***Review Article***

**ENHANCING CANCER TREATMENT: INTEGRATING PHARMACOMETRICS AND PERSONALIZED MEDICINE IN ONCOLOGY**

**ABSTRACT**

Cancer remains a major global contributor to mortality, with 19.3 million new diagnoses and 10 million fatalities reported in 2020. Despite significant advancements in treatment, improving patient outcomes remains a major challenge. Recently, there has been increasing interest in combining pharmacometrics with personalized medicine to enhance cancer therapies and improve patient care. Pharmacometrics aids in developing precise dosing regimens, while personalized medicine uses genetic and biomarker data to identify the most effective treatments for individual patients. The integration of these approaches shows promise in optimizing cancer treatment. This review discusses the synergy between pharmacometric modeling—focused on understanding drug behavior and patient response—and personalized medicine, which tailors treatment to an individual’s genetic, environmental, and lifestyle factors. Combining these strategies can improve treatment outcomes, minimize side effects, and enhance patient stratification, ensuring that therapies are better suited to each patient’s unique characteristics. The integration of computational modeling and multi-omics data in oncology is revolutionizing cancer treatment. With the rise of high-throughput technologies, oncologists can access a wide array of data, including genomic, transcriptomic, and clinical information. By incorporating these diverse data types, computational models provide a deeper understanding of cancer biology and patient-specific responses to treatment. Key methodologies such as mechanistic modeling, machine learning algorithms, systems biology, and population pharmacokinetics (PopPK) models are increasingly being used to predict cancer dynamics and optimize drug dosing, offering clinicians tailored treatment plans.This review highlights how integrating pharmacometrics and personalized medicine can significantly improve cancer treatment effectiveness and reduces treatment-related toxicity.

**Key words:** Pharmacometrics, Personalized medicine, Cancer, Computational models, Oncology, Population pharmacokinetics (PopPK) models, Precision Oncology, Biomarkers, Systems Biology.

**INTRODUCTION**

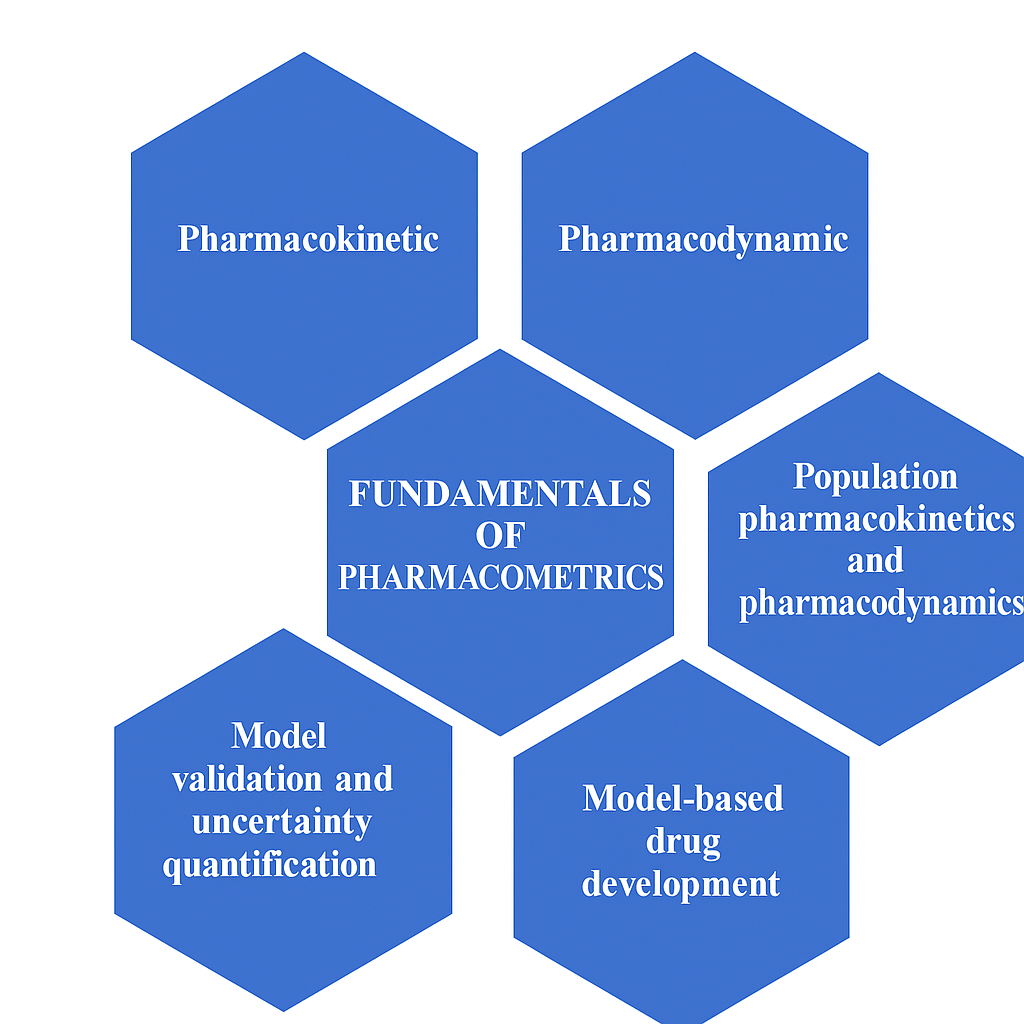
**TO THE PHARMACOMETRICS AND PERSONALIZED MEDICINE:**

Pharmacometrics and personalized medicine are revolutionizing healthcare by providing a more precise and practical approach to drug treatment. Pharmacometrics, the science of quantitative drug modelling, enables the optimization of drug dosing and treatment regimens. It combines mathematical modelling, statistics, and computer simulations to understand and predict the pharmacokinetics and pharmacodynamics of drugs in individuals. On the other hand, personalised medicine involves tailoring treatment to individual patients based on their unique genetic, environmental, and lifestyle factors. By incorporating pharmacometrics into personalized medicine, we can adapt the drug therapy to each individual's unique characteristics, maximizing the efficacy and minimizing the risks of treatment, leading to better patient outcomes and reduced adverse reactions.Oncology is a complex and dynamic field in which effective treatment strategies are crucial for improving patient outcomes. Pharmacometrics, the science of quantitative drug modelling, has emerged as a vital tool in optimizing cancer therapy. By leveraging advanced statistical and computational methods, pharmacometrics enables the development of personalized treatment plans, predicts drug efficacy and toxicity, and streamlines drug development processes.

