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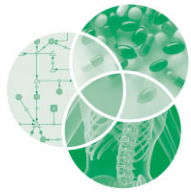

Personalizing oncology treatments by predicting drug efficacy, side-effects, and improved therapy: mathematics, statistics, and their integration

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Despite its great promise, personalized oncology still faces many hurdles, and it is increasingly clear that targeted drugs and molecular biomarkers alone yield only modest clinical benefit. One reason is the complex relationships between biomarkers and the patient's response to drugs, obscuring the true weight of the biomarkers in the overall patient's response. This complexity can be disentangled by computational models that integrate the effects of personal biomarkers into a simulator of drug–patient dynamic interactions, for predicting the clinical outcomes. Several computational tools have been developed for personalized oncology, notably evidence-based tools for simulating pharmacokinetics, Bayesian-estimated tools for predicting survival, etc. We describe representative statistical and mathematical tools, and discuss their merits, shortcomings and preliminary clinical validation attesting to their potential. Yet, the individualization power of mathematical models alone, or statistical models alone, is limited. More accurate and versatile personalization tools can be constructed by a new application of the statistical/mathematical nonlinear mixed effects modeling (NLMEM) approach, which until recently has been used only in drug development. Using these advanced tools, clinical data from patient populations can be integrated with mechanistic models of disease and physiology, for generating personal mathematical models. Upon a more substantial validation in the clinic, this approach will hopefully be applied in personalized clinical trials, *P-trials*, hence aiding the establishment of personalized medicine within the main stream of clinical oncology.

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INTRODUCTION

Conventionally, cancer patients have been treated following the 'one-size-fits-all' paradigm, by drug protocols that showed acceptable results in many patients with a similar diagnosis. However, progress in human genetics has made it increasingly clear that cancers of primary sites vary genetically and hence, respond differently to drugs. The concept emerging today is to overcome this problem by personalizing drug treatment according to the specific molecular characteristics of the patient's tumor. Indeed, advances in pharmacogenomics have led both to the design of personalized drugs that target particular molecular sites, and to the accelerated search for biomarkers that can predict how the patient

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will respond to a drug (predictive biomarkers).[1–3] At present, the repertoire of biomarkers approved for clinical use in oncology is rather limited.[4] It includes key regulators, such as the epidermal growth factor receptor (EGFR) for patients with non-small cell lung cancer, the estrogen receptor (ER) protein, the Human Epidermal Growth Factor Receptor (HER2) amplification biomarker, the breast cancer susceptibility type 1 and 2 (BRCA-1, 2) for patients of breast cancer (BC) and a few newer ones. Such a small repertoire is insufficient, especially in view of the emerging complexity entailed in the use of some of these biomarkers.[5]

The concept of 'personalized medicine' represents an important step forward in the evolution of medical science, toward greater mechanistic understanding of health, disease, and treatment. But several impediments still prevent its bold acceptance. These include the insufficient validation of the suggested predictive biomarkers, the current drug development methodology which is unsuitable for personalized medicine, the cost of new technologies and the doctors' reluctance about their acceptance.[6] These caveats are further elaborated below.

Biomarker Validation

The clinical benefit of predictive biomarkers is still obscured by many difficulties, and many potential biomarkers that have been identified *a priori*, subsequently proved to be of poor clinical benefit.[7] The generally poor achievements of molecular biomarkers are not surprising given the emerging recognition that single mutations do not encompass the whole array of genetic alterations that characterize a progressing tumor, and that cancer will increasingly be seen as a disease defined by its genetic fingerprint.[8,9] Moreover, a disturbing confusion exists between surrogate biomarkers, which can represent treatment endpoints for drug regulatory approval, and predictive biomarkers which can stratify patients according to their expected response to specific treatments. The latter biomarkers, essential for personalized medicine, do not require as stringent validation as the former. Yet, drug and diagnostic developers imagine that the overwhelming validation barriers to the use of surrogate end points also apply to regulatory issues that are pertinent to predictive biomarkers.[6]

How should predictive biomarkers be validated? Over the last few years, considerable attention of statisticians has been given to this subject, and many trial designs have been analyzed with respect to their efficiency and reliability in validating predictive biomarkers under different clinical settings.[10,11] One useful classification distinguishes between analytical validation, clinical validation, and clinical utility validation. Analytical validation of predictive biomarkers checks that, based on the biomarker in question, one can be more accurate in predicting the patient's response than by a gold standard predictor. Clinical validation checks that the biomarker quantity correlates with a clinical end point or characteristic. Clinical utility validation requires that the use of the biomarker results in improved response in patients.[12] None of these different approaches are, however, standardized and applied in reality. Below we show how the use of biomarkers and their validation can be improved by their integration into computational personalization support tools.

Clinical Trials

The overall success rate of most clinical trials is challenged by the large variability among patients, requiring large study populations to reach statistical confidence.[13] In contrast, patient stratification often reduces the number of patients that can be recruited to personalized-therapy trials; traditional statistical methods for clinical trials do not apply in such cases. Another limitation of current trial designs is that they apply the given drug to the patient in an unchanging regimen. This forces the clinicians to use these regimens, in spite of problems that may oblige flexible personal regimens, such as the slowly emerging drug resistance. It appears, then, that a different paradigm is needed in personalized drug development.[6] The recently suggested concept of personalized clinical trials (*p-trials*) introduces the idea of flexible personalized treatment schedules, based on personalized mathematical models.[14] The latter dynamic personalization method will be described below.

Doctors' Compliance

One of the main caveats in embedding personalized medicine in the clinical practice is the conservatism of physicians and the healthcare system, in general. Physicians are biased toward interventions that permeate the healthcare system and are reluctant to adopt new technologies, even when they lead to better outcomes.[6,15] In addition, personalized medicine depends on a substantial reliance on electronic medical records and decision support systems, but the healthcare industry is still not comfortable with information technology.[16] A vicious circle exists here, in which acceptance by the clinical community is a primary prerequisite for the demonstration of success of personalized medicine technologies. At the same

time, success of these technologies is a primary prerequisite for acceptance by the clinical community.

A new comprehensive framework for reducing the barriers to successful personalized medicine is needed, and can be provided by a combined statistical and mathematical modeling approach. Using such an approach, drug–patient interactions can be captured on many levels of biological organization, so that forces as diverse as molecular effects on a patient's disease and population variability of molecular biomarkers can be put together and implemented in a decision support algorithm. The algorithm should be able to quantify the comprehensive effect of plural clinical and molecular measurements on the patient's parameters of the drug-driven disease progression model, thus improving predictability of biomarkers and forecasting improved personal treatment regimens. As a result, personalized medicine will eventually be better integrated within clinical trials and the cost-effectiveness of clinical treatment will increase. Below we review several test cases, demonstrating the use of statistical and mathematical models in personalized medicine, as well as put forward a more advanced methodology, integrating statistical and mathematical models for improved personalization.

USE OF MATHEMATICAL MODELS IN PERSONALIZING ONCOLOGY TREATMENTS

The disillusionment with predictive biomarkers can be explained by the complexity of drug–patient interactions. Highly nonlinear relationships exist between a molecular biomarker and its realization in the patient's reaction to treatment. For example, the effect of HER2 on the patient's response to trastuzumab is often obscured by genetic and epigenetic changes that limit the binding of drug to HER2.[3,17] The inability to see the direct reflection of the marker in the patient's response calls for an intermediate system which can simulate disease complexity, factoring in the patient's molecular profile and the desired clinical treatment. Mathematical modeling can be used for constructing such an intermediate system, because of its power to describe, quantify and predict multifaceted behavior in a succinct formal language, enabling to scrutinize the system's behavior under various initial conditions.[18]

Many mathematical models investigating various dynamic aspects of known mechanisms in cancer growth and therapy have been put forward over the last 40 years,[19–21] and mechanism-based models have analyzed common methodologies of chemotherapy and suggested new approaches.[22–24] Typically, however, parameterization of these models is coarse, and often done in a theoretical manner or reliant on laboratory data or literature-derived data. Therefore, they fall short of capturing any specific clinical scenario, and while contributing to development of bio-modeling methodologies and to understanding of general treatment concepts, these models are still not used for prescribing specific treatment schedules at the clinical level.

