

REVIEW ARTICLE

Computational and nanotechnology strategies for colorectal cancer detection and therapy: A narrative review and conceptual framework for magnesium–manganese nanoparticles

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Abstract

Colorectal cancer (CRC) remains a leading cause of global cancer-related mortality, where patient prognosis is heavily dictated by the timing of detection. While CRC encompasses both colon and rectal malignancies, this narrative review focuses primarily on the early detection of colon tumors, which represent the majority of CRC cases and serve as a primary target for biomarker-driven strategies. Despite the utility of conventional screening methods such as colonoscopy, limitations regarding invasiveness and accessibility persist. This review synthesizes interdisciplinary progress from 2019 to 2025, highlighting how the convergence of computational biology and nanotechnology offers a promising path forward. Computational strategies, particularly machine learning and omics analysis, have accelerated the discovery of predictive biomarkers. In parallel, nanotechnology platforms—including gold nanoparticles and quantum dots—have emerged as high-sensitivity tools for biosensing. A central feature of this review is a conceptual framework on magnesium–manganese nanoparticles, which provides a theoretical framework for their dual roles as biosensors and imaging agents. This framework underscores the translational potential of combining *in silico* biomarker discovery with nanomaterial design. Finally, the review examines the hurdles to clinical translation and outlines a roadmap for using artificial intelligence-driven optimization to achieve precise, non-invasive early detection of colon-specific malignancies across the CRC spectrum.

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1. Introduction

Colorectal cancer (CRC) remains a pressing global health concern, ranking among the most frequently diagnosed malignancies and leading causes of cancer-related mortality.¹ Despite advances in prevention and treatment, the global burden is projected to rise substantially by 2040, necessitating a shift toward more proactive screening and intervention strategies.^{2,3}

Current diagnostic strategies rely predominantly on colonoscopy, imaging, and serum biomarkers, such as carcinoembryonic antigen (CEA) and various carbohydrate antigens.^{4–7} While colonoscopy is the diagnostic gold standard, its invasiveness often results in poor patient compliance.⁸ Furthermore, conventional biomarkers frequently suffer from low sensitivity in early-stage disease. These limitations hinder early intervention, frequently leading to advanced-stage diagnoses and significantly reduced survival.

While CRC encompasses both colon and rectal cancers, this review places a strategic emphasis on colon tumors. The colon's unique physiological landscape—characterized by specific pH gradients and a dense microbial environment—presents both challenges for delivery and opportunities for highly localized, biomarker-driven detection.

The transition toward precision oncology is currently bottlenecked by the complexity of multi-omic data and the physical barriers to early-stage imaging. Computational biology—the use of artificial intelligence (AI) to model biological systems—has reached a stage where it can

identify patterns in tumor behavior previously invisible to clinicians, even with the addition of nanotechnology; however, these *in silico* insights require a physical vehicle for clinical translation.^{9–11} Nanotechnology provides this vehicle, offering the sensitivity needed to turn computational predictions into tangible diagnostic tools. Yet, a gap remains: few frameworks effectively integrate the digital discovery of biomarkers with the material design of nanoproboscopes (Figure 1).

To illustrate this integration, while similar integrative concepts have been discussed,^{9–11} this review explores the potential of magnesium (Mg) and manganese (Mn) with a conceptual framework. Mn offers exceptional contrast properties for magnetic resonance imaging (MRI),¹² while Mg provides a biocompatible, biodegradable scaffold that can modulate the probe's release and activity.¹³ Together, they represent a dual-function system that exemplifies how material science can be tailored to meet the specific demands of the colon's microenvironment.

This narrative review synthesizes literature published between January 2019 and June 2025. Relevant studies

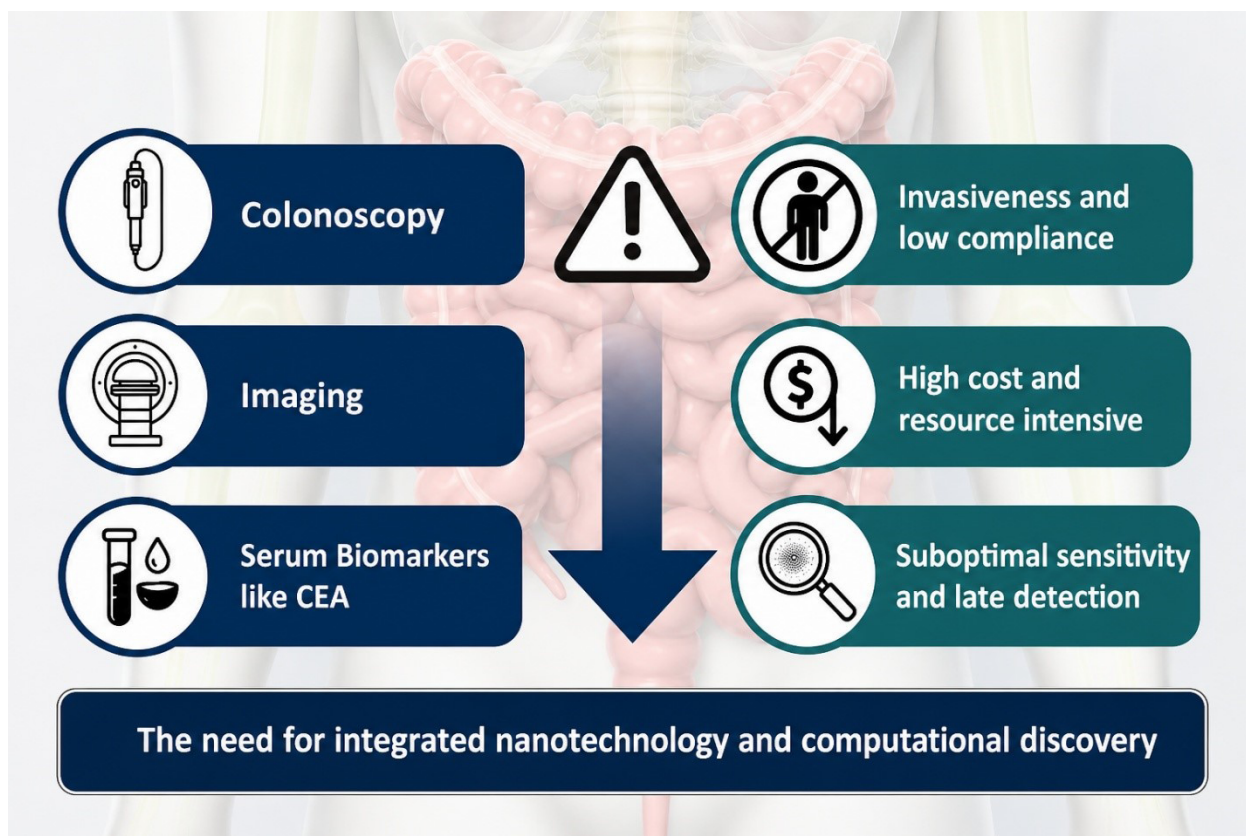


Figure 1. The current landscape of colorectal cancer screening. Image created by the authors.
Abbreviation: CEA: Carcinoembryonic antigen.

were retrieved from PubMed, Scopus, and Web of Science, focusing on the convergence of biomarker discovery, computational modeling, and nanotechnology-enabled detection. This narrative is limited by its non-systematic nature and focus on conceptual rather than validated systems. The objective of this review is to provide a comprehensive framework that bridges recent technological advances with clinical needs. By proposing an integrative model—highlighted by the conceptual framework for Mg–Mn nanoparticles—we outline a roadmap toward precise, non-invasive, and clinically translatable early detection of colorectal malignancies.

2. Methodology

This study employed a structured narrative review approach to synthesize recent advances in computational biomarker discovery and nanotechnology-based strategies for CRC detection and therapy. The review integrated developments in AI-driven biomarker identification with emerging nanotechnology platforms for diagnostic and therapeutic applications. The review was conducted in accordance with the Scale for the Assessment of Narrative Review Articles guidelines for narrative reviews, with elements of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework considered to enhance transparency in literature identification.^{14,15}

A literature search was conducted across major scientific databases, including PubMed, Scopus, and Web of Science, to identify relevant peer-reviewed publications. The search focused on studies published between 2019 and 2025 to capture recent developments in AI, multi-omics biomarker discovery, and nanotechnology applications in oncology. Representative search queries combined keywords such as “colorectal cancer,” “CRC biomarkers,” “machine learning (ML),” “artificial intelligence,” “multi-omics,” “nanotechnology,” “nanoparticles,” “nanotheranostics,” and “computational biology.”

