Review article

Predictive Modeling of Tumor Growth in Personalized Oncology: Current Trends and Future Directions

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ABSTRACT -

Cancer is still a major global health concern, which is why individualized therapies that are based on each patient's unique genetic, environmental, and lifestyle characteristics are replacing generic ones. Enhancing therapeutic results, directing clinical judgment, and personalizing care are all made possible by predictive modelling. This interdisciplinary field models tumour growth, treatment responses, and disease progression by combining clinical insights, mathematics, and computational science. By combining a variety of factors, predictive modelling increases accuracy; it facilitates individualized treatment planning by combining genetic and tumour-specific data; and it helps with prognosis and drug development by using in silico simulations and early detection. Models of tumour growth can be empirical (Gompertz, Logistic), mechanistic (reaction-diffusion), or hybrid, and they are calibrated using data from genomics, multi-omics, and clinical imaging. Adaptive therapy techniques, real-time model updates, patient-specific parameter estimation, and the combination of pathomics and radiomics for thorough cancer analysis are some recent developments. Across all cancer types, deep learning improves

early detection, classification, and diagnosis. Optimizing treatment plans with digital twins, anticipating immunotherapy and other therapy responses, comprehending drug resistance and tumour evolution, and facilitating virtual clinical trials are some of the key applications in personalized oncology.

KEYWORDS: - *Predictive modelling, Tumor growth dynamics, Personalized oncology, Computational oncology, Mathematical modelling, Artificial intelligence (AI), Machine learning, Deep learning*

1. INTRODUCTION:

Background and motivation:

Cancer is a major global health concern, claiming millions of lives each year and straining healthcare systems. Its increased prevalence is attributed to an ageing population, lifestyle changes, and avoidable risk factors such as smoking and poor diet. (1) Historically, cancer treatment used a generalised strategy. However, due to cancer's intrinsic complexity, there is a rising concentration on personalised therapy. This approach tailor’s treatment to individual genetic, environmental, and lifestyle factors in order to improve outcomes and minimise negative effects. (2) The main motivation of predictive modelling is to help physicians make better treatment choices, customise care, and enhance therapeutic results. Numerous factors, such as immunological responses, angiogenesis, cell proliferation rates, genetic abnormalities, and treatment-induced alterations, affect the formation of tumours. The goal of predictive models is to include these intricate, dynamic processes in computer simulations that can predict how tumours will behave in certain scenarios (3).

Importance of Predictive Modelling in Oncology:

1. Prediction modelling Improves Predictive Accuracy: Although certain risk variables are frequently associated with medical events, concentrating just on these may reduce the predictive accuracy. When compared to risk categorisation alone, research indicates that incorporating a variety of variables—including demographic, clinical, genetic, and lifestyle data—into cancer prediction models improves performance. It has been demonstrated that multivariable models increase outcome prediction accuracy and provide more useful information for clinical staging decisions (4).

2. Personalized Treatment Planning: By combining a patient's genetic profile, tumour features, and clinical history, predictive models allow for individualised therapy plans. These models aid in determining

the most successful treatments, such as which chemotherapy treatments are most likely to be successful or whether immunotherapy will be beneficial for a patient. This precision method lessens side effects and increases therapeutic success (5)

3. Prognostic assessment: By calculating outcomes like overall survival, disease-free survival, and recurrence risk, predictive models aid in prognosis. These evaluations assist patients and physicians in making well-informed choices on long-term care and treatment plans. One genomic test, Oncotype DX, for example, uses gene expression profiles to predict the chance of breast cancer recurrence and determine whether chemotherapy is necessary in instances that are still in the early stages (6).

4. Drug developments and clinical trials: By detecting early indicators of treatment response, improving clinical trial design, and classifying patients who are most likely to benefit from investigational medicines, predictive modelling plays a crucial role in speeding up drug development. Early-stage drug development and testing can be shortened in terms of time, expense, and ethical burden by using in silico models, which computationally recreate intricate biological processes (7).

5. Predictive modelling by Artificial intelligence (AI) and machine learning (ML): Oncology is changing quickly as a result of AI and ML advancements that improve predictive modelling. These technologies, which are fuelled by strong computer systems, AI-based platforms, and increased accessibility to electronic health information, are able to spot intricate patterns in big datasets. Research indicates that AI and ML models can improve accuracy and decision-making by surpassing human clinicians in some cancer prediction and diagnosis activities (8).

Scope and structure of review:

The multidisciplinary topic of predictive modelling of cancer progression combines computational science, mathematics, and oncology. In order to estimate tumour progression and improve treatment plans, this study focuses on both data-driven methods (like artificial intelligence and machine learning) and mechanistic approaches. The scope covers the fundamentals of cancer biology, such as immune response, angiogenesis, and genetic alterations, as well as how these elements are mathematically portrayed in prediction models. Metzcar et al.'s recent work from 2024 offers a thorough review of mechanistic learning, especially hybrid models that combine neural networks and physics-based systems to improve cancer modeling's prediction ability (9). The paper also looks at AI-powered frameworks that use imaging, multi-omics, and clinical data to provide individualised prognostic and treatment recommendations. emphasis on the clinical usefulness of digital twins and patient-specific models, emphasising how they can be used to simulate individual therapy responses and guide therapeutic decisions (10). The importance of predictive modelling in oncology, modelling framework categories, the

function of AI/ML, clinical applications, and a discussion of limitations, validation issues, and ethical considerations are all included in the review's structure. These observations are intended to aid in the creation of precise, up-to-date, and patient-focused instruments for individualised cancer treatment (9).

