

Beyond Molecular Residual Disease: The Gastroseed Artificial Intelligence (AI) Paradigm for Early Prediction of Metastatic Progression After Curative Gastrointestinal Cancer Surgery

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Abstract

Background: Circulating tumor DNA (ctDNA) detection has revolutionized Molecular Residual Disease (MRD) assessment in gastrointestinal cancer, yet the "recurrence paradox" persists some ctDNA-negative patients relapse while ctDNA-positive patients remain disease-free, suggesting that tumor biology alone does not determine metastatic outcomes.

Objective: To propose the GastroSeed-AI paradigm, a systems-oncology framework integrating five biological domains (molecular residual disease, tumor genomics, gut microbiota, host immunometabolic status, and perioperative biology) with artificial intelligence to predict metastatic progression after curative gastrointestinal cancer surgery.

Methods: This is a translational narrative synthesis integrating current evidence from molecular oncology, surgical biology, microbiome research, immunometabolism, and machine learning. We conducted a comprehensive literature search across PubMed, Scopus, and Web of Science (2018-2026) using search terms including "circulating tumor DNA," "molecular residual disease," "gastrointestinal neoplasms," "gut microbiota," "immunometabolic status," and "perioperative complications." Evidence was synthesized thematically and integrated into a conceptual framework.

Results: The GastroSeed-AI paradigm proposes that metastatic recurrence results from the interaction between the "seed" (tumor cells with metastatic potential) and the "soil" (host environment). Five biological domains were identified as critical determinants: (1) molecular residual disease as a marker of tumor burden; (2) tumor genomics defining intrinsic metastatic potential; (3) gut microbiota composition influencing immune competence; (4) host immunometabolic status reflecting capacity for tumor control; and (5) perioperative biology creating windows of vulnerability.

Artificial intelligence is proposed as the essential tool to synthesize these heterogeneous, high-dimensional datasets into a single actionable risk score.

Conclusion: The GastroSeed-AI paradigm represents a paradigm shift from tumor-centric to systems-oncology approaches in predicting metastatic recurrence. This framework provides a roadmap for prospective validation, computational prototype development, and eventual clinical implementation over a 6-year translational pathway.

Keywords: Circulating Tumor DNA; Molecular Residual Disease; Gastrointestinal Neoplasms; Gut Microbiota; Machine Learning

Introduction

Metastatic recurrence remains the Achilles' heel of curative gastrointestinal cancer surgery. Despite advances in surgical technique, chemotherapy, and targeted therapy, approximately 30–50% of patients with stage II–III colorectal cancer, gastric cancer, and esophageal cancer develop distant metastases within 5 years of curative resection [1]. This persistent recurrence rate reflects our incomplete understanding of the biological mechanisms underlying metastatic progression and our inability to identify high-risk patients who would benefit from intensified adjuvant therapy.

The discovery of circulating tumor DNA (ctDNA) in the bloodstream of cancer patients has fundamentally transformed our approach to Molecular Residual Disease (MRD) detection [2]. Unlike traditional tumor markers, ctDNA provides a direct molecular signature of tumor burden and can detect minimal residual disease with exquisite sensitivity [3].

Postoperative ctDNA detection independently predicts recurrence and survival in multiple cancer types, including colorectal cancer [4], gastric cancer [5], and esophageal cancer [6]. This breakthrough has led to the hypothesis that ctDNA-guided adjuvant therapy could improve outcomes by identifying patients with occult metastatic disease [7].

However, a critical paradox has emerged: not all ctDNA-positive patients develop recurrence, and some ctDNA-negative patients' relapse [8]. This "recurrence paradox" suggests that tumor biology alone as reflected by ctDNA detection—does not fully determine metastatic destiny.

The presence of tumor cells in the circulation is necessary but not sufficient for metastatic progression. Rather, metastatic success depends on the interaction between the tumor cell (the "seed") and the host environment (the "soil"), a concept articulated over a century ago by Stephen Paget [9].

The host environment encompasses multiple biological systems that either promote or inhibit metastatic progression. These include the gut microbiota, which influences systemic immunity and metabolic homeostasis [10]; the host immunometabolic status, which reflects the capacity for tumor control [11]; and perioperative biology, which creates transient windows of immunosuppression and inflammation that may facilitate metastatic seeding [12]. Despite the recognized importance of these factors, current recurrence prediction models remain largely tumor-centric, incorporating only molecular and clinicopathological variables [13].

