistance softening, fine-tuning the sequencing and promotion of the biomarker-driven therapies. The main focuses of the research include Immunotherapy revolutions for microsatellite-stable (MSS) tumors,

using new checkpoints combination (e.g., PD-1/LAG-3 inhibition) and microenvironment modulation (e.g., TGF-β blockade), Dual-targeted approaches (e.g., EGFR/MET co-inhibition, BRAF/MEK suppression) to disrupt parallel signaling pathways and circumvent resistance. As these innovations step off the premises of clinical trials and enter into the real-life scene, CRC management will embrace the model of precision oncology more and more, which will be the result of all this: molecular profiling, real-time monitoring, and adaptive therapeutic strategies will be combined as one. In addition to the extra survival benefits, the concentration of the emphasis will also switch to enhancing the patient-centric aspects to the highest level including the improvement of the life quality and functional preservation. The next great problem in CRC is necessitating a double assault: on the one hand, it is to demolish the tumor's molecular fortifications; on the other hand, it is to demolish the immunosuppressive stronghold of the metastasis niche. The advent of this reformatory stage will be powered through groundbreaking collaboration; bench scientists, doctors, and patients will work together to design clinical trials that will blur the boundary between research and real-world practice. In the upcoming days, we are at the crossroads; CRISPR-engineered microbes could outsmart chemoresistance, while the community-based spatial transcriptomics may decrypt the niche-driven relapse path within the tumor, and the AI-curated combined treatment will make stage IV cancer a chronic condition. The breakthrough, of course, brings up the question of equity: democratizing the dendritic access to these tools on the part of people through decentralized trials and global molecular tumor boards; hence, a more disciplined route to progress is clear:

i. Precision Overhaul: Liquid biopsy-guided adaptive therapies that evolve with the tumor's genomic drift

ii. Niche Domination: Stroma-targeting nano-therapies and engineered immune cells to break metastatic sanctuaries

iii. Systems Warfare: Fusing deep learning with multi-omics to predict and PREEMPT treatment escape routes.

This isn't not just minor changes but a fundamental re-conceptualization of the whole architecture of cancer care. The tools exist. The science is ripe. Now we must build the ecosystem to deliver cures, not just care

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Statement of Transparency and Principals:

- Author declares no conflict of interest
- Study was approved by Research Ethic Committee of author affiliated Institute.
- Study's data is available upon a reasonable request.
- All authors have contributed to implementation of this research.

References

1. Siegel RLGANJA. Erratum to "Cancer statistics, 2024". CA: a cancer journal for clinicians. 2024;74(2):203. https://doi.org/10.3322/caac.21830
2. Ghorbaninezhad F, Nour MA, Farzam OR, Saeedi H, Vanan AG, Bakhshivand M, Jafarlou M, Hatami-Sadr A, Baradaran B. The tumor microenvironment and dendritic cells: Developers of pioneering strategies in colorectal cancer immunotherapy?. Biochimica Et Biophysica Acta. Reviews on Cancer. 2025 04;1880(2):189281. https://doi.org/10.1016/j.bbcan.2025.189281
3. Li Y, Cheng Z, Li S, Zhang J. Immunotherapy in colorectal cancer: Statuses and strategies. Heliyon. 2025 01 15;11(1):e41354. https://doi.org/10.1016/j.heliyon.2024.e41354
4. Balboa-Barreiro V, Pértega-Díaz S, García-Rodríguez T, González-Martín C, Pardeiro-Pértega R, Yáñez-González-Dopeso L, Seoane-Pillado T. Colorectal cancer recurrence and its impact on survival after curative surgery: An analysis based on multistate models. Digestive and Liver Disease: Official Journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2024 07;56(7):1229-1236. https://doi.org/10.1016/j.dld.2023.11.041
5. Baxter NN, Kennedy EB, Bergsland E, Berlin J, George TJ, Gill S, Gold PJ, et al. Adjuvant Therapy for Stage II Colon Cancer: ASCO Guideline Update. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2022 03 10;40(8):892-910. https://doi.org/10.1200/JCO.21.02538
6. Karahan SN, Gorgun E. Modern rectal cancer management: A review of total neoadjuvant therapy and current practices. American Journal of Surgery. 2025 03;241:116145. https://doi.org/10.1016/j.amjsurg.2024.116145
7. Kaviyarasan V, Das A, Deka D, Saha B, Banerjee A, Sharma NR, Duttaroy AK, Pathak S. Advancements in immunotherapy for colorectal cancer treatment: a comprehensive review of strategies, challenges, and future prospective. International Journal of Colorectal Disease. 2024 Dec 28;40(1):1. https://doi.org/10.1007/s00384-024-04790-w
8. Waterson AG. Switching It up with New KRAS Inhibitors. Journal of Medicinal Chemistry. 2025 05 08;68(9):9126-9128. https://doi.org/10.1021/acs.jmedchem.5c00998
9. Perretta S, Guerrero V, Garcia-Aguilar J. Surgical treatment of rectal cancer: local resection. Surgical Oncology Clinics of North America. 2006 01;15(1):67-93. https://doi.org/10.1016/j.soc.2005.10.001
10. Rahbari NN, Ulrich AB, Bruckner T, Münter M, Nickles A, Contin P, Löffler T, et al. Surgery for locally recurrent rectal cancer in the era of total mesorectal excision: is there still a chance for cure?. Annals of Surgery. 2011 03;253(3):522-533. https://doi.org/10.1097/SLA.0b013e3182096d4f
11. Wisselink DD, Klaver CEL, Hompes R, Bemelman WA, Tanis PJ. Curative-intent surgery for isolated locoregional recurrence of colon cancer: Review of the literature and institutional experience. European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2020 09;46(9):1673-1682. https://doi.org/10.1016/j.ejso.2020.04.021
12. Reddy K, Gharde P, Tayade H, Patil M, Reddy LS, Surya D. Advancements in Robotic Surgery: A Comprehensive Overview of Current Utilizations and Upcoming Frontiers. Cureus. 2023 Dec;15(12):e50415. https://doi.org/10.7759/cureus.50415