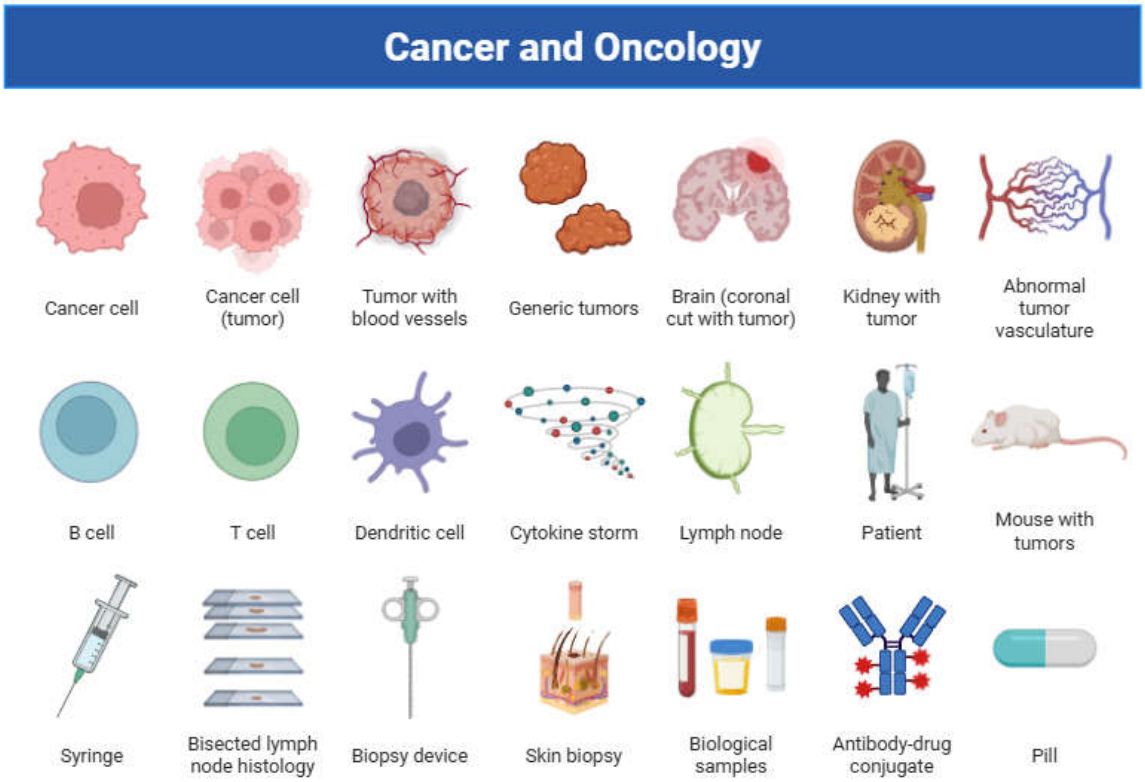

Figure 1: Cancer & Oncology

2. FUNDAMENTALS OF TUMOR GROWTH MODELING:

Biological Basis of Tumour Progression:

For more than a century, the term "tumour progression" has been used to describe the slow development of tumours into more aggressive and malignant forms. Foulds established the groundwork for contemporary knowledge of tumour development and malignancy in 1954 by emphasizing that this process proceeds step-by-step through discrete qualitative stages (11). The ability of neoplastic cells to infiltrate and metastasize is one of the characteristics that determine malignancy. Proteolytic enzymes, adhesion molecules, angiogenic factors, and platelet interactions have all been found to play important roles. Understanding these pathways, particularly angiogenesis, has opened up new therapeutic options (12). Growth rates are often elevated, and local regulatory limitations are evaded when tumours advance. The primary cause of this is a greater growth percentage, which means that more cells actively multiply

rather than differentiating or dying. Changes in cytokine or hormone signalling brought on by receptor loss may be the cause of this dysregulation (13). In addition to disturbed development, tumour progression also includes defective apoptosis, which is particularly associated with BCL2 in lymphomas. Inappropriate protein expression, altered metabolism, and loss of differentiation are also frequent. Retinoic acid receptor alterations prevent normal myeloid differentiation in acute promyelocytic leukaemia (14). The development of medication resistance and immune surveillance evasion—a notion put forth in the 1950s—are frequent features of tumour progression. Through processes such as immunological tolerance, MHC class I downregulation, immunosuppressive factor release, and regulatory T cell activation, tumours may evade immune recognition. These pathways demonstrate the intricacy and unpredictability of tumour evolution, which can happen gradually or suddenly and frequently exhibits notable intratumorally heterogeneity (15).

Mathematical and Computational Models:

Computational and mathematical modelling has emerged as a key tool for comprehending the intricate dynamics of tumour growth and its response to treatment throughout the last 20 years. Researchers can test theories, forecast treatment results, and improve therapeutic approaches thanks to these models' insightful information on tumour development. These models can be broadly divided into three classes: discrete, continuum, and hybrid (16).

Discrete models are useful for simulating single cells or small clusters, frequently utilising cellular automata (CA) or cellular Potts models. These models are ideal for capturing behaviours at the cell level, including as signalling, mutation, and response to therapy. But they are not scalable or have tissue-scale dynamics (17).