Artificial Intelligence (AI) offers a transformative opportunity to integrate these disparate biological domains into a unified predictive framework. Machine learning algorithms can identify complex, non-linear interactions among molecular, microbial, immunological, and perioperative variables that would be impossible to detect through conventional statistical approaches [14]. However, the development of such models requires a conceptual framework that explicitly acknowledges the multidimensional nature of metastatic progression.

We propose the GastroSeed-AI paradigm: a systems-oncology framework that integrates five biological domains molecular residual disease, tumor genomics, gut microbiota, host immunometabolic status, and perioperative biology with artificial intelligence to predict metastatic progression after curative gastrointestinal cancer surgery. This framework is grounded in translational evidence and provides a roadmap for prospective validation and clinical implementation.

Methodology

Study Design and Methodological Approach

This is a translational narrative synthesis designed to integrate current evidence across multiple biological disciplines and propose a novel conceptual framework for predicting metastatic progression in gastrointestinal cancer. The narrative synthesis approach was selected because it allows for the integration of diverse study designs (mechanistic studies, observational cohorts, clinical trials, and computational models) and the synthesis of evidence across disciplinary boundaries [15].

Literature Search Strategy

A comprehensive literature search was conducted across PubMed, Embase, Scopus, and Web of Science databases covering the period from January 2018 to June 2026. This timeframe was selected to capture recent advances in ctDNA science, microbiome

research, immunometabolism, and machine learning applications in oncology.

Search Terms and Information Sources

Primary search terms included: "circulating tumor DNA," "ctDNA," "molecular residual disease," "MRD," "gastrointestinal neoplasms," "colorectal cancer," "gastric cancer," "esophageal cancer," "gut microbiota," "microbiome," "immunometabolic," "sarcopenia," "frailty," "perioperative complications," "anastomotic leak," "machine learning," "artificial intelligence," "deep learning," and "cancer recurrence prediction." Boolean operators (AND, OR, NOT) were used to refine searches and identify relevant studies.

Study Selection Process

Studies were selected based on the following criteria: (1) original research or systematic reviews published in peer-reviewed journals; (2) focus on one or more of the five biological domains (MRD, tumor genomics, microbiota, immunometabolism, perioperative biology); (3) relevance to gastrointestinal cancer or cancer biology more broadly; (4) publication in English and (5) availability of full-text articles. Studies were excluded if they focused exclusively on non- gastrointestinal malignancies without translational relevance to GI cancer biology.

Eligibility Criteria and Evidence Prioritization

Eligible studies included prospective cohort studies, randomized controlled trials, mechanistic studies, and systematic reviews. Evidence was prioritized according to the following hierarchy:

- (1) Prospective cohort studies with multivariate analysis
- (2) Randomized controlled trials
- (3) Mechanistic studies in animal models or cell culture
- (4) Retrospective cohort studies
- (5) Expert opinion or narrative reviews.

This prioritization ensured that the framework was grounded in the highest-quality available evidence.

Evidence Synthesis and Thematic Integration

Evidence was synthesized thematically around each of the five biological domains. For each domain, we identified: (1) the biological rationale for inclusion; (2) key studies supporting the domain's relevance to metastatic progression; (3) current gaps in knowledge; and (4) opportunities for integration with other domains. Evidence was then integrated into a unified conceptual framework that acknowledges the interdependencies among domains.

Gap Analysis and Identification of Research Priorities

A systematic gap analysis was performed to identify: (1) areas where evidence is robust and ready for clinical translation; (2) areas where evidence is emerging but requires further validation and (3) areas where evidence is sparse and requires foundational research. This gap analysis informed of the proposed roadmap for future development.

Conceptual Framework Development and Evidence Triangulation

The GastroSeed-AI framework was developed through iterative synthesis of evidence across disciplines. Evidence triangulation was employed to identify convergent findings across different research domains that support the proposed framework. The framework was then evaluated for internal consistency, biological plausibility, and clinical applicability.

Results and Discussion

Challenges in Contemporary Recurrence Prediction Models

Current risk stratification models for gastrointestinal cancer rely primarily on clinicopathological variables (tumor stage, grade, histology) and, increasingly, on molecular markers such as Microsatellite Instability (MSI) and Mismatch Repair (MMR) status [16]. While these models have improved prognostic accuracy, they remain imperfect predictors of individual patient outcomes [17]. The addition of ctDNA detection has enhanced predictive performance, but the recurrence paradox persists [18].

