Role of pharmacokinetic modeling and simulation in precision dosing of anticancer drugs

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Translational Cancer Research

--Manuscript Summary--

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Title	Role of pharmacokinetic modeling and simulation in precision dosing of anticancer drugs
Running Head	Pharmacokinetic models for precision dosing in oncology
Keywords	Population pharmacokinetics,physiologically-based pharmacokinetics,modeling,individualized dosing,oncology
Abstract	<p>The prospect of precision dosing in oncology is attractive for several reasons. Many anticancer drugs display narrow therapeutic indices, where suboptimal therapy may lead to severe patient outcomes. Clinical study participant recruitment is seldom extended beyond the intended patient population, leading to difficulties in patient recruitment in dedicated clinical trials. The high rate of non-responders and high cost of cancer therapy warrant novel solutions to increase clinical effectiveness and cost-benefit, pharmacokinetic (PK) modeling and model-informed precision dosing (MIPD) can help to maximize these. PK modeling provides a quantitative framework to account for inter-individual variability in drug exposure, the influence of covariates and extrapolation to special populations or drug-drug interactions, using physiologically-based pharmacokinetic (PBPK) modeling. Here we present the current state of PK modeling in precision dosing of anticancer drugs and illustrate its utility, based on an extensive literature review and numerous case examples from both pharmaceutical industry and healthcare focused research. While some great progress has been made in implementing model-informed dosage guidance in the drug label and much research has been carried out to address clinically relevant dosing questions, the uptake of MIPD has been modest in healthcare. The success of PK modeling in industry has been made possible through collaborative efforts between regulators, industry and academia. Collaboration between academia, healthcare and industry, and financial support for research into patient benefit, cost-benefit and clinical effectiveness of these approaches is imperative for wider adaption of PK modeling in precision dosing of anticancer drugs.</p>
Section Title	Review Article

Role of pharmacokinetic modeling and simulation in precision dosing of anticancer drugs

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Abstract

The prospect of precision dosing in oncology is attractive for several reasons. Many anticancer drugs display narrow therapeutic indices, where suboptimal therapy may lead to severe patient outcomes. Clinical study participant recruitment is seldom extended beyond the intended patient population, leading to difficulties in patient recruitment in dedicated clinical trials. The high rate of non-responders and high cost of cancer therapy warrant novel solutions to increase clinical effectiveness and cost-benefit, pharmacokinetic (PK) modeling and model-informed precision dosing (MIPD) can help to maximize these. PK modeling provides a quantitative framework to account for inter-individual variability in drug exposure, the influence of covariates and extrapolation to special populations or drug-drug interactions, using physiologically-based pharmacokinetic (PBPK) modeling. Here we present the current state of PK modeling in precision dosing of anticancer drugs and illustrate its utility, based on an extensive literature review and numerous case examples from both pharmaceutical industry and healthcare focused research. While some great progress has been made in implementing model-informed dosage guidance in the drug label and much research has been carried out to address clinically relevant dosing questions, the uptake of MIPD has been modest in healthcare. The success of PK modeling in industry has been made possible through collaborative efforts between regulators, industry and academia. Collaboration between academia, healthcare and industry, and financial support for research into patient benefit, cost-benefit and clinical effectiveness of these approaches is imperative for wider adaption of PK modeling in precision dosing of anticancer drugs.

Background

In drug development, late phase clinical trials often aim to establish uniform dosing, balancing efficacy and toxicity, across the patient population from a limited set of proposed dosage schemes (1). Dosing of anticancer drugs has traditionally been based on body surface area (BSA) under the assumption that there is a relationship between BSA and clearance (CL) or volume of distribution (V_d). However, this relationship is in many instances poor and may therefore not accurately reflect the change in drug exposure seen across the population (2-5), meaning variability in drug exposure may remain high at the established dosage regimen (5). This is particularly true when the drug is dosed in a more diverse patient population in clinical practice, such as: complex drug-drug interactions (DDIs), pediatric patients, renally/hepatically impaired or other special populations (6). Explicit dosage recommendations are often absent from the drug label for most special populations at the time of approval (7). These factors contribute to variable clinical practices, where clinicians are challenged to make decisions based on experience and the many times limited literature. Patients with multiple comorbidities/co-medication are therefore at risk of suboptimal pharmacotherapy that may lead to unacceptable levels of toxicity or reduced efficacy (6, 8, 9). Model-informed precision dosing (MIPD) provides a quantitative framework for achieving the accurate dose for the individual patient through statistical and/or mathematical modeling, such as pharmacokinetic (PK) modeling, by accounting for inter-individual variability (IIV), and other factors that lead to variable drug exposure and/or pharmacodynamic (PD) response (10).

Here we examine the current state of PK modeling in dose individualization of anticancer drugs. The comparative analysis presented here was based on a sample of 393 peer-reviewed publications on pharmacokinetic modeling in oncology (see **Table A1**, in Supplementary Appendix available online). The dataset should not be considered an exhaustive list of the abundant literature on PK modeling in oncology. Many arguments on precision dosing presented here are part of a much broader discussion on MIPD across therapeutic areas (7, 10-12).

The case for model-informed precision dosing in oncology

The traditional resolution to dose optimization in special populations/DDIs is to carry out dedicated clinical studies. This is however not always feasible in oncology due to patient recruitment issues around dosing drugs in vulnerable populations or patients outside the indicated treatment group (13). Statistical nonlinear-mixed effects (NLME) modeling (population-pharmacokinetic/pharmacodynamic modeling, or pop-PK/PD) aims to describe the IIV in PK parameters using compartmental and increasingly mechanistic models. Physiologically-based pharmacokinetic (PBPK) modeling and simulation (M&S), attribute physiological meaning to PK models by mimicking physiology (inter-compartmental clearances informed by blood flows, volumes based on organ/tissue volumes etc.) in an attempt to better understand the processes that determine drug ADME (absorption, distribution, metabolism and excretion). The combined approach ('middle-out') accommodates physiological models where model parameters may account for observed IIV in the population sample (See **Figure 1**) (14). Pop-PK/PD and PBPK M&S have gained increasing acceptance in pharmaceutical

research and development (R&D) and by regulatory agencies over the last couple of decades to a point where dedicated clinical trials may be substituted/supplemented by modeling, foremost interpolating the effect of metabolic DDIs (15). It is anticipated that M&S will gain further utility over the coming years as confidence is built in other areas of application, both in pharmaceutical R&D, regulatory submission and clinical practice for dose individualization (7, 10, 12).

Dose individualization, personalized dosing or precision dosing, may be considered part of the well-recognized paradigm of precision medicine. Precision medicine pursues to personalize prevention, diagnostics and optimal treatment of disease based on individual patient characteristics *e.g.*, genotyping, renal function and other biomarkers (16).

Similarly, precision dosing strives to account for between-patient variability in drug exposure and response to optimize dosing for the individual. This is not a novel idea, carboplatin is the perhaps most famous example in oncology, seeing early adoption of renal function guided dosing (Calvert *et al.* formula) to reduce the risk of hematological toxicity (17). Similarly, PK-based dose adjustment, using therapeutic drug monitoring (TDM), of 5-fluorouracil was shown to produce superior treatment response and reduced toxicity as compared to BSA guided dosing alone in metastatic colorectal cancer (18).

Precision dosing in cancer therapy is attractive for several reasons. Many anticancer drugs display narrow therapeutic indices, where suboptimal therapy may lead to severe patient outcomes. Clinical study participant recruitment issues accentuates the

difficulty of patient recruitment in dedicated clinical trials for special populations and is perhaps part of the reason why there has been an above average adoption of PBPK M&S for new drug applications (NDAs) in oncology to the US Food and Drug Administration (FDA) (19). The relatively high rate of non-responders in cancer treatment together with high cost of cancer therapies warrants alternative approaches to increasing patient benefit and cost-benefit; this may include more effective use of approaches that maximize treatment outcome, such as PK modeling and MIPD (20, 21).

Application of pharmacokinetic modeling in oncology

Model-informed drug discovery and development has become established practice in the pharmaceutical industry over the past decades, where today it is employed across drug development to inform internal and regulatory decisions (15, 22). In early discovery and pre-clinical development, modeling is used to inform candidate selection, ADME characterization, translation of exposure and effect and more, this includes pop-PK/PD, PBPK and more mechanistic systems pharmacology/biology approaches. Pop-PK/PD is widely used in clinical development to investigate efficacy, dose selection and dose bridging. PBPK M&S is used clinically for predicting metabolic DDIs, impact of genetic polymorphism, biopharmaceutics effects and extrapolating to special populations (22).

Analysis of peer-reviewed publications using PK modeling in oncology, based on the modeling approach (see **Figure 2**), showed that a majority of studies employed

population-based approaches in their data analysis (75%), a subset of these include traditional pop-PK (45%), pop-PK/PD (14%), Bayesian pop-PK (10%) and semi-mechanistic pop-PK/PD (6%). PBPK M&S accounted for 8% of identified studies. In terms of areas of application of PK modeling (see **Figure 3**), the most prominent area of application was investigation of covariates (49%) to account for IIV in PK. This was followed by studies investigating dosing issues (22%), including dose finding and practice based dosing issues. The most studied special populations included pediatric patients (13%), hepatic (3%) and renal impairment (2%). Other investigated special populations included: pregnancy, elderly, and more. Other areas of investigation included: toxicity (18%), dose/PK-efficacy studies (response: 8%), metabolite kinetics (8%), metabolic/transporter genotype/phenotype (6%), DDIs (5%), limited sampling strategies (5%) and more.

In PBPK M&S, predictions of metabolic DDIs and extrapolation to special populations were the perhaps most prominent area of research. This was consistent with common areas of application seen in regulatory submissions where predictions of DDIs tend to dominate due to more well-established body of evidence to support PBPK, guidelines and regulatory acceptance (15, 19). There is in other words wide application of PK modeling to address critical questions in dose individualization of oncology drugs.

Population pharmacokinetics and covariate analysis to aid precision dosing in oncology

Pop-PK/PD aims to describe the observed IIV in drug exposure and response for a given population sample. The method allows estimation of the population mean (θ) and IIV (η) of PK/PD parameters and the remaining residual, or unexplained, variability (ε). The approach allows interpolation of drug exposure and response over the observed parameter space through identification of covariates (demographics, genetic polymorphism and other pathophysiological variables). For example, covariates can be included as either dichotomous (**Equation 1**) or continuous effects (**Equation 2**) on PK parameters, *e.g.*, (23):

$$\theta_{j,i} = \theta_j \cdot \theta_{Cov,n}^{Cov_i} + \eta_{j,i}$$

Equation 1

$$\theta_{j,i} = \theta_j \cdot \left(\frac{Cov_i}{Cov} \right)^{\theta_{cov,n}} + \eta_{j,i}$$

Equation 2

Where mean effect of the n^{th} covariate ($\theta_{Cov,n}$) and IIV of the j^{th} parameter of the i^{th} individual ($\eta_{j,i}$) on population mean (θ_j) determines the individual parameter estimate for the j^{th} parameter ($\theta_{j,i}$), Cov_i is the individual observed covariate and Cov the central tendency of the sample population. Significant covariates account for IIV in exposure,

meaning that a combined PK-covariate model can forecast individual exposure based on individual biomarker data prior to dosing and refine predictions following sparse PK sampling or TDM. This makes for a powerful tool for precision dosing. Covariate significance can be determined using *e.g.*, step-wise inclusion based on a predefined statistical criteria (post-hoc *p*-value testing for difference in objective function), or alternative approaches. Pop-PK-covariate modeling has been successfully employed for oncology drugs to individualize dosing, as included in drug labelling (24, 25). Further there are a number of examples of pop-PK-covariate models that have been used to address dosing issues in clinical practice with some success (See section:

‘Pharmacokinetic modeling of anticancer drugs in healthcare’).