13. Siddaiah-Subramanya M, Tiang KW, Nyandowe M. A New Era of Minimally Invasive Surgery: Progress and Development of Major Technical Innovations in General Surgery Over the Last Decade. Surgery Journal (New York, N.Y.). 2017 Oct;3(4):e163-e166. https://doi.org/10.1055/s-0037-1608651
14. Collins A, Phillips A. Sentinel lymph node mapping in the modern management of gynaecological malignancy. The Obstetrician & Gynaecologist. 2023;25(3):210–9.
15. Calvert GT. Role of Surgery in Oligometastatic Disease. In: Metastatic Bone Disease. Cham: Springer International Publishing. 2024;:279-95.
16. Chesney TR, Metz JJ, Nadler A, Quereshy FA, Ashamalla S, Acuna SA, Swallow CJ. Long-term outcomes of resection for locoregional recurrence of colon cancer: A retrospective descriptive cohort study. European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2021 09;47(9):2390-2397. https://doi.org/10.1016/j.ejso.2021.05.003
17. Pandey S, Yadav P. Liquid biopsy in cancer management: Integrating diagnostics and clinical applications. Practical Laboratory Medicine. 2025 01;43:e00446. https://doi.org/10.1016/j.plabm.2024.e00446
18. Dickens E, Ahmed S. Principles of cancer treatment by chemotherapy. Surgery (Oxford). 2021;39(4):215–20.
19. Sievers CK, Kratz JD, Zurbriggen LD, LoConte NK, Lubner SJ, Uboha N, Mulkerin D, Matkowskyj KA, Deming DA. The Multidisciplinary Management of Colorectal Cancer: Present and Future Paradigms. Clinics in Colon and Rectal Surgery. 2016 09;29(3):232-238. https://doi.org/10.1055/s-0036-1584292
20. Wu Z, Deng Y. Capecitabine Versus Continuous Infusion Fluorouracil for the Treatment of Advanced or Metastatic Colorectal Cancer: a Meta-analysis. Current Treatment Options in Oncology. 2018 Nov 27;19(12):77. https://doi.org/10.1007/s11864-018-0597-y
21. Hirsch BR, Zafar SY. Capecitabine in the management of colorectal cancer. Cancer Management and Research. 2011;3:79-89. https://doi.org/10.2147/CMR.S11250
22. Petrelli F, Zaniboni A, Ghidini A, Ghidini M, Turati L, Pizzo C, Ratti M, Libertini M, Tomasello G. Timing of Adjuvant Chemotherapy and Survival in Colorectal, Gastric, and Pancreatic Cancer. A Systematic Review and Meta-Analysis. Cancers. 2019 04 17;11(4):550. https://doi.org/10.3390/cancers11040550
23. Yang Y, Lu Y, Tan H, Bai M, Wang X, Ge S, Ning T, et al. The optimal time of starting adjuvant chemotherapy after curative surgery in patients with colorectal cancer. BMC cancer. 2023 05 09;23(1):422. https://doi.org/10.1186/s12885-023-10863-w
24. Vasefifar P, Najafi S, Motafakkerazad R, Amini M, Safaei S, Najafzadeh B, Alemohammad H, Jafarlou M, Baradaran B. Targeting Nanog expression increased Cisplatin chemosensitivity and inhibited cell migration in Gastric cancer cells. Experimental Cell Research. 2023 08 15;429(2):113681. https://doi.org/10.1016/j.yexcr.2023.113681
25. Nour MA, Kheradmand F, Rasmi Y, Asadzadeh Z, Doustvandi MA, Jafarlou M, Hajiasgharzadeh K, Baradaran B. Nicotinic Acetylcholine Receptor Subunit Alpha-7 Mediates PD-L1 and CTLA-4 Expression in HepG2 Cells. ImmunoAnalysis. 2021 Dec 28;1(1):10-10. https://doi.org/10.34172/ia.2021.10
26. Atreya CE, Yaeger R, Chu E. Systemic Therapy for Metastatic Colorectal Cancer: From Current Standards to Future Molecular Targeted Approaches. American Society of Clinical Oncology Educational Book. American Society of Clinical Oncology. Annual Meeting. 2017;37:246-256. https://doi.org/10.1200/EDBK_175679
