

Perspective

The Gut–Nutrient–Genome Axis: A Host-Integrated Perspective on Genomic Instability in Cancer

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Simple Summary

Cancer cells steadily accumulate damage to their DNA, and this genomic instability helps tumors grow and resist treatment. Most therapies focus on the tumor itself, yet the body's wider physiological condition also influences how well cells protect and repair their DNA. This includes the health of the gut and its microbes, nutrient levels, inflammation, body-clock and sleep rhythms, hydration, and chronic stress. In this perspective, we propose that these host factors act together and change over time to shape when and how genomic instability develops and that outwardly visible disease may lag behind these underlying biological changes. We also describe how carefully limited artificial intelligence could combine many kinds of patient data to identify which host factors matter most for each individual. Importantly, these host-focused strategies are intended to support, not replace, standard cancer treatments, with the aim of helping patients tolerate therapy better and helping treatments work for longer.

Abstract

Genomic instability is a defining feature of cancer progression and therapeutic resistance, yet contemporary oncology interprets it largely through tumor-intrinsic genetic alterations, with less attention to the evolving host physiological context in which DNA damage accumulates and genome maintenance operates. In this perspective, we propose a longitudinal host-transfer-state framework that treats host physiology not as a static background but as a continuously evolving adaptive system. Gut microbial ecology, micronutrient physiology, inflammatory signaling, circadian organization, hydration, environmental exposures, and chronic stress are framed as interacting biologic transfer systems that shape DNA repair fidelity, oxidative buffering, immune coordination, and adaptive tumor behavior over time. These influences are proposed to vary by tumor type, treatment context, and individual physiologic reserve, and clinically observable disease may lag behind deeper latent biologic dynamics. We further outline how longitudinal multi-omic integration and constrained, bounded artificial intelligence—used for longitudinal data integration, normalization, contextualization, and bounded analytical support rather than autonomous decision-making—could identify patient-specific constraints on genome maintenance and treatment tolerance. Host-directed strategies are presented as complementary to, not replacements for, established tumor-directed therapies.

Keywords: genomic instability; gut microbiome; micronutrient; diet; cancer; carcinogenesis; DNA repair; host physiology; artificial intelligence; therapeutic resistance



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1. Introduction

Genomic instability, characterized by chromosomal aberrations, aneuploidy, impaired DNA repair fidelity, and elevated mutation rates, is a defining feature of many solid tumors and a central driver of tumor evolution, therapeutic resistance, and disease progression [1–3] (Appendix A). Contemporary oncology has increasingly focused on targeting tumor-intrinsic vulnerabilities, including oncogenic signaling pathways, homologous recombination defects, immune evasion mechanisms, and adaptive metabolic dependencies. Although these approaches can produce substantial initial responses, durable disease control remains limited for many patients, as resistance frequently emerges through intra-tumoral heterogeneity, adaptive selection pressures, and genomic plasticity [4,5].

Immune checkpoint inhibitors demonstrate a median time to acquired resistance of approximately 7.3 months (95% confidence interval [CI], 6.4–8.2), with most initial responders progressing within 24 months [6]. Poly (ADP-ribose) polymerase (PARP) inhibitors similarly demonstrate variable but often limited durability depending on tumor histology, *BRCA* mutation status, and prior therapeutic exposure [7,8]. These treatment failures reflect the capacity of genetically unstable tumor populations to adapt under sustained selective pressure through dynamic evolutionary mechanisms [9]. In this context, the capacity of genetically unstable tumor populations refers to their ability—by virtue of high mutational and chromosomal diversity—to continuously generate heritable genetic and phenotypic variants, such that therapeutic selection favors pre-existing or newly arising resistant subclones that survive treatment and repopulate the tumor. Despite major advances in tumor genomics and molecular oncology, prevailing models of resistance remain predominantly tumor-centered and less frequently incorporate the broader host physiological conditions under which DNA damage accumulates, repair mechanisms operate, inflammatory signaling evolves, and adaptive tumor behavior emerges longitudinally over time [10].

Environmental toxicant exposure, dietary instability, circadian disruption, hydration status, chronic psychosocial stress, and sedentary behavioral patterns together constitute a composite host exposome capable of influencing genomic integrity through simultaneous effects on DNA damage burden, oxidative stress regulation, inflammatory signaling, immune coordination, and repair capacity [11–14]. Gut microbiome dysbiosis and micronutrient insufficiencies—including deficiencies in zinc, folate, selenium, magnesium, and B vitamins—may further impair DNA repair enzyme activity, alter redox buffering capacity, disrupt epithelial integrity, and accelerate age-associated genomic decline [15]. Increasing evidence additionally suggests that chronic inflammatory signaling, microbiome-derived metabolites, neuroimmune interactions, and circadian dysregulation may influence the biologic conditions under which mutagenesis, immune escape, and adaptive tumor evolution occur [16–18].

However, despite growing recognition that host physiology may influence genomic stability, these observations remain fragmented across microbiome science, nutritional biology, stress physiology, circadian biology, immunology, and cancer genomics. Most current frameworks emphasize static tumor-state characterization while less frequently accounting for the evolving host physiological context through which nutrients, inflammatory signals, environmental perturbations, and therapeutic interventions are biologically processed over time.

In this perspective, we propose a longitudinal host-transfer-state framework in which host physiology is interpreted not as a static background condition but as a continuously evolving adaptive system. Host-state refers to the composite, longitudinally evolving physiologic condition of the organism—including microbiome ecology, inflammatory signaling, micronutrient physiology, circadian organization, and environmental exposure burden—while gut microbial ecology and lifestyle-associated behaviors function as inter-

acting transfer modifiers shaping genome maintenance capacity over time. We propose that genomic instability may emerge not solely from tumor-autonomous molecular processes, but also from evolving host-state conditions that shape the biologic environment in which DNA repair dysfunction, oxidative stress accumulation, and adaptive tumor evolution occur; these influences are not assumed to operate uniformly across cancers or patient populations. Clinically relevant host-state assessment may begin at multiple temporal anchoring points (T_0), and observable disease may lag deeper latent biologic dynamics, emphasizing longitudinal trajectory interpretation rather than isolated tumor-state assessment alone.