A physician dealing with an individual patient may be interested in precise short-term goals, such as, are three treatment cycles sufficient for stabilizing tumor progression in patient X, or should a more aggressive regimen be administered? Will the scheduled drug dose be tolerable in patient X? etc. Such patient-oriented short-term questions can possibly be tackled by a dynamic tumor model, a capacity which is beyond the scope of current statistical methodologies. Below it is shown how such treatment decisions can be supported by dynamically personalized mathematical models, making the need to use mass historic data redundant.

Therapy-Induced Neutropenia

Chemotherapy-induced neutropenia (CIN), a disorder in granulocyte development, is the major toxicity of chemotherapy. It is associated with substantial morbidity, mortality, and excessive hospital admissions.[25] The appearance of grade III/IV CIN frequently leads to delayed chemotherapy administration, or dose reduction, both associated with poor clinical outcomes.[26,27] These complications motivated the development of models for predicting CIN and for analyzing granulopoiesis, as affected by granulocyte colony stimulating factor (G-CSF) support.[28–31] One of these models focused on predicting the individual time to neutrophil nadir in patients treated by chemotherapy, a clinically valuable factor in the physician's decision making process.[32,33] The personalization accuracy of this model was validated by retrospective clinical data, as described below.

The model describes granulopoiesis from myeloid progenitors through the different bone marrow compartments, to blood neutrophils. It also features explicit cell-cycle in mitotic compartments and the effects of G-CSF, the feedback molecule governing bone marrow maintenance of a quasisteady neutrophil levels in blood. The secretion, diffusion, clearance, and interactions of G-CSF with different cell compartments in the normal neutrophil development were described as well. The parameters of the

granulopoiesis model were estimated based on extensive literature data and neutrophil profiles in cancer patients subject to chemotherapy.[30,34]

The granulopoiesis model was integrated with a docetaxel pharmacokinetic (PK)/pharmacodynamics (PD) model, in order to predict blood toxicity in individual docetaxel-treated patients.[30,34] A three-compartment population PK model with linear elimination was assumed,[35] and PK model parameters were estimated using data from patients treated by docetaxel (100 mg/m^2, 1-h i.v infusion[33]); the resulting PK model was then validated by independent data.[36] Docetaxel's effect on granulopoiesis was modeled as a direct killing of neutrophil proliferating progenitors, the most likely targets of docetaxel in granulopoiesis.[32]

Model personalization was done in two stages: (1) adapt the granulopoiesis model to represent the patient population, and (2) test the population model for its accuracy in predicting neutropenia profiles in individual patients, taken from a new dataset. To this end, blood counts were collected from 38 docetaxel-treated metastatic BC patients (from Nottingham City Hospital, UK, and Soroka Hospital, Israel). Patients were randomly divided into a training set ($n = 12$), and a validation set ($n = 26$; 16 receiving a tri-weekly docetaxel regimen and 10 receiving a weekly regimen). Docetaxel schedules and neutrophil baselines (median 5080 neutrophils/μL; range 1800–15,500) were used as model input. Some population model parameters were re-estimated by fitting to training data, resulting in a single parameter set common for all patients, excluding individual initial baseline neutrophil counts and individual treatment regimen.[30,34] Then, the baseline neutrophil counts and the treatment regimen of each patient in the validation set were input into the population model for predicting the patients' CIN. Model predictions were compared to clinical neutrophil profiles in the validation set patients. The model showed high predictive accuracy of the timing of the personal nadir, i.e. timing of lowest observed neutrophil count at each cycle ($r = 0.99$, 95% confidence interval (CI): 0.98–1; Figure 1), and a good prediction of the neutropenia grade for each patient from the validation set, positive and negative predictive values of grade 3–4 neutropenia being 86% and 83%, respectively ($\kappa = 0.69$, $P < 0.001$).[30,34] Thus, even with this small dataset, the model gave accurate personal predictions of neutrophil nadir, a highly significant factor for chemotherapy design in the clinic.

It should be noted that the prediction accuracy required for evaluating the timing of nadir was much lower than would be required for predicting, for example, the actual neutrophil value at nadir in each patient. Thus, the small patient cohort sufficed for this purpose. Moreover, the requirement for a large dataset was made redundant here by use of data from additional sources. The neutropenia model, being designed also on the basis of extensive literature, was not dependent on the clinical dataset only. Rather, most of the model parameters-mostly system parameters-were already estimated at the population level based on data from literature, and only a few PK/PD parameters required re-estimation based on the clinical dataset of the 12 patients in the training set. Additionally, the variability aspect of this model was relatively simple, in that the only individually variable factor was the initial neutrophil count, whereas the rest of the processes were described on the population level. Despite this low variability, the model succeeded in predicting the requested time to nadir individually. In summary, the prediction goal of the model and its variability level are key factors in determining the size of the clinical dataset required for its validation, and small datasets can be complemented by additional data from the literature.

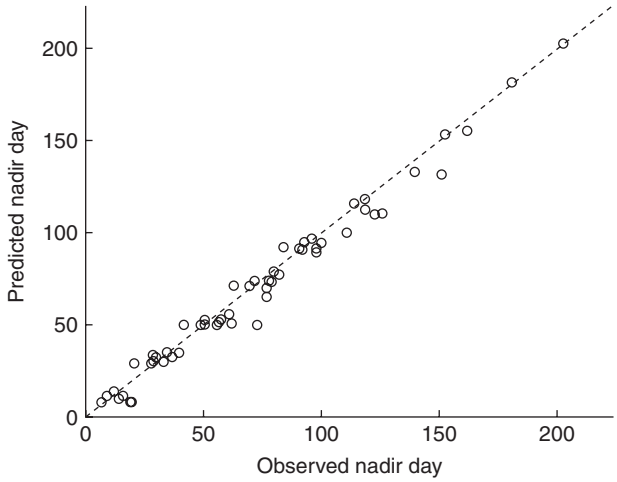

FIGURE 1 | Model-predicted neutrophil counts over time compared to the observed neutrophil counts of metastatic BC patients, treated with different docetaxel schedules. Model predictions of the nadir days at each cycle vs. the observed nadir days (circles; $N = 66$; calculated correlation coefficient is $r = 0.99$). The dashed line represents the identity line.

Efficacy Response in Mesenchymal Chondrosarcoma

In this subsection we briefly describe a work that combines mathematical models and xenograft experiments for personalizing treatment protocols. The rationale underlying this work was to generate xenografts from the patient's resected metastases,

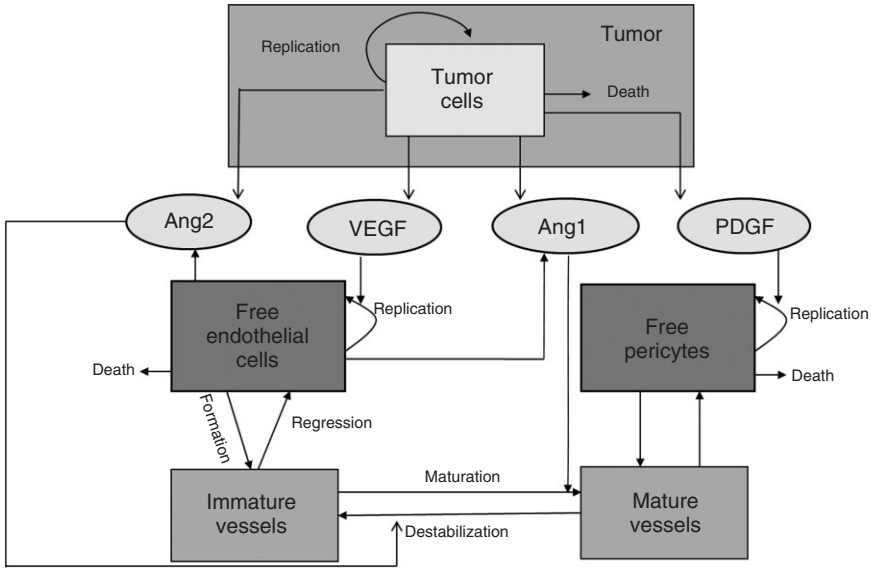

FIGURE 2 | Vascular tumor growth dynamics. A schematic description of the multiscale mathematical model for vascular tumor growth. Tissues (medium gray), cells (dark gray), and molecules (light gray) interact as marked by the arrows. Vascular endothelial growth factor (VEGF) and platlet-derived growth factor (PDGF) are secreted by the tumor cells. VEGF binds to endothelial cells and PDGF to pericytes, to generate new and mature blood vessels, respectively; the ratio of Angiopoietin1 (Ang1) and Angiopoietin2 (Ang2), secreted both by the tumor and by endothelial cells, affects the stability of the mature vessels.