Several factors contribute to the limitations of current models. First, they are predominantly tumor-centric, focusing on intrinsic tumor characteristics while largely ignoring the host environment [19]. Second, they treat biological variables as independent predictors rather than acknowledging the complex interactions among molecular, immunological, and metabolic systems [20]. Third, they do not account for the dynamic nature of the host-tumor relationship, which evolves over time in response to surgery, chemotherapy, and other interventions [21].

Bridging the Biological Gap Between Molecular Residual Disease and Clinical Recurrence

The recurrence paradox wherein some ctDNA-positive patients do not relapse, and some ctDNA-negative patients do suggests that ctDNA detection alone is insufficient to predict metastatic progression [22]. This paradox can be understood through the lens of the seed-and- soil hypothesis: ctDNA represents the "seed" (tumor cells with metastatic potential), but the "soil" (host environment) determines whether these seeds will germinate into clinically manifest metastases [23].

Recent evidence suggests that the biological characteristics of Circulating Tumor Cells (CTCs) and ctDNA fragments may influence their metastatic potential. Representative studies supporting each biological domain are presented in Table 1, demonstrating the robust evidence base for the GastroSeed-AI framework [24].

Biological Domain	Key Study	Year	Study Type	Key Finding	Relevance to Framework
MRD	Tie, et al., Circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer	2022	RCT	ctDNA-guided adjuvant therapy improved recurrence-free survival	Demonstrates clinical utility of ctDNA for treatment decisions
MRD	Reinert, et al., Analysis of plasma cell-free DNA by ultradeep sequencing in patients with stages I to III colorectal cancer	2019	Prospective cohort	ctDNA detection independently predicts recurrence	Validates ctDNA as prognostic biomarker
Tumor Genomics	Guinney, et al., The consensus molecular subtypes of colorectal cancer	2015	Meta- analysis	Identified 4 molecular subtypes with distinct outcomes	Demonstrates importance of tumor genomics in prognosis
Microbiota	Lynch C Pedersen, The human microbiome and the immune system	2016	Review	Microbiota composition influences systemic immunity	Establishes biological rationale for microbiota domain
Immunometabolism	Hotamisligil, Inflammation, metaflammation and immunometabolic disorders	2017	Review	Metabolic dysfunction impairs immune function	Links metabolism to anti-tumor immunity
Sarcopenia	Shachar, et al., Prognostic value of sarcopenia in adults with cancer: a meta-analysis and systematic review	2016	Meta- analysis	Sarcopenia independently predicts poor outcomes	Demonstrates clinical relevance of immunometabolic status

Perioperative Biology	Neeman, et al., A new approach to perioperative	2016	Review	Surgery induces immunosuppression	Establishes biological rationale for perioperative domain
Biological Domain	Key Study	Year	Study Type	Key Finding	Relevance to Framework
	cancer management			that promotes metastasis	
Perioperative Complications	Krarup, et al., Anastomotic leak increases distant recurrence and long-term mortality	2014	Cohort study	Anastomotic leak associated with increased recurrence	Demonstrates clinical impact of perioperative complications
AI in Oncology	Esteva, et al., Dermatologist- level classification of skin cancer with deep neural networks	2017	Validation study	Deep learning achieves dermatologist-level accuracy	Demonstrates feasibility of AI for cancer diagnosis
Machine Learning	Rajkomar, et al., Machine learning in medicine	2019	Review	Machine learning improves prediction of clinical outcomes	Establishes rationale for AI integration in framework

Table 1: Representative studies supporting the biological and translational foundations of the GastroSeed-AI framework.

For example, ctDNA fragments derived from primary tumors with high genomic instability may have greater metastatic potential than those from more stable tumors [25]. Additionally, the presence of specific mutations (such as TP53 mutations) in ctDNA may predict higher recurrence risk [26]. These observations suggest that not all ctDNA is equivalent, and that the molecular characteristics of ctDNA may provide additional prognostic information beyond its mere presence or absence. Furthermore, the timing of ctDNA detection relative to surgery may influence its prognostic significance [27]. ctDNA detected in the immediate postoperative period may reflect residual disease from the primary tumor, whereas ctDNA detected weeks or months after surgery may reflect true metastatic seeding [28]. This temporal dimension has not been adequately incorporated into current prediction models.