27. Fujiwara Y, Kato S, Kurzrock R. Evolution of Precision Oncology, Personalized Medicine, and Molecular Tumor Boards. Surgical Oncology Clinics of North America. 2024 04;33(2):197-216. https://doi.org/10.1016/j.soc.2023.12.004
28. Malone ER, Oliva M, Sabatini PJB, Stockley TL, Siu LL. Molecular profiling for precision cancer therapies. Genome Medicine. 2020 01 14;12(1):8. https://doi.org/10.1186/s13073-019-0703-1
29. De Felice F, Miccini M, Botticelli A, Roberto M, Petrucciani N. The multidisciplinary management of locally advanced rectal cancer. Expert Review of Anticancer Therapy. 2024 07;24(7):581-587. https://doi.org/10.1080/14737140.2024.2349137
30. Tseng M, Soon YY, Vellayappan B, Ho F, Tey J. Radiation therapy for rectal cancer. Journal of Gastrointestinal Oncology. 2019 Dec;10(6):1238-1250. https://doi.org/10.21037/jgo.2018.12.04
31. Iv AA, Koprowski MA, Nabavizadeh N, Tsikitis VL. The evolution of rectal cancer treatment: the journey to total neoadjuvant therapy and organ preservation. Annals of Gastroenterology. 2022;35(3):226-233. https://doi.org/10.20524/aog.2022.0712
32. Brændengen M, Glimelius B. Preoperative radiotherapy or chemoradiotherapy in rectal cancer - Is survival improved? An update of the "Nordic" LARC study in non-resectable cancers. Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology. 2018 06;127(3):392-395. https://doi.org/10.1016/j.radonc.2018.05.004
33. Aref A, Abdalla A. Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer: Induction or Consolidation Chemotherapy?. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2022 08 10;40(23):2515-2519. https://doi.org/10.1200/JCO.22.00506
34. Chang G, Halabi WJ, Ali F. Management of lateral pelvic lymph nodes in rectal cancer. Journal of Surgical Oncology. 2023 06;127(8):1264-1270. https://doi.org/10.1002/jso.27317
35. Hope TA, Gollub MJ, Arya S, Bates DDB, Ganeshan D, Harisinghani M, Jhaveri KS, et al. Rectal cancer lexicon: consensus statement from the society of abdominal radiology rectal & anal cancer disease-focused panel. Abdominal Radiology (New York). 2019 Nov;44(11):3508-3517. https://doi.org/10.1007/s00261-019-02170-5
36. Guibert EE, Petrenko AY, Balaban CL, Somov AY, Rodriguez JV, Fuller BJ. Organ Preservation: Current Concepts and New Strategies for the Next Decade. Transfusion Medicine and Hemotherapy: Offizielles Organ Der Deutschen Gesellschaft Fur Transfusionsmedizin Und Immunhamatologie. 2011;38(2):125-142. https://doi.org/10.1159/000327033
37. Yoo RN, Kim HJ. Organ Preservation Strategies After Neoadjuvant Chemoradiotherapy for Locally Advanced Rectal Cancer. Annals of Coloproctology. 2019 04;35(2):53-64. https://doi.org/10.3393/ac.2019.04.15.1
38. Stieb S, Kiser K, Dijk L, Livingstone NR, Elhalawani H, Elgohari B, McDonald B, et al. Imaging for Response Assessment in Radiation Oncology: Current and Emerging Techniques. Hematology/Oncology Clinics of North America. 2020 02;34(1):293-306. https://doi.org/10.1016/j.hoc.2019.09.010
39. Thorwarth D. Functional imaging for radiotherapy treatment planning: current status and future directions-a review. The British Journal of Radiology. 2015 07;88(1051):20150056. https://doi.org/10.1259/bjr.20150056

