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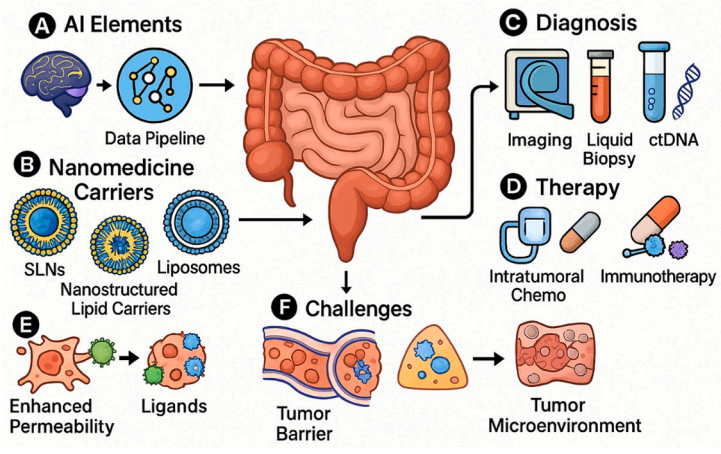
Review article

Artificial intelligence assisted design of nanomedicines for colorectal cancer diagnosis and therapy: Advances, challenges, and future directions

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GRAPHICAL ABSTRACT



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ABSTRACT

Colorectal cancer (CRC) remains one of the leading causes of cancer-related morbidity and mortality worldwide, with an increasing incidence in both high- and low-income countries. Despite advances in colonoscopy, imaging, molecular biomarker testing, and multimodal therapeutic regimens, limitations in early detection, tumor heterogeneity, and resistance to conventional therapy continue to hinder effective management of CRC. Nanomedicine offers transformative opportunities for precision diagnosis and therapy by enabling targeted delivery, controlled drug release, and multimodal imaging. Concurrently, artificial intelligence (AI), including machine learning (ML), deep learning (DL), and emerging transformer-based architectures, has revolutionized the interpretation of biomedical data and guided the rational design of nanocarriers for drug delivery applications. The synergistic integration of artificial intelligence and nanotechnology has accelerated the discovery of CRC-specific biomarkers, improved formulation optimization, enabled predictive pharmacokinetic/

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pharmacodynamic modeling, and facilitated the design of adaptive clinical trials. Recent breakthroughs include AI-driven histopathology and imaging analysis for early CRC detection, with AI-assisted colonoscopy demonstrating sensitivity improvements of up to 94%–97% and accuracy gains of 10%–20% compared to standard methods. However, major challenges remain, including limited access to large, annotated CRC datasets, the interpretability of AI models in clinical decision-making, the reproducibility of complex nanoparticle synthesis, and regulatory gaps in nanomedicine. This review synthesizes the current advances in AI-assisted nanomedicine for CRC diagnosis and therapy, critically evaluates the translational barriers, and outlines future research trajectories. Ultimately, multidisciplinary collaboration across oncology, nanotechnology, the design of adaptive clinical trials, science, and regulatory science is essential to realize the full potential of AI-powered nanomedicine in CRC management

1. Introduction

Colorectal cancer (CRC) is the third most common malignancy and the second leading cause of cancer-related deaths worldwide, with an estimated 1.9 million new cases and 904,000 deaths reported in 2022. GLOBOCAN.[1] Its incidence is steadily rising among younger populations and in low- and middle-income countries, emphasizing the urgent need for improved strategies for early detection, prevention, and treatment.[2,3] Incidence rates show epidemiological differences, with higher rates in Western populations (approximately 40 per 100,000) compared to varying rates in Asian populations, where countries like Japan and Korea exhibit rates around 45 per 100,000 due to Westernization of lifestyles, while rates are lower in India and China but increasing rapidly; for instance, Japanese Americans have 25% higher rates in men compared to White Americans. Conventional diagnostic approaches, including colonoscopy, computed tomography (CT), magnetic resonance imaging (MRI), and serological biomarkers such as carcinoembryonic antigen play a crucial role but are constrained by their invasiveness, operator dependence, limited sensitivity for small or right-sided lesions, and poor specificity.[4,5] Colonoscopy remains the gold standard, yet it is subject to variable detection rates depending on preparation quality and operator skill.[6] Similarly, radiological modalities are effective for staging but may fail to detect early lesions, while serological and stool-based tests often lack the sensitivity required for early disease detection.[7] On the therapeutic front, standard regimens such as chemotherapy (FOLFOX and FOLFIRI), targeted agents against EGFR and VEGF, and immune checkpoint inhibitors have shown variable efficacy, largely due to tumor heterogeneity, late-stage diagnosis, drug resistance, and the presence of an immunosuppressive tumor microenvironment.[8,9] Immunotherapy has transformed the treatment landscape for MSI-H/dMMR CRC, which accounts for approximately 15% of cases, but microsatellite-stable tumors remain largely refractory to immune-based therapies.[10,11] These persistent diagnostic and therapeutic challenges underscore the need for more precise, predictive, and individualized strategies in CRC management. The convergence of artificial intelligence (AI) and nanotechnology represents a major paradigm shift in addressing these gaps. AI technologies enable high-throughput data processing, early biomarker discovery, predictive modeling, and real-time decision support, thereby enhancing diagnostic precision and therapeutic planning [12–14]. In parallel, nanocarriers can be rationally engineered to target CRC-specific molecular signatures, improve drug solubility and stability, achieve controlled or

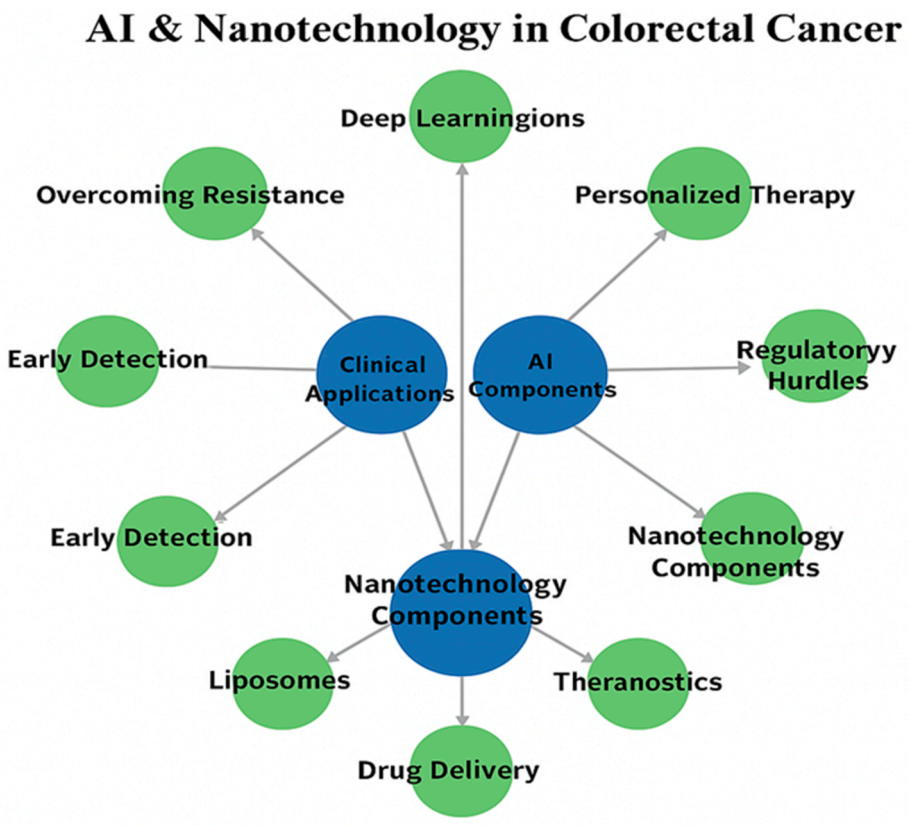


Fig. 1. Overview of AI–Nanomedicine integration in colorectal cancer.

Table 1
Comparison of traditional and AI-Powered diagnostic tools in colorectal cancer.

Method	Conventional Sensitivity/Specificity	AI-Augmented	Key Improvement	Ref
Optical Colonoscopy	75%–95%/~90%	Sensitivity 90–98%, ADR 14–24%	Real-time detection	21,22
CT Colonography	70%–90% (>6 mm)	↑15–20% for < 6 mm polyps	Flat & small lesion detection	23
FIT	70%–80%	ML panels: 85–92%[24]	Non-invasive screening	24
Serum CEA/CA19-9	40%–60%	Multi-marker + ML: 78–88%	Early recurrence monitoring	25,26

stimuli-responsive release, and enable theranostic applications for simultaneous diagnosis and therapy.[15–17] By integrating these complementary approaches, it becomes possible to overcome key barriers associated with late detection, treatment resistance, and tumor heterogeneity, paving the way for precision oncology strategies that are tailored to individual patient and tumor profiles.[18–20] This review synthesizes the latest advances in AI-assisted nanomedicine for CRC, examines existing challenges, and outlines a translational roadmap, illustrating how this multidisciplinary approach has the potential to revolutionize CRC diagnosis, prognosis, and treatment.[19,20] Fig. 1 highlights the major domains and subcategories where AI and nanotechnology intersect in CRC research (Figures: Created by using BioRender software), while Table 1 compares conventional diagnostic methods with AI-augmented approaches, emphasizing their advantages in sensitivity, specificity, and clinical utility.[19,20]

2. Traditional diagnostic tools and limitations

Accurate and timely diagnosis of colorectal cancer is critical for improving outcomes; however, conventional methods have significant limitations, leading to late-stage detection, false negatives, and variability.[27] Colonoscopy, the gold standard, enables visualization, biopsy, and polypectomy but is invasive, operator-dependent, and limited by patient compliance, incomplete bowel preparation, and miss rates of up to 19%–26% for adenomas and up to 6% for cancers, especially for right-sided and flat lesions.[28] CT colonography and MRI assist in staging but struggle to detect small polyps (< 6 mm), incur high costs, expose patients to radiation, or have reduced sensitivity for flat lesions (MRI).[29] The serological biomarkers CEA and CA19-9 lack sensitivity and specificity for early CRC, whereas the stool tests FOBT and FIT have reduced sensitivity for proximal disease and compliance issues.[30] Liquid biopsies, such as ctDNA, CTCs, and exosomes, are promising but are limited by low tumor-derived material, preanalytical variability, and high costs in the early stages. These shortcomings highlight the need for next-generation diagnostics, where AI-integrated nanotechnology platforms can transform CRC detection through real-time image analysis, molecular profiling, and multiplexed biomarker evaluation with enhanced precision.[31] Table 1 represents a comparison of conventional diagnostic methods with AI-augmented approaches.