Immunometabolic Vulnerability as a Determinant of Metastatic Destiny

Emerging evidence demonstrates that the host immunometabolic status encompassing immune competence, metabolic homeostasis, and nutritional status plays a critical role in determining whether circulating tumor cells can successfully establish metastases [29]. Multiple factors contribute to immunometabolic vulnerability in the perioperative period.

Sarcopenia and Frailty: Sarcopenia (loss of skeletal muscle mass) and frailty are increasingly recognized as independent predictors of poor outcomes in cancer patients [30]. Sarcopenia is associated with impaired immune function, reduced chemotherapy tolerance, and increased infection risk [31]. In gastrointestinal cancer patients, preoperative sarcopenia predicts worse overall survival and higher recurrence rates [32]. The mechanisms underlying this association include reduced production of immune-modulating myokines, impaired mitochondrial function, and increased systemic inflammation [33].

Metabolic Dysfunction: Cancer cachexia and metabolic dysfunction are hallmarks of advanced cancer and persist in the perioperative period [34]. These conditions are characterized by insulin resistance, dyslipidemia, and altered amino acid metabolism, all of which impair immune function [35]. Recent evidence suggests that metabolic reprogramming of immune cells (immunometabolism) is essential for effective anti-tumor immunity [36]. Patients with metabolic dysfunction may have impaired capacity for tumor control due to altered immune cell metabolism [37].

Micronutrient Deficiency: Perioperative nutritional depletion, particularly of micronutrients such as vitamin D, zinc, and selenium, impairs immune function and increases infection risk [38]. Vitamin D deficiency is associated with impaired T cell differentiation and increased regulatory T cell (Treg) populations, which may promote tumor progression [39]. These observations suggest that nutritional optimization in the perioperative period may enhance anti-tumor immunity.

Perioperative Biology and the Hidden Determinants of Recurrence

Surgery, while curative in intent, paradoxically creates a biological environment that may promote metastatic progression [40]. This "surgery-induced immunosuppression" is mediated by multiple mechanisms, including acute inflammatory responses, release of Damage-Associated Molecular Patterns (DAMPs), and activation of immunosuppressive pathways [41].

Surgical Stress and Inflammation: Major surgery triggers a systemic inflammatory response characterized by elevated levels of pro-inflammatory cytokines (IL-6, TNF- α , IL-1 β) and acute phase reactants [42]. This inflammatory response, while necessary for wound healing, may also promote metastatic seeding by increasing vascular permeability, promoting angiogenesis, and activating pro-metastatic immune cells [43]. The magnitude and duration of this inflammatory response vary depending on the extent of surgery, operative time, and perioperative complications [44].

Surgical Complications and Metastatic Risk: Perioperative complications, particularly anastomotic leaks and surgical site infections, are associated with increased recurrence risk [45]. These complications trigger prolonged inflammatory responses and may create a "second hit" that promotes metastatic progression [46]. Recent evidence suggests that the inflammatory milieu created by surgical complications may activate dormant disseminated tumor cells and promote their outgrowth into clinically manifest metastases [47].

Anesthesia and Immune Function: Perioperative anesthesia and analgesia have complex effects on immune function [48]. While some anesthetic agents (such as propofol) have immunosuppressive properties, others (such as volatile anesthetics) may have immunomodulatory effects [49]. The choice of anesthetic technique and perioperative analgesic strategy may influence postoperative immune function and recurrence risk [50].

Transfusion and Immune Modulation: Perioperative blood transfusion is associated with increased recurrence risk in some studies, possibly through Transfusion-Related Immunomodulation (TRIM) [51]. This association suggests that the perioperative immune environment is malleable and can be modified by therapeutic interventions [52].

Artificial Intelligence and the Need for Multimodal Biological Integration

The fundamental challenge in predicting metastatic progression is integrating information from multiple biological domains — each with its own dimensionality, temporal dynamics, and measurement uncertainty — into a single actionable risk score [53]. Traditional statistical approaches are limited in their ability to capture complex, non-linear interactions among these domains [54]. Machine learning and artificial intelligence offer transformative potential for this integration [55]. Deep learning algorithms can identify patterns in high-dimensional data that would be invisible to conventional analysis [56]. Recurrent neural networks can capture temporal dynamics in longitudinal data [57]. Graph neural networks can model the complex interactions among biological variables [58]. Ensemble methods can combine predictions from multiple models to improve robustness [59].