40. Saberian E, Jenča A, Petrášová A, Zare-Zardini H, Ebrahimifar M. Application of Scaffold-Based Drug Delivery in Oral Cancer Treatment: A Novel Approach. Pharmaceutics. 2024 06 14;16(6):802. https://doi.org/10.3390/pharmaceutics16060802
41. Sadrabad MJ, Saberian E, Izadi A, Emami R, Ghadyani F. Success in Tooth Bud Regeneration: A Short Communication. Journal of Endodontics. 2024 03;50(3):351-354. https://doi.org/10.1016/j.joen.2023.12.005
42. Patel R, Klein P, Tiersten A, Sparano JA. An emerging generation of endocrine therapies in breast cancer: a clinical perspective. NPJ breast cancer. 2023 04 05;9(1):20. https://doi.org/10.1038/s41523-023-00523-4
43. Mohammadinezhad F, Talebi A, Allahyartorkaman M, Nahavandi R, Vesal M, Khiyavi AA, Velisdeh ZJ, et al. Preparation, Characterization and Cytotoxic Studies of Cisplatin-containing Nanoliposomes on Breast Cancer Cell Lines. Asian Pacific Journal of Cancer Biology. 2023 07 30;8(2):155-159. https://doi.org/10.31557/apjcb.2023.8.2.155-159
44. Murphy N, Strickler HD, Stanczyk FZ, Xue X, Wassertheil-Smoller S, Rohan TE, Ho GYF, et al. A Prospective Evaluation of Endogenous Sex Hormone Levels and Colorectal Cancer Risk in Postmenopausal Women. Journal of the National Cancer Institute. 2015 Oct;107(10):djv210. https://doi.org/10.1093/jnci/djv210
45. Rudolph A, Toth C, Hoffmeister M, Roth W, Herpel E, Jansen L, Marx A, Brenner H, Chang-Claude J. Expression of oestrogen receptor β and prognosis of colorectal cancer. British Journal of Cancer. 2012 08 21;107(5):831-839. https://doi.org/10.1038/bjc.2012.323
46. Barry EL, Peacock JL, Rees JR, Bostick RM, Robertson DJ, Bresalier RS, Baron JA. Vitamin D Receptor Genotype, Vitamin D3 Supplementation, and Risk of Colorectal Adenomas: A Randomized Clinical Trial. JAMA oncology. 2017 05 01;3(5):628-635. https://doi.org/10.1001/jamaoncol.2016.5917
47. Na S, Kim KB, Lim YJ, Song HJ. Vitamin D and Colorectal Cancer: Current Perspectives and Future Directions. Journal of Cancer Prevention. 2022 09 30;27(3):147-156. https://doi.org/10.15430/JCP.2022.27.3.147
48. Nikasa M, Karimi P, Rajavand H, Afshari F, Jafarlou M, Soltanali M. High Cholesterol Diet Increases Expression of Cholesterol 24-Hydroxylase and BACE1 in Rat Hippocampi: Implications for the Effect of Diet Cholesterol on Memory. Iranian Red Crescent Medical Journal (IRCMJ). 2016 Dec 01;18(12):1-8. https://doi.org/kkkkk
49. Ghahramanipour Z, Alipour S, Masoumi J, Rostamlou A, Hatami-Sadr A, Heris JA, Naseri B, Jafarlou M, Baradaran B. Regulation of Dendritic Cell Functions by Vitamins as Promising Therapeutic Strategy for Immune System Disorders. Advanced Biology. 2023 Dec;7(12):e2300142. https://doi.org/10.1002/adbi.202300142
50. Peters G, Gongoll S, Langner C, Mengel M, Piso P, Klempnauer J, Rüschoff J, Kreipe H, Wasielewski R. IGF-1R, IGF-1 and IGF-2 expression as potential prognostic and predictive markers in colorectal-cancer. Virchows Archiv: An International Journal of Pathology. 2003 08;443(2):139-145. https://doi.org/10.1007/s00428-003-0856-5
51. Vigneri PG, Tirrò E, Pennisi MS, Massimino M, Stella S, Romano C, Manzella L. The Insulin/IGF System in Colorectal Cancer Development and Resistance to Therapy. Frontiers in Oncology. 2015;5:230. https://doi.org/10.3389/fonc.2015.00230