Tumours are treated as continuous media in *continuum models*, which describe bulk phenomena including nutrition diffusion, proliferation, and mechanics using ordinary or partial differential equations. Although they don't address single-cell details, these models provide insights at the tissue level. Specifically, multiphase continuum models use mixture theory or TCAT to depict mass and momentum transfer while differentiating between phases like cells, interstitial fluid, and extracellular matrix (18). Discrete agents for cells and continuum fields for the microenvironment are common examples of *hybrid models* that combine discrete and continuum frameworks. These multiscale models help applications such as tumour invasion and angiogenesis by capturing both tissue-level interactions and cell behaviours (19). By effectively simulating tumour growth and treatment response, mathematical models reduce biological variability and experimental expenses. They evaluate theories about tumour growth and direct treatment planning after being calibrated with clinical data (20-22). Differential equations and agent-based models

are two methods that provide insights into the dynamics of cancer and prediction capability. Their use in oncology research is still growing (23-25).

3. TYPES OF TUMOUR GROWTH MODEL:

Empirical model (e.g. Gompertz model):

Oncology's mathematical modelling has advanced more slowly than disciplines like immunology, in part because there isn't a unifying framework like Jerne's network theory [26]. Though understudied, the autocrine/paracrine theory [27] provides a possible conceptual framework. Due to a lack of high-quality data, many of the various tumour models that are available are unvalidated [28–30]. Reproducible growth curves are provided by multicellular tumour spheroids, allowing for thorough model testing [31]. These systems have demonstrated cell-cell interactions-driven spontaneous regression [32]. To increase the realism and prediction capacity of tumour growth models, autocrine signalling strength can be measured using a "magnification factor" [33].

For instance,

1. ***The Gompertz model*** is a popular mathematical model for describing tumour growth because it can accurately depict the sigmoidal (S-shaped) growth pattern seen in many solid tumours (34).

   Gompertz Equation;

$$\frac{dV(t)}{dt} = \lambda V(t) In(\frac{K}{V(t)})$$

   where, V(t): Tumour volume at time t

   λ: Initial growth rate

   K: Carrying capacity (maximum sustainable tumor volume)

2. ***The logistic model*** also another popular mathematical model which shows that when tumour size gets closer to a maximum limit known as the carrying capacity, the rate of growth slows. Because it takes into consideration constraints like nutrient availability, space, and immunological reaction, it is more practical than exponential growth (35).

   Logistic equation;

$$V(t) = \frac{K}{1 + (\frac{K - V0}{V0})e^{-rt}}$$

   Where, V(t): Tumour volume at time t

   V0: Initial tumour volume at t=0t = 0t=0

K: Carrying capacity (maximum tumour size) , r: Intrinsic growth rate, t: Time

Mechanistic model:

Rather than merely fitting observed data, mechanistic models of tumour growth seek to explain the biological mechanisms underlying tumour development. In contrast to empirical models, mechanistic models use mathematical equations derived from systems biology, biochemistry, and biophysics to account for angiogenesis, immunological interactions, cell proliferation, and nutrient diffusion (36).

For instance, *reaction–diffusion models* are a class of mechanistic tumour growth models that explain how tumour cells interact with their surroundings and move through tissue by combining spatial diffusion (such as migration and nutrient transport) with local reactions (such as cell proliferation and apoptosis) (37).

These models frequently consist of:

1. Evaluation of tumour cell density
2. Diffusion and absorption of nutrients and oxygen
3. Interaction with extracellular matrix (ECM) or immune cells.

$$\frac{\partial C(x,t)}{\partial t} = D\nabla^2 C(x,t) + R(C,N)$$

where C(x,t) is tumour cell density, D is the diffusion coefficient, and R (C, N) represents net cell proliferation dependent on nutrient N.

Hybrid model:

In order to more accurately depict the intricate, multiscale nature of tumour evolution and its dynamic interactions with the microenvironment, including vasculature, immune response, and treatment effects, a hybrid model for tumour growth integrates a variety of modelling strategies. Typically, this combines data-driven techniques like statistical inference and machine learning with mechanistic approaches like deterministic differential equations or agent-based simulations (38).

$$\frac{\partial C(x,t)}{\partial t} = \nabla \cdot (D(C)\nabla C) + \lambda(t,\theta)C(1 - K(x)C)$$

Where, C(x,t) be the tumour cell density at location x and time t

D(C) be the diffusion coefficient (may be density-dependent)

$\lambda(t,\theta)$ be the proliferation rate estimated from data

$K(x)$ be the spatially varying carrying capacity

4. DATA SOURCES FOR MODEL PERSONALIZATION:

Clinical data of imaging biomarker: Imaging biomarkers (IBs) are characteristics, such as physiologic or radiographic features, that are measured as markers of pathogenic or normal biological processes or responses to interventions. They can be categorical or quantitative (numerical). IBs are used on a daily basis in oncology and are essential to the routine management of cancer patients. Their clinical applications include cancer screening, diagnosis, and staging; treatment targeting; patient stratification guidance; and the prediction and tracking of therapeutic efficacy and toxicity. (39)