in order to validate the model's ability to predict shrinkage of the patient's tumor under a variety of treatment protocols. This intermediate validation instrument was necessary, since there was no other way to develop a personalized mathematical model, test its ability to predict an improved treatment on the same patient, and still use the model for improving treatment of this patient. Once the model is validated by these xenograft experiments, it is up-scaled to humans and employed for suggesting an improved treatment schedule for the patient. The latter computational step was necessary as the xenograft experiments on their own cannot practically test a large number of potential treatment schedules, as the validated mathematical model can do.

Initially, a mechanistic model for vascular tumor growth in mesenchymal chondrosarcoma (MCS) was developed.[37] This model was based on a pre-existing vascular tumor model, which accounts for the molecular, cellular, and organ level interactions in tumor growth, angiogenesis, and vessel maturation. Four proteins that mediate blood vessel formation and maturation were modeled: vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), angiopoietin-1 (Ang-1), and angiopoietin-2 (Ang-2). Coupled with estimation of model parameters from the literature and laboratory results, the former model suitably predicted tumor and vasculature dynamics in human ovary carcinoma spheroids xenografted in mice[37–39] (Figure 2). This model was adapted to describe treatment personalization for the MCS patient, as described below.

A 45-year old male was in excellent health until a growing mediastinal mass was found. The primary tumor was resected and defined as MCS, but multiple new bilateral pulmonary nodules were discovered immediately after the operation. Following a long period under chemotherapy, the disease was still progressing and the patient suffered severe pancytopenia. An advisory panel was thus formed for identifying an improved drug treatment for this patient.

Tumor fragments, obtained from the MCS patient were subcutaneously implanted in nude male mice (xenografts). Once tumors grew to 50–150 mm^3 in size, animals were pair-matched by tumor size into treatment and control groups, and treatment animals were administered drugs by different monotherapy or combination regimens. In parallel, the initial vascular tumor model was adjusted to describe the MCS xenograft dynamics. This was done by fitting to tumor growth dynamics in the untreated mice. Using the xenograft-adjusted model, growth of the MCS xenografts and their response to various drug therapies was simulated, in conjunction with the PK/PD models of the relevant drugs, and with the applied dosing regimens. Where available, patient-specific chemosensitivity information was used to construct PK/PD models. Otherwise, publicly available data were used. This

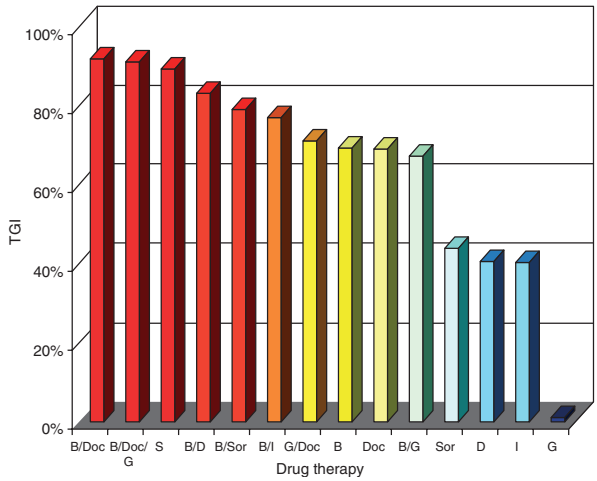

FIGURE 3 | Mathematical model predictions of tumor growth inhibition (TGI), calculated as TGI (%) = $100 \cdot (1 - (T - T_0)/(C - C_0))$, where T_0, C_0 are initial tumor sizes of the treated and the control tumor xenografts, respectively; T and C are sizes of treated or control tumor xenografts, respectively. The drug protocols that were simulated are shown at the bottom of each histogram bar: B/Doc denotes bevacizumab, 10 mg/kg, IV, Q3Dx10 +docetaxel, 25 mg/kg, IV, Q7Dx3; B/Doc/G denotes bevacizumab, 6.7 mg/kg, IV, day 1,8 + docetaxel, 25 mg/kg, IV, Q7Dx3 + gemcitabine, 160 mg/kg, IV infusion, 24 hr (single dose); S denotes sunitinib, 40 mg/kg, PO b.i.d x28; B/D denotes bevacizumab, 5 mg/kg, IP, Q4Dx6 + docetaxel, 3 mg/kg, IV, QDx8; B/Sor denotes bevacizumab, 5 mg/kg, IP, Q4Dx6 + Sorafenib, 85 mg/kg, PO, QDx10; other bars denote predicted TGI by drugs and drug protocols as above.

model was used to evaluate tumor growth inhibition (TGI) in the xenografted MCS patient tumors, by simulating different monotherapies and combinations of two or three cytotoxic and anti-angiogenic drugs. Model predictions suggested efficacy (TGI) differences between the different drug protocols, applied to the MCS patient's xenografts (Figure 3). The combination of bevacizumab and docetaxel was predicted to be most efficacious in inhibiting the growth of tumors originating at the MCS lung metastasis. Model predictions were compared to the experimentally observed values with 87.1% prediction accuracy.[40]

The personalized MCS xenograft model served as basis for the human model. Gene expression analyses of key proteins in the patient's metastases and in the xenografted tumor (denoted as Met/F1 ratio) were used to up-scale relevant xenograft parameters. For example, gene expression analysis shows that the Met/F1 ratio of Ang-2 is 0.7; values of corresponding parameters in the xenograft model were multiplied by this coefficient to yield a new value in the human model. Published data on the involved drugs were used to model their PK in the MCS patient. The PD functions used in the human modeling were those of the murine models.

Owing to the above mentioned xenograft predictions and *in vitro* results, the mathematical MCS patient model was used to study the patient's response to many different docetaxel/bevacizumab combination regimens. Simulations show that in this patient, bevacizumab in combination with *once-weekly* docetaxel was most efficacious in suppressing tumor growth (Figure 4), consistent with the above CIN model that suggested minimized risk of docetaxel-driven neutropenic toxicity when the drug is applied once weekly, rather than at other dosing schedules (see above).[34] Subsequently, the MCS patient himself received bevacizumab in combination with once weekly docetaxel, showing dramatic disease stabilization and a substantial recovery of hemoglobin, white blood cells, and platelets.[40]

This work shows the benefit of the mathematical model in a prospective trial, albeit in one patient. Hopefully, following more extensive clinical trials, models such as the one described will replace intermediate experimental tests. However, we do not exclude the possibility that in some treatment personalization cases, the combined *in vitro* xenograft and *in silico* modeling approach will still be necessary to identify personal PD effects. Since this combined methodology is costly, time consuming, and difficult to practice routinely in clinics, more practical methodologies for model personalization should be sought. Some of the alternatives are described below.

