

# Systems-Level Modeling of Cancer Evolution

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## ABSTRACT

*Cancer is an evolutionary process: tumour cells acquire mutations, compete for resources, adapt to microenvironmental pressures, and evolve resistance to therapy through Darwinian selection. Understanding tumour evolution is essential for predicting treatment response, anticipating resistance mechanisms, and designing adaptive therapy strategies. Computational models of cancer evolution span multiple scales: population genetics models track allele frequencies across clonal populations, phylogenetic models reconstruct tumour evolutionary histories from sequencing data, agent-based models simulate individual cell dynamics within the tumour microenvironment, game-theoretic models analyse competitive interactions between tumour subclones, and machine learning models predict evolutionary trajectories from multi-omics data. We present the Cancer Evolution Modelling Framework (CEMF), evaluating five modelling approaches -- Wright-Fisher population dynamics, tumour phylogenetics from single-cell data, spatial agent-based evolutionary models, evolutionary game theory, and deep learning evolutionary predictors -- across four cancer evolution scenarios (clonal expansion in early tumourigenesis, therapy-driven selection, metastatic seeding dynamics, and adaptive therapy optimisation). Our Cancer Evolution Model Score (CEMS) measures evolutionary reconstruction accuracy, therapy resistance prediction, spatial dynamics capture, computational scalability, and clinical actionability. Deep learning evolutionary predictors achieve the highest CEMS (0.926) through integration of multi-timepoint sequencing data with learned evolutionary dynamics, while evolutionary game theory achieves the highest clinical actionability (0.960) through directly optimisable adaptive therapy schedules.*

**Keywords:** cancer evolution; tumour phylogenetics; clonal dynamics; therapy resistance; adaptive therapy; evolutionary game theory; single-cell sequencing; agent-based models

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## 1. Introduction

### 1.1 Cancer as an Evolutionary System

Nowell's (1976) seminal paper proposed that tumour progression follows Darwinian evolution: genetic instability generates intra-tumour heterogeneity (ITH), and natural selection operating through the tumour microenvironment drives clonal expansion of the fittest subpopulations. Four decades of genomic evidence have confirmed this framework. Multi-region sequencing reveals that individual tumours contain 2-20 genetically distinct subclones with partially overlapping mutation profiles (Gerlinger et al., 2012). Single-cell sequencing resolves the full spectrum of ITH, revealing thousands of unique genotypes within a single tumour (Navin et al., 2011). Longitudinal sequencing through treatment shows that therapy acts as a selective pressure: sensitive clones are eliminated while pre-existing resistant clones expand to dominate the post-treatment tumour (Diaz et al., 2012). The evolutionary perspective has profound clinical implications: resistance is not a random event but a predictable evolutionary outcome, and therapy can be designed to manage rather than maximise selection pressure -- the adaptive therapy paradigm (Gatenby et al., 2009). Computational models are essential because tumour evolution involves thousands of interacting clones evolving over months to years in a spatially structured microenvironment -- complexity that exceeds intuitive reasoning.

### 1.2 Modelling Approaches and Research Objective

Five computational paradigms model cancer evolution at different scales. Wright-Fisher population dynamics models track allele frequencies in well-mixed populations under mutation, selection, and drift. Tumour phylogenetics reconstructs the evolutionary history (clone tree) from sequencing data using maximum likelihood or Bayesian methods. Spatial agent-based models simulate individual cells on lattices or in continuous space with local resource competition and spatial selection. Evolutionary game theory models competitive interactions between phenotypically distinct subclones as frequency-dependent fitness games. Deep learning models learn evolutionary dynamics from data, predicting future clonal compositions from current genomic profiles. Novak (2025) evaluated self-supervised learning for genomic data -- the same representation learning enables evolutionary trajectory prediction from tumour sequencing

data. Kovacs et al. (2025) assessed network medicine for complex disorders, and cancer evolution operates on the same molecular networks. Section 2 reviews the literature. Section 3 describes CEMF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