In oncology, pharmacometrics has shown promise in enhancing the management of various cancer types, including breast, lung, and colon cancer. Personalized medicine in oncology refers to using individualized treatment approaches based on a patient's unique genetic makeup, molecular profile, and other specific characteristics. This approach allows for more targeted and effective therapies, reduced side effects, and improved patient outcomes. Advances in genomics, precision biomarkers, and targeted therapies have enabled the development of innovative personalized approaches, such as immunotherapy and gene editing.

This review aims to provide a comprehensive overview of pharmacometrics and personalized medicine in oncology. It highlights its principles, applications, challenges, and the latest advancements and opportunities for improving patient outcomes and advancing cancer treatment strategies.

**FUNDAMENTALS OF PHARMACOMETRICS:**

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**Fig 1: Pharmacometric Modeling Workflow**

Pharmacometrics integrates mathematical modeling, statistics, and computational tools to understand drug pharmacokinetics (PK) and pharmacodynamics (PD). Below are its core components:

1. **Pharmacokinetics**: Pharmacokinetics describes how a drug is absorbed, distributed, metabolized, and excreted in the body. Pharmacometric models can describe and predict a drug's concentration-time profile in various tissues and body fluids. For example, PK models for chemotherapy drugs like docetaxel optimize infusion schedules to balance efficacy and toxicity.
2. **Pharmacodynamics**: Pharmacodynamics studies how a drug affects the body. Pharmacometric models can quantify the relationship between drug concentration and pharmacological response, allowing for drug efficacy and safety prediction.
3. **Population pharmacokinetics and pharmacodynamics:** Population pharmacokinetic and pharmacodynamic modelling involves analysing data from multiple individuals to estimate the average drug behaviour in a population. This method can detect factors contributing to differences in drug response and refine drug dosing schedules.
4. **Model-based drug development:** Pharmacometric models can be used throughout drug development to inform drug design, dosing, and patient selection decisions. By integrating data from preclinical studies, clinical trials, and post-marketing surveillance, pharmacometrics modelling can help optimize the development and use of new medicines.
5. **Model validation and uncertainty quantification:** A key aspect of pharmacometrics is validating models and quantifying uncertainty in model predictions. Validation techniques such as cross-validation and bootstrapping can help assess the accuracy and reliability of pharmacometrics models.

**GENOMICS AND BIOMARKERS IN PERSONALIZED MEDICINE**:

Genomics and biomarker testing are pivotal in personalized medicine, enabling tailored healthcare by identifying individual patient characteristics. These tools predict disease risk, diagnose conditions, and guide targeted therapies, particularly in oncology, where precision medicine leverages tumor genetics to optimize treatment.

**Role of Genomics in Personalized Medicine**:

Genomics involves studying the structure, function, and evolution of genomes through techniques like DNA sequencing, genetic variation analysis, and gene expression profiling. In personalized medicine, it identifies genetic variations linked to disease risk or treatment response, improving diagnosis, treatment efficacy, and disease prevention. Key applications include:

**Table 1: Overview of Genomic Technologies and Their Applications in Personalized Cancer Treatment**

|  |  |  |  |
| --- | --- | --- | --- |
| **Category** | **Subcategory** | **Details/Examples** | **Applications** |
| **Role of Genomics** | Genetic Testing | Detects inherited mutations (e.g., BRCA1/2) | Assesses breast and ovarian cancer risk, influences disease/treatment outcomes |
| Pharmacogenomics | Predicts drug response and toxicity | Optimizes medication selection and dosing |
| Targeted Therapies | Drugs like Trastuzumab (Herceptin) for HER2-positive breast cancer, Imatinib (Gleevec) for BCR-ABL-positive leukemia | Treats specific cancer types based on genetic markers |
| Precision Medicine Trials | Uses genomics for patient enrolment | Guides treatment allocation |
| Non-Invasive Prenatal Testing | Screens for fetal chromosomal abnormalities | Early detection of genetic conditions |
| Liquid Biopsies | Analyzes circulating tumor DNA | Cancer diagnosis and monitoring |
| **Technologies in Genomics** | Next-Generation Sequencing (NGS) | High-throughput sequencing | Rapid genomic analysis |
| Whole-Genome Sequencing (WGS) | Comprehensive genome analysis | Detailed genetic insights |
| Exome Sequencing | Focuses on protein-coding regions | Targeted genetic analysis |
| Genotyping Arrays | High-throughput genotyping | Genetic variation analysis |
| RNA Sequencing (RNA-seq) | Analyzes gene expression profiles | Understands disease mechanisms |
| **Examples of Genomic Applications** | BRCA1/2 Testing | Assesses genetic mutations | Breast and ovarian cancer risk assessment |
| Trastuzumab (Herceptin) | Targets HER2-positive breast cancer | Treatment for specific breast cancer subtype |
| Imatinib (Gleevec) | Targets BCR-ABL-positive leukemia | Treatment for specific leukemia subtype |
| Pembrolizumab (Keytruda) | Targets PD |  |

**BIOMARKERS**

A biomarker is a biological marker present in bodily fluids or tissues that indicates the occurrence of a normal or abnormal process, condition, or disease. In the context of oncology, a cancer biomarker is a specific indicator that accurately and reliably identifies characteristics of cancer. Cancer biomarkers are crucial for diagnosing cancer, forecasting patient outcomes, and anticipating treatment responses. They can forecast the likelihood of disease progression (prognostic biomarkers) or anticipate how a patient will respond to a particular treatment (predictive biomarkers), enabling personalized treatment approaches.

The NIH Biomarkers Definition Working Group describes a biomarker as "a feature that can be objectively measured and evaluated to serve as a predictor of healthy biological functions, disease states, or the efficacy of a medicinal intervention." Biomarkers might be useful at different stages of drug development, from preclinical to after the drug is on the market. In oncology, the total tumour load changes several biomarkers, which makes it possible to evaluate how well a treatment works and anticipate how the disease will progress. The need to uncover predictive biomarkers has come from the need to figure out which individuals respond to treatment and which ones are likely to relapse.

In oncology, it is thought that tumour cells produce tumour markers into the blood that flows through the body. This means that having a tumour in the body will indirectly increase the production of biomarkers.