Several IBs are well-established and used routinely in healthcare worldwide. Clinical TNM stage, derived from various imaging modalities, is a categorical IB that guides the management of nearly every patient with a solid tumor and is prognostic in almost all cancers. It can also be predictive in certain contexts, such as distinguishing localized from locally advanced prostate cancer to predict the benefit from bicalutamide monotherapy. The assessment of objective response, defined by criteria like RECIST, is an ordered categorical IB derived from CT, MRI, and PET. It is used worldwide to guide decisions on whether to continue, discontinue, or switch therapy and has been extensively validated and qualified by regulators for approving new drugs. Left ventricular ejection fraction (LVEF), measured by scintigraphy, ultrasound, or MRI, is a safety and monitoring IB that guides the management of many cancer patients, particularly those receiving therapies like trastuzumab. A confirmed decrease in LVEF is a key indicator of cancer therapy-related cardiac dysfunction. A safety and monitoring indicator that directs the treatment of many cancer patients, especially those undergoing treatments like trastuzumab, is left ventricular ejection fraction (LVEF), which can be determined by scintigraphy, ultrasound, or MRI. One important sign of cardiac dysfunction brought on by cancer treatment is a verified drop in LVEF. (39-40)

Genomic and proteomic data:

According to high stringency analyses, the human genome and proteome are both more than 90% complete as of 2020, primarily because of significant technological advancements over the previous 20 years. The present trend toward precision and personalized medicine is being bolstered by these accomplishments. The proteome is characterized as highly dynamic, whereas the genome is thought to be relatively static and contains the blueprint for about 19,773 predicted proteins. Splice variations, extensive post-translational modifications (PTMs) like glycosylation, phosphorylation, and acetylation, and single amino acid polymorphisms (SAPs) are some of the causes of this dynamism.

Proteogenomic is the term used to describe the combining of data from various 'omics' platforms, especially proteomics and genomics. This method combines important data combinations to provide a more thorough understanding of health and illness. In order to better understand carcinogenesis mechanisms, find therapeutic targets, and assess treatment efficacy, proteogenomic is essential for advancing precision oncology research and clinical practice. The creation and dissemination of genomic and proteomic data in relation to cancer is the focus of numerous programs and resources. With the intention of comprehending biology by means of proteomics, the Human Protein Organization (HUPO) established the HPP in order to populate the human proteome. (41)

Longitudinal patient monitoring

Longitudinal patient monitoring in oncology offers substantial benefits over single-timepoint analysis by repeatedly gathering a variety of data over time. Because cancer is a disease that is dynamic and always changing, this strategy is essential. Longitudinal monitoring allows for the dynamic modification of treatment plans and the prompt identification of abnormalities by capturing temporal patterns. (42)

The cfDNA concentration and variant allele fraction (VAF) of genetic alterations, measured at baseline (T1) and at an early timepoint during treatment (T2), are important longitudinal data. The analysis focuses on how outcomes like Early Death (ED) and Hyper progression (HPD) are predicted by changes in these markers between T1 and T2. According to the study, ED risk is significantly correlated with cfDNA concentration at T2 and its variation (T2-T1), whereas HPD risk is correlated with the relative change in maxVAF (T2-T1/T1). With the help of this temporal data, a two-step risk assessment model based on predetermined cut-offs can be proposed, assisting in the early identification of high-risk patients and promoting treatment customization. (43)

Multi-omics integration:

In cancer, multi-omics integration includes multiple data types. Including liquid biopsy (cfDNA, CTCs), this also includes technologies like transcriptomics, proteomics, and spatial genomics. A thorough analysis of the molecular structure and functional characteristics of tumors is the aim. The establishment of novel biomarkers requires the integration of these intricate datasets, which are frequently aided by deep learning models. This strategy is essential for developing precision oncology, facilitating individualized treatment plans, and attempting to enhance patient outcomes. However, difficulties as clinical implementation and prospective validation exists. (44) One important technology for this is liquid biopsy, which offers information from circulating tumor cells (CTCs) and circulating tumor DNA (cfDNA) (43-44). Patients with breast cancer can have their survival outcomes predicted by integrating multiple omics. The neural network model with feature selection is used to classify patients into high- or low-risk groups

based on a variety of clinical features and omics data types. This combined strategy produced an AUROC of 0.98 and a high predictive accuracy of 94% (45). Timely abnormality detection and dynamic treatment strategy adaptation are made possible by longitudinal data collection (44-45).

Data Source	Description	Applications in Personalization	References
Clinical Imaging Biomarkers	Radiographic or physiological features used to assess disease processes and responses. Includes TNM staging, RECIST criteria, LVEF.	Diagnosis, staging, treatment guidance, efficacy/toxicity monitoring, therapy modification	(39-40)
Genomic and Proteomic Data	Genome: relatively stable; Proteome: dynamic (with PTMs, splice variants, SAPs). Supports the understanding of molecular biology of cancer.	Identifying mutations, therapeutic targets, drug sensitivity, resistance profiling	(41)
Proteogenomics	Integration of proteomics and genomics for a systems-level view.	Understanding tumor biology, discovering therapeutic targets, precision medicine implementation	(41)
Longitudinal Monitoring Data	Time-series tracking of biomarkers like cfDNA, maxVAF at baseline (T1) and during treatment (T2).	Early identification of ED and HPD, dynamic treatment planning, high-risk patient stratification	(42-43)
Multi-Omics Integration	Integration of transcriptomics, proteomics, spatial genomics, cfDNA, CTCs. Supports deep molecular tumor profiling.	Biomarker discovery, patient-specific risk classification, treatment response prediction	(44)
Liquid Biopsy (cfDNA, CTCs)	Non-invasive blood tests that provide real-time molecular insights.	Monitoring tumor progression, resistance, treatment response, and aiding in multi-omics integration	(43-44)
AI-Enhanced Omics Analysis	Application of neural networks and feature selection on combined clinical and omics data.	High-accuracy patient stratification (e.g., AUROC 0.98 for survival prediction in breast cancer)	(45)