Studies were considered eligible if they met the following inclusion criteria: (i) peer-reviewed research articles or reviews addressing CRC diagnostics, biomarker discovery, or therapeutic technologies; (ii) studies involving computational or machine learning (ML) approaches for biomarker identification; (iii) investigations describing nanotechnology-based diagnostic or therapeutic platforms relevant to CRC; and (iv) publications written in English. Exclusion criteria included conference abstracts without full methodological descriptions, articles not directly related to CRC, and publications lacking sufficient scientific detail to support meaningful synthesis.

Following database searches, retrieved records were screened for relevance based on titles and abstracts,

and duplicate records were removed prior to full-text assessment. Articles meeting the inclusion criteria were subsequently examined to identify key developments in computational biomarker analysis, nanotechnology platforms, and emerging integrative strategies linking digital biomarker discovery to nanomaterial-based diagnostics and therapeutics. Because the objective of this work is conceptual integration rather than quantitative comparison, the review emphasizes qualitative synthesis and critical interpretation of current research trends, highlighting opportunities and translational challenges in combining computational oncology with nanotechnology-based theranostic systems. Figure 2 illustrates the PRISMA flow diagram showing the narrative review methodology. A total of 250 records were initially identified through database searches and manual screening. After removal of duplicates and title/abstract screening, 130 full-text articles were assessed for eligibility. Following full-text review, 103 studies were included in the synthesis. This flow demonstrates transparent methodology and study selection. This flow demonstrates transparent methodology and study selection, guided by established narrative review reporting standards (Table 1).

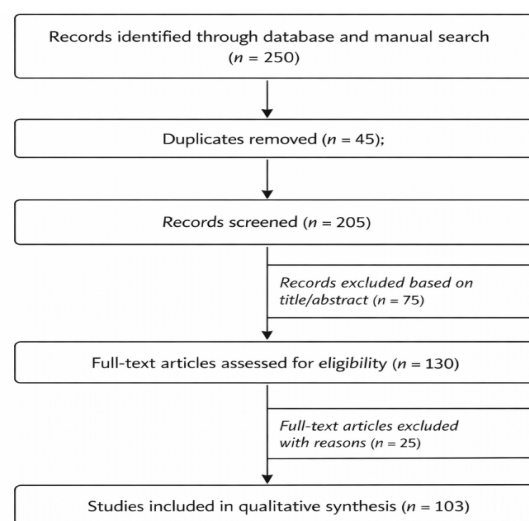


Figure 2. Preferred Reporting Items for Systematic Reviews and MetaAnalyses flow diagram showing the narrative review methodology. Image created by the authors.

3. Computational biomarker discovery

Computational approaches have moved beyond mere data processing to become analytical frameworks capable of identifying molecular signatures hidden within complex biological noise. For example, AI-driven proteomics enables robust biomarker discovery with high precision¹¹, while the comprehensive characterization of the cancer

Table 1. Scale for the Assessment of Narrative Review Articles (SANRA) checklist for assessment of narrative review quality

No.	SANRA item	Description
1	Justification of the article's importance for the readership	Explains why the review is relevant and necessary for the target audience
2	Statement of concrete aims or formulation of questions	Clearly defines the objective(s) or guiding questions of the review
3	Description of literature search	Explains how studies were identified, including databases and search strategy
4	Referencing	Ensures appropriate, relevant, and sufficient citation of sources
5	Scientific reasoning	Provides critical analysis, synthesis, and interpretation of the included literature
6	Appropriate presentation of data	Ensures clear, logical, and coherent organization of information

matrisome provides new opportunities to identify localized tumor-environment interactions.¹⁶ This transition from *in silico* prediction to clinical utility requires navigating high-dimensional big data challenges; here, automatic feature selection and the decoding of competing endogenous RNA networks play a vital role in identifying the most stable predictive markers.^{17,18} Figure 3 illustrates the progressive refinement of high-dimensional biological data into clinically relevant targets. Stage 1 begins with aggregating diverse multi-omics datasets from public repositories (The Cancer Genome Atlas [TCGA], Gene Expression Omnibus [GEO], ArrayExpress) to ensure statistical robustness and mitigate population bias. Stage 2 utilizes a layered analytical approach, moving from basic statistical differential expression to context-aware pathway and network analyses, finally employing ML algorithms for non-linear feature selection. Stage 3 represents the final output: a prioritized set of high-confidence “candidate biomarkers” ready for subsequent experimental validation and nanotechnology integration.

3.1. Data sources

High-quality public repositories form the foundation of these discovery pipelines. While TCGA provides high-depth multi-omic layers (genomic, transcriptomic, and clinical),^{19,20} the GEO and ArrayExpress offer the necessary breadth through diverse patient cohorts and functional genomics data.^{21,22}

Combining these databases is essential for improving robustness; a biomarker identified in TCGA but not reproducible in GEO cohorts is unlikely to survive clinical validation. Nevertheless, researchers must account for significant limitations, including batch effects (technical variations between labs) and population bias, which can lead to overfitted models that do not generalize across different ethnic or demographic groups.

3.2. Analytical methods

The current landscape of computational analysis in biomarker discovery is shaped by a strategic balance

between statistical interpretability and predictive performance. On one hand, traditional statistical methods provide clarity, reproducibility, and straightforward biological insights, making them easily interpretable by researchers and clinicians. On the other hand, advanced ML and network-based models offer superior predictive power, capturing complex, non-linear relationships across high-dimensional multi-omics datasets that conventional approaches may overlook. Navigating this trade-off is critical: choosing methods that are too simplistic may miss subtle but clinically relevant patterns, while relying solely on highly complex models can obscure mechanistic understanding, creating a gap between prediction and actionable biological insight. Major analytical methods are highlighted in the following sections.

3.2.1. Statistical methods

Implementation of edgeR, DESeq2, and limma provides robust statistical frameworks for identifying differentially expressed genes across experimental conditions.²³⁻²⁶ These tools use models such as negative binomial distributions and empirical Bayes variance estimation to quantify changes in gene expression while controlling false discovery rates. Their transparency, reproducibility, and well-defined assumptions make them widely used for initial feature reduction in high-dimensional omics analyses. However, these methods primarily detect linear relationships and independent gene effects, which may limit their ability to capture the complex, non-linear interactions that characterize tumor biology. Consequently, modern pipelines often combine differential expression analysis with systems biology and ML approaches to better identify predictive biomarkers within multi-omics datasets.^{27,28}

3.2.2. Systems biology and network analysis

Pathway enrichment and protein–protein interaction network analyses provide a systems-level approach for identifying key regulatory molecules involved in tumor development. Rather than focusing solely on individual genes, these methods evaluate coordinated biological

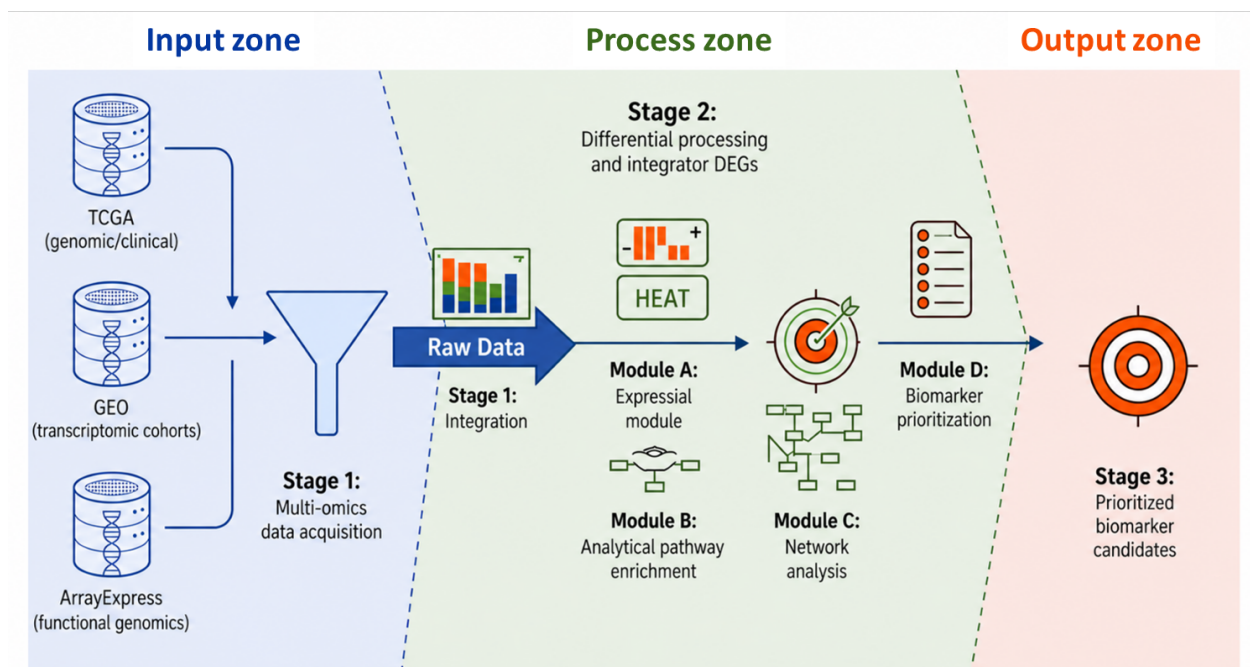


Figure 3. A structured computational pipeline for early colon tumor biomarker discovery. Image created by the authors. Abbreviations: DEGs: Differentially expressed genes; GEO: Gene Expression Omnibus; TCGA: The Cancer Genome Atlas.