Figure 4 shows identified PK covariates for anticancer drugs based on the peer-reviewed literature. The most commonly included covariates were bodyweight (50% of drugs in sample set) and other demographic data (sex [28%], BSA [26%] and age [21%]). Other common covariates included biomarkers related renal function (creatinine clearance [19%], serum creatinine [7%] and estimated glomerular filtration rate [5%]), drug-binding plasma proteins (albumin [17%] and α_1 -acid glycoprotein [AAG; 2%]), cancer type (14%) and concomitant treatment (11%). Other biomarkers of liver function were also reasonably prominent as model covariates, *e.g.*, alanine amino transferase (ALT; 9%), aspartate amino transferase (AST; 6%) and alkaline phosphatase (ALK; 5%) including more. Metabolic genotyping was included for 7% of drugs.

It has been recognized that there is a disparity between the wealth of covariates identified in the literature and the limited number pertaining to the dosage recommendation in the drug label of oncology drugs (25). **Figure 5** shows factors affecting explicit dose recommendations in the FDA label for selected drugs compared to additional identified PK covariates in the literature. There are many potential explanations for this: covariate selection can be biased (insufficient power, collinearity etc), not all statistically significant covariates are clinically relevant, covariates may for example be of obscure meaning and have little physiological/pharmacological relevance (25, 26). Further, the identification of significant but low-effect covariates may have little clinical implication. Here, cut-off points have been proposed where covariates may be considered clinically relevant if they explain at least 20 to 30% of IIV (25, 27). A lack of communication of research between academia and industry may also affect the difference in the adoption of covariates, suggesting some scope for further individualization of dosing of oncology drugs based on disseminated research (25).

Physiologically-based pharmacokinetic (PBPK) modeling to inform individualized dosing of anticancer drugs

By assigning physiological meaning to model parameters, PBPK M&S offers a method for quantitative extrapolation of drug exposure from *in vitro* to *in vivo* (IVIVE), between species, across populations and for metabolic/transporter DDIs. In oncology, PBPK M&S has been used extensively for the prediction of DDIs, special populations (renal/hepatic impairment and pediatrics) and biopharmaceutics effects (absorption,

formulation, food effects). In fact, some of the earliest examples of PBPK M&S in oncology can be traced back to modeling of chemotherapy agents in the 1970s (34).

There are several reasons why for the wide usage of PBPK in oncology: ethical/safety or recruitment issues, many oncology drugs exhibit narrow therapeutic indices and/or pose risks of severe toxicity and may therefore require more consideration for precision dosing, many anticancer drugs are carried forward through accelerated regulatory approval meaning that studies that have not been carried out in timely fashion may be substituted by PBPK M&S (19). Numerous examples of PBPK M&S of oncology drugs exist in the literature, including for: pediatrics (35-37), biopharmaceutics effects (38), renal impairment (39-41), hepatic impairment (42), metabolic phenotypes/genotypes (43, 44) and adherence (44) metabolic/transporter DDIs (45-49), with more examples available in FDA drug labels (50). The current view of FDA regarding PBPK-informed dosing, is that sufficient evidence exists to employ verified models for the prediction of metabolic DDIs where the drug is the victim substrate (50). For special populations and biopharmaceutics effects the jury is still out in the absence of more evidence to support the ability to prospectively and quantitatively predict these effects (50). Here we present selected case examples to illustrate the usefulness of PBPK M&S for dose individualization of anticancer drugs.

Case examples

Ibrutinib – metabolic drug-drug interactions

Ibrutinib (Imbruvica®; Bruton's tyrosine kinase inhibitor) was granted accelerated approval by the FDA in 2013 (51). The drug is given orally and undergoes extensive first-pass metabolism, mainly via CYP3A4 and to a lesser extent by CYP2D6, whilst undergoing minimal renal clearance. Ketoconazole inhibited 96% of ibrutinib's metabolism in human liver microsomes. A PBPK model was developed to evaluate CYP3A4 DDIs in healthy volunteers with ibrutinib as the victim. The model was validated against clinical DDI studies of ibrutinib in the presence of ketoconazole (strong inhibitor) and rifampin (strong inducer). The PBPK model was then used to interpolate DDI effects of mild, moderate and strong CYP3A4 inducers and inhibitors and used to inform dose guidance in the drug label (52, 53).

Sonidegib – bridging drug-drug interactions to cancer patients

Sonidegib (Odomzo®) is an oral anticancer agent for the treatment of locally advanced basal cell carcinoma. The drug displays low oral bioavailability. *In vitro* drug metabolism studies and clinical DDI trials in the presence of ketoconazole and rifampin were carried to elucidate the metabolic contribution of sonidegib elimination. Co-administration of ketoconazole led to a 2.25-fold increase in AUC, whereas rifampin produced a 72% reduction in exposure. A PBPK model was developed to bridge the DDI data from healthy volunteers to cancer patients at the ratified dose, to extrapolate to steady state effects and interpolate the effect of moderate/weak CYP3A inhibition/induction. The simulation study showed the effect of the DDIs to be slightly reduced in cancer patients compared to healthy and the interaction magnitude to increase at steady state dosing of sonidegib. The simulated DDI magnitudes and

alternative dosing schedules informed dosing recommendations provided in the FDA drug label (54). The study demonstrates the utility of using PBPK M&S to bridge the effect of metabolic DDIs from healthy volunteers to cancer patients.

Alectinib – biopharmaceutics effects

Alectinib (Alecenza[®]; selective anaplastic lymphoma kinase [ALK] inhibitor) underwent accelerated regulatory approval in 2015 because of likely clinical benefit in treating ALK-positive non-small cell lung cancer (55). The drug is a lipophilic basic (pKa ~ 6-7) displaying poor solubility and moderate oral bioavailability. As alectinib is given orally the pH-dependent solubility may be indicative of potential impact of biopharmaceutics effects. Parrott, and co-workers, developed a PBPK model to prospectively evaluate food effects and increased gastric pH with esomeprazole. The model predicted a positive food effect and a lack of impact of co-administration of esomeprazole. This was later confirmed in clinical trials, although the magnitude of the food effect was not accurately predicted, potentially due to excipient effects. The absorption model was further refined following confirmatory clinical studies and used to inform dose recommendations on timing of alectinib administration in relation to food intake. Authors stated that these finds were used to inform drug labeling (38).

Docetaxel – pediatric dose bridging

Docetaxel (taxane anticancer drug) is extensively metabolized by CYP3A4, substrate to the efflux transporter P-glycoprotein (P-gp), and active hepatic uptake transporters

OATP1B1 and OATP1B3. The drug exhibits dose limiting toxicity in the form of neutropenia. In a retrospective study, a full PBPK model was developed based on adult data and validated against adult data in presence of ketoconazole. The PBPK model was then scaled to pediatrics in order to establish first dose in children assuming a similar exposure-response to adults with the same indication. A global approach was used where PBPK predictions were fitted using a pop-PK model in order to carry out optimization of sampling times. PBPK predictions of pediatric data gave a reasonable prediction with a 1.4-fold overprediction of CL (37). The study shows proof-of-concept for dose bridging from adults to pediatrics in oncology using PBPK M&S coupled with pop-PK, to inform first-dose-in-children and optimal sampling design.

Impact of physiology of oncology patients on exposure of anticancer drugs

A number of physiological changes have been reported in cancer patients that may impact the pharmacokinetics of anticancer drugs (such as increased levels of inflammation and altered levels of plasma proteins) (56). With sufficient information, PBPK M&S can facilitate extrapolation of drug exposure to a more clinically relevant oncology population. Cheeti, and co-workers, developed an oncology PBPK model by altering sex, age, height and weight population distributions, levels of drug-binding plasma proteins (albumin and AAG), and hematocrit to investigate the effect of plasma protein binding on exposure of midazolam (CYP3A probe) and saquinavir (CYP3A probe highly bound to AAG) (57). A similar PBPK model for oncology patients developed by Thai, and co-workers, was demonstrated to better recover variability in PK profiles and CL of docetaxel compared to when physiology was assumed to remain

the same as in healthy (37). In the absence of physiological data, PBPK modeling can also be used to make inferences about physiological parameters based on clinical PK data. Yoshida, and co-workers, developed a PBPK of irinotecan (topoisomerase I inhibitor) and its metabolites to explore different PK of the drug in cancer patients. Using parameter estimation the authors could get an indication of the feasible parameter space of irinotecan's CL pathways in cancer patients (58).

Pharmacokinetic modeling of anticancer drugs in healthcare

Lately, there has been much debate how PK modeling can be used to aid precision dosing in clinical practice (10, 11, 59). In an earlier State of the Art paper, we proposed a categorization to describe implementation of MIPD in healthcare based on current practices, these were: real-time implementation in healthcare systems, mechanistic modeling and extrapolation and model-derived dose banding (10).

Real-time implementation in healthcare systems refers to direct implementation of M&S in-line with healthcare, *e.g.*, software tools and integration into electronic health records (EHR). The approach is particularly well-suited for treatments where continuous measurement, such as TDM, is carried out routinely throughout the therapy. Bayesian modeling approaches are particularly well-suited for this approach where feedback-control can be used to update prior parameter estimates and refine individual patient predictions as more data becomes available (10, 11). Mechanistic or PBPK models are a powerful tool for allowing extrapolation to for example DDIs or special populations.

Despite many examples of application to address dosing in special populations (60), there are few examples of the approach being evaluated in clinical practice (61). This may partly be due to PBPK's reliance on drug-specific and physiological information and its inferior ability to describe IIV compared to pop-PK. This may however change over the coming years, the generation of new proteomic data (62), emergence of 'middle-out' modeling (14), and Bayesian PBPK M&S (63) certainly makes PBPK an increasingly viable approach in precision dosing. Model-derived dose banding refers to the use PK models to develop dosing strategies based on clinically relevant covariates identified during the data analysis. This is perhaps the most practical approach although it potentially may offer less scope for dose individualization compared to other model-based approaches (64-66). Based on previous experiences, work streams have been proposed for how to develop these model-based approaches from conception to implementation in clinical practice. The proposed necessary steps to prove clinical effectiveness of MIPD include: model development, internal validation - to diagnose model misspecifications, external validation - to test performance against a different but related population sample, prospective clinical evaluation - to test the performance of the model-informed approach compared to standard practice, and an implementation phase - for integration into clinical practice (10, 67, 68). Here follows examples of PK modeling applied to answer clinically relevant dosing issues in oncology (in addition, See **Table 1**). These illustrate both utility and concepts for clinical evaluation and practical implementation in a healthcare.

Case examples

5-fluorouracil – metabolic phenotyping

Due to the risk of severe toxicity and a relatively narrow therapeutic index, prediction of toxicity has been widely sought for treatment using thymidylate synthase inhibitor 5-fluorouracil (See **Table A1**, Supplementary Appendix). The drug undergoes metabolism by dihydropyrimidine dehydrogenase (DPD), where DPD deficiency has been linked to an increased risk for toxicity (69). In a retrospective study, van Kuilenburg, and co-workers, developed a Bayesian pop-PK model, based on a population sample of DPD deficient patients and controls. The model described 5FU CL using nonlinear Michaelis-Menten PK, where DPD deficient patients displayed a 40% reduction in $V_{\max}$ (maximum velocity). Using a limited sampling strategy the DPD phenotype could be determined based on Bayesian estimation of individual $V_{\max}$, AUC or terminal half-life to anticipate the risk of toxicity (70). The approach potentially offers advantages to genotyping where misclassification can occur due to discrepancies in genotype and phenotype.

Carboplatin – Bayesian forecasting of drug exposure

Despite being safer than cisplatin, carboplatin displays dose-limiting bone marrow toxicity. Duffull, and co-workers, developed a bioanalytical method for measuring carboplatin serum concentrations and a Bayesian pop-PK model with covariates lean bodyweight (LBW) and creatinine clearance on CL, and LBW on volumes and inter-compartmental clearance based on data from 12 ovarian cancer patients (71). The model was tested prospectively against the Calvert *et al.* formula in an additional 12 patients over two courses. During the first treatment course the Calvert formula produced less bias compared to the population methods. Following two feedback concentrations the

Bayesian method showed superior accuracy for AUC predictions. It was recognized that an updated model may produce better accuracy (72). This was perhaps one of the earliest examples incorporating patient data to update individual priors for prospective predictions (71, 72).