Several frequently used biomarkers in personalized oncology include:

**Table 2: Functional Roles and Status of Cancer Biomarkers Across Tumor Types**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Category** | **Biomarker Type** | **Examples** | **Associated Cancers/Conditions** | **Applications** | **Status** |
| **Genetic Biomarkers** | Mutations | BRCA1/2 | Breast, Ovarian | Risk assessment, Targeted therapies | Used widely |
|  | KRAS | Colorectal | Targeted therapies | Popular |
|  | BRAF | Melanoma | Targeted therapies | Widely used |
|  | EGFR | Non-small cell lung cancer | Targeted therapies | Used widely |
|  | ALK | Non-small cell lung cancer | Targeted therapies | Popular |
|  | PIK3CA | Breast | Targeted therapies | Research/Developing |
|  | JAK2 | Myeloproliferative neoplasms | Targeted therapies | Research/Developing |
|  | CALR | Myeloproliferative neoplasms | Targeted therapies | Research/Developing |
|  | NTRK | Various (Breast, Lung, Colon) | Targeted therapies | Research/Developing |
| **Protein Biomarkers** | Proteins | HER2 | Breast | Diagnosis, Prognosis, Treatment decisions | Widely used |
|  | PSA | Prostate | Diagnosis, Prognosis, Treatment decisions | Widely used |
|  | CA 125 | Ovarian | Diagnosis, Prognosis, Treatment decisions | Widely used |
|  |  | CEA | Colorectal | Diagnosis, Prognosis, Treatment decisions | Widely used |
|  | VEGF | Various (Breast, Lung, Colon) | Prognosis, Treatment decisions | Research/Developing |
|  | p53 | Various (Breast, Lung, Colon) | Prognosis, Treatment decisions | Research/Developing |
|  | AFP | Liver | Diagnosis, Prognosis | Research/Developing |
|  | Thyroglobulin | Thyroid | Diagnosis, Prognosis | Research/Developing |
|  | CA 19-9 | Pancreatic | Diagnosis, Prognosis | Research/Developing |
| **Immunological Biomarkers** | Immune-related proteins | CTLA-4 | Various | Predicts how immunotherapy will work | Widely used |
|  | PD-L1 | Non-small cell lung cancer | Immunotherapy response predicted | Popular |
|  | CD4/CD8 ratio | Various | Immune response monitoring | Widely used |
|  | FoxP3 | Various | Immune response monitoring | Widely used |
|  |  | PD-1 | Various | Predict immunotherapy response | Widely used |
|  | CEA | Colorectal | Monitor cancer progression | Widely used |
|  | CA 125 | Ovarian | Monitor cancer progression | Widely used |
|  | HLA-G | Various | Immune response regulation | Research/Developing |
|  | IDO | Various | Immune response regulation | Research/Developing |
|  | ARG1 | Various | Immune response regulation | Research/Developing |
|  | TGF-β | Various | Immune response, Tumor progression | Research/Developing |
|  | IFN-γ | Various | Immune response regulation | Research/Developing |
| **Circulating Tumor Cells (CTCs)** | CTC Markers | EpCAM positive | Breast, Lung, Colon, Prostate | Early detection, Treatment response | Widely used |
|  | CK19 positive | Breast, Lung, Colon | Early detection, Treatment response | Widely used |
|  |  | CD45 negative | Melanoma, Others | Early detection, Treatment response | Widely used |
|  | EGFR positive | Lung, Colon | Early detection, Treatment response | Widely used |
|  | HER2 positive | Breast | Early detection, Treatment response | Widely used |
|  | EMT markers (vimentin, Twist) | Various (Breast, Lung, Colon) | Early detection, Treatment response | Research/Developing |
|  | Circulating tumor microemboli (CTMs) | Various | Early detection, Treatment response | Research/Developing |
|  | Stem cell markers (CD133, CD44) | Various (Breast, Lung, Colon) | Early detection, Treatment response | Research/Developing |
|  | Tumor-specific mutations (KRAS, BRAF) | Various (Lung, Colon, Melanoma) | Early detection, Treatment response | Research/Developing |
|  | Cancer-related genes (c-Myc, Cyclin D1) | Various | Early detection, Treatment response | Research/Developing |
| **MicroRNA Biomarkers** | MicroRNAs | miR-21 | Breast, Lung, Colon | Diagnosis, Prognosis, Treatment response, and Early detection | Widely used |
|  | miR-155 | Breast, Lung, Lymphoma | Diagnosis, Prognosis, Response to Treatment, Early detection | Used widely |
|  | miR-34a | Various | Assessment, Prediction, Treatment response, Early detection | Popular |
|  | miR-210 | Breast, Lung, Colon | Assessing, Forecast, Treatment response, Early diagnosis | Widely used |
|  | miR-200 | Breast, Colorectal, Ovarian | Diagnosis, Prognosis, Treatment response, Early detection | Widely used |
|  |  | miR-205 | Breast, Colorectal, Ovarian | Diagnosis, Prognosis, Treatment to the response, Early assessment | Used widely |
|  | miR-221 | Lung, Liver | Detection, Prediction, Treatment response, Early detection | Popular |
|  | miR-222 | Liver | Diagnosis, Prognosis, Treatment response, Early detection | Widely used |
|  | miR-224 | Liver | Assessment, Prediction, Reaction, Early diagnosis | Widely used |

**DATA INTEGRATION AND COMPUTATIONAL MODELING IN ONCOLOGY:**

Data integration in oncology is becoming increasingly important in the field of pharmacometrics.

**Table 3: Pharmacometric modeling approaches used in cancer types**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **S.No** | **Type of cancer** | **Models** | **Authors** | **Published year** | **References** |
| 1. | Colorectal Cancer | 5-Fluorouracil pharmacokinetics and pharmacodynamics | K. Saif, M. Choma, A. Salamoun, et al. | 2020 | Saif, M. W., *et al.,* "Pharmacokinetics and pharmacodynamics of 5-fluorouracil: “Applications in colorectal cancer.” *Anticancer Research*, 2020. |
| 2. | Breast cancer | Population Pharmacokinetics (PopPK), Mechanistic Modeling | Druker BJ et al. | 2001 | Druker BJ *et al.,* The effectiveness and safety of a particular inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukaemia. New England Journal of Medicine. April 5, 2001; 344(14): 1031-7. |
| 3. | Pediatric Leukemia | Physiologically-Based Pharmacokinetic (PBPK) Modeling | Zhou J, Xu B | 2013 | Zhou J, Xu B *et al.,* Cancer Chemotherapy Pharmacology. 2013;72(1):139-49. |
| 4. | Solid Tumors | Pharmacokinetic-Pharmacodynamic (PK-PD) Models | Bruno R, Mercier F, Claret L | 2014 | Bruno R, *et al.,* Pharmacokinetic Pharmacodynamic. 2014;41(3):281-93. |
| 5. | Metastatic Breast Cancer | Tumor Growth Inhibition (TGI) Modeling | Dawson SJ et al. | 2013 | Dawson SJ *et al.,* N Engl J Med. 2013;368(13):1199-209. |
| 6. | Lung Cancer | Bayesian Modeling, Machine Learning Approaches | Brahmer JR et al. | 2012 | Brahmer JR *et al.,* N Engl J Med. 2012;366(26):2455-65. |
| 7. | Multiple Cancer Types | Systems Pharmacology, Model-Informed Drug Development (MIDD) | Marshall SF et al. | 2016 | Marshall SF *et al.,* CPT Pharmacometrics Syst Pharmacol. 2016;5(3):93-105. |
| 8. | Vascular Tumors | Hybrid QSP-PKPD Modeling | Ribba B et al. | 2014 | Ribba B *et al.,* PLoS Computer Biolgics. 2014;10(12):e1003889. |