Hormone Therapy in Prostate Cancer

Another example of a clinically-oriented efficacy model was shown in the prostate cancer (PCa) case. A mechanistic mathematical model of the form of a piecewise-linear dynamical ordinary differential equation (ODE) system,[41,42] was developed in order to identify the optimal conditions for replacing continuous hormone (androgen suppression) therapy in PCa patients—the conventional treatment mode—with intermittent hormone therapy, which has been hypothesized as more advantageous. Signaling pathways evolving with epigenetic and mutational changes in PCa cells can result in reversible or irreversible androgen independence. Therefore, the mechanistic model describes three populations of tumor cells which are sensitive or reversibly/irreversibly insensitive to hormone ablation therapy: (1) androgen-dependent (AD) cells; (2) androgen-independent (AI) cells resulting from reversible changes; (3) AI cells arising from irreversible changes of genetic mutations. Under hormone treatment conditions, cells of state (1) may

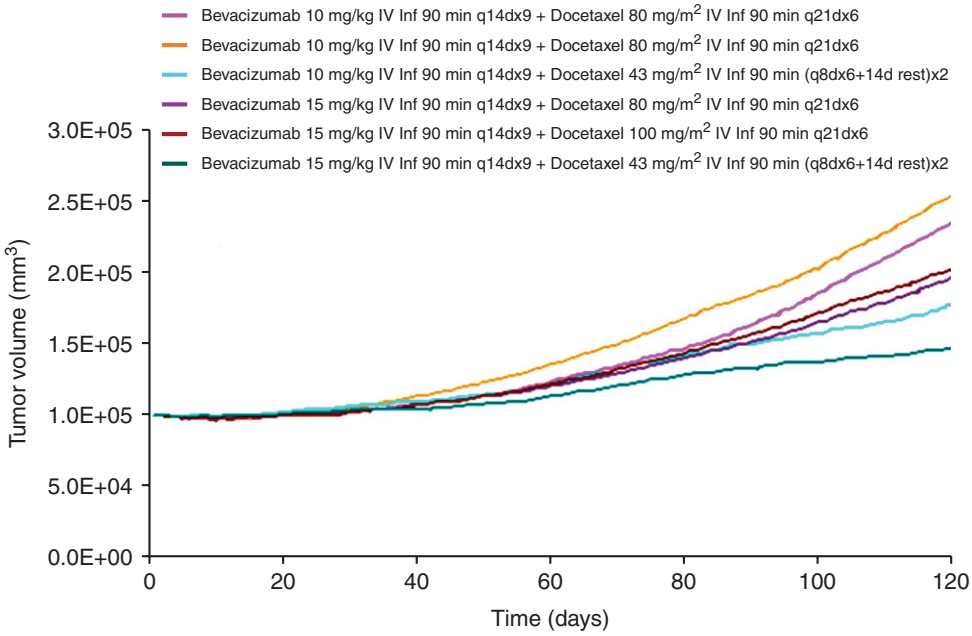

FIGURE 4 | Model predicted effects of different bevacizumab and docetaxel combination regimens on tumor growth in the MCS patient.

change to those of state (2) or (3), and cells of state (2) may change to those of state (3). Under no treatment, cells of state (2) may return to ones of state (1).

The model was tested in 177 PCa patients from three medical centers. Clinical measurements of the PCa tumor biomarker prostate specific antigen (PSA), taken during the first 2.5 treatment cycles, were used for personalizing the model, and model predictions for PSA counts in subsequent treatment cycles were made. Visual comparison to the observed results appeared in line with the PSA dynamics observed clinically (Figure 5). The model also showed that PSA dynamics can be sufficiently described by a linear equation for each of on/off-treatment periods. The evaluation was done by comparing the prediction errors of the radial basis function, a generic nonlinear model, with those of linear model. Model analysis revealed that patients can be classified into three treatment groups, in which (1) relapse can be prevented by intermittent therapy, if appropriately scheduled, (2) relapse can only be delayed by intermittent therapy, and (3) continuous therapy is preferred to intermittent therapy. Correlations between the classification by medical doctors' judgments and the classification by the mathematical model proved significant. It still remains to be seen whether this simple model can adequately describe more radical PCa therapies, where disease dynamics may be completely different.

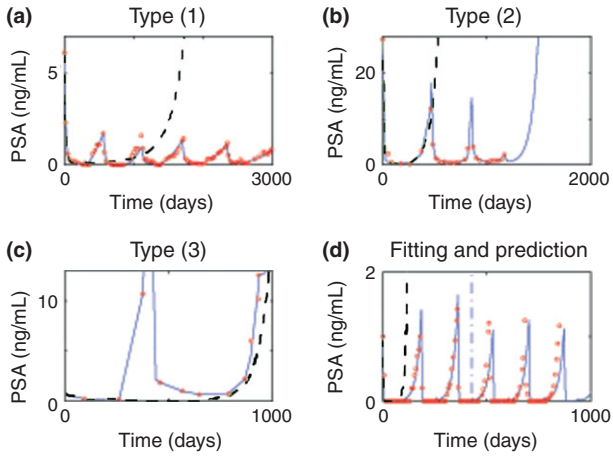

FIGURE 5 | Clinical and predicted PSA dynamics. Panels (a), (b), and (c) are the respective examples of type (1), type (2), and type (3) patients from the American cohort of 79 patients. In each panel, actual PSA values (red circles) are shown across intermittent therapy fits (blue solid lines) and continuous therapy fits (green dashed line). In another example (d) data from the first two and half treatment cycles was used to predict the following cycles.

USE OF STATISTICAL MODELS IN PREDICTING SURVIVAL OF ONCOLOGY PATIENTS

Clinicians have long been interested in estimating survival, for example in order to identify cancer patients that are likely to live at least three months, who would then derive some benefit from surgery.[43]

Statistical tools that predict survival have been based on population studies and on personal attributes, such as tumor size, performance status, pathological stage, etc.[43,44]

A systematic review of biostatistical survival models in renal cell carcinoma suggested that the variability in their predictive power is a function of the role of tumor histotype in the statistical analyses, of the consistency of prognostic impact of certain variables in different histotypes, of the level of model validation, etc. Possibly, the predictive success of statistical models may be improved if patients are categorized according to tumor histotype, or other disease characteristics.[45] Yet this would require a large and rich initial patient group as a basis for model development, thus rendering the task more difficult.

Skeletal Metastatic Diseases

Personalized survival estimates are important for clinical decision-making at different stages of disease progression, for example, in skeletal metastatic disease, as they can help identify which patient will benefit from surgery and which surgical procedure may be most appropriate. Based on data collected from the Scandinavian Skeletal Metastasis Registry for model training, two Bayesian classifiers, denoted Bayesian-Estimated Tools for Survival (BETS) models, have been developed for estimating the likelihood that a patient will survive more than 3 or 12 months (BETS3 and BETS12, respectively[43]); two separate models had to be developed as Bayesian classifiers are suited to provide probabilities of one particular outcome only. Both models were internally validated using 10-fold cross-validation methods. Subsequently, the two models were successfully validated by an independent dataset comprising 815 records that varied from the training set in the distributions of the demographic and clinical Parameters.[43]

The successful validation of the BETS models, via independent data, demonstrates that statistical tools can predict survival quite accurately and, therefore, can assist decision-making at important medical crossroads. The Bayesian Classifier methodology can account for data uncertainty. In addition, BETS generate a joint distribution function describing the probabilistic relationships between various prognostic factors and display it graphically.[43] These two aspects of BETS are certainly an advantage when doctors' compliance is at stake.

But the BETS method also has disadvantages. It is highly specific to estimations in patients with specific medical conditions (e.g., locations of metastases), undergoing specific interventions (e.g., surgery), under specific treatment philosophies. In addition, it can estimate the probability of a defined outcome (e.g., 3 month survival), but not a dynamic personal behavior profile (e.g., tumor growth over time), which is often critical to predict in the clinical setting.

Overall, the available statistical algorithms for prognosis (e.g., nomograms for metastatic BC and prostate cancer patients) are centered on statistical analysis of past clinical trials. Rather than modeling dynamical processes, these tools analyze retrospective patient data where one or more specific endpoints have been monitored. Therefore, they are limited to prediction of a patient's state at only a few predetermined time-points (typically, survival probability at 1–2 years and median survival months), and only for the same treatment protocols which were historically applied, excluding the ability to predict the outcomes of any treatment modification. As such, these algorithms cannot satisfy all the specific needs of the physician, which in many cases fall outside the historically defined aims.