pathways and molecular interaction networks to detect hub molecules—highly connected nodes that play central roles in cellular signaling and tumor progression. Because these hubs often regulate multiple downstream processes, they can serve as more reliable biomarkers than isolated gene alterations, reflecting broader biological mechanisms driving colorectal carcinogenesis.^{16,18,27,28–36} However, a key challenge in this area is the methodological gap between interpretability and predictive performance. Traditional statistical and systems biology tools provide clearer biological explanations and are easier for clinicians to interpret, but they may lack strong predictive capability. In contrast, network-based ML models often achieve higher accuracy by capturing complex, non-linear interactions within biological systems, yet they frequently function as “black boxes,” making it difficult to fully interpret the underlying biological rationale for their predictions.

3.2.3. Machine learning and algorithm comparisons

Different computational frameworks have been applied to prioritize candidate biomarkers from high-dimensional multi-omics datasets. Classical statistical methods such as edgeR, DESeq2, and limma provide transparent differential expression analysis,^{24–26} but may miss non-linear relationships between genes. In contrast, network-

based ML models can capture complex interactions and higher-order dependencies in biological networks,^{28,29} often yielding superior predictive performance. Comparisons across these approaches indicate a trade-off between interpretability and predictive power: while statistical methods are easier for clinicians to understand, ML-based models typically outperform in accuracy, particularly when integrating multi-modal omics data.^{34,35} Performance metrics such as area under the curve (AUC), sensitivity, and specificity are commonly used to evaluate these models, allowing standardized comparisons across algorithmic strategies.³⁵

3.2.4. Model validation and limitations

Models undergo rigorous cross-validation, bootstrapping, and, where possible, external validation in independent cohorts to ensure robust performance.³⁵ Despite these measures, several key limitations persist. High-dimensional multi-omics datasets are prone to overfitting if feature selection is not carefully constrained, potentially inflating predictive accuracy in the training set.^{17,18,34} Variations across datasets or sequencing platforms, commonly referred to as batch effects, can further bias model predictions,^{22,23} while improper separation of training, validation, and test datasets may introduce data leakage, leading to overestimation of model performance.^{34,35}

Finally, complex ML models often face an interpretability gap, producing predictive biomarkers whose mechanistic rationale is unclear, necessitating subsequent experimental validation to confirm biological relevance.^{11,16,27}

3.3. Emerging trends and limitations

Recent trends emphasize the use of ML to integrate disparate multi-omics datasets and enhance prioritization. ML frameworks are uniquely capable of uncovering non-linear patterns and predicting patient-specific behavior.^{11,19} Despite significant advances, several limitations hinder the clinical translation of ML-derived biomarkers in CRC. A key concern is overfitting, in which models capture noise rather than the true biological signal, yielding excellent performance during cross-validation but poor generalization to independent cohorts. Batch effects arising from differences in sequencing platforms, sample handling, or laboratory protocols can introduce systematic biases, further compromising reproducibility.¹⁹ Data leakage—where information from the test set inadvertently informs the training process—can inflate apparent model performance and mask true predictive utility.

Another critical challenge is the lack of external validation. Although reported models often achieve high performance metrics, such as AUC values exceeding 0.85 in cross-validation, their predictive accuracy frequently drops when applied to independent populations due to population stratification, technical variability, or heterogeneity across clinical cohorts.¹⁹

Finally, rare clinical transitions illustrate the difficulty of moving from discovery to routine implementation. For instance, although numerous *in silico* CRC biomarkers have been proposed, few have entered clinical practice for early detection or prognostication. Established tests like Oncotype DX colon cancer recurrence score represent one of the few widely used informed genomic assays, whereas early detection biomarkers for CRC remain largely

absent from standard screening panels.^{1-3,26-32} These gaps highlight the persistent translational bottleneck between computational discovery and clinical utility, emphasizing the need for robust validation pipelines, standardized datasets, and prospective clinical trials.

As summarized in Table 2, the current computational landscape is dominated by multi-omics integration and systems biology approaches.²⁹⁻³⁶ A critical synthesis of these studies reveals two major trends: first, a shift toward deep learning approaches, moving away from single-gene markers toward panel-based signatures (e.g., serum protein panels or methylation markers); and second, an increasing reliance on computational frameworks to handle complex clinical-genomic datasets.

Despite these advances, a significant gap remains: the majority of these studies are preclinical. Future efforts must move beyond retrospective data (re-analyzing existing databases) and toward prospective, AI-optimized validation to ensure these digital signatures perform reliably in real-world clinical settings. Figure 4 illustrates the integration of multi-omics datasets (TCGA, GEO, ArrayExpress) to discover CRC biomarkers. Stage 1 involves data aggregation to ensure statistical robustness. Stage 2 represents computational analysis, including differential expression (edgeR, DESeq2, limma), pathway/network analysis, and ML algorithms with algorithm comparisons. Stage 3 shows model validation using cross-validation, bootstrapping, and external cohort testing, with performance metrics including AUC, sensitivity, and specificity. Key limitations—including overfitting, batch effects, data leakage, and interpretability gaps—are highlighted to ensure transparency and guide experimental follow-up.

4. Nanoparticle-based detection

Nanomaterials, particularly nanoparticles, have emerged as promising candidates for cancer detection, bridging critical

Table 2. Computational studies identifying early colon tumor biomarkers

Study	Dataset/approach	Biomarkers identified	Notes/method highlights
Suleman <i>et al.</i> ³⁰	Experimental + computational	Multiple candidate genes	Integrated <i>in silico</i> modeling with validation.
Ivancic <i>et al.</i> ³¹	Serum proteomics	CEA, CA19-9, novel proteins	Focused on non-invasive serum panels.
Wu <i>et al.</i> ³²	Literature + multi-omics	Expression and methylation	Comprehensive review of screening markers.
Dhillon <i>et al.</i> ³³	Multi-omics datasets	Prognostic/diagnostic markers	High-level machine learning strategies for discovery.
Al-Tashi <i>et al.</i> ³⁴	Machine learning	Predictive biomarkers	Focus on prognostic accuracy.
Skrede <i>et al.</i> ³⁵	Deep learning (genomic + clinical)	Outcome prediction markers	Discovery using histopathology and genomics.
Oh and Joo ³⁶	Literature + bioinformatics	Novel CRC biomarkers	Targeted diagnostic and prognostic markers.
Rahman <i>et al.</i> ³⁷	Systems biology	Prognostic signatures	Integrated biology and candidate drug discovery.

Abbreviations: CA19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; CRC: Colorectal cancer.