A study published in Clinical Pharmacology & Therapeutics found that pharmacometric modelling reduced chemotherapy dose adjustments by 30% in cancer patients. According to the American Society of Clinical Oncology (ASCO), pharmacometrics can improve cancer treatment outcomes by 20-30%.

A review of 150 pharmacometric studies in oncology found that 75% focused on chemotherapy, 15% on targeted therapies, and 10% on immunotherapies. The National Cancer Institute reports that 80% of cancer patients have genetic mutations that can inform personalized treatment. A study in Nature Medicine found that personalized medicine approaches increased overall survival by 12.5 months in advanced cancer patients.

According to a survey by the Personalized Medicine Coalition, 70% of oncologists use biomarkers to guide treatment decisions. Research published in Cancer Research found that integrating pharmacometrics and genomics improved the predictive accuracy of treatment outcomes by 40%.

A review in Clinical Cancer Research highlighted the potential of pharmacometric modelling to optimize dosing regimens for targeted therapies. The FDA has approved several pharmacogenomic-based tests for guiding cancer treatment, including those for KRAS, BRAF, and EGFR mutations. Next-generation sequencing (NGS) can identify potential biomarkers for personalized cancer treatment in 80% of patients.

**COMPUTATIONAL MODELING:**

Computational modeling in oncology uses advanced simulations to study cancer biology, aid drug discovery, and optimize treatments. These models integrate mathematical, physical, and engineering principles with molecular signatures (genomic, proteomic), imaging (MRI, microscopy), and clinical data to mimic biological systems. Tumor behavior is modeled using discrete (individual-based), continuum (population-based), or hybrid approaches. Continuum models excel at capturing large-scale tumor growth, like extracellular matrix dynamics, and are less sensitive to small genetic or cellular fluctuations. In silico methods, leveraging data repositories, machine learning, network analysis, and pharmacophore mapping, identify cancer-related molecular patterns and defective pathways. They also support the design of specific, optimized drug-like molecules by analyzing absorption, toxicity, and other properties. These cost-effective, efficient methods accelerate oncology research by complementing traditional experiments.

1. **Population Pharmacokinetics (popPK) and Pharmacodynamics (popPK-PD):**

Pharmacokinetic (PK) and Pharmacodynamic (PD) models are vital tools in drug development and therapeutic optimization, particularly in oncology. These models are instrumental in predicting drug behavior in the body and its effects on cancer cells, enabling better dosing strategies and improved treatment outcomes.

**Pharmacokinetics (PK)** focuses on the processes of drug absorption, distribution, metabolism, and excretion (ADME). It provides a detailed understanding of how drug concentrations vary over time:

* **Absorption (A):** The process by which the drug enters the bloodstream.
* **Distribution (D):** The dispersal of the drug across body tissues.
* **Metabolism (M):** The chemical transformation of the drug, often in the liver, into more soluble compounds.
* **Excretion (E):** The elimination of the drug or its metabolites, primarily through urine or faeces.

**Pharmacodynamics (PD)** examines the relationship between drug concentration and its effects, focusing on therapeutic and adverse outcomes. Key aspects include:

* **Efficacy:** The best therapeutic impact a medication can have.
* **Potency:** The amount of substance needed to get a certain effect.
* **Dose-Response Relationship:** How variations in drug dose influence the magnitude of effects.

PK/PD models integrate these dimensions, offering quantitative analyses of the relationship between drug concentration and pharmacological effects. These models optimize dosing regimens, predict therapeutic results, and minimize adverse effects. For instance, in chemotherapy, PK/PD models assist in determining dosing schedules that balance efficacy and toxicity.

**Population PK (popPK) and PD (popPK-PD)** approaches extend these models to assess variability across patient populations. PopPK evaluates how drugs are distributed, metabolized, and eliminated among diverse groups, accounting for factors like age, weight, gender, and genetics. PopPK-PD integrates pharmacodynamic data to explore drug exposure-response relationships. Using nonlinear mixed-effects modeling, these methods predict typical values and variability in parameters, identify patients needing dose adjustments, and simulate clinical trials, reducing the need for large-scale studies.

The software’s used for this popPK-PD model is:

1. **NONMEM** (Nonlinear Mixed Effects Modelling):

It is a widely used software tool in pharmacometrics for analysing and interpreting population pharmacokinetics (popPK) and pharmacodynamics (popPK-PD) data. It applies advanced statistical methods to model complex drug behaviour and effects in diverse patient populations, optimising drug therapy and personalized medicine. It's a powerful program for analysing complex pharmacokinetic and pharmacodynamic data. This software program is designed to handle nonlinear mixed-effects modelling. It primarily analyses pharmacokinetic (PK) and pharmacodynamic (PD) data, incorporating population and individual variability. This tool is essential for understanding how drugs interact with the body and how these interactions vary among individuals.

1. **Mixed-Effects Modeling**:

NONMEM combines fixed effects (population average) and random effects (individual variability) to understand drug behaviour comprehensively. Mixed effects modelling, or multilevel modelling, is a statistical approach to analyse data with complex structures, where observations are nested within different levels or groups. This method is particularly valuable in pharmacometrics. Fixed effects are parameters that are assumed to be constant across all individuals or groups in the study. Fixed effects represent population-average parameters that apply to the entire study population. They represent the average effect of predictors on the response variable. In pharmacokinetics, fixed effects might include average drug clearance rate or mean drug absorption time.