52. Greiner TU, Koh A, Peris E, Bergentall M, Johansson MEV, Hansson GC, Drucker DJ, Bäckhed F. GLP-1R signaling modulates colonic energy metabolism, goblet cell number and survival in the absence of gut microbiota. Molecular Metabolism. 2024 05;83:101924. https://doi.org/10.1016/j.molmet.2024.101924
53. Singh A, Sohal A, Batta A. GLP-1, GIP/GLP-1, and GCGR/GLP-1 receptor agonists: Novel therapeutic agents for metabolic dysfunction-associated steatohepatitis. World Journal of Gastroenterology. 2024 Dec 28;30(48):5205-5211. https://doi.org/10.3748/wjg.v30.i48.5205
54. Yu D, Lu Z, Wang R, Xiang Y, Li H, Lu J, Zhang L, et al. FXR agonists for colorectal and liver cancers, as a stand-alone or in combination therapy. Biochemical Pharmacology. 2023 06;212:115570. https://doi.org/10.1016/j.bcp.2023.115570
55. Zhang Y, Xie Y, Xia S, Ge X, Li J, Liu F, Jia F, et al. The Novel Dual GIP and GLP-1 Receptor Agonist Tirzepatide Attenuates Colon Cancer Development by Regulating Glucose Metabolism. Advanced Science (Weinheim, Baden-Wurttemberg, Germany). 2025 05;12(19):e2411980. https://doi.org/10.1002/advs.202411980
56. Shahverdi M, Hajiasgharzadeh K, Sorkhabi AD, Jafarlou M, Shojaee M, Jalili Tabrizi N, Alizadeh N, et al. The regulatory role of autophagy-related miRNAs in lung cancer drug resistance. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2022 04;148:112735. https://doi.org/10.1016/j.biopha.2022.112735
57. Winder T, Lenz H. Vascular endothelial growth factor and epidermal growth factor signaling pathways as therapeutic targets for colorectal cancer. Gastroenterology. 2010 06;138(6):2163-2176. https://doi.org/10.1053/j.gastro.2010.02.005
58. Xie Y, Chen Y, Fang J. Comprehensive review of targeted therapy for colorectal cancer. Signal Transduction and Targeted Therapy. 2020 03 20;5(1):22. https://doi.org/10.1038/s41392-020-0116-z
59. Ghorbaninezhad F, Masoumi J, Bakhshivand M, Baghbanzadeh A, Mokhtarzadeh A, Kazemi T, Aghebati-Maleki L, et al. CTLA-4 silencing in dendritic cells loaded with colorectal cancer cell lysate improves autologous T cell responses in vitro. Frontiers in Immunology. 2022;13:931316. https://doi.org/10.3389/fimmu.2022.931316
60. Hajiasgharzadeh K, Doustvandi MA, Khiabani NA, Mohammadi M, Dastmalchi N, Jafarlou M, et al. The Effects of siRNA-Mediated Gene Silencing of Alpha-7 Nicotinic Acetylcholine Receptors on Drug Resistance to Oxaliplatin in Colorectal Cancer Cells. Biology Bulletin. 2022;49.
61. Benson AB, Venook AP, Adam M, Chang G, Chen Y, Ciombor KK, Cohen SA, et al. Colon Cancer, Version 3.2024, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network: JNCCN. 2024 06;22(2 D):e240029. https://doi.org/10.6004/jnccn.2024.0029
62. Jafarlou M, Baradaran B, Saedi TA, Jafarlou V, Shanehbandi D, Maralani M, Othman F. An overview of the history, applications, advantages, disadvantages and prospects of gene therapy. Journal of Biological Regulators and Homeostatic Agents. 2016;30(2):315-321.
63. Mohd Abas MD, Mohd Asri MF, Yusafawi NAS, Rosman NAZ, Baharudin NAZ, Taher M, Susanti D, Khotib J. Advancements of gene therapy in cancer treatment: A comprehensive review. Pathology, Research and Practice. 2024 09;261:155509. https://doi.org/10.1016/j.prp.2024.155509
64. Oishi T, Ito M, Koizumi S, Horikawa M, Yamamoto T, Yamagishi S, Yamasaki T, et al. Efficacy of HSV-TK/GCV system suicide gene therapy using SHED expressing modified HSV-TK against lung cancer brain metastases. Molecular Therapy. Methods & Clinical Development. 2022 09