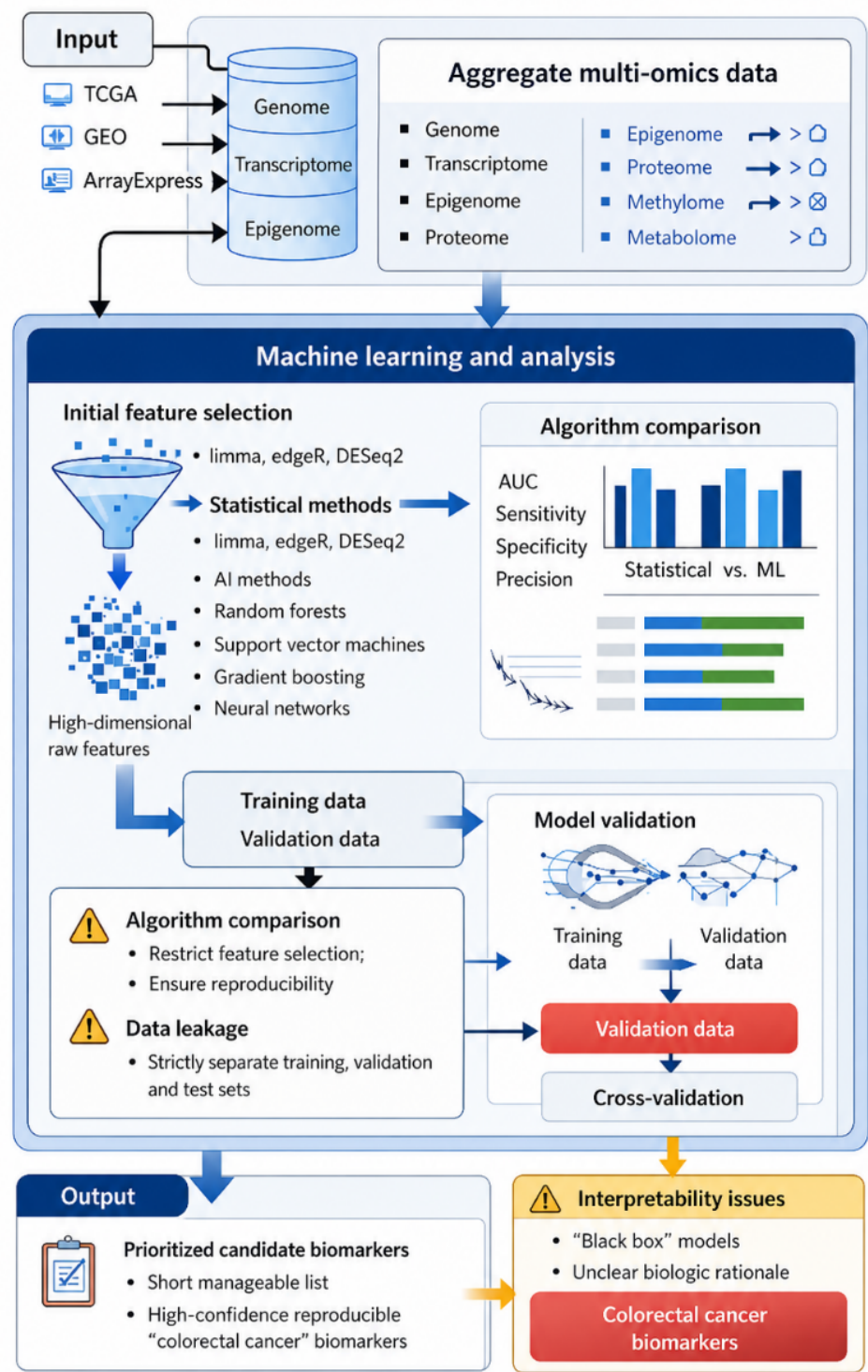


Figure 4. ML-assisted biomarker prioritization and validation workflow. Image created by the authors.
Abbreviations: AI: Artificial intelligence; AUC: Area under the curve; GEO: Gene Expression Omnibus; ML: Machine learning; TCGA: The Cancer Genome Atlas.

limitations of conventional diagnostic techniques.^{37–39} Their nanoscale dimensions enable intimate interactions with biological systems, while their adaptable surface chemistry allows selective targeting of tumor-specific biomarkers.^{38–43} As a result, nanoparticle-based diagnostic platforms offer improved signal amplification, early-stage detection, and multi-modal imaging capabilities, positioning nanotechnology as a transformative force in precision oncology. Figure 5 categorizes the diverse range of nanoplatforms currently utilized in CRC diagnostics and therapy. Each class is mapped to its primary functional role, ranging from the high-sensitivity optical properties of gold nanoparticles (AuNPs) and quantum dots (QDs) to the specialized delivery capabilities of liposomes and polymeric nanoparticles. The Mg–Mn nanoparticles and hybrid systems highlight the move toward multifunctional, dual-mode agents capable of simultaneous imaging and sensing.

4.1. Functional classification of nanoplatforms

Rather than viewing nanoparticles solely by their

material composition, they are better categorized by their functional role within the diagnostic–therapeutic pipeline. This perspective focuses on what the nanoplatform is designed to achieve—such as enhancing imaging sensitivity, enabling targeted drug delivery, or improving biosensing capabilities. Such a framework aligns with the growing field of theranostics, in which nanomaterials integrate diagnostic and therapeutic functions within a single system, enabling researchers to better evaluate their translational potential and clinical relevance.

4.1.1. Contrast and imaging agents

Gold nanoparticles, QDs, and ferrite-based nanomaterials exhibit superior optical and magnetic properties, making them highly suitable for non-invasive cancer visualization and diagnostic imaging.^{44–47} AuNPs and QDs exhibit unique surface plasmon resonance and fluorescence characteristics, enabling highly sensitive optical detection and enhanced molecular-level imaging contrast.^{44–50} Ferrite systems, on the other hand, possess strong magnetic properties, enabling their use in MRI and magnetic

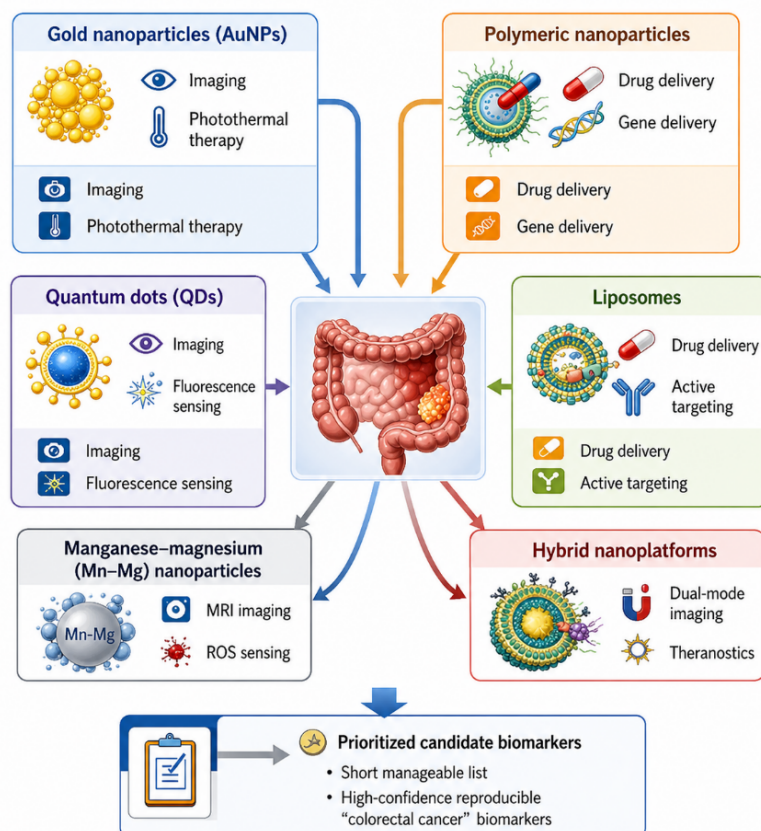


Figure 5. Nanoparticle classes used in early colon tumor detection. Image created by the authors.

targeting applications.⁵⁰ Together, these nanoplateforms enhance signal sensitivity, improve imaging resolution, and enable early detection of tumor-associated biomarkers in CRC.