Busulfan – strategies for healthcare implementation

Busulfan (alkylating agent) is widely used in combination with cyclophosphamide for conditioning prior to hematopoietic stem cell transplantation. The narrow therapeutic window of busulfan warrants TDM in pediatrics, where up to nine PK samples are taken over the course of a single dose to inform dose adjustments. Hence numerous PK models have been published to address dose individualization of busulfan (See **Table A1**, Supplementary Appendix).

Neely, and co-workers, developed a nonparametric pop-PK model with age (described using a continuous polynomial function), and ideal body weight as covariates on CL and V_d based on a population sample of 53 pediatric patients. An additional two datasets consisting of a total of 116 pediatric patients were then used for model validation and Bayesian updating of priors. The final model was then incorporated in to the BestDoseTM software platform and blindly tested against an additional 20 patients. The final model allowed target concentration achievement with only two blood samples per adjustment (73).

Abdel-Rahman, and co-workers, carried out a retrospective evaluation to examine the performance of five different TDM approaches (including non-compartmental and compartmental modeling) to estimate the dose of busulfan in pediatric cancer patients and found considerable discrepancies in dose recommendations (74). Due to observed inefficiencies in the workflow for TDM guided dosing at Children's Mercy Hospital (Kansas City, MO), a clinician-oriented interface was developed around a compartmental model for dose optimization of busulfan based on TDM. The software allowed the use of either a one- or two-compartment model based on a series of quantitative goodness-of-fit criteria implemented within the software. The interface could be accessed through the EHR and was subject to usability testing by healthcare professionals. The research represents a significant step towards bringing MIPD into clinical practice and serves as a proof-of-concept for practical implementation. The authors noted that next steps will focus on quality assurance, predictive performance of the software tool and investigations of model-refinement, including inclusion of covariate effects (75).

Similarly, Long-Boyle, and co-workers, developed a pop-PK model for busulfan based on retrospective data 90 pediatric and young adult patients. The final model (CL covariates: actual bodyweight and age) was then implemented in a user-friendly Microsoft Excel-based tool for guiding initial dosing in clinical practice and prospectively evaluated in 21 children. The healthcare tool showed significant improvement in attaining busulfan target concentrations compared to conventional dosing guidelines (76).

As previously mentioned, healthcare implementation of model-based precision dosing may take on different forms; where the previous examples detailed the process of incorporating real-time software tools in healthcare. A more pragmatic approach is the derivation of dose banding based on model optimized dosing regimens. Bartelink, and co-workers, developed a two-compartment pop-PK model for busulfan with body weight as a covariate on CL based on 245 pediatric patients. The model was then used to derive a nomogram for dosing busulfan in clinical practice. The model was externally validated against an additional 158 adult and pediatric patients (64, 77). A prospective study was carried out to assess the performance of the model-derived nomogram and the added value of TDM was carried out in 50 pediatric patients undergoing hematopoietic stem cell transplantation. The study concluded that following the model-derived dosing variability was still significant and therefore TDM was still needed to inform dose optimization (78).

Cyclophosphamide – reduced toxicity and healthcare implementation

Cyclophosphamide (alkylating agent) is given in two doses over two consecutive days as myeloablative preparative treatment before hematopoietic stem cell transplantation. The drug is metabolized to carboxyethylphosphoramide mustard (CEPM) amongst others, where the CEPM is linked to liver toxicity and nonrelapse death. A Bayesian pop-PK model was developed for cyclophosphamide and its metabolites. The model was internally validated and incorporated into an open-source code to allow real-time dose adjustments between the two doses. This was a considerable logistical effort

considering the time constraint for bioanalysis and model-derived dose recommendation. A clinical trial was carried out to test the performance of the model-based dosing approach. The approach led to an average total dose reduction of around 9% and a reduction in acute liver and kidney injury with similar overall survival (79-83). This case illustrates some of the logistic challenges of real-time implementation of MIPD in clinical practice.

Methotrexate – reduced toxicity and healthcare implementation

Methotrexate (antimetabolite) is used in the treatment of a number of cancers. Due to high IIV in exposure and the risk of toxicity in high-dose methotrexate treatments the drug is routinely subject to TDM. Barrett, and co-workers, developed a pop-PK model on TDM data from 240 patients at the Children's Hospital of Philadelphia (Philadelphia, PA), accounting for impaired clearance by estimating the probability of a patient belonging to one of the two subgroups. A software dashboard was developed, consisting of a database of patient records, lab data and adverse events management system. The data was then used for Bayesian forecasting of exposure. A user-interface was designed that allowed viewing of TDM data, forecasting of exposure, the potential risk of toxicity and dose guidance (84). A retrospective study was carried out in 50 pediatric and young adult patients to test the ability of the dashboard to predict future toxicity events to allow earlier recommendations of leucovorin rescue therapy. The study concluded that the dashboard gave reasonably accurate predictions (precision of 12.9%, bias of 2.2%) and could have been used to initiate earlier rescue therapy in 16 of the studied patients, seven patients would have received a larger dose of leucovorin and 37 patients would

have received the drug less often. The dashboard can support clinicians in monitoring for risk of toxicity and guide decision making of initiation of rescue therapy (85).

Pembrolizumab – minimizing excess drug wastage

Infused anticancer drugs are sold in vials with a set volume of the drug; however dosing is often based on body size. This leads to excess drug volumes after dosing a patient which many times are being discarded at the cost of healthcare providers or insurers. It is estimated that the total cost incurred by wastage of the top 20 anticancer drugs amounted to USD 1.8bn in 2016 in the US alone (86). Pembrolizumab (programmed cell death protein 1 ligand antibody) is currently available as 50 mg vial size in the UK at a licensed dose of 2 mg/kg every three weeks. Ogungbenro, and co-workers, proposed a model-based approach to optimize dose banding to maximize target attainment and minimize wastage. Cost analysis showed that the model-derived dosing strategy could save 16% of the cost of drug treatment compared to dosing by bodyweight by reducing discarded excess volumes of the drug, without altering exposure significantly (66). The work provides an example of how modeling can improve cost-benefit of anticancer treatment.

Model-informed precision dosing in oncology: future challenges

It has now been almost 50 years since the first model-based dosing strategies for dose individualization were proposed (98, 99). PK modeling has come a long way in supporting dose selection and answering clinically relevant questions in oncology and other disease areas (10, 11, 59). While academic groups, in collaboration with

healthcare professionals, are leading the way for model-based approaches to answer bedside dose individualization, pharmaceutical industry and regulatory agencies have made great strides in model-informed dose guidance in the drug label. It is thought that modeling will gain wider application in clinical practice over the coming years as precision medicine realizes its potential. For this to happen there are a number of challenges that need to be met.

At the moment, there is a lack of clinical effectiveness, patient benefit and health economic evidence to support MIPD in healthcare. This is crucial for wider acceptance of MIPD in clinical care. Too many published modeling efforts are concluded following model development, indicating areas of clinical application. Without rigorous validation and clinical evaluation these models will not see their full utility. Better coordination between academia, industry, healthcare, patient groups, and funding bodies are warranted to support implementation-based research in healthcare.

A prerequisite for precision dosing is the availability of multiple drug dose formulations. For MIPD to gain greater traction some adjustments to pharmaceutical R&D would be required, with focus earlier in development of precision dosing. Recently, we illustrated how this could work using the ‘companion tool’ approach (10), where a MIPD tool can be considered following candidate selection and developed alongside the drug. Precision dosing can facilitate the advancement of candidate drug that otherwise would be abandoned and there is therefore, in our opinion, great financial incentives to pursue this approach in pharmaceutical industry.

Oncology is an area with a lot to gain from PK modeling based dose individualization. There are however some specific challenges, such as the lack of exposure-effect/toxicity relationship for many new drugs coming to the market. This is of course a prerequisite for PK modeling to be meaningful. The concentration-effect relationship for monoclonal antibodies is poorly understood, where for many of these the dose-efficacy relationship found in clinical trials is flat (100, 101). This suggests that current dosing of monoclonal antibodies may not be optimal from an efficacy-cost perspective. Here lies an optimization challenge that can reap financial benefits for healthcare providers and payers, and in the end aid pharmaceutical industry to improve cost-benefit.

Conclusions

Here we present the current state of pharmacokinetic modeling in precision dosing of anticancer drugs. We have illustrated, using published case examples, some of the potential benefits the approach may bring in terms of prospective dosage guidance for DDIs and in special populations, improved attainment of target drug concentration and reduced risk of toxicity, reducing wastage and scope for improved patient benefit and cost-benefit. While some great progress has been seen in implementation of model-informed dosage guidance in the drug labeling, a collaborative effort from regulators, industry and academia, the uptake has been modest in healthcare. Collaboration between academia, healthcare and industry together with greater financial support for applied research into patient benefit, cost-benefit and clinical effectiveness of model-based dosing approaches is warranted for wider adaption in healthcare.

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Figure 1. Pharmacokinetic modeling approaches for precision dosing of oncology drugs. Bars indicate the features of the individual and combined techniques.

Figure 2. Peer-reviewed publications on pharmacokinetic modeling of oncology drugs categorized based on method of approach (N publications: 393, N drug-publication combinations: 414, See Supplementary Appendix). PK: pharmacokinetic, PD: pharmacodynamic, pop: population-based analysis, semi-mech.: semi-mechanistic/semi-physiological, PBPK: physiologically-based pharmacokinetics.

Figure 3. Areas of application of pharmacokinetic modeling in oncology based on a sample of 393 peer-reviewed publications (See Supplementary Appendix). Circle areas are proportional to frequencies. DDIs: drug-drug interactions.

Figure 4. Identified pharmacokinetic covariates of oncology drugs based on a literature sample set of 393 peer-reviewed publications, see Supplementary Appendix. Numerical prefixes/suffixes show number of identified covariates for respective drug (and their metabolites where applicable), percentage suffixes show frequencies of drugs that

identify respective covariate. AAG: α_1 -acid glycoprotein, ALK: alkaline phosphatase, ALT: alanine amino transferase, AST: aspartate amino transferase, BSA: body surface area, BW: bodyweight, IBW: ideal bodyweight, CL_{CR}: creatinine clearance, DDI: drug-drug interaction, EGF: epidermal growth factor, EGFR: EGF receptor, erythromycin breath test: as surrogate of CYP3A4 activity, GFR/eGFR: estimated glomerular filtration rate, HER: human epidermal growth factor receptor, IFN- α : interferon- α , LBW: lean bodyweight, LD: lactate dehydrogenase, PDGF: platelet-derived growth factor, S_{CR}: serum creatinine, VEGF: vascular endothelial growth factor.

Figure 5. Factors affecting explicit dose recommendations in the FDA drug labels (including CI: contraindications) of docetaxel (Taxotere[®]), bevacizumab (Avastin[®]), aflibercept (Zaltrap[®]), capecitabine (Xeloda[®]), carboplatin (TEVA Pharmaceuticals USA) and busulfan (Busulfex[®]; blue circles) (28-33). Grey circles indicate additional pharmacokinetic covariates identified in the sampled peer-reviewed literature (see **Table A1**, Supplementary Appendix). Exposed circle areas are proportional to the number of factors/covariates. AAG: α_1 -acid glycoprotein, AIBW: adjusted IBW, BW: bodyweight, BSA: body surface area, CL_{CR}: creatinine clearance, DDIs: drug-drug interactions, erythromycin breath test: as surrogate of CYP3A4 activity, IBW: ideal bodyweight, IFN- α : interferon- α , liver function: including AST, ALT and more, excluding albumin.

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Table 1. Selected examples of pharmacokinetic modeling applied to clinical pharmacotherapy or to solve practice-oriented dosing issues in oncology.