However, the development of clinically useful AI models requires more than algorithmic sophistication [60]. Models must be:

- (1) Interpretable, allowing clinicians to understand which biological variables drive predictions [61]
- (2) Validated on independent cohorts to ensure generalizability [62]
- (3) Prospectively evaluated in clinical trials to demonstrate clinical utility [63]
- (4) Integrated into clinical workflows in a way that enhances rather than replaces clinical judgment [64]

Toward a Comprehensive Biological Model of Metastatic Progression

The GastroSeed-AI paradigm proposes that metastatic recurrence results from the dynamic interaction among five biological domains. The principal biological domains and their key components are summarized in Table 2. These five domains are not independent; rather, they interact dynamically:

Biological Domain	Key Components	Biological Rationale	Clinical Relevance
Molecular Residual Disease (MRD)	ctDNA detection, quantity, molecular characteristics (mutations, copy number)	Reflects tumor burden and metastatic potential; independent predictor of recurrence	Guides intensity of adjuvant therapy; Identifies high-risk patients
Tumor Genomics	Mutation burden, driver mutations (TP53, KRAS, APC), chromosomal instability, MSI/MMR status	Determines intrinsic metastatic potential; influences treatment response	Predicts recurrence risk independent of ctDNA; guides targeted therapy
Gut Microbiota	Microbial composition, diversity, functional capacity (short-chain fatty acid production)	Influences systemic immunity, metabolic homeostasis, anti-tumor immunity	Dysbiosis associated with poor outcomes; modifiable through intervention
Host Immunometabolic Status	Immune competence (T cell phenotyping, cytokine profiles), metabolic status (glucose, lipid metabolism), nutritional status (sarcopenia, micronutrients)	Determines capacity for tumor control; reflects host vulnerability	Sarcopenia predicts poor outcomes; modifiable through nutrition and exercise
Perioperative Biology	Surgical stress (operative time, blood loss), complications (anastomotic leak infection), inflammatory markers, immune recovery trajectory	Creates transient window of immunosuppression and inflammation; promotes metastatic seeding	Complications Associated with increased recurrence; modifiable through enhanced recovery protocols

Table 2: Biological architecture of the GastroSeed-AI framework.

1. Molecular Residual Disease (the "Seed"): ctDNA detection and characterization provide a molecular signature of tumor burden and metastatic potential. The presence, quantity, and molecular characteristics of ctDNA inform the likelihood of metastatic seeding
2. Tumor Genomics: The intrinsic genomic characteristics of the primary tumor (mutation burden, specific driver mutations, chromosomal instability) determine metastatic potential independent of ctDNA detection
3. Gut Microbiota (the "Soil"): The composition and function of the gut microbiota influence systemic immunity, metabolic homeostasis, and anti-tumor immunity. Dysbiosis may promote metastatic progression
4. Host Immunometabolic Status: The capacity of the host immune system to control metastatic disease depends on immune competence, metabolic homeostasis, and nutritional status. Immunometabolic vulnerability creates windows of opportunity for metastatic seeding
5. Perioperative Biology: Surgery creates a transient biological environment characterized by inflammation, immunosuppression, and activation of pro-metastatic pathways. The magnitude and duration of this perioperative perturbation influence metastatic risk

These five domains are not independent; rather, they interact dynamically. For example, gut microbiota influences immune function, which in turn influences the capacity to control metastatic disease. Perioperative complications trigger inflammatory responses that may activate dormant disseminated tumor cells. Nutritional status influences both immune function and microbiota composition (Fig. 1).