4.1.2. Molecular biosensors

The Mg–Mn hybrid nanoplateforms represent an emerging class of multifunctional nanoplateforms capable of acting as ultra-sensitive detectors for circulating biomarkers. The Mn component contributes to magnetic responsiveness and paramagnetic properties that enhance contrast in T1-weighted MRI, allowing for the detection of minute tumor lesions,^{12,51} while Mg provides structural stability, biocompatibility, and favorable surface chemistry for functionalization with targeting ligands.^{13,51} These complementary physicochemical features enable Mg–Mn nanoplateforms to interact selectively with tumor-derived molecules, such as circulating tumor DNA (ctDNA), miRNAs, and protein biomarkers, amplifying detection signals far beyond the limits of conventional assays.^{9,51} By leveraging both magnetic and chemical properties, these particles enable highly sensitive signal transduction across multiple modalities—including MRI, fluorescence, and electrochemical readouts—thereby supporting real-time or near real-time molecular monitoring.^{9,51,52} Unlike traditional serum-based tests, which often rely on bulk biomarker concentrations and may miss early-stage disease, Mg–Mn and hybrid nanoplateforms offer dynamic, multi-modal biosensing that improves diagnostic precision and enables continuous monitoring of CRC progression and therapeutic response.⁵¹

4.1.3. Targeted delivery vehicles

Lipid- and polymer-based nanoparticles—including liposomes, dendrimers, and chitosan-based systems—are designed for precise, localized drug delivery in CRC. Lipid- and polymer-based nanoparticles—including liposomes, dendrimers, and chitosan-based systems—are designed for precise, localized drug delivery in colorectal cancer. These nanoplateforms enable encapsulation of chemotherapeutic agents and bioactive molecules with improved tumor targeting, reduced systemic toxicity, and enhanced bioavailability. Liposomal and ligand-functionalized nanoparticle systems have been widely explored for targeted delivery of therapeutic cargos in colorectal cancer.^{53–56} Advances in hybrid nanostructures and optomagnetic nanosystems further support improved diagnostic sensitivity and theranostic performance.^{57–59} In addition, quantum dot-based and photothermally active nanomaterials contribute to enhanced imaging and therapeutic precision within integrated nanotheranostic platforms.^{60,61} Polyphenol-based and polymeric

nanoparticle systems, including chitosan-based oral delivery platforms, have also demonstrated strong potential in improving colorectal cancer treatment efficacy.^{62,63} Active targeting through surface functionalization with ligands, antibodies, or polymers—such as epithelial cell adhesion molecule (EpCAM) aptamers or hyaluronic acid—further improves tumor-specific recognition and cellular uptake.^{53,55} Hybrid systems integrating QDs, silica, or AuNPs enable simultaneous drug delivery and diagnostic monitoring, facilitating real-time assessment of therapeutic response.^{57,59,60} Chitosan-based platforms provide additional advantages for oral delivery, combining biocompatibility with controlled release to enhance local efficacy.⁶³ These nanoparticles also help circumvent chemoresistance by promoting intracellular delivery of drugs and RNA therapeutics, establishing them as versatile tools for improving both safety and efficacy in CRC treatment.⁶¹

4.2. Mechanisms of diagnostic action

The utility of these nanomaterials in CRC applications arises from three principal mechanisms that collectively enhance specificity, sensitivity, and real-time monitoring: active targeting, signal amplification, and biosensing.

4.2.1. Active targeting

Surface functionalization of nanoparticles with targeting ligands—such as aptamers, antibodies, or peptides—enables active recognition of tumor-specific antigens, ensuring precise delivery to CRC cells and high signal-to-noise ratios in detection. Initial work on nanosized barium titanate-coated spinel ferrites demonstrated selective cytotoxicity and biocompatibility in CRC models.⁵² EpCAM aptamer-functionalized cationic liposomes have been employed for targeted miRNA delivery, improving uptake and therapeutic efficacy,⁵³ while broader reviews have highlighted lipid- and polymer-based nanocarriers as versatile platforms for receptor-mediated targeting.^{54–56} Hyaluronic acid-decorated liposomes provide tumor-selective delivery of 5-fluorouracil into HT-29 cells, enhancing intracellular accumulation.⁵⁵ Hybridized systems combining QDs, silica, and AuNPs exploit ligand-directed targeting for precise chemo-radiotherapy.⁵⁷ Recent advances in targeted nanomaterials for CRC diagnostics and therapy demonstrate improved specificity through surface modifications.^{58–61} Polyphenol-based nanoparticles and chitosan-based oral nanocarriers further utilize active targeting mechanisms to enhance tumor selectivity and therapeutic efficacy.^{62,63} Reviews on molecular pathogenesis and nanotechnology approaches confirm the growing importance of functionalized surfaces for tumor-specific delivery and detection.⁶⁴ Advanced DNA methylation-

targeted nanoparticles enable ultrasensitive biomarker detection,⁶⁵ while near-infrared polymeric nanoparticles have been developed for active optical imaging of tumors.⁶⁶ Nanosensors for miRNA detection exemplify ligand-based recognition strategies in molecular diagnostics,⁶⁷ and ferrocene-labeled peptide nucleic acid electrochemical sensors provide tumor-specific, high-sensitivity detection through active targeting.⁶⁸ Collectively, these studies establish surface functionalization as the cornerstone of active targeting, forming the mechanistic basis for precise biomarker detection and selective therapeutic delivery in CRC.

4.2.2. Signal amplification

Nanoparticles significantly enhance signal amplification in imaging modalities such as MRI, fluorescence, and optomagnetic sensing, enabling the detection of subtle molecular changes that conventional methods may miss. Mn-based nanoparticles provide strong T1-weighted MRI contrast, critical for identifying small or early-stage colorectal lesions.^{59,66} QDs and hybrid nanoparticle systems further amplify fluorescence signals, allowing multiplexed imaging of multiple biomarkers with high specificity and sensitivity.^{57,60} Optomagnetic nanoplatforms, including cadmium selenide/cadmium sulfide/zinc sulfide nanocrystals decorated with Fe₃O₄, transduce biomolecular interactions into amplified optical and magnetic signals, facilitating rapid, point-of-care detection of circulating tumor biomarkers.⁵⁹ Through these mechanisms, nanoparticles act as signal enhancers, improving both the resolution and reliability of CRC imaging and laying the foundation for precise early diagnostics.^{57-60,66}

4.2.3. Biosensing sensitivity

By interacting with ctDNA or miRNAs, these nanoplatforms achieve ultrahigh sensitivity, detecting malignancies at concentrations far below the threshold of conventional laboratory assays.^{65,67} The exceptional performance is largely attributable to the nanoscale interface, which maximizes surface area and enhances ligand-target interactions. Figure 6 illustrates the functional workflow of nanodiagnostics, beginning with the surface functionalization of nanoparticles with specific ligands, such as antibodies, aptamers, or peptides, which selectively recognize key biomarker classes, including CEA, ctDNA, and miRNA. Upon binding, the nanoparticles transduce these molecular interactions into measurable diagnostic signals across multiple modalities, including fluorescence emission, MRI contrast modulation, or electrochemical changes, amplifying otherwise weak biological signals into detectable outputs.⁶⁹ This biosensing capability enables real-time, minimally invasive monitoring of early-stage tumors, providing sensitivity and specificity that surpass traditional serological or imaging assays and supporting rapid clinical decision-making.

4.3. The role of computational integration

Computational modeling has become the architectural phase of nanoparticle design. Molecular docking and molecular dynamics (MD) simulations allow researchers to predict how a nanoparticle will interact with the colon's mucus layer or tumor cell receptors before a single experiment is performed.⁷⁰⁻⁷⁴ By simulating these interactions *in silico*, researchers can optimize binding affinity and predict the stability of the nano-bio interface,

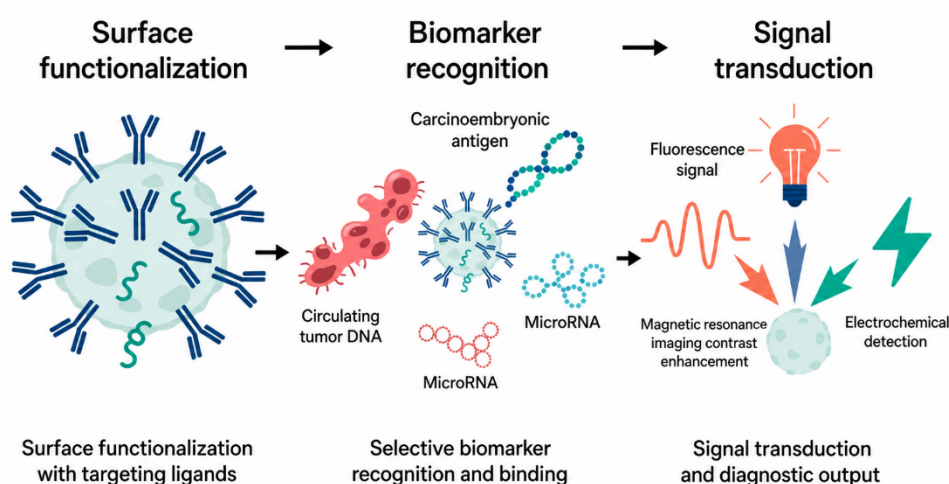


Figure 6. Mechanisms of nanoparticle-biomarker interaction in colon cancer. Image created by the authors.
Abbreviations: MRI: Magnetic resonance imaging.

significantly reducing the experimental trial-and-error cost and accelerating the development of new probes. Figure 7 presents a split-panel schematic that illustrates the transition from *in silico* modeling to physical implementation. The left panel depicts the use of molecular docking and MD simulations to predict the binding affinity and orientation between nanoparticle surface ligands and target tumor biomarkers. This digital refinement allows for the rational design of probes with maximum sensitivity. The right panel shows the optimized nanoparticle, synthesized according to computational parameters to ensure high stability and capture efficiency during experimental validation.