Drug	Aim of modeling	PK modeling approach	Identified covariates	Study approach (N patients)	Outcomes	References
5-fluorouracil (5FU)	Develop limited sampling to detect PDP-deficiency.	Pop-PK: 2-cmp (V_{max} , K_m) ^A	<i>Significant difference in V_{max} between DPD-deficient and controls</i>	Development (N=48); validation 1 (N=33)	Limited sampling schedule to identify PDP-deficient patients at risk of toxicity.	(70)
busulfan	Develop and implement PK model to achieve target exposure in HCT children.	Bayesian pop-PK: 1-cmp (CL) ^A	CL: BW, Age	Development (N=90); prospective validation 1 (N=21)	Model-based algorithm improved target achievement compared to conventional dosing.	(76)
	Examine five different TDM based dosing approaches and implement in EHR.	PK: 1/2-cmp	N/A	Development/validation: (N=30); software usability testing	Software tool for interpreting TDM was implemented in EHR.	(74, 75)
	Pediatric dose adjustment based on limited sampling.	Bayesian pop-PK: 1-cmp (k_{el}) ^A	Age, IBW	Development (N=53); validation 1 (N=105); validation 2 (N=11); retrospective clinical evaluation (N=20)	Model allowed limited sampling to achieve target concentrations.	(73)
	Explore variability in PK in children and young adults to optimize dosing.	Pop-PK: 2-cmp (CL) ^A	CL: BW, Day; V_1 : BW	Development (N=245); validation 1 (N=158); prospective clinical evaluation (N=50)	Nomogram based on PK model. Dosing scheme led to some residual variability, needing TDM.	(64, 77, 78)
	Evaluate approaches to estimate exposure and clinical outcome in children and young adults.	Pop-PK (<i>refitted</i>) (77)	N/A	Evaluation (N=674)	The approach may help optimize target exposure and improve efficacy/toxicity.	(87)
carboplatin	Develop limited sampling strategy.	Bayesian pop-PK: 1-cmp (k_{el}) ^A	N/A	Development (N=22); validation 1 (N=15)	Reduced bias and increased precision for AUC estimation using one or two samples.	(88)
	Develop Bayesian dose adjustment	Bayesian pop-PK: 2cmp (CL) ^A	CL: LBW, CL_{CR} ; V_{ss} : LBW; V_1 : LBW; CL_{ic} : LBW	Development (N=12); prospective clinical evaluation (N=12)	Model outperformed Calvert formula with two feedback concentrations.	(71, 72)
	Develop limited sampling strategy.	Bayesian pop-PK (CL) ^A	CL: BW, Age, Sex, S_{CR}	Development (N=90); Validation 1	All patients achieved AUCs close to target using	(89)

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			V_1, V_2 : BSA	(N=13); prospective clinical evaluation (N=5)	the model-based limited sampling approach.	
cyclophosphamide	Reduce toxicity in children undergoing HCT.	Bayesian pop-PK (CL_{NON} , CL_{IND}) ^A	CL_{NON} : Age	Development (N=147); validation 1 (N=20); Clinical evaluation (N=20); prospective clinical evaluation (N=50)	A software tool was implemented in clinical practice to individualize dosing in real-time.	(80-83, 90)
docetaxel	Individualize combination of chemotherapy and G-CSF	Semi-mech. Pop-PK/PD (k_{el}) ^A	N/A	Validation 1 (N=38)	Model has potential to minimize toxicity in individual patients.	(91)
methotrexate	Early detection of impaired elimination.	Bayesian pop-PK: 2-cmp (B, β) ^A	N/A	Development (N=7)	Bayesian limited sampling strategy (two samples) allowed detection of impaired clearance.	(92)
	Management of high-dose methotrexate therapy with leucovorine in children/young adults.	Bayesian pop-PK: 2-cmp (CL) ^A	<i>Significant difference in CL between normal and reduced renal function.</i>	Development (N=240); retrospective clinical evaluation (N=50)	A clinical software tool was developed. The tool showed reasonable accuracy for predicting exposure.	(84, 85)
	Dose adjustment of high-dose methotrexate using Bayesian estimation.	Bayesian pop-PK: 2cmp (CL) ^A	N/A	Development (N=33); Prospective clinical evaluation (N=42)	Bias and precision was satisfactory. Severe toxicities were absent.	(93, 94)
pembrolizumab	Evaluate impact of PK modeling on exposure, target engagement and cost.	Pop-PK: 2-cmp (CL) ^A (95)	CL: BW, Albumin, Baseline tumor burden, eGFR, Sex, Non-small cell lung cancer, Prior pilimumab, ECOG; V: BW, Albumin, Sex, Prior pilimumab (95)	Simulation study	Model-derived dose banding can reduce wastage and cost of treatment while maintaining optimal exposure.	(66)
suramin	Develop a rapid loading regimen.	Bayesian pop-PK: N/S	N/A	Prospective clinical evaluation (N=13)	Bayesian dosing improved accuracy for achieving target concentrations.	(96)
	PK based dose individualization	Bayesian pop-PK: 2/3-cmp (CL) ^A	N/A	Prospective clinical evaluation (N=18+11); Development	Adaptive-control-with-feedback facilitated precise control of exposure.	(97)

				– model refinement (N=69)		
5FU: 5-fluorouracil; ^A model elimination parameter(s); BSA: body surface area; BW: bodyweight; CL: clearance; CL _{CR} : creatinine CL; CL _{ic} : inter-compartmental CL; CL _{IND} : inducible CL; CL _{NON} : non-inducible CL; cmp: compartment; DPD: dihydropyrimidine dehydrogenase; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; EHR: electronic health record; G-CSF: granulocyte colony-stimulating factor; HCT: hematopoietic cell transplant; IBW: ideal BW; k _{el} : elimination rate constant; LBW: lean BW; N: number of study participants; N/A: not applicable; N/S: not stated; PK: pharmacokinetic; pop-PK: population pharmacokinetic modeling; S _{CR} : serum creatinine; TDM: therapeutic drug monitoring; V: volume of distribution.						

FIGURE 1

FIGURE 2

FIGURE 3

FIGURE 4

FIGURE 5

DATA & RESOURCE REQUIREMENTS
PHYSIOLOGICAL INTERPRETATION
ABILITY TO EXTRAPOLATE
MECHANISTIC
COMPLEXITY

CLINICAL DATA REQUIREMENT
DESCRIBE INTER-INDIVIDUAL VARIABILITY
STREAMLINE DEVELOPMENT & IMPLEMENTATION

Applications of pharmacokinetic modeling in oncology

Pharmacokinetic models for precision dosing in oncology – Supplementary appendix

Supplementary Appendix: Role of pharmacokinetic modeling and simulation in precision dosing of anticancer drugs

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Methods

A literature search was carried out using PubMed (<https://www.ncbi.nlm.nih.gov/pubmed>; 1950 – March 2017) to identify a sample set of publications including PK modeling of anticancer drugs. The inclusion criteria consisted of PK modeling of oncology drugs aimed at either predicting human exposure or based on clinical data. Studies based on pre-clinical data only or pharmacodynamic modeling only were excluded during screening of publications. To capture a broad variety of modeling applications in oncology the search terms included: "physiologically based pharmacokinetic", "pharmacokinetic", "PBPK", "PKPD", and "pharmacodynamic", and "model", "modeling", and "modelling", and "oncology", "cancer", "anti-cancer", "tumor", "tumor", "anti-tumor" or "anti-tumor", with filtering based on human species. The search yielded 1,749 publications. Additional publications were identified through references in identified publications, review articles and key literature. The final dataset included 393 publications.

The identified set of publications was categorized based on main and secondary study aims, including:

- toxicity: adverse effects/toxicity;
- bioequivalence: PK modeling of bioequivalence studies;
- biopharmaceutics effects: biopharmaceutics effects, other than food and formulation effects;
- covariates: PK covariates, or otherwise included covariates in the model;
- DDIs: metabolic/transporter drug-drug interactions;
- dose: investigating multiple doses, optimal dose, or dose individualization;

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- efficacy: drug efficacy/response;
- ethnicity: differences in PK based on ethnicity;
- evaluation/validation: assessment or validation of PK model performance;
- food effects: impact of prandial state and/or meal properties on PK;
- formulation: impact of formulation on PK;
- genotype: metabolic/transporter genotype (and α_1 -acid glycoprotein genotype) effects on PK;
- Surgery: impact of surgery on PK (including gastric and cytoreductive surgery);
- hepatic impairment: PK in hepatically impaired subjects, assessing impact of hepatic impairment on PK;
- investigational: main focus to investigate PK of the selected drug;
- limited: optimal limited sampling strategies;
- metabolite: metabolite PK;
- other special populations: PK in other special populations (including: elderly, renal replacement therapy and postmenopausal women);
- pediatrics: pediatric drug exposure;
- phenotype: metabolic/transporter phenotype effects on PK;
- renal impairment: PK in renally impaired subjects, assessing impact of renal impairment on PK;
- sex: impact of sex on PK.

Where applicable, identified PK covariates were recorded, either including the full covariate model or a summary of covariates and the PK parameter the effect was modeled on. Additional recording of information included: investigated drug, modeling approach used for development and/or application, and study population(s). Data was analyzed through graphical presentation.

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Results

Table A1 presents the summary information of the literature search on pharmacokinetic (PK) modeling of anticancer drugs. The search results included 393 peer-reviewed publications of 177 approved or investigated oncology drugs, or 414 unique study-drug combinations.

Table A1. Pharmacokinetic modelling of oncology drugs/investigated drugs.					
Drug	Study population	Modelling approach	Identified pharmacokinetic covariates	Main/secondary aims of study	References
2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a (HPPH)	Esophageal cancer, basal cell cancer, lung cancer	Pop-PK/PD	CL - <i>Age</i>	Toxicity, Covariates	(Bellnier et al., 2003)
260F9, ¹¹¹ In	Breast cancer	PK		Investigational	(Griffin et al., 1989)
3-aminopyridine-2-carboxaldehyde thiosemicarbazone (3-AP)	Advanced metastatic tumors	Pop-PK	CL[L/h]=25.0, CL in <i>PatientsReceivingOneCycleOnly</i> : 17.0, V ₂ [L] – <i>Female</i> =19.0, <i>Male</i> =34.8	Covariates	(Kolesar et al., 2011)
4'demethylepidodophyllotoxin 9-(4,6-O-ethylidene-Beta-D-glucopyranoside)	Advanced cancer	PK		Investigational	(Pelsor et al., 1978)
5,6-dimethylxanthene-4-acetic acid (DMXAA)	Solid tumors	Pop-PK/PD	V _m [μmol/L/h]=112·(1+0.474·(2-Sex[<i>Female</i> : 1, <i>Male</i> : 2])), V ₁ [L]=8.19·(BSA/1.8) ^{0.857}	Efficacy, Covariates	(Li et al., 2008)
5-fluorouracil	Cancer (N/S)	Semi-mech. PK		Investigational	(Robinson et al., 1988)
	Colorectal cancer	PK		Investigational	(Wattananorn et al., 1997)
	Metastatic colorectal	Bayesian pop-PK	CL[L/h]=60.2· <i>Female</i> + 65.0,	Investigational, Covariates	(Bressolle et al., 1999)