3. Limitations of traditional CRC therapies

Colorectal cancer therapy still faces major challenges. Standard regimens, such as FOLFOX and FOLFIRI, extend survival but are limited by dose-related toxicities, neuropathy, diarrhoea, myelosuppression, and resistance mechanisms, including ABC transporter overexpression, EMT, and CSC enrichment.[32] Targeted agents, such as anti-EGFR antibodies cetuximab and panitumumab, benefit RAS wild-type tumors but are constrained by KRAS/NRAS/BRAF mutations and alternative signaling pathways.[33] In contrast, anti-VEGF agents such as bevacizumab offer only modest gains owing to compensatory angiogenesis.[34] Immunotherapy with PD-1/PD-L1 inhibitors produces durable responses in approximately 15% of dMMR/MSI-H patients but is largely ineffective in MSS tumors due to an immunologically "cold" microenvironment with poor T cell infiltration and immunosuppressive signaling.[35] Microsatellite-stable (MSS) tumors (about 85% of cases) exhibit low tumor mutational burden, poor T-cell infiltration, and dense stromal immunosuppression driven by cancer-associated fibroblasts (CAFs) and tumor-associated macrophages (TAMs), creating major barriers to immunotherapy. AI-guided nanocarriers are emerging to co-deliver immunomodulators and convert "cold" to "hot" tumors. The dense CRC tumor microenvironment, characterized by hypoxia, acidic niches, and stromal cells, including CAFs, TAMs, and Tregs, further impedes drug delivery and supports tumor survival.[36] Recent advances highlight AI-driven nanomedicine as a promising strategy to bypass these barriers, co-deliver synergistic therapies, and target resistance pathways to KRAS mutations, thereby enhancing the precision and efficacy of CRC treatment. Fig. 2 illustrates a Conceptual schematic contrasting traditional CRC management, empirical drug selection, non-targeted delivery with AI-enabled nanomedicine innovations, ML-optimized nanocarriers, and predictive modeling for personalized therapy.

4. AI-driven design and development of nanomedicine nanocarriers

Artificial intelligence accelerates every stage of nanocarrier development by integrating multi-scale datasets. Key innovations include graph neural networks (GNNs) for ligand–receptor prediction,

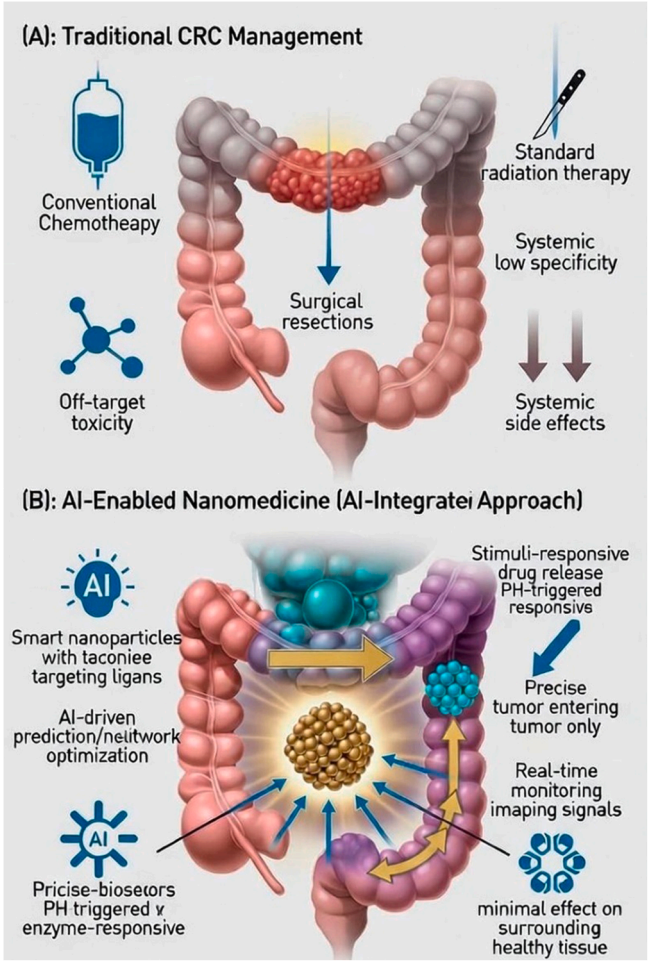


Fig. 2. Comparison between traditional and AI-Nanomedicine approaches.

reinforcement learning, and digital twins for GMP-compliant scale-up, and federated learning for privacy-preserving collaboration across institutions, Through the integration of large biological, chemical, and clinical datasets, AI streamlines drug discovery, pre-formulation, formulation optimization, and quality assurance, reducing experimental costs, improving precision, and accelerating translation to the clinic. The following sections detail how ML and DL approaches are reshaping each stage of nanocarrier development for CRC seen in Fig. 3.

4.1. Role of ML and DL nanocarrier design

Machine learning and deep learning are revolutionizing nanomedicine, particularly in the design of nanocarriers for colorectal cancer.[37] The operational mechanisms of artificial intelligence involve a series of sophisticated processes that enable machines to emulate human-like intelligence illustrated in Fig. 4. AI algorithms model nanoscale materials, optimize drug delivery, and scale production with precision tailored to the complex tumor microenvironment of CRC. ML methods, such as support vector machines and random forests, predict optimal nanostructures from material-property datasets, improving biocompatibility and tumor uptake. DL models, including convolutional neural networks, analyze high-resolution imaging to simulate atomic interactions and refine nanocarrier design, while reinforcement learning and digital twins enhance synthesis, reduce batch variability, and ensure GMP compliance.[38] Transformer-based DL integrates multi-omics data to functionalize nanocarriers with targeting ligands, and QSAR models support controlled drug release. Generative adversarial networks accelerate drug–nanocarrier screening, whereas federated learning and explainable AI improve data security and regulatory trust.[39,40] Collectively, these approaches increase efficacy, reduce toxicity, and personalize CRC therapy, ushering in a new era of scalable, patient-centric nanomedicine.

4.2. Machine learning

In recent years, several studies have demonstrated the power of machine learning in CRC diagnosis and prognosis. Sadoughi et al. showed that SVMs achieved superior diagnostic performance across

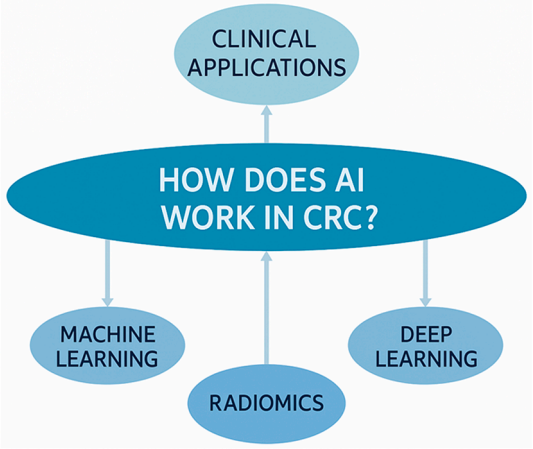


Fig. 4. The operational mechanisms of artificial intelligence involve a series of sophisticated processes that enable machines to emulate human-like intelligence.

imaging modalities, reducing false positives and improving classification accuracy.[41,42] Byrne et al. further demonstrated the potential of ANN-based models to distinguish between benign and malignant polyps during live colonoscopy with real-time feedback. More advanced workflows combine multiple algorithms for feature selection and classification. Atban et al. integrated transfer learning (ResNet18) with metaheuristic algorithms, including PSO, ASO, and EO, to select discriminative features from histopathological datasets. These features were then classified using SVM, KNN, and decision trees, achieving an impressive F-score of 97.75%,[43] including DeePathNet and Pathformer, which integrate genomics/proteomics for CRC subtyping, achieving 85–90% accuracy in predicting nanocarrier targets. Chen et al. developed CRC classification and prognosis models using XGBoost, random forest, logistic regression, and KNN, showing that XGBoost achieved the best performance with a recall of 1.00 and an overall score of 1.01 ± 0.980.[44] Collectively, these recent studies demonstrate that machine learning has evolved from simple image analysis to

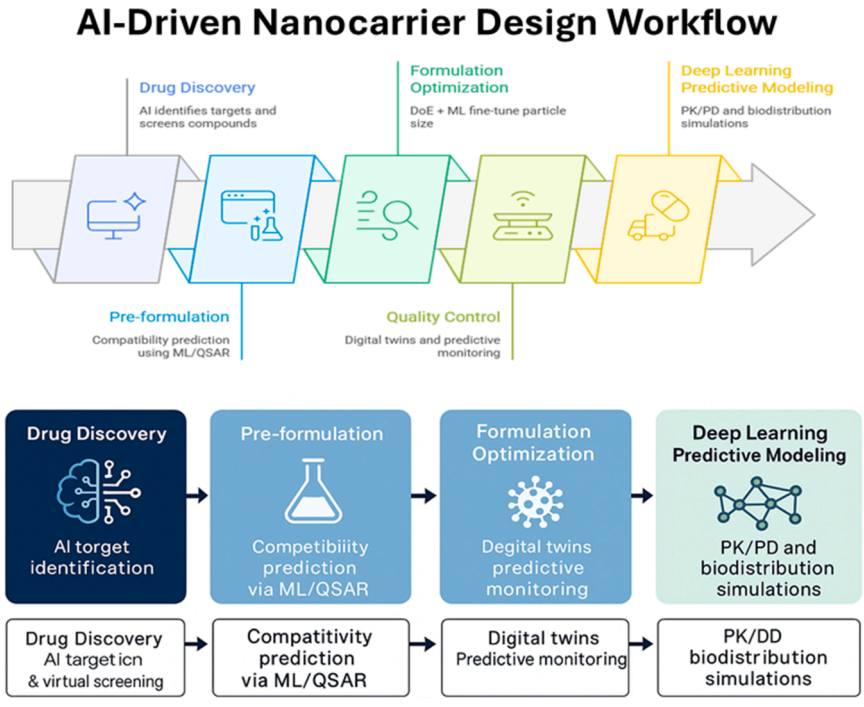


Fig. 3. AI-driven nanocarrier design workflow.

sophisticated multimodal integrative approaches, playing a central role in colorectal cancer screening, diagnosis, biomarker discovery, and prognosis prediction. Dataset bias and class imbalance represent major hidden limitations in many AI models applied to colorectal cancer. Most publicly available CRC datasets are dominated by samples from Western populations and tertiary care centers, leading to demographic and spectrum bias. In screening datasets, the number of normal images often vastly exceeds the number of cancer images, causing a class imbalance that can artificially inflate the accuracy and AUC without reflecting the true clinical performance. Moreover, many studies rely on internal validation only, without testing models on external multicenter cohorts. The lack of external validation limits generalizability, and models that perform well in controlled datasets may fail in real-world settings with different populations, imaging systems and disease prevalence.