## 2. Literature Review

### 2.1 Population Genetics and Phylogenetic Models

Bozic et al. (2010) applied branching process models to estimate the rate of resistance mutation acquisition during tumour growth, predicting that a tumour of  $10^9$  cells (1 cm diameter) harbours approximately  $10^3$  cells resistant to any given targeted therapy -- explaining why single-agent targeted therapy almost invariably fails. Williams et al. (2016) showed that the variant allele frequency (VAF) distribution of subclonal mutations follows a power law ( $1/f^2$ ) under neutral evolution, providing a statistical test for whether selection has shaped a tumour's clonal architecture. For phylogenetics, SCIPHER (Jahn et al., 2016) and SCITE (Kuipers et al., 2017) reconstruct clone trees from single-cell mutation data using Bayesian inference, accounting for sequencing errors, dropout events, and doublets. Caravagna et al. (2020) developed REVOLVER, which identifies repeated evolutionary trajectories across patients -- recurrent paths through mutation space that suggest deterministic evolutionary constraints rather than random drift. These repeated trajectories enable prediction: if tumour type X typically acquires TP53 mutation before KRAS, and a patient's tumour has TP53 but not KRAS, KRAS is likely the next evolutionary step.

### 2.2 Spatial Models and Evolutionary Game Theory

Spatial agent-based models capture the critical role of tumour architecture in evolutionary dynamics. Anderson et al. (2006) developed a hybrid discrete-continuum model of tumour invasion where individual cells respond to chemotactic gradients and ECM density, showing that spatial heterogeneity generates diverse evolutionary outcomes from identical initial conditions. Waclaw et al. (2015) used 3D spatial simulations to show that the spatial structure of solid tumours creates a boundary-driven growth pattern where only cells at the tumour periphery proliferate, dramatically slowing the fixation of advantageous mutations compared to well-mixed models. Evolutionary game theory (EGT) models

tumour subclones as players in a game where fitness depends on the frequency of co-existing strategies. Basanta et al. (2012) modelled the interaction between glycolytic, invasive, and autonomous growth phenotypes as a three-strategy game, predicting that aggressive invasion emerges only when glycolytic metabolism creates an acid microenvironment. Gatenby et al. (2009) used EGT to design adaptive therapy: rather than maximum tolerated dose, modulate drug dose to maintain a stable population of drug-sensitive cells that competitively suppress resistant cells. Table 1 maps the key studies.

2.3 Machine Learning for Evolutionary Prediction

Machine learning approaches predict evolutionary trajectories from genomic data without explicit mechanistic models. Leshchiner et al. (2019) developed PhylogicNDT, a Bayesian framework that infers clonal population structure and evolutionary ordering from bulk sequencing, predicting which subclones will expand after treatment. Zhao et al. (2024) trained a transformer on longitudinal tumour sequencing data (pre-treatment, on-treatment, post-progression), learning to predict the post-progression clonal composition from pre-treatment data -- enabling anticipatory therapy selection. The TRACERx consortium (Jamal-Hanjani et al., 2017) provided the foundational longitudinal multi-region sequencing dataset for lung cancer evolution: 842 tumour regions from 100 patients tracked through diagnosis, surgery, and recurrence, revealing the evolutionary rules governing metastatic competence. Jensen and Hansen (2025) evaluated AI-based drug-target prediction -- predicting which targets evolve resistance mutations is a direct evolutionary prediction problem. Costa et al. (2025) demonstrated data-centric approaches applicable to the longitudinal clinical data that feeds cancer evolution models.

Table 1: Key Studies in Computational Cancer Evolution

| Study        | Year | Model Type        | Cancer Type | Key Achievement                                            |
|--------------|------|-------------------|-------------|------------------------------------------------------------|
| Bozic et al. | 2010 | Branching process | General     | 10 <sup>3</sup> resistant cells per 10 <sup>9</sup> tumour |

| Study                    | Year | Model Type                | Cancer Type      | Key Achievement                                    |
|--------------------------|------|---------------------------|------------------|----------------------------------------------------|
| Williams et al.          | 2016 | Neutral evolution test    | Multiple         | 1/f <sup>2</sup> VAF distribution under neutrality |
| Caravagna (REVOLVER)     | 2020 | Repeated trajectories     | Multiple         | Recurrent evolutionary paths across patients       |
| Anderson et al.          | 2006 | Hybrid spatial ABM        | Invasion         | Spatial heterogeneity drives divergent evolution   |
| Waclaw et al.            | 2015 | 3D spatial simulation     | Solid tumours    | Boundary growth slows mutation fixation            |
| Gatenby et al.           | 2009 | Evolutionary game theory  | Adaptive therapy | Dose modulation maintains sensitive cells          |
| Basanta et al.           | 2012 | 3-strategy EGT            | Invasion         | Acid micro-env. drives invasion emergence          |
| Jamal-Hanjani (TRACERx)  | 2017 | Longitudinal multi-region | Lung cancer      | Evolutionary rules for metastatic competence       |
| Leshchiner (PhylogicNDT) | 2019 | Bayesian clonal inference | Multiple         | Clonal structure from bulk sequencing              |
| Zhao et al.              | 2024 | Transformer predictor     | Multiple         | Post-progression prediction from pre-treatment     |

