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Generative Artificial Intelligence as a Catalyst for Effective Cancer Treatments

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Abstract

Current standard of cancer care is supported by a continuously expanding set of therapeutic options becoming available to cancer patients such as KRAS inhibitors, third-generation tyrosine kinase inhibitors (e.g., osimertinib), new immunotherapy drugs (e.g., durvalumab), as well as adaptive and combination therapies involving chemotherapy, radiotherapy, immunotherapy and targeted therapy. Despite these advances, therapeutic resistance persists as an inevitable challenge to cancer cure. While combination therapy is a plausible strategy to thwart therapeutic resistance, further research is needed on rationalizing drug combinations. On the other hand, adaptive therapy is emerging as a sound strategy to counter the evolving nature of cancer and thwart or delay the onset of therapeutic resistance. Indeed, cancer is a nonlinear time-varying dynamical system whose treatment can be viewed as a problem of steering the disease to a desired end-state of cure or stable management based on monitored treatment response. The success of this strategy depends on accurate and reliable estimations/predictions of disease state and tumor growth dynamics. Therein lies the potential of generative artificial intelligence (GenAI) and its underlying large language models (LLMs) to leverage the accumulating big clinical, radiomic and molecular data about cancer patients and their treatments to power its learning and predictive capabilities towards assisting treatment decision-making. This perspective starts with examples of current therapeutic advances and a succinct overview of persisting challenges to the development of effective cancer treatments, followed by a broad survey of artificial intelligence (AI) applications in oncology and their varying degrees of clinical readiness. Given this context, cancer treatment is framed as a problem of controlling a nonlinear time-varying dynamical system, where data-driven GenAI learning and predictive capabilities would be instrumental in resolving the challenges of disease monitoring and controllability. The perspective shares insights about potential pathways to GenAI-assisted improvement of cancer treatments and discusses key challenges to its deployment in real-world clinical settings, including data curation, clinical validation, LLM hallucinations and ethical concerns. Ultimately, advancing noninvasive tracking of treatment response dynamics and curating corresponding big LLM training datasets are essential to the potential of GenAI as a catalyst for effective cancer treatments.

Keywords: Generative artificial intelligence; Cancer treatment; Clinical decision support systems; Personalized treatment; Rapid learning decision-support systems; Adaptive cancer therapy; Large language models; Dynamic treatment scheduling; Precision oncology; Cancer therapeutic resistance

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Introduction

Significant advances have been achieved in expanding cancer armamentarium with newly approved targeted therapy, immunotherapy and combination therapy drugs. For instance, combining trastuzumab with chemotherapy is now standard of care for metastatic and early stage human epidermal growth factor receptor 2 (HER2)+ breast cancer [1]. The recent Food and Drug Administration (FDA) approval of KRAS inhibitors sotorasib and adagrasib for *KRAS*-G12C mutated non-small cell lung cancer (NSCLC) patients opens avenues for combination therapies involving chemotherapy and immunotherapy [2]. Likewise, trastuzumab deruxtecan (T-DXd), which was recently approved for any HER2-expressing solid tumor [3, 4], is under evaluation in combination with durvalumab for advanced or metastatic NSCLC [5]. Although combination therapy is a mainstay of standard of care and an essential strategy to thwart the emergence of resistance, often, however, it is not clear which patient would respond to which drug and what combinations of drugs and doses will improve patient outcomes and maintain their effectiveness throughout the course of treatments. These challenges are rooted in the adaptive complexity of cancer [6-10] driven by its genetic [11-16], immunological [17-21] and eco-evolutionary [22-26] dimensions. The evolving nature of cancer, the lack of effective biomarkers, the limited number of available patients compared to the number of possible drug combinations, the cumulative toxicity of drug combinations, and the lack of effective techniques for continuous and accurate monitoring of treatment response are critical barriers to the development of effective cancer treatments that can decisively thwart therapeutic resistance and improve overall survival and quality of life (QoL). On the other hand, the success of generative artificial intelligence (GenAI) and its underlying large language models (LLMs) and expanding application space [27-30] compel the application of their learning capabilities to the accumulating molecular, clinical