4.3. Deep learning

Deep learning networks incorporate multiple layers, often structured as convolutional neural networks, to perform advanced image processing that exceeds the capabilities of traditional feature-based machine learning classifiers.[45] Unlike conventional methods that depend on manual or automatic feature extraction, deep learning models process raw images directly, enabling higher layers to autonomously learn complex representations and classify images with high accuracy. Deep learning has significantly advanced the detection of colorectal cancer using multiple imaging modalities.

In colonoscopy, CNN-based systems have achieved real-time polyp detection with high accuracy, improving adenoma detection rates in large prospective studies. In ultrasonography, deep CNNs have enhanced sensitivity and specificity by reliably identifying microcalcifications and masses, while in histopathology, CNNs have demonstrated high accuracy in differentiating malignant from benign glandular structures in whole-slide images. In MRI, deep segmentation networks such as U-Net have enabled precise rectal tumor localization and staging by distinguishing between tissue types with high Dice similarity scores. Recent methodologies have integrated deep and machine-learning approaches to further improve CRC classification and segmentation. Zheng et al. developed an AdaBoost framework enhanced with CNN features, which significantly boosted performance and demonstrated rapid deployment potential. Another approach combined geometric mean filtering for preprocessing, AlexNet for feature extraction, and multiple classifiers, including least-squares SVM, KNN, random forest, and naïve Bayes, achieving high accuracy in CRC image classification. Hu et al proposed a deep multi-magnification network (DMMN) for histopathological whole-slide image analysis, leveraging 20 ×, 10 ×, and 5 × magnifications to enhance segmentation performance through multi-scale feature map integration.[46] While these methods have shown impressive results, the segmentation of well-differentiated carcinomas remains limited owing to insufficient annotated training data. Deep learning has played a transformative role in digital pathology, supporting personalized treatment planning and improving diagnostic accuracy in colorectal cancer. Model interpretability is increasingly important for clinical and regulatory acceptance. Tools such as SHAP, LIME, Grad-CAM, and attention maps help identify influential features in imaging, ligand selection, and toxicity prediction. Explainable AI improves clinician trust and supports regulatory review by making model decisions more transparent.

4.4. Drug discovery

AI-driven drug discovery for CRC nanocarriers applies ML and DL to identify therapeutic targets and optimize ligand–target interactions with high precision.[47] ML algorithms, such as support vector machines and random forests, analyze multi-omics datasets, TCGA, and GEO to identify CRC-specific targets, such as CD44, EpCAM, CLDN18.2, and GUCY2C, enabling selective nanocarrier functionalization.[48] Generative models, including VAEs and GANs, virtually screen chemical libraries to identify druggable candidates for polymeric, lipid, or inorganic nanocarriers, which are particularly valuable for hard-to-treat targets, such as mutant KRAS (KRAS G12D and KRAS G13D), found in 40%–50% of CRC cases.[49] QSAR models predict ligand-binding affinities, accelerating the selection of small molecules or biologics, siRNA, and CRISPR-Cas for delivery. Recent transformer-based approaches have integrated multi-omics data with chemical properties to forecast synergistic drug combinations, such as co-delivering 5-FU with KRAS inhibitors to enhance preclinical efficacy in CRC models.[50] Generative models, including VAEs and GANs, virtually screen chemical libraries. GANs generate *de-novo* ligand candidates and predict binding affinities to CRC-specific markers (EpCAM, GUCY2C), improving active targeting efficiency by 20%–30% *in silico* before synthesis. Transformer-based models (MOT-2024, DeePathNet) integrate TCGA multi-omics data with $>$ 90% accuracy in consensus molecular subtyping (CMS1–4), guiding personalized nanocarrier functionalization. Most AI models identify statistical correlations rather than biological causality. Therefore, predictions related to ligand selection, tumor targeting, or therapeutic response should be interpreted as hypothesis-generating rather than mechanistic proof. Experimental validation is essential to establish causality and confirm that AI-identified features drive biological behavior.

4.5. Pre-formulation studies

Pre-formulation studies ensure drug–nanocarrier compatibility, and AI enhances this process by predicting solubility, encapsulation efficiency, and stability.[51] ML models trained on large drug–polymer datasets forecast the behavior of CRC drugs, such as irinotecan, oxaliplatin, and 5-FU, in carriers such as PLGA, PEGylated liposomes, and chitosan nanoparticles. ANNs and QSAR analyses model pH- and enzyme-triggered release kinetics tailored to the colonic microenvironment, including acidic pH and enzymes such as β-glucuronidase and azoreductase. ML-driven approaches have optimized irinotecan encapsulation in liposomes, improving systemic stability and controlled release in the tumor microenvironment (TME). Recent advances include Bayesian optimization for predicting drug–polymer miscibility and GNNs for mapping molecular interactions between payloads and nanocarrier matrices, enabling the design of stimuli-responsive systems that release drugs in response to CRC-specific conditions, such as hypoxia or microbial enzymes.[52]

4.6. Formulation optimization

Formulation optimization tailors nanocarrier properties, such as size, polydispersity, zeta potential, ligand density, and drug loading, to maximize the biodistribution, tumor uptake, and therapeutic efficacy.[53] AI combines the design of experiments (DoE) with ML algorithms, such as support vector regression and gradient boosting, to optimize parameters. For example, hybrid chitosan–lipid nanoparticles encapsulating 5-FU were fine-tuned using SVR for controlled release and enhanced colonic retention. DL models, including CNNs, analyze imaging and biodistribution data to refine the nanoparticle size to 50–150 nm for the EPR effect and surface modifications, PEGylation, and folate ligands. Reinforcement learning iteratively adjusts formulation parameters using *in vitro* and *in vivo* feedback, thereby improving stability and tumor targeting, as demonstrated with SN-38-loaded liposomes in CRC xenograft models.[54,55] Although the enhanced permeability and retention (EPR) effect is robust in rodent tumors, its reliability in human colorectal cancer is variable. Clinical imaging studies suggest that nanoparticle accumulation is inconsistent, particularly in fibrotic, hypovascular, and microsatellite-stable tumors (MSI). The dense extracellular matrix, high interstitial pressure, and poor vascular permeability often limit passive accumulation. These findings indicate that EPR alone is insufficient and must be complemented by active targeting, transcytosis-based delivery,

or microenvironment-modulating strategies.These AI-driven strategies reduce trial and error and enable rapid patient-specific customization for CRC subtypes, such as CMS3 metabolic and CMS4 mesenchymal subtypes.

4.7. Quality assurance and control

Nanoparticle manufacturing often faces batch-to-batch variability, which limits its scalability and regulatory approvals.[55] AI-driven quality assurance addresses these issues through predictive control and real-time monitoring of the production process. ML models, such as decision trees and ensemble methods, analyze synthesis parameters, mixing rates, solvent evaporation, and temperature to ensure consistency and GMP compliance. For instance, AI monitoring of PLGA nanoparticle synthesis can detect anomalies in particle size or drug loading, thereby reducing manufacturing failures. DL models, including RNNs, predict temporal deviations in production processes, whereas digital twins for PLGA synthesis can reduce variability by 20%–30%, and federated learning for secure multi-site data sharing simulates and optimizes workflows for complex nanocarriers, such as metal–organic frameworks and exosome-mimetic systems.[56,57] These AI-driven approaches improve reproducibility, reduce costs, and support the clinical translation of CRC nanomedicine (Table 2).

4.8. AI-based nanotoxicity prediction

The rapid generation of AI-designed nanocarriers for CRC therapy requires early, high-throughput safety screening. Deep learning tools such as DeepTox and Nano-QSAR, trained on large nanomaterial databases, predict cytotoxicity, immunotoxicity, genotoxicity, and organ accumulation (AUC 0.89–0.96, $R^2 > 0.85$) using descriptors including size, zeta potential, surface chemistry, and protein-corona fingerprint. AI-based nanotoxicity prediction is limited by the lack of standardized toxicity endpoints. Different laboratories use various cell lines, animal models, exposure times, and toxicity readouts, making cross-study comparisons difficult. Interlaboratory variability reduces reproducibility and weakens regulatory confidence. Harmonized toxicity frameworks aligned with OECD and FDA guidelines are required to generate reliable datasets for training and validating AI nanotoxicity models.[58]

4.9. Deep learning in nanocarrier design

Deep learning in nanocarrier design represents a cutting-edge advancement in nanomedicine, particularly for targeted therapies addressing colorectal cancer, by harnessing complex, high-dimensional data to enhance precision and efficacy.[58] DL algorithms, such as convolutional neural networks, excel in analyzing intricate datasets, including whole-slide images of CRC tissues, to stratify tumors by molecular subtype and map the spatial expression of therapeutic targets, guiding the rational selection of surface ligands for nanocarriers. Recurrent neural networks and long short-term memory models process longitudinal omics and treatment-response data to predict resistance mechanisms, enabling the design of adaptive nanocarriers that co-deliver synergistic agents.[59] Transformer-based architectures integrate genomic, transcriptomic, proteomic, and microbiome data to create comprehensive molecular profiles and identify patient-specific vulnerabilities that inform the development of tailored nanocarriers for targeted therapy.[60] These models optimize physicochemical properties, such as size, shape, and drug release kinetics, by simulating interactions within the tumor microenvironment, thereby improving the biodistribution and therapeutic outcomes. DL accelerates development by reducing the reliance on extensive experimental trials, and its ability to handle unstructured data enhances its scalability and personalization. This approach marks a transformative step toward the development of efficient and patient-centric CRC nanomedicine.