Table 1: Data Sources for Model Personalization

5. CURRENT TRENDS IN PREDICTIVE ONCOLOGY:

Patient-specific parameter Estimation:

The estimation of patient-specific parameters is essential for customizing mechanistic tumor models to predict growth and response to treatment. Recent developments for model initialization and calibration over time include repeated imaging and biomarker measurements. Artificial intelligence helps to identify parameters from a variety of data sources, including genetic profiles and medical imaging. One new method for this estimation is the use of integrated frameworks, such as biology-informed neural networks (46). For diagnosis and staging, imaging biomarkers such as clinical TNM stage are used using AI models (39,46).

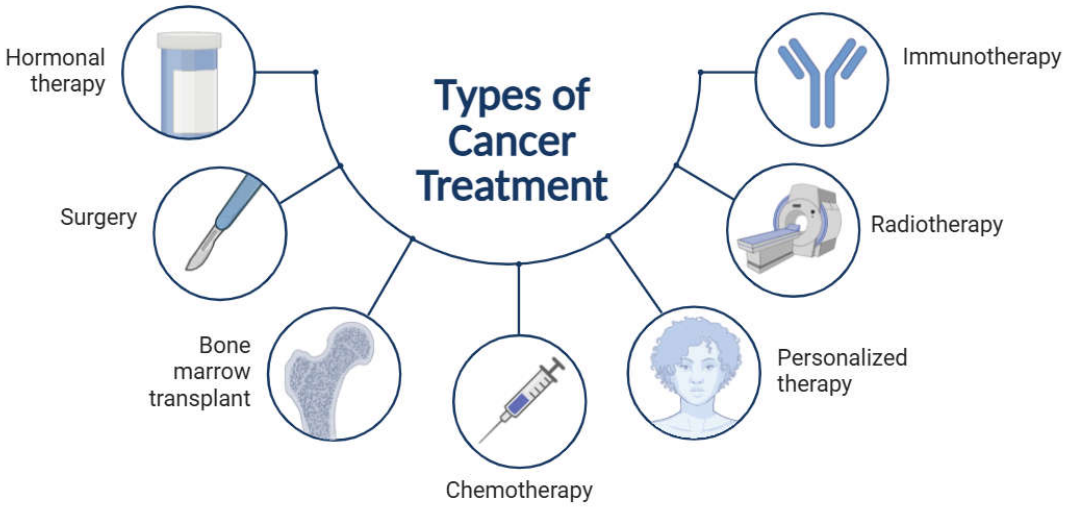

Figure 2: Types of Cancer Cell

Real-Time Model Updating and Adaptive Therapy

Adaptive therapy is intended to improve the accuracy, efficiency, and informational value of drug development, particularly in complex fields like oncology, (48) which can be divided into two categories:

- **Dose-skipping adaptive therapy:**
- **Dose-modulation adaptive therapy**

Real-time model updating is a crucial component of adaptive therapy in the context of cancer treatment, allowing for flexible and patient-specific treatment choices. A thorough explanation of real-time model updating is provided below:

Adequate Patient Observation: Sufficient monitoring of a patient's condition using relevant clinical markers is necessary for accurate real-time prediction. The extent of the disease (e.g., hormone-sensitive versus castration-resistant prostate cancer, localized versus metastatic) and the frequency of data collection to track the course of the disease determine the biomarker selection.

Calculating and Validating Mathematical Models: The selected mathematical model needs to be calibrated and verified to precisely depict patient-specific biomarker dynamics before predictions can be made. This entails evaluating the model's parameters for identifiability and sensitivity in relation to the data at hand. (47)

Biomarkers as an auxiliary marker: In adaptive trials, biomarkers serve as auxiliary markers; however, the main inferential focus is still on clinical endpoints such as progression-free survival (PFS) or overall survival (OS). Yet, for these endpoints to be beneficial, biomarkers do not have to be ideal stand-ins. (48)

Integration with Radiomics and Pathomics:

A recent and quickly developing trend in oncology treatment is the integration of path omics and radiomics, which aims to provide a more thorough and accurate understanding of cancer dynamics. This method goes beyond what single-modal analysis can provide in terms of diagnostic, prognostic, and predictive capabilities by utilizing multi-modal data. Developing a more accurate prognostic or predictive test is the ultimate objective. (50) These methods open up new ways to improve neoadjuvant therapy strategies and could lead to powerful predictive tools. (51)

Radiomics: Radiomics is the high-throughput extraction of quantitative features from X-ray, CT, MRI, and PET images. It provides insights into underlying sub-visual tissue heterogeneity that may not be visible to the human eye by capturing the macroscopic anatomical and functional features of tumors. Although radiomics features offer macroscopic spatial information, but they lack cytological detail. (50)