We further outline how longitudinal multi-omic integration and constrained AI-assisted systems analysis may support structured longitudinal systems analysis and contextual interpretation within complex host–tumor systems. Within this framework, AI is conceptualized not as an autonomous clinical decision-maker, but as a bounded data integration tool for longitudinal interpretability. The novelty of this perspective lies not in linking microbiome, micronutrients, inflammation, or stress physiology to cancer individually, but in integrating these domains into a unified longitudinal architecture for investigating how evolving host physiology may shape genome maintenance, adaptive tumor behavior, and therapeutic resistance over time.

2. Deconstructing the Host–Transfer–Genome Axis

We propose a longitudinal host-transfer-state framework in which environmental exposures, gut ecology, micronutrient physiology, inflammatory signaling, and genome maintenance capacity function as dynamically interacting components of an evolving host system rather than as isolated biologic variables. Within this framework, genomic instability emerges through a sequential and partially self-reinforcing cascade in which environmental and lifestyle perturbations alter biologic transfer fidelity, impair systemic resilience, and progressively constrain genome maintenance capacity over time. Importantly, the framework does not propose a universal mechanism applicable across all malignancies, but rather a systems-level architecture through which host physiological conditions may differentially influence genomic stability depending on tumor type, treatment context, environmental exposure burden, and individual host reserve.

2.1. Environmental and Lifestyle Perturbations of Host Transfer Physiology

Environmental toxicant exposure, pro-inflammatory dietary patterns, chronic psychosocial stress, circadian disruption, hydration instability, sedentary behavioral patterns, and sleep dysregulation may collectively perturb host physiologic organization through convergent effects on gut ecology, neuroimmune signaling, epithelial integrity, and inflammatory regulation [19–23]. Within the proposed framework, these variables are interpreted not merely as isolated risk modifiers, but as interacting host-state transfer perturbations capable of influencing how nutrients, metabolites, inflammatory mediators, and adaptive physiologic responses are biologically processed and assimilated longitudinally over time.

Gut microbial dysbiosis represents a central transfer disturbance within this model. Chronic stress-associated glucocorticoid signaling, circadian instability, environmental toxicants, and dietary disruption may alter microbial diversity, impair epithelial barrier integrity, reduce short-chain fatty acid (SCFA) production, and promote inflammatory microbial states [20,21]. These perturbations compromise absorptive architecture and intestinal signaling networks while increasing permeability and systemic inflammatory exposure [22,23]. As a result, the gut microbiome is interpreted not solely as a biomarker of disease state, but as a dynamic biologic transfer layer regulating nutrient assimilation, inflammatory signaling, oxidative buffering, microbial metabolite production, and immune coordination across evolving host-state trajectories.

2.2. Disrupted Micronutrient Physiology and Genome Maintenance Capacity

Compromised epithelial integrity and dysregulated gut ecology may reduce the efficiency of micronutrient absorption and utilization while simultaneously increasing inflammatory interference with metabolic and repair pathways [24]. Dysbiotic microbial communities may additionally compete for essential micronutrients or generate metabolites that alter nutrient bioavailability and host utilization. Within the proposed framework, micronutrient physiology is therefore interpreted longitudinally as a transfer-dependent component of genome maintenance capacity rather than as a static nutritional variable alone.

Several micronutrients participate directly in DNA repair fidelity, redox buffering, methylation dynamics, and genome maintenance processes. Folate and vitamin B12 serve as methyl donors in one-carbon metabolism, sustaining thymidylate synthesis and S-adenosylmethionine-dependent DNA methylation. Deficiency states may promote uracil accumulation within DNA, base excision repair-mediated strand breaks, and dysregulated CpG methylation at tumor suppressor loci [25]. Zinc functions as a structural cofactor for numerous DNA repair and checkpoint proteins, including the zinc-finger domains of p53 and the nucleotide excision repair protein XPA (xeroderma pigmentosum complementation group A), such that zinc depletion may impair both lesion recognition and repair coordination [26,27]. Selenium, incorporated into glutathione peroxidases and thioredoxin reductases, contributes to intracellular redox regulation and protection against oxidative replication stress [28]. Vitamin D signaling additionally influences transcriptional regulation of DNA repair pathways and immune coordination [29].

Importantly, this framework does not propose that micronutrient supplementation universally improves cancer outcomes. Rather, the biologic relevance appears most plausible in states of documented deficiency or impaired physiologic transfer, where restoration of deficient cofactors may recover impaired enzymatic or repair function. Clinical trials performed in nutritionally sufficient populations, including SELECT [30] and CARET [31], demonstrated no benefit and, in some cases, potential harm from indiscriminate supplementation. Furthermore, the contribution of host micronutrient physiology to genomic instability is unlikely to be uniform across malignancies. In tumors dominated by strong tumor-intrinsic mutational processes, such as APOBEC-driven mutagenesis or mismatch repair deficiency, host physiologic contribution may be comparatively secondary, whereas in cancers characterized by inflammatory remodeling, oxidative stress burden, or impaired repair fidelity, host-state conditions may exert greater influence on genome maintenance trajectories.

2.3. Host-State Contributions to Genomic Instability

Within the proposed host-transfer-state framework, genomic instability may emerge through convergent interactions among inflammatory signaling, impaired repair fidelity, oxidative stress accumulation, microbiome-derived genotoxic metabolites, and disrupted host transfer physiology. Dysbiotic microbial communities may directly contribute to genotoxic stress through metabolites including colibactin and hydrogen sulfide [32], while increased intestinal permeability permits translocation of microbial products into systemic circulation, sustaining chronic inflammatory signaling and reactive oxygen species generation [33,34]. These processes may create biologic conditions permissive to DNA damage accumulation, clonal diversification, adaptive selection pressure, and therapeutic resistance [35] (Figure 1).