1. **Phoenix NLME:**

This software application, developed by Certara, is explicitly designed for nonlinear mixed effects modelling (NLME). It is widely used to analyze population pharmacokinetics (popPK) and pharmacodynamics (popPD) data in pharmacometrics. Phoenix NLME provides a comprehensive suite of model development, estimation, and validation tools, making it a valuable resource for researchers and clinicians in drug development and personalized medicine. Phoenix NLME is a component of the Phoenix platform, a comprehensive suite of pharmacometric tools. It focuses on nonlinear mixed effects modelling, which allows for analysing complex pharmacokinetic and pharmacodynamic data, accounting for variability within and between individuals. Phoenix NLME will enable users to import and manage large datasets, perform data transformations, and prepare data for modelling. Users can construct and customize pharmacokinetic models, including one-compartment, two-compartment, and more complex structures. The software supports both linear and nonlinear models. Phoenix NLME models drug concentration-time profiles, helping optimize dosing regimens based on population data. Analyzes variability in pharmacokinetic parameters across different patients, considering factors like age, sex, weight, and genetic factors. It supports various PD model structures, including Emax models, indirect response models, and disease progression models.

1. **Monolix:**

Monolix is a software package that uses nonlinear mixed effects models to analyse population pharmacokinetics and pharmacodynamics data. It provides a comprehensive suite of model development, estimation, simulation, and validation tools. Monolix is a specialized software for nonlinear mixed effects modelling developed by Lixoft, a part of the Certara group. It is designed to handle complex pharmacokinetic (PK) and pharmacodynamic (PD) modelling tasks, offering a robust platform for population-based analyses. Monolix is renowned for its user-friendly interface, advanced modelling capabilities, and powerful estimation algorithms. It supports extensive simulation capabilities for predicting drug behaviour and responses under various scenarios. Monolix supports importing and managing large datasets from clinical trials, with functionalities for data cleaning and preprocessing. It helps design optimal dosing regimens by predicting drug concentration-time profiles across patient subgroups. Monolix enables integrating pharmacokinetic and pharmacodynamic data to model the relationship between drug concentrations and their effects.

Some standard PD models include:

1. Empirical models (e.g., Emax, sigmoidal)
2. Mechanistic models (e.g., receptor binding, signal transduction)
3. Semi-mechanistic models (hybrid approach)
4. **EMPIRICAL MODELS:**

Empirical PK/PD modelling models are mathematical descriptions of drug behaviour and effects based on observed data rather than underlying biological mechanisms. They aim to capture drug exposure and response relationships using simplified, data-driven approaches.

1. **Emax model**:

The Emax model (also known as the maximum effect model) is a widely used pharmacodynamic model that describes the relationship between drug dose or concentration and the effect. This model is beneficial in pharmacology and clinical research to know how the strength of a drug's effect fluctuates with different doses or concentrations. It describes a drug's maximum effect (Emax) and the concentration required to achieve half of Emax (EC50). The Emax model is designed to explain how increasing doses of a drug produce a response until a maximum effect (Emax) is reached. It provides a quantitative relationship between the drug's concentration (or dose) and pharmacological effect.

The Emax model can be expressed using the following equation:

Where:

* E is the observed effect.
* E0​ is the baseline effect (when the drug concentration is zero).
* Emax​ is the maximum possible effect.
* EC50​ is the concentration at which the effect is 50% of Emax​.
* C is the drug concentration.

1. **Sigmoid Emax model**:

The sigmoid Emax model is a refinement of the basic Emax model designed to represent better dose-response relationships, significantly when the drug's effect does not increase linearly with dose but instead follows a sigmoidal (S-shaped) curve. This model is beneficial in pharmacodynamics for capturing more complex dose-response relationships.

This model is similar to the Emax model but includes a Hill coefficient to describe the steepness of the concentration-effect curve. The sigmoid Emax model improves upon the Emax model by incorporating a Hill coefficient to account for situations where the response curve has a steeper slope, reflecting a more gradual or non-linear increase in response with dose.

The sigmoid Emax model is expressed as:

Where:

* E is the observed effect.
* ​ is the baseline effect.
* ​ is the maximum possible effect.
* is the concentration at which the effect is 50% of .
* C is the drug concentration.
* h is the Hill coefficient, which adjusts the curve's steepness.

These (popPK-PD) models help identify patients who may require adjusted dosing or alternative treatments. They also better predict treatment outcomes and potential adverse events. These models can simulate clinical trials, reducing the need for large-scale studies.

1. **Systems Biology Models:**

Systems biology models are comprehensive frameworks used to understand and predict the behaviour of biological systems through the integration of various biological, chemical, and physical processes. These models aim to capture the complex interactions and dynamics within biological systems, often at the molecular, cellular, or tissue level. Systems biology models integrate data from genomics, proteomics, metabolomics, and other high-throughput technologies to provide a holistic view of biological systems. They predict how changes in one part of the system affect the entire system, allowing for simulations of biological processes under different conditions.

Types of system biology models:

1. **Mathematical and Computational Models:**

**a)** Ordinary Differential Equations (ODEs): Used to describe the dynamics of biological systems by modelling the rates of change of system components (e.g., gene expression, protein concentrations).

**b)** Partial Differential Equations (PDEs): Applied to spatially distributed systems, such as diffusion processes or tissue dynamics.

**c)** Stochastic Models: Incorporate randomness and variability, which help model biochemical reactions with inherent noise and uncertainty. d)Agent-Based Models (ABMs): Simulate the interactions of individual entities (e.g., cells, molecules) and their effects on the overall system.

1. **Network-Based Models:**

**a)** Gene Regulatory Networks (GRNs): Describe interactions between genes and their regulatory elements, helping to understand gene expression control.

**b)** Protein-Protein Interaction Networks (PPINs): These networks model the interactions between proteins, which are crucial for studying cellular processes and signalling pathways.

**c)**Metabolic Networks: Represent metabolic pathways and the flow of metabolites, aiding in the analysis of metabolic processes and their regulation.

1. **Flux Balance Analysis (FBA):** Used primarily in metabolic network models to optimize and predict the flow of metabolites through metabolic pathways under given constraints. The main objective is to maximize or minimize a particular objective function (e.g., growth rate, production of a metabolite) subject to constraints derived from the network.

Systems biology models can simulate tumour growth and progression, considering genetic, epigenetic, and environmental factors. These models can predict how tumours respond to various treatments, including chemotherapy, targeted therapy, and immunotherapy. They also help identify potential drug targets by understanding the interactions and pathways involved in disease processes.

1. **Tumor Growth Models:**

Tumor growth models are mathematical and computational frameworks used to describe and predict the growth and development of tumours over time. These models are crucial in oncology for studying tumour behaviour, evaluating treatment strategies, designing clinical trials, and predicting patient outcomes.