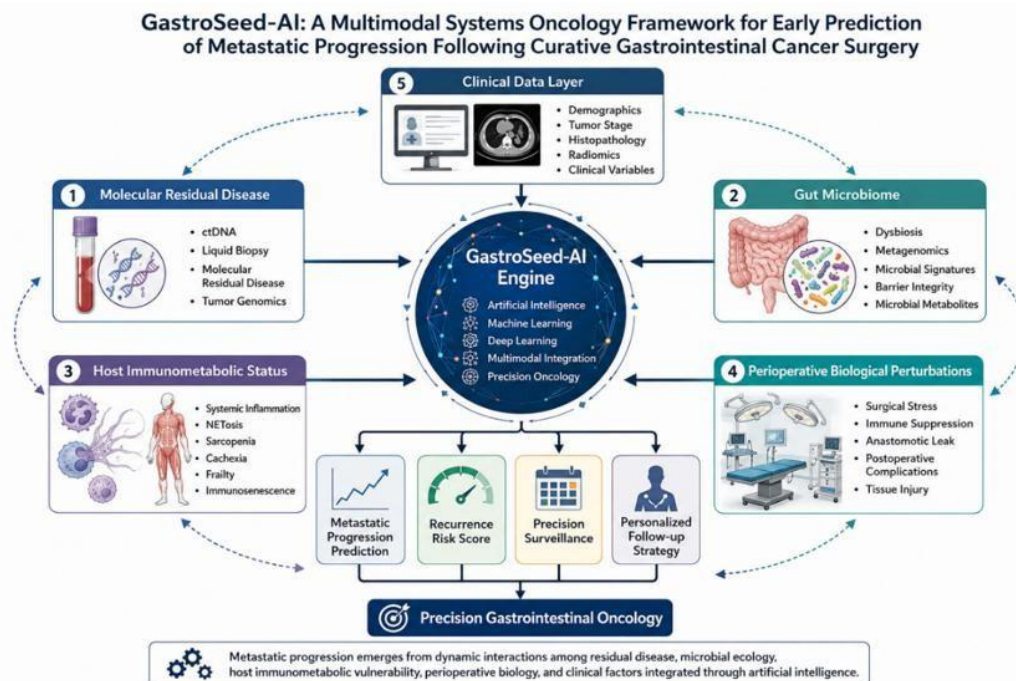


Figure 1: GastroSeed-AI: A Multimodal Systems Oncology Framework for Predicting Metastatic Progression in Gastrointestinal Cancer. The framework integrates five biological domains (molecular residual disease, tumor genomics, gut microbiota, host immunometabolic status, and perioperative biology) through artificial intelligence to predict metastatic progression. The "seed" (circulating tumor DNA and metastatic potential) interacts with the "soil" (host environment) to determine metastatic destiny. Machine learning algorithms synthesize high-dimensional, heterogeneous data into a single actionable risk score.

Artificial intelligence is proposed as the essential tool to synthesize these interactions into a unified predictive framework. A multimodal AI model would integrate:

- Molecular data: ctDNA characteristics, tumor genomics, circulating biomarkers
- Microbiota data: 16S rRNA sequencing, metagenomic analysis, functional predictions
- Immunological data: T cell phenotyping, cytokine profiles, immune checkpoint expression
- Metabolic data: glucose metabolism, lipid profiles, amino acid metabolism
- Perioperative data: operative time, blood loss, complications, inflammatory markers
- Clinical data: patient demographics, comorbidities, treatment received

Such a model would generate a dynamic risk score that evolves over time as new data becomes available, allowing for adaptive therapeutic interventions.

Clinical and Biotechnological Implications

The GastroSeed-AI paradigm has profound implications for clinical practice and biotechnological innovation. First, it suggests that current approaches to adjuvant therapy – which are largely based on tumor stage and ctDNA detection may be suboptimal. A more nuanced understanding of the host-tumor interaction could enable more precise therapeutic targeting.

Second, the framework identifies multiple therapeutic targets beyond the tumor itself. Interventions to optimize immunometabolic status (nutritional support, exercise, immune modulation), modify the microbiota (probiotics, dietary interventions), and reduce perioperative complications (enhanced recovery protocols, minimally invasive surgery) may all contribute to improved outcomes.

Third, the framework provides a roadmap for the development of novel biomarkers and therapeutic strategies. For example, microbiota-derived metabolites (such as short-chain fatty acids) may serve as biomarkers of anti-tumor immunity and therapeutic targets for immune modulation.

Strengths and Limitations of the Review

Strengths

This review synthesizes evidence across multiple biological disciplines to propose a novel, integrative framework for predicting metastatic progression. The framework is grounded in translational evidence and acknowledges the complexity of the host-tumor interaction. The proposed roadmap for development is realistic and achievable, with clear milestones and timelines.

Limitations

This is a narrative synthesis rather than a systematic review, and therefore subject to selection bias. The framework is conceptual and has not yet been prospectively validated. Some of the proposed biological mechanisms remain incompletely understood, and the relative importance of each domain in determining metastatic risk is unknown. The framework is specific to gastrointestinal cancer and may not be generalizable to other cancer types.