Pathomics: Pathomics is the process of extracting and mining computer-derived measurements from digital histopathology images. It is also referred to as quantitative histomorphometry analysis. The "gold standard" for conclusive tumor diagnosis is still traditional histological examination, but path omics goes one step further by revealing "sub-visual" prognostic image cues and facilitating a microscopic spatial interrogation of the entire tumor landscape. Tumor-infiltrated lymphocyte (TIL) nuclear arrangement, texture, orientation, and spatial arrangement can all be measured. As Usually, path omics depends on biopsy samples, which can have sampling problems because of intra-tumor heterogeneity. Additionally, some associations between pathetic features and clinical behavior may not have clear biological explanations. (50)

Multi-omics Integration (Radiophonic): The combination of path omics and radiomics, or radiophonic, is a significant development. By combining macroscopic and microscopic features, this method greatly improves the predictive power of models and offers a more thorough picture of tumor heterogeneity. In predicting the effectiveness of neoadjuvant therapy, especially for breast and rectal cancers, this combination has produced promising results. (51)

A recent study combined characteristics from preoperative CT scans (radiomics) and H&E-stained pathological slides (path omics) to create a radiophonic model for gastric cancer. This model sought to predict pathological staging (Stage I-II vs. Stage III) by mainly using the SVM algorithm. It outperformed unimodal approaches in terms of discriminative ability. This demonstrates that precise preoperative staging is feasible and could support precision treatment for gastric cancer. (49)

AI and Deep Learning Enhancements:

Recent developments in artificial intelligence (AI) and deep learning are transforming the treatment of cancer by providing the capacity to independently learn abstract data representations that are essential for early detection and classification. The challenges of managing various inputs, high-dimensional features, and subtle patterns in medical imaging data are addressed by this changing environment. In one study, indeterminate biliary strictures were diagnosed using AI in conjunction with digital single-operator Chol angioscopy (D-SOC). More than 84,000 images from 129 procedures were used to train a convolutional neural network. The model's 82.9% accuracy, 83.5% sensitivity, and 82.4% specificity showed how AI could improve the detection of malignancy in biliary diseases. (52). Another study emphasizes how crucial it is to use deep learning for early breast cancer detection by highlighting the drawbacks of manual screening and advocates for automated AI-based techniques to increase accuracy. (52-53). They are transforming cancer treatment in many ways. It helps detect skin cancer early, enhances urological cancer diagnosis and treatment, and uses CNNs to accurately analyze voice signals in laryngeal carcinoma (52). Advanced CNNs support the use of biomarkers in clinical trials by automating the measurement of metabolic tumor volume from PET-CT scans in DLBCL. (52,39)

Mechanistic models of tumor growth greatly benefit from artificial intelligence (AI), which can improve their capabilities and address some of their inherent limitations, especially through synergistic integration. This combination creates new possibilities for comprehending tumor growth and creating individualized treatment plans (9). By gathering patient-specific information from imaging, genetics, and clinical history to initialize mechanistic models such as ODEs and PDEs, AI helps with parameter identification. This enables more precise tumor growth forecasts that are customized for each patient. AI also makes it possible to create surrogate models that roughly represent intricate mechanistic systems, which are helpful

for large-scale simulations and quick clinical decisions. These surrogate models provide both computational efficiency and predictive power, and they are frequently constructed using sophisticated architectures like transformers. Furthermore, by adding biological constraints to the learning process, Biology-Informed Neural Networks (BINNs) integrate neural networks with biomechanistic models. For instance, mathematical tumor growth models can be used to guide the training of recurrent neural networks on serial imaging data (46).