INTEGRATION OF MECHANISTIC MATHEMATICAL MODELS WITHIN DATA-DRIVEN STATISTICS

The application of PK models in drug development has always been difficult,[46] but over the last years a useful extension of these models has led to a significant step forward in the ability to predict population and personal PK. When data from many patients are available, population PK models together with interpatient PK variability can be used for distinguishing biomarkers of the patient's PK, so that subpopulations of patients that would respond differently to drug can be singled out.[47–51] This methodology belongs to a group of population-based statistical and mathematical models-nonlinear mixed effects (NLMEM) models, which has been increasingly applied for drug development. Termed pharmacometrics, these applications quantify beneficial effects and side effects of drugs.[52] Generally, oncological pharmacometrics include, in addition to the mathematical population-based PK/PD models, also simple disease models that are limited to linear, exponential, or logistic description of tumor cell growth. But, unlike the 'bottom-up' development of mechanism-based models, the model building process in pharmacometrics is of the 'top-down' methodology, essentially evaluating a range of plausible models for their accuracy in reproducing results from large clinical trials.[52–55]

Pharmacometric models have significantly impacted drug approval, labeling and trial design decisions.[56,57] Consequently, the number of drug

submissions to the Food and Drug Administration (FDA), which included pharmacometric analyses, has increased by sixfold over the years 2000–2008.[58] Still, this type of modeling has remained descriptive over the years, using simple mathematical portrayal of cancer growth, and focusing on retrieval of the population behavior. But given the large interpatient variability, such models cannot precisely describe drug–patient interactions on the individual level. In order to anticipate the response of specific individual patients within a real-time clinical scenario, NLMEM models must ascend to the individual perspective. Two examples of such modeling are given below.

Chemotherapy-Induced Neutropenia

When a chemotherapeutic drug has cytotoxic side-effects (e.g., CIN), its dose is reduced by fixed decrements. Attempting to replace this crude method by a better approach, a semimechanistic NLMEM myelosuppression model was recently transformed into a patient-specific dosing tool. The tool, implemented in MS Excel, is based on a Bayesian estimation procedure. The procedure uses PK or PD information processed from neutrophil counts of a previous treatment cycle in order to adjust the subsequent cycle dose for obtaining a desired nadir. In simulations with a hypothetical etoposide-like drug,[59] the prevailing stepwise procedure of dose adjustment was compared to the model-based dose adjustment, the latter being superior in targeting a desired nadir, in terms of number of patients on target with no increased severe toxicity. In contrast to the standard method, model-based adjustment may allow to increase dose for patients with a subtoxic levels.[60]

Underlying the development of this NLMEM/MS Excel tool is the view that CIN is highly variable between patients and between treatment cycles in the same patients. In contrast, the above described fully mathematical CIN model did not assume a significant interpatient and intercycle variability. Yet, it yielded accurate personal predictions of neutrophil counts over several treatment cycles, using only baseline neutrophil counts. A prospective clinical study for comparing the two approaches may be worthwhile. Note, however, that each of these models aimed at achieving different endpoints: the NLMEM model in the current example was developed for predicting the neutrophils counts at the nadir, and for assisting the adequate adjustments of these minimal values through dose individualization. In contrast, the purely mathematical CIN model mentioned above was clinically evaluated for its ability to predict the nadir itself and the neutrophil profile of the individual patient.

Metastatic BC

The NLMEM modeling strategy has been recently applied for personalizing chemotherapy in metastatic BC, the most common cancer among women. Taxanes are commonly used cytotoxic treatments in BC,[61] specifically docetaxel, which yields a 47% objective response rate and an overall survival of 15 months.[62] Since taxanes are expected to remain a principal chemotherapeutic agent for BC, the ability to quantify and predict response in a patient-specific manner is expected to assist in the personalized approach to BC treatment. Recently, a clinically applicable statistical/mathematical model for BC patients treated with docetaxel was developed, using an NLMEM approach, in order to accommodate the distribution of PK/PD and biological parameters, naturally observed among patients, and to account for errors in data measurement (Kheifetz et al., in preparation).

Data from 33 metastatic BC patients (altogether 64 tumor lesions) under docetaxel treatment were used for creating the disease/PD model describing the dynamics of tumor volume, angiogenic capacity, and long-term effects of docetaxel. Merged with a population PK model for docetaxel (designed using a study in 521 patients from 22 Phase II trials[35]), the full NLMEM model was implemented and calibrated in Monolix. Twelve molecular biomarkers measured in the patients (estrogen receptor and VEGF expression, proliferation and mitotic indices, etc.) were tested for inclusion as covariates, potentially linking clinical parameters to individual lesion outcomes via their direct effects on model parameters. The model successfully fit the observed lesion dynamic data, with an R^2 value of 0.98 for individual fits. Stringent model selection criteria that are normally applied in NLMEM methodology were all satisfied (nonsingular Fisher Matrix value, low p-values for covariate coefficients, realistic interindividual variability of parameters, low condition number of correlation matrices of estimations of parameters, low Akaike information criterion value, small standard errors of parameter values, etc.). The sole biomarker found to be well correlated with lesion elimination was the mitotic index, high values of which indicated good response to docetaxel.

Results show that, using three lesion data points (one baseline and two in-treatment) measured in the individual patient, the personalized NLMEM model (simulated via a Bayesian Predictor) reliably predicts the subsequent dynamic response (change of lesion size over time) in that patient, during two months following the last measurement. This work shows the ability of such models to predict personal patient responses to chemotherapy, based on early data, and to help personalize treatment

regimens that will divert the tumor lesion towards elimination. Implementation of model predictions in clinical decision-making can be done upon a large scale model validation and adaptation to the clinical needs. This can be done by identifying the critical decision-making junctions during treatment, in which one protocol out of several authorized ones has to be elected. In BC, for example, this can be implemented for patients with recurrent disease, where recurrence is systemic, or in patients having stage IV disease with distant metastases when first diagnosed. If such patients are also estrogen-receptor-positive, the doctor needs to choose between different hormone therapies, or between aromatase inhibitors and antiestrogen drugs, etc. In such decision-making junctions, the mathematical model can serve for providing the patient's individual prognosis for progression or survival and for predicting response to the pertinent therapies. This method extends to other malignancies, and attests to efficient integration of mixed-effects, biomathematical/statistical, modeling in the personalized oncotherapy realm.

ADAPTING CLINICAL TRIALS TO PERSONALIZED TREATMENT PROTOCOLS BY USE OF COMPUTATIONAL MODELS

One may argue that computational methods carry little value for clinical medicine, as it may be impossible, from the regulatory point of view, to make changes in an ongoing treatment plan on the basis of model predictions. Yet in reality, a great deal of medical deliberation is involved in determining the therapy route the patient will go through. In PCa, for example, oncologists base their treatment decisions on the clinical stage of the disease and on the evaluation of the primary surrogate marker PSA. This is done even though the oncologists are aware that PSA alone is not sufficient for navigating the patient's treatment, and it is widely believed that to gain the maximal therapeutic effect, treatment of PCa patients must be personalized.[14,63] For example, hormone sensitive PCa patients with potentially good prognosis are generally over-treated by the standard, androgen deprivation therapy (ADT), suffering unnecessary adverse event and, possibly, accelerated emergence of hormone resistance. In contrast, poor-prognosis hormone sensitive patients who progress rapidly, do not benefit from standard ADT; they ought to be initially treated more aggressively, for example, with ADT combined with the new second-line hormone therapy. In addition, 35–55% of castrate resistant PCa patients do not respond to Docetaxel, the first line chemotherapy, making treatment futile (Dr. Manish Kohli, personal communication).

We note that, similarly to other cancers, PCa progression is realized in a transition at different rates, from a local stage to an advanced stage disease, with resistance to different drugs emerging and establishing themselves at different rates. Nevertheless, the current paradigm in oncology is inflexible and does not follow the personal disease-drug dynamics: adaptation, when made, is made *a posteriori*, rather than in 'real-time.' It is therefore important to show that the time-window at which the patient is most responsive to a particular treatment protocol can be dynamically calculated. This will enable to properly plan a cost-efficient individual therapeutic strategy, which will extend the patient's survival and enhance the quality of life. A computational model based on an adequate mathematical description of the patient's drug-affected disease dynamics may be of aid in this policymaking process.