4.4. Translational evidence and the preclinical bottleneck

Despite the high efficacy shown in preclinical models—including organoids and animal subjects—there is a notable translational gap. As summarized in Table 3, the majority of advanced nanoplatforms currently sit at a low technology readiness level. While AuNPs have reached early clinical phases,^{44,45} most systems, including Mg–Mn and hybrid composites, remain in the preclinical stage. Challenges such as nanoparticle toxicity, long-term clearance from the liver/spleen, and the complexity of large-scale manufacturing continue to hinder clinical translation. Figure 8 illustrates the rigorous journey of a nanodiagnostic agent from initial laboratory discovery to clinical implementation. The horizontal pipeline is divided into distinct stages, each separated by critical “translational bottlenecks.” These include the primary challenges of

systemic toxicity during the transition to *in vivo* models, the complex regulatory requirements for human clinical trials, and the logistical barriers of large-scale, cost-effective manufacturing. Addressing these bottlenecks early in the development phase is essential for bridging the gap between innovative laboratory research and bedside patient care.

5. Illustrative conceptual discussion: Potential of magnesium–manganese nanoparticles in colorectal cancer

This section presents a conceptual framework for a dual-mode Mg–Mn nanoplatform. While individual components of this system have been validated in isolation, their integration into a single smart probe for colon tumor detection remains a theoretical model aimed at bridging the gap between *in silico* design and clinical application.

5.1. Scientific rationale for the magnesium–manganese synergy

The selection of Mn and Mg is motivated by their complementary biological and physicochemical properties. Mn serves as a potent T1-weighted MRI contrast agent, enabling sensitive visualization of early-stage lesions.⁷⁸ When incorporated into multifunctional nanocuboids or graphene chelates, Mn-based systems can carry therapeutic loads such as 5-fluorouracil while simultaneously providing real-time imaging.^{79–81} Evidence supports additional functionalities, including

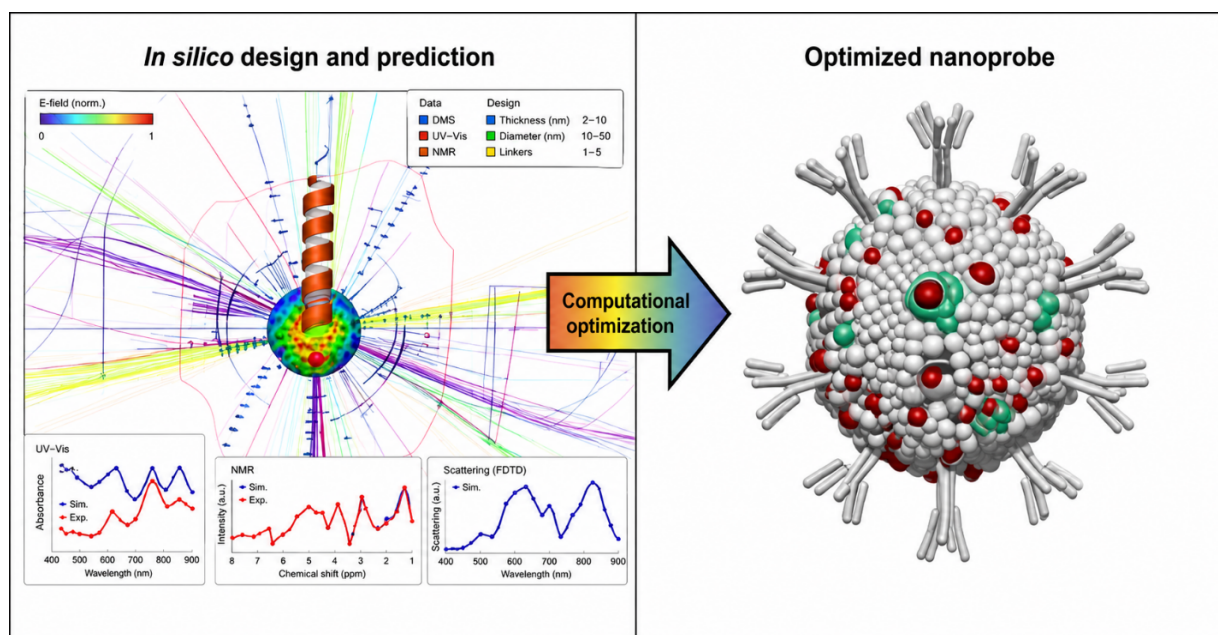


Figure 7. Computational optimization of nanoparticle–biomarker interactions. Image created by the authors.

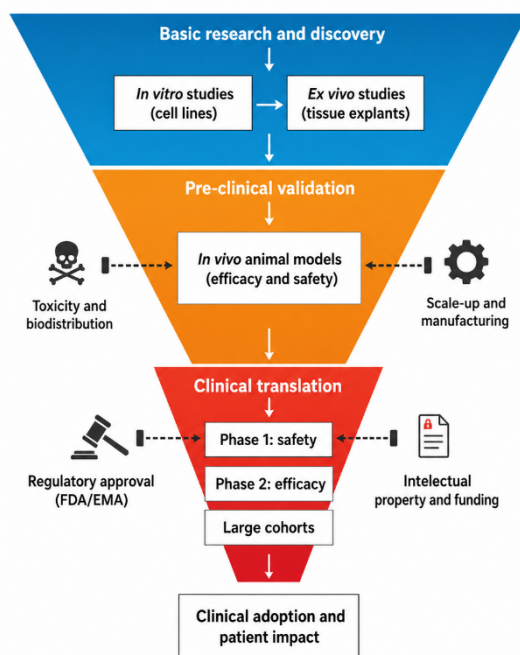


Figure 8. Translational pathway and bottlenecks in nanoparticle-based colon cancer detection. Image created by the authors.

tumor microenvironment (TME)-responsive release and enhanced imaging sensitivity. However, Mn accumulation poses well-documented neurotoxicity risks—manganism—including basal ganglia deposition and Parkinsonism-like symptoms, particularly with systemic exposure. Colon-localized delivery may mitigate but does not fully eliminate these risks; rigorous biodistribution and clearance studies are essential.⁷⁸ Controlled ion release under acidic TME conditions is currently extrapolated from Mn dioxide-based systems; the stability, degradation kinetics, and systemic safety of combined Mg carbonate/Mn dioxide composites have not been tested.

Magnesium acts primarily as a biocompatible stabilizer and structural scaffold. Evidence indicates that Mg ions can modulate colorectal tumor cell proliferation, potentially by regulating cell cycle pathways and calcium-dependent intracellular signaling.^{82–84} Its structural role supports nanoparticle integrity and may influence degradation kinetics in physiological conditions.

Combined Mg–Mn systems remain largely speculative. Hypothetical synergy could include enhanced nanoparticle stability, tunable degradation, and the simultaneous ability to deliver therapeutic payloads while providing high-sensitivity imaging. However, these potential benefits require experimental validation. Risks remain, particularly regarding Mn neurotoxicity even at low doses if systemic leakage occurs.⁷⁸ Other properties, such as controlled ion

release in acidic TME or selective tumor targeting, are extrapolated from studies on individual Mn- or Mg-oxide systems and have not been experimentally verified in combined formulations.