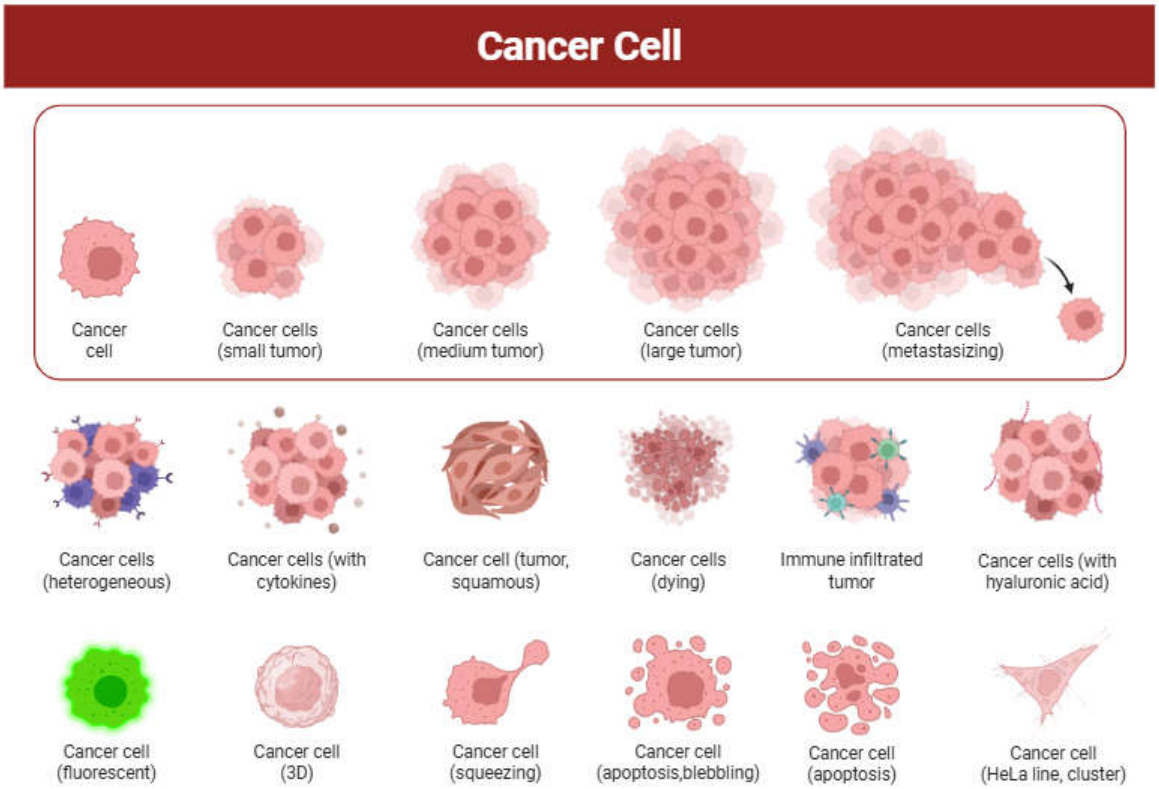

Figure 3: Various Types of Cancer Cell

6. APPLICATIONS IN PERSONALIZED CANCER THERAPY:

Treatment Planning and Optimization:

In order to predict tumor growth and treatment response, mechanistic models provide a framework that is both interpretable and biologically based. This allows for customized, patient-specific simulations, which are similar to "n=1 clinical studies." To customize treatment according to unique tumor characteristics, these models combine data from digital pathology, MRI, PET scans, and omics (such as single-cell RNA sequencing). Optimization frameworks such as the Optimal Control Theory (OCT) aid in modifying treatments (such as radiation and drug dosage) to minimize toxicity and lessen tumor burden (46). Virtual

tumor replicas, or "digital twins," use real-time data to continuously monitor and modify treatment regimens. These resources work together to provide cancer treatment that is safer, more efficient, and highly individualized. (54).

Predictive modeling using AI and ML is being used more and more in personalized cancer therapy with the goal of improving treatment planning and optimization by taking into account the unique characteristics of each patient and tumor. (52). In order to evaluate tumor heterogeneity and forecast treatment response or biomarker expression in cancers such as lung, breast, and rectal cancers, radiomics extracts quantitative features from medical images (CT, MRI, PET). In order to predict prognosis, recurrence, and biomarkers like MSI and CDKN2A, path omics uses artificial intelligence (AI) to analyze digital pathology slides and capture microscopic tumor details. Both provide affordable, non-invasive methods to improve individualized cancer treatment. (51). Deep learning improves the early diagnosis, classification, and detection of many types of cancer, including hematological, biliary, and urological cancers. Accuracy and interpretability are enhanced by methods like hybrid models and explainable AI. Additionally, through in silico simulations, mathematical modeling helps predict tumor growth and optimize treatment plans. (51)

Prognosis and Response Prediction:

Advanced predictive tools are being used more and more in personalized cancer therapy to predict treatment efficacy. Radiomics uses quantitative features extracted from imaging (CT, MRI, PET) to evaluate the microenvironment and tumor heterogeneity, allowing for non-invasive biomarker expression and therapy response prediction. Path omics analyzes histopathology images using artificial intelligence (AI), providing microscopic insights for biomarker, prognosis, and recurrence prediction. Dynamic response prediction is enhanced by delta radiomics, which monitors feature changes throughout treatment. While radiophonic integrates macro- and microscopic imaging data to enhance the prediction of neoadjuvant therapy outcomes, radio genomics associates imaging features with genetic mutations. (50-51).

Drug Resistance and Tumor Evolution:

According to a pharmacometrics modeling study conducted on erlotinib-treated NSCLC patients, acquired resistance—primarily brought on by EGFR T790M mutations—is the main obstacle to treatment success. Different sensitive and resistant cell populations were found using tumor dynamics models, and baseline ctDNA, particularly EGFR variant allele frequency (VAF), was found to predict tumor growth and response to treatment. Given that efficacy seemed to be saturated at standard dosage, the study raises the possibility of dose optimization. Notwithstanding the paucity of available data, the results demonstrate

the clinical value of ctDNA as an early biomarker and lend support to tailored approaches to predict and treat drug resistance in cancer treatment. (57)

Drug resistance arises from gene-gene, protein-protein, and transcriptional regulatory networks within cells, as well as dynamic crosstalk with stromal and immune cells outside the primary tumor, which functions as a complex ecosystem. While recent single-cell studies indicate cell-autonomous resistance, models such as non-cell-autonomous tumor growth demonstrate interconal cooperation. The need for clinic genomic models that incorporate high-quality clinical and genomic data specific to cancer type and stage is highlighted by these divergent opinions on tumor evolution and drug response. This will enhance individualized treatment plans. (58).