1. **Exponential Growth Models:**

Exponential tumour growth models are among the most straightforward and commonly used mathematical representations for understanding how tumours expand over time. These models assume that the tumour's growth rate is constant, leading to a rapid increase in tumour size. In an exponential growth model, the tumour size increases at a rate proportional to its current size. This means that as the tumour grows, the growth rate also accelerates. Exponential models do not account for the limitations of resources such as nutrients and space, leading to unrealistic long-term predictions. They also fail to capture the complex interactions within the tumour microenvironment and changes in growth dynamics over time.

1. **Advanced Tumor Growth Models:**

Advanced tumour growth models are mathematical and computational frameworks that simulate and predict the growth and progression of tumours in response to various biological factors. These models can be used to understand tumour dynamics, optimize treatment strategies, and explore the effects of different therapies. Advanced tumour growth models incorporate more complexity and realism than basic models, aiming to capture the intricate dynamics of tumour development, progression, and interaction with the microenvironment. These models address the limitations of more straightforward approaches by including additional factors such as spatial distribution, genetic variability, and interactions with the tumour microenvironment.

**CLINICAL APPLICATIONS OF PHARMACOMETRICS IN ONCOLOGY:**

Pharmacometrics is the science of interpreting and describing pharmacological data using mathematical models. It has been increasingly applied in oncology to optimize drug development, dosing regimens, and therapeutic strategies. Population pharmacokinetics (popPK) and pharmacodynamics (popPK-PD) are two of the most important pharmacometrics methods. They are used in many different ways in drug development and to find the right dose at the right time.

Pharmacometrics can help determine optimal dosing regimens for anticancer agents, especially with patient factors such as age, body surface area, and comorbidities. Using population pharmacokinetics (PopPK) models, we can tailor doses to individual patient profiles, improving efficacy while reducing toxicity.

Oncology often involves combination therapies. Pharmacometrics can model drug interactions, helping identify optimal dosing sequences and schedules that maximize therapeutic effects while minimizing adverse effects.

Pharmacometrics can incorporate biomarkers to inform drug efficacy and safety, leading to a precision medicine approach. It can aid in identifying and validating biomarkers that predict response to treatment. Pharmacometrics models can support the development of personalised treatment plans by correlating drug exposure with biomarker changes (e.g., tumour shrinkage and progression-free survival).

We can understand how drugs behave in diverse patient populations using population pharmacokinetics. This includes variability due to genetic factors, organ function (e.g., liver or kidney impairment), and other patient-specific variables. This information is crucial for effective treatments across the heterogeneous cancer patient population.

Pharmacometrics models predict patient treatment responses, enabling clinicians to make informed decisions and adapt treatment plans. Pharmacometrics helps identify, validate, and integrate biomarkers for early response assessment, treatment monitoring, and patient stratification. Pharmacometrics improves understanding of immune responses, informing strategies to enhance efficacy and mitigate toxicity. Pharmacometrics models predict the risk of adverse effects based on drug concentrations and patient characteristics.

Pharmacometric models can predict potential drug-drug interactions, critical in oncology, where patients often receive multiple therapies. For example, the interaction between the anticancer agent erlotinib and other drugs can be predicted and managed to avoid adverse effects. Pharmacometric models also assist in adjusting drug regimens to mitigate interactions and optimize therapeutic outcomes. Pharmacometrics models analyze long-term outcomes and survival data, helping to predict patient prognosis based on treatment regimens and individual patient factors. Based on predictive models, follow-up schedules and supportive care can be tailored to improve overall patient management and quality of life.

**ETHICAL AND REGULATORY CONSIDERATIONS:**

When integrating pharmacometrics and personalized medicine in oncology, several ethical and regulatory considerations must be addressed to ensure these advanced methodologies' safe, effective, and equitable use.

**Ethical Considerations:**

1. **Informed consent:** Patients must be fully informed about the benefits and risks of personalized medicine approaches, including pharmacometric modelling. They should understand how their genetic and clinical information will be used in treatment decisions.
2. **Privacy and Confidentiality:** Personal health information, including genetic data and treatment responses, must be protected to maintain patient confidentiality. Safeguarding sensitive data from unauthorized access and ensuring proper data handling practices are crucial, especially when using advanced modelling techniques. Genetic data, in particular, require stringent measures to prevent misuse. Protecting patient information and obtaining explicit consent for data usage in research and treatment is essential.
3. **Equity and Access:** Ensuring that advancements in personalized medicine are accessible to all patients, regardless of socioeconomic status, race, or geographic location.
4. **Potential for Discrimination:** Using genetic and pharmacometrics data could lead to discrimination in insurance and employment. Ethical frameworks must be established to prevent misuse of such sensitive information.
5. **Patient Autonomy:** Personalized medicine often involves shared decision-making between the patient and healthcare provider. Respecting patient preferences and values is crucial in tailoring treatment strategies.

**Regulatory considerations:**

1. **Approval Processes:** Regulatory agencies like the FDA (Food and Drug Administration) and EMA (European Medicines Agency) must evaluate and approve new personalized therapies. This involves rigorous assessment of pharmacometrics models to ensure they meet safety and efficacy standards.
2. **Guidelines for Biomarker Development:** Clear regulatory guidelines are needed to develop and validate biomarkers used in personalized oncology treatments. These guidelines should ensure that biomarkers are clinically relevant and benefit patient outcomes.
3. **Post-market Surveillance:** Continuous monitoring of personalized therapies post-approval is essential to assess long-term effectiveness and safety. Ongoing monitoring and surveillance are required to evaluate the real-world efficacy and safety of personalized treatments. Regulatory bodies must establish frameworks for reporting adverse effects and real-world outcomes.
4. **Adaptive Trial Designs:** Integrating pharmacometrics in clinical trials can lead to more efficient adaptive designs. Regulatory agencies are gradually adapting guidelines to accommodate these innovative trial designs, which can improve the speed of bringing personalized therapies to market.
5. **Collaboration Between Stakeholders:** Effective communication and collaboration among regulators, industry, and healthcare providers are necessary to implement personalized medicine in oncology successfully. Stakeholders must address regulatory challenges together to streamline processes without compromising safety.

**CHALLENGES IN PHARMACOMETRICS AND PERSONALIZED MEDICINE IN CANCER TREATMENT:**

Despite the promising potential of integrating pharmacometrics and personalized medicine in oncology, several challenges hinder their widespread clinical application. These challenges span scientific, technological, ethical, and clinical domains, requiring strategic solutions to optimize their impact in cancer treatment.

1. **Complexity of Multi-Omics Data Integration**

* Cancer is highly heterogeneous, making it difficult to integrate multi-omics data, including genomic, proteomic, metabolomic, and transcriptomic information, into predictive models.
* The sheer volume of data requires advanced computational tools and bioinformatics expertise for meaningful interpretation.
* Standardization of data formats and ensuring interoperability across different databases remain major obstacles.