4.10. AI-driven predictive modeling

AI-driven predictive modeling is central to CRC nanomedicine, using machine learning and deep learning to forecast outcomes, optimize therapies, and guide clinical decisions.[61] ML methods, such as random forests and support vector machines, identify critical variables, such as nanoparticle size, zeta potential, and ligand density, to predict the biodistribution and tumor uptake in the CRC microenvironment. DL models, including CNNs and transformers, analyze complex datasets, including whole-slide images and multi-omics profiles, to anticipate resistance mechanisms and tailor nanocarrier designs. Predictive modeling simulates PK/PD profiles, enabling real-time optimization of drug delivery, reducing toxicity, and supporting adaptive clinical trials through patient stratification and outcome prediction. By integrating real-time data from liquid biopsies and imaging, AI-driven predictive modeling advances personalized, scalable, and precise nanomedicine for CRC.

5. Pharmacokinetic/pharmacodynamic (PK/PD) modeling

Artificial intelligence is transforming PK/PD modeling in CRC nanomedicine by enabling predictive analytics, capturing nonlinear biodistribution, and integrating heterogeneous preclinical, imaging, and clinical datasets.[62] ML algorithms, including random forests, SVM, gradient boosting, and k-NN, predict pharmacokinetic parameters, such as clearance, half-life, and distribution volume, based on nanoparticle properties. DL approaches, including ANN, CNN, and RNN, model complex time–concentration profiles and tumor-specific accumulation kinetics of radiopharmaceuticals. Adaptive Bayesian modeling refines PK/PD predictions using patient-specific data, whereas reinforcement learning optimizes individualized dosing in real time. Traditional simulation platforms, such as NONMEM, Monolix, Phoenix WinNonlin, Simcyp, and GastroPlus, are increasingly enhanced with AI modules, improving predictive accuracy, accelerating nanomedicine development, and reducing empirical trial-and-error experimentation.

Machine learning (ML) and deep learning (DL) methods further

Table 2
AI techniques used in colorectal cancer (CRC) diagnostics.

AI Technique	Application	Advantages
Convolutional Neural Networks (CNNs)	Real-time polyp detection and classification during colonoscopy; lesion segmentation in CT/MRI	High sensitivity and specificity; reduction of missed lesions
Support Vector Machines (SVMs)	Biomarker discovery using genomic and proteomic data; molecular subtype classification.	Effective with small and high-dimensional datasets
Recurrent Neural Networks (RNNs)	Temporal analysis of patient outcomes, recurrence prediction, and treatment response modeling	Effective at recognizing longitudinal patterns over time
Deep Reinforcement Learning (DRL)	Optimizing screening schedules and treatment strategies	Adaptive and dynamic decision-making
Generative Adversarial Networks (GANs)	Synthetic augmentation of colonoscopy and histopathology datasets to improve model training	Enhances performance in limited data settings
Multi-omics Integration Models (MOIMs)	Integrating imaging, genomic, transcriptomic, and clinical data for precision diagnosis and risk stratification	Comprehensive analysis for personalized medicine

enhance PK/PD modeling by learning nonlinear exposure–response relationships directly from *in-vivo* CRC datasets. ML algorithms such as random forests, support vector machines, gradient boosting, and k-NN predict PK parameters (AUC, C_{max}, tumor-to-plasma ratios) from nanoparticle physicochemical features and imaging signatures. DL models including ANN, CNN, RNN, and LSTM architectures–capture complex temporal concentration profiles, nanoparticle retention dynamics within CRC tumors, and drug-induced tumor regression trajectories. Adaptive Bayesian modeling integrates individual *in vivo* measurements to refine PK/PD parameters in near real time, while reinforcement learning frameworks optimize personalized nanomedicine dosing strategies by simulating tumor exposure and therapeutic outcomes under varying regimens. Traditional PK/PD platforms such as NONMEM, Monolix, Phoenix WinNonlin, Simcyp, and GastroPlus increasingly incorporate AI-assisted modules to assimilate *in vivo* CRC datasets, allowing mechanistic models to be augmented with ML-driven insights. Collectively, AI-enabled PK/PD modeling enhances predictive accuracy, accelerates optimization of nanoparticle formulations, and reduces empirical experimentation by translating *in vivo* CRC data into actionable design and dosing strategies. Traditional physiologically based pharmacokinetic (PBPK) models offer mechanistic interpretability but require extensive parameterization and assumptions to be made. In contrast, AI-driven PK/PD models excel at learning nonlinear patterns from large datasets but often lack physiological transparency. Hybrid AI–PBPK frameworks may combine the strengths of both approaches by integrating biological structure with data-driven learning.

6. AI-Driven Drug Development and Personalized CRC Therapy

ADME Modeling, AI, including ML and DL, is instrumental in predicting the absorption, distribution, metabolism, and excretion of drugs, optimizing dosing, evaluating toxicity, and guiding safety.[63] Computational tools, such as pharmacophore modeling, virtual screening, and molecular docking, streamline candidate identification and refinement. Integrating ML with molecular modeling accelerates drug development by enabling rapid ADMET predictions and efficient evaluation of compounds as safe and effective therapeutics.[64]

6.1. Regulatory submissions

AI enhances regulatory processes by analyzing adverse event reports, real-world data, and literature, thereby improving pharmacovigilance, risk–benefit assessments, and safety evaluations.[65] QSAR, pharmacophore modeling, and docking tools, including SwissADME, PreADMET, ADMEWORKS, GastroPlus, and ADMETlab 2.0, support these predictions and facilitate faster approval.[66] Coordination among researchers, industry, and regulators, combined with XAI and real-world evidence, ensures the safe translation of CRC nanomedicines.[67]

6.2. Continuous post-market surveillance

AI enables proactive post-marketing safety monitoring by detecting rare, delayed, or population-specific toxicities of nanoparticle formulations, thereby supporting adaptive therapy management.[68]

6.3. Target identification

ML analyzes complex biological datasets to identify CRC-specific therapeutic targets, including immune checkpoints, monoclonal antibodies, and small-molecule inhibitors, thereby supporting precision therapy.[69] PBPK modeling assists in predicting the toxicity, pharmacokinetics, tumor targeting, payload optimization, and multiscale analysis of nanocarriers. Personalized Medicine: ML algorithms process patient genomic, proteomic, and clinical data to deliver individualized therapies, predict drug–drug interactions, optimize dosage, and reduce adverse effects. Virtual clinical trials simulate drug performance in diverse populations, thereby accelerating the development of tailored nanoparticle-based therapies. AI stratifies CRC patients by molecular subtype CMS1–4, MSI/TMB status, and pharmacogenomics to guide formulation selection, such as immune-activating nanoparticles for MSI-H tumors and EGFR-targeted carriers for CMS2 tumors.[70,71]

6.4. Predictive modeling for clinical trials

The integration of artificial intelligence into nanomedicine design is rapidly translating into clinical candidates for colorectal cancer, particularly in historically undruggable KRAS-mutant and microsatellite-stable disease. Generative adversarial networks have enabled virtual high-throughput screening of ligand-nanoparticle conjugates, yielding pH-responsive polymeric nanoparticles loaded with KRAS G12D/V inhibitors that achieved 65%–78% tumour regression in patient-derived xenografts with minimal off-target toxicity. Landmark ongoing trials reflecting AI-accelerated pipelines include NCT06838338 (JAB-21822), NCT06252649 (CodeBrek), NCT05462717 (RMC-6291), and NCT05382559 (ASP3082). These studies, underpinned by AI-driven target validation, ligand optimization, and patient stratification, suggest that AI-optimized regimens could improve median overall survival by 20%–30% in KRAS-driven metastatic CRC [72–76], provided combination toxicities and biomarker validation are resolved, marking a pivotal shift from empirical to precision nano-oncology summarised in Table 3.

6.5. Predictive analytics

AI-driven analytics integrate experimental and clinical data to forecast therapeutic outcomes, optimize nanocarrier design, personalize treatment, and enhance supply chain management.[81] ML models, such as LightGBM, Random Forest, SVR, and PLS, have successfully predicted liposome formulation properties, size, zeta potential, encapsulation efficiency, and nanoparticle cytotoxicity, enabling dose optimization and improved tumor infiltration. This comprehensive AI-driven framework bridges drug design, regulatory compliance, clinical translation, and personalized CRC therapy, promoting safer, more effective, and patient-specific nanomedicine strategies for CRC treatment in the future.

7. AI-driven prediction and optimization in CRC nanomedicine

AI and ML algorithms provide comprehensive predictive tools for colorectal cancer nanomedicine, enabling the rational design and optimization of drug delivery systems (DDSs). ML models forecast molecular loading and release kinetics, including co-encapsulation strategies for biologics, such as siRNA targeting KRAS-G12D. Support vector machines and neural networks predicted cellular uptake in CRC cell lines HT29, HCT116, and SW480, and optimized endocytosis efficiency. Nano-QSAR approaches estimate cytotoxicity in intestinal organoids and 3D CRC spheroids, minimizing the reliance on animal models. AI also predicts nanocarrier stability by modeling protein corona formation and aggregation in the gastrointestinal tract, whereas computational simulations of solubility, mucosal diffusion, and permeability guide oral bioavailability and gastrointestinal protection. Furthermore, AI-driven optimization of physicochemical properties, such as surface charge, size, hydrophobicity, and morphology, enhances drug entrapment, DDS efficiency, and physical stability. Collectively, these predictive and design strategies accelerate the translation from bench to bedside while reducing attrition rates.

7.1. Particle size and polydispersity

The particle size, shape, and polydispersity index (PDI) critically influence the biological behavior of nanocarriers in colorectal cancer therapy. Nanoparticles sized 10–200 nm enhance tumor accumulation via the EPR effect, whereas smaller particles ($<$ 10 nm) are rapidly cleared by the kidneys. Spherical nanoparticles have prolonged

Table 3
Translational Significance: Representative ongoing clinical trials of AI-Optimized or AI-Enabled therapeutics for colorectal cancer.

