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Game Theoretical AI for Precision Medicine

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How To Cite: Guo, S.; Wu, D. Game Theoretical AI for Precision Medicine. *Transactions on Artificial Intelligence* **2025**, *1*(1), 170–196. https://doi.org/10.53941/tai.2025.100011

Received: 2 July 2025
Revised: 11 August 2025
Accepted: 19 August 2025
Published: 29 August 2025

Abstract: Current clinical decision-making relies heavily on doctors' experience, often leading to generic treatments that overlook individual patient factors. A lack of clinical expertise, especially in resource-limited regions, hinders optimal decisions and contributes to higher patient mortality. To address this, traditional AI systems have modeled clinical decision-making as a predator-prey game. However, such approaches fail to recognize that disease agents, such as cancer cells, can exhibit adaptive, human-like intelligence. Immunological studies reveal that malignant tumors evade the immune system through camouflage, coercion, and cytoprotection. To counter these adaptive strategies, game-theoretic approaches are essential. In this paper, we present Game Theoretical AI (GTAI)—a novel approach that formalizes and automates strategic reasoning to enhance clinical decision-making against complex diseases. Inspired by Sun Tzu's *The Art of War* and the Thirty-Six Stratagems, GTAI mimics expert clinical reasoning through four stages: (1) observation and diagnosis, (2) treatment planning, (3) execution, and (4) outcome evaluation. Within this framework, GTAI can dynamically select and carry out high-level tactics analogous to humans' stratagems at each decision stage. This unified approach yields six major discoveries that bridge theory and practice. Collectively, these advances demonstrate the power of integrating strategic intelligence with computational models, opening new avenues for the application of AI in precision medicine and adaptive clinical practice.

Keywords: game-theoretic AI (GTAI); adaptive clinical decision-making; precision medicine strategies

1. Introduction

Clinical decision-making remains one of the most complex challenges in healthcare, requiring physicians to integrate vast amounts of patient data, medical knowledge, and experiential wisdom to formulate effective treatment strategies. Despite advances in medical technology and evidence-based medicine, clinical outcomes continue to vary significantly based on physician expertise, geographic location, and resource availability [1]. This variability is particularly pronounced in resource-limited settings, where the scarcity of experienced clinicians directly correlates with increased patient mortality and morbidity [2].

The advent of artificial intelligence (AI) in healthcare promised to democratize access to expert-level clinical decision-making. Traditional AI approaches have modeled the clinical encounter as a relatively straightforward optimization problem, often employing predator-prey dynamics to represent the interaction between treatment strategies and disease progression [3]. However, these models fundamentally mischaracterize the nature of many diseases, particularly cancer, by treating them as passive targets rather than adaptive adversaries.

Recent advances in tumor immunology have revealed that cancer cells exhibit sophisticated evasion strategies, indicating that cancer cells are intelligent. Malignant cells employ camouflage to avoid immune detection, coerce surrounding healthy cells to support tumor growth, and develop cytoprotection to resist therapeutic interventions [4]. This adaptive intelligence of cancer cells suggests that effective clinical decision-making requires not just optimization

but strategic thinking that anticipates and outwits the disease's evolving tactics.

Game theory provides a natural framework for modeling strategic interactions between intelligent agents [5,6]. While game-theoretic approaches have been applied to various medical scenarios, existing implementations typically assume static or minimally adaptive disease models [7]. This limitation becomes critical when confronting diseases that exhibit learning-like behavior and strategic adaptation. To address this, traditional AI systems have often modeled clinical decision-making as a predator-prey game. However, such formulations overlook the fact that disease agents, such as cancer cells, can display adaptive human-like intelligence. For example, immunological studies have demonstrated that malignant tumors evade immune surveillance through sophisticated tactics including camouflage, coercion, and cytoprotection. Effectively combating these adaptive disease strategies requires an explicit strategic and game-theoretic approach.

The dynamic interaction between clinicians and diseases closely parallels the timeless lessons found in classical military strategy. Sun Tzu's *The Art of War* and the Thirty-Six Stratagems emphasize principles such as anticipation, deception, and leveraging the opponent's weaknesses—tactics directly analogous to the challenges faced in modern medicine. Just as military commanders must contend with a cunning and evolving adversary, clinicians must anticipate and counteract the adaptive responses of diseases. Drawing from these classical texts provides not only a rich vocabulary of tactical options but also a mindset oriented toward flexibility, indirect action, and long-term strategic thinking. By infusing clinical reasoning with these ancient strategic insights, medical decision-making is elevated from a reactive process to a dynamic, adversarial game where both sides continually adapt.

In this paper, we introduce Game-Theoretical AI (GTAI), a novel computational approach that reconceptualizes clinical decision-making as a strategic interaction between two intelligent agents: the clinician (augmented by AI) and the disease. Our approach draws inspiration from Sun Tzu's *Art of War* [8] and the Thirty-Six Stratagems [9], translating military strategic principles into clinical contexts. This cross-disciplinary insight enables GTAI to systematically incorporate concepts such as deception, leverage, and escape into medical treatment planning, empowering clinicians to anticipate, outmaneuver, and adapt to the evolving strategies of diseases.

The GTAI framework operates through four interconnected stages that mirror expert clinical reasoning: (1) observation and diagnosis, where the system analyzes patient data to infer the disease's current state and strategic posture; (2) treatment planning, where multiple strategic options are evaluated considering the disease's likely adaptations; (3) execution, involving the implementation of chosen strategies with real-time monitoring; and (4) outcome evaluation, where results inform the system's evolving understanding of the disease's strategic behavior.

Our contributions are threefold:

- **Theoretical Foundation:** We formally define the GTAI framework as a two-player strategic game modeling clinical decision-making as dynamic interactions between the clinician-AI agent and adaptive disease entities. Unlike optimization-based approaches treating diseases as passive targets, our game-theoretic foundation captures disease strategic intelligence, particularly cancer's immune evasion and adaptive resistance capabilities.
- **Architectural Innovation:** We present a four-stage architecture operationalizing game-theoretic principles across clinical workflows: observation and diagnosis, treatment planning, execution, and outcome evaluation. This architecture enables anticipatory reasoning and real-time strategic adaptation, distinguishing it from conventional rule-based clinical decision support systems.
- **Clinical Impact:** We demonstrate GTAI's effectiveness through six discoveries that translate strategic concepts into actionable clinical insights. These range from uncovering novel disease mechanisms (cancer's coordinated camouflage strategy) to developing innovative therapeutic approaches (controllable anaerobic gradients for bacterial therapy), advancing both AI methodology and clinical outcomes.

Major Discoveries Enabled by GTAI:

1. *Discovery of a novel immune escape mechanism:* GTAI reveals that cancer cells can evade immune surveillance via a coordinated camouflage strategy, combining low tumor mutation burden (TMB) with high PD-L1 expression. This phenotype underlies hyperprogressive disease (HPD) during immunotherapy, where treatment paradoxically accelerates tumor growth through dual immune escape—weakening T cell recognition (TMB↓) and suppressing residual T cell function (PD-L1↑).
2. *Dynamic model for immune efficacy evaluation:* By adopting a differential dynamic perspective, GTAI introduces a tumor volume stratification standard distinguishing pseudo-progression (growth rate > 0, acceleration < 0) from true response (both < 0). This approach overcomes limitations of current irRC criteria, enabling more accurate and timely assessment of immunotherapy efficacy.
3. *Ecological strategy in microbiota transplantation:* GTAI elucidates that colonization resistance in fecal microbiota transplantation follows the principle of "Befriending the distant enemy while attacking a nearby enemy (远交近攻)". When donor and recipient flora are closely related, competition for intestinal niches inten-

sifies, reducing transplantation success; when distantly related, niche complementarity increases, facilitating successful engraftment.

4. *Interdisciplinary validation of cocktail therapy:* Leveraging mathematical modeling, military strategy, and logical reasoning, GTAI demonstrates that multi-drug combination therapy for HIV (cocktail therapy) drastically lowers the probability of drug resistance ($P_{\text{resist}} = \prod_{i=1}^{n}(1 - P_i)$), especially as the number of drugs increases. This mirrors the "divide and conquer" military stratagem, effectively blocking viral escape routes.
5. *Bacterial therapy targeting via controllable anaerobic gradient:* GTAI introduces a strategy to enhance the precision of bacterial therapy in early-stage tumors, where the anaerobic microenvironment and its natural "siphon effect" are insufficient to attract anaerobic bacteria. Pharmacologically accelerating local oxygen consumption within the tumor, such as through mitochondrial respiratory chain inhibition or induction of oxidative stress, rapidly expands the oxygen potential difference between the tumor and normal tissue. This creates a negative-pressure "siphon" that, via biochemical reactions and fluid dynamic diffusion, drives anaerobic bacteria like *Salmonella* to aggregate in low-oxygen tumor regions selectively. This controllable potential difference creation not only overcomes the hypoxia limitation of early tumors but also provides a spatiotemporal window for precise, regulated bacterial targeting.
6. *Ferroptosis as a self-sacrificing anti-tumor mechanism:* GTAI uncovers that specific stromal cells (e.g., fibroblasts) can relieve GPX4 inhibition and induce their own ferroptosis, releasing oxidized lipid signals that trigger lipid peroxidation and death in nearby tumor cells. This "self-sacrificing" effect exemplifies the classical stratagem of "Palming off substitute for the real thing (李代桃僵)" from the Thirty-Six Strategies, whereby one component is purposefully sacrificed to achieve a greater therapeutic gain for the whole.

These discoveries highlight how GTAI's integration of strategic reasoning, adaptive modeling, and cross-disciplinary insights leads to a deeper understanding of disease behavior and novel avenues for precision therapy.

2. Related Work

The intersection of game theory and healthcare has seen significant evolution, moving from static resource allocation models to more dynamic frameworks that attempt to capture the adaptive nature of disease. Here, we review the progression of relevant approaches and their limitations, motivating the need for Game Theoretical AI.

2.1. Game Theory and Disease Modeling

Early applications of game theory in medicine focused on resource allocation, vaccination strategies, and antibiotic resistance, usually treating diseases as passive entities responding mechanistically to interventions [10–13]. The predator-prey model, adapted from ecology, became a standard for modeling treatment-disease interactions, with therapies acting as predators and disease cells as prey [14,15]. However, these models rely on fixed behavioral assumptions and do not account for the adaptive intelligence seen in diseases like cancer [16,17]. Recent advances in medical AI have highlighted the need to systematically measure AI reliance and decision calibration in such frameworks, as these factors can significantly affect clinical outcomes and trust in automated systems [18,19]

Evolutionary game theory represented a significant advance, revealing that cancer cells compete not only with healthy tissue but also among themselves, resulting in complex population dynamics [20, 21]. Adaptive therapy, such as intermittent androgen deprivation therapy (IADT), leverages the competition between drug-sensitive and drug-resistant cancer cell populations to manage tumor burden and delay resistance-driven progression [22]. However, even these models generally define cancer adaptation through static fitness landscapes, rather than as intentional strategic behavior.

2.2. Machine Learning, Multi-Agent Systems, and Opponent Modeling

Parallel progress in machine learning has produced clinical decision support systems that leverage deep learning and reinforcement learning (RL) for diagnosis and treatment optimization [23–28]. In related domains, advanced generative and predictive models have also been developed to optimize molecular properties and accelerate drug discovery [29–32]. However, standard RL assumes stationary or slowly changing environments, making these systems vulnerable to adaptive diseases [33,34]. Recent adversarial RL work shows that intelligent opponents can exploit learned policies [35,36], but such methods are rarely integrated into healthcare applications.

Multi-agent systems (MAS) offer a framework for modeling complex healthcare interactions, including resource management and epidemic control [37–41]. While some MAS research incorporates adversarial roles, most treat pathogens as having fixed or limited strategies [42].

Opponent modeling, widely studied in competitive games and security domains, has begun to influence medical AI [43–45]. Techniques for inferring opponent behavior and reasoning about intent (theory of mind) [46,47] hold

promise for anticipating disease adaptation, but practical applications remain limited by partial observability and high clinical stakes.

2.3. Strategic Reasoning and Cross-Disciplinary Insights

The translation of military strategy to medicine is not new—concepts such as "surveillance" and "containment" have long been borrowed from strategic studies [48]. Classical texts like Sun Tzu's *Art of War* emphasize the importance of understanding both oneself and the adversary [8], a principle directly relevant to adaptive disease management. The Thirty-Six Stratagems further illustrate complex concepts such as deception, leverage, and escape [9], which suggest novel therapeutic analogues. However, systematic integration of these strategic principles into computational decision frameworks is lacking.