Future Directions and Research Priorities

Deciphering the Biology of Metastatic Progression

Future research must elucidate the mechanisms by which each of the five biological domains influences metastatic progression. This requires integrated mechanistic studies combining *in-vitro*, *in-vivo*, and clinical approaches. For example, studies should investigate how specific microbiota-derived metabolites influence T cell differentiation and anti-tumor immunity, and how perioperative complications alter the trajectory of immune recovery.

Longitudinal Characterization of the Host-Tumor Interaction

The GastroSeed-AI paradigm emphasizes the dynamic nature of the host-tumor relationship. Future studies should employ intensive longitudinal sampling (blood, stool, tissue) to characterize how molecular, microbial, immunological, and metabolic variables evolve over time in relation to recurrence risk. Such studies should include frequent sampling in the perioperative period, when the host environment is most malleable.

Integrating Molecular, Microbial, Immunological, and Metabolic Data

Large prospective cohort studies should be designed to collect comprehensive data across all five biological domains. These studies should employ standardized protocols for sample collection, processing, and analysis to ensure data quality and comparability. Biobanking of samples should enable future validation studies and mechanistic investigations.

Development of Computational Prototypes and Machine Learning Models

Computational prototypes integrating data from the five biological domains should be developed and validated on existing cohorts. These models should employ interpretable machine learning approaches (such as SHAP values) to identify which biological variables drive predictions. Models should be validated on independent cohorts and prospectively evaluated in clinical trials.

Translational Innovation and Digital Health Integration

Digital health platforms should be developed to integrate ctDNA testing, microbiota analysis, immune profiling, metabolic assessment, and perioperative monitoring into a unified clinical decision-support system. Such platforms should provide real-time risk stratification and enable adaptive therapeutic interventions.

Roadmap for Future Development

Phase 1 (Years 1–2): Retrospective Validation

- Assemble existing cohorts with comprehensive molecular, clinical, and outcome data
- Develop computational prototypes integrating available data
- Validate models on retrospective cohorts
- Identify key biological variables driving predictions

Phase 2 (Years 2–3): Prospective Cohort Development

- Initiate prospective cohort studies with intensive longitudinal sampling
- Standardize protocols for sample collection and analysis
- Establish biobanks for future mechanistic studies
- Refine computational models based on prospective data

Phase 3 (Years 3–5): Clinical Trial Development

- Design and initiate randomized controlled trials testing AI-guided therapeutic interventions
- Compare AI-guided risk stratification to standard approaches
- Evaluate clinical utility and cost-effectiveness
- Assess patient and clinician acceptance

Phase 4 (Years 5–6): Regulatory Approval and Clinical Implementation

- Seek regulatory approval for AI-based risk prediction tools
- Develop clinical implementation protocols
- Train clinicians in interpretation and use of AI predictions
- Monitor real-world performance and safety

Future Perspective

The GastroSeed-AI paradigm represents a fundamental shift in how we conceptualize and predict metastatic progression in gastrointestinal cancer. By integrating molecular, microbial, immunological, and metabolic data through artificial intelligence, we can move beyond tumor-centric approaches toward a systems-oncology framework that acknowledges the complexity of the host-tumor interaction. This framework has the potential to improve outcomes for patients with gastrointestinal cancer by enabling more precise risk stratification and targeted therapeutic interventions.

Conclusion

Circulating tumor DNA has revolutionized our ability to detect molecular residual disease in gastrointestinal cancer patients. However, the recurrence paradox—wherein some ctDNA-positive patients do not relapse and some ctDNA-negative patients do—demonstrates that tumor biology alone does not determine metastatic destiny. The GastroSeed-AI paradigm proposes a systems-oncology framework integrating five biological domains (molecular residual disease, tumor genomics, gut microbiota, host immunometabolic status, and perioperative biology) with artificial intelligence to predict metastatic progression. This framework is grounded in translational evidence and provides a realistic roadmap for prospective validation, computational development, and clinical implementation. By embracing the complexity of the host-tumor interaction, we can move toward more precise, personalized approaches to cancer care.

Conflict of Interest

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

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement

Informed consent was obtained from all participants included in the study.

Authors' Contributions

J.R.A. and I.A.F. conceived the study and designed the experiments. J.R.A. performed the data collection. A.C.M.R. and I.A.F. analyzed the data. J.R.A., A.C.M.R., and I.A.F. wrote the manuscript. All authors read and approved of the final manuscript.

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