08;26:253-265. https://doi.org/10.1016/j.omtm.2022.07.001
65. Sultan MH, Zhan Q, Wang Y, Xia Y, Jia X. Precision oncolytic viral therapy in colorectal cancer: Genetic targeting and immune modulation for personalized treatment (Review). International Journal of Molecular Medicine. 2025 07;56(1):104. https://doi.org/10.3892/ijmm.2025.5545
66. Jafarlou M, Baradaran B, Shanehbandi D, Saedi TA, Jafarlou V, Karimi P, Othman F. Silencing of myeloid cell leukemia-1 by small interfering RNA improves chemosensitivity to etoposide in u-937 leukemic cells. Journal of Biological Regulators and Homeostatic Agents. 2016;30(1):55-65. https://doi.org/hhhh
67. Alizadeh N, Kazemi T, Hemmat N, Jafarlou M, Baradaran B. The Combination of PD-L1 and CTLA-4 Suppression Significantly Decreased the Expression Levels of Cancer Stem Cell Factors in the Pancreatic Cancer Cell Line. ImmunoAnalysis. 2023 Jun 26;3:6.
68. Hosseinkhani N, Hemmat N, Baghbani E, Baghbanzadeh A, Kazemi T, Mokhtarzadeh A, Jafarlou M, Amin Doustvandi M, Baradaran B. Dual silencing of tumor-intrinsic VISTA and CTLA-4 stimulates T-cell mediated immune responses and inhibits MCF7 breast cancer development. Gene. 2024 02 20;896:148043. https://doi.org/10.1016/j.gene.2023.148043
69. Jung E, Choi J, Kim J, Han T. MicroRNA-Based Therapeutics for Drug-Resistant Colorectal Cancer. Pharmaceuticals (Basel, Switzerland). 2021 02 08;14(2):136. https://doi.org/10.3390/ph14020136
70. Uddin F, Rudin CM, Sen T. CRISPR Gene Therapy: Applications, Limitations, and Implications for the Future. Frontiers in Oncology. 2020;10:1387. https://doi.org/10.3389/fonc.2020.01387
71. Younis MA, Tawfeek HM, Abdellatif AAH, Abdel-Aleem JA, Harashima H. Clinical translation of nanomedicines: Challenges, opportunities, and keys. Advanced Drug Delivery Reviews. 2022 02;181:114083. https://doi.org/10.1016/j.addr.2021.114083
72. Saberian E, Jenča A, Jenča A, Zare-Zardini H, Araghi M, Petrášová A, Jenčová J. Applications of artificial intelligence in regenerative dentistry: promoting stem cell therapy and the scaffold development. Frontiers in Cell and Developmental Biology. 2024;12:1497457. https://doi.org/10.3389/fcell.2024.1497457
73. Dabbaghipour R, Ahmadi E, Entezam M, Farzam OR, Baghbanzadeh A, Sichani AS, et al. Regulatory Effects of Long Non-coding RNAs on Th17/Treg Differentiation and Imbalance [Internet]. Available from: http://ijaai.tums.ac.ir.