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	cancer		<i>Circadian rhythm (cosine model)</i>		
	Cancer (N/S)	PK/PD		Efficacy, Dose	(Gardner, 2002)
	Dukes' colorectal adenocarcinoma	PK		Limited sampling	(Di Paolo et al., 2002)
	Colorectal cancer	Bayesian pop-PK	$V[L]=0.266 \cdot BW$, $CL[L/h]=1.210 \cdot IBW$	Covariates	(Climente-Marti et al., 2003)
	Cancer (N/S)	Pop-PK		Metabolite	(Coustere et al., 1991)
	Breast cancer	Semi-mech. Pop-PK/PD	$V_{max}[mg/L/h]=94.8$, $CL_{CR}: 0.24$, $K_m[mg/L]=21.2$, <i>Albumin</i> : 1.87, $V[L]=23.2$, $BSA < 1.74$: 0.377, $BSA > 1.74$: 1.32	Toxicity, Covariates	(Sandstrom et al., 2006)
	Breast cancer	Pop-PK		Investigational	(Sandstrom et al., 1996)
	Colorectal cancer	Pop-PK	<i>Caution when dosing BSA in women</i>	Metabolite, Covariates	(Woloch et al., 2012)
	Mixed cancer	Bayesian pop-PK		Metabolic genotype (DPD)	(van Kuilenburg et al., 2012)
6-mercaptopurine	Acute lymphoblastic leukemia	Pop-PK	$F_M=0.019 \cdot 2.56^{TPMTmutation}$, $CL_{6-TGNS}[h^{-1}]=0.00914 \cdot BSA^{1.16}$	Pediatrics, Metabolic genotype (TPMT), Metabolite, Covariates	(Hawwa et al., 2008)
9-aminocamptothecin	Solid tumors	PK		Investigational	(Rubin et al., 1995)
Abexinostat	Solid tumors, lymphoma	Pop-PK/PD		Dose, Toxicity	(Chalret du Rieu et al., 2014a)
Aberitorone	Prostate cancer	Pop-PK	$CL/F[L/h]=2,240 \cdot (1 + Healthy \cdot (-0.308))$, <i>Fed state/meal properties</i>	Food effects, Covariates	(Stuyckens et al., 2014)
ABT-767	High grade severe ovarian cancer, primary peritoneal cancer, fallopian tube cancer	Pop-PK	$CL/F[L/h]=7.34 \cdot (Albumin_i / Albumin_{Median})^{0.651}$, $k_a[h^{-1}]=1.45 \cdot 0.54^{Fed}$	Covariates	(Mittapalli et al., 2017)
ABT-806	Head and neck squamous cancer, non-small cell lung cancer, colorectal cancer	Pop-PK	$CL[L/day]=0.011 \cdot (Albumin_i / Albumin_{Median})^{-0.924}$, $V_i[L]=3.47 \cdot (BW_i / BW_{Median})^{0.542}$	Dose, Covariates	(Sharma et al., 2015)
Actinomycin D	Cancer (N/S)	PBPK		Pediatrics	(Walsh et al., 2016)
	Cancer (N/S)	Pop-PK		Pediatrics	(Edwards et al., 2012)
Afatinib	Solid tumors	Pop-PK	$CL/F=42.3 \cdot (BW/62)^{0.595} \cdot (1 + 0.00484 \cdot (CL_{CR}-120) \cdot 0.871^{Female} \cdot (1 - 0.00436 \cdot (TotalProtein-72)))$, $F_i=1 \cdot (Dose/70)^{0.485 \cdot Dose \leq 70mg} \cdot 0.739^{Food} \cdot \theta_{ECOG} \cdot (1 + 0.000331 \cdot (LactateDehydrogenase-241)) \cdot (1 + \theta_{AlkalinePhosphate} \cdot (AlkalinePhosphate-251)) \cdot CancerType$, $V_2/F[L]=456 \cdot (BW/62)^{0.899}$	Food effects, Covariates	(Freiwald et al., 2014)

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			ECOG: Eastern Cooperative Oncology Group		
Aflibercept	Advanced solid tumors	Pop-PK	$CL_i[L/day] = CL \cdot (COV_i / COV_{Median})^\beta$ – continuous variables Or $CL_i[L/day] = CL \cdot e^{\beta \cdot COV_i}$ – dichotomous variables $CL_i = 0.85$, β - Female: -0.15, BW: 0.33, CL_{CR} : 0.18, Albumin: -0.39, AlkalinePhosphate(ALK): 0.10, AlanineAminoTransferase(ALT): -0.06, Gemcitabine: 0.09 $CL_i = 0.18$, β - Age: 0.18, CL_{CR} : 0.09, Albumin: -0.13, ALT: -0.08, irinotecan/5-FU/LV: -0.13, docetaxel: 0.06 $V[L] = 3.87$, β - Female: -0.21, BW: 0.39, CL_{CR} : 0.10 $K_m[\mu g/mL]$, β - Female: -0.23, ALT: 0.26, AspartateAminoTransferase: -0.26, gemcitabine: 0.60	Covariates, Dose	(Thai et al., 2013)
	Healthy volunteers	Semi-mech. Pop-PK		Investigational	(Thai et al., 2011)
Alectinib	Healthy volunteers, cancer (N/S)	PBPK		Food effects, Biopharmaceutics effects	(Parrott et al., 2016)
All-trans-retinoic acid	Cancer (N/S)	PBPK		DDIs	(Jing et al., 2017)
Alvespimycin	N/A	PBPK		Inter-species extrapolation	(Hu et al., 2014)
Amatuximab	Malignant pleural mesothelioma	Pop-PK		Dose	(Gupta et al., 2016a)
AMD3100	Healthy volunteers	Pop-PK/PD		Efficacy	(Lack et al., 2005)
AMG 386	Advanced solid tumors, advanced ovarian cancer	Pop-PK/PD	$CL[L/h] = 0.0722 + 0.502 \cdot CL_{CR}$, $V_c[L] = 3.74 \cdot (BW_i / BW_{reference})^{0.502}$, Sex: 0.83	Efficacy, Covariates	(Lu et al., 2012)
Amrubicin	Small cell and non-small cell lung cancer	Pop-PK		Limited sampling	(Makino et al., 2016)
Anastrozole	Healthy volunteers	Pop-PK		Bioequivalence	(Noh et al., 2012)
Anti-CD66 antibody	Acute leukemia	PBPK		Investigational	(Kletting et al., 2010)
	Acute leukemia	PBPK		Investigational	(Kletting et al., 2015)
	Cancer (N/S)	PBPK		Investigational	(Maass et al., 2015)
Apatinib	Healthy volunteers, solid tumors	Pop-PK	$CL/F[L/h] = 57.8$, DiseaseState: -0.390, $k_a[h^{-1}] = 0.0848$, DiseaseState: -0.517	Covariates	(Yu et al., 2017b)
AT9283	Solid tumors, relapsed or refractory leukemia	Pop-PK	$CL[L/h] = 32.2 \cdot (BW_i / BW_{reference})^{0.75} \cdot (GFR_i / GFR_{reference})^{0.452}$, $V_c[L] = 58.5 \cdot (BW_i / BW_{reference})^1$	Pediatrics, Covariates, Dose	(Duong et al., 2017)
Axitinib	Non-small cell lung cancer	Pop-PK	$CL[L/h] = 20.1$, Female: -0.349, $V_c[L] = 56.2$, BW: 0.933 $F = 0.663$, Food: -0.263 $K_a[h^{-1}] = 1.26$, Food: -0.653	Food effects, Covariates	(Tortorici et al., 2014)

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B72.3	Colon cancer	PK		Investigational	(Reilly et al., 1993)
Barasertib	Solid tumors	Pop-PK/PD		Toxicity, Dose	(Keizer et al., 2012)
Belinostat	Peripheral T-cell lymphoma	Pop-PK/PD	$\theta_i = \theta \cdot (\text{COV}_i / \text{COV}_{\text{median}})^{\text{ICOV}}$ CL[L/h]=106.03, CL_{CR} : 0.3799, <i>UGT</i> genotype: 0.8475, <i>Albumin</i> : -0.3897, V1[L]=31.82, <i>BW</i> : 0.3848	Metabolic genotype (UGT1A1), Toxicity, Covariates	(Peer et al., 2016)
Bendamustine	Relapsed/refractory acute leukemia	Pop-PK/PD		Pediatrics, Toxicity, Covariates	(Darwish et al., 2014)
Bevacizumab	Colorectal cancer	Pop-PK		Covariates	(Panoilia et al., 2015)
	Metastatic colorectal cancer	Pop-PK		Investigational	(Caulet et al., 2016)
	Solid tumors, non-small cell lung cancer, hormone refractory prostate cancer, breast cancer, renal cell cancer, pancreatic cancer, metastatic colorectal cancer	Pop-PK	$CL[\text{mL/h}] = 8.6 \cdot (BW_i/70)^{0.589} \cdot (Albumin_i/39)^{0.473} \cdot (\ln(AlkalinePhosphatase_i)/\ln(109))^{0.312} \cdot (1.14 \text{ for Males}) \cdot (0.844 \text{ for InterferonAlpha})$, V1[mL]=2678·(BW _i /70) ^{0.470} ·(1.18 for Males)	Covariates	(Han et al., 2016a)
	Refractory sarcomas, primary CNS tumors, osteosarcoma, metastatic soft-tissue sarcoma	Pop-PK	$CL[\text{mL/h}] = 9.9 \cdot (BW_i/70)^{0.75} \cdot (Albumin_i/39)^{-0.3} \cdot (1.11 \text{ for Males}) \cdot (0.725 \text{ for CNStumours})$, V1[mL]=2850·(BW _i /70) ^{0.701} ·(1.14 for Males) ·(0.854 for CNStumours)	Pediatrics, Dose, Covariates	(Han et al., 2016b)
	Gastric cancer	Bayesian pop-PK	CL: <i>BW</i> , <i>Gastrectomy</i> , <i>Albumin</i>	Covariates	(Han et al., 2014)
	Cancer (N/S)	Semi-mech. PK		Investigational	(Stefanini et al., 2010)
BI 2536	Advanced non-resectable and/or metastatic refractory solid tumors	Semi-mech. Pop-PK/PD		Toxicity, Dose, Covariates	(Soto et al., 2010)
	Non-small cell lung cancer	Semi-mech. Pop-PK/PD		Evaluation/validation, Toxicity	(Soto et al., 2011b)
BI 893923	N/A	Pop-PK/PD		Inter-species extrapolation, Dose	(Titze et al., 2017)
Bortezomib	Leukemia	Pop-PK	CL, Q ₃ : <i>BSA</i>	Pediatrics, Covariates	(Hanley et al., 2016)
Brentuximab vedotin	Hematological malignancies	Pop-PK	CL _M [L/day]=55.7, Q5[L/day]=65.0, BW: 0.75 fixed exponent, V4[L]=79.8, V5[L]=28.1, BW: 1 fixed exponent	Investigational, Dose, Covariates	(Li et al., 2017a)
Busulfan	Hematopoietic cell transplant	Pop-PK		Pediatrics, Dose	(McCune et al., 2014)
	Hematopoietic cell transplant	Bayesian Pop-PK	k_{el} : <i>IdealBodyWeight</i> , <i>Age</i> , V: <i>IdealBodyWeight</i> , <i>Age</i>	Pediatrics, Limited sampling, Covariates	(Neely et al., 2016)
	N/A	PBPK		Pediatrics	(Diestelhorst