2.4. Limitations of Existing Approaches

Current AI and game-theoretic models in medicine suffer from fundamental limitations when confronting adaptive diseases, mischaracterizing the clinical decision-making problem. First, they employ *static disease models* that assume fixed behavioral patterns, failing to capture strategic adaptation exhibited by cancers and drug-resistant pathogens. For instance, cancer cells demonstrate intelligent behaviors such as immune camouflage (mimicking normal tissue markers), therapeutic resistance evolution (developing multi-drug efflux mechanisms), and microenvironmental manipulation (inducing angiogenesis and immune suppression), yet existing models treat these as stochastic variations rather than strategic adaptations. Second, these frameworks operate *reactively*, responding to observed behaviors without anticipating future adaptations. This temporal limitation is critical because clinical decision-making requires anticipating multi-step disease responses and modeling how diseases "learn" from interventions to develop counter-strategies over time. Third, they lack formal mechanisms for representing strategic concepts essential to adversarial interactions–deception, leverage, and escape remain outside their computational vocabulary. Fourth, existing immunotherapy response criteria exemplify these limitations by failing to distinguish true progression from pseudoprogression, leading to premature treatment discontinuation in patients who might benefit from continued therapy. Finally, the artificial separation of diagnosis and treatment planning prevents integrated strategic reasoning, as diseases actively respond to and anticipate clinical interventions requiring holistic strategic approaches. These limitations collectively render existing approaches inadequate against diseases that function as intelligent adversaries.

3. Game Theoretical AI: A New Approach in Medicine

We introduce Game-Theoretical AI (GT-AI), a fundamentally new conceptual framework that, for the first time, reconceptualizes the disease-clinician interaction as a strategic game between two intelligent, adaptive agents. While existing approaches in medical AI and computational game theory have made significant contributions, they universally treat diseases as passive targets or mechanistic systems. In contrast, our pioneering GT-AI framework explicitly acknowledges that diseases—particularly cancers—function as strategic adversaries: they gather information, adapt to interventions, deploy deceptive tactics, and evolve counter-strategies.

This novel paradigm, which we are the first to formally propose and implement, emerges from an unprecedented synthesis of three intellectual traditions: (1) *modern game theory*, providing mathematical frameworks for strategic interaction; (2) *classical military strategy*, offering time-tested principles for adversarial engagement; and (3) *adaptive AI*, enabling real-time learning and counter-adaptation. No existing framework has attempted this integration, making GT-AI the first computational system capable of truly anticipating and countering sophisticated disease strategies.

3.1. Core Innovations

GTAI introduces four system-level innovations that distinguish it from existing AI in medicine. These innovations are architectural and methodological in nature, enabling the framework to anticipate, adapt, and counter the strategic behavior of complex diseases. Sections IV–V detail GTAI's computational architecture and a concrete instantiation of its Dynamic Strategy Libraries capability using ancient strategic wisdom (Section VI).

Bidirectional Strategic Modeling: For the first time in medical AI, we model both clinician and disease as agents that maintain explicit models of their opponent. This bidirectional modeling enables anticipatory rather than reactive strategies—a capability absent from all existing medical decision support systems. The disease's utility function, uniquely formulated in our framework, incorporates survival, resource acquisition, immune evasion, and information concealment, reflecting its multi-objective strategic nature.

Dynamic Strategy Libraries: GT-AI is the first system to operationalize the Thirty-Six Stratagems and

principles from Sun Tzu's *Art of War* as formal computational policies in medicine. These strategies—including deception, leverage, and escape-provide a new vocabulary for clinical action that has never been computationally implemented in medical AI.

Integrated Decision Cycles: Unlike any existing framework, GT-AI unifies observation, planning, execution, and evaluation into a coherent strategic process. This integration, first achieved in our system, ensures that each stage informs and constrains the others, enabling truly adaptive responses to unexpected disease behaviors.

Meta-Strategic Learning: In a first for medical AI, GT-AI not only learns specific strategies but also learns *how* diseases learn. This meta-strategic capability, which we pioneered, enables the system to anticipate and preempt adaptive responses across patient populations—a level of strategic reasoning previously unattained in computational medicine.

To directly address the limitations identified in Section II, GTAI integrates mechanisms specifically designed for the challenges of incomplete observational data and the high clinical risk inherent in predicting adaptive disease behavior. Incomplete data are handled by the Observer Module through strategic particle filtering with deception-aware likelihoods, enabling robust inference under partial observability. High-risk predictions of disease adaptability are mitigated via integrated strategic risk assessment, which combines patient-specific causal estimates with probabilistic modeling of aggressive disease strategies, supplemented by sensitivity analyses and negative control checks. Table 1 summarizes how GTAI's components map to each limitation discussed in Section II, ensuring that the framework not only introduces novel strategic reasoning but also directly overcomes the shortcomings of prior approaches.

Table 1. Limitations in related work and corresponding GTAI features.

Limitation in Related Work	GTAI Feature That Addresses It
Static disease models	Bidirectional Strategic Modeling with adaptive opponent learning.
Reactive strategies only	Integrated Decision Cycles enabling anticipatory actions.
Lack of strategic vocabulary	Dynamic Strategy Libraries (Sun Tzu; Thirty-Six Stratagems operationalized).
Incomplete observational data	Observer Module with Strategic Particle Filtering and Bayesian updates under deception.
High clinical risk in predicting adaptability	Integrated Strategic Risk Assessment, sensitivity analysis, and adaptive execution triggers.

4. Theoretical Foundation of GTAI

Game-Theoretical AI rests on a fundamental reconceptualization: diseases are not merely biological processes but strategic agents capable of adaptive behavior. This section formalizes this perspective through mathematical frameworks that capture the dynamic, strategic nature of disease-clinician interactions.

4.1. Problem Formalization

We formulate the clinical encounter as a two-player extensive-form game with imperfect information. Let $\mathcal{G} = \langle \mathcal{N}, \mathcal{H}, \mathcal{A}, \mathcal{Z}, \chi, \rho, \sigma, u, \mathcal{I} \rangle$, where:

- $\mathcal{N} = \{C, D\}$ denotes the players: Clinician (C) and Disease (D).
- $\mathcal{H}$ is the set of all action histories (finite sequences of actions taken).
- $\mathcal{A}$ is a (single) set of actions.
- $\mathcal{Z} \subseteq \mathcal{H}$ is the set of terminal histories.
- $\chi : \mathcal{H} \to 2^{\mathcal{A}}$ assigns to each choice node a set of possible actions.
- $\rho : \mathcal{H} \to \mathcal{N}$ assigns to each non-terminal node h a player $i \in \mathcal{N}$ who chooses an action at h.
- σ represents successor function. $\sigma : \mathcal{H} \times \mathcal{A} \to \mathcal{H} \cup \mathcal{Z}$ maps a choice node and an action to a new choice node or terminal node such that for all h_1, $h_2 \in \mathcal{H}$ and $a_1, a_2 \in \mathcal{A}$, if $\sigma(h_1, a_1) = \sigma(h_2, a_2)$ then $h_1 = h_2$ and $a_1 = a_2$.
- $u = (u_C, u_D)$ are the utility functions for the clinician and the disease, respectively.
- $\mathcal{I} = (\mathcal{I}_1, \ldots, \mathcal{I}_n)$, where $\mathcal{I}_i = (\mathcal{I}_{i,1}, \ldots, \mathcal{I}_{i,k_i})$is an equivalence relation on (that is, a partition of) $\{h \in \mathcal{H} : \rho(h) = i\}$ with the property that $\chi(h) = \chi(h')$ and $\rho(h) = \rho(h')$ whenever there exists a j for which $h \in \mathcal{I}_{i,j}$ and $h' \in \mathcal{I}_{i,j}$

Unlike traditional models, the disease's utility function u_D is explicitly constructed to reflect multi-faceted,

strategic objectives beyond mere survival:

$$u_D(z) = \alpha \cdot S(z) + \beta \cdot R(z) + \gamma \cdot E(z) + \delta \cdot I(z) \tag{1}$$

where $z \in \mathcal{Z}$ is a terminal history; $S(z)$ denotes survival probability, $R(z)$ quantifies resource acquisition (such as host nutrients), $E(z)$ measures successful evasion of treatment, and $I(z)$ reflects information concealment or uncertainty induced in the clinician. The non-negative weights $\alpha, \beta, \gamma, \delta$ can be tuned based on disease type and stage.

Correspondingly, the clinician's utility function u_C may be expressed as:

$$u_C(z) = \eta_1 \cdot H(z) - \eta_2 \cdot T(z) - \eta_3 \cdot C(z) - \eta_4 \cdot I(z) \tag{2}$$

where $H(z)$ reflects patient health or survival, $T(z)$ measures treatment side effects or toxicity, $C(z)$ accounts for resource or financial cost, $I(z)$ penalizes information concealment or uncertainty induced by the disease, and $\eta_1, \eta_2, \eta_3, \eta_4 \geq 0$ are tunable weights reflecting clinical priorities.

This formulation enables both agents—the clinician and the disease—to pursue rich, adaptive strategies, supporting the core premise of GTAI.

4.2. Belief Dynamics and Information Sets

Both players maintain beliefs about hidden states. The clinician's information set $I_C(h)$ includes observable symptoms, test results, and treatment responses, while the disease's information set $I_D(h)$ encompasses detected treatments, immune responses, and environmental conditions.

We model belief updates using a modified Bayesian framework that accounts for strategic deception:

$$\mu_{C,t+1}(s_D|h_t, a_t, o_{t+1}) = \frac{P(o_{t+1}|s_D, a_t; \theta_D) \cdot \mu_{C,t}(s_D|h_t)}{\sum_{s'_D} P(o_{t+1}|s'_D, a_t; \theta_D) \cdot \mu_{C,t}(s'_D|h_t)} \tag{3}$$

where θ_D represents the disease's deception parameter, capturing its ability to mask true states.

5. Solution Approach

5.1. Strategic Interaction Dynamics

The interaction between clinician and disease unfolds over discrete time steps. At each step t:

1. The clinician observes $o_t \in \mathcal{O}$ (symptoms, test results)
2. Based on beliefs $\mu_{C,t}$, the clinician selects action $a_{C,t} \in \mathcal{A}_C$
3. The disease observes the clinical action and updates beliefs $\mu_{D,t}$
4. The disease selects response $a_{D,t} \in \mathcal{A}_D$
5. Nature determines outcomes based on both actions
6. Both players update beliefs for the next iteration

This framework captures the adaptive nature of both players, with strategies evolving based on observed opponent behavior.

5.2. Strategic Principles from Military Theory

We formalize key strategic principles from Sun Tzu and the Thirty-Six Stratagems as computational operators:

5.2.1. Know Yourself and Your Enemy

This principle translates to maintaining accurate belief distributions over both self-state and opponent state:

$$\mathcal{K}(t) = H(\mu_{C,t}(s_C)) + H(\mu_{C,t}(s_D)) \tag{4}$$

where $H(\cdot)$ denotes entropy. Lower entropy indicates better knowledge, guiding information-gathering actions.

5.2.2. Decamping Being the Best

Formalized as temporarily accepting suboptimal immediate outcomes to achieve better long-term positions:

$$\pi_{retreat}(h_t) = \arg\max_{a \in \mathcal{A}_C} \left[-\lambda u_{C,immediate}(a) + \mathbb{E}[u_{C,future}(a, h_{t+k})]\right] \tag{5}$$

where $\lambda < 1$ weights immediate losses against expected future gains.

5.2.3. Deception and Misdirection

The clinician may employ therapeutic feints to reveal disease characteristics:

$$a_{feint} = \arg \max_{a \in \mathcal{A}_{C,suboptimal}} \mathbb{I}[D(a)|\mu_{C,t}] \tag{6}$$

where $\mathbb{I}[D(a)|\mu_{C,t}]$ measures the information gain from observing the disease's response to action a.

5.3. Equilibrium Concepts for Adaptive Games

Traditional Nash equilibrium proves insufficient for games with adaptive agents. We introduce the concept of *Strategic Adaptive Equilibrium* (SAE), where strategies must be robust to opponent learning:

Definition 1 (Strategic Adaptive Equilibrium)**.** *A strategy profile* (π_C^*, π_D^*) *constitutes an SAE if:*

1. *Neither player can improve by unilateral deviation:* $\forall \pi_C, k \leq K : u_C(\pi_C^*, \Phi^k(\pi_D^*)) \geq u_C(\pi_C, \Phi^k(\pi_D^*)) - \epsilon$
2. *Both strategies remain approximately optimal under opponent adaptation:* $\forall \pi_D, k \leq K : u_D(\Phi^k(\pi_C^*), \pi_D^*)) \geq u_D(\Phi^k(\pi_C^*), \pi_D) - \epsilon$
3. *The strategies induce bounded belief divergence over time:* $\max_k D_{KL}(\mu_k \parallel \mu_0) \leq \delta$

where adaptation operator $\Phi(\pi) = \pi + \eta \nabla u(\pi, \pi_{opp})$.

Formally, for adaptation operator Φ and tolerance ϵ:

$$\begin{aligned} u_C(\pi_C^*, \Phi^k(\pi_D^*)) &\geq u_C(\pi_C, \Phi^k(\pi_D^*)) - \epsilon, \forall \pi_C, k \leq K \\ u_D(\Phi^k(\pi_C^*), \pi_D^*) &\geq u_D(\Phi^k(\pi_C^*), \pi_D) - \epsilon, \forall \pi_D, k \leq K \end{aligned} \tag{7}$$

5.4. Learning and Meta-Strategy

Both players employ hierarchical learning, updating not just strategies but meta-strategies governing adaptation:

$$\begin{aligned} \pi_{t+1} &= \Gamma(\pi_t, h_t, \omega_t) \\ \omega_{t+1} &= \Lambda(\omega_t, \{\pi_\tau, h_\tau\}_{\tau \leq t}) \end{aligned} \tag{8}$$

where π_t denotes the player's current strategy at time t, h_t represents the observed history up to t, ω_t encodes the meta-strategy or adaptation policy at time t, Γ represents strategy updates and Λ governs meta-strategy evolution.

6. Computational Architecture and Algorithms

The GTAI framework operationalizes its theoretical foundation through a modular computational architecture designed for real-time strategic clinical decision support. This section presents the core system architecture, algorithms, and implementation strategies that collectively enable GTAI to anticipate and counter adaptive disease behavior.

6.1. System Architecture Overview

GTAI is structured around four tightly interconnected modules: the Observer, Strategist, Executor, and Evaluator (see Figure 1). Together, these components mirror the workflow of expert clinicians, systematically progressing from patient assessment through action and continuous learning.

6.2. Module Interactions and Workflow

The Observer Module initiates the cycle by performing real-time state inference and risk assessment, drawing on strategic particle filtering and causal inference to synthesize available clinical data. Insights from the Observer feed into the Strategist Module, which formulates and updates both immediate tactics and long-term treatment strategies based on the evolving patient state. These strategies are then enacted by the Executor Module, which translates plans into concrete clinical interventions, monitors for unexpected disease responses, and triggers adaptive replanning as necessary. The Evaluator Module completes the loop by systematically analyzing intervention outcomes, capturing feedback that informs future state estimation and strategic refinement.

By structuring GTAI around these four modules, the architecture not only supports robust, adaptive clinical reasoning but also closely emulates the decision-making processes of experienced human clinicians, enabling seamless integration of strategic intelligence into real-world healthcare.

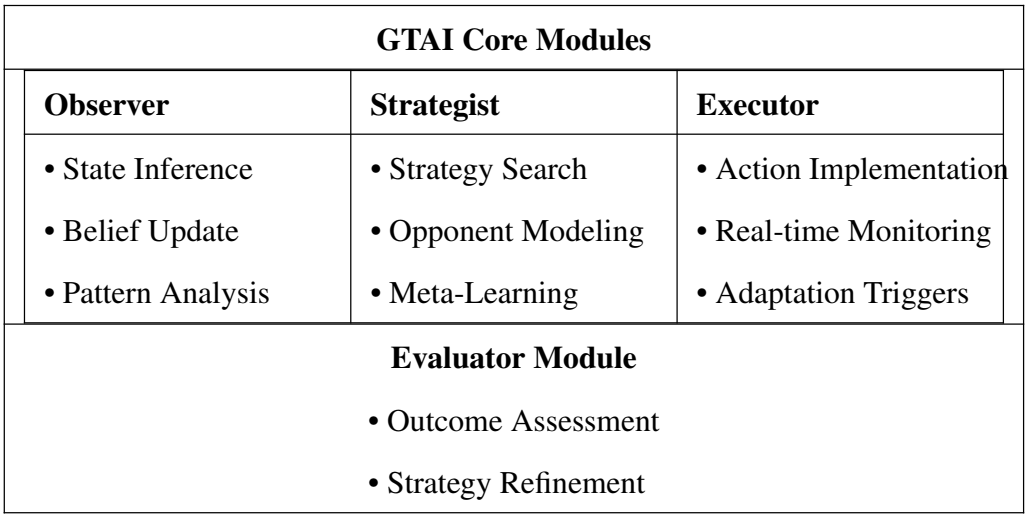

Figure 1. GTAI System Architecture. The four modules (Observer, Strategist, Executor, Evaluator) are organized in an iterative loop. At the Strategist module, the system branches into alternative tactical choices (e.g., deception, leverage, escape), forming a decision-tree workflow that guides clinical decision-making.

6.3. Observer Module: Strategic State Inference

The Observer Module serves as the sensory and analytical foundation of GTAI, combining strategic particle filtering with causal inference to provide comprehensive disease state assessment and treatment risk quantification.

6.3.1. Strategic Particle Filter

The Observer Module infers disease states from partial observations using a particle filter augmented with strategic reasoning (see Algorithm 1).

Algorithm 1 Strategic Particle Filter

Require: Observation o_t, previous particles $\{x_{t-1}^{(i)}, w_{t-1}^{(i)}\}_{i=1}^{N}$
Ensure: Updated particles $\{x_t^{(i)}, w_t^{(i)}\}_{i=1}^{N}$
for $i = 1$ to N **do**
  Sample $x_t^{(i)} \sim P(x_t|x_{t-1}^{(i)}, \pi_D)$ // Strategic transition
  $w_t^{(i)} = w_{t-1}^{(i)} \cdot P(o_t|x_t^{(i)}, \theta_D)$ // Deception-aware
end for
Normalize weights: $w_t^{(i)} = w_t^{(i)} / \sum_j w_t^{(j)}$
if $ESS < N_{threshold}$ **then**
  Resample particles using strategic importance
end if
Update deception parameter: $\theta_D = \Psi(\{x_t^{(i)}, o_t\})$
return $\{x_t^{(i)}, w_t^{(i)}\}_{i=1}^{N}$

The key innovation is incorporating the disease's strategic policy π_D into state transitions and accounting for potential deception through parameter θ_D.

6.3.2. Causal Inference for Treatment Risk Quantification

Beyond state inference, the Observer Module employs causal inference to quantify treatment risks, translating observed relationships into actionable clinical insights. Since randomized controlled trials are often infeasible in clinical contexts due to ethical or practical constraints, most treatment data are observational. Consequently, minimizing confounding bias becomes critical for valid causal inferences.

Accounting for Unmeasured Confounding

In clinical reality, many sources of confounding, such as epigenetic factors or environmental exposures, may be unmeasured or unknown. While we collect ten routinely available covariates (e.g., age, gender, comorbidities) to form a provisional backdoor set X:

- **Patient's condition**: Directly affects treatment choice
- **Age**: Impacts response and tolerance to treatment
- **Gender**: Influences disease incidence and treatment efficacy
- **Ethnicity**: Affects disease progression and treatment response due to genetic differences
- **Disease type**: Determines applicability of specific therapies
- **Pre-existing conditions**: Comorbidities that may impact health status
- **Allergy history**: Limits drug choice and safety
- **Smoking history**: May increase disease risk and reduce treatment efficacy
- **Family genetic history**: Provides key information for diagnosis and treatment
- **Medical complications**: Unfavorable results of disease or treatment [49]

To mitigate residual bias from unmeasured factors (e.g., epigenetics, environmental exposures), we implement a dual-layer robustness strategy:

1. *Sensitivity analysis*: For every causal estimate, we compute an *E-value* [50] to quantify the minimum confounding strength required to nullify the observed effect. Additionally, we perform a Rosenbaum Γ-test [51] to assess robustness to hidden biases under varying Γ sensitivity parameters.
2. *Negative controls*: Where empirically justified (e.g., availability of non-target biomarkers or placebo data), we incorporate negative-control outcomes and/or exposures to detect latent confounding structures [52].

This approach explicitly acknowledges the provisional nature of X while providing quantitative bounds for residual confounding.

Minimizing Confounding: The Backdoor Criterion

To control for confounding, we utilize the backdoor criterion, which states that a set of variables $\mathbf{W}$ satisfies the backdoor criterion for estimating the causal effect of treatment T on outcome Y if:

1. $\mathbf{W}$ blocks all non-causal (backdoor) paths from T to Y.
2. $\mathbf{W}$ does not include any descendants of T.

In practice, we attempt to control for confounding by conditioning on observed patient covariates X. However, the validity of the backdoor adjustment,

$$P(y \mid do(t)) = \sum_{X} P(y \mid t, X)P(X), \tag{9}$$

requires the assumption of no unmeasured confounding given X. Given the possibility of unobserved factors, our risk estimates should be interpreted with appropriate caution and, where possible, supplemented with sensitivity analyses.

Integrated Strategic Risk Assessment

We define the strategic treatment risk as follows:

$$\text{Risk}_{\text{strategic}}(T, s_t) = \mathbb{E}[Y \mid T, X = x_j] \cdot P(s_D = \text{aggressive} \mid \mu_t) \tag{10}$$

where:

- T is the treatment assignment,
- Y is the clinical outcome (e.g., response, adverse event),
- X denotes patient covariates,
- s_t represents the inferred disease strategic state at time t,
- $P(s_D = \text{aggressive} \mid \mu_t)$ is the probability that the disease adopts an aggressive strategy, as estimated by the particle filter given current belief state μ_t.

Here, $\mathbb{E}[Y \mid T, X = x_j]$ estimates the expected causal effect of treatment T for patients with covariates $X = x_j$, and $P(s_D = \text{aggressive} \mid \mu_t)$ quantifies the current risk that the disease is acting aggressively.

6.3.3. Real-Time Belief and Risk Updates

The Observer Module continuously updates both disease state beliefs and treatment risk assessments(see Algorithm 2).

Algorithm 2 Integrated State and Risk Update

Require: New observation o_t, patient information X
1: Update disease state beliefs using Strategic Particle Filter
2: Compute causal risk for available treatments:
3: **for** each treatment $T_i \in \mathcal{T}$ **do**
4: $r_i \leftarrow \mathbb{E}_{G_i}[Y_i \mid T_i, X]$
5: Adjust for strategic disease behavior
6: **end for**
7: Propagate risk assessments to Strategist Module
8: **return** Updated beliefs μ_t and risk vector $\mathbf{r}$

This integrated approach ensures that treatment recommendations account for both the dynamic disease state and patient-specific causal risk factors, providing a comprehensive foundation for strategic clinical decision-making.

6.4. Strategist Module: Multi-Level Strategic Planning

The Strategist Module generates treatment strategies through hierarchical planning that combines immediate tactics with long-term strategic goals. This is achieved through two-stage approaches: first, a Monte Carlo Tree Search (MCTS) algorithm with integrated opponent modeling efficiently explores potential treatment paths; second, GTAI incorporates meta-learning to enhance adaptability and improve strategic reasoning across diverse patient encounters.

6.4.1. Strategy Search Algorithm

GTAI employs Monte Carlo Tree Search (MCTS) enhanced with opponent modeling, as outlined in Algorithm 3.

Algorithm 3 Strategic MCTS with Opponent Modeling

Require: Root state s_0, computational budget B
Ensure: Best action a^*
1: Initialize tree $\mathcal{T}$ with root s_0
2: **for** $b = 1$ to B **do**
3: $s_{leaf} \leftarrow$ TreePolicy($\mathcal{T}$, s_0)
4: $\pi_D \leftarrow$ InferOpponentStrategy(s_{leaf})
5: $v \leftarrow$ Rollout(s_{leaf}, π_C, π_D)
6: Backup($\mathcal{T}$, s_{leaf}, v)
7: UpdateOpponentModel(π_D, v)
8: **end for**
9: **return** $\arg\max_a Q(s_0, a) + \xi \cdot S(s_0, a)$

Algorithm 3 implements the standard MCTS procedure, consisting of expansion (*TreePolicy*), simulation (*Rollout*), and backpropagation (*Backup*). At each leaf node, the disease strategy π_D is inferred to enable opponent modeling. Simulations are conducted using both the clinician's policy π_C and the inferred disease policy π_D. The algorithm selects the action that maximizes the sum of the expected value $Q(s_0, a)$ and a strategic bonus $S(s_0, a)$, weighted by ξ. This formulation enables the selection of actions that balance immediate clinical benefits with long-term strategic advantages, such as risk mitigation and information gain.

Opponent Modeling Network

The opponent model uses a recurrent neural network to predict disease strategies:

$$\begin{aligned} h_t &= \text{LSTM}(h_{t-1}, [o_t, a_{t-1}]) \\ \mu_{\pi_D} &= \text{Softmax}(\text{MLP}(h_t)) \\ \pi_D &\sim \text{Categorical}(\mu_{\pi_D}) \end{aligned} \tag{11}$$

where h_{t-1} denotes the previous LSTM hidden state, encoding historical information, while $[o_t, a_{t-1}]$ represents the current observation and previous action as inputs. The LSTM updates its hidden state to h_t, which is then transformed by a multi-layer perceptron (MLP) followed by a softmax function to produce μ_{π_D}, a probability distribution over possible disease strategies. The disease strategy π_D is subsequently sampled from the categorical

distribution defined by μ_{π_D}, capturing the model's probabilistic estimate of the disease's current strategic behavior based on observed data. This architecture captures temporal dependencies in disease behavior while maintaining uncertainty over strategic patterns.

6.4.2. Meta-Learning for Strategic Adaptation

Furthermore, to enhance the system's ability to generalize and adapt across diverse clinical scenarios, GTAI employs meta-learning to improve strategic reasoning across patient encounters:

$$\theta_{meta} = \arg\min_{\theta} \mathbb{E}_{\mathcal{D}\sim p(\mathcal{D})} \left[\mathcal{L}(\theta - \alpha\nabla_{\theta}\mathcal{L}_{\mathcal{D}_{train}}(\theta), \mathcal{D}_{test})\right] \tag{12}$$

where $\mathcal{D}$ represents disease-specific strategic patterns and α controls adaptation speed.

6.5. Executor Module: Adaptive Implementation

The Executor Module translates strategic plans into concrete clinical actions while monitoring for unexpected disease responses, as shown in Algorithm 4.

Algorithm 4 Adaptive Strategy Execution

Require: Strategy π_C, monitoring threshold τ
1: $a_0 \leftarrow \pi_C(s_0)$
2: Execute clinical action a_0
3: **while** treatment ongoing **do**
4: Observe response o_t
5: $\Delta_{surprise} \leftarrow D_{KL}(P(o_t|\mu_t)\|P(o_t|\hat{\mu}_t))$
6: **if** $\Delta_{surprise} > \tau$ **then**
7: Trigger strategic reassessment
8: $\pi'_C \leftarrow$ AdaptStrategy(π_C, o_t)
9: $\pi_C \leftarrow \pi'_C$
10: **end if**
11: $a_t \leftarrow \pi_C(s_t)$
12: Execute action a_t
13: **end while**

The module translates the current strategic policy π_C into clinical actions while continuously monitoring patient responses for unexpected changes. At each step, it quantifies the surprise of the observed response o_t using the Kullback–Leibler (KL) divergence between the predicted and actual response distributions. If this surprise exceeds a threshold τ, the system triggers a reassessment and adapts the policy via AdaptStrategy, ensuring clinical decisions remain responsive to evolving patient conditions. This adaptive process repeats throughout the treatment episode.

6.6. Evaluator Module: Closing the Feedback Loop

The Evaluator Module is the critical feedback and optimization component of GTAI. After treatment actions are executed, this module systematically assesses clinical outcomes, such as therapeutic efficacy, adverse events, and disease progression, relative to the strategic intent. By analyzing both quantitative and qualitative results, the Evaluator identifies which aspects of the chosen strategies were successful and where adjustments are needed. These insights are then fed back to the Strategist and Observer Modules, supporting continual strategy refinement and adaptive learning in future decision cycles. This feedback loop ensures the architecture's integrity and enables GTAI to dynamically optimize its tactics in response to real-world outcomes.

6.7. From Architecture to Strategic Reasoning

This integrated architecture enables GTAI to operationalize advanced strategic reasoning in clinical contexts, systematically applying a library of classical strategies to outmaneuver adaptive diseases. Drawing from Sun Tzu's *Art of War* and the Thirty-Six Stratagems, GTAI translates ancient strategic wisdom into practical, algorithmic tools for modern precision medicine.

6.8. Strategic Principle Implementation: Algorithmic Examples

To illustrate this process, we present concrete implementations of several classical strategies within the GTAI framework:

6.8.1. Escape Stratagems Algorithm

When faced with aggressive disease progression, GTAI may recommend escape stratagems, temporarily shifting focus from direct confrontation to stabilization and preparation for future counteroffensive actions (see Algorithm 5).

Algorithm 5 Escape Stratagems

Require: Current state s_t, disease momentum m_D
if $m_D > m_{critical}$ AND $P(success|aggressive) < p_{threshold}$ **then**
  $targets \leftarrow$ IdentifySecondaryObjectives(s_t)
  $a_{escape} \leftarrow$ OptimizeForStabilization($targets$)
  Schedule future counteroffensive
  return a_{escape}
else
  return standard treatment
end if

6.8.2. Deceptive Therapy Planning

To reveal hidden disease characteristics, GTAI can design therapeutic feints—actions that maximize information gain while minimizing risk:

$$a_{feint} = \arg \max_{a \in \mathcal{A}_{probe}} [\mathbb{I}(s_D; o|a) - \lambda \cdot \text{Risk}(a)] \tag{13}$$

where $\mathbb{I}(s_D; o|a)$ represents the expected mutual information between the disease state and observed outcomes, and λ balances exploration with safety.

These algorithmic modules exemplify how GTAI leverages strategic principles to enhance adaptive clinical decision-making. The following section details how GTAI systematically draws from Sun Tzu's *Art of War* and the Thirty-Six Stratagems, using them as a strategic library of advanced tactics—such as deception, leverage, root cause removal, and escape—that are algorithmically deployed across all stages of clinical decision-making. This approach transforms ancient strategic wisdom into a practical, adaptive toolkit for modern precision medicine.

7. Strategic Library: Operationalizing Ancient Wisdom in GTAI

The Thirty-Six Strategies and *The Art of War* serve as a rich strategic library for GTAI, providing a repertoire of advanced tactics—including deception, leverage, removing the root cause, and escape—that can be operationalized within each stage of clinical decision-making. In this approach, GTAI functions as the decision engine, while these classical strategies constitute the high-level actions or tactics available at every step in the clinical workflow.

The strategies in the decision library are organized into three principal categories:

- **Deception**: Concealing true intentions or actions to mislead the disease, thereby reducing its ability to mount an effective defense and increasing the likelihood of therapeutic success.
- **Leverage**: Exploiting external or internal factors to steer the clinical situation toward a favorable outcome. This includes the subclass **Removing the Root Cause**, which targets the fundamental driver of disease progression, such as eradicating the tumor microenvironment or disrupting essential metabolic pathways, to prevent recurrence and achieve lasting control.
- **Escape**: Recognizing the limitations of aggressive intervention, clinicians may strategically shift to supportive or palliative care, prioritizing patient quality of life when curative treatment is no longer feasible.

In practice, GTAI maps these strategies to the four core stages of decision support:

- **Observation and Diagnosis:** GTAI identifies disease behaviors such as camouflage or immune evasion, enabling the deployment of strategies like "unmasking the enemy" to improve detection and characterization.
- **Treatment Planning:** The system can formulate indirect or adaptive approaches—for example, planning a "feint" with a milder therapy to manipulate disease adaptation, or a "retreat" to minimize resistance development.

- **Execution:** GTAI dynamically selects and adjusts strategies during treatment, such as "encircling Wei to rescue Zhao"—targeting disease-supporting microenvironments rather than the primary lesion.
- **Outcome Evaluation:** The effectiveness of each tactic is rigorously evaluated, informing the selection and refinement of future strategies.

This integration transforms ancient strategic wisdom into a practical, algorithmic toolkit for modern medicine. As detailed in the Appendix A, GTAI's deployment of specific stratagems results in improved diagnostic accuracy, treatment personalization, and adaptive therapeutic success. This systematic framework empowers clinicians to tailor patient-specific strategies through enhanced causal reasoning and adaptive risk management.

8. Computational Feasibility and Clinical Safety Considerations

The practical implementation of GTAI in clinical environments requires careful consideration of computational requirements and rigorous safety protocols. This section addresses the feasibility challenges and safety measures necessary for responsible clinical deployment.

Computational Feasibility

The bidirectional strategic modeling inherent in GTAI introduces computational complexity beyond traditional unidirectional medical AI systems. Maintaining simultaneous belief and strategy models for both clinician and disease agents theoretically increases computational load compared to static approaches. However, several architectural design strategies can effectively mitigate these computational burdens while preserving strategic reasoning capabilities.

Hierarchical abstraction represents a key optimization approach, employing coarse-grained opponent models at higher decision levels with fine-grained updates triggered only when critical clinical thresholds are reached. This selective refinement strategy significantly reduces continuous computational overhead while maintaining strategic accuracy during pivotal decision points. Complementing this approach, opponent model compression techniques such as policy distillation and dimensionality reduction can substantially reduce both storage requirements and update costs without compromising essential strategic information.

Adaptive update frequencies provide another computational efficiency mechanism, as opponent models need not be updated at every decision cycle. Update intervals can be dynamically adjusted based on the stability of observed opponent behavior, with more frequent updates during periods of rapid disease evolution and reduced frequency during stable phases. Modern computational infrastructure further supports GTAI implementation through parallelization capabilities, where contemporary GPUs and distributed computing systems can support real-time inference across the core modules: Observer, Strategist, Executor, and Evaluator.

Clinical Trial Safety and Security

Clinical deployment of GTAI requires comprehensive safety protocols addressing both technical reliability and patient protection. These measures must be integrated into every phase of development and implementation to ensure responsible translation from theoretical framework to clinical practice.

Physician-in-the-loop control forms the fundamental safety principle, ensuring that all GTAI recommendations remain subject to final approval and oversight by trained clinicians. This human oversight mechanism guarantees that no autonomous clinical decision is executed without expert review, maintaining clinical accountability while leveraging AI strategic insights. The system functions as an advanced decision support tool rather than an autonomous agent, preserving essential human judgment in patient care.

Staged validation protocols provide systematic risk mitigation through progressive implementation phases. Clinical deployment should proceed through rigorous in-silico simulations using synthetic patient data, followed by retrospective analyses of historical clinical datasets, and culminating in carefully designed limited-scope pilot studies before advancing to large-scale clinical trials. Each validation stage must demonstrate safety and efficacy benchmarks before progression to subsequent phases.

Regulatory compliance represents a critical implementation requirement, with GTAI systems adhering to established medical device regulations including FDA and EMA guidelines for AI-based decision support systems. Compliance extends to comprehensive data privacy protections under HIPAA and GDPR frameworks, algorithm transparency requirements for clinical decision support, and established protocols for AI system validation in healthcare settings.

Fail-safe mechanisms provide essential safety redundancy through predefined fallback strategies embedded within the Executor Module. These mechanisms activate when model outputs deviate from expected clinical norms or exceed predetermined risk thresholds, automatically reverting to established standard-of-care protocols. Such

safety systems ensure that technical failures or unexpected model behavior cannot compromise patient safety, maintaining clinical care continuity even during system anomalies.

The integration of these computational and safety considerations ensures that GTAI can be responsibly developed and deployed while maintaining the strategic advantages that distinguish it from conventional medical AI approaches. These foundational safeguards enable clinical translation while preserving the innovative strategic reasoning capabilities that make GTAI uniquely suited for confronting adaptive diseases.

9. Conclusions

This work presents Game Theoretical AI (GTAI) as a unified, strategic framework for clinical decision-making against adaptive diseases. By formalizing clinical reasoning as a dynamic, multi-stage process inspired by classical stratagems, GTAI addresses the limitations of traditional AI and captures the complexity of adversarial patient-disease interactions. The six key discoveries illustrate GTAI's capacity to bridge theoretical modeling with practical clinical needs, enabling real-time, adaptive treatment planning that closely mimics expert reasoning.

GTAI's modular structure facilitates personalized, context-specific care, offering particular promise in resource-constrained settings where clinical expertise is limited. By automating strategic and tactical aspects of care, GTAI can reduce clinician workload and improve patient outcomes. Future work will focus on large-scale validation and integration into clinical workflows. Overall, GTAI highlights the transformative potential of embedding strategic intelligence within computational medicine for precision and adaptive healthcare.

Author Contributions

S.G.: Conceptualization, investigation, writing, and revision. D.W.: Conceptualization, investigation, writing, and revision. All authors have read and agreed to the published version of the manuscript.

Funding

This paper is partially supported by Hong Kong Innovation and Technology Commission (ITC) grant #MHP/034/22.

Conflicts of Interest

The authors declare no conflict of interest. Given the role as Editor-in-Chief, Dapeng Oliver Wu had no involvement in the peer review of this paper and had no access to information regarding its peer-review process. Full responsibility for the editorial process of this paper was delegated to another editor of the journal.

Appendix A. Application of 36 Stratagems in Disease Treatment

The integration of ancient strategic wisdom with modern computational intelligence marks a fundamental shift in clinical decision-making strategies. The Thirty-Six Stratagems and The Art of War, a collection of Chinese military tactics refined over millennia, offers profound insights into strategic thinking that transcend their original martial context. When combined with GTAI's computational framework, these stratagems provide a sophisticated vocabulary for conceptualizing and executing complex clinical strategies against adaptive diseases.

GTAI serves as the computational engine that operationalizes strategic reasoning through its four-stage cycle: observation and diagnosis, treatment planning, execution, and outcome evaluation. At each stage, the system can invoke specific stratagems from its strategic library, translating abstract tactical concepts into concrete clinical actions. This synthesis enables clinicians to move beyond reactive treatment protocols toward proactive strategic engagement with disease.

The stratagems are not merely metaphorical; they represent fundamental patterns of strategic interaction that emerge whenever intelligent agents compete for resources or survival. In the clinical context, diseases—particularly cancers and drug-resistant pathogens—exhibit behaviors remarkably analogous to military adversaries: they gather intelligence, adapt to threats, deploy deceptive tactics, and evolve counter-strategies. Recognizing these parallels allows us to apply time-tested strategic principles to modern medicine.

Our categorization of the Thirty-Six Stratagems for clinical application follows three primary strategic modalities:

- **Deception (12 stratagems)**: Concealing true intentions or actions to mislead the disease, thereby reducing its ability to mount an effective defense and increasing the likelihood of therapeutic success.
- **Leverage (21 stratagems)**: Exploiting external or internal factors to steer the clinical situation toward a favorable outcome. This includes the subclass **Removing the Root Cause**, which targets the fundamental

driver of disease progression, such as eradicating the tumor microenvironment or disrupting essential metabolic pathways, to prevent recurrence and achieve lasting control.

- **Escape (1 stratagem)**: Recognizing the limitations of aggressive intervention, clinicians may strategically shift to supportive or palliative care, prioritizing patient quality of life when curative treatment is no longer feasible.

This appendix presents detailed mappings between classical stratagems and their clinical implementations, demonstrating how ancient wisdom can enhance modern medical practice through computational intelligence.

Appendix A.1. Deception (12 Stratagems)

Deception stratagems provide GTAI with the ability to mislead, distract, or confuse disease processes, thereby undermining the disease's adaptive responses. By concealing true therapeutic intentions or introducing diagnostic ambiguity, GTAI can reduce the effectiveness of resistance mechanisms, gain critical information about hidden disease states, and increase the likelihood of successful intervention. In clinical practice, these tactics translate to approaches such as stealthy diagnostics, therapeutic feints, or protocol modifications that exploit the disease's uncertainty. The deception category comprises 12 stratagems, each detailed in Tables A1–A12.

Table A1. Deception Stratagems 1: Crossing the sea under camouflage (瞒天过海).

Clinical Application Scenarios
During radiotherapy, doctors can use this strategy: First, play lullabies and let patients wear headphones to sleep, diverting their attention from the claustrophobic environment. Then, push patients into a small radiotherapy room while they are unconscious (a small space can reduce radiation energy requirements and reduce systemic damage). This not only avoids triggering claustrophobia (patients are unaware of the real environment), but also ensures accurate and efficient treatment, achieving "painless" radiotherapy.

Table A2. Deception Stratagems 2: Making a feint to the east and attacking in the west (声东击西).

Clinical Application Scenarios
Combination of Immunotherapy and Chemotherapy: Feint Attack: The treatment begins with a course of chemotherapy agents, such as gemcitabine, administered to the patient. This initial intervention prompts the tumor to activate its intrinsic drug resistance mechanisms, including the upregulation of DNA repair pathways and efflux pumps. Consequently, the tumor perceives chemotherapy as the principal therapeutic threat, directing its adaptive responses towards countering cytotoxic damage. **Main Attack:** Following this, immunotherapy is introduced—typically through agents like immune checkpoint inhibitors (e.g., PD-1/PD-L1 antibodies). At this stage, the tumor's defense mechanisms remain primarily oriented against chemotherapy, rendering it vulnerable to immune-mediated destruction. Additionally, the prior chemotherapy phase not only reduces tumor burden but also disrupts the tumor microenvironment by depleting immunosuppressive cells and factors. This creates a more favorable landscape for immune cell infiltration and activity. The immune system, now less inhibited, can more effectively recognize and eradicate residual malignant cells. Through this sequential strategy, the synergistic effect of combining chemotherapy-induced immunogenic modulation with targeted immunotherapy maximizes anti-tumor efficacy while minimizing tumor evasion.

Table A3. Deception Stratagems 3: Advancing secretly by an unknown path (暗渡陈仓).

Clinical Application Scenarios
Example: Biomimetic Trojan Horse Nanoparticles for Targeted Cancer Therapy. A novel example of a "secret attack" strategy is the use of biomimetic Trojan Horse nanoparticles, such as Mel-SiO_2@CCM. In this approach, a mesoporous silica nanoparticle (SiO_2) is loaded with bee venom peptide (Mel) and then cloaked with membranes derived from colon cancer cells (CCM). This cancer cell membrane camouflage allows the nanoparticle to evade immune detection and facilitates its entry into tumor tissue by mimicking native cancer cells. Once inside, the Mel-SiO_2@CCM nanoparticle delivers its bee venom peptide payload directly into the cancer microenvironment. This dual-action design enables targeted elimination of both tumor cells and the cancer-promoting bacteria *Fusobacterium nucleatum* (*F. nucleatum*), which is often enriched in colon cancer. By exploiting the cancer cell's own membranes as a disguise, these nanoparticles infiltrate via a route the tumor does not defend, releasing their cytotoxic cargo precisely where it is needed and achieving highly selective, effective therapy against both cancer and its microbial allies [53].

Table A4. Deception Stratagems 4: Creating something out of nothing (无中生有).

Clinical Application Scenarios
Relieving Phantom Limb Pain with Brain-Computer Interface (BMI): Patients with bone or soft tissue sarcomas (e.g., osteosarcoma, Ewing's sarcoma) sometimes require amputation if the tumor invades critical vessels or nerves, or is unresponsive to other therapies. After amputation, abnormal nerve activity at the stump may trigger phantom limb pain, as the brain misinterprets residual nerve signals. Using a brain-computer interface (BMI), patients undergo repeated virtual movement training, such as simulated grasping and touching. This approach suppresses abnormal pain signals and gradually restores the functional connection between the motor and somatosensory cortices, effectively reducing phantom limb pain [54].

Table A5. Deception Stratagems 5: Covering the dagger with a smile (笑里藏刀).

Clinical Application Scenarios
Fucoidan-Nanoparticles Targeting P-Selectin for Brain Tumor Therapy. Clinical Scenario: Delivering potent anticancer drugs directly to brain tumors is a significant clinical challenge due to the restrictive nature of the blood-brain barrier (BBB), which limits drug penetration and protects healthy neural tissue from potentially toxic agents. **Innovative Solution:** Researchers at Memorial Sloan Kettering Cancer Center have developed fucoidan-based nanoparticles engineered to target P-selectin, a cell adhesion molecule overexpressed in tumor vasculature. These nanoparticles are loaded with the anticancer drug Vismodegib (Roche), aiming to enhance drug delivery specificity and efficacy while minimizing systemic side effects. **Mechanism:** 1. **Enhanced Permeation:** The nanoparticles possess a small diameter (136 nm), which facilitates their passage across the BBB by increasing transmembrane permeability. 2. textbf Targeted Binding: Fucoidan, a natural sulfated polysaccharide, contains sulfate groups on its L-fucose backbone that specifically bind to P-selectin on tumor blood vessels. This interaction triggers receptor-mediated endocytosis, ensuring selective uptake by tumor cells. 3. **Controlled Release:** The nanocarrier exhibits pH-responsive properties, releasing Vismodegib preferentially in the acidic tumor microenvironment, which enhances localized drug action. Fucoidan itself is biocompatible and seemingly harmless; it functions as a stealth carrier, efficiently delivering Vismodegib to the tumor, where the drug is released and exerts targeted cytotoxic effects on malignant cells.

Table A6. Deception Stratagems 6: Luring the tiger out of his den (调虎离山).

Clinical Application Scenarios
Heavy Particle Radiotherapy for Deep-Seated Tumors. Heavy particle radiotherapy is a cutting-edge treatment modality that accelerates carbon ions to approximately 70% of the speed of light, generating a high-energy carbon ion beam for precise tumor irradiation. Its principal advantage lies in the unique physical properties of carbon ions: as the beam penetrates tissue, it deposits minimal energy along its entry path and releases the majority of its energy, the Bragg peak, precisely at the tumor site. This targeted energy delivery minimizes collateral damage to adjacent healthy tissues, making it especially effective for treating deep-seated, radioresistant solid tumors that respond poorly to conventional photon radiotherapy. **Comparison with Photon Radiotherapy: Precision:** Photon radiotherapy emits energy continuously along its path, affecting both tumor and normal tissues. In contrast, heavy particle radiotherapy deposits maximal energy only at the tumor, significantly reducing harm to surrounding healthy structures. **Biological Effectiveness:** Photons primarily induce single-strand DNA breaks, which are often reparable. Heavy particles, however, cause complex double-strand DNA breaks, leading to more thorough tumor cell eradication. Deep tumors are analogous to "tigers hiding in the mountains." Heavy particle radiotherapy, by accurately confining radiation to the tumor and maximizing destructive power at the target, effectively "lures the tiger from the mountain" and eliminates it with precision.

Table A7. Deception Stratagems 7: Letting the enemy off in order to catch him (欲擒故纵).

Clinical Application Scenarios
Metronomic Chemotherapy: An Innovative Approach for Resistant Tumors. Traditional chemotherapy for malignant tumors utilizes the maximum tolerated dose (MTD), targeting rapidly dividing tumor cells. However, this approach often fails to eradicate tumors, as it eliminates chemotherapy-sensitive cells but spares resistant clones, leading to acquired resistance and eventual relapse. Metronomic chemotherapy offers an alternative strategy, particularly for recurrent and drug-resistant advanced cancers. It involves the regular, frequent administration of low-dose chemotherapy (1/10–1/3 of MTD) without extended breaks, primarily targeting tumor vasculature, especially endothelial cells and circulating endothelial progenitors (CEPs). The clinical results demonstrate that metronomic chemotherapy is an effective, safe, and feasible option for advanced, treatment-resistant malignancies [55].

Table A8. Deception Stratagems 8: Slipping away by casting off a cloak; getting away like the cicada sloughing its skin (金蝉脱壳).

Clinical Application Scenarios
CAR-T Therapy: Precision Immunotherapy for Cancer. In the battle against cancer, CAR-T therapy employs a strategic "divide and conquer" approach. Initially, T cells are isolated from the patient's blood; since only a small number are extracted, tumor cells remain unaware of the intervention. These T cells are then genetically engineered to express chimeric antigen receptors (CARs), enabling them to recognize specific tumor antigens such as CD19 or BCMA. The modified T cells are expanded in vitro, creating a powerful army equipped for targeted attack. Once reinfused into the patient, CAR-T cells precisely seek out and destroy cancer cells, while the body's original immune system remains intact. This process—comprising T cell extraction, genetic modification, amplification, and reinfusion—allows for accurate and efficient elimination of malignant cells. CAR-T therapy not only enhances immune targeting but also provides ongoing surveillance, significantly improving outcomes for patients with refractory or relapsed cancers.

Table A9. Deception Stratagems 9: Attacking the enemy by passing through a common neighbor (假道伐虢).

Clinical Application Scenarios
Stepwise Targeting of Tumor Support Systems in Cancer Therapy. Doctors sometimes employ a strategic two-step approach in cancer treatment. Initially, they exploit certain support cells or physiological pathways—such as tumor-associated macrophages (TAMs) or angiogenesis—to enhance drug delivery or weaken the tumor. For example, TAMs can be used as delivery vehicles, utilizing their natural tumor-homing abilities to transport chemotherapy agents, liposomes, or nanoparticles directly to the tumor site. After the primary tumor burden is reduced, doctors then target these same support systems to prevent cancer recurrence. For instance, therapies such as the CSF1R inhibitor pexidartinib can be administered to eliminate TAMs, which might otherwise shift to a pro-tumor M2 phenotype and promote tumor regrowth. This sequential strategy maximizes treatment efficacy by first "borrowing" a natural ally to attack the tumor, then removing the ally to prevent it from aiding future cancer progression or relapse.

Table A10. Deception Stratagems 10: Stealing the beams and pillars and replacing them with rotten timbers (偷梁换柱).

Clinical Application Scenarios
Biological Control of Mosquito-Borne Diseases via Sterile Mosquito Release. To combat diseases like malaria and dengue, a novel strategy is employed: releasing genetically engineered sterile female mosquitoes into the wild. Instead of directly eliminating mosquitoes, this approach reduces their population by preventing reproduction. Sterile females, created through genetic modification (e.g., CRISPR/Cas9 knockout of oogenesis-related genes such as *doublesex* or *Nix*) or by Wolbachia-induced cytoplasmic incompatibility, mate but cannot produce viable eggs. As these sterile mosquitoes replace fertile ones, the overall mosquito population declines across generations, significantly impeding disease transmission.

Table A11. Deception Stratagems 11: Removing the ladder after the enemy has climbed up the roof (上屋抽梯).

Clinical Application Scenarios
Radiosensitizers: Forcing Cancer Cells Out of Hiding. Rapid tumor growth depletes oxygen within the tumor, causing cancer cells to "hide" in the resting G1 phase, where enhanced DNA repair mechanisms make them resistant to radiation. However, when cancer cells transition to the S phase for DNA synthesis, they lose much of this repair capacity. Doctors exploit this vulnerability using radiosensitizers—drugs that mimic oxygen and deceive cancer cells into perceiving a well-oxygenated environment. This "trick" induces cancer cells to exit the protective G1 phase and enter the S phase. Once in the S phase, radiotherapy is administered. Because cancer cells in this phase cannot effectively repair radiation-induced DNA breaks, they are much more susceptible to apoptosis. This strategy combines radiosensitizers and precise timing of radiotherapy, ensuring that cancer cells are targeted when they are least able to defend themselves, thereby improving the effectiveness of cancer treatment and reducing tumor survival.

Table A12. Deception Stratagems 12: Feigning the madness without becoming insane (假痴不癫).

Clinical Application Scenarios
Hypoxia-Activated Prodrugs: Outsmarting Cancer's Defenses. Cancer cells often evade therapy by exploiting their hypoxic microenvironment, which results from rapid growth and poor oxygen supply. In hypoxia, cells predominantly remain in the G1 phase, upregulate DNA repair enzymes, and become less sensitive to conventional radiotherapy and chemotherapy. To counter this, doctors employ a "deceptive" strategy using hypoxia-activated prodrugs (HAPs), such as tirapazamine (TPZ). Rather than forcing cancer cells out of the G1 phase, therapy allows them to remain "comfortable," then targets them when least expected. (1) TPZ is minimally toxic under normal oxygen conditions, but in the hypoxic tumor microenvironment, it is activated by cellular reductases, generating cytotoxic agents. (2) Activated TPZ inhibits DNA repair enzymes, so DNA breaks in cancer cells cannot be repaired. (3) This approach kills cancer cells even in the protective G1 phase, overcoming their resistance and leveraging their adaptive strategies against them.

Appendix A.2. Leverage (21 Stratagems)

Leverage strategies enable GTAI to exploit external or internal factors, such as patient-specific vulnerabilities, environmental influences, or systemic weaknesses, to shift the therapeutic balance in favor of the patient. These stratagems may involve using combination therapies, harnessing immune responses, or manipulating the tumor microenvironment to improve clinical outcomes. By systematically applying leverage, GTAI can steer the clinical trajectory toward safer, more effective, and more durable treatment responses. The leverage category comprises 21 stratagems, each detailed in Tables A13–A33.

Table A13. Leverage Stratagems 1: Relieving the state of Zhao by besieging the state of Wei (围魏救赵).

Clinical Application Scenarios
Ipilimumab: Reactivating T Cells by Blocking CTLA-4. Cancer cells excel at evading immune detection by exploiting immune checkpoints. The CTLA-4 protein, a key negative regulator on T cells, binds to the B7 protein on antigen-presenting cells (APCs), delivering an inhibitory signal that suppresses T cell activation. By leveraging this pathway, cancer cells effectively send a "stop" signal to T cells, preventing an immune attack. Ipilimumab, an immune checkpoint inhibitor, targets this mechanism. It binds specifically to CTLA-4, blocking its interaction with B7. This action prevents CTLA-4 from transmitting inhibitory signals, thereby "releasing the brakes" on T cell activation. With the "stop" signal interrupted, T cells are reactivated, recognize cancer cells as threats, and mount a renewed immune response against the tumor. Through CTLA-4 blockade, ipilimumab empowers the immune system to overcome cancer's defenses and enhances the effectiveness of immunotherapy in cancer treatment.

Table A14. Leverage Stratagems 2: Plundering a burning house (趁火打劫).

Clinical Application Scenarios
Oncolytic Viruses: Selective Cancer Cell Lysis and Immune Activation. Oncolytic viruses (OVs) are natural or genetically engineered viruses that selectively infect and destroy cancer cells while stimulating anti-tumor immunity. Common OVs include herpes simplex virus type 1 (HSV-1), vesicular stomatitis virus, and vaccinia virus. For example, modified HSV-1 targets melanoma by entering tumor cells via specific receptors (e.g., gD-HVEM), then replicates extensively, causing cell lysis and releasing new viral particles to propagate infection. Simultaneously, OVs recruit $CD8^+$ T cells, enhancing the immune response and promoting collaborative tumor cell killing.

Table A15. Leverage Stratagems 3: Killing someone with a borrowed knife (借刀杀人).

Clinical Application Scenarios
Targeted Treatment of Acute Promyelocytic Leukemia with Arsenic Trioxide. Acute promyelocytic leukemia (APL), a highly aggressive form of leukemia, results from a chromosomal translocation that creates the PML-RARA fusion gene. This gene encodes the abnormal PML-RARα fusion protein, which disrupts the normal maturation and programmed death of white blood cells, leading to their uncontrolled accumulation. Effective treatment requires targeting and inhibiting the PML-RARα protein to restore normal white blood cell development. Remarkably, doctors have discovered that arsenic trioxide—a substance historically known for its toxicity—can inhibit the synthesis and promote the degradation of PML-RARα. By blocking the activity of this fusion protein, arsenic trioxide enables the maturation and apoptosis of leukemic cells, allowing normal blood cell production to resume. Although arsenic is inherently toxic, its controlled use in APL therapy transforms a harmful compound into a life-saving drug, exemplifying the power of targeted molecular treatment in modern oncology.

Table A16. Leverage Stratagems 4: Waiting at one's ease for the exhausted enemy (以逸待劳).

Clinical Application Scenarios
Prone Ventilation Therapy: A Life-Saving Strategy for Severe Respiratory Failure. Prone ventilation therapy involves positioning patients face-down using specialized beds or manual turning, allowing them to breathe or receive mechanical ventilation in a prone posture. This technique is crucial for severe pneumonia or acute respiratory distress syndrome (ARDS), where conventional ventilation may fail. **Clinical Case:** A patient with severe pneumonia and respiratory failure deteriorated despite maximal ventilatory support and antibiotics. After switching to prone ventilation, nurses repositioned the patient and managed all medical lines. Within an hour, blood oxygen saturation increased to 95%, and respiratory function steadily improved. After five days, the patient was weaned off the ventilator and discharged from the ICU. **Physiological Rationale:** Prone positioning uses gravity to aid drainage of pulmonary secretions, preventing alveolar collapse. It also relieves compression of the dorsal lung regions by the heart and abdominal organs, enhancing oxygen exchange. This approach maximizes alveolar recruitment, reduces ventilation-perfusion mismatch, and significantly improves outcomes in ARDS patients.

Table A17. Leverage Stratagems 5: Watching a fire from the other side of the river (隔岸观火).

Clinical Application Scenarios
Pseudoprogression in Immunotherapy: Identification and Dynamic Evaluation. Cancer patients receiving PD-1/PD-L1 inhibitors may experience pseudoprogression—an initial increase in tumor size or appearance of new lesions (meeting RECIST progression criteria), followed by rapid regression or stabilization. This phenomenon arises from two mechanisms: delayed immune activation allows continued tumor growth, and extensive T cell infiltration induces inflammation, necrosis, and edema, temporarily enlarging the tumor on imaging. Correctly distinguishing pseudoprogression is critical, as premature discontinuation of effective therapy can occur if misidentified. The American Society of Clinical Oncology (ASCO) recommends immunotherapy-specific response criteria (irRC) over traditional RECIST. The irRC incorporates new lesions into total tumor burden, defining true progression only if the burden increases by $\geqslant$25%. **To enhance assessment accuracy, we propose a kinetic evaluation model: during pseudoprogression, tumor growth rate is positive but decelerating (acceleration ¡ 0); during true response, both growth rate and acceleration are negative, reflecting accelerated tumor shrinkage. This dynamic approach enables more precise monitoring of immunotherapy outcomes.**

Table A18. Leverage Stratagems 6: Palming off substitute for the real thing (李代桃僵).

Clinical Application Scenarios
Real Case: Life-Saving Surgery for the sacrifice of a section of the small intestine. A patient presented with intestinal obstruction from acute appendicitis, exhibiting pallor, confusion, and signs of shock. During surgery, the doctor discovered continuous bleeding and fluid in the abdomen. Examination revealed the appendix adhered to the small intestine, creating a constrictive loop that caused ischemia and necrosis of approximately 1.2 meters of distal ileum. To save the patient, the necrotic segment was surgically removed. Following the procedure, the patient recovered consciousness and his life was successfully preserved, demonstrating the critical importance of timely surgical intervention in severe abdominal emergencies.

Table A19. Leverage Stratagems 7: Resurrecting a dead soul by borrowing a corpse (借尸还魂).

Clinical Application Scenarios
New Uses for Old Drugs: Expanding Therapeutic Potential. "Old drugs" are medications already approved or in clinical trials; "new uses" involve identifying novel indications for these agents. Because old drugs have extensive clinical histories and well-established safety profiles, repurposing them can accelerate drug development and reduce risks. Examples: (1) Propranolol, a non-selective β-blocker originally used for coronary heart disease and hypertension, is now being explored for treating osteoporosis and melanoma. (2) Cimetidine, the first histamine H2 receptor antagonist for peptic ulcers, has shown efficacy in conditions such as chronic obstructive pulmonary disease and HIV infection, highlighting the promise of drug repurposing.

Table A20. Leverage Stratagems 8: Catching the thief by closing/blocking his escape route (关门捉贼).

Clinical Application Scenarios
Antibody Drug Conjugates (ADCs): Targeted Cancer Therapy. Antibody drug conjugates (ADCs) are innovative therapeutics created by chemically linking a monoclonal antibody to a potent cytotoxic molecule via a stable linker. This design allows ADCs to deliver cytotoxins specifically to cancer cells, minimizing systemic toxicity. For example, gemtuzumab ozogamicin (Mylotarg, Pfizer) targets CD33 on leukemia cells. Its antibody component binds to CD33, enabling the ADC-antigen complex to be internalized by the tumor cell. This complex is trafficked through endosomes and ultimately fuses with lysosomes, effectively "closing the door" on the cancer cell. Inside the lysosome, the cytotoxin calicheamicin is released, causing DNA damage and triggering apoptosis—"catching the thief" within the cell.

Table A21. Leverage Stratagems 9: Befriending the distant enemy while attacking a nearby enemy (远交近攻).

Clinical Application Scenarios
Ecological strategy in microbiota transplantation. GTAI elucidates that colonization resistance in fecal microbiota transplantation (FMT) follows the principle of "Befriending the distant enemy while attacking a nearby enemy." When the donor and recipient microbiota are closely related, competition for intestinal ecological niches is intense, resulting in high colonization resistance and reduced transplantation success. Conversely, when donor and recipient microbiota are distantly related, niche complementarity increases, colonization resistance decreases, and engraftment is more successful. FMT introduces probiotics, fungi, or bacteriophages from healthy donors to patients, restoring gut flora and treating disease. Colonization resistance refers to the inability of transplanted microbes to persist in the recipient's gut. Using distantly related donors, such as in children with autism spectrum disorder and gastrointestinal symptoms, lowers colonization resistance and improves therapeutic outcomes, highlighting the strategic advantage of genetic distance in microbiota transplantation.

Table A22. Leverage Stratagems 10: Mudding the water to catch the fish; fishing in troubled waters (混水摸鱼).

Clinical Application Scenarios
Interdisciplinary validation of cocktail therapy. Acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV), a retrovirus that targets the immune system. HIV enters host cells through endocytosis. Once inside, HIV reverse transcriptase undertakes three critical functions: 1. Using its own RNA as a template, reverse transcriptase synthesizes DNA, initially forming an RNA-DNA hybrid. 2. The enzyme then generates gaps in the RNA strand of the hybrid, producing short RNA fragments. 3. These RNA fragments act as primers; reverse transcriptase uses them with single-stranded DNA as a template to synthesize double-stranded DNA. This viral DNA is then integrated into the host genome, where it is replicated, transcribed, and translated alongside host DNA, establishing persistent infection. Following integration, viral DNA is transcribed and translated by the host cell to produce the Gag-Pol polyprotein. This polyprotein strategy enables rapid viral replication, akin to "economies of scale." HIV-1 protease subsequently cleaves the polyprotein into functional viral proteins, including reverse transcriptase itself. HIV's high mutation rate allows it to rapidly develop resistance to monotherapy. To counteract this, clinicians employ "cocktail therapy" (Highly Active Antiretroviral Therapy, HAART), which combines 2–4 drugs from at least two classes: reverse transcriptase inhibitors (NRTIs/NNRTIs) and protease inhibitors (PIs). This multi-drug approach targets different stages of the viral life cycle, greatly reducing the chance of resistance. **Interdisciplinary validation:** Leveraging mathematical modeling, military strategy, and logical reasoning, GTAI demonstrates that multi-drug combination therapy for HIV (cocktail therapy) drastically lowers the probability of drug resistance, especially as the number of drugs increases. This mirrors the "divide and conquer" military stratagem, effectively blocking viral escape routes. **Theoretical Model and Formulas:** Let P_i represent the probability that drug i kills the virus ($i = 1, 2, 3, 4$). The probability that a virus survives a single drug is $1 - P_i$. Assuming independence, the probability of resistance to all four drugs is: $$P_{\text{resist}_{\text{all}}} = \prod_{i=1}^{4}(1 - P_i)$$ The overall kill rate for combination therapy is: $$P_{\text{combined}} = 1 - P_{\text{resist}_{\text{all}}} = 1 - \prod_{i=1}^{4}(1 - P_i)$$ **Example:** If $P_i = 0.9$ for each drug, then $P_{\text{resist}_{\text{all}}} = 0.1^4 = 0.0001$, so the combination kill rate is 0.9999.

Table A23. Leverage Stratagems 11: Putting artificial flowers on trees (树上开花).

Clinical Application Scenarios
Iodine Contrast Agents in X-ray Imaging. In standard X-ray imaging, the similar densities of muscles, blood vessels, fat, and organs result in comparable X-ray attenuation and overlapping grayscale images. Intravenous injection of iodine contrast agents introduces regions with higher X-ray attenuation due to iodine's density, distinguishing these areas from surrounding tissues. This differential transmittance creates enhanced contrast on X-ray images, clearly revealing the distribution of iodine within organs and blood vessels. As a result, iodine contrast agents significantly improve the visualization of anatomical structures, enabling doctors to more accurately detect and diagnose abnormalities within the body.

Table A24. Leverage Stratagems 12: Presenting a bold front to conceal unpreparedness (空城计).

Clinical Application Scenarios
Placebo Effect: Mechanism and Clinical Application. The placebo effect describes symptom relief in patients who receive an inactive treatment, driven by their expectation or belief in its efficacy. Examples include administering sugar pills or performing sham surgeries (superficial incisions without actual intervention). Mechanistically, when mice anticipate pain relief, neurons in the anterior cingulate cortex activate signals to the pontine nucleus, an area rich in opioid receptors. This expectation-driven signaling enhances endogenous opioid activity, resulting in real pain reduction. Clinically, doctors may prescribe placebos to patients with sleep disorders who are discontinuing medication, helping to ease anxiety related to withdrawal. The placebo effect thus harnesses the power of expectation to produce measurable physiological and psychological benefits.

Table A25. Leverage Stratagems 13: Turning from the guest into the host (反客为主).

Clinical Application Scenarios
From Passive Treatment to Active Prevention: The Case of Cervical Cancer. The transition from passive disease treatment to active prevention exemplifies the strategy of "turning the tables." Cervical cancer, largely caused by human papillomavirus (HPV), is highly preventable. Instead of being a "guest" who only acts after illness arises, individuals can take charge as "hosts" by proactively seeking vaccination. Gardasil 9, a 9-valent HPV vaccine, protects against nine HPV types responsible for about 90% of cervical cancer cases. Including women and men aged 27–45 in vaccination programs effectively prevents HPV infection. Notably, 5–8 years after widespread vaccination, the infection rates of high-risk HPV16 and HPV18 declined by 83% in women aged 13–19 and 66% in those aged 20–24.

Table A26. Leverage Stratagems 14: Beating the grass to frighten the snake (打草惊蛇).

Clinical Application Scenarios
"Alerting the Snake": Systematic Diagnosis Uncovers a Hidden Threat. When a patient presents with vague or generalized symptoms, GTAI will give a systematic clinical approach to uncover the true cause. **Real case:** An elderly woman arrived at a Shanghai emergency department with diffuse discomfort, sweating, sneezing, runny nose, and a sudden loss of movement in her hands and feet lasting over ten minutes. Initial examination revealed normal muscle strength, a low fever, and mild respiratory symptoms. However, the doctor recognized the acute limb paralysis as a possible neurological event and immediately ordered a head CT scan. Imaging revealed a subarachnoid hemorrhage—an acute hemorrhagic stroke. Prompt surgical intervention was arranged, ultimately saving the patient's life. This case exemplifies the importance of thorough clinical reasoning and timely investigation.

Table A27. Leverage Stratagems 15: Picking up something in passing (顺手牵羊).

Clinical Application Scenarios
Example: Simultaneous Management of Multiple Lesions. In surgical oncology, GTAI will assess for additional lesions during the removal of a primary tumor. **Medical scenario:** A patient's gastroscopy revealed gastric antral mucosal carcinoma. During endoscopic resection of the primary lesion, the surgeon identified an additional suspicious area at the gastric cardia. Seizing the opportunity, the surgeon performed endoscopic submucosal dissection to remove both the newly discovered lesion and another small lesion concurrently. Final pathology confirmed that the cardia lesion was a high-grade intraepithelial neoplasia—one step away from invasive gastric cancer.

Table A28. Leverage Stratagems 16: Giving the enemy something to induce him to lose more valuable things (抛砖引玉).

Clinical Application Scenarios
mRNA Vaccines: Safe and Effective. Traditional vaccines introduce antigenic proteins or attenuated pathogens to stimulate the host immune response. However, there is a risk that incomplete inactivation of the virus during production could lead to unintended host infection. In contrast, mRNA vaccines avoid this risk entirely, as they do not contain any virus particles. Instead, these vaccines use messenger RNA (mRNA) coding for a viral protein, such as the SARS-CoV-2 spike protein, encapsulated in lipid nanoparticles for delivery. Upon injection, the mRNA is taken up by host cells, which then produce the spike protein. The immune system responds by generating antibodies and activating T cells against the spike protein. Later, if the vaccinated individual encounters the actual virus, the immune system rapidly recognizes the spike protein and mounts a swift, effective response, neutralizing the pathogen before it can cause disease.

Table A29. Leverage Stratagems 17: Reviling/abusing the locust tree while pointing to the mulberry (指桑骂槐).

Clinical Application Scenarios
Coupling Strategy: The Case of Bevacizumab. When two biological processes, A and B, are tightly coupled, targeting one inevitably affects the other. Criticizing or inhibiting A is, in effect, a means of influencing B. The GTAI drug design approach leverages this coupling: by impairing A, B is also compromised. Bevacizumab exemplifies this strategy. As an anticancer drug, it inhibits angiogenesis (A) by specifically binding to vascular endothelial growth factor A (VEGF-A). Since angiogenesis is essential for providing nutrients and oxygen (B) to tumors, blocking this pathway deprives cancer cells of critical resources. Consequently, tumor growth is suppressed and tumor size is reduced. Thus, targeting angiogenesis indirectly but effectively limits tumor progression through this biologically coupled relationship.

Table A30. Leverage Stratagems 18: Sowing discord among the enemy (反间计).

Clinical Application Scenarios
Anaerobic *Salmonella* YB1 as an Anti-Tumor Agent: Mechanism and Safety. Salmonellosis is a common zoonotic infection caused by *Salmonella*, typically transmitted through contaminated food or water. Symptoms include fever, abdominal pain, diarrhea, nausea, and dehydration. Genetically engineered anaerobic *Salmonella* YB1 offers a novel cancer therapy. YB1 is designed to proliferate exclusively within the hypoxic microenvironment of tumors, sparing normal oxygen-rich tissues. When liposome-encapsulated YB1 is injected into the patient, the bacteria colonize tumors and release cytotoxic factors, such as flagellin, directly killing cancer cells. In breast cancer mouse models, YB1 slowed tumor growth by approximately 50% and completely inhibited lung metastasis. However, a major challenge to clinical application is infection-related toxicity. Although gene editing approaches, such as deleting the msbB virulence gene, can reduce Salmonella toxicity by 99.99%, residual toxicity to normal tissues remains a safety concern and must be carefully managed in future therapies.

Table A31. Leverage Stratagems 19: Using seductive women to corrupt the enemy (美人计).

Clinical Application Scenarios
Hidden Harm: The Warburg Effect and 2-Deoxyglucose. GTAI designs a solution that appears to be beneficial to cancer cells but actually harms them. The Warburg effect illustrates how tumor cells seem to benefit by favoring anaerobic glycolysis for rapid ATP production, even in oxygen-rich environments. This pathway, while generating ATP at twice the rate of oxidative phosphorylation, appears to support uncontrolled cellular proliferation. During glycolysis, each glucose molecule first consumes 2 ATP, then produces 4 ATP, resulting in a net gain of 2 ATP. However, this perceived advantage becomes a hidden vulnerability. Administration of 2-deoxyglucose (2-DG), a glucose analogue, exploits this metabolic trait. 2-DG competes with glucose for hexokinase binding, consuming 1 ATP but halting subsequent glycolysis steps. As a result, no ATP is produced, and cancer cells suffer lethal energy deprivation.

Table A32. Leverage Stratagems 20: Deceiving the enemy by torturing one's own man (苦肉计).

Clinical Application Scenarios
Toward Universal Antivenom: Innovations Inspired by Snake Collector Tim Friede. Antivenom serum is the standard treatment for venomous snakebites, but each serum is typically specific to only one or a few closely related snake species. Most venomous snakes lack dedicated antivenom, and even for the same species, antivenom effectiveness can vary widely due to geographic genetic differences. Tim Friede, a snake enthusiast, sought to build immunity by actively exposing himself to snake venom—over 600 injections and 200 bites, for a total of 856 immunizations. Researchers analyzed the memory B cells in his blood and identified two potent antibodies: LNX-D09 (targeting long-chain neurotoxins) and SNX-B03 (targeting short-chain neurotoxins). When combined with Varespladib, a phospholipase A2 (PLA2) inhibitor that blocks venom-induced muscle and nerve damage, these antibodies form a "three-in-one" therapy. This novel treatment effectively neutralized venom from 19 of the world's most dangerous snakes, including the king cobra, black mamba, and taipan.

Table A33. Leverage Stratagems 21: Coordinating one stratagem with another (连环计).

Clinical Application Scenarios
Quadruple Therapy for *Helicobacter pylori* Infection: Mechanism and Clinical Application. *Helicobacter pylori* infection is the primary cause of chronic gastritis, gastric ulcers, and gastric cancer. The recommended treatment is quadruple therapy, which consists of two antibiotics, a proton pump inhibitor (PPI), and a bismuth agent, administered over 10–14 days. This regimen eradicates *H. pylori* through a coordinated, synergistic approach. First, a bismuth agent (e.g., potassium bismuth citrate) is taken 30 minutes before meals. In the acidic gastric environment, it forms a protective layer over ulcerated areas, shielding the mucosa from gastric acid, digestive enzymes, and food particles. Next, a PPI (e.g., omeprazole, lansoprazole, or esomeprazole) is taken after an interval of 15–30 minutes to suppress gastric acid secretion, creating unfavorable conditions for *H. pylori* survival. To maximize efficacy and minimize irritation, two antibiotics (such as amoxicillin, clarithromycin, metronidazole, or levofloxacin) are taken after meals. The dual-antibiotic approach targets *H. pylori* while reducing the likelihood of resistance. Together, these four agents act in concert—protecting the gastric lining, reducing acidity, and delivering potent antibacterial action—to efficiently eliminate *H. pylori* and promote mucosal healing.

Removing the Root Cause (2 Stratagems)

A critical subclass within leverage, the "Remove the Root Cause" stratagems focus on identifying and eradicating the fundamental drivers of disease progression. This may involve targeting the underlying molecular pathways, dismantling supportive disease niches, or interrupting feedback loops that sustain pathology. By addressing root causes rather than only symptoms, GTAI aims to achieve deeper, more sustained control and reduce the risk of recurrence. The removing the root cause category comprises 2 stratagems, each detailed in Tables A34 and A35.

Table A34. Removing the Root Cause Stratagems 1: Capturing the ringleader first in order to capture all the followers (擒贼擒王).

Clinical Application Scenarios
The Ringleader: Cancer Stem Cells. Cancer stem cells (CSCs) are a distinct subpopulation within tumors, characterized by stem-like features: (1) high proliferative capacity, (2) multi-lineage differentiation potential, and (3) notable drug resistance. Tumors are typically composed of a small number of CSCs and a large number of ordinary cancer cells. Most CSCs reside in the G1 phase and possess robust DNA repair mechanisms, rendering them relatively insensitive to conventional chemotherapy and radiotherapy. As a result, standard treatments often eliminate the bulk of ordinary cancer cells, but CSCs survive, proliferate, and differentiate, leading to tumor regrowth and recurrence. For example, during a typical radiotherapy regimen—daily sessions of 10–15 minutes at 20 mGy for 30 days—a tumor may shrink from 5 cm to 4 cm. However, residual CSCs can drive tumor relapse. This issue is particularly pronounced in triple-negative breast cancer, known for its strong drug resistance and lack of effective molecular targets. To address this challenge, researchers at the Icahn School of Medicine at Mount Sinai have developed a novel multikinase inhibitor, 108600, which selectively induces apoptosis in breast cancer stem cells. This targeted approach significantly inhibits both the growth and metastatic spread of triple-negative breast cancer, offering new hope for improved outcomes.

Table A35. Removing the Root Cause Stratagems 2: Extracting the fire wood from under the cauldron (釜底抽薪).

Clinical Application Scenarios
Addressing the Root Cause: An Illustrative Case. Treating only the symptoms of a disease is akin to addressing the smoke without extinguishing the fire; true healing requires identifying and eradicating the root cause. **Case example:** A 35-year-old man developed sudden stomach pain and self-medicated for relief, but his symptoms worsened. Without prompt medical attention, he eventually fainted at home. Emergency evaluation revealed an acute myocardial infarction, not a primary gastrointestinal issue. Immediate coronary angiography showed complete blockage of the right coronary artery. Two cardiac stents were implanted, restoring blood flow and saving the patient's life within half an hour. The connection between heart disease and stomach pain lies in their anatomical proximity: the stomach and the heart's lower wall are separated only by the diaphragm and share an autonomic nerve supply. Thus, heart pain can manifest as stomach pain. This case highlights the importance of thorough diagnosis and addressing underlying causes, rather than merely alleviating symptoms.

Appendix A.3. Escape (1 Stratagem)

The escape stratagem equips GTAI with the capacity to recognize when aggressive intervention is no longer beneficial or safe. In such scenarios, the system can recommend shifting to supportive or palliative strategies that prioritize patient quality of life and symptom management. By integrating escape tactics, GTAI ensures flexible, patient-centered care, adapting to the evolving risk-benefit landscape and respecting individual treatment goals. The removing the root cause category comprises 2 stratagems, each detailed in Tables A36.

Table A36. Escape Stratagems 1: Decamping being the best; runnning away as the best choice (走为上).

Clinical Application Scenarios
Palliative Care: Definition, Objectives, and Principles. Palliative care refers to comprehensive medical support for patients with life-limiting illnesses who are no longer responsive to curative treatment and have a limited life expectancy. Its primary goal, as defined by the WHO, is to improve the quality of life for patients and their families by preventing and alleviating suffering through early identification, accurate assessment, and effective management of pain and other physical, psychological, and spiritual issues. Key principles include relieving pain and distressing symptoms, affirming life while recognizing dying as a natural process, and neither accelerating nor delaying death. Palliative care integrates psychological and spiritual support, helping patients live as actively as possible until death. Families receive ongoing support, including bereavement counseling. A multidisciplinary team approach addresses the holistic needs of patients and families. Palliative care can be introduced early alongside life-prolonging treatments, contributing to better symptom control, improved quality of life, and potentially influencing disease progression.

References

1. Saeed, S.A.; Masters, R.M. Disparities in health care and the digital divide. *Curr. Psychiatry Rep.* **2021**, *23*, 1–6.
2. Persad, G.; Wertheimer, A.; Emanuel, E.J. Principles for allocation of scarce medical interventions. *Lancet* **2009**, *373*, 423–431.
3. Hamilton, P.T.; Anholt, B.R.; Nelson, B.H. Tumour immunotherapy: Lessons from predator–prey theory. *Nat. Rev. Immunol.* **2022**, *22*, 765–775.
4. Galassi, C.; Chan, T.A.; Vitale, I.; et al. The hallmarks of cancer immune evasion. *Cancer Cell* **2024**, *42*, 1825–1863.
5. Shoham, Y.; Leyton-Brown, K. *Multiagent Systems: Algorithmic, Game-Theoretic, and Logical Foundations*; Cambridge University Press: Cambridge, UK, 2008.
6. Lu, J.; Zhang, H.; Zhou, P.; et al. Fedlaw: Value-aware federated learning with individual fairness and coalition stability. In Proceedings of the IEEE Transactions on Emerging Topics in Computational Intelligence, Online, 18 September 2024.
7. Chang, S.L.; Piraveenan, M.; Pattison, P.; et al. Game theoretic modelling of infectious disease dynamics and intervention methods: A review. *J. Biol. Dyn.* **2020**, *14*, 57–89.
8. Tzu, S. The art of war. In *Strategic Studies*; Routledge: Abingdon, UK, 2008; pp. 63–91.
9. Verstappen, S.H. The Thirty-Six Strategies. 2017. Available online: https://www.chinastrategies.com/wp-content/uploads/2017/04/The-Thirty-Six-Strategies.pdf (ccessed on 30 July 2025).
10. Wang, S.; de Véricourt, F.; Sun, P. Decentralized resource allocation to control an epidemic: A game theoretic approach. *Math. Biosci.* **2009**, *222*, 1–12.
11. Mamani, H.; Chick, S.E.; Simchi-Levi, D. A game-theoretic model of international influenza vaccination coordination. *Manag. Sci.* **2013**, *59*, 1650–1670.
12. Abedrabboh, K.; Al-Majid, L.; Al-Fagih, Z.; et al. Mechanism design for a fair and equitable approach to global vaccine distribution: The case of COVID-19. *PLOS Global Public Health* **2023**, *3*, e0001711.
13. Smith, D.L.; Levin, S.A.; Laxminarayan, R. Strategic interactions in multi-institutional epidemics of antibiotic resistance. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 3153–3158.
14. Kareva, I.; Berezovskaya, F. Cancer immunoediting: a process driven by metabolic competition as a predator–prey–shared resource type model. *J. Theor. Biol.* **2015**, *380*, 463–472.
15. Kareva, I.; Luddy, K.A.; O'Farrelly, C.; et al. Predator-prey in tumor-immune interactions: A wrong model or just an incomplete one? *Front. Immunol.* **2021**, *12*, 668221.
16. Hausser, J.; Alon, U. Tumour heterogeneity and the evolutionary trade-offs of cancer. *Nat. Rev. Cancer* **2020**, *20*, 247–257.
17. Vitale, I.; Shema, E.; Loi, S.; et al. Intratumoral heterogeneity in cancer progression and response to immunotherapy. *Nat. Med.* **2021**, *27*, 212–224.
18. Hu, L.; Wu, Y. Predict to minimize swap regret for all payoff-bounded tasks. In Proceedings of the 2024 IEEE 65th Annual Symposium on Foundations of Computer Science (FOCS), Chicago, IL, USA, 27–30 October 2024; pp. 244–263.
19. Guo, Z.; Wu, Y.; Hartline, J.D.; et al. A decision theoretic framework for measuring ai reliance. In Proceedings of the 2024 ACM Conference on Fairness, Accountability, and Transparency, Rio de Janeiro, Brazil, 3–6 June 2024; pp. 221–236.
20. Yu, J.; Zhang, Y.; Sun, C. Multi-agent evolutionary reinforcement learning based on cooperative games. In Proceedings of the IEEE Transactions on Emerging Topics in Computational Intelligence, Virtual, 5 September 2024.
21. Salvioli, M.; Garjani, H.; Satouri, M.; et al. Stackelberg evolutionary games of cancer treatment: What treatment strategy to choose if cancer can be stabilized? *Dyn. Games Appl.* **2024**,*2024*, 1–20.
22. Lu, Y.; Chu, Q.; Li, Z.; et al. Deep reinforcement learning identifies personalized intermittent androgen deprivation therapy for prostate cancer. *Briefings Bioinform.* **2024**, *25*, bbae071.
23. Sun, C.; Li, Y.; Marini, S.; et al. Phylogenetic-informed graph deep learning to classify dynamic transmission clusters in infectious disease epidemics. *Bioinform. Adv.* **2024**, *4*, vbae158.
24. Zhang, Z.; Huang, M.; Jiang, Z.; et al. Patient-specific deep learning model to enhance 4d-cbct image for radiomics analysis. *Phys. Med. Biol.* **2022**, *67*, 085003.
25. Handawi, K.A.; Kokkolaras, M. Optimization of infectious disease prevention and control policies using artificial life. *IEEE Trans. Emerg. Top. Comput. Intell.* **2021**, *6*, 26–40.
26. Ouyang, H.; Liu, D.; Li, S.; et al. Two-stage deep feature selection method using voting differential evolution algorithm for pneumonia detection from chest x-ray images. In Proceedings of the IEEE Transactions on Emerging Topics in Computational Intelligence, Virtual, 26 July 2024.
27. Zhao, L.; Zhang, Y.; Luo, X.; et al. Selecting heterogeneous features based on unified density-guided neighborhood relation for complex biomedical data analysis. In Proceedings of the 2023 IEEE International Conference on Bioinformatics and Biomedicine (BIBM), Istanbul, Turkiye, 5–8 December 2023; pp. 771–778.
28. Chen, Q.; Xie, W.; Zhou, P.; et al. Multi-crop convolutional neural networks for fast lung nodule segmentation. *IEEE Trans. Emerg. Top. Comput. Intell.* **2021**, *6*, 1190–1200.
29. Yau, T.; Galle, P.R.; Decaens, T.; *et al.* Nivolumab plus ipilimumab versus lenvatinib or sorafenib as first-line treatment for unresectable hepatocellular carcinoma (checkmate 9dw): An open-label, randomised, phase 3 trial. *Lancet* **2025**, *405*, 1851–1864.

30. Guo, S.; Guan, J.; Zhou, S. Diffusing on two levels and optimizing for multiple properties: A novel approach to generating molecules with desirable properties. In Proceedings of the IEEE/ACM Transactions on Computational Biology and Bioinformatics, Virtual, 26 July 2024.
31. Jin, C.; Guo, S.; Zhou, S.; et al. Effective and explainable molecular property prediction by chain-of-thought enabled large language models and multi-modal molecular information fusion. *J. Chem. Inf. Model.* **2025**, *65*, 5438–5455.
32. Li, Y.; Zhou, D.; Zheng, G.; et al. Dyscore: A boosting scoring method with dynamic properties for identifying true binders and nonbinders in structure-based drug discovery. *J. Chem. Inf. Model.* **2022**, *62*, 5550–5567.
33. Zhu, J.; Wei, Y.; Kang, Y.; et al. Adaptive deep reinforcement learning for non-stationary environments. *Sci. China Inf. Sci.* **2022**, *65*, i202204.
34. Liu, Z.; Lu, J.; Zhang, G.; et al. A behavior-aware approach for deep reinforcement learning in non-stationary environments without known change points. *arXiv* **2024**, arXiv:2405.14214.
35. Brown, N.; Bakhtin, A.; Lerer, A.; et al. Combining deep reinforcement learning and search for imperfect-information games. *Adv. Neural Inf. Process. Syst.* **2020**, *33*, 17057–17069.
36. Meta Fundamental AI Research Diplomacy Team (FAIR); Bakhtin, A.; Brown, N.; et al. Human-level play in the game of diplomacy by combining language models with strategic reasoning. *Science* **2022**, *378*, 1067–1074.
37. Li, Z.; Duan, Z.; Chen, G.; et al. Consensus of multiagent systems and synchronization of complex networks: A unified viewpoint. *Trans. Circuits Syst. I Regul. Pap.* **2009**, *57*, 213–224.
38. Hao, Q.; Xu, F.; Chen, L.; et al. Hierarchical multi-agent model for reinforced medical resource allocation with imperfect information. *ACM Trans. Intell. Syst. Technol.* **2022**, *14*, 1–27.
39. Chen, X.; Yi, H.; You, M.; *et al.* Enhancing diagnostic capability with multi-agents conversational large language models. *NPJ Digit. Med.* **2025**, *8*, 159.
40. Vyklyuk, Y.; Manylich, M.; Škoda, M.; et al. Modeling and analysis of different scenarios for the spread of covid-19 by using the modified multi-agent systems–evidence from the selected countries. *Results Phys.* **2021**, *20*, 103662.
41. Zhang, Y.; Zhou, Y.; Jiang, C.; et al. Plug-in electric vehicle charging with multiple charging options: A systematic analysis of service providers' pricing strategies. *IEEE Trans. Smart Grid* **2020**, *12*, 524–537.
42. Jin, W.; Du, H.; Zhao, B.; et al. A comprehensive survey on multi-agent cooperative decision-making: Scenarios, approaches, challenges and perspectives. *arXiv* **2025**, arXiv:2503.13415.
43. Hou, Y.; Sun, M.; Zhu, W.; et al. Behavior reasoning for opponent agents in multi-agent learning systems. *IEEE Trans. Emerg. Top. Comput. Intell.* **2022**, *6*, 1125–1136.
44. Nashed, S.; Zilberstein, S. A survey of opponent modeling in adversarial domains. *J. Artif. Intell. Res.* **2022**, *73*, 277–327.
45. Wu, J.; Li, J.; Wang, Y.; et al. Optimal defense strategy against evasion attacks. In Proceedings of the 2020 16th International Conference on Mobility, Sensing and Networking (MSN), Tokyo, Japan, 17–19 December 2020; pp. 323–329.
46. Jing, Y.; Liu, B.; Li, K.; et al. Opponent modeling with in-context search. *Adv. Neural Inf. Process. Syst.* **2024**, *37*, 61549–61591.
47. Yu, X.; Jiang, J.; Lu, Z. Opponent modeling based on subgoal inference. *Adv. Neural Inf. Process. Syst.* **2024**, *37*, 60531–60555.
48. Hartman, A.L. The role of military strategies in medical thinking. *Perspect. Biol. Med.* **1993**, *36*, 177–183.
49. Tomic, D.; Shaw, J.E.; Magliano, D.J. The burden and risks of emerging complications of diabetes mellitus. *Nat. Rev. Endocrinol.* **2022**, *18*, 525–539.
50. VanderWeele, T.J.; Ding, P. Sensitivity analysis in observational research: introducing the e-value. *Ann. Intern. Med.* **2017**, *167*, 268–274.
51. Rosenbaum, P.R.; Rosenbaum, P.R. *Overt Bias in Observational Studies*; Springer: Berlin, Germany, 2002.
52. Lipsitch, M.; Tchetgen, E.T.; Cohen, T. Negative controls: A tool for detecting confounding and bias in observational studies. *Epidemiology* **2010**, *21*, 383–388.
53. Wu, W.; Guo, F.; Wang, C.; et al. Biomimetic "trojan horse" nanoparticles with biotactic behavior toward tumor-associated bacteria for targeted therapy of colorectal cancer. *Cell Biomater.* **2025**, *1*, 100092.
54. Yoshimura, M.; Kurumadani, H.; Hirata, J.; et al. Case report: Virtual reality training for phantom limb pain after amputation. *Front. Hum. Neurosci.* **2023**, *17*, 1246865.
55. Simsek, C.; Esin, E.; Yalcin, S. Metronomic chemotherapy: a systematic review of the literature and clinical experience. *J. Oncol.* **2019**, *2019*, 5483791.