1. **Limited Availability of High-Quality Data**

* Pharmacometric models and personalized treatment strategies rely on large, high-quality clinical datasets, which are often incomplete or restricted.
* Biased datasets can lead to inaccuracies in predictive models, limiting their reliability.
* Ethical and legal restrictions on patient data sharing further complicate data acquisition.

1. **Variability in Patient Responses and Tumor Evolution**

* Cancer patients exhibit diverse treatment responses due to genetic variability, tumor microenvironment factors, and immune system interactions.
* Tumors evolve over time, leading to acquired drug resistance, necessitating continuous model adaptation.
* Pharmacometric models must account for dynamic tumor biology to maintain predictive accuracy.

1. **Challenges in Model Validation and Clinical Translation**

* Many pharmacometric models remain experimental and require extensive clinical validation before routine use.
* Translating theoretical models into real-world clinical decision-making requires collaboration between computational scientists and oncologists.
* Regulatory approval for new pharmacometric-driven approaches can be time-consuming, delaying implementation.

1. **Ethical and Regulatory Barriers**

* Personalized medicine raises ethical concerns related to genetic testing, patient consent, and potential genetic discrimination.
* Regulatory frameworks impose strict guidelines that can slow the adoption of innovative pharmacometric approaches.
* Data privacy laws, such as GDPR and HIPAA, restrict how patient data is collected, stored, and shared.

1. **Cost and Accessibility Issues**

* Implementing pharmacometric and personalized medicine strategies requires costly technologies such as next-generation sequencing (NGS) and artificial intelligence (AI).
* Low- and middle-income countries often lack the necessary infrastructure for these advanced methods.
* Insurance and reimbursement policies frequently do not cover personalized therapies, limiting patient access.

1. **Need for Interdisciplinary Collaboration**

* Successful integration of pharmacometrics and personalized medicine requires collaboration among oncologists, pharmacologists, data scientists, and regulatory experts.
* Communication gaps and differences in expertise between these fields can hinder progress.
* Limited training programs in pharmacometrics and personalized medicine contribute to a shortage of skilled professionals.

Addressing these challenges requires a multi-pronged approach, including improved data integration, refined computational models, regulatory reforms, and increased accessibility to personalized therapies. Overcoming these obstacles will help advance pharmacometrics and personalized medicine, ensuring that cancer treatment becomes more precise, effective, and tailored to individual patients.

**FUTURE DIRECTIONS EMERGING TECHNOLOGIES:**

1. **Artificial Intelligence (AI) and Machine Learning (ML) for predictive modelling & personalized treatment planning:** AI and ML can help with pharmacometric modelling by predicting how drugs will affect people based on their unique traits. Machine learning algorithms may look at a lot of different kinds of patient data (genomic, phenotypic, and clinical) to find the best treatment regimens. New technologies like artificial intelligence (AI) and machine learning (ML) could help speed up the objective of precision medicine. This is especially true when they are used with more data from more sources and more ways to treat patients. Combining AI and ML with pharmacometric modelling to make predictions more accurate and create treatment plans that are tailored to each patient. AI can help doctors choose the best personalised cancer treatments by predicting how patients will respond to certain therapy. Based on a patient's genomic profile and past clinical data, ML models may predict how well a treatment will work, how toxic it will be, and what bad reactions might happen.
2. **Genomic Medicine and Precision Oncology**: **Next-Generation Sequencing (NGS)** for comprehensive genomic profiling is revolutionizing cancer treatment by allowing for comprehensive tumour genomic profiling. This can help identify actionable mutations, enabling highly personalized treatment plans.

**Pharmacogenomics**: Integrating pharmacogenomics with pharmacometrics allows a better understanding of how genetic variations impact drug metabolism and response. Emerging technologies in gene editing, such as CRISPR-Cas9, can offer new ways to target cancer-causing mutations directly.

**Liquid Biopsies:** Non-invasive liquid biopsy techniques are used for genomic profiling of tumour DNA from blood samples. These tests enable continuous monitoring of cancer progression and treatment response, helping to adjust therapies in real time. ctDNA-based tests can serve as liquid biopsies to detect minimal residual disease (MRD) and monitor treatment response.

1. **Nanotechnology for targeted drug delivery:**

The development of nanoscale devices for targeted drug delivery improves efficacy and reduces toxicity. Nanoparticles can be designed to selectively target cancer cells, reducing side effects and improving treatment efficacy. This can be integrated with pharmacometrics modelling to optimize dosing regimens. Nanoparticles can be designed to provide real-time feedback on PK/PD parameters, enabling more accurate modelling and simulation. Nanoparticles can be used as contrast agents for imaging techniques, enabling earlier cancer detection and monitoring.

Nanoparticles can be engineered to deliver drugs directly to the tumour site, reducing systemic toxicity and increasing drug concentration at the target. Personalized nanoparticles can be designed to account for the specific characteristics of an individual’s cancer. Integrating pharmacometrics with nanomedicine can optimize the design of personalised drug delivery systems based on the patient’s specific tumour biology, enabling better drug targeting to the tumour.

1. **3D Printing for personalised medicine manufacturing:**

Creating personalized tissue models for cancer research and tailored treatment strategies. 3D printing enables the creation of customized implants and prosthetics tailored to individual patient's needs, improving functional outcomes and quality of life. 3D printing can create customized drug delivery systems, such as implants or tablets, with specific release profiles, enhancing treatment efficacy and reducing side effects. 3D printing can create customized tumour models for research and testing, enabling the development of more effective cancer treatments. 3D printing can improve functional outcomes, quality of life, and patient satisfaction.

Creating patient-specific 3D tumour models or organoids from biopsy samples to test how different drugs perform against an individual's cancer cells. This could enable more accurate predictions of which therapies would be effective, complementing pharmacometric modelling. Microfluidic devices that simulate the human tumour microenvironment allow testing of drug efficacy in a patient-specific manner, integrating both pharmacokinetics and pharmacodynamics. By creating organoids from individual tumours, researchers can identify how specific treatments affect a patient's cancer cells, facilitating the development of highly personalized treatment strategies. Using pharmacokinetic modelling on organoid cultures allows researchers to simulate the in vivo response of drugs, ensuring better predictions of patient-specific treatment responses.

1. **Internet of Medical Things (IoMT) for real-time patient monitoring**: The Internet of Medical Things (IoMT) is an emerging technological concept that refers to the network of connected medical devices and applications that enable real-time monitoring of patients, collecting and transmitting health data to healthcare providers for analysis and decision-making. In personalized cancer treatment and pharmacometrics, the IoMT can significantly enhance the ability to monitor and adjust treatment strategies in real time, leading to more tailored and effective care.