Trial ID (ClinicalTrials.gov)	Phase	Intervention/Agent	AI Role in Development/ Optimization	Key Population (CRC)	Status (Dec 2025)	Interim/ Reported Efficacy Highlights	Reference
NCT06838338	II	JAB-21822 (KRAS G12C inhibitor) + chemotherapy ± bevacizumab	AI-driven patient stratification & dosing via multi-omics transformer	KRAS G12C-mutant mCRC, 2nd line	Recruiting ($n = 120$)	ORR 35%, DCR 75%, mPFS 8.2 mo	[77,78]
NCT06252649 (CodeBreaK 301)	III	Sotorasib + panitumumab + FOLFIRI vs. standard therapy	AI-optimized triplet combination & biomarker enrichment (GAN screening)	1st-line KRAS G12C-mutant mCRC	Recruiting ($n = 420$)	Expected ORR about 45% (phase II precursor: ORR 30%, mPFS 6.9 mo)	[79,72]
NCT05462717 (RMC-6291-001)	I	RMC-6291 (oral KRAS G12C ON inhibitor)	Deep learning pharmacokinetic prediction & virtual screening	Advanced solid tumors incl. KRAS G12C CRC	Recruiting ($n = 200$)	ORR 40% in CRC cohort, durable responses in prior G12C failures	[72]
NCT05382559	I/II	ASP3082 (first-in-class KRAS G12D inhibitor)	AI-enriched biomarker cohorts & predictive toxicity modelling	KRAS G12D-mutant solid tumors incl. CRC	Recruiting ($n = 150$)	ORR 25% in KRAS G12D-enriched CRC, well-tolerated	[73]
NCT07066046 (pre-IND 2026)	–	GAN-designed pH-responsive PLGA nanoparticle + KRAS G12D/V inhibitor (MRTX1133 analog)	Full AI pipeline: GAN ligand design, RL formulation optimization, DeepTox safety	Planned: KRAS G12D/V-mutant mCRC	Preclinical → IND 2026	65%–78% tumour regression in PDX, minimal systemic toxicity	[74,80]
NCT05679674 (A2B694 CAR-T)	I	AI-optimized mesothelin-targeted CAR-T + nanocarrier preconditioning	Transformer-based antigen selection & nano-preconditioning design	MSLN-positive advanced CRC	Recruiting ($n = 60$)	Early signals: 30% partial response in CRC subset	[75,76]

circulation compared to rod-shaped nanoparticles, which extravasate faster but have shorter half-lives. Optimizing the PDI (< 0.2) ensures uniform drug loading and release, directly improving therapeutic efficacy, as exemplified by liposomal doxorubicin with a size of about 100 nm and low PDI, which minimizes off-target toxicity and maximizes tumor penetration. Surface modifications, such as PEGylation, reduce opsonization, prolong circulation, and enhance MRI contrast. Techniques such as atomic force microscopy, static and dynamic light scattering, and centrifugal liquid sedimentation are used to measure particle size, whereas factors such as polymer molecular weight, ionic concentration, and temperature influence nanocarrier dimensions. For example, predictive modeling of chitosan nanoparticles showed that higher polymer concentrations reduced disintegration, whereas extreme pH levels increased it.

7.2. Morphology

The shape of nanocarriers, whether spherical, rod-like, or discoidal, critically influences their interactions with biological barriers in colorectal cancer. Spherical nanoparticles demonstrate superior margination in chaotic tumor vasculature, whereas rod-shaped particles achieve higher cellular uptake but may trigger immune responses. For instance, discoidal mesoporous silica nanoparticles evade macrophage clearance more effectively than spherical nanoparticles, enhancing tumor accumulation. Anisotropic shapes, such as gold nanorods, facilitate photothermal therapy via localized surface plasmon resonance, enabling precise hyperthermic treatment. However, irregular geometries can hinder deep tumor penetration because of steric hindrance within the dense extracellular matrix. Computational modeling, including finite element analysis integrated with AI-driven design, can predict optimal morphologies to overcome these limitations. Comparative studies have shown that rod-shaped nanoparticles extravasate faster, whereas spherical nanoparticles have longer circulation times. The nanocarrier architecture and polymer design further enhance drug transport. High-resolution morphological analysis was achieved using atomic force microscopy, whereas SEM and TEM provided structural insights, SEM for dried, metal-coated samples, and TEM for detailed morphology. Dissipative particle dynamics simulations suggest that rod-like and elongated nanoparticles exhibit superior margination, tumor accumulation, and encapsulation efficiency compared with spherical nanoparticles.

8. Nanocarrier physicochemical properties and AI-driven optimization

Nanocarrier characteristics critically influence drug delivery, cellular uptake, and therapeutic efficacy in colorectal cancer. Surface charge determines bioavailability, stability, and endocytosis, which are influenced by pH, size, composition, medium, and ionic concentration. The zeta potential is measured via TRPS, ELS, or PALS, and neural networks have been used to correlate the structure with the ζ-potential. Nanoparticle adhesion to vessel walls affects tumor targeting, and ANN models predict attachment based on size and shear stress. Surface modification, including PEGylation, improves circulation by reducing aggregation and phagocytosis, whereas cavitation techniques enhance the stability of metal nanoparticles. Hydrophobicity governs membrane penetration and distribution. Coarse-grained molecular dynamics simulations have shown that hydrophobic particles penetrate membranes efficiently, whereas semi-hydrophilic particles primarily adsorb onto membranes. Concentration and elasticity influence uptake: optimal nanoparticle concentrations maximize penetration, and flexible nanoparticles initially envelop membranes faster but may slow over time because of receptor recruitment dynamics, whereas rigid particles maintain steady internalization. Molecular loading metrics, such as drug loading content and drug Loading efficiency, depend on the drug structure and loading method, with covalent bonding generally resulting in higher drug incorporation. Drug release is optimized using AI models that analyze patient data, drug properties, and multi-omics datasets to predict dissolution, absorption, interactions, and target engagement. Cellular uptake prediction relies on nano-QSAR models to forecast endocytosis efficiency based on size, charge, and surface properties, which are validated using FCM, CLSM, STEM, and ICP-MS. Cytotoxicity prediction leverages computational models to assess nanoparticle safety,

reducing the reliance on animal testing and identifying potential organ toxicity. Safety prediction integrates design strategies for low-toxicity cores and biocompatible coatings, such as silica and metal oxides, to enhance stability and biocompatibility. Collectively, AI-driven modeling enables rational design, optimization, and safety assessment of nanocarriers, accelerating translation from bench to clinical application.

8.1. Stability, Solubility, and Permeability Predictions

Nanocarrier stability is critical for effective drug delivery, as vesicular systems, such as liposomes, may undergo phospholipid oxidation, reduced zeta potential, Ostwald ripening, bilayer fusion, or drug leakage. In self-assembled systems, such as micelles, stability is reflected by the critical micelle concentration, with lower values indicating better retention of hydrophobic drugs. The formation of a protein corona in biological environments can also affect nanocarrier behavior, toxicity, and targeting. AI and ML facilitate stability prediction by analyzing large datasets, modeling degradation pathways, and forecasting shelf life, thereby improving nanomedicine safety and efficacy. Solubility prediction leverages machine learning techniques, including deep neural networks and random forests, to accelerate the identification of promising drug candidates. AI enables the comprehensive analysis of nanoparticle interactions and optimization of formulations, while in silico simulations combined with experimental validation refine the predictive accuracy. Permeability prediction is essential for evaluating a drug's ability to cross biological barriers and influence ADME profiles. ML and AI models assess molecular features, such as lipophilicity, hydrogen bonding, and molecular weight, across diverse datasets, thereby guiding candidate selection and enhancing clinical efficacy.

8.2. Biological activities and AI-driven ADME predictions

AI, including machine learning and deep learning, is increasingly employed to predict the pharmacokinetics of nanodrugs in colorectal cancer therapy. ADME predictions use ML models, such as Bayesian networks, random forests, and neural networks, together with QSAR methods, to forecast absorption, distribution, metabolism, and excretion based on chemical structures. Absorption prediction addresses protein corona formation, which affects cellular recognition and biological activity. ML integrated with molecular simulations can predict nanodrug interactions, thereby improving their safety and efficacy. Distribution predictions evaluate post-absorption biodistribution, which is influenced by nanoparticle size, zeta potential, PEGylation, blood protein binding, and tissue perfusion. ML, multiple linear regression, and physiologically based pharmacokinetic (PBPK) models simulate tissue accumulation and clearance, including mucociliary and biliary pathways, for formulations such as PLGA-mPEG495 and AgNPs. Metabolism predictions focus on nanocarrier processing by liver enzymes and the mononuclear phagocyte system, which affects metabolite formation. Hill function-based PBPK simulations provide preliminary insights from *in vitro* and *in vivo* data. Excretion predictions examine renal and hepatobiliary clearance, with size and surface charge as the key determinants. Studies on TiO_2 and AuNPs have demonstrated the use of PBPK and computational modeling to anticipate pharmacokinetic behavior, aiding in safety evaluation and nanodrug design. Collectively, AI-driven ADME predictions provide a robust framework for optimizing nanodrug performance and guiding the development of safe and effective therapeutics for colorectal cancer.

9. Types of AI-optimized nanocarriers

AI-based computational modeling and simulation are powerful tools for analyzing complex systems and enhancing performance in healthcare, materials research, engineering, and environmental sustainability fields.[82] By processing large datasets, AI identifies trends and builds predictive models for virtual testing, thereby reducing the reliance on costly experiments. In nanotechnology, AI accelerates the design and optimization of innovative nanocarriers, enables real-time monitoring, improves efficiency, and fosters multidisciplinary collaborations.[83] The integration of neural networks with nanotechnology has facilitated applications such as neuromorphic circuits in medical diagnostics and robotics. Recent advances have produced intelligent nanomaterials with tunable optical properties, enhanced absorption, biocompatibility, immune evasion, targeted cellular interactions, and controlled drug release, which offer transformative therapeutic potential. AI further streamlines drug discovery by employing ML and DL to analyze chemical and clinical datasets, predict molecular activities, and perform virtual screenings. For effective intelligent nanoparticle development, nanoscale carriers must meet the following criteria: biocompatibility, biodegradability, size stability, stimulus responsiveness, low toxicity, high encapsulation efficiency, and an adjustable surface charge. Thirteen commonly used nanocarriers have been examined in this context. Fig. 5 illustrates the Classification of AI-optimized nanocarriers.

9.1. Polymeric nanoparticles

Polymeric nanoparticles are pivotal in colorectal cancer nanomedicine, enabling improved drug delivery, controlled release, and targeting strategies.[84] Their versatility fosters collaboration among biologists, chemists, engineers, and clinicians to enhance therapeutic outcomes. Intelligent polymeric systems have been applied in CRC to co-encapsulate chemotherapeutic drugs (5-fluorouracil and oxaliplatin) with tailored release profiles, enhancing circulation and therapeutic efficacy. PEG–drug conjugates increase stability, prolong half-life, and reduce immunogenicity, addressing challenges such as poor solubility and rapid clearance of conventional CRC drugs.[85] Machine learning has been increasingly applied to optimize formulation parameters, such as polymer–drug ratios, particle size, and encapsulation efficiency, for CRC-targeted polymeric carriers. The integration of materials informatics with polymer science holds significant promise for accelerating the translation of polymer-based gene therapies and chemo–immunotherapy combinations into effective CRC treatment.