But is it possible to validate the prediction accuracy of personalized mathematical models and still use them to navigate long-term treatments of individual patients? It has been shown theoretically that this can be achieved by a method which entails dynamic modification of the personalized model and consequently, of the personalized treatment. This method was developed on the basis of the notion that for fully accomplishing personalized medicine, not only drug entities but also drug regimens should be dynamically personalized[64] (see below). When this happens, current large-scale clinical trials, yielding approved 'packages' of both drug entity and accompanying *fixed* drug regimen, are no more valid. A new clinical trial methodology, denoted *p-trials*, has been suggested, which accommodates approval of flexible personal drug regimens. In the suggested *p-trials*, the range between the minimally effective dose and the maximally tolerated dose will be determined in a Phase I clinical trial, as is conventionally done, whereas the flexible personal treatment schedule for the individual patient (within the above determined range) will be governed using personalized mathematical models.[14]

The above marks a change in the perception of the patient's treatment at any given moment as predetermined. Upon recognition by the clinical community of the advantage in flexible personalized regimens, the necessary change to be made in the clinical trial paradigm is relatively minor: the current paradigm of clinical trials is predicated on the statistical methodology of hypothesis testing, geared to ensure that the end result of a clinical trial is

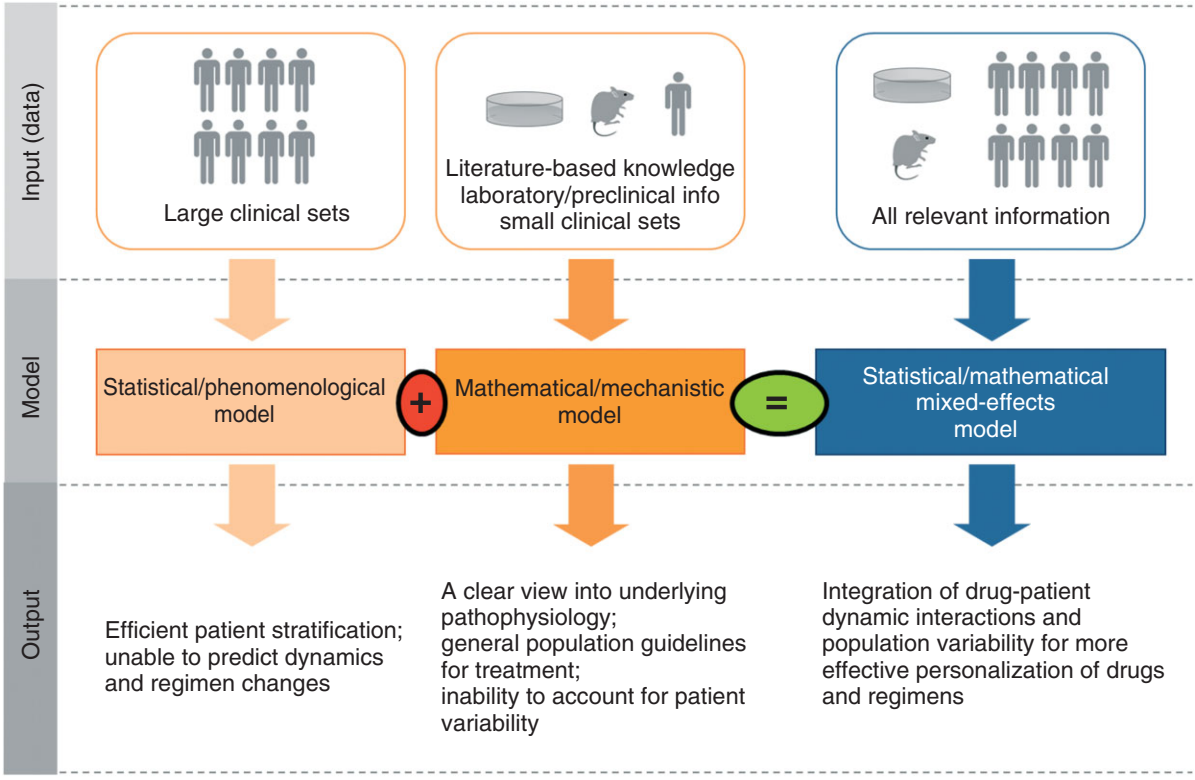

FIGURE 6 | The suggested approach for creating personalized response predictors uses nonlinear mixed effects modeling to integrate clinical information with mechanistic mathematical models of drug–patient dynamic interactions.

provided with the prescribed statistical power and statistical significance. For example, in Phase III, the trial answers the question, 'is there convincing evidence that treatment A (i.e., the package containing one or several molecules and doses and treatment intervals and other elements) has a better therapeutic effect than treatment package B?' This paradigm provides a method to determine the necessary number of subjects in the clinical trial. A failure in a clinical trial indicates nothing more precise than the failure of the tested treatment as a whole package. The same paradigm and the same significance of the conclusions should hold for testing treatment A versus treatment B in *p-trials*. The only difference between the conventional methodology and *p-trials* is that in the latter, the treatment regimen of the patient is flexible. The necessary number of subjects in a *p-trial* should be determined statistically, as is done in conventional clinical trials and in adaptive clinical trials.

The *p-trials* methodology is briefly exemplified below.

Immunotherapy in Prostate Cancer

The goal of this work was to show that it is feasible to create personalized patients models, validate them in early Phase II trials and use them in real-time for suggesting an improved treatment regimen, to be applied to the patient during the same clinical trial phase. This feasibility test was made using data from a Phase II clinical trial in PCa immunotherapy, an area in which personalized therapy is desperately needed.

Designing drug regimens in PCa, a slowly progressing malignancy, is not an easy task, since patients display highly variable PSA profiles. Immunotherapy design in PCa is even more complicated, as such treatments must adapt to the continuously evolving immunoediting of the tumor, one of the key processes responsible for the high interindividual variability among cancer patients. A mechanistic mathematical model for PCa immunotherapy, describing the dynamic interactions of tumor cells, immune cells and the vaccine, was developed for predicting PSA progression in advanced PCa patients treated by whole-cell autologous immunotherapy in a Phase II study. A method was designed for both personalizing the model and for validating the accuracy of its personalized predictions early in-trial. To prove its feasibility, personal PSA counts collected pretreatment and in the early stages of treatment were used for calibrating the model

for each of the patients, and reliability of patient-specific PCa models was demonstrated. In 7 out of 9 patients tested, the model-suggested personalized vaccination regimens were predicted to stabilize PSA levels, if applied immediately after individual model validation.[64,65] This could significantly improve efficacy of this particular cellular immunotherapy, which in the actual clinical study failed to show a meaningful response.[66]

The latter study was unique in demonstrating the feasibility and clinical benefit in an individualized *ad hoc* modeling strategy, namely, to create personalized patients models, validate them early on in the given patient, and use them in real-time for suggesting an improved treatment regimen to be applied to that patient during the same clinical trial phase. In the broad context, this study highlights why individual treatments (particularly in immunotherapy, but also in other oncotherapy modalities) should ideally be flexible within an approved range of doses, as the new dynamic personalization and *p-trial* concepts suggest.[14,63]

CONCLUSIONS

'Personalized medicine is the future. The only remaining question is how soon it will come about.'[6] By reviewing computational predictive tools that were developed for personalizing oncology treatments, we hope to contribute to further acceptance of this approach and, by that, to speeding up the establishment of personalized medicine as a main stream clinical practice.

A new type of decision support tools for personalized medicine is put forward, by which statistical-oriented mixed-effects PK/PD modeling is merged with mathematical mechanistic modeling of cellular and molecular processes at the core of the drug–patient interactions. This method increases the probability of proper model selection, via objective testing of a variety of reasonable model alternatives, having maximal parsimony and predictive ability, and minimal bias to data. An important feature of this method is its comprehensiveness, enabling long-range versatile predictions, in contrast to existing decision-support tools which usually estimate single features, such as survival at a given time point[43] (Figure 6).