**Real-time patient monitoring** is a vital part of personalized oncology. Through IoMT, continuous patient data can be collected and transmitted to healthcare professionals for immediate analysis. This is for patients undergoing complex treatment regimens such as chemotherapy, targeted therapy, or immunotherapy, where timely adjustments are crucial. Wearable Devices, such as smartwatches or biosensors, can track vital signs and monitor cancer-related biomarkers in sweat, blood, or interstitial fluid, allowing for the real-time assessment of a patient’s response to treatment. Innovative injectors connected to the IoMT can record data on dosage, timing, and administration for cancer patients using immunotherapies or other injectable medicines. Smart Pill Bottles and Infusion pump devices can monitor medication intake and infusion parameters (e.g., dose, time, frequency).

The continuous data collected from IoMT can be integrated into pharmacometrics models to predict drug behaviour in real time. This helps to optimize dosing schedules and determine the effectiveness of treatments based on a patient’s unique responses, such as how their body metabolizes a particular drug. It also helps detect potential drug resistance early in the treatment process. IoMT devices can help identify changes in a patient’s risk profile over time by continuously monitoring vital health metrics.

1. **Integrating multi-omics data (genomics, transcriptomics, proteomics) for comprehensive patient profiling:** Combining genomics, transcriptomics, proteomics, and metabolomics for a more complete picture of cancer biology, aiding in discovering new biomarkers for better therapeutic targeting. Integrating genomics, transcriptomics, and proteomics allows a holistic view of tumour biology. This comprehensive profile provides crucial information, such as:

* The presence of specific oncogenic mutations or gene fusions.
* Gene expression changes that influence the tumour’s growth and metastatic potential.
* Proteomic alterations (e.g., protein overexpression or biomarker identification) that affect therapeutic response.

Cancer cells often develop drug resistance through complex interactions between genetic mutations, altered gene expression, and protein modifications. By integrating multi-omics data, we can predict how a cancer will respond to therapies and detect early signs of resistance, allowing for timely adjustments to treatment plans. Integrating multi-omics data supports identifying specific molecular targets that existing or novel therapies can target. For instance, knowing the exact mutation in a gene (from genomics) and the associated protein dysregulation (from proteomics) enables the development of targeted therapies aimed at those specific alterations. Multi-omics integration can lead to the discovery of novel biomarkers for cancer diagnosis, prognosis, and monitoring. As technologies improve, it will become possible to perform dynamic profiling of tumours over time, assessing changes in multi-omics data in response to treatment. This would allow real-time treatment efficacy monitoring and guide adaptive therapy strategies. Integrating multi-omics data can be crucial in developing personalized cancer vaccines. By identifying unique neoantigens (tumour-specific proteins), multi-omics profiling can guide the development of vaccines tailored to a patient’s tumour biology.

1. **Augmented Reality (AR) and Virtual Reality (VR) in Personalized Medicine:** Augmented Reality (AR) and Virtual Reality (VR) are emerging technologies that have shown great promise in enhancing personalized medicine, particularly in oncology. These technologies provide immersive, interactive experiences that can improve cancer treatment's precision, effectiveness, and patient experience.AR and VR technologies could be used to visualize complex patient data (e.g., 3D tumour scans and molecular profiles) more intuitively, assisting clinicians in planning and personalizing cancer treatment.

Virtual Reality (VR) creates fully immersive, 3D environments that can simulate real-world or conceptual scenarios. In personalized medicine, VR enhances the diagnosis and treatment of cancer patients by providing detailed, interactive visualizations of a patient’s unique tumour biology, anatomy, and treatment responses. VR enables patients to visualize their treatment options and understand potential outcomes. VR has been used to distract patients during painful procedures or long hospital stays.

**Augmented Reality (AR)** overlays digital information, such as images, text, or videos, onto the real-world environment. AR’s ability to enhance the perception of reality in real time makes it a powerful tool for personalized medicine, particularly for real-time guidance and decision-making in cancer treatment. AR can provide real-time guidance to clinicians during surgery or radiation treatment planning. AR can also be used to visualize real-time data during patient treatment sessions, including chemotherapy, radiation, or immunotherapy.

* Developing pharmacometric models incorporating real-world data (RWD) and electronic health records (EHRs).
* Investigating microbiome's role in cancer treatment and pharmacometrics.
* Exploring synthetic lethality approaches for targeted cancer therapies.
* Advancing precision medicine through functional genomics and CRISPR technology.
* Developing point-of-care diagnostics for personalized cancer treatment.
* Creating personalized cancer vaccines using AI-driven approaches.

**CONCLUSION**

Integrating pharmacometrics with personalized medicine in oncology marks a significant advancement in cancer treatment. By utilizing pharmacometric modeling and simulation, clinicians can more accurately predict drug efficacy and toxicity, leading to optimized dosing strategies tailored to individual patients. Personalized medicine, which relies on genomic, proteomic, and clinical data, complements pharmacometric approaches by identifying patient-specific biomarkers and therapeutic targets. Together,these strategies enhance treatment effectiveness, minimize adverse effects, and promote a patient-centered approach to oncology. As innovations in data science, bioinformatics, and pharmacology continue to evolve, integrating these disciplines paves the way for more effective, efficient, and equitable cancer therapies. However, successfully bridging these fields requires interdisciplinary collaboration, rigorous clinical validation, and the translation of advancements into routine practice.

Advanced technologies such as multi-omics data analysis, artificial intelligence (AI), augmented reality (AR), virtual reality (VR), and real-time patient monitoring through the Internet of Medical Things (IoMT) are driving this transformation. These innovations enable treatments that not only align with the genetic profile of a patient’s cancer but also adapt to the disease’s dynamic nature. This approach facilitates more accurate treatment predictions, optimized dosing regimens, and strategies to combat therapeutic resistance. Additionally, AR and VR technologies enhance surgical planning and treatment visualization, reducing errors and improving patient outcomes.

Despite these advancements, challenges remain, including integrating multi-omics data, addressing data privacy concerns, and ensuring broad accessibility to these technologies. Overcoming these obstacles will be crucial in improving survival rates, reducing side effects, and tailoring treatments to the unique molecular characteristics of each patient. Ultimately, combining pharmacometrics and personalized medicine will shape the next generation of cancer therapies, fostering a holistic, patient-centric approach that not only extends life but also enhances the quality of life for cancer patients worldwide. Continued research, innovation, and clinical application of these methodologies will be vital in transforming the future of cancer care.

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