9.2. Mesoporous silica nanoparticles

Mesoporous silica nanoparticles are widely utilized in colorectal cancer therapy for controlled drug delivery owing to their large surface area, tunable pore size, and biocompatibility.[86] Surface modification

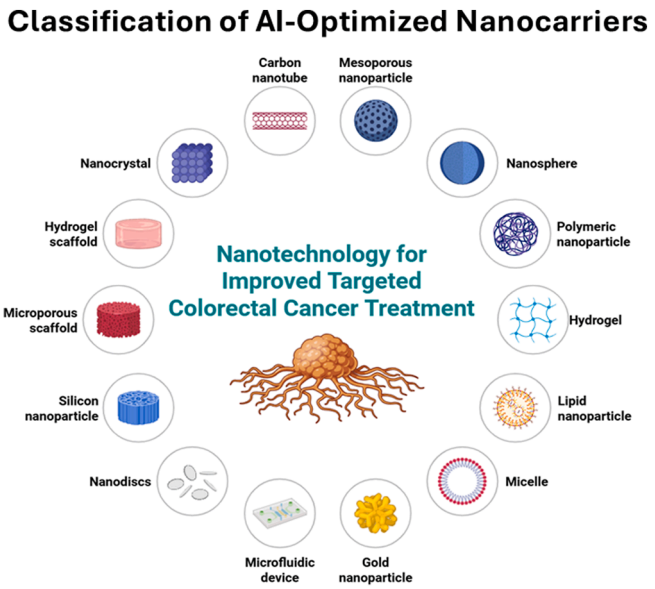


Fig. 5. Classification of AI-Optimized nanocarriers.

with polyethylene glycol has been shown to enhance circulation time and tumor accumulation via the enhanced permeability and retention effect in CRC models. MSNs loaded with irinotecan or doxorubicin demonstrated increased cytotoxicity against CRC cell lines HCT-116 and SW480, with pH-responsive coatings enabling tumor-specific release of the drug. Machine learning methods have been applied to MSN synthesis to predict coating thickness and morphology from spectroscopic features,[87] enabling precise engineering of CRC-targeted MSN formulations.

9.3. Peptide-based nanoparticles

Peptide-based nanoparticles have emerged as promising delivery systems in colorectal cancer immunotherapy and drug delivery owing to their amphiphilic self-assembly properties.[88] Peptide amphiphiles have been used to deliver ellipticine and doxorubicin in CRC models, achieving high tumor accumulation and stimulus-responsive release. In addition, peptide-based platforms are being explored for CRC vaccine development, leveraging multivalency to enhance immune responses against tumor-associated antigens such as CEACAM5 and MUC1. Advanced peptide screening approaches, including machine learning–assisted algorithms, are increasingly employed to design sequences with optimal stability, low immunogenicity, and efficient tumor targeting, thereby accelerating CRC-focused peptide nanocarrier development.[89]

9.4. Dendrimers

Dendrimers, such as polyamidations, are being actively studied for CRC drug delivery because of their precise size control, high drug loading capacity, and targeting capabilities.[90] PAMAM dendrimers have been used to enhance the colon-specific delivery of 5-fluorouracil and SN-38, improving bioavailability and reducing systemic toxicity. Machine learning approaches have been applied to predict dendrimer cytotoxicity and optimize branching architectures for CRC applications by generating 3D dendrimer structures and extracting physicochemical descriptors to inform safe and efficient designs.[91]

9.5. Polymer micelles

Polymer micelles have shown great potential in CRC therapy by improving the solubility and stability of hydrophobic anticancer drugs such as camptothecin and curcumin. pH-responsive micelles have been designed to release drugs specifically in the acidic tumor microenvironment, typical of colorectal tumors, pH 6.5 to 7.0, thereby minimizing off-target effects and enhancing the therapeutic index.[92] Machine learning has been applied to predict micelle viscosity and dispersion based on the molecular structure, which can be adapted to CRC drug carriers to optimize their release kinetics and tumor targeting.

9.6. Liposomes

Liposomes are among the most clinically relevant nanocarriers for colorectal cancer therapy. PEGylated liposomal doxorubicin has demonstrated an extended circulation half-life 55 h vs. 10 min for the free drug and enhanced tumor accumulation through the EPR effect.[93] Folate-targeted liposomal doxorubicin increased tumor uptake by 3.5-fold and reduced cardiotoxicity by 40% in HER2-negative CRC murine models. Pluronic-modified liposomes (SP1049C) overcame P-glycoprotein-mediated resistance in aggressive CRC xenografts, achieving 70% tumor regression compared to 25% with the free drug. Machine learning models have been used to predict critical liposomal formulation parameters, particle size, and encapsulation efficiency, enabling the rapid optimization of CRC liposomal delivery systems.[94]

9.7. Protein-based nanoparticles

Protein-based nanoparticles derived from soy, milk, and serum have been evaluated as CRC drug carriers because of their biocompatibility and high drug binding capacity.[95] Bovine serum albumin nanoparticles have demonstrated efficient encapsulation and sustained release of 5-fluorouracil and SN-38 in colon cancer models. Machine learning has been applied to predict protein corona formation on engineered nanomaterials, including CRC-relevant nanocarriers, using fluorescence change descriptors, thereby improving the prediction of protein–nanoparticle interactions and safety assessments.

9.8. Cell membrane-coated nanoparticles

CMCNs offer enhanced immune evasion, prolonged circulation, and tumor-specific targeting in CRC therapy.[96] For example, platelet membrane-coated nanoparticles co-loaded with doxorubicin and TRAIL demonstrated potent anticancer activity in CRC xenograft models. The combination of mesoporous silica cores with erythrocyte membranes has enabled pH-triggered release and prolonged systemic circulation in colorectal tumor-bearing mice. AI approaches are increasingly being used to design CMCN formulations and monitor drug release in real time, thereby improving targeting precision and treatment personalization.

9.9. Metallic nanoparticles

Metallic nanoparticles, particularly superparamagnetic iron oxide nanoparticles (SPIONs) and gold nanoparticles, have been explored for CRC imaging and treatment.[97] SPIONs enable high-resolution MRI of CRC lesions and facilitate targeted drug delivery when functionalized with colon-targeting ligands. Gold nanoparticles have been employed for the targeted photothermal ablation of CRC cells, enhancing tumor reduction with minimal damage to healthy tissues.[98] Machine learning has been integrated with spectroscopy (XANES) to model the size and morphology of platinum or gold nanoparticles during synthesis, improving precision engineering for CRC applications.[99]

9.10. Gold nanoparticles

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9.11. Metal–organic framework nanoparticles

MOFs have been explored as multifunctional CRC nanocarriers for chemotherapy and photodynamic therapy because of their high porosity and tunable structures.[100] Core-shell and Janus MOF architectures have improved drug loading and release in colon cancer models. Machine learning, particularly artificial neural networks, has been used to predict MOF structural outcomes and drug-loading efficiency, thereby accelerating CRC MOF design pipelines.

9.12. Quantum dots (QDs)

Quantum dots offer exceptional imaging capabilities in CRC diagnostics because of their tunable emission spectra and photostability.[101] QDs conjugated with colon-specific ligands enable real-time

intraoperative tumor visualization. Machine learning has been employed to optimize QD synthesis parameters and predict the zeta potential, enhancing their application in CRC nanomedicine and imaging.

9.13. Carbon nanotubes

Carbon nanotubes (CNT), including single-walled carbon nanotubes (SWCNT) and multi-walled carbon nanotubes (MWCNT) types, are pivotal in nanotechnology and biomedical applications.[102] Their strong near-infrared absorption enables targeted therapy. MWCNT toxicity depends on morphology and ROS generation, and quasi-QSAR models help predict cytotoxicity in pulmonary cells, thereby supporting safer applications of MWCNT. CNTs can deliver drugs, such as camptothecin and cisplatin, thereby enhancing therapeutic efficacy; however, further studies are required for clinical translation. The integration of molecular dynamics simulations with AI improves the modeling of nanoscale materials with high aspect ratios, enabling accurate and efficient nanotoxicology predictions.

10. Advancements in AI for colorectal cancer diagnostics

Artificial intelligence is rapidly transforming colorectal cancer diagnostics by significantly improving the precision, speed, and breadth of conventional diagnostic methods.[103] The application of machine learning and deep learning algorithms to complex datasets, such as colonoscopic images, radiology scans, histopathology slides, and multi-omics data, enables earlier detection and more accurate characterization of tumors. In endoscopy, artificial intelligence-assisted colonoscopy has increased adenoma detection rates while reducing the miss rates of diminutive and flat lesions.[104] Convolutional neural network-based models have achieved sensitivities exceeding 94 percent and specificities of approximately 92 percent for lesion classification, outperforming traditional manual interpretation.[105] In radiology, artificial intelligence systems applied to computed tomography and magnetic resonance imaging facilitate automated lesion segmentation, tumor staging, and volumetric analysis.[106] Notably, three-dimensional U-Net architectures have demonstrated high Dice similarity scores (greater than 0.85) for rectal tumor delineation, while the integration of convolutional neural networks into diagnostic workflows has reduced missed diagnoses by up to 30 percent.[107] Beyond imaging, machine learning-driven analyses of genomic and proteomic data have advanced biomarker discovery, identifying key alterations such as KRAS, NRAS, and BRAF mutations, microsatellite instability, HER2 amplification, and specific methylation signatures.[108] These biomarkers are crucial for patient stratification and guiding targeted and immunotherapeutic interventions. Radiomic biomarkers provide non-invasive insights into tumor phenotypes, complementing molecular diagnostics to support precision treatment planning.[77] Despite these significant advancements, widespread clinical adoption remains constrained by challenges such as the need for large, diverse, and well-annotated datasets, external validation across populations, regulatory approvals, and the “black-box” nature of many artificial intelligence models.[78] Most nanocarrier efficacy data are derived from xenograft or patient-derived xenograft (PDX) models, which have significant limitations. These models lack a fully functional human immune system and do not accurately reproduce human stromal architecture, microbiome interactions, or vascular heterogeneity. Consequently, they often overestimate therapeutic benefits and poorly predict human responses, particularly with immune-modulating nanocarriers. Advanced models, such as organoids, humanized mice, and microfluidic tumor-on-chip systems, are needed to improve translational relevance. As explainable artificial intelligence frameworks evolve and robust validation strategies are established, the integration of these tools into clinical workflows holds great promise for enhancing early detection, reducing diagnostic variability, enabling personalized therapy, and ultimately transforming colorectal cancer diagnosis and patient care in the future.[79]

11. Innovations in nanotechnology for colorectal cancer therapy

Nanotechnology has revolutionized colorectal cancer treatment by enabling precise drug delivery and Theranostics.[72] Engineered nanocarriers, including liposomes, gold nanoparticles, and polymeric micelles, directly deliver chemotherapy to tumor cells, thereby reducing systemic toxicity and enhancing therapeutic efficacy.[73] Theranostic platforms combine diagnostic imaging with treatment capabilities, allowing real-time monitoring of therapeutic responses.[74] Biogenically synthesized gold nanoparticles further enhance the anticancer efficacy while minimizing the side effects.[75] Overall, nanotechnology improves clinical outcomes by providing highly effective and safe treatment strategies for colorectal cancer.