Virtual Clinical Trials:

In oncology treatment, virtual clinical trials are developing to take advantage of scientific, technological, and methodological advancements to give participants a more dynamic and adaptable experience, with an eye toward future improvements. Optimizing the digitalization of clinical trials is intended to greatly increase the quality and accessibility of oncology trials. (60) Natural language processing (NLP) AI platforms are being used by cancer centers more and more to extract structured and unstructured patient data from electronic medical records (EMRs), determine eligibility, and match patients to pertinent clinical trials. This strategy is becoming more and more significant as eligibility requirements expand and biomarker-based therapy selection becomes more common.(59) In response to changing regulatory objectives and the emergence of precision medicine, artificial intelligence (AI) tools—in particular, those that use natural language processing (NLP)—connect individual patient data from electronic medical records (EMRs) to genomically-annotated trial registries, speeding up enrollment for rare genomic groups and improving recruitment effectiveness and trial inclusivity.(60)

LIMITATIONS:

Data quality and availability:

The development of prediction tumour growth models in personalised oncology is severely hampered by the scarcity and poor quality of clinical data. Genomic sequencing efforts frequently lack full patient treatment histories and outcome records, which limits their therapeutic value (61). Data privacy and ownership constraints further limit access, preventing model validation with real-world evidence. As a result, researchers rely significantly on pre-clinical models such as cancer cell lines and patient-derived xenografts (PDXs). While cell lines are extensively utilised, they exhibit transcriptional drift and loss of fidelity to the original tumour biology over time (62-63)

Furthermore, interpreting genomic data is difficult—co-occurring driver mutations may result from mutagenesis mechanisms such as chromosomal instability rather than actual functional synergy (64-65). Co-occurring driver mutations may result from chromosomal instability rather than real synergy, which complicates genomic interpretation (64-65). Key biological cues in non-coding areas, methylation, and expression are frequently overlooked (66-67). Thus, genetic profiling supplemented but did not replace clinical judgement (68). Expensive and slow prediction validation impedes clinical adoption (69)

Model Interpretability and Validation:

One of the most significant issues in predicting tumour modelling is a lack of experimental validation and model interpretability. While in silico models can predict gene editing effectiveness, nanocarrier stability, and tumour regression (70), they are just theoretical until tested in vivo. Biological testing has shown tumour targeting, pharmacokinetics, and safety (71). Models can be built to reveal mechanisms such as drug synergy or spatial dispersion, rather than acting as black boxes (72). However, the transfer to clinical relevance is dependent on thorough experimental confirmation (73-74), therefore real-world validation is an essential step.

Regulatory and ethical considerations:

Integrating generative AI into personalised oncology creates significant regulatory and ethical issues. A fundamental difficulty is a lack of transparency: many AI systems operate as black boxes, making clinical judgements difficult to explain (75). In healthcare, interpretability is critical for confidence and acceptance. Data privacy and ownership are especially important, as personalised models rely on sensitive patient information (76). Bias in training data might result in unfair or erroneous predictions, endangering patient safety (77). Researchers are investigating synthetic data to protect privacy and reduce prejudice, although these methods are still in development (78). Furthermore, the lack of consistent regulations hinders responsible AI deployment. Without explicit monitoring, tools can be exploited or misunderstood (79).

Scalability and Clinical Translation:

Integrating predictive oncology models into clinical settings faces two significant challenges: scalability and clinical translation. Scalability requires big, diverse datasets, which are often produced from high-throughput drug screens employing preclinical cancer models. Immortalised cancer cell lines provide scalability but fail to recreate the intricacy of the tumour microenvironment, limiting their clinical utility (80). More physiologically authentic models, such as patient-derived organoids (PDOs) and xenografts (PDXs), better simulate in vivo settings, but they are more expensive, have lower throughput, and take

longer to prepare (81). Furthermore, clinical databases, while growing, remain restricted in size and diversity, making it challenging to capture inter-patient variation (82).

Generalisability continues to be a major difficulty in clinical translation. Models trained on homogenous data frequently perform poorly in varied patient populations due to differences in age, genetics, and treatment procedures (83). Many models also fail to predict clinically relevant outcomes like progression-free or overall survival. The clinical usefulness of data inputs, particularly omics-based profiles, remains restricted (84). Furthermore, opaque AI architectures such as deep learning undermine clinical trust and adoption (85). Infrastructure, legal complexity, and budgetary constraints all impede adoption, especially in low-resource environments.
To address these challenges, models should be verified using real-world clinical datasets, developed with interpretability in mind, and backed by FAIR-compliant data sharing policies (86).

FUTURE DIRECTIONS:

To advance digital twin technology for tumour therapy, current limitations must be overcome and its use in clinical practice expanded. The focus areas for development are clear. Increasing data diversity and availability is essential. Global multi centre data sharing platforms are needed to build large and representative datasets for training and validating models. These should integrate information from clinical trials and real-world patient data across regions to improve generalization and support international collaboration. Interoperability and standardization are also critical. This includes creating common tools, data formats, interface guidelines, and validation methods. Standardization helps manage data fragmentation and supports the integration of multiple data types. This makes the technology more useful and comparable in different clinical settings. The first steps include building interoperable platforms and forming public private partnerships. Establishing international digital twin partnerships will help define shared standards [87]. Digital twins are seen as dynamic models of a patient's tumour and organ systems. They use clinical data, genetic information, imaging, and lab results to simulate tumour behaviour. One goal is to test treatment strategies like chemotherapy, radiation, and immunotherapy virtually to find the best approach with the least risk. As patients go through treatment, the digital twin updates with new data and helps guide decisions, follow up plans, and long-term care. Beyond clinical application, digital twins will support research by improving our understanding of cancer and helping to create new detection methods and therapies [88].

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