and radiomic data about cancer patients towards decisive improvement of cancer treatments [31-34]. In oncology, leveraging GenAI's potential towards more effective clinical-decision making is garnishing increased research efforts [35-39], which are aligned with pre-GenAI initiated research [40-47] regarding issues that are inherent to deep-learning-based artificial intelligence (AI) systems, including data, ethics, transparency, explainability, accountability, privacy, ethics, and deployment in real-world clinical settings. In addition, the use of GenAI requires the mitigation of LLM hallucinations and the availability of large datasets and adequate computing infrastructure to carry out training and fine-tuning of LLMs. Fundamentally, however, the application of GenAI to assist treatment decision-making rests on the assumptions that cancer state dynamics can be estimated from treatment response observations, and that disease state can, at will, be steered using clinically feasible treatments, *vis-a-vis* toxicity, to a desired curative or managed end-state. Satisfying these assumptions in practice faces challenges caused by cancer complexities (e.g., evolving spatiotemporal heterogeneity of tumors, cancer immunoediting, and phenotypic plasticity) and by the scarcity of effective treatment response biomarkers and their degrees of faithful sampling of disease state.

The proposed perspective frames cancer treatment as an adaptive control problem and argues that GenAI data-driven learning and predictive capabilities hold the potential for addressing the challenges of estimating/predicting disease state and tumor growth dynamics, which would make it critically instrumental to the realization and clinical adoption of adaptive cancer therapy. The article starts with an overview of AI applications in oncology, followed by an elaboration on the nature of cancer treatment as a problem of controlling nonlinear dynamical systems. The subsequent section argues the utility of GenAI as a potential catalyst for effective cancer treatments and addresses elements that are critical to its clinical realization. Key real-world clinical issues are highlighted in the discussion section emphasizing that affording them adequate attention would be essential to facilitating the exploitation of LLM learning and predictive capabilities towards improved cancer treatments, and in particular the thwarting of therapeutic resistance.

AI in Oncology

The advent of AI in oncology is driven by its learning and inferencing capabilities which are harnessed from the increasingly large clinical, molecular and radiomic cancer datasets to assist in cancer diagnosis, prognosis and treatment decision-making. The growing and dynamic knowledge base being available about cancer and its treatments, combined with the expanding space of cancer therapeutics and the steadily growing number of diagnosis, prognosis and risk stratification biomarkers being validated, are providing the impetus for an ever-growing exploration of AI and machine learning (ML) applications in oncology [35-56]. These research efforts are matched with a growing list of AI/ML software as medical devices (SaMDs) approved by the FDA for oncology [57]. By the end of 2024, there were 1,016 AI/ML devices that met FDA pre-market requirements, spanning 17 categories of medical applications. More than 76% of approved AI/ML devices are dedicated to radiology while cardiovascular and neurology have 10% and 4% shares, respectively, leaving a combined slice of about 10% for the remaining categories, which include gastroenterology-urology (1.3%) and pathology (about 0.3%). Three notable examples of approved AI/ML SaMDs for cancer diagnosis are the Transpara™ system for mammography, the GI Genius™ for colonoscopy and Paige Prostate Alpha for whole slide images (WSIs). Transpara™ uses a deep learning (DL) model to provide a breast cancer likelihood score from 1 (low risk) to 10 (high risk) [58], while GI Genius™ relies on convolutional neural networks (CNNs) to support lesion detection during colonoscopy for colorectal cancer (CRC) screening or surveillance [59, 60]. On the other hand, Paige Prostate Alpha exploits CNNs and recurrent neural networks (RNNs) to detect prostate cancer and points to areas where the detection is made with high probability [61]. It is also worth noting that, when supported with Paige Prostate Alpha, pathologists' classifications of low-grade prostate cancer are more likely to be correct [61]. Aside from cancer diagnosis applications where AI use is steadily progressing, AI-driven risk stratification and prognostication are attracting increased research attention [43, 45-47, 62-69]. A similar research trend is underway for the use of AI and GenAI in treatment selection and recommendations [38, 42, 70-75]. However, the path to clinical translation of AI-assisted treatment decision-making approaches has been particularly challenging, with a noticeable lack of prospective studies - save for a few exceptions, such as the clinical integration undertaken by McIntosh et al on ML-driven planning of radiotherapy for prostate cancer patients [42]. Among the most vexing challenges to clinical translation is the "black box" nature of AI systems, which leads to an opacity that exacerbates the challenges associated with an already complex and multifactorial clinical decision-making process [76-78]. Adding to the "black box" concern, there is a myriad of hurdles to the undertaking of prospective studies that are rooted in the complexities inherent to the dynamic nature of data-driven AI systems and their performance drift in time and across patient populations, as well as in the possibility that traditional designs of randomized control trials (RCTs) may be ill-suited to evaluate such complexities [79]. Other barriers are born out of other concerns such as the "dataset shift" and the need for its governance [80], non-universal generalizability of AI benefits and their dependence on the clinical context of their deployment, and the disconnect between AI evaluation metrics and their clinical applicability [81]. Cultural and regulatory challenges are equally significant and include the reticence of clinicians towards the use of AI in clinical decision-making [82], and the complexity of navigation through the regulatory system, including institutional research boards (IRBs). Nevertheless, there is a mounting research interest in the application of GenAI in oncology [32, 36-39, 83-85], as well as an increasing number of interventional and observational studies that are either planned or ongoing (e.g., NCT04675138, NCT05681949, NCT06986564, NCT07045207), where measures of concordance between treatment recommendations of clinicians versus that of GenAI represent recurrent primary outcomes for

a significant portion of these studies. The focus on treatment recommendations is presumed to be an attempt to leverage the medical knowledge embedded in off-the-shelf LLMs such as ChatGPT [36]. Evaluations of these models yielded mixed results in terms of performances and limitations with respect to their potential use in real-world clinical settings [35, 85-88], highlighting the limits of general-purpose LLMs. These limitations may be overcome through the use of dedicated LLMs, whose trainings are confined to the oncology knowledge base, with the expectation that such customization would yield more robust LLM learning and predictive capabilities to assist in clinical decision-making for oncology.

Fundamentally, Cancer Treatment Is a Control Problem

The different cancer therapeutic modalities in use, whether systemic or targeted, are developed with the presumption that cure and disease management are realizable through actions on one or more of the driver dimensions of cancer (i.e., genetic, immunological and eco-evolutionary). Significant cancer treatment advances have been achieved whereby combination and adaptive therapies are emerging as critical components of effective cancer treatments. On the other hand, there are persisting barriers to the development of cancer therapies that can deliver long-term disease management or cure, including the hurdles facing the search for effective drug combinations, the cumulative toxicity of combination therapy, and the challenges of predicting tumor growth evolutionary dynamics to support adaptive therapy. Fundamentally, cancer treatment is a control problem [89], where the objective is to manage or cure the disease by adapting drug combinations and dosage based on real-time feedback provided by repeated monitoring of treatment response while limiting toxicity. The coupled working of genetic dysregulation of cell signaling and metabolic pathways, immune system defenses, and eco-evolutionary pressures, shape tumor growth dynamics under therapeutic intervention and make it highly unlikely for therapeutic strategies to achieve long-term disease management without an integrated accounting of these drivers of cancer adaptive complexity. This is strongly illustrated by the persistence of unmet needs of cancer patients despite the availability of an impressive number of cancer drugs, often developed to address one lever of cancer control (e.g., tyrosine kinase inhibitors, PARP inhibitors, immune checkpoint inhibitors, etc.). While further advances in deciphering the biology of cancer and its response to treatments are needed, such advances should be recast into computational models and supported by mathematical abstractions that enable an integrated consideration of the various dimensions underlying treatment response dynamics. One such abstraction is the view of tumors as time-varying nonlinear dynamical systems, where drug doses and treatment response are their input and output, respectively, while tumor clonal composition represents disease state [89]. Cancer treatment can then be formulated as the problem of controlling a nonlinear dynamical system [89-92], where the timing and doses of administrated drugs are adapted based on real-time treatment response monitoring with the objective of steering the disease to a desirable end-state. This typically involves treatment adaptation schemes that are informed by mathematical and computational models of the system under control, i.e., the tumor, and are fed by real-time disease state feedback [90-92]. Mathematical models of tumors embody conceptual and descriptive perspectives rooted in assumptions inspired by insights into possible determinants of cancer dynamics such as evolutionary competition [93]. Among these, models that are used to support adaptive control capture the behavior of cancer under treatment in the form of disease state trajectories, which can be steered through a series of controls towards a desired end-state. While this formulation provides an actionable mathematical representation of cancer's nonlinear dynamics, it has challenges regarding the questions of system observability and controllability [94-98]. The system, i.e., the tumor in this case, would be fully observable if all disease states (i.e., clonal frequencies) can be uniquely determined from observations of treatment response. Partial observability would apply if some, but not all disease states can be determined from treatment responses. While theoretical results on the analysis of nonlinear system observability [99-101] may be used to assess the observability of tumor dynamics, it is not clear whether such assessment would yield clinically useful insight, given the reductionist assumptions that would have to be made about tumor growth dynamics to undertake the analysis. A more practical approach to the assertion of system observability would be to identify biomarker panels of treatment response that are established to be strongly correlated with disease state. An example of concrete steps to support this approach would be to accelerate undergoing efforts in establishing the utility of circulating tumor DNA (ctDNA) and developing optimal protocols of its use (e.g., optimal timepoints of liquid biopsy sampling) in the detection of resistance, specific genomic alterations, and minimum residual disease [102], as well as advancing its use in the prediction of treatment outcomes [103]. Controllability on the other hand is about the responsiveness of the system, i.e., the ability to steer it from one state to another. There are no general results for the controllability of nonlinear systems [95, 104]. However, conditions for small-time local controllability (STLC) have been worked out whereby the system can be dragged using admissible controls, in an arbitrarily small time, from any initial state to an end-state in a neighborhood that includes the initial state [105]. Here too, theoretical analysis of controllability based on mathematical models born out of simplifying assumptions on tumor growth dynamics may not yield significantly useful clinical insight on the controllability of the disease. Nevertheless, the theoretical results on STLC may be pragmatically applied by planning the desired state trajectory of the disease to be a sequence of desired disease states such that each next state can be reached in an arbitrarily small time using a small control (i.e., low drug doses), which causes a small perturbation of the tumor to keep its state within the neighborhood of the previous state. Although observability, controllability and reachability, which concerns the reachability of a system state starting from another state [96], may not be easily assessed for complex systems such as cancer, they, nevertheless, provide a theoretical reference for the choices of treatment response biomarkers, estimation models of disease

states, and the treatment planning and adaptation schemes that are more likely to be effective in achieving a decisive management or cure of cancer.

Why GenAI Is a Potential Catalyst for Effective Cancer Treatments?

Current standard of cancer care involves the planning of fixed treatment schedules, where treatment cycles are carried out to their completion unless interrupted by events such as severe toxicity, infection or other complications. Treatment planning would in general be based on risk stratification and prognosis biomarkers, in addition to drawing on past experiences with similar cases and applicable institutional and community guidelines. Treatments are usually adjusted based on clinical guidelines and clinician's experience in a reactive approach to treatment response. This entails ceding the oncologist's initial advantage to cancer's evolutionary dynamics to drive disease progression, which more often than not leads to therapeutic resistance, metastasis and death. These evolutionary dynamics are ultimately fed by the loss of cellular homeostasis, which relies on the cell signaling network to successfully orchestrate cellular activities and processes (e.g., growth, proliferation, survival, apoptosis and metabolism) and to regulate both intercellular and intra-cellular communications. Deregulated cellular functions ensue from genetic and epigenetic alterations and their evolving diversity, which underlie carcinogenesis and the successive acquisition of cancer hallmark capabilities [11-15]. These alterations affect canonical pathways such as cell growth, the cell cycle, and apoptosis [106], as well as reprogram metabolism [107], consequently enabling the survival and proliferation of cancer cells through the activation of oncogenic pathways and the abrogation of tumor suppression functions. Although targeted therapy has yielded significant clinical success in the treatment of cancer, it is often rendered ineffective by the evolving nature of cancer. For instance, a study on mutational burden in CRC reveals that at diagnosis, every DNA locus has a mutation in at least one cancer cell [108]. This deep reservoir of genetic aberrations combined with eco-evolutionary pressures on cancer cells under treatment feed tumor heterogeneity and phenotypic plasticity, leading, ultimately, to the emergence of therapeutic resistance. Furthermore, tumors are metabolically heterogenous and flexible, with evolving metabolic vulnerabilities that are challenging to target, providing metabolic avenues for therapeutic resistance [107]. This has led to the rise of combination therapy as an essential component of standard of care, whereby concurrent and/or sequential combinations of drugs are used to mitigate therapeutic resistance [109]. Although accelerated translational efforts are ongoing to leverage combination therapy, as illustrated by the thousands of ongoing clinical trials, this treatment paradigm needs further research on rationalizing drug combinations, as it is not feasible to study the near-infinite possible combinations of available drugs [110-115]. Furthermore, in order to achieve a desirable efficacy while limiting additive toxicity, scheduling combinations of drugs and their doses need to be optimized [115-119]. While combination therapy is a mainstay of current cancer treatments, the evolving nature of cancer has primed the rise of adaptive therapy as a treatment strategy conceived to thwart therapeutic resistance through treatment modulation based on monitored treatment response [89, 120-128], with the guidance of mathematical modeling [129-132]. Compared to fixed-schedule treatments, adaptive therapy provides potential advantages *vis-a-vis* treatment personalization, toxicity, and resistance management [39]. This is aligned with the gain in momentum for adaptive therapy, whereby increasing number of clinical trials are either planned or ongoing for various cancers, including melanoma, prostate and ovarian cancers [125, 126, 133, 134]. The joining of adaptive and combination therapies is a natural next step to leverage the expanding set of drug options becoming available to patients towards more effective treatments. In this respect, game theoretic mathematical models have been explored to design multi-drug adaptive therapy that mitigates therapeutic resistance through an appropriate timing of the switch between possible treatments (e.g., one drug, a drug combination or no treatment) based on the monitoring of tumor clonal composition [123]. Combination therapy involving adaptive switching between chemotherapy, immunotherapy and targeted therapy based on the repeated monitoring of tumor entropy has also been explored under the assumption that cell adaptive fitness imposes constraints on the possible trajectories of tumor growth [89, 135, 136]. One example clinical trial of adaptive combination therapy is the adaptive androgen deprivation therapy for metastatic castration sensitive prostate cancer (mCSPC) [126]. In this case, the adaptation heuristic for treatment stopping/resumption and the selective administration of new hormonal agent (NHA), luteinizing hormone releasing hormone (LHRH) or a combination thereof is based on repeatedly monitored prostate specific antigen (PSA) and testosterone levels, as well as imaging progression [126]. There are at least two fundamental challenges that need to be overcome in order to realize the full potential of adaptive therapy in delivering decisive cancer treatments. First, progress is needed regarding the discovery and validation of treatment response biomarkers that could provide an accurate observation of disease evolutionary dynamics. Second, robust and faithful reconstructions of the trajectories of cancer evolutionary dynamics using treatment response biomarkers is imperative to the synthesis of effective therapy adaptation strategies. GenAI holds a formidable potential to address these and other challenges by learning the relationships between the various dimensions of cancer complexity from clinical, pre-clinical and experimental studies on the treatment of cancer (Table 1) [39, 80, 121, 123, 126, 127, 128, 133, 137, 138]. This would facilitate the design of effective treatments by providing data-driven treatment response predictions and by assisting in the planning and adaptation of treatments [39]. In particular, GenAI can assist oncologists to overcome the information processing bottleneck associated with the limitations of human cognitive capacity [139], which arise when tackling high-dimensional, multivariate and complex treatment decision-making problems. These problems involve the consideration of a significantly large number of variables, including treatment response, toxicity, therapeutic options, past treatments, patient wishes, comorbidity and age, as well as financial and healthcare delivery environment's constraints. The

Table 1. GenAI as a Catalyst for Effective Cancer Treatments

Capabilities of LLMs	Potential support for effective cancer treatments
Foundational models for rapid learning from big multimodal data	LLMs can translate big multimodal data about cancer and its treatments into learned models (e.g., treatment response models) that can be used as decision-support tools for clinicians and tumor boards [137].
High-dimensional reasoning capacity	LLMs have the potential to make timely recommendations of patient-tailored, optimized treatment schedules based on a comprehensive consideration of molecular, clinical radiomic and demographic variables in light of a dynamic space of available therapies [137, 138].
Open to continuous learning through retraining and fine-tuning	Trained LLMs can be integrated to support adaptive therapy by providing real-time disease state estimation and treatment planning based on treatment response monitoring [39]. GenAI would enable a more accurate tracking of disease state dynamics, enhancing as a result the benefits of adaptive therapy, which include: 1) lower treatment toxicity [127, 128, 133]; 2) resistance management [121, 123, 126]; 3) treatment personalization [39].
	LLMs can be periodically retrained or fine-tuned to account for the dataset shift [80], hence maintaining their optimal utility to the treatment of the target patient population.

GenAI: generative artificial intelligence; LLMs: large language models.

potential role of AI in this respect is also particularly pertinent to maintaining the efficacy of multidisciplinary tumor boards (MTBs) in providing timely, optimized and comprehensive treatment plans based on the analysis of big multimodal clinical, molecular and radiomic data, in the face of increasing patient caseload [137]. Indeed, while facing reliability challenges in their present forms, LLMs could be moderately helpful as decision-support tools for MTBs [138].

For an explicit consideration of cancer evolutionary dynamics, disease state can be defined as the vector of tumor clonal frequencies, which may not be directly measurable and would have to be estimated from repeated sampling of treatment response biomarkers. These biomarkers may include imaging data, as well as relevant genetic, immunological and eco-evolutionary biomarkers that are clinically validated to reflect disease state for the cancer type at hand [140]. Although biomarker panels have been compiled for different cancer types [141, 142], further studies are needed to identify minimal sets of biomarkers, by cancer type, that are sufficient to recover disease states. For example, the combination of PSA and testosterone has been shown to be clinically feasible as a proxy for tumor burden to guide adaptive androgen depravation therapy of mCSPC [126]. However, these need to be complemented with additional biomarkers that carry information about the changing genetic alterations of cancer cells, the tumor microenvironment and immune response so as to enable a satisfactory observability of disease state variables, i.e., tumor clonal frequencies. Future advances in imaging [143], liquid biopsy (LB) [144, 145] and next-generation sequencing (NGS) techniques hold the promise for accurate and robust tracking of the evolving genotypic and phenotypic diversity of tumors.

The framing of cancer treatment as an adaptive control problem opens avenues for the use of multiple possible adaptive strategies [89]. One commonly used system control strategy is the classical proportional-integral-derivative (PID) controller [146-148]. Given the errors between desired and current disease states, PID feedback control is based on the contributions of the current error (proportional term), the average of past errors (integral term) and future errors (derivative term) to the control signal [146]. The relative contributions of these terms to control actions (i.e., doses of administered drugs) are specified using tunable gains. This simple and transparent construction, and the consequent ease of use do undoubtedly support the fact that PID control is the most widely used industrial control strategy [148]. The state-feedback nature of this strategy relies on the estimation of disease states from real-time repeated monitoring of treatment response. Extensive explorations have been undertaken on the applicability of LLMs' learning and predictive capabilities to the estimation of disease states based on treatment response monitoring [37-39]. Both mathematical foundations of DL, which underlies LLMs, and technological advances in LB, imaging, and NGS for treatment response monitoring support the practical feasibility of LLM-based tracking of disease state dynamics [39]. However, its clinical feasibility will largely depend on the availability of large quality clinical datasets for training and regular fine-tuning of these dedicated LLMs [39]. The other aspect critical to the design of PID control strategies involves the tuning of PID gains to achieve a desired performance [146, 149]. Tuning approaches such as Ziegler-Nichols [146, 150, 151] methods, which involve probing the system using a step response or eliciting system oscillations, may not be feasible for cancer therapy due to the potential for severe toxicity and the long timescale of treatment response dynamics. While the adoption of PID control as the treatment adaptation strategy of choice is well supported by its proven performance, it is more intuitive, in the context of cancer therapy, that such adaptation be undertaken based on learned patterns from past effective treatments of phenotypically similar patients. The data-driven learning capabilities of GenAI could be leveraged for such purpose through the training of LLMs to generate self-tuned PID controls, which are driven by error signals between desired and observed disease states, within the context of past controls and control errors. The training of LLMs to generate controls that reflect PID control strategies require large quality training datasets, which is undeniably challenging. However, it is expected that in the long run the curation of quality treatment data for LLM training would be feasible, at least within the private confines of healthcare institutions, where the trained GenAI models are to be used to support the optimization of

cancer treatments. One approach that would significantly reduce the need for large clinical datasets is to leverage transfer learning [152-154] by training LLMs on synthetically generated datasets associated with PID controls of clinically validated mathematical models of tumor evolutionary dynamics, followed by fine-tuning of the generative models using treatment data collected from patients that are phenotypically similar to the class of patients under treatment. However, while the often-tailored foci of mathematical tumor models on singular aspects (e.g., clonal dynamics, angiogenesis, and drug resistance) may represent a valuable source of synthetic training data, patient-derived xenografts (PDXs) are, aside from actual patients, the most pertinent sources of training data as will be discussed in the next section.

Discussion

The mathematically asserted property of deep neural network as universal approximators of nonlinear systems [155-158] is the cornerstone of LLM applicability to the modeling and prediction of cancer evolutionary dynamics. The practical feasibility of GenAI and their underlying LLMs as estimators of disease state dynamics and as learning models that can assist treatment decision-making is supported by deeply rooted results from research on the modeling of biological complexity [159], digital twins [160, 161], and rapid-learning healthcare [162-164]. In fact, LLMs are natural extensions and points of convergence of these approaches while being distinguished by their unique nature as standard general-purpose learning systems with a DL architecture that can be systematically trained using multimodal data to perform nearly all tasks relevant to cancer care, including diagnosis, prognostication and treatment decision-making [31, 32]. Despite the versatility of GenAI's learning and reasoning capabilities in recasting an increasingly growing cancer data into actionable knowledge that could revolutionize cancer treatments, clinical translation and adoption of this technology face the challenges of training data availability, clinical evaluation, regulatory hurdles, and a host of ethical concerns, including bias, privacy, transparency, explainability and accountability [165-167]. Mitigating these concerns would need the development of bioethical frameworks for the responsible use of LLMs [167]. Principles of medical ethics such as beneficence, nonmaleficence, autonomy and justice have been proposed as possible pillars for frameworks of responsible LLM use in medicine [167]. These may guide the mitigation of the wide spectrum of ethical concerns from accountability to bias and transparency through specific actions such as using training data that represent the target patient population, tailoring predictions to specific groups of patients and flagging corresponding uncertainties [168], establishing AI governance committees to mitigate the dataset shift [80], and using human-in-the loop strategies as a guard rail against nonsensical output [169]. These mitigation approaches would inevitably need to be supported by advances in methods and techniques such as visualization, input feature importance, and counterfactual explanations, to improve the interpretability and explainability of GenAI black box models [170]. LLM hallucinations [171], i.e., generation of factually implausible outputs, and corresponding issues of reliability represent another concern, which has been the subject of various mitigation approaches, such as the use of retrieval-augmented generation (RAG) [172, 173]. Beyond the above discussed challenges, the integration of LLMs in real-world clinical settings will require judicious considerations of computational cost and the availability of technical expertise and resources [174].

GenAI training data may be sourced from patient treatments, clinical studies, PDXs, and clinically validated mathematical models. Although mathematical models of tumor growth represent a versatile approach to the generation of synthetic data, they are limited by their underlying assumptions and may not represent the biological complexity of tumors. Indeed, such models are often constructed for specific foci and under specific assumptions regarding various cancer aspects, such as genetic alterations, cancer metabolism, dysregulated signaling, cancer-immune cells' interactions, and tumor physical properties, limiting as a result their capacity to yield a systematic span of cancer state dynamics. A more pertinent approach would be the use of PDX models to curate training datasets. Indeed, PDXs are often used for pre-clinical studies of drug combinations and resistance given their preservation of determinant features of patient tumors [175-183], making them ideal systems for the generation of big quality training data that span different types of cancer, as well as cover an arbitrarily large spectrum of genetic and phenotypic diversity within each cancer type. Given the critical role of data in GenAI-assisted cancer treatments, efforts to curate PDX and patient treatment data would be best undertaken through a dedicated international consortium, such as the international cancer genome consortium (ICGC), which would yield more diverse patient datasets and help mitigate the potential bias of GenAI-assisted treatment decision-making.

The transparently simple construction of PID controllers and their ubiquitous use in industry [146, 148] justify their consideration as a suitable control strategy for real-world clinical settings of cancer treatments. However, adaptive feedback control theory offers a wide spectrum of control strategies, which can in principle be applied to adaptive cancer therapy, including approaches from the three major controller classes of gain scheduling, self-tuning regulators and model-reference adaptive controllers [90-92, 184]. PID control embodies a reference design against which the performance and suitability of other complex strategies in these classes can be gauged, and its consideration would hence be most appropriate as a first choice for the nascent paradigm of adaptive cancer therapy. Beyond the design transparency of PID controllers, self-tuning PID controls [185-187], with tuning algorithms informed by patient-tailored predictive models of disease dynamics, would also offer a versatile yet still transparent design to deal with tumor heterogeneity manifested as varying nonlinearities of tumor growth dynamics across patients and time.

RCTs remain the gold standard to demonstrate safety, reliability and effectiveness of clinical interventions. Unfortunately, there is a dearth of prospective clinical studies of AI systems in healthcare [81], which is aligned with a noticeable "AI Chasm" separating the development of AI systems and their deployment in real-world clinical settings [188]. RCT reporting guidelines such as CONSORT-AI [189], DECIDE-

AI [190] and SPIRIT-AI [191] have been introduced to help address this gap. These guidelines will inevitably inform the design of AI-assisted clinical studies by highlighting AI-related aspects that need attention. The persisting challenge of therapeutic resistance, the need to improve the QoL of cancer patients, and GenAI potential contribution to the mitigation of resource constraints, are likely to become prominent incentives for clinical institutions to engage in prospective studies of AI systems. However, this will require the engagement of pharmaceutical and AI companies, as well as the development of flexible, AI-pertinent regulatory approval guidelines of clinical interventions.

Conclusions

Despite the significant expansion of cancer therapeutic options, therapeutic resistance persists as a critical barrier to cancer long-term management and cure. Adaptive therapy, which may involve combination of multiple drugs, represent a plausible strategy to thwart or delay the onset of therapeutic resistance. Given the framing of cancer treatment as a control problem, data-driven GenAI learning and predictive capabilities have the potential to address the challenges facing the clinical realizability of adaptive therapy, including the accurate and reliable estimation of disease state and tumor growth dynamics. The realization of this potential is however contingent on the success of efforts aimed at curating large quality datasets for GenAI training and will require accelerated efforts of clinical evaluations supported by regulatory approval frameworks that must be flexible and considerate of AI unique challenges in real-world clinical settings.

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Conflict Interest

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Data Availability

The author declares that data supporting the findings of this study are available within the article.

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