Another milestone in nanomedicine is the development of multifunctional theranostic nanoparticles that combine diagnostic and therapeutic capabilities on a single platform.[76] These platforms enable simultaneous tumor imaging and therapy, thereby enhancing the efficacy of cancer treatment. For example, magnetic nanoparticles can act as both drug carriers and MRI contrast agents, creating versatile nanoplatforms for precise diagnosis and therapy. Quantum dots and gold nanoparticles improve imaging resolution, facilitating early and accurate tumor detection. Modified gold nanostars have been engineered for the targeted imaging and photothermal therapy of triple-negative colorectal cancer, demonstrating enhanced imaging and therapeutic efficacy. Such theranostic nanoparticles offer a promising strategy for personalized colorectal cancer treatment, potentially improving patient outcomes.

AI has revolutionized nanoparticle design for cancer therapy by analyzing tumor-specific features, including microenvironmental pH, receptor expression, and vascular characteristics.[109,110] Machine learning enables the optimization of nanoparticles tailored to tumor-specific parameters, thereby improving their therapeutic efficacy. A central focus is the development of pH-sensitive nanoparticles that selectively release drugs in the acidic tumor microenvironment, thereby minimizing exposure to healthy tissues, reducing side effects, and enhancing treatment outcomes. AI also addresses challenges in the tumor microenvironment, such as elevated interstitial fluid pressure and irregular vasculature, which can hinder nanoparticle delivery. Furthermore, AI-guided nanomaterials, including quantum dots and gold nanoparticles, enhance imaging resolution, enabling earlier and more precise tumor detection and therapy initiation.[48,111] The integration of AI in nanoparticle design represents a major advancement in personalized cancer treatment, facilitating precise, effective, and tumor-specific therapeutic strategies for cancer treatment. Table 4 summarizes the types of nanocarriers, their properties, and their applications.

12. AI in clinical CRC diagnostics

Artificial intelligence has transitioned from research tools to clinically approved systems that are now routinely used in colorectal cancer screening and diagnosis, markedly improving adenoma detection rates, reducing interval cancers, and enhancing diagnostic confidence in real-world settings. Colorectal cancer is a major cause of mortality among women worldwide.[114,115] Its pathophysiology is complex and is influenced by factors such as sex, genetics, heredity, environmental exposure, and occupational risk factors. Effective management relies heavily on early screening, which significantly reduces the mortality rate. Advanced AI techniques are enhancing these screening methods, improving the accuracy and efficiency of colorectal cancer detection and diagnosis through imaging and biopsy data analyses.[116,117] The integration of AI into screening workflows holds great promise for improving diagnostic precision and treatment outcomes.[111] Current research suggests that AI-assisted colorectal cancer screening can further reduce mortality and enhance patient outcomes.[57,118] Fig. 6 illustrates the capabilities of AI in colorectal cancer imaging.

Table 4
Properties and applications of nanocarriers in colorectal cancer (CRC).

Nanoparticle Type	AI Enhancement Example	Experimental Status	Clinical Development Stage	Key Reference (2022–2025)
Liposomes	ML-guided optimization of PEGylated formulations for doxorubicin encapsulation and pH-responsive release	*In vivo* (CRC xenografts: reduced toxicity, enhanced EPR uptake)	Phase II (e.g., Onivyde® analogs for irinotecan)	[94]
Polymeric NPs (e.g., PLGA)	RL + DoE for size/shape optimization; GANs for KRAS G12D inhibitor loading	Preclinical (3D spheroids: 70% tumor regression)	Preclinical/Phase I (NCT05382559: ASP3082 for KRAS mutants)	[53]
Mesoporous Silica NPs	ML for synthesis optimization (pore size, coating); GNNs for ligand screening	*In vitro/in vivo* (HCT-116 cells: high cytotoxicity, low immunogenicity)	Phase I (targeted MSN for irinotecan)	[87]
Gold NPs	Deep learning for photothermal ablation design; XANES-ML for morphology prediction	Preclinical (murine models: 3.5-fold tumor uptake)	Phase I/II (AuNP-DOX conjugates)	[99,112]
Iron Oxide NPs (SPIONs)	CNNs for MRI contrast enhancement; predictive ML for targeting ligands	*In vivo* (lymph node mapping in CRC models)	Phase II (Ferumoxytol® for metastasis detection)	[97]
Carbon Nanotubes	Transformer models for toxicity prediction; QSAR for functionalization	Preclinical (photothermal therapy in xenografts)	Preclinical (SWCNT for siRNA delivery)	[102,113]

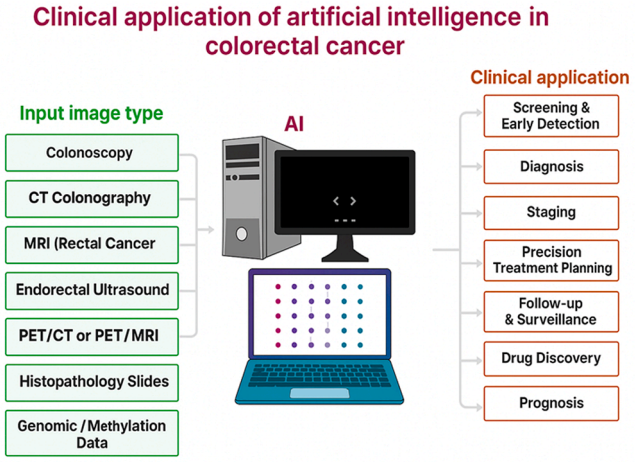


Fig. 6. Clinical applications of AI in colorectal cancer.

12.1. *FDA-approved AI systems for real-time colonoscopy*

Two systems have received full FDA approval and are commercially deployed: GI Genius™ and CAD EYE™. Both function as computer-aided detection platforms providing real-time visual and auditory alerts for potential polyps. Large-scale randomized trials and post-market studies consistently demonstrate absolute ADR increases of 14%–22% in average-risk screening populations, with the greatest benefit observed in community practice settings where baseline ADR is lower.[119,21] These systems have been integrated into routine clinical workflows in over 5000 endoscopy units worldwide.

12.2. *Detection of right-sided sessile serrated polyps*

Right-sided sessile serrated lesions are flat, mucus-capped, and represent a major cause of interval cancers (up to 50–60% of post-colonoscopy CRCs originate from missed proximal serrated lesions). Latest-generation CNN-based systems achieve sensitivity of 85–92% for SSLs versus 55–65% for unaided endoscopists in prospective studies, with particular improvement during the withdrawal phase in the proximal colon.[120,121] This has translated into a significant reduction in missed precursor lesions that disproportionately contribute to aggressive, microsatellite-stable interval cancers.

12.3. *AI-augmented virtual colonoscopy*

AI dramatically improves the performance of CT colonography, especially for sub-centimeter polyps that are traditionally challenging. Deep learning algorithms applied to CTC datasets increase sensitivity for polyps < 6 mm by 15%–20% and reduce false-positive rates by 30%–40% through automated 3D reconstruction, prone/supine registration, and electronic cleansing.[122,22] Multicenter trials (2024–2025) have validated AI-CTC as a viable non-invasive alternative for patients unwilling or unable to undergo optical colonoscopy, with per-patient sensitivity approaching 95% for clinically relevant (≥ 6 mm) lesions.[23]

12.4. *Correlation with post-resection pathology*

Contemporary AI systems now provide real-time histological prediction ("optical biopsy") with sensitivity of 90%–96% and specificity 85–93% for distinguishing adenomatous from hyperplastic diminutive polyps, meeting or exceeding PIVI thresholds established by ASGE.[24,25] This "diagnose-and-leave" or "resect-and-discard" strategy has been shown to reduce pathology costs by $> 70\%$ while maintaining surveillance interval accuracy $> 95\%$ in large prospective cohorts (2023–2025). Implementation of these capabilities is rapidly shifting clinical practice toward AI-supported, pathology-sparing management of diminutive colorectal polyps. These clinically validated AI applications collectively address the major limitations of conventional CRC diagnostics: operator dependency, miss rates for subtle/proximal lesions, and over-reliance on histopathology, paving the way for higher-quality, more efficient, and cost-effective colorectal cancer prevention programs.[123,124]

13. Challenges and future directions

The integration of nanotechnology and AI in colorectal cancer diagnosis and therapy offers great potential but faces significant challenges. Ensuring data integrity and accessibility remains difficult, as high-quality, representative datasets, especially for underrepresented populations, are scarce, and privacy concerns and fragmented data-sharing systems further limit access. Deep learning models often function as "black boxes," reducing clinical trust and adoption; explainable AI (XAI) with interpretable layers or attention mechanisms may improve confidence and facilitate regulatory approval. Scaling nanocarrier production is also challenging, as uniformity in particle size, shape, and surface properties is essential for safety and efficacy.[125,126] Additionally, CRC's molecular heterogeneity and drug resistance complicate therapy design, making single-agent nanocarriers insufficient for addressing complex tumor biology. High costs, resource requirements, and extensive clinical validation, particularly in resource-limited settings, further constrain development. Future research should prioritize centralized, open-access databases with anonymized clinical data to enhance diversity and improve model reliability. Transparent AI decision-making, alongside stringent quality standards for nanocarrier synthesis, will facilitate clinical translation. Beyond data privacy, ethical concerns include algorithmic bias. AI models trained on non-representative

datasets may perform poorly in certain age groups, ethnicities, or tumor locations. Underrepresentation of low- and middle-income populations risks widening health disparities. Fairness-aware model design, diverse training datasets, and continuous post-deployment auditing are required to ensure equitable clinical performance. The development of multifunctional, stimuli-responsive nanocarriers that adapt to the tumor microenvironment, integrate therapeutic and imaging functions, and deliver multiple agents may overcome tumor heterogeneity and resistance. Regulatory frameworks must remain adaptable to keep pace with rapid innovations. Collaboration among researchers, industry, and regulatory agencies is essential for standardizing evaluations, accelerating approvals, and reducing costs. AI-driven robotic automation in nanoparticle synthesis can lower production costs while ensuring consistent quality, improving affordability and access. Compared with conventional CRC therapy, AI-guided nanomedicine offers higher targeting precision and potential efficacy but involves greater cost, technical complexity, and regulatory burden. Conventional therapies are cheaper and widely accessible but less personalized and often more toxic. A balanced risk–benefit evaluation is therefore essential when considering clinical adoption. The validation of these nanotechnology approaches will require large-scale, multicenter clinical trials that include diverse patient populations. Adaptive trial designs can improve the efficiency of clinical translation by allowing modifications to procedures based on interim results. Equally important are sustainability and ethical considerations in the production and application of nanoparticles. Researchers must adopt sustainable practices and ensure that the benefits of these technologies are distributed equitably among patients from different socioeconomic backgrounds.[127,128] Table 5 represents key challenges and future directions for integrating AI and nanotechnology in breast cancer management.