The success in predicting efficacy response, as exemplified in this review, calls for a careful consideration of the promise, the suggested concept may have, for the future of personalized medicine. For example, the mathematical/statistical predictor described in the metastatic BC example may reduce the need for laborious biomarker validation, since, by this method, the correlation of measured biomarkers to the system's parameters and endpoints is stringently evaluated in the patient population. Biomarkers not correlating with response may still be significantly linked with a parameter of the disease process, affecting response indirectly via synergism with other parameter-correlated biomarkers. Analysis of such effects is part of the suggested methodology, so that biomarker validation is embedded within the validation of the model-based tool.

Using the personalized models in clinical trials may be an important leap forward in the acceptance of personalized medicine; the new dynamic personalization strategy is expected to increase the significance of agents that are highly effective in part of the patients, yet fail to demonstrate significant overall efficacy under the standard clinical trial paradigm. Moreover, similarly to the conventional practice in drug development, we suggest that the currently available modeling approaches will be implemented in the clinic only following an acceptable regulatory process.

Upon successful prospective clinical validation, novel strategies highlighted in this review will hopefully take the theoretical modeling approaches being applied in today's biomedical research and drug development arenas one step further, effectively extending them to the actual clinical arena where a personalized treatment schemes should be applied to all cancer patients.

REFERENCES

1. Oldenhuis CN, Oosting SF, Gietema JA, de Vries EG. Prognostic versus predictive value of biomarkers in oncology. *Eur J Cancer* 2008, 44:946–953.

2. Sarker D, Workman P. Pharmacodynamic biomarkers for molecular cancer therapeutics. *Adv Cancer Res* 2007, 96:213–268.

3. La Thangue NB, Kerr DJ. Predictive biomarkers: a paradigm shift towards personalized cancer medicine. *Nat Rev Clin Oncol* 2011, 8:587–596.

4. Rhea JM, Molinaro RJ. Cancer biomarkers: surviving the journey from bench to bedside. *MLO Med Lab Obs* 2011, 43:10–12 16, 18; quiz 20, 22.

5. Sawyers CL. The cancer biomarker problem. *Nature* 2008, 452:548–552.
6. Woodcock J. The prospects for ''personalized medicine'' in drug development and drug therapy. *Clin Pharmacol Ther* 2007, 81:164–169.
7. Diamandis EP. Cancer biomarkers: can we turn recent failures into success? *J Natl Cancer Inst* 2010, 102:1462–1467.
8. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000, 100:57–70.
9. Cancer Genome Atlas Research N, Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, Shen H, Robertson AG, Pashtan I, Shen R, et al. Integrated genomic characterization of endometrial carcinoma. *Nature* 2013, 497:67–73.
10. Buyse M, Sargent DJ, Grothey A, Matheson A, de Gramont A. Biomarkers and surrogate end points—the challenge of statistical validation. *Nat Rev Clin Oncol* 2010, 7:309–317.
11. Mandrekar SJ, Sargent DJ. Clinical trial designs for predictive biomarker validation: one size does not fit all. *J Biopharm Stat* 2009, 19:530–542.
12. Simon R. Clinical trial designs for evaluating the medical utility of prognostic and predictive biomarkers in oncology. *Per Med* 2010, 7:33–47.
13. Simon R. Advances in clinical trial designs for predictive biomarker discovery and validation. *Curr Breast Cancer Rep* 2009, 1:216–221.
14. Agur Z, Vuk-Pavlovic S. Mathematical modeling in immunotherapy of cancer: personalizing clinical trials. *Mol Ther* 2012, 20:1–2.
15. Dutton G. Companion Dx and personalized medicine. *Wall Street Biobeat* 2012. Available at: http://www.genengnews.com/gen-articles/companion-dx-and-personalized-medicine/4577/. (Accessed January 28, 2014).
16. Abrahams E, Ginsburg GS, Silver M. The personalized medicine coalition: goals and strategies. *Am J Pharmacogenomics* 2005, 5:345–355.
17. Ahn ER, Wang E, Gluck S. Is the improved efficacy of trastuzumab and lapatinib combination worth the added toxicity? A discussion of current evidence, recommendations, and ethical issues regarding dual HER2-targeted therapy. *Breast Cancer (Auckl)* 2012, 6:191–207.
18. Agur Z. Biomathematics in the development of personalized medicine in oncology. *Future Oncol* 2006, 2:39–42.
19. Rubinow SI, Lebowitz JL. Model of cell kinetics with applications to the acute myeloblastic leukemic state in man. *Biosystems* 1977, 8:265–266.
20. Schmidt W, Eisen M. Mathematical Models in Cell Biology and Cancer Chemotherapy. Lecture Notes in Biomathematics, vol. 30. Springer-Verlag, Berlin-Heidelberg-New York 1979. IX, 431 S., 70 Abb., 17 Tab., DM 39. *Biom J* 1981, 23:519–520.
21. Hart D, Shochat E, Agur Z. The growth law of primary breast cancer as inferred from mammography screening trials data. *Br J Cancer* 1998, 78:382–387.
22. Norton L, Simon R. Tumor size, sensitivity to therapy, and design of treatment schedules. *Cancer Treat Rep* 1977, 61:1307–1317.
23. Tannock I. Cell kinetics and chemotherapy: a critical review. *Cancer Treat Rep* 1978, 62:1117–1133.
24. Agur Z, Arnon R, Schechter B. Reduction of cytotoxicity to normal tissues by new regimens of cell-cycle phase-specific drugs. *Math Biosci* 1988, 92:1–15.
25. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. *Cancer* 2004, 100:228–237.
26. Cameron D. Management of chemotherapy-associated febrile neutropenia. *Br J Cancer* 2009, 101(Suppl 1):S18–22.
27. Krell D, Jones AL. Impact of effective prevention and management of febrile neutropenia. *Br J Cancer* 2009, 101(Suppl 1):S23–26.
28. Foley C, Mackey MC. Mathematical model for G-CSF administration after chemotherapy. *J Theor Biol* 2009, 257:27–44.
29. Shochat E, Rom-Kedar V. Novel strategies for granulocyte colony-stimulating factor treatment of severe prolonged neutropenia suggested by mathematical modeling. *Clin Cancer Res* 2008, 14:6354–6363.
30. Vainstein V, Ginosar Y, Shoham M, Ranmar DO, Ianovski A, Agur Z. The complex effect of granulocyte colony-stimulating factor on human granulopoiesis analyzed by a new physiologically-based mathematical model. *J Theor Biol* 2005, 234:311–327.
31. Vainstein V, Ginosaur Y, Shoham M, Ianovski A, Rabinovich A, Kogan Y, Selitser Z, Agur Z. Improving cancer therapy by doxorubicin and granulocyte colony-stimulating factor: insights from a computerized model of human granulopoiesis. *Nat Phenom* 2006, 1:70–80.
32. Ozawa K, Minami H, Sato H. Population pharmacokinetic and pharmacodynamic analysis for time courses of docetaxel-induced neutropenia in Japanese cancer patients. *Cancer Sci* 2007, 98:1985–1992.
33. van Zuylen L, Sparreboom A, van der Gaast A, van der Burg ME, van Beurden V, Bol CJ, Woestenborghs R, Palmer PA, Verweij J. The orally administered P-glycoprotein inhibitor R101933 does not alter the plasma pharmacokinetics of docetaxel. *Clin Cancer Res* 2000, 6:1365–1371.
34. Vainas O, Ariad S, Amir O, Mermershtain W, Vainstein V, Kleiman M, Inbar O, Ben-Av R, Mukherjee A, Chan S, et al. Personalising docetaxel and G-CSF schedules in cancer patients by a clinically validated computational model. *Br J Cancer* 2012, 107:814–822.
35. Bruno R, Vivier N, Vergniol JC, De Phillips SL, Montay G, Sheiner LB. A population pharmacokinetic model for

docetaxel (Taxotere): model building and validation. *J Pharmacokinet Biopharm* 1996, 24:153–172.