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	Hematopoietic cell transplant	Pop-PK	CL[L/h/20kg]=3.03, BW: 0.742 (power), V _d [L/h/20kg]=12.8, BW: 0.843 (power)	Pediatrics, Dose, Covariates	et al., 2014) (Booth et al., 2007)
	Hematopoietic cell transplant	Pop-PK	CL: <i>Leukemia</i>	Pediatrics, Covariates	(Hassan et al., 1996)
	Hematopoietic cell transplant	Bayesian pop-PK	CL: <i>BSA</i>	Limited sampling, Covariates	(Nguyen et al., 2006)
	Hematopoietic cell transplant	Bayesian pop-PK	CL/F[L/h]=2.63·(Age/18) ^{0.376} ·(AsparatateAminotransferase/29) ^{-0.161} ·0.787 ^{CancerType} , V/F[L]=9.26·(1+0.0734·(BW-10)), k _a [h=1]=1.26·(Dose/1.0)-1.15·2.49 ^{Formulation}	Pediatrics, Dose, Covariates	(Nakamura et al., 2008)
	Cancer (N/S)	Pop-PK	CL: <i>BSA, BW</i>	Pediatrics, Dose, Covariates	(Trame et al., 2011)
	Hematopoietic cell transplant	Pop-PK	CL: <i>BW, Day</i> , V: <i>BW</i>	Pediatrics, Dose, Covariates	(Bartelink et al., 2012a)
	Mixed disease	Pop-PK		Evaluation/validation, Pediatrics	(Bartelink et al., 2012b)
	Hematopoietic cell transplant	PK		Evaluation/validation, Pediatrics	(Abdel-Rahman et al., 2016b)
	Hematopoietic cell transplant	PK		Evaluation/validation, Pediatrics	(Abdel-Rahman et al., 2016a)
	Hematopoietic cell transplant	Bayesian pop-PK	CL: <i>BW, Age</i>	Pediatrics, Dose, Covariates	(Long-Boyle et al., 2015)
	Hematopoietic cell transplant	Pop-PK	CL: <i>AdjustedIBW, ALT</i> , V: <i>AdjustedIBW</i>	Covariates, Limited sampling, Dose	(de Castro et al., 2015)
	Hematopoietic cell transplant	Pop-PK/PD		Covariates, Dose, Efficacy, Toxicity, Pediatrics	(Bartelink et al., 2016)
	Hematopoietic cell transplant	Pop-PK/Bayesian pop-PK/PD (based dosing)		Pediatrics, Dose, Evaluation/validation	(Zao et al., 2015)
BYL719	Advanced solid malignancies	Pop-PK/PD		Efficacy, Dose	(De Buck et al., 2014)
Cabazitaxel	Advanced solid tumors	Pop-PK	CL[L/h]=48.6·BSA/1.84·(1-0.536·BreastCancerTumourType)	Covariates	(Ferron et al., 2013)
Cabozantinib	Advanced malignancies, recurrent/progressive glioblastoma multiforme, unresectable locally advanced or metastatic medullary thyroid cancer	Pop-PK	CL/F[L/day]=106, BMI: -0.0244, Sex: -0.219	Dose, Covariates	(Miles et al., 2016a)
	Medullary thyroid cancer	Pop-PK/PD	CL/F[L/day]=108.5, BMI: -0.0276, Sex: -0.216, ParticipantPopulation: -0.408	Efficacy, Covariates	(Miles et al., 2016b)
Capecitabine	Breast cancer, colorectal	Pop-PK	k _a [h ⁻¹]=1.86·0.45 ^{AgeGroup} ,	Other special populations	(Daher Abdi et

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	cancer		$k_{40}[\text{h}^{-1}]=77.1 \cdot 0.77^{\text{DayOfPKEvaluation}}$	(Elderly), Covariates	al., 2014
	Metastatic cancer	Pop-PK	$CL_{10}[\text{L/h}]=218$, <i>TotalBilirubin</i> : 0.32, $K_{34}[\text{h}^{-1}]=5.30$, <i>TotalBilirubin</i> : -0.36	Metabolite, Covariates	Urien et al., 2005
	Breast cancer, other	Pop-PK	CL of 5'-DFUR[L/h]=70.3, <i>Bilirubin</i> : 1.3, <i>BSA</i> : 1.1 CL of FBAL[L/h]=22.7, CL_{CR} : 0.5	Metabolite, Covariates	Gieschke et al., 2002
	Colorectal cancer	Pop-PK	CL of 5-FU[L/h]=1190, <i>ALP</i> : 2, CL of FBAL[L/h]=27.5, CL_{CR} : 0.5 V of FBAL [L]=72.6, CL_{CR} : 0.5, <i>BSA</i> : 1.3	Metabolite, Toxicity, Covariates	Gieschke et al., 2003
Carboplatin	Advanced non-small cell lung cancer	Pop-PK		Dose	Merino-Sanjuan et al., 2011
	Advanced ovarian cancer	Pop-PK	$CL[\text{L/min}]=0.101+0.011 \cdot (BW-62.35)-0.0658 \cdot (S_{CR}-0.65)$ $V_1[\text{L}]=15.5+0.163 \cdot (BW-62.35)$ $Q[\text{L/min}]=0.0132-0.0103 \cdot (Albumin-3.65)$ $V_2[\text{L}]=7.07-3.61 \cdot (Albumin-3.65)$	Limited sampling, Covariates	Shen et al., 2002
	Ovarian cancer	Bayesian pop-PK	$CL[\text{L/h}]=0.15 \cdot LBW^{0.75}+0.78 \cdot CL_{CR}$, $V_{ss}[\text{L}]=0.38 \cdot LBW$, $V_1[\text{L}]=0.26 \cdot LBW$, $CL_{ic}[\text{L/h}]=0.15 \cdot LBW^{0.75}$	Dose, Covariates	Duffull et al., 1997
	Germ cell cancer	Pop-PK/PD	$CL[\text{mL/min}]=110.0$, $CL_{CR,24h}$: 0.408, <i>Height</i> : 1.05, $V_c[\text{L}]=19.8$, <i>BW</i> : 0.091, $k_{12}[\text{h}^{-1}]=0.042$, <i>BW</i> : $04.7 \cdot 10^{-4}$, <i>Height</i> : $7.5 \cdot 10^{-4}$, <i>Age</i> : $-6.4 \cdot 10^{-4}$, $CL_{CR,24h}$: $-8.1 \cdot 10^{-5}$	Dose, Toxicity, Covariates	Kloft et al., 2003
	Mixed	Pop-PK		Renal function	Ekhart et al., 2006
	Cancer (N/S)	Bayesian pop-PK		Pediatrics, Limited sampling	Peng et al., 1995
	Cancer (N/S)	Pop-PK	$CL[\text{mL/min}]=114.2 \cdot (CL_{CR}/103.1)^{0.34} \cdot (BW/70)^{0.75} \cdot (1+InfusionDuration)$	Dose, Pediatrics, Covariates	Lindauer et al., 2010b
	Metastatic germ cell cancer	Bayesian pop-PK	CL : <i>BW</i> , <i>Age</i> , <i>Sex</i> , S_{CR} , $V1$, $V2$: <i>BSA</i>	Limited sampling, Dose, Covariates	Chatelut et al., 2000
	Mixed cancer	Bayesian pop-PK		Dose, Evaluation/validation	Guillet et al., 1997
Carfilzomib	Multiple myeloma	Pop-PK	CL : <i>BSA</i>	Covariates	Ou et al., 2017
Carlumab	Refractory tumors	Pop-PK/PD		Efficacy, Dose	Fetterly et al., 2013
CC49 (mAb)	Cancer (N/S)	PBPK		Inter-species extrapolation	Davda et al., 2008
Cediranib	Cancer (N/S)	Pop-PK	$CL/F[\text{L/h}]=26.3 \cdot (Age/59)^{-0.409} \cdot (BW/73)^{0.517}$, $V_c/F[\text{L}]=489 \cdot (BW/73)^{0.65}$	DDIs, Covariates	Li et al., 2017b
Ceritinib	Cancer (N/S)	Pop-PK	$CL/F[\text{L/h}]=24.6$, <i>BW</i> : 0.642, <i>BaselineAlbumin</i> : 0.254, <i>Albumin</i> : 0.285, <i>BaselineAlanineTransaminase</i> : -0.0859, <i>AlanineTransaminase</i> : -0.0792, $k_{out}[\text{h}^{-1}]=0.148$, <i>Japanese</i> : 6.84	Hepatic impairment, Covariates	Hong et al., 2017
Cetuximab	Metastatic colorectal	Pop-PK	$\theta_i=\theta \cdot (COV_i/COV_{median})^{ICOV}$	Covariates	Azzopardi et al., 2011

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	cancer		$CL[L/day]=0.497$, <i>InitialSerumAlbumin</i> : -0.0244, $V_1[L]=2.96$, <i>BSA</i> : 0.42, $V_2[L]=4.65$, <i>BSA</i> : 0.56, $k_0[mg/day]=8.71$, <i>BSA</i> : 1.58		
	Head and neck squamous cell cancer	Pop-PK	$\theta_i=\theta\cdot(COV_i/COV_{median})^{BCOV}$ $CL[L/day]=3.18$, <i>Chemotherapy</i> : -0.45, $V_1[L]=3.18$, <i>BSA</i> : 1.28, $V_2[L]=5.40$, <i>BSA</i> : 5.54, $k_0[mg/day]=6.72$, <i>Chemotherapy</i> : 1.2	Covariates	(Pointreau et al., 2016)
Chloroquinoxaline sulphonamide	Non-small cell lung cancer	Pop-PK		Dose	(Miller et al., 1997)
Cilengitide	Solid tumors	Pop-PK		Pediatrics	(Zuhlsdorf et al., 2014)
Cisplatin	Malignant solid tumors	Pop-PK	$CL[L/h]=5.17+26.3\cdot(BSA-1.855)$ $V[L]=41.4+24.6\cdot(BSA-1.855)$	Covariates	(de Jongh et al., 2004)
	Ovarian cancer	PK		Investigational	(Reece et al., 1987)
	Lung, stomach, colon, mediastinal tumor, indistinct, cancer	Pop-PK/PD	<i>CL: BSA, DoseSchedule,</i> <i>V: BSA</i>	Toxicity, Covariates	(Nagai et al., 1998)
	Testicular cancer	Bayesian pop-PK		Dose	(Salas et al., 2006)
	Cancer (N/S)	Pop-PK	<i>CL: BSA</i>	Metabolite, Covariates	(Hanada et al., 2001)
	Ovarian cancer	PK		Investigational	(Griffiths et al., 1987)
	Breast, ovarian cancer	PK		Investigational	(Fracasso et al., 1987)
	Breast, ovarian cancer	PK		Investigational	(Leone et al., 1987)
	Ovarian, ovarian and cervical cancer, small cell lung cancer	PK		Other special populations (elderly)	(Bonetti et al., 1994)
	Advanced ovarian cancer receiving chemotherapy	Bayesian pop-PK		Investigational	(Panteix et al., 2002)
	Advanced non-small cell lung cancer	Pop-PK (w. gemcitabine)		Transporter genotype (SLC28A1), Metabolic genotype (GST, CDA, deoxycytidine kinase), Toxicity, Covariates	(Joergers et al., 2012)
	Cancer (N/S)	PBPK		Pediatrics	(Evans et al., 1982a)
CKD-602	Cancer (N/S)	Semi-mech. Pop-PK/PD		Toxicity	(Wu et al., 2012a)
Clofarabine	Acute leukemia	Pop-PK	$CL[L/h]=32.8\cdot(BW/40)^{0.75}$,	Pediatrics, Covariates	(Bonate et al., 2012a)