Importantly, no molecular docking outputs, release kinetics, or *in vivo* data for combined Mg–Mn systems are currently reported in the literature. Future studies should focus on developing synthesis protocols, comprehensive physicochemical characterization (e.g., particle size, zeta potential, stability), *in vitro* cytotoxicity testing (e.g., HT-29 cells), and preclinical pharmacokinetics to establish safety, efficacy, and translational potential.⁸⁵

5.2. Computational modeling of the nano-bio interface

Building on this physicochemical rationale, computational modeling provides a predictive framework for optimizing nanoparticle–biomarker interactions. Computational modeling is the predictive engine of this framework, enabling digital prototyping of the Mg–Mn probe. *In silico* simulations—specifically MD—are utilized to predict binding affinity by modeling the interaction between functionalized Mg–Mn surfaces and colon-specific biomarkers (e.g., CEA or mutated *KRAS*) to ensure high targeting specificity^{79,84} and simulate ion release by predicting how the acidic microenvironment of a colon tumor (pH 5.5–6.5) triggers the release of Mn ions for imaging and Mg for therapy.^{79,83}

Table 3. Nanoparticles used in early colon tumor detection

Nanoparticle type	Targeting/mechanism	Imaging/detection modality	Study type	Toxicity concerns	Clinical status
AuNPs	Antibody/aptamer surface functionalization	MRI, fluorescence	Preclinical/early clinical ⁴⁴⁻⁴⁸	Generally low; potential accumulation in liver/spleen	Early clinical evaluation
Mg–Mn nanoparticles	Dual biosensor; binds tumor antigens	MRI, biosensing, fluorescence	Preclinical ⁵¹	Neurotoxicity risk (Mn), biodegradation byproducts	Preclinical
Liposomes	Encapsulation of RNA/drugs; ligand-targeted	Fluorescence, drug monitoring	Preclinical ^{53,55,56}	Immunogenicity, infusion reactions	Some formulations clinically approved for other cancers; CRC mostly preclinical
Polymeric/dendrimers	Controlled release; tumor-specific uptake	Optical imaging, tracking	Preclinical ^{40,56,66}	Cytotoxicity depends on polymer type; cationic surface can be toxic	Preclinical
QDs	Fluorescent probes for biomarkers	Fluorescence	Preclinical ^{57,59}	Heavy metal toxicity (Cd, Se)	Preclinical
Ferrite nanoparticles	Magnetic hyperthermia and imaging	MRI	Preclinical ^{50,52}	Iron overload, oxidative stress	Preclinical
Hybrid (QD–gold–silica)	Multifunctional imaging/delivery	Fluorescence, optomagnetic	Preclinical ^{57,59}	Combination of QD and AuNP toxicity; biodistribution unknown	Preclinical
Chitosan-based	Oral delivery; targeted colon uptake	Fluorescence, release monitoring	Preclinical ^{63,75–77}	Generally low; possible gastrointestinal irritation	Preclinical; colon delivery faces a mucus barrier, variable pH, and limited oral/rectal success stories

Abbreviations: AuNPs: Gold nanoparticles; Cd: Cadmium; CRC: Colorectal cancer; Mg: Magnesium; Mn: Manganese; MRI: Magnetic resonance imaging; QD: Quantum dots; Se: Selenium.

Although these interactions are grounded in established thermodynamic principles, the precise kinetics of a combined Mg–Mn system in a complex human gut environment remain hypothetical and require further validation through multi-scale modeling.

5.3. Experimental feasibility and safety considerations

Following computational optimization, experimental feasibility and safety considerations become critical for translation. Experimental evidence from related bimetallic and green nanoplatforms supports the feasibility of this model. For instance, inulin-coated Mn oxide nanocuboids have successfully reversed tumorigenesis in murine models, proving that Mn-based platforms can survive the gastrointestinal environment.⁸³ Furthermore, plant-

mediated green synthesis (e.g., *Moringa oleifera* or chromium-based methods) offers a non-toxic pathway for producing these particles at a lower cost.^{84–89} Within this framework, magnesium-related bioactivity has been explored for its potential role in inhibiting colorectal tumor cell progression.⁸⁴ Sustainable bimetallic nanoparticle systems capped with plant extracts demonstrate strong antioxidant and anti-biofilm properties, highlighting their therapeutic relevance.⁸⁵ Magnetic and multifunctional nanomaterials further expand applications in cancer theranostics through improved targeting and diagnostic performance.⁸⁶ Biocompatibility assessments of nanomaterials support their safe integration into medical applications.⁸⁷ Green biosynthesis of chromium-based nanoparticles using plant extracts has shown promising anticancer activity against colorectal cancer models.⁸⁸

Similarly, *Moringa oleifera*-derived silver nanoparticles have demonstrated significant anti-colon cancer effects in human cell lines, reinforcing the value of plant-mediated synthesis routes.⁸⁹

The transition to clinical use is hindered by long-term safety concerns. While Mg is highly biocompatible, the potential for Mn-induced neurotoxicity (manganism) if the particles accumulate systemically is a critical risk factor.⁸⁷ Future experimental designs must prioritize clearing-by-design strategies to ensure that the particles degrade and are excreted once the diagnostic task is complete.

5.4. Translational roadmap and challenges

The translational promise of Mg–Mn nanoparticles lies in their all-in-one diagnostic and therapeutic potential. However, the path to clinical integration must navigate the gap between successful animal studies and human trials. Some of these hurdles are regulatory violations, scale-up consistency, and clinical reproducibility, among others. Figure 9 shows a structured workflow—integrating computational optimization, robust preclinical safety testing, and focused clinical validation—required to move this conceptual framework into the realm of practical oncology.

6. Integrative framework and future perspectives

6.1. The integrated computational-nanotechnology pipeline

The success of early colon tumor detection depends on a structured pipeline that seamlessly integrates digital

discovery with physical application. Recent bioinformatics-driven frameworks have enabled systematic mining of large-scale repositories, such as the Sequence Read Archive, providing the reproducible data foundations necessary for identifying high-confidence biomarkers.^{90–94}

Integrating these reproducible datasets with the computational design of Mg–Mn nanoparticles ensures that selected biomarkers are not only statistically significant but also physically accessible for nanoparticle binding. This approach reduces translational noise, which often causes diagnostic projects to fail in early development by aligning material design with the complexities of real-world genomic and proteomic data.⁹⁵

The overarching workflow begins with the acquisition of multi-omics data, which is processed via AI-driven computational analysis to identify robust targets. These insights guide the rational design and synthesis of optimized nanoparticles, culminating in highly specific platforms for early tumor detection. Importantly, each stage—from computational prediction to nanoparticle fabrication—requires rigorous experimental validation, including physicochemical characterization, *in vitro* cytotoxicity (e.g., HT-29 cells), and preclinical pharmacokinetics, to ensure translational feasibility.^{80–85} Figure 10 illustrates this pipeline, highlighting the synergistic progression from big data to bedside application while emphasizing critical validation checkpoints to mitigate clinical translation risks.

6.2. Natural compounds as adjunct biomarker modulators

An emerging strategy in the proposed framework is the

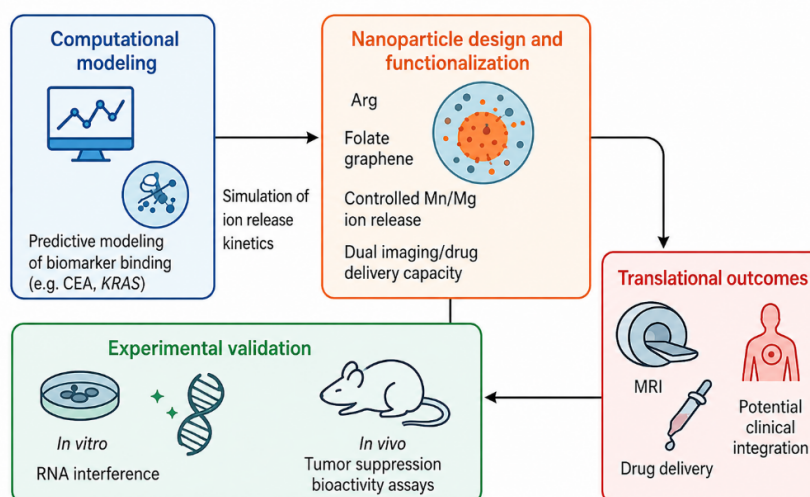


Figure 9. Proposed pathway of Mg–Mn nanoparticle application in colorectal cancer. Image created by the authors.

Abbreviations: Arg: Arginine; CEA: Carcinoembryonic antigen; Mg: Magnesium; Mn: Manganese; MRI: Magnetic resonance imaging.

use of natural compounds, or phytochemicals, as adjunct modulators of tumor biomarkers. Experimental evidence suggests that compounds such as *Arachis hypogaea* extracts can influence carcinogenesis pathways, potentially altering the tumor environment in ways that improve biomarker detectability.^{96,97}

In the context of nanotechnology, these natural products may serve two primary roles. First, they can modulate the expression of specific surface antigens, potentially enhancing recognition and binding by Mg–Mn nanoparticle probes. Second, phytochemicals may be incorporated into nanoparticle platforms to provide a low-toxicity bioactive layer, although robust mechanistic and efficacy data specific to CRC remain limited.^{98,99}

In summary, the use of plant-derived bioactives in this context remains preliminary. Future work requires rigorous characterization, including verification of biomarker modulation, assessment of nanoparticle encapsulation efficiency, and evaluation in relevant preclinical models, before translational claims can be made.

6.3. Critical limitations to translation

Despite the promise of this integrative framework, several formidable challenges hinder near-term clinical translation. Data heterogeneity remains a primary concern, as AI-based detection models often show reduced reproducibility when moving from controlled datasets to the biological variability present across diverse patient populations.^{99–101} Nanoparticle safety is another critical issue: while Mg is generally biocompatible, the long-term metabolic fate of Mn and its neurotoxicity risks—including basal ganglia deposition and Parkinsonism-like

effects—require rigorous biodistribution and clearance studies.^{102–104} These technical challenges are compounded by the high cost and complexity of manufacturing multifunctional probes at scale, as well as substantial regulatory hurdles for combination products that function simultaneously as diagnostic devices and therapeutic agents.^{100,105} Collectively, these barriers underscore the need for systematic validation, scalable synthesis protocols, and careful alignment with regulatory frameworks before clinical adoption is feasible.

6.4. Future perspectives: Toward precision oncology

The next generation of CRC care will be defined by the convergence of AI, nanomedicine, and interdisciplinary collaboration across chemistry, physics, and oncology. In the near term, AI-driven epitope prediction represents a particularly promising approach, enabling identification of ultra-specific therapeutic targets—such as *SMAD4*-specific epitopes—that can be programmed onto Mg–Mn nanoparticle surfaces to achieve high diagnostic precision.^{87,103}

Integrating real-time biosensing data from circulating nanoprobe with AI-driven drug resistance profiling could allow clinicians to dynamically adjust treatments in response to the tumor's evolving molecular signature.¹⁰² However, the translation of these approaches into clinical practice requires a robust bench-to-bedside loop. Interdisciplinary teams must refine computational pipelines, optimize biocompatible and cost-effective nanoparticle platforms, and generate rigorous preclinical and clinical validation data, as illustrated in Figure 10.

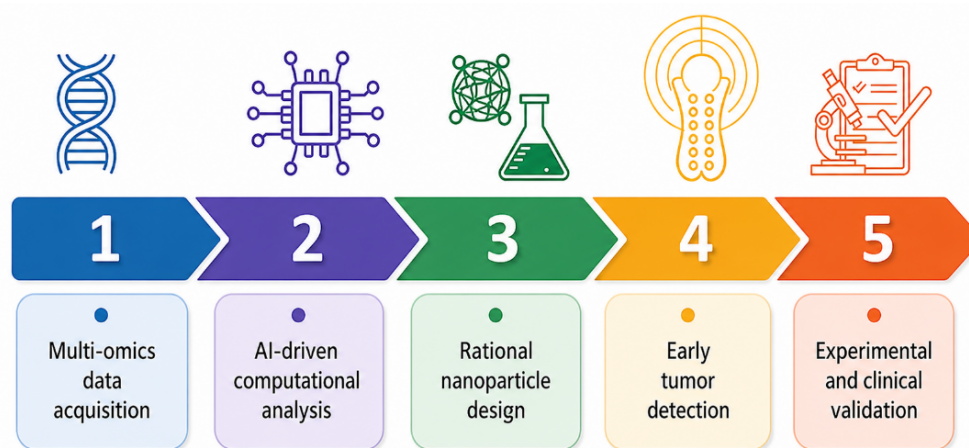


Figure 10. Integrated computational–nanotechnology pipeline for colon cancer research and early detection. Image created by the authors. Abbreviation: AI: Artificial intelligence.

Figure 11 presents a phased roadmap for advancing nanoparticle-based CRC detection platforms from the laboratory to clinical use. The timeline recognizes critical developmental stages: near-term efforts focus on manufacturing standardization and preclinical validation; mid-term stages address regulatory approval, safety trials, and early clinical feasibility; long-term objectives include large-scale validation, final regulatory approval, and integration into routine oncological workflows. By systematically navigating these stages, precision oncology can move from theoretical promise to practical implementation while maintaining safety, efficacy, and cost-effectiveness.

7. Conclusion

Colorectal cancer remains a significant global health

challenge, with patient outcomes strongly influenced by early detection and timely intervention. Conventional screening approaches, such as colonoscopy, are essential but limited by invasiveness, accessibility, and patient adherence, leading to numerous diagnoses at advanced stages. Emerging computational biology methods—particularly ML-assisted multi-omics analyses for biomarker prioritization—combined with nanotechnology-based biosensing platforms, offer complementary strategies for sensitive, non-invasive detection, especially in the colon, where physiological factors such as pH gradients and microbial composition may facilitate localized targeting.

Mg–Mn nanoparticle systems illustrate potential design principles in this context. Evidence for Mn-based nanoparticles supports their use in T1-weighted MRI

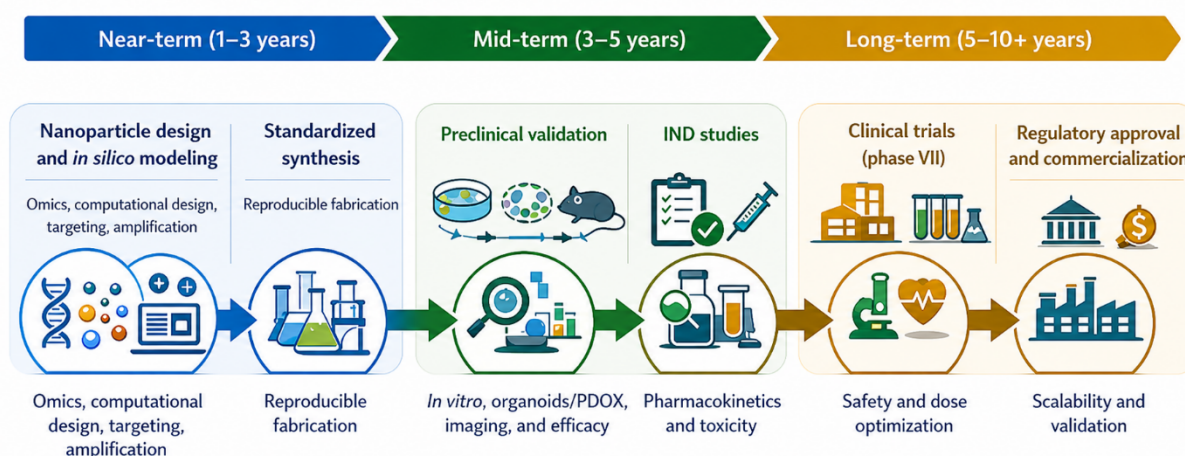


Figure 11. Future perspectives and realistic clinical translation timeline. Image created by the authors. Abbreviations: IND: Investigational New Drug; PDOX: Patient-derived orthotopic xenograft.

contrast and TME-responsive release, while Mg contributes biocompatibility and preliminary anti-proliferative effects. No integrated Mg–Mn system for CRC has been experimentally validated, and proposed synergistic effects remain hypothetical. Mn neurotoxicity—including basal ganglia accumulation, blood–brain barrier penetration, and manganism—requires rigorous biodistribution, clearance, and toxicological evaluation. Claims of therapeutic modulation by Mg remain preliminary and mechanistically unverified in combined systems.

Translational application of these strategies faces challenges, including reproducibility limitations in computational modeling, preclinical-to-clinical gaps in nanomedicine, manufacturing complexity, regulatory hurdles for combination diagnostic-therapeutic products, and the need for multi-cohort validation. Clinical

implementation will require harmonized data standards, robust safety assessment, and well-designed trials to evaluate efficacy, feasibility, and patient benefit.

The convergence of computational oncology and nanotechnology represents a promising research frontier for complementary CRC screening strategies. Realizing these opportunities demands evidence-driven development, interdisciplinary collaboration, and careful attention to toxicity, manufacturability, and translational barriers.

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Further disclosure

Limited use of large language models (specifically Grok by xAI, accessed in early 2026) was employed solely for minor language polishing, grammar correction, sentence restructuring suggestions, and assistance with word-count expansion in selected draft sections. No AI tool generated original scientific content, interpretations, conclusions, figures, tables, or the conceptual framework of the manuscript. All core ideas, critical analysis, literature synthesis, and final scientific writing were conceived and performed by the author. Every AI-suggested edit underwent thorough human review, manual revision, and proofreading to ensure accuracy, scientific integrity, and alignment with the author's voice. The estimated AI contribution to the final submitted text is below 30%.

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