36. Baker SD, Zhao M, Lee CK, Verweij J, Zabelina Y, Brahmer JR, Wolff AC, Sparreboom A, Carducci MA. Comparative pharmacokinetics of weekly and every-three-weeks docetaxel. *Clin Cancer Res* 2004, 10:1976–1983.
37. Arakelyan L, Vainstein V, Agur Z. A computer algorithm describing the process of vessel formation and maturation, and its use for predicting the effects of anti-angiogenic and anti-maturation therapy on vascular tumor growth. *Angiogenesis* 2002, 5:203–214.
38. Agur Z, Arakelyan L, Daugulis P, Ginosar Y. Hopf point analysis for angiogenesis models. *Disc Contin Dyn Syst Ser B* 2004, 4:29–38.
39. Arakelyan L, Merbl Y, Agur Z. Vessel maturation effects on tumour growth: validation of a computer model in implanted human ovarian carcinoma spheroids. *Eur J Cancer* 2005, 41:159–167.
40. Gorelik B, Ziv I, Shohat R, Wick M, Hankins WD, Sidransky D, Agur Z. Efficacy of weekly docetaxel and bevacizumab in mesenchymal chondrosarcoma: a new theranostic method combining xenografted biopsies with a mathematical model. *Cancer Res* 2008, 68:9033–9040.
41. Hirata Y, Akakura K, Higano CS, Bruchovsky N, Aihara K. Quantitative mathematical modeling of PSA dynamics of prostate cancer patients treated with intermittent androgen suppression. *J Mol Cell Biol* 2012, 4:127–132.
42. Hirata Y, Tanaka G, Bruchovsky N, Aihara K. Mathematically modelling and controlling prostate cancer under intermittent hormone therapy. *Asian J Androl* 2012, 14:270–277.
43. Forsberg JA, Wedin R, Bauer HC, Hansen BH, Laitinen M, Trovik CS, Keller JO, Boland PJ, Healey JH. External validation of the Bayesian Estimated Tools for Survival (BETS) models in patients with surgically treated skeletal metastases. *BMC Cancer* 2012, 12:493.
44. Zisman A, Pantuck AJ, Dorey F, Chao DH, Gitlitz BJ, Moldawer N, Lazarovici D, deKernion JB, Figlin RA, Belldegrun AS. Mathematical model to predict individual survival for patients with renal cell carcinoma. *J Clin Oncol* 2002, 20:1368–1374.
45. Galfano A, Novara G, Iafrate M, Cavalleri S, Martignoni G, Gardiman M, D'Elia C, Patard JJ, Artibani W, Ficarra V. Mathematical models for prognostic prediction in patients with renal cell carcinoma. *Urol Int* 2008, 80:113–123.
46. Gobburu JV, Marroum PJ. Utilisation of pharmacokinetic-pharmacodynamic modelling and simulation in regulatory decision-making. *Clin Pharmacokinet* 2001, 40:883–892.
47. de Jonge ME, Huitema AD, Schellens JH, Rodenhuis S, Beijnen JH. Individualised cancer chemotherapy: strategies and performance of prospective studies on therapeutic drug monitoring with dose adaptation: a review. *Clin Pharmacokinet* 2005, 44:147–173.
48. Evene E, Chatelut E, Tranchand B, Canal P, Lochon I, Iliadis A, Ardiet CJ. Bayesian estimation of pharmacokinetic parameters of etoposide. *Bull Cancer* 1997, 84:699–703.
49. Sheiner LB, Beal SL. Some suggestions for measuring predictive performance. *J Pharmacokinet Biopharm* 1981, 9:503–512.
50. Sheiner LB, Beal SL. Evaluation of methods for estimating population pharmacokinetic parameters. II. Biexponential model and experimental pharmacokinetic data. *J Pharmacokinet Biopharm* 1981, 9:635–651.
51. Tranchand B, Amsellem C, Chatelut E, Freyer G, Iliadis A, Ligneau B, Trillet-Lenoir V, Canal P, Lochon I, Ardiet CJ. A limited-sampling strategy for estimation of etoposide pharmacokinetics in cancer patients. *Cancer Chemother Pharmacol* 1999, 43:316–322.
52. Barrett JS, Fossler MJ, Cadieu KD, Gastonguay MR. Pharmacometrics: a multidisciplinary field to facilitate critical thinking in drug development and translational research settings. *J Clin Pharmacol* 2008, 48:632–649.
53. Zhang L, Pfister M, Meibohm B. Concepts and challenges in quantitative pharmacology and model-based drug development. *AAPS J* 2008, 10:552–559.
54. Ette EI, Williams PJ. *Pharmacometrics : The Science of Quantitative Pharmacology*. Hoboken, NJ: John Wiley & Sons; 2007.
55. Grasela TH, Dement CW, Kolterman OG, Fineman MS, Grasela DM, Honig P, Antal EJ, Bjornsson TD, Loh E. Pharmacometrics and the transition to model-based development. *Clin Pharmacol Ther* 2007, 82:137–142.
56. Bhattaram VA, Bonapace C, Chilukuri DM, Duan JZ, Garnett C, Gobburu JV, Jang SH, Kenna L, Lesko LJ, Madabushi R, et al. Impact of pharmacometric reviews on new drug approval and labeling decisions—a survey of 31 new drug applications submitted between 2005 and 2006. *Clin Pharmacol Ther* 2007, 81:213–221.
57. Goldberger MJ, Singh N, Allerheiligen S, Gobburu JV, Lalonde R, Smith B, Ryder S, Yozviak A. ASCPT Task Force for advancing pharmacometrics and integration into drug development. *Clin Pharmacol Ther* 2010, 88:158–161.
58. Lee JY, Garnett CE, Gobburu JV, Bhattaram VA, Brar S, Earp JC, Jadhav PR, Krudys K, Lesko LJ, Li F, et al. Impact of pharmacometric analyses on new drug approval and labelling decisions: a review of 198 submissions between 2000 and 2008. *Clin Pharmacokinet* 2011, 50:627–635.
59. Wallin JE, Friberg LE, Karlsson MO. A tool for neutrophil guided dose adaptation in chemotherapy. *Comput Methods Prog Biomed* 2009, 93:283–291.
60. Wallin JE, Friberg LE, Karlsson MO. Model-based neutrophil-guided dose adaptation in chemotherapy: evaluation of predicted outcome with different types

and amounts of information. *Basic Clin Pharmacol Toxicol* 2010, 106:234–242.

61. Murray S, Briasoulis E, Linardou H, Bafaloukos D, Papadimitriou C. Taxane resistance in breast cancer: mechanisms, predictive biomarkers and circumvention strategies. *Cancer Treat Rev* 2012, 38:890–903.
62. Chan S, Friedrichs K, Noel D, Pinter T, Van Belle S, Vorobiof D, Duarte R, Gil Gil M, Bodrogi I, Murray E, et al. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. *J Clin Oncol* 1999, 17:2341–2354.
63. Agur Z, Vuk-Pavlovic S. Personalizing immunotherapy: balancing predictability and precision. *Oncoimmunology* 2012, 1:1169–1171.
64. Kogan Y, Halevi-Tobias K, Elishmereni M, Vuk-Pavlovic S, Agur Z. Reconsidering the paradigm of cancer immunotherapy by computationally aided real-time personalization. *Cancer Res* 2012, 72:2218–2227.
65. Kronik N, Kogan Y, Elishmereni M, Halevi-Tobias K, Vuk-Pavlovic S, Agur Z. Predicting outcomes of prostate cancer immunotherapy by personalized mathematical models. *PLoS One* 2010, 5:e15482.
66. Michael A, Ball G, Quatan N, Wushishi F, Russell N, Whelan J, Chakraborty P, Leader D, Whelan M, Pandha H. Delayed disease progression after allogeneic cell vaccination in hormone-resistant prostate cancer and correlation with immunologic variables. *Clin Cancer Res* 2005, 11:4469–4478.