14. Regulatory and health-economics perspectives

As AI-assisted nanomedicine advances toward clinical integration for colorectal cancer management, robust regulatory frameworks and economic analyses are essential to ensure safety, efficacy, and equitable access, particularly in diverse global contexts.

14.1. Regulatory frameworks for AI as software as a medical device (SaMD) and nanotechnology products

The convergence of artificial intelligence and nanotechnology in colorectal cancer theranostics falls under dual regulatory oversight by the U.S. Food and Drug Administration and the European Medicines Agency. AI components integrated into diagnostic or therapeutic systems are classified as Software as a Medical Device and regulated through risk-based pathways. The FDA's 2025 Final Guidance on "Artificial Intelligence-Enabled Device Software Functions" adopts a Total Product Lifecycle approach and permits Predetermined Change Control Plans, allowing pre-specified algorithm modifications, retraining on new CRC imaging datasets without requiring new submissions, provided performance and safety are maintained.[129,130] Nanotechnology-specific considerations are addressed in FDA Guidance for Industry (2018, updated 2024) entitled "Drug Products, Including Biological Products, that Contain Nanomaterials," which mandates detailed physicochemical characterization (particle size distribution, zeta potential, morphology, dissolution rate, surface chemistry) and long-term biodistribution/toxicity studies.[131,132]

In the European Union, AI-SaMD is governed by the Medical Device Regulation (EU) 2017/745 and the upcoming Artificial Intelligence Act (2024/1689), with most real-time colonoscopy CADe systems classified as Class IIa or IIb. The EMA's Innovation Task Force briefing meetings and the 2024 Reflection Paper on Nanotechnology-Based Medicinal Products emphasize risk-based evaluation of immunogenicity, persistence, and environmental impact, supported by enhanced post-market surveillance via EudraVigilance.[133,134] Harmonization efforts through the International Medical Device Regulators Forum and adoption of Good Machine Learning Practice principles ensure transparency, bias mitigation, and continuous monitoring critical for approval of AI-optimized nanocarriers targeting KRAS-mutant or microsatellite-stable CRC subtypes.[135,136]

14.2. Health-economics implications in resource-limited settings

In low- and middle-income countries (LMICs), where colorectal cancer incidence is projected to increase 2–3-fold by 2040 and currently accounts for approximately 70% of global cancer-related mortality due to late-stage diagnosis and limited therapeutic access, AI-integrated nanomedicine offers transformative cost-effectiveness potential.[137,138] Markov modeling and real-world evidence from India, Brazil, and sub-Saharan Africa (2023–2025) indicate that AI-assisted colonoscopy systems (GI Genius™, CAD EYE™) yield incremental cost-effectiveness ratios (ICERs) of US$1200–$3800 per quality-adjusted life year (QALY) gained by increasing adenoma detection rates and reducing downstream treatment costs.[139,140] Scalable nanomedicine platforms such as oral pH-responsive polymeric nanoparticles for 5-fluorouracil or irinotecan eliminate cold-chain requirements and reduce hospitalization needs by 40%–60%, achieving ICERs below US$2000/QALY in rural settings.[141,142] Despite high initial development costs, technology transfer initiatives, local GMP manufacturing partnerships, and tiered

Table 5
Future directions and challenges in AI–Nanotechnology integration for colorectal cancer.

Challenge	Description	Proposed Solution
Data Accessibility	Limited availability of large, diverse, and high-quality datasets integrating colonoscopy, histopathology, imaging, and multi-omics information.	Establish centralized, anonymized CRC repositories combining colonoscopy images, CT/MRI data, histopathology slides, genomic/methylation profiles, and therapeutic response data to train robust AI-nanotechnology models.
Model Interpretability	Lack of transparency in AI predictions limits clinician trust and regulatory acceptance.	Develop explainable AI (XAI) models for polyp classification, drug response prediction, and nanocarrier optimization; integrate visual feature maps to support clinical interpretability and decision-making.
Nanocarrier Scalability	Inconsistent large-scale production of CRC-targeted nanocarriers leads to variable physicochemical properties.	Use AI-driven automated formulation systems to optimize lipid ratios, surfactant levels, and drug loading; employ reinforcement learning and Bayesian optimization for scale-up of NLCs, SLNs, and polymeric nanoparticles for CRC therapy.
Tumor Heterogeneity	Significant molecular variability between and within CRC tumors reduces uniform treatment efficacy.	Design multifunctional, stimuli-responsive nanocarriers using AI-guided multi-omics clustering to target heterogeneous subpopulations; integrate DL models to match nanoparticle surface ligands with tumor receptor expression patterns.
Formulation Optimization	Traditional formulation relies on trial-and-error, leading to high cost and long timelines.	Apply ML/DL algorithms (SVM, ANN, RF) to predict critical quality attributes (size, PDI, zeta potential, EE%) and optimize formulation parameters through DoE-AI hybrid models for faster and more reproducible CRC nano formulation design.
Regulatory and Ethical Barriers	Regulatory frameworks lag behind rapid AI-nanotechnology innovations in CRC diagnostics and therapy.	Establish adaptive regulatory pathways, standardized AI reporting guidelines, and global collaborations to accelerate translation of AI-driven nano formulations while ensuring safety and equity in access.

pricing models supported by WHO and the Medicines Patent Pool are projected to lower per-patient costs by 55%–70% by 2035, making AI-nanomedicine combinations cost-saving in high-burden LMICs while averting an estimated 450,000–600,000 premature CRC deaths annually.[143,144]

15. Conclusion

The convergence of artificial intelligence and nanomedicine represents a transformative paradigm in colorectal cancer management, offering unprecedented opportunities to overcome the limitations of conventional diagnostics and therapies. AI enables data-driven optimization of nanocarrier design, pharmacokinetics, and drug release, while nanomedicine provides versatile platforms for theranostics, controlled delivery, and modulation of the immunosuppressive tumor microenvironment, collectively addressing chemoresistance and systemic toxicity. By integrating multi-omics and real-time clinical data, these technologies advance truly personalized oncology tailored to molecular subtypes, tumor heterogeneity, and individual patient profiles. Although many reports highlight successful AI-guided nanocarrier designs, several approaches have failed to translate beyond preclinical testing. Some AI-optimized formulations showed excellent in silico binding or *in vitro* cytotoxicity but failed *in vivo* due to rapid clearance, poor stability, immune recognition, or inadequate tumor accumulation. In some cases, high predicted ligand–receptor affinity did not translate into effective tumor targeting because of biological barriers such as protein corona formation or stromal exclusion. Negative or neutral outcomes are often underreported, creating publication bias and an overly optimistic view of AI-guided nanomedicine. Integrated modelling from global oncology consortia projects that widespread adoption of AI-enhanced screening and AI-guided nanomedicine could increase 5-year overall survival rates by 10%–15% across all stages of CRC, driven by absolute adenoma detection rate gains of 20%–50% in routine practice, corresponding reductions in interval cancers, earlier stage migration, and improved systemic control of metastatic disease through precision targeting of KRAS-driven and microsatellite-stable tumors. Realising this potential will require continued multidisciplinary collaboration, transparent and explainable AI frameworks, scalable GMP manufacturing, and equitable global access strategies, particularly in low- and middle-income regions facing the fastest-rising CRC burden. When fully implemented, AI-driven nanomedicine has the capacity to redefine CRC from a frequently lethal malignancy to a chronically manageable condition, dramatically improving both survival and quality of life worldwide.

CRediT authorship contribution statement

Yogananthan Dhanapal: Writing – review & editing, Conceptualization. **Duraisamy Sridhar:** Writing – review & editing, Conceptualization. **Sulekha Khute:** Writing – review & editing, Conceptualization. **Paranthaman Subash:** Writing – review & editing, Conceptualization. **Subramaniam AnandaThangadurai:** Writing – review & editing, Conceptualization.

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List of abbreviations

ADR	Adenoma Detection Rate
AI	Artificial Intelligence
CAF	Cancer-Associated Fibroblast
CNN	Convolutional Neural Network
CRC	Colorectal Cancer
dMMR	Deficient Mismatch Repair
DL	Deep Learning
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EPR	Enhanced Permeability and Retention
FDA	Food and Drug Administration
FIT	Fecal Immunochemical Test
FOLFOX	Folinate + Fluorouracil + Oxaliplatin
GAN	Generative Adversarial Network
GNN	Graph Neural Network
KRAS	Kirsten Rat Sarcoma Viral Oncogene
ML	Machine Learning
MSI-H	Microsatellite Instability-High
MSS	Microsatellite Stable
PD-1	Programmed Death-1
PK/PD	Pharmacokinetic/Pharmacodynamic
PLGA	Poly(lactic-co-glycolic acid)
QSAR	Quantitative Structure-Activity Relationship
SaMD	Software as a Medical Device
SPION	Superparamagnetic Iron Oxide Nanoparticle
TAM	Tumor-Associated Macrophage
TME	Tumor Microenvironment
VEGF	Vascular Endothelial Growth Factor

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