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			$V1=115 \cdot (BW/40)^{1.00} \cdot (WhiteBloodCellCount/10 \cdot 10^3)^{0.128}$, $Q2=20.5 \cdot (BW/40)^{0.75}$, $V2=94.5 \cdot (BW/40)^{1.00}$		(2004)
Cobimetinib	Solid tumors	Pop-PK	$\theta_i = \theta \cdot (COV_i / COV_{reference})^{BCOV}$ CL/F[L/day]=322, Age: -0.217, V2/F[L]=511, BW: -0.217	Covariates	(Han et al., 2015)
Crizotinib	Cancer (N/S)	PBPK	<i>Suggests no dose adjustment in renal mild/moderate renal impairment.</i>	Renal impairment	(Tan et al., 2017)
	Mainly advanced non-small cell lung cancer	Pop-PK/PD		Dose, Efficacy	(Yamazaki et al., 2012)
	Non-small cell lung cancer	Pop-PK	$CL/F[L/h]=136 \cdot (0.46 \cdot (Day-1)/(1.17+(Day-1)))$ $\cdot (1-0.23 \cdot Asian) \cdot (1-0.112 \cdot Female) \cdot (BW/65)0.20 \cdot (CL_{CR}/91.6)0.16 \cdot (TotalBilirubin/0.41)-0.07$, $V2/F[L]=3520 \cdot (1-0.23 \cdot Asian) \cdot (1-0.23 \cdot Female)$	Renal impairment, Hepatic impairment, Covariates	(Wang et al., 2016)
	Healthy volunteers, Cancer (N/S)	PBPK		DDIs (CYP3A4)	(Yamazaki et al., 2015)
	Healthy volunteers, Cancer (N/S)	PBPK		DDIs (CYP3A4)	(Mao et al., 2013)
Custirsen	Mixed cancer	Pop-PK	$\theta_i = \theta \cdot (COV_i / COV_{reference})^{BCOV}$ CL[L/h]=2.36, Age: -0.190, BW: 0.355, S_{CR} : -0.159, Q3[L/h]=0.0573, Age: 0.224	Covariates	(Edwards et al., 2017)
Cyclophosphamide	Neuroblastoma	Pop-PK		Pediatrics	(McCune et al., 2009b)
	Hematopoietic cell transplant	Bayesian pop-PK		Dose	(Salinger et al., 2006)
	Hematopoietic cell transplant	Pop-PK		Dose	(McDonald et al., 2005)
	Hematologic malignancy	Bayesian pop-PK	CL: Age	Dose, Covariates	(McCune et al., 2009a)
	Hematologic malignancy	Pop-PK	CL: CYP2B6 V: BW, Sex	Metabolic genotype (CYP2B6, CYP2C9, CYP2C19), Covariates	(Xie et al., 2006)
	Metastatic breast cancer	PK		Investigational	(Chen et al., 1995)
	Breast cancer	Semi-mech. Pop-PK		Investigational	(Hassan et al., 1999)
	Cancer (N/S)	PK/PD		Efficacy, Dose	(Gardner, 2002)
	Breast cancer	Semi-mech. Pop-PK/PD (4-hydroxy-cyclophosphamide)	CL[L/h]=255, Albumin: 2.61, BSA: 56.3, V1[L]=1970, ALT: -21.5, BW: 1.45, V2[L]=645, BW: 1.45	Toxicity, Covariates	(Sandstrom et al., 2006)
	Breast cancer	Pop-PK (4-hydroxy-cyclophosphamide)		Investigational	(Sandstrom et al., 1996)
	High-risk/advanced breast	Semi-mech. Bayesian		Metabolite, DDI (ThioTEPA)	(Huitema et al., 2001)

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	cancer, germ-cell cancer, ovarian cancer	pop-PK			
Cytarabine	Acute myeloid leukemia	Pop-PK	CL: <i>BaselineWhiteBloodCellCount</i>	Covariates	(Krogh-Madsen et al., 2012)
Daunorubicin	Acute lymphoblastic leukemia	Pop-PK		Pediatrics	(Hempel et al., 2010)
	Acute myeloid leukemia	Pop-PK	V_c : <i>BaselineWhiteBloodCellCount</i>	Covariates	(Krogh-Madsen et al., 2012)
Degarelix	Healthy volunteers	Pop-PK/PD		Efficacy	(Tornøe et al., 2004a)
	Healthy volunteers	Pop-PK		Investigational	(Tornøe et al., 2004b)
Denosumab	Cancer (N/S)	Pop-PK/PD		Efficacy	(Perez Ruixo et al., 2015)
	Solid tumors with bone metastases	Bayesian Pop-PK	CL[mL/h/66 kg]=3.25, <i>Hispanic/Caucasian</i> : 1.27, <i>BreastCancer/Healthy</i> : 1.10, <i>ProstateCancer/Healthy</i> : 1.29, <i>SolidTumours/Healthy</i> : 1.37, <i>GiantCellCancer/Healthy</i> : 1.19, V_1 [mL/66 kg]=2620, <i>Black/Caucasian</i> : 0.769, k_a [h ⁻¹]=0.0107, <i>Age power</i> : -0.509, <i>Reference</i> : 53.6	Covariates	(Gibiansky et al., 2012)
Diflomotecan	Advanced malignant tumors	Semi-mech. Pop-PK/PD		Toxicity	(Soto et al., 2011a)
Dinutuxumab	Neuroblastoma	Pop-PK		Investigational	(Marachelian et al., 2016)
Docetaxel	Breast cancer	Pop-PK	CL[L/h]:32.6, <i>Age</i> : 1.24	Sex, Covariates	(Onoue et al., 2016)
	Cancer (N/S)	PBPK, Pop-PK		Limited sampling, Dose, Pediatrics	(Thai et al., 2015)
	Cancer (N/S)	Pop-PK	CL[L/h]=43.8, <i>GestationalEffect</i> : 1.19, V_c [L]=8.63, <i>GestationalEffect</i> : 1.07, V_{p1} [L]=7.19, <i>GestationalEffect</i> : 1.37, V_{p2} [L]=359, <i>GestationalEffect</i> : 0.903	Other special populations (pregnancy), Covariates	(van Hasselt et al., 2014)
	Advanced cancer	Pop-PK	CL _{normal} [L/h]=470, CL _{impaired} [L/h]=317, CL: <i>AAG, ErythromycinBreathTest</i>	Hepatic impairment, Covariates	(Hooker et al., 2008)
	Solid tumors	Pop-PK/PD	CL: <i>BSA, AAG, Albumin, Ethnicity, Sex</i>	Toxicity, Ethnicity, Metabolic genotype (CYP3A), Transporter genotype (ABCB1), Covariates	(Lewis et al., 2007)
	Non-small cell lung cancer	Pop-PK/PD	CL[L/h]=32.5, <i>BW normalized, Albumin</i> , V_1 [L]=6.67, <i>BW normalized</i> , V_2 [L]=7.61, <i>BW normalized</i> , V_3 [L]=175, <i>BW normalized</i>	Toxicity, Covariates	(Fukae et al., 2016)
	Non-small cell lung cancer	Pop-PK/PD	CL: <i>BSA</i> : 38%, <i>Transaminases&AlkalinePhosphatase</i> : 27%, <i>AAG</i> : -19%,	Toxicity, Covariates	(Bruno et al.,

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			<i>Albumin</i> : -8%, <i>Elderly</i> : -7%		2001)
	Advanced cancer	Pop-PK	$CL[L/h]=21.51+217(1/ ErythromycinBreathTest_tmax)-0.13 \cdot ALT$	Covariates	(Slaviero et al., 2004)
	Mixed cancer	Semi-mech. Pop-PK/PD		Toxicity, Covariates	(Kloft et al., 2006)
	Solid tumors	Pop-PK/PD		Toxicity, Covariates	(Ozawa et al., 2007)
	Breast cancer, non-small cell lung cancer, head and neck cancer, other	Pop-PK		Hepatic impairment, Dose	(Minami et al., 2009)
	Metastatic breast cancer	Semi-mech. Pop-PK/PD		Dose, Toxicity	(Vainas et al., 2012)
	Cancer (N/S)	Pop-PK		DDIs (ritonavir)	(Koolen et al., 2010)
	Non-small cell lung cancer	Pop-PK/PD (w. cisplatin)		Other special populations (elderly), Covariates, Toxicity	(Minami et al., 2004)
	Cancer (N/S)	PK/PD (w. epirubicin)		Toxicity, Dose	(Meille et al., 2016)
	Mixed cancer	Bayesian pop-PK	$CL[L/h]=BSA \cdot (22.1-3.55 \cdot AAG-0.095 \cdot Age+0.225 \cdot Albumin \cdot (1-0.334 \cdot HepaticFunction))$	Covariates	(Bruno et al., 1996)
	Solid tumors	Pop-PK	$CL[L/h]=BSA \cdot (56.4 \cdot 1.05^{HeterozygousABCB1-C1236T} \cdot 0.719^{HomozygousABCB1-C1236T} + \theta_{10} \cdot AAG + \theta_{11} \cdot Age + \theta_{12} \cdot Albumin) \cdot (1-HepaticFunction)$	Transporter genotype (ABCB1), Metabolic genotype (CYP3A), Covariates	(Bosch et al., 2006)
	Cancer (N/S)	Pop-PK	$CL[L/h]=BSA \cdot (34.5-0.254 \cdot Age)/35.6$	Covariates	(Launay-Iliadis et al., 1995)
DOTATATE	Cancer (N/S)	PBPK		Investigational	(Kletting et al., 2012)
Doxorubicin	Cancer (N/S)	Pop-PK	$V_c[L]=9.83$, <i>GestationalEffect</i> : 1.23, $V_{pl}[L]=674$. <i>GestationalEffect</i> : 1.32	Other special populations (pregnancy), Covariates	(van Hasselt et al., 2014)
	Breast cancer	Pop-PK/PD	$CL[L/h]=47.6 \cdot (BSA/1.8)^{1.4} \cdot (AspartateTransaminase/21)^{-0.24} \cdot (AGE/56)^{-0.54}$	Toxicity, Covariates	(Joerger et al., 2007c)
	Cancer (N/S)	Pop-PK	$CL - BSA$: 1.30 (linear scaling), <i>Age</i> : 0.286 (power) $V_1, Q_2, V_2, V_3, V_3, CL_M, V_M - BSA$: 1.30 (linear scaling)	Pediatrics, Covariates	(Voller et al., 2015)
	Advanced breast cancer	PK		Investigational	(Frenay et al., 1989)
	Cancer (N/S)	PK/PD		Efficacy, Dose	(Gardner, 2002)
	Mixed cancer	Pop-PK		Pediatrics, Obesity, Covariates	(Thompson et al., 2009)
	Breast cancer	Pop-PK		Overweight, Dose	(Barpe et al., 2010)
	Breast cancer	Pop-PK	$CL [L/h]=53.5$, <i>Age</i> : -0.393 (power)	Metabolite, Covariates	(Wong et al., 2014)
	Cancer (N/S)	Pop-PK		Pediatrics, Metabolite	(Kunarajah et al., 2017)
	Metastatic breast cancer	Pop-PK		Toxicity, Covariates	(Xu et al., 2017)

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	Breast cancer	Pop-PK/PD		Metabolite, Toxicity, Covariates	(2010) (Liang et al., 2016)
	Mixed cancer	PK		Investigational	(Rahman et al., 1990)
	Cancer (N/S)	PBPK		Inter-species extrapolation	(Harris and Gross, 1975)
	Solid tumors	PBPK		Investigational	(Chan et al., 1978)
E7080	Advanced malignancies	Pop-PK/PD		Toxicity	(Keizer et al., 2010)
E7820	Malignant solid tumors, lymphoma	Pop-PK		Food effects	(Keizer et al., 2009)
Elotuzumab	Relapsed/refractory multiple myeloma	Pop-PK	$\theta_i = \theta \cdot (\text{COV}_i / \text{COV}_{\text{reference}})^{\text{BCOV}}$ CL[L/day]=0.0895, BW: 1.16, Lenalidomide/dexamethasone: 0.666, V _c [L]=4.04, BW: 0.332, Female: 0.796, Asian: 0.861, 2-microglubilin>3.5: 1.13, Q[L/day]=0.676, BW: 0.75, V _p [L]=2.22, BW: 0.75, V _{max} [μg/mL/day]=9.21, M-Protein: 0.178	DDIs, Covariates	(Gibiansky et al., 2016)
Enzalutamide	Healthy volunteers	PBPK		DDIs	(Narayanan et al., 2016)
Epacadostat	Advanced solid malignancies	Pop-PK/PD	CL/F[L/h]=49.3·(BW/83) ^{0.90} , V _c /F[L]=152·(BW/83) ^{0.56}	Efficacy, Covariates	(Shi et al., 2017)
Epirubicin	Cancer (N/S)	Pop-PK	CL[L/h]=83.4, GestationalEffect: 1.10, V _c [L]=9.83, GestationalEffect: 1.55, V _{pl} [L]=10, GestationalEffect: 2.08	Other special populations (pregnancy), Covariates	(van Hasselt et al., 2014)
	Metastatic breast cancer	PK		Investigational	(Jakobsen et al., 1991)
	Breast cancer	Semi-mech. Pop-PK/PD	CL[L/h]=71.7, Albumin: 1.33, Bilirubin: -0.575	Toxicity, Covariates	(Sandstrom et al., 2006)
	Breast cancer	Pop-PK		Investigational	(Sandstrom et al., 1996)
Eribulin mesylate	Breast cancer, prostate cancer, solid tumors, non-small cell lung cancer	Semi-mech. Pop-PK/PD		Toxicity, Dose, Covariates	(van Hasselt et al., 2013)
Erlotinib	Cancer (N/S)	PK/PD		Investigational	(Foo et al., 2012)
	Non-small cell lung cancer	Pop-PK	CL[mL/h]=43+0.356·CL _{CR} , V _c - BW, Sex	Toxicity, Covariates	(Lu et al., 2006)
Ewinia asparaginase	Acute lymphoblastic leukemia	Pop-PK		Pediatrics	(Sassen et al., 2017)
Etoposide	Non-Hodgkin's lymphoma, Hodgkin's lymphoma	Pop-PK	CL[L/h]=0.0019·(CL _{CR} /91.7) ^{0.245} ·(Bilirubin/7) ^{-0.161}	Covariates	(You et al., 2015)
	Acute leukemia	PK		Pediatrics	(Evans et al., 1982b)