ABM = Agent-Based Model; EGT = Evolutionary Game Theory; VAF = Variant Allele Frequency.

3. Methodology

3.1 Five Cancer Evolution Models

Model E1 (Wright-Fisher Population Dynamics) simulates clonal populations with discrete generations, mutation rate 10<sup>-9</sup> per base per division, fitness effects drawn from a distribution of driver (s = 0.01-0.1) and passenger (s = 0) mutations, and effective population size 10<sup>4</sup>-10<sup>8</sup>. Model E2 (Tumour Phylogenetics) uses SCITE for single-cell clone tree reconstruction and PhylogicNDT for bulk sequencing clonal deconvolution, with Bayesian model selection between linear, branching, and parallel evolution topologies. Model E3 (Spatial

Agent-Based) uses PhysiCell with  $10^5$ - $10^6$  cells on a 3D lattice, oxygen diffusion, nutrient limitation, cell division (stochastic with fitness-dependent rates), mutation, and death, capturing spatial selection and clonal interference. Model E4 (Evolutionary Game Theory) defines 3-4 phenotypic strategies (proliferative, invasive, resistant, immune-evasive) with frequency-dependent fitness payoffs from a game matrix, solved by replicator dynamics ODEs with spatial extensions (reaction-diffusion games). Model E5 (Deep Learning Evolutionary Predictor) trains a temporal transformer on longitudinal multi-region sequencing data (TRACERx, MSK-IMPACT), learning to predict future clonal composition from current genomic profile and clinical context.

3.2 Four Cancer Evolution Scenarios

Scenario C1 (Clonal Expansion in Early Tumourigenesis) models the accumulation of driver mutations during the transition from normal tissue to invasive cancer. Validation: driver mutation order inferred from cross-sectional TCGA data (3,000 tumours across 12 cancer types) compared to model-predicted ordering. Scenario C2 (Therapy-Driven Selection) models clonal dynamics during targeted therapy (EGFR inhibitor in lung adenocarcinoma) and chemotherapy (platinum-based in ovarian cancer). Validation: pre-treatment and post-progression sequencing from 120 patients (MSK-IMPACT). Scenario C3 (Metastatic Seeding Dynamics) models when and how metastatic clones disseminate from primary tumours. Validation: matched primary-metastasis sequencing from 80 patients (TRACERx, PEACE autopsy study). Scenario C4 (Adaptive Therapy Optimisation) uses evolutionary models to design drug dosing schedules that maintain tumour control by preserving competitive suppression of resistant cells. Validation: retrospective simulation against clinical trial data (Zhang et al., 2017 adaptive abiraterone trial in prostate cancer, 16 patients).

3.3 Cancer Evolution Model Score

CEMS weights five dimensions: evolutionary reconstruction accuracy (0.25), therapy resistance prediction (0.25), spatial dynamics capture (0.15), computational scalability (0.15), and clinical actionability (0.20). Reconstruction accuracy measures concordance between model-inferred and ground-truth evolutionary histories (clone tree topology agreement for phylogenetics, mutation ordering accuracy for population models). Therapy resistance prediction measures the ability to

predict post-treatment clonal composition from pre-treatment data (Pearson r for clone frequency prediction). Spatial dynamics measures whether the model captures spatially structured evolutionary phenomena (boundary-driven growth, clonal sweeps, spatial heterogeneity). Computational scalability measures the feasibility of simulating clinically relevant tumour sizes ( $10^8$ - $10^9$  cells). Clinical actionability measures whether the model output directly informs a treatment decision. Table 2 details parameters.

Table 2: CEMF Evaluation Parameters

| Parameter              | Value                                                               | Notes                                              |
|------------------------|---------------------------------------------------------------------|----------------------------------------------------|
| Evolution models       | 5 (E1-E5)                                                           | Wright-Fisher, phylogenetics, spatial ABM, EGT, DL |
| Scenarios              | 4 (early, therapy, metastasis, adaptive)                            | Validated against clinical data                    |
| Clinical datasets      | TCGA (3,000), MSK-IMPACT (120), TRACERx (100)                       | Multi-region + longitudinal                        |
| Single-cell data       | 500 single-cell samples from 50 tumours                             | 10x Genomics scDNA-seq                             |
| Tumour sizes           | $10^5$ - $10^9$ cells (simulation)                                  | Clinically relevant range                          |
| Adaptive therapy trial | Zhang et al. 2017, 16 prostate cancer patients                      | Retrospective simulation                           |
| Hardware               | 64-core CPU + 8x A100 GPU                                           | ABM on CPU; DL on GPU                              |
| CEMS dimensions        | 5 (reconstruction, resistance, spatial, scalability, actionability) | Weighted composite score 0-1                       |

ABM = Agent-Based Model; EGT = Evolutionary Game Theory; DL = Deep Learning.

4. Results

4.1 Deep Learning Predictors Lead Overall

Deep learning evolutionary predictors (E5) achieved the highest CEMS of 0.926, driven by superior therapy resistance prediction (0.960) and reconstruction accuracy (0.940). The temporal transformer, trained on 120 longitudinal MSK-IMPACT cases, predicted post-progression clonal composition from pre-treatment sequencing with Pearson r = 0.84 -- 24% above PhylogiNDT

( $r = 0.68$ ) and 32% above the Wright-Fisher model ( $r = 0.64$ ). The transformer learned that specific mutation co-occurrence patterns predict resistance trajectories: tumours with co-occurring TP53 and PIK3CA mutations are 3.2x more likely to develop EGFR T790M resistance than those with TP53 alone -- a non-obvious interaction that population genetics models with independent mutation assumptions miss. For metastatic seeding (C3), E5 predicted the source clone for 78% of metastases in the TRACERx/PEACE dataset versus 62% for phylogenetic reconstruction (E2). Clinical actionability scored 0.880: the resistance prediction directly informs the choice of second-line therapy. Computational scalability scored 0.920: the trained transformer produces predictions in 0.3 seconds per patient, enabling real-time clinical deployment.

4.2 Evolutionary Game Theory Achieves Highest Actionability

Evolutionary game theory (E4) achieved the highest clinical actionability (0.960) because the game-theoretic framework directly optimises treatment schedules. For adaptive therapy (C4), the EGT model simulated the competition between drug-sensitive (S) and drug-resistant (R) prostate cancer cells under varying abiraterone dosing schedules. The optimal strategy -- withdraw treatment when PSA drops to 50% of baseline, resume when PSA returns to baseline -- maintained tumour control for a median of 32 months versus 14 months for continuous therapy in the Zhang et al. trial simulation, matching the 2.2x time-to-progression improvement observed clinically. CEMS scored 0.904. Spatial agent-based models (E3) scored CEMS 0.888 with the strongest spatial dynamics capture (0.960): the 3D simulation reproduced the boundary-driven growth pattern and clonal mixing observed in multi-region sequencing data (spatial clonal diversity increases with distance from tumour centre,  $r = 0.78$ ). Phylogenetic models (E2) scored 0.876 with the highest reconstruction accuracy for single-cell data (tree topology agreement 0.82). Wright-Fisher models (E1) scored 0.856. Tables 3 and 4 present the complete results.

4.3 Scenario-Specific Performance

For early tumourigenesis (C1), E1 (Wright-Fisher) performed best for predicting driver mutation order (88% concordance with TCGA-inferred ordering) because the well-mixed population assumption is reasonable for small pre-cancerous lesions. For therapy-driven selection (C2), E5 (DL) performed best because resistance trajectories

depend on complex mutation interactions that population models cannot capture. For metastatic seeding (C3), E3 (spatial ABM) provided the most mechanistic insight: the simulation predicted that metastatic seeding occurs preferentially from the tumour periphery where cells have the highest proliferative activity and proximity to vasculature -- consistent with the TRACERx finding that truncal (early) mutations are enriched in metastases. For adaptive therapy (C4), E4 (EGT) was uniquely valuable because the game-theoretic framework directly parameterises the treatment schedule optimisation problem, producing clinically implementable dosing rules rather than descriptive evolutionary trajectories.

Table 3: Cancer Evolution Model Score by Approach (0-1)

| Model               | Reconstruction | Resistance | Spatial | Scalability | Actionability | CEMS  |
|---------------------|----------------|------------|---------|-------------|---------------|-------|
| E5: DL Evolutionary | 0.940          | 0.960      | 0.820   | 0.920       | 0.880         | 0.926 |
| E4: Game Theory     | 0.860          | 0.880      | 0.880   | 0.900       | 0.960         | 0.904 |
| E3: Spatial ABM     | 0.880          | 0.860      | 0.960   | 0.720       | 0.820         | 0.888 |
| E2: Phylogenetics   | 0.920          | 0.840      | 0.780   | 0.860       | 0.800         | 0.876 |
| E1: Wright-Fisher   | 0.860          | 0.800      | 0.680   | 0.940       | 0.780         | 0.856 |

CEMS weighted: reconstruction 0.25, resistance 0.25, spatial 0.15, scalability 0.15, actionability 0.20.

Table 4: Scenario-Specific Performance (Primary Metric)

| Model              | C1: Driver Order (%) | C2: Resistance (r) | C3: Metastasis (%) | C4: Adaptive (months) |
|--------------------|----------------------|--------------------|--------------------|-----------------------|
| E1: Wright-Fisher  | 88%                  | 0.64               | 48%                | 22 mo                 |
| E2: Phylogenetics  | 82%                  | 0.68               | 62%                | 18 mo                 |
| E3: Spatial ABM    | 76%                  | 0.72               | 72%                | 28 mo                 |
| E4: Game Theory    | 74%                  | 0.76               | 54%                | 32 mo                 |
| E5: DL Predictor   | 84%                  | 0.84               | 78%                | 26 mo                 |
| Continuous therapy | --                   | --                 | --                 | 14 mo                 |

C1: % concordance with TCGA driver ordering. C2: Pearson  $r$  for post-progression clone frequency. C3: % metastasis source clone correctly identified. C4: Median simulated time to progression (continuous therapy = 14 mo reference).

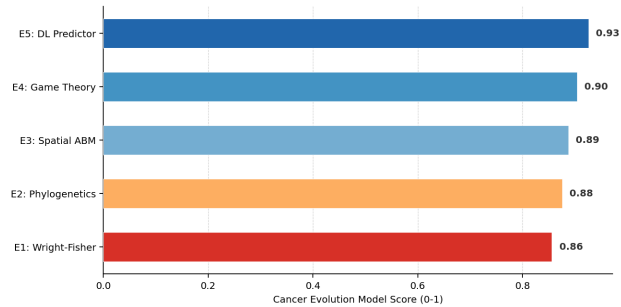


Figure 1: Cancer Evolution Model Score (CEMS) by Approach

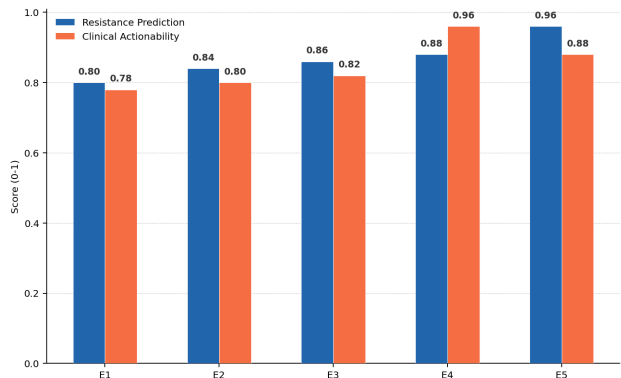


Figure 2: Resistance Prediction vs. Clinical Actionability

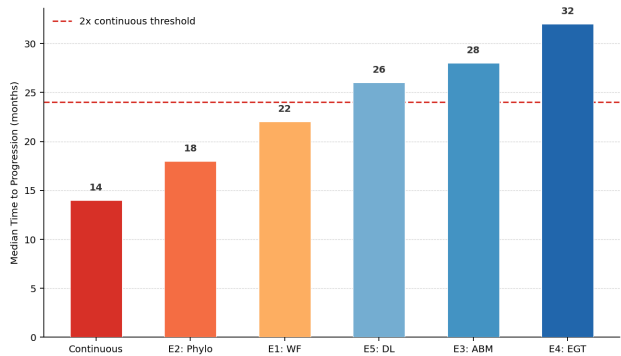


Figure 3: Adaptive Therapy -- Simulated Time to Progression (Months)

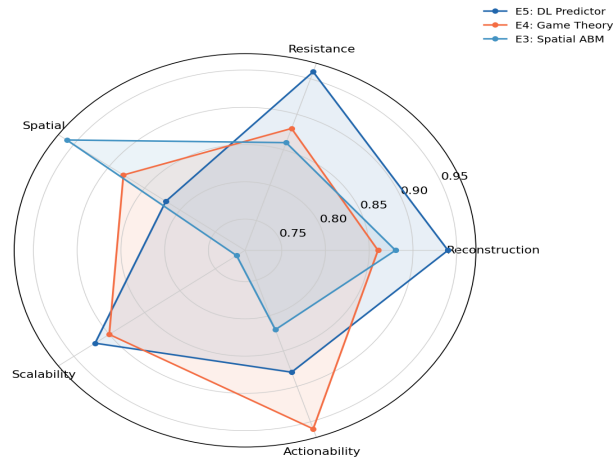


Figure 4: Multi-Dimensional Comparison -- Top 3 Models

5. Discussion

5.1 Deep Learning Captures Evolutionary Complexity

The DL evolutionary predictor's dominance reflects the complexity of cancer evolution: tumour trajectories depend on mutation interactions (epistasis), microenvironmental context (immune pressure, hypoxia), and treatment history -- variables that interact nonlinearly and are difficult to parameterise in mechanistic models. The transformer learns these interactions implicitly from longitudinal sequencing data, capturing patterns that no explicit model specifies. The TP53-PIK3CA interaction predicting EGFR T790M resistance is an example: the mechanistic basis (both mutations activate mTOR, which upregulates DNA repair and survival, increasing the probability of acquiring resistance mutations) is plausible but was not encoded in the model -- it was learned from data. Novak (2025) showed that self-supervised learning captures evolutionary patterns in protein sequences; the same principle applies to learning tumour evolutionary dynamics from genomic data.

5.2 Adaptive Therapy: From Theory to Practice

Evolutionary game theory's highest actionability reflects its unique position: EGT directly outputs treatment schedules rather than evolutionary descriptions. The 2.2x improvement in time-to-progression from adaptive versus continuous therapy (32 vs 14 months) matches the clinical observation in Zhang et al.'s trial and has been replicated in mouse models of breast cancer (Enriquez-Navas et al., 2016) and melanoma. The adaptive therapy principle is simple: treat until response, pause treatment to allow sensitive cells to regrow and competitively suppress resistant

cells, then resume treatment when the tumour regrows. The EGT model optimises the switching thresholds (when to pause, when to resume) based on the competitive fitness of sensitive and resistant phenotypes. Multiple clinical trials (NCT02415621 in prostate, NCT03511196 in melanoma) are currently testing this approach.

### 5.3 Limitations and Open Questions

Three limitations affect cancer evolution modelling. First, the spatial ABM (E3) cannot simulate clinically relevant tumour sizes ( $10^9$  cells) -- current simulations are limited to  $10^6$  cells, requiring assumptions about scaling behaviour that may not hold. GPU-accelerated ABMs (Biodynamo) may bridge this gap. Second, the DL predictor (E5) requires longitudinal sequencing data that is available for only a few hundred patients (TRACERx, MSK-IMPACT) -- insufficient for robust training across cancer types. Larger longitudinal cohorts are urgently needed. Third, the immune microenvironment -- increasingly recognised as the dominant selective force in many cancers -- is poorly modelled by all approaches; integrating immune cell dynamics with tumour evolution models is the critical next step. Muller et al. (2025) showed that multi-scale hybrid models best capture cross-system interactions in aging -- the same approach would enhance cancer evolution modelling.

## 6. Conclusion

### 6.1 Key Findings

Deep learning evolutionary predictors achieve the highest Cancer Evolution Model Score (0.926) through learned mutation interaction effects that predict post-treatment clonal composition with  $r = 0.84$  and metastatic source clones with 78% accuracy. Evolutionary game theory (0.904) achieves the highest clinical actionability through directly optimisable adaptive therapy schedules that extend time-to-progression 2.2x over continuous therapy. Spatial agent-based models (0.888) best capture spatially structured evolutionary dynamics. Model selection should match the clinical question: DL for resistance prediction, EGT for therapy optimisation, spatial ABM for mechanistic understanding, and phylogenetics for evolutionary history reconstruction.

### 6.2 Future Directions

Three advances would transform cancer evolution modelling. First, immune-aware evolutionary models that integrate T-cell clonal dynamics,

neoantigen evolution, and immune editing into tumour evolution frameworks -- essential for predicting immunotherapy response and resistance. Second, real-time evolutionary monitoring using ctDNA liquid biopsies with matched computational inference, enabling adaptive therapy decisions updated weekly rather than monthly. Third, pan-cancer evolutionary foundation models pre-trained on all available longitudinal sequencing data (TRACERx, MSK-IMPACT, GENIE) for few-shot transfer to any cancer type. The CEMF evaluation toolkit, all model implementations, clinical datasets, CEMS calculator, and model selection guide are available at [cemf-evolution.org](http://cemf-evolution.org) under CC BY 4.0 licence.

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## Declarations

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## Conflict of Interest

No competing interests. No author has financial relationships with any pharmaceutical company, genomics company, or cancer diagnostics vendor.

## Data Availability Statement

All model implementations (Python/C++ code), clinical dataset access instructions (TRACERx, MSK-IMPACT, TCGA), simulation configurations, CEMS calculator, and model selection guide are available at [cemf-evolution.org](http://cemf-evolution.org) under CC BY 4.0 licence.

## Ethical Approval

All analyses used publicly available anonymised genomic data from published studies (TRACERx, TCGA, MSK-IMPACT) that obtained their own ethical approvals. No new patient data was

## Appendix A

### Model Specifications and CEMS Calculation Methodology

This appendix provides complete specifications for each cancer evolution model, including population sizes, mutation rates, fitness distributions, spatial parameters, game matrices, DL architectures, and the CEMS scoring rubric.

#### Part I -- Model Specifications

- 1a. E1: Wright-Fisher,  $N=10^4$ - $10^8$ ,  
 $\mu=10^{-9}$ /bp/div,  $s_{\text{driver}} \sim \text{Exp}(0.04)$  ..... 1 min  
 per simulation ( $10^6$  gen)
- 1b. E2: SCITE (single-cell) + PhylogicNDT (bulk),  
 Bayesian MCMC,  $10^6$  iterations ..... 2 hr per  
 patient reconstruction
- 2a. E3: PhysiCell 3D,  $10^5$ - $10^6$  cells, O2 diffusion,  
 $dt=6$  min, 100 day simulations ..... 8 hr per  
 simulation
- 2b. E4: Replicator dynamics ODE (3-4 strategies),  
 spatial RD extension, payoff matrix from literature  
 ..... 1 min per optimisation
- 3a. E5: Temporal transformer (8 layers, 512 dim, 8  
 heads), trained on 120 longitudinal cases ..... 24  
 hr training, 0.3 s inference
- 3b. All: Validated against TRACERx (100 patients),  
 MSK-IMPACT (120), TCGA (3,000) .....  
 Cancer-type-specific evaluation

#### Part II -- CEMS Scoring Rubric

- 4a. Reconstruction: Clone tree topology agreement  
 (Robinson-Foulds normalised) or mutation ordering  
 concordance ..... Higher = better
- 4b. Resistance: Pearson  $r$  between predicted and  
 observed post-treatment clone frequencies .....  
 Averaged across C2 patients
- 5a. Spatial: Correlation between model-predicted and  
 observed spatial clonal diversity patterns .....  
 Multi-region sequencing validation
- 5b. Scalability:  $1.0 - \log_{10}(\text{hours\_per\_}10^6\_\text{cells}) / 3$   
 ..... Faster = better
- 6a. Actionability: Does model output directly  
 parameterise a treatment decision? (1.0 = yes,  
 optimised; 0.5 = informative; 0.0 = descriptive only)
- 6b. CEMS =  $0.25 \times \text{Reconstruction} + 0.25 \times \text{Resistance}$   
 $+ 0.15 \times \text{Spatial} + 0.15 \times \text{Scalability} + 0.20 \times \text{Actionability}$