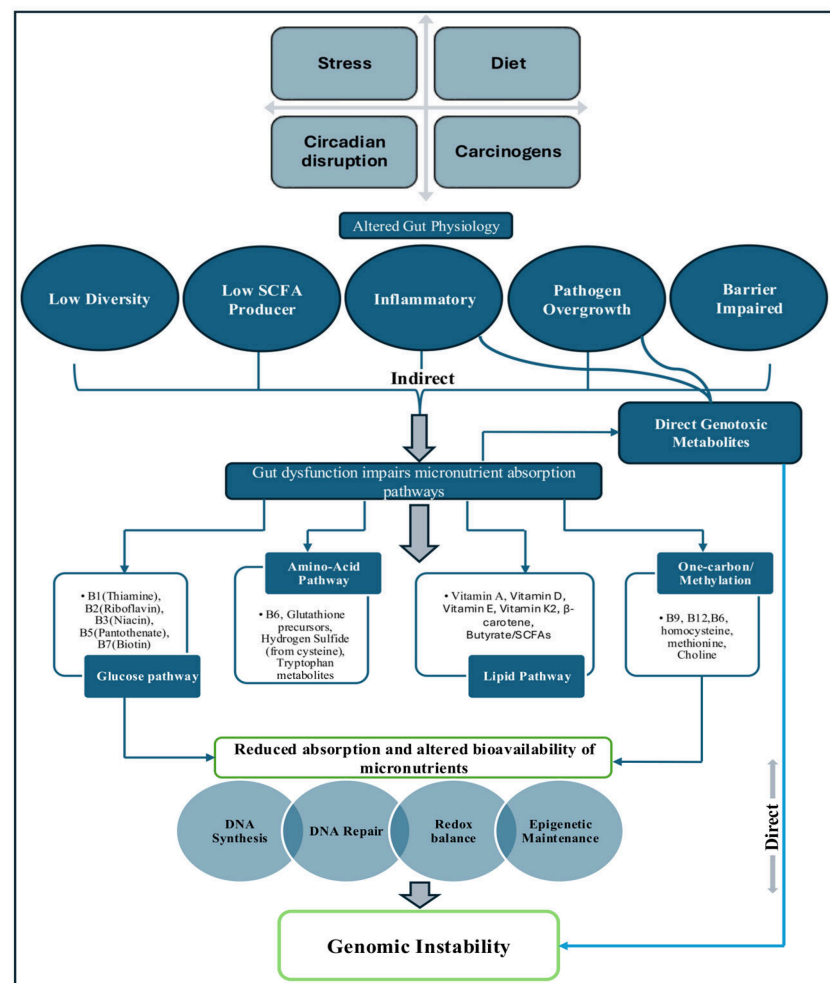


Figure 1. Conceptual host pathway linking gut physiology to genome maintenance. This figure illustrates a proposed systems model, not a strict causal pathway, highlighting one host-centered route through gut ecology, micronutrient physiology, and genome maintenance. Chronic stress, diet, circadian disruption, and dietary carcinogens (connected by bidirectional arrows) interact reciprocally and converge on altered gut physiology, including dysbiosis, reduced SCFA producers, inflammatory states, pathogen overgrowth, and impaired barrier integrity. Gut dysfunction impairs micronutrient absorption across glucose-dependent (B1, B2, B3, B5, B7), amino acid-dependent (B6, glutathione precursors, tryptophan metabolites), lipid-dependent (vitamins A, D, E, K2, SCFAs), and one-carbon/methylation (B9, B12, methionine, choline) pathways. Indirectly, reduced micronutrient bioavailability compromises DNA synthesis, repair, redox balance, and epigenetic maintenance; directly, dysbiotic microbiota produce genotoxic metabolites including colibactin and hydrogen sulfide. Both routes converge on genomic instability. SCFA, short-chain fatty acid.

At a mechanistic level, host-associated genomic instability may involve at least three partially overlapping pathways. First, chronic inflammatory signaling mediated through NF-κB activation, inducible nitric oxide synthase (iNOS), and NADPH oxidase may generate reactive oxygen and nitrogen species capable of inducing oxidative DNA lesions and double-strand breaks [36]. When repair pathways such as base excision repair or homologous recombination are impaired, these lesions may contribute to mutational accumulation and chromosomal instability [37,38]. Second, micronutrient insufficiency may impair multiple nodes of genome maintenance, including thymidylate synthesis, methylation regulation, redox buffering, checkpoint activation, and nucleotide excision repair [25–28,39,40]. Third, microbiome-derived metabolites may exert both genotoxic and epigenomic effects,

including colibactin-mediated double-strand breaks and butyrate-associated modulation of chromatin accessibility and histone deacetylase activity [41,42].

Importantly, the relative contribution of these pathways is likely highly tumor-type dependent. In inflammation-associated colorectal carcinogenesis, microbial genotoxicity and inflammatory remodeling are strongly supported by molecular and translational evidence. In contrast, in malignancies such as lung adenocarcinoma, tobacco carcinogen exposure and *APOBEC*-associated mutational processes dominate the genomic landscape, and the contribution of host-transfer physiology to genomic instability remains less clearly defined [43]. Accordingly, this framework should not be interpreted as a universal explanatory model for all cancers, but rather as a structured conceptual architecture for investigating how evolving host physiological conditions may interact with tumor-intrinsic processes to shape genomic instability, adaptive tumor evolution, and therapeutic resistance longitudinally over time.

3. Computational Integration for Longitudinal Host–Tumor Systems Analysis

Identifying host-level physiologic constraints on genome maintenance and adaptive tumor behavior requires integration of diverse and temporally evolving data streams, including genomics, metabolomics, microbiome profiling, inflammatory biomarkers, nutritional status, environmental exposures, behavioral physiology, and longitudinal clinical trajectories. The scale, heterogeneity, and dynamic nature of these data exceed the interpretive capacity of unaided clinical analysis and therefore necessitate structured computational approaches capable of longitudinal contextualization and systems-level integration [44,45].

Within the proposed host-transfer-state framework, computational analysis is conceptualized not as an autonomous decision-making system, but as a bounded infrastructure for structured longitudinal analysis, contextualization, and interpretation across evolving host-state trajectories. Importantly, the novelty of this framework does not reside in the isolated application of artificial intelligence to oncology, but rather in the proposal that host physiology, tumor biology, environmental exposures, and longitudinal behavioral dynamics can be integrated within a unified systems architecture designed to investigate how evolving host-state conditions may influence genome maintenance capacity, adaptive tumor behavior, and therapeutic resistance over time.

Under this framework, computational integration may support three primary functions. First, multimodal longitudinal phenotyping of host physiological state across interacting biologic domains, including micronutrient physiology, inflammatory signaling, microbiome composition, circadian organization, metabolic resilience, hydration status, and behavioral physiology. Second, structured analytical inference intended to identify potential host-state constraints on genome maintenance while distinguishing biologically plausible signals from confounded or weakly associated variables. Third, longitudinal monitoring of dynamic biologic endpoints—including circulating cell-free DNA measures of chromosomal instability [46], inflammatory markers, microbiome composition, metabolomic signatures, and physiologic state variables—to evaluate whether observed trajectory changes are directionally consistent with anticipated biologic effects of intervention (Figure 2).

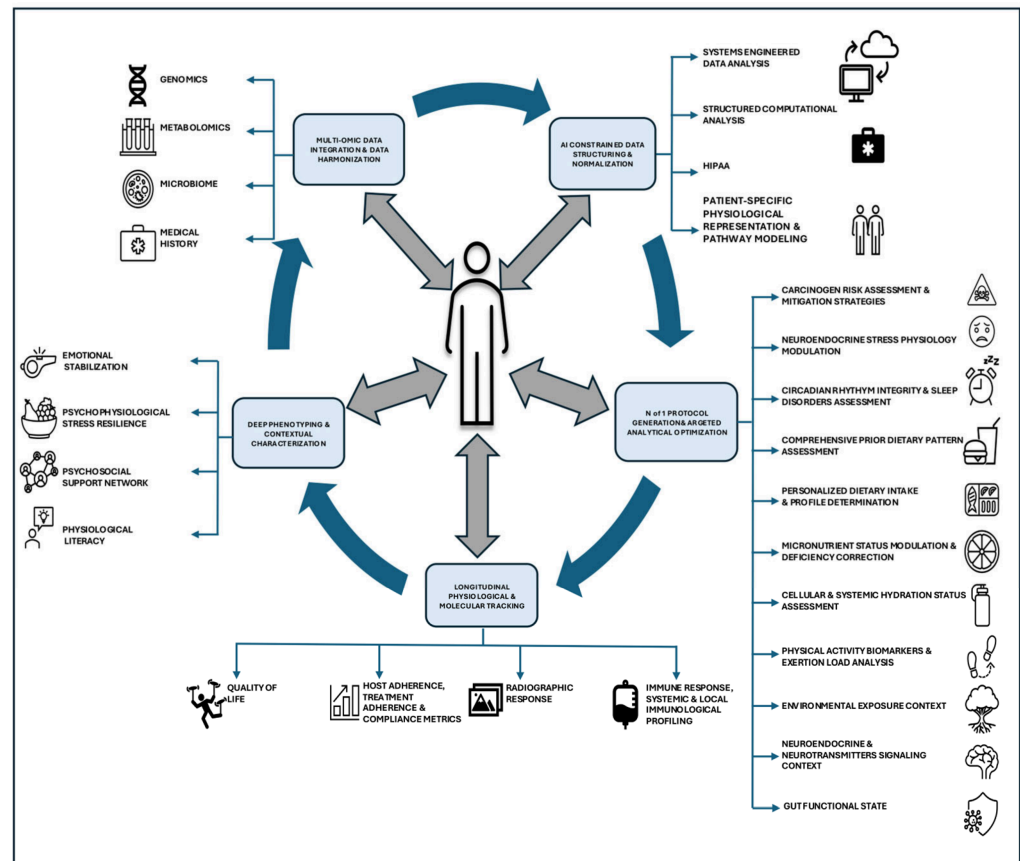


Figure 2. Conceptual architecture for AI-enabled, patient-specific analysis of host physiology in oncology (patient digital twin). Multimodal data streams—genomics, metabolomics, microbiome profiling, medical history, and longitudinal clinical data—are integrated and harmonized to construct an individualized, dynamic representation of host physiological state (a patient-specific “digital twin”) rather than a population-level average. AI-constrained data structuring and normalization support deep phenotyping, N-of-1 longitudinal study structuring, and longitudinal physiological and molecular tracking across domains including micronutrient status, inflammatory signaling, circadian organization, hydration, environmental exposures, and gut function. Outputs are intended to characterize patient-specific physiological constraints on genome maintenance and treatment tolerance and to support longitudinal analysis, contextualization, and interpretation, not autonomous clinical decision-making. The asterisked domains represent contextual host factors shaping the personalized model rather than prescriptive clinical services. AI, artificial intelligence.

Within this architecture, host-state reconstruction may begin at multiple temporal anchoring points (T_0), including pre-oncogenic physiologic instability, diagnosis, treatment initiation, recurrence, or therapeutic resistance. Rather than relying solely on isolated static measurements, the framework emphasizes longitudinal trajectory interpretation, recognizing that clinically observable disease states may represent delayed projections of deeper latent biologic dynamics evolving over time. Computational systems are therefore used to contextualize temporal relationships among host-state variables, tumor evolution, inflammatory burden, microbiome dynamics, and treatment response within partially observable adaptive systems.

Importantly, the framework distinguishes two levels of analysis that should not be conflated. Population-level observations—drawn from epidemiologic studies, cohort analyses, and cross-sectional multi-omic surveys—provide biological knowledge that can inform interpretation of host–tumor relationships. In contrast, patient-level implementation focuses on longitudinal host-state reconstruction within an individual, integrating serial physiologic, microbiome, micronutrient, behavioral, and clinical data to interpret that

patient's evolving transfer-state trajectory. Population-derived knowledge informs which variables merit monitoring; patient-level analysis determines how those variables behave over time in a specific clinical context.

To conceptually formalize this framework, host physiology may be represented as an evolving longitudinal system in which biologic state changes dynamically over time according to interacting transfer conditions:

$$H(t+1) = H(t) + S(G_{transfer}, L_{transfer}, E) - D(I, O, R)$$

where $H(t)$ represents host-state at time t ; $G_{transfer}$ represents gut-associated transfer physiology regulating nutrient assimilation, microbial signaling, and epithelial integrity; $L_{transfer}$ represents lifestyle-associated transfer physiology including sleep organization, hydration status, stress regulation, circadian stability, and behavioral execution; E represents environmental exposures; and $D(I, O, R)$ represents destabilizing influences associated with inflammatory burden (I), oxidative stress (O), and impaired repair capacity (R).

Within this model, genome maintenance capacity may similarly be conceptualized as a dynamic systems property rather than a fixed biologic characteristic:

$$GMC(t) = f(N(t), I(t), M(t), C(t))$$

where $GMC(t)$ represents genome maintenance capacity; $N(t)$ represents micronutrient sufficiency and bioavailability; $I(t)$ represents inflammatory signaling burden; $M(t)$ represents microbiome state and microbial diversity; and $C(t)$ represents circadian organization and physiologic rhythmicity. Under this framework, genomic stability emerges from the interaction of these longitudinally evolving host-state variables rather than from isolated molecular pathways alone.

Importantly, the framework further proposes that observed clinical states may incompletely represent underlying biologic dynamics due to delayed physiologic observability:

$$ObservedState_t \approx LatentState_{t-\tau}$$

where τ represents the temporal lag between latent biologic state evolution and clinically observable manifestation. This formulation reflects the possibility that inflammatory destabilization, microbiome disruption, repair dysfunction, or adaptive tumor evolution may evolve longitudinally before becoming detectable through imaging, laboratory measurements, or overt clinical progression.

A central concept within the host-transfer-state model is that biologic effect is not necessarily equivalent to therapeutic or nutritional input alone:

$$B_{delivered}(t) = Input(t) \times T_{host}(t)$$

where $B_{delivered}(t)$ represents the effective biologic impact of a therapeutic, nutritional, or behavioral intervention and $T_{host}(t)$ represents the evolving host transfer-state through which the intervention is processed, absorbed, regulated, and biologically integrated. Under this interpretation, two patients receiving similar interventions may experience substantially different biologic outcomes depending on differences in microbiome composition, inflammatory signaling, circadian organization, absorptive integrity, physiologic reserve, and behavioral stability.

These equations are presented as conceptual abstractions intended to formalize the proposed longitudinal host-transfer-state framework rather than as validated predictive models. Their purpose is to provide a structured systems architecture capable of supporting

structured translational investigation into how evolving host physiology may interact with tumor biology across time.

Existing machine learning and multi-omic integration approaches demonstrate the feasibility of integrating heterogeneous biologic datasets and generating individualized analytical outputs [47–49]. However, these systems remain limited by inconsistent data standardization, population bias, limited longitudinal resolution, lack of mechanistic interpretability, and minimal validation against biologic endpoints directly relevant to genomic instability or therapeutic resistance. Accordingly, the framework proposed here should be interpreted as exploratory and hypothesis-generating rather than clinically validated.

Importantly, AI-assisted analysis within this framework is intentionally constrained and bounded. Computational systems are conceptualized as structured data integration and normalization tools operating within sequential analytical architectures designed to reduce unstructured inference and improve longitudinal interpretability. Where multiple biologically plausible interpretations emerge from integrated data analysis, outputs are not treated as equivalent or automatically actionable. Rather, competing biological interpretations are intended to be prioritized according to biologic plausibility, temporal consistency across independent data streams, concordance with established oncologic evidence, safety considerations, and prospective testability. Interpretations that cannot be linked to measurable biologic endpoints or that conflict with established mechanistic evidence are considered low-priority within the analytical hierarchy.

At the present stage of oncology research, realistically feasible applications of this framework are limited to structured longitudinal data integration, normalization, contextualization, and interpretation within research or complementary-care settings. Adaptive predictive modeling, autonomous clinical inference, and large-scale prospective validation of host-state reconstruction remain future objectives requiring standardized data architectures, mechanistic endpoint validation, and rigorous clinical study designs before translational implementation can be responsibly considered.

Several important methodological and translational challenges remain. These include harmonization of longitudinal data across clinical and research systems, biologic variability across tumor types and patient populations, model interpretability for clinical use, algorithmic bias in underrepresented populations, regulatory oversight for adaptive computational systems, and uncertainty regarding which host-state variables exert meaningful causal influence on genomic instability across specific malignancies [50,51]. These limitations are not merely technical constraints but define the conditions under which computational systems can be responsibly integrated into translational oncology research.

Accordingly, computational integration within the proposed host-transfer-state framework should presently be viewed as analytical infrastructure for longitudinal data integration and contextual interpretation rather than as a replacement for clinical judgment or established tumor-directed therapeutic decision-making. Prospective longitudinal studies integrating biologic endpoint measurement, tumor-state characterization, and host-state reconstruction will ultimately be required to determine whether incorporation of host-level physiologic dynamics meaningfully improves understanding of genomic instability, therapeutic resistance, and treatment durability within complex host–tumor systems.

4. Discussion

4.1. Reframing Genomic Instability Through a Longitudinal Host-State Lens

The framework proposed here invites a broader reinterpretation of genomic instability in oncology—not solely as a tumor-intrinsic molecular phenomenon but also as a dynamic process potentially influenced by the evolving physiologic environments in which tumor cells emerge, adapt, and evolve over time [3]. Contemporary cancer models have largely

emphasized tumor-centered mechanisms, including mutational burden, clonal selection, oncogenic signaling pathways, and immune evasion. While these processes remain fundamental, they occur within host physiological systems that regulate inflammatory tone, nutrient availability, oxidative stress buffering, repair fidelity, immune coordination, and adaptive resilience longitudinally across the disease trajectory [52].

Within the proposed host-transfer-state framework, host physiology is interpreted not as a static background condition but as a continuously evolving adaptive system governed by interacting biologic transfer functions. Gut microbial ecology, absorptive integrity, circadian organization, hydration status, stress burden, diet, and behavioral physiology may collectively shape how inflammatory signals, nutrients, environmental perturbations, and therapeutic pressures are biologically processed and assimilated over time. Under this interpretation, genomic instability may emerge not solely through autonomous mutational processes within tumor cells, but also through evolving host-state conditions that influence the biologic context in which genome maintenance operates.

Importantly, the framework does not propose that host-state physiology replaces tumor genomics as the primary driver of cancer evolution, nor does it imply that these interactions operate uniformly across all malignancies. Rather, it proposes that host physiological organization may function as a modifying systems layer capable of influencing the conditions under which mutagenesis, adaptive selection, inflammatory remodeling, and therapeutic resistance evolve longitudinally. In malignancies dominated by strong tumor-intrinsic mutational processes, host-state influence may be comparatively limited, whereas in cancers characterized by chronic inflammation, oxidative stress burden, microbiome perturbation, or impaired repair fidelity, host physiologic dynamics may exert greater biologic relevance.

A central conceptual contribution of this framework is the interpretation of host-state dynamics through longitudinal trajectory reconstruction rather than isolated static assessment alone. Within this model, clinically observable disease states may represent delayed projections of deeper latent biologic dynamics evolving over time, as formalized in Section 3.

Similarly, the framework proposes that biologic response may depend not solely on therapeutic or nutritional input itself, but also on the evolving host transfer-state through which that input is biologically processed, as formalized in Section 3.

4.2. Synergy with Standard Cancer Therapies

We emphasize that host-directed modulation of the proposed host-transfer-state axis is conceived as strictly complementary to established tumor-directed therapies rather than as a replacement for standard oncologic care. In principle, correcting documented micronutrient deficiencies, improving aspects of microbiome stability, restoring circadian organization, reducing chronic inflammatory burden, and improving physiologic resilience may influence treatment tolerance and tissue recovery within nonmalignant host systems during cytotoxic therapy, targeted therapy, immunotherapy, or radiation exposure [53,54].

However, substantial caution remains warranted. For example, high-dose antioxidant supplementation administered concurrently with cytotoxic therapies may theoretically attenuate oxidative mechanisms central to the efficacy of certain chemotherapeutic agents and radiation therapy [55]. Existing evidence regarding antioxidant co-administration remains heterogeneous, and the net effect on therapeutic index likely depends on tumor biology, treatment modality, timing, dose, and underlying host physiologic state. Consequently, indiscriminate supplementation strategies cannot be justified based on current evidence alone.

Early mechanistic and clinical studies suggest that selected host-directed interventions may reduce treatment-related toxicity or alter biologic markers associated with inflammatory burden and DNA damage in nonmalignant tissues [56]. Nevertheless, high-quality randomized evidence demonstrating improved oncologic outcomes remains limited, and the contexts in which such interventions may be beneficial, neutral, or harmful remain incompletely defined [57]. The proposed framework should therefore be interpreted as exploratory and investigational rather than prescriptive.

4.3. Validation and Translational Pathways

In our view, the most immediate translational application of this framework is prospective longitudinal evaluation rather than direct clinical implementation. Initial studies could investigate whether integrating host-state reconstruction alongside standard oncologic care meaningfully alters biologic trajectories associated with genomic instability, treatment tolerance, or therapeutic resistance.

A proposed translational pathway under this framework may involve sequential integration across five longitudinal domains (Figure 3):

1. **Host-State Reconstruction:** Multimodal characterization of baseline host physiology, including micronutrient status, microbiome composition, inflammatory signaling, circadian organization, hydration status, metabolic resilience, and behavioral physiology.
2. **Tumor-State Characterization:** Integration of tumor genomics, mutational signatures, treatment history, immune phenotype, and disease burden.
3. **Longitudinal Systems Monitoring:** Serial assessment of dynamic biologic endpoints, including circulating cell-free DNA measures of chromosomal instability [46,58], inflammatory biomarkers, metabolomic signatures, microbiome dynamics, physiologic state variables, and patient-reported outcomes.
4. **Trajectory Analysis:** Longitudinal interpretation of temporal relationships among host-state dynamics, therapeutic exposure, inflammatory burden, microbiome evolution, and adaptive tumor behavior.
5. **Prospective Biological Endpoint Evaluation:** Evaluation of whether targeted host-state interventions produce biologically measurable changes consistent with improved genome maintenance capacity, treatment tolerance, or delayed emergence of therapeutic resistance.

Conceptual schematic illustrating how evolving host physiology may modify therapeutic and environmental inputs and influence their clinical observability over time. The framework is anchored at clinically meaningful temporal reference points (T_0 – T_5), spanning pre-oncogenic instability through treatment response and resistance emergence. External inputs—including standard oncologic therapies, supportive interventions, nutrients, and lifestyle or environmental exposures—interact with a dynamic host transfer-state representing the composite longitudinal physiological condition of the individual. The model integrates interacting domains including gut microbial ecology, micronutrient physiology, inflammatory burden, circadian organization, immune coordination, hydration status, and metabolic resilience. It further distinguishes latent biologic dynamics from clinically observable states, emphasizing that changes in genome maintenance capacity, adaptive tumor behavior, treatment tolerance, and resistance may precede detectable clinical manifestations. The framework is presented as a conceptual architecture to support investigation of host-state dynamics and observability constraints in oncology rather than as a validated predictive model.

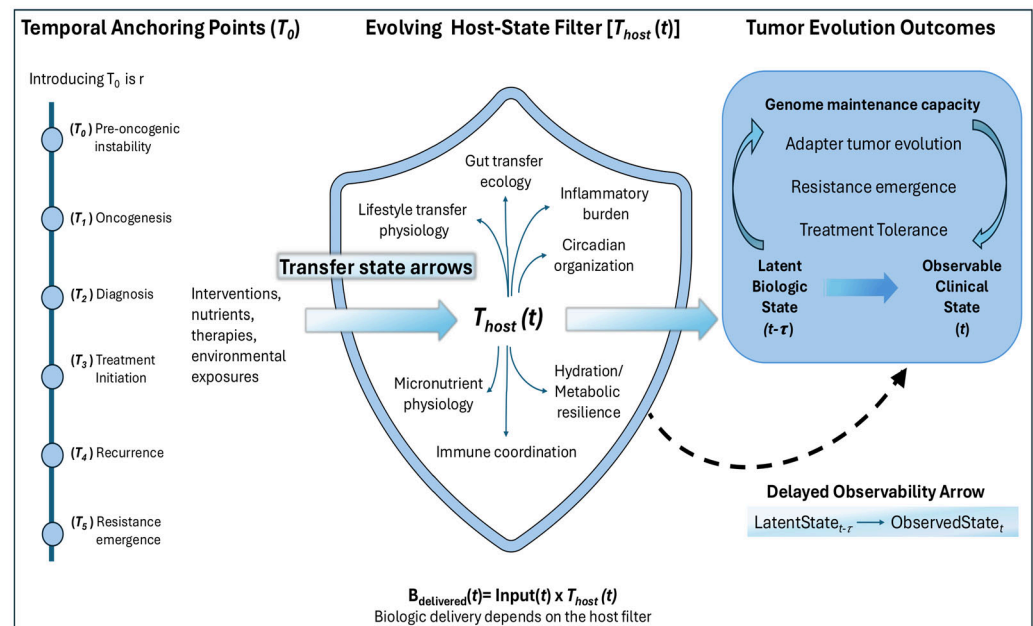


Figure 3. Longitudinal Host-State Observability and Transfer-State Architecture.

Under this architecture, computational systems are not intended to function as autonomous clinical decision-makers, but rather as structured analytical tools supporting longitudinal analysis, contextualization, and interpretation within partially observable adaptive systems.

As an illustrative example of how constrained longitudinal systems integration could be operationalized, a bounded computational workflow employing sequential extraction, validation, transformation, and analytical normalization steps could be used to integrate longitudinal clinical, physiologic, and treatment-related data under predefined evidence constraints within standard oncologic care pathways. Such an approach would be intended to support prospective longitudinal host-state reconstruction and biologic endpoint tracking in complementary oncology settings rather than to provide validation of the host-transfer-state framework proposed here. Any preliminary observations arising from such implementations should be regarded as exploratory and preliminary, would be constrained by small sample sizes and non-randomized designs, and would require rigorous prospective validation before any clinical inference could be drawn.

As an initial proof-of-concept population, patients with *BRCA*-mutated ovarian cancer receiving PARP inhibitors may represent a tractable translational cohort. In this setting, genomic instability constitutes a defined therapeutic target [8], treatment-related toxicity remains clinically significant [59], and resistance emergence is relatively predictable [60], potentially enabling longitudinal assessment of whether host-state modulation measurably alters biologic trajectories associated with treatment durability or adaptive resistance [46].

Importantly, such studies should not initially aim to demonstrate superiority over established therapies, but rather to determine whether incorporation of host-state dynamics meaningfully improves interpretation of biologic evolution, treatment tolerance, or resistance trajectories within complex host–tumor systems.

4.4. Challenges, Limitations, and Open Questions

Substantial conceptual, methodological, and translational challenges remain before host-directed longitudinal systems approaches can be responsibly integrated into oncology practice. Equitable access, longitudinal data capture burden, privacy protection, algorithmic

bias, interpretability of computational systems, regulatory oversight, and accountability within AI-assisted analytical environments all represent major considerations [51,61].

Biologic uncertainties remain similarly substantial. The temporal dynamics governing host-state modulation remain poorly characterized, including the speed at which microbiome composition, inflammatory signaling, micronutrient physiology, circadian organization, or metabolic resilience can be altered, as well as the lag interval required before downstream biologic effects on genome maintenance become clinically detectable [49]. The relative contribution of dysbiosis, inflammatory burden, oxidative stress, micronutrient insufficiency, behavioral physiology, and environmental exposures to genomic instability likely varies substantially across tumor types, treatment modalities, and individual patients, arguing strongly against uniform or one-size-fits-all approaches [3].

Importantly, the equations and systems abstractions presented in this framework are conceptual rather than validated predictive models. Their inclusion is intended to formalize the proposed host-transfer-state architecture and support structured hypothesis testing rather than to imply quantitative predictive certainty. At present, the framework remains exploratory and requires rigorous prospective validation.

4.5. Heterogeneity and Limitations of Current Evidence

The evidence supporting individual components of the proposed host-transfer-state framework remains heterogeneous, and several areas of direct contradiction warrant explicit acknowledgment. Regarding microbiome-directed interventions, observational studies consistently associate greater microbial diversity with improved immunotherapy outcomes [62], yet prospective microbiome manipulation trials have produced inconsistent results. Routy et al. demonstrated associations between gut microbiome composition and anti-PD-1 response across epithelial tumors [63], whereas subsequent fecal microbiota transplantation studies suggested that microbiome transfer alone may be insufficient to reverse resistance in the absence of adequate tumor immunogenicity [64]. More recent studies, including the PERFORM trial in metastatic renal cell carcinoma, have demonstrated feasibility and preliminary biologic signals, though oncologic efficacy endpoints remain preliminary [65].

Nutritional intervention studies similarly demonstrate mixed results. Meta-analyses suggest that nutritional support during chemoradiotherapy may reduce treatment-related toxicity, yet objective response improvements and survival advantages remain inconsistently demonstrated [56]. Furthermore, supplementation trials involving individual micronutrients have not reliably reproduced the protective associations suggested by epidemiologic observations. The SELECT trial demonstrated no reduction in prostate cancer incidence with selenium or vitamin E supplementation in nutritionally sufficient populations [30], while the CARET trial identified increased lung cancer incidence associated with high-dose beta-carotene supplementation in high-risk smokers [31]. These findings underscore the importance of distinguishing correction of documented physiologic deficiency from indiscriminate supplementation strategies.

Collectively, these inconsistencies likely reflect substantial biologic heterogeneity across tumor types, treatment contexts, baseline host physiology, microbiome composition, environmental exposure burden, intervention timing, dosing, and longitudinal adaptive dynamics. Most existing studies were not designed to evaluate the integrated mechanistic cascade proposed within the host-transfer-state framework, thereby limiting direct inference regarding causality [3].

Accordingly, the host-transfer-state framework should presently be understood as a structured conceptual architecture intended to organize existing biologic observations and support structured translational investigation into how evolving host physiology may

interact with tumor biology over time. It should not be interpreted as a validated clinical model or as evidence that host-directed interventions alone can meaningfully control cancer progression independent of established oncologic therapies.

5. Conclusions

This perspective proposes a longitudinal host-transfer-state framework that reframes genomic instability not solely as a tumor-intrinsic molecular phenomenon, but also as a process shaped by evolving host physiology. Its novelty lies not in linking microbiome, nutrition, inflammation, or stress to cancer individually, but in integrating these domains into a unified longitudinal systems architecture in which host physiology acts as a continuously evolving transfer-state, and in which clinically observable disease may represent a delayed projection of deeper latent biologic dynamics. Importantly, the framework does not propose that host-state physiology supersedes tumor genomics or replaces established therapies; rather, host-directed interventions are conceived as complementary, exploring whether stabilizing host physiologic organization can influence the biologic environments in which tumors evolve. Constrained AI-assisted analysis and longitudinal multi-omic integration are envisioned as bounded tools for longitudinal analysis, contextualization, and interpretation, not autonomous clinical decision-making.

Substantial uncertainty remains regarding the causal significance, temporal dynamics, tumor-specific applicability, and translational feasibility of the proposed mechanisms, and the framework should be regarded as exploratory and hypothesis-generating rather than clinically validated. Rigorous prospective longitudinal studies will be required to determine whether incorporating evolving host physiology meaningfully improves understanding of genomic instability and therapeutic resistance. Nevertheless, by extending precision oncology beyond isolated tumor genomics toward systems-level interpretation of host–tumor interactions, this framework offers a structured basis for generating testable longitudinal research questions on host-state dynamics rather than providing a validated model of cancer causation or treatment response.

6. Patents

A provisional patent application (35 U.S.C. §111(b)) titled ‘Systems and Methods for AI-Driven Host Modulation in Cancer Care Using Multi-Layer Modeling, Machine Learning Models, Digital Twin Dynamics, and Adaptive Therapeutic Orchestration’ was filed on 26 January 2026 by R.H.O. (BTBC Oncologic, Inc., Crawfordsville, IN 47933, USA).

Author Contributions: Conceptualization, R.H.O.; Writing—Original Draft Preparation, R.H.O. and S.R.; Writing—Review and Editing, R.H.O. and S.R.; Visualization, R.H.O. and S.R. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: R.H.O. is the founder and holds equity in BTBC Oncologic, Inc., a pre-revenue company developing AI-guided host modulation systems, and is the inventor of a provisional patent application (filed 26 January 2026) related to AI-driven host modulation in cancer care. The concepts presented in this perspective remain at the conceptual and investigational stage. S.R. declares no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AI	Artificial intelligence
APOBEC	Apolipoprotein B mRNA-editing enzyme catalytic polypeptide
BER	Base excision repair
BRCA	Breast cancer gene
cfDNA	Circulating cell-free DNA
COSMIC	Catalogue of Somatic Mutations in Cancer
DSB	DNA double-strand break
EHR	Electronic health record
FMT	Fecal microbiota transplantation
GPx	Glutathione peroxidase
HIPAA	Health Insurance Portability and Accountability Act
iNOS	Inducible nitric oxide synthase
ML	Machine learning
NADPH	Nicotinamide adenine dinucleotide phosphate
NER	Nucleotide excision repair
NF- κ B	Nuclear factor kappa B
PARP	Poly (ADP-ribose) polymerase
PERFORM	Preventing Toxicity in Renal Cancer Patients Treated with Immunotherapy Using Fecal Microbiota Transplantation
PROMs	Patient-reported outcome measures
QALYs	Quality-adjusted life years
ROS	Reactive oxygen species
SCFA	Short-chain fatty acid
TrxR	Thioredoxin reductase
VDR	Vitamin D receptor
XPA	Xeroderma pigmentosum complementation group A

Appendix A. Definitions of Key Terms

Genomic instability. An increased tendency of the genome to acquire alterations—including point mutations, small insertions and deletions, copy-number changes, chromosomal rearrangements, and aneuploidy—arising from elevated rates of DNA damage and/or deficient DNA repair, replication, and checkpoint surveillance. It is typically quantified through mutational burden, chromosomal instability metrics, or microsatellite instability, and is regarded as an enabling characteristic of cancer.

Genomic plasticity. The capacity of a tumor cell population to tolerate, regulate, and exploit genomic change so as to generate heritable genetic and epigenetic diversity that supports adapting to selective pressures such as therapy. Whereas genomic instability denotes the underlying propensity to accumulate genomic alterations, genomic plasticity emphasizes the adaptive use of that variation to produce phenotypic flexibility and clonal evolution.

Overlap between the two terms. The concepts overlap because genomic instability frequently provides the substrate of heritable variation on which genomic plasticity operates; however, they are not synonymous. Instability refers primarily to the rate and type of genomic change, whereas plasticity refers to the functional and evolutionary consequences of that change. A tumor may, in principle, display high instability with limited adaptive plasticity, or harness comparatively modest instability with high plasticity.

Biological uncertainties. In this perspective, the term refers to aspects of the proposed host–tumor relationships that are not yet established with mechanistic or causal confidence. These include the direction and magnitude of causal effects of host-state variables on genome maintenance, the temporal dynamics and lag times between host modulation and

measurable biologic change, the degree to which findings generalize across tumor types and patient populations, and the extent to which observed associations reflect causation rather than confounding. These uncertainties define where prospective experimental validation is required before clinical inference can be drawn.

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