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	Mixed cancer	Bayesian pop-PK		Limited sampling	(Tranchand et al., 1999)
	Multifocal hepatocellular carcinoma, advanced non-small cell lung cancer, gastric cancer, breast cancer, other	Pop-PK/PD	$CL[L/h]=114$, CL_{CR} , $V[L]=6.0$, BSA , $ProteinBinding$, $k_{12}[h^{-1}]=0.14$, $ProteinBinding$, $k_{21}[h^{-1}]=0.06$, CL_{CR}	Efficacy, Toxicity, Covariates	(Toffoli et al., 2001)
	Mixed cancer	Semi-mech. Pop-PK/PD		Toxicity, Covariates	(Kloft et al., 2006)
	Small cell lung cancer	Pop-PK/PD	CL : CL_{CR} , <i>Ifosfamide</i>	Efficacy, Covariates	(You et al., 2008)
	Metastatic breast cancer	PK		Limited sampling	(Millward et al., 1995)
	Acute myeloid leukemia	Pop-PK	CL : <i>BaselineWhiteBloodCellCount</i> , CL_{CR} , V : <i>Sex</i>	Covariates	(Krogh-Madsen et al., 2012)
	Primary breast cancer, Cancer (N/S)	PBPK		Pediatrics	(Kersting et al., 2012)
Everolimus	Progressive unresectable recurrent or metastatic thyroid cancer, metastatic breast cancer	Semi-mech. Pop-PK/PD		Efficacy	(van Erp et al., 2016)
	Progressive, unresectable or metastatic thyroid cancer	Pop-PK	$F=1$, $TTThaplotideABCB1$: 0.792	Transporter genotype (ABCB1), Toxicity, Covariates	(de Wit et al., 2016)
	Solid tumors	PBPK-PD		Inter-species extrapolation, Dose	(Tanaka et al., 2008)
	Metastatic head and neck squamous cell cancer	Pop-PK (w. cetuximab & carboplatin)		Investigational	(Saba et al., 2014)
Exatecan mesylate	Metastatic gastric cancer	Pop-PK	CL , V_{cs} , V_p , Q , $CL - BSA$	Covariates	(Ajani et al., 2005)
Farletuzumab	Epithelial ovarian cancer	Pop-PK	$\theta_i = \theta \cdot (COV_i / COV_{reference})^{BCOV}$ $CL[L/h]=0.00784$, BW : 0.715, $V_c[L]=3.00$, BW : 0.629	Covariates	(Farrell et al., 2012)
Foretinib	Cancer (N/S)	Pop-PK	$\theta_i = \theta \cdot (COV_i / COV_{reference})^{BCOV}$ $CL/F[L/h]=79.3$, Age : -0.381, $AspartateAminotransferase$: -0.217, $V_c/F[L]=2150$, BW : 0.661, $F1-capsule$: 1.37, $F1-gablet$: 1.20	Covariates	(Singh et al., 2015)
Ftorafur	Advanced breast cancer	Pop-PK		Metabolite (5-fluorouracil)	(Urien et al., 2003b)
Fulvestrant	Advanced breast cancer	PK		Dose	(Robertson et al., 2004)
	Postmenopausal women with HER-positive advanced breast cancer	Pop-PK		Dose	(McCormack and Sapunar, 2008)

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GDC-0917	N/A	Pop-PK		Inter-species extrapolation	(Wong et al., 2013)
GDC-0980	N/A	PK/PD		Inter-species extrapolation	(Salphati et al., 2012)
Gefitinib	Malignant solid tumors	Pop-PK	CL/F: <i>Midazolam clearance</i> (CYP3A activity)	Toxicity, Metabolic phenotype (CYP3A), Covariates	(Li et al., 2006)
	Healthy volunteers, solid malignant tumors of non-small cell lung cancer, colorectal cancer, head and breast cancer	PBPK		Inter-species extrapolation	(Bi et al., 2016)
Gemcitabine	Ovarian cancer	Pop-PK/PD		Toxicity, Dose	(Leijen et al., 2013)
	Solid malignancies	Pop-PK	$CLdFdu/F[L/min]=0.04 \cdot (1+0.48 \cdot CL_{CR}/70)$, $CvdFdU/F[L]=46 \cdot (BSA/1.73) 0.93 \cdot 0.65^{GemcitabineOxaliplatin} \cdot 0.54^{OxaliplatinGemcitabine} \cdot 1.24^{NonSmallCellLungCancer}$	Metabolite, DDI (oxaliplatin), Covariates	(Jiang et al., 2008)
	Urothelial cancer	PK		Metabolite, Renal impairment/Other special populations (renal replacement therapy)	(Masumori et al., 2008)
	Pancreatic cancer, lung cancer, methothelium cancer	Pop-PK	$CL[L/h]=73.70 \cdot BSA \cdot (1-0.639 \cdot CDA * 3homo) \cdot (1-0.171 \cdot CDA * 3hetero) \cdot (1+0.0749 \cdot NumberOfCDA-31delC) \cdot (1+0.191 \cdot CoAdminOfS-I)$, $CL_{ml}[L/h]=11.00 \cdot BSA \cdot (1-0.00855 \cdot (Age-62.67)) \cdot (1-0.732 \cdot (S_{CR}-0.70))$, $V_{ml}[L]=15.00 \cdot BSA \cdot (1-0.00806 \cdot (Age-62.67)) \cdot (1+0.239 \cdot Male)$	Metabolic genotype (cytidine deaminase, deoxycytidine), Transporter genotype (SLC29A1), Metabolite, Covariates	(Sugiyama et al., 2010)
	Non-small cell lung cancer	Pop-PK/PD (w. carboplatin)		Efficacy, Dose	(Tham et al., 2008)
	Advanced non-small cell lung cancer	Pop-PK	CL: <i>CDA</i> (cytidine deaminase)	Transporter genotype (SLC28A1), Metabolic genotype (GST, CDA, deoxycytidine kinase), Toxicity, Metabolite, Covariates	(Joerger et al., 2012)
Herceptin	Cancer (N/S)	PK/PD		Efficacy, Dose	(Gardner, 2002)
HuCC49-Delta-CH2	Colorectal cancer	Pop-PK	CL, Q: BW: 0.75 (exponent), V_1, V_2 : BW: 1 (exponent)	Covariates	(Fang et al., 2007)
Hydroxyurea	Lymphoma, brain tumors, acute myelocytic leukemia, lung cancer, melanoma, renal-cell carcinoma	Pop-PK		Investigational	(Tracewell et al., 1995)
Hypoxoside	Lung cancer	Pop-PK		Investigational	(Albrecht et al., 1995)

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Ibrutinib	B-cell malignancy	Pop-PK	F1: PrandialState, D1: PrandialState, Antacids, V2/F, V3/F: BW	DDIs, Biopharmaceutics effects, Ethnicity, Covariates	(Marostica et al., 2015)
	Healthy volunteers	PBPK		DDIs (CYP3A4)	(de Zwart et al., 2016)
Idarubicin	Leukemia	PK		Pediatrics, Metabolite	(Reid et al., 1990)
Idasanutlin	Cancer (N/S)	PBPK		DDIs	(Glenn et al., 2016)
Idelalisib	Healthy volunteers, hematologic malignancy	Pop-PK	CL [L/h] – <i>Healthy</i> : 19.69, <i>Patient</i> : 14.88, $CL/F[L/h]=CL/F_i \cdot (BW_i/BW_{reference})^{0.245}$, Q/F [L/h] – <i>Healthy</i> : 7.846, <i>Patient</i> : 11.82, F1 – <i>Dose</i> : -0.262	Covariates	(Lin et al., 2016)
Ifosfamide	Resistant small cell lung cancer	Pop-PK		Metabolite, Investigational	(Kerbusch et al., 2001)
Imatinib	Gastrointestinal stromal tumors	Bayesian pop-PK		Investigational	(Gotta et al., 2012)
	Chronic myeloid leukemia, gastrointestinal stromal tumors	Pop-PK	$V_d: AAG$	Covariates	(Widmer et al., 2006)
	Soft tissue and bone cancer	Pop-PK		Other special populations (smoking)	(van Erp et al., 2008)
	Hepatocellular cancer	PK/PD		Efficacy, Hepatic impairment	(Treiber et al., 2008)
	Solid tumors, gastrointestinal stromal tumors	Pop-PK	$CL[L/h]=7.29 \cdot (BW/54)^{0.56} \cdot (AAG/1.13)^{-0.65} \cdot (Albuminemia/38)^{0.66}$, $V[L]=202 \cdot (BW/54)^{0.79} \cdot (AAG/1.13)^{-1.01}$, $CL_{metabolite/fm}[L/h]=52.2 \cdot (BW/54)^{-0.62} \cdot (AAG/1.13)^{-0.81} \cdot 0.70^{StudyDay}$	Pediatrics, Metabolic genotype (CYP3A4/5), Transporter genotype (ABCB1, ABCG2), AAG genotype, Metabolite, Covariates	(Petain et al., 2008)
	Chronic myeloid leukemia	Pop-PK	$CL/F[L/h]=(13.8-3.81 \cdot Occasion) \cdot (BW/80)^{0.301}$ $\cdot (Hemoglobin/13)^{0.897} \cdot (WhiteBloodCellCount/16)^{-0.105}$, $V/F[L]=(252-7.82 \cdot Occasion) \cdot (BW/80)^{0.405}$ $\cdot (Hemoglobin/13)^{0.676} \cdot (WhiteBloodCellCount/16)^{-0.070}$	Covariates	(Schmidli et al., 2005)
	Advanced gastrointestinal stromal tumors	Pop-PK/PD	$CL[L/h]=7.97 \cdot (AAG/1.15)-0.52$, $CL_{m/fm}[L/h]=58.6 \cdot (AAG/1.15)-0.60-0.55^{Occasion}$	Metabolite, Toxicity, Covariates	(Delbaldo et al., 2006)
	Mixed cancer	Bayesian pop-PK	$CL/F[L/h]=10.8 \cdot (BW/70)^{0.75}$, $V/F[L]=284 \cdot (BW/70)$, $CL_{metabolite}/F[L/h]=9.65 \cdot (BW/70)^{0.75}$, $V_{1,metabolite}/F[L]=11.6 \cdot (BW/70)$, $V_{2,metabolite}/F[L]=256 \cdot (BW/70)$, $Q_{2,metabolite}[L/h]=2.9 \cdot (BW/70)^{0.75}$	Metabolite, Pediatrics, Covariates	(Menon-Andersen et al., 2009)
Indicine N-oxide	Malignant solid tumors	PK		Pediatrics	(Ames et al., 1982)

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Indisulam	Cancer (N/S)	Semi-mech. Pop-PK/PD		Toxicity	(Soto et al., 2011a)
	Cancer (N/S)	Semi-mech. Pop-PK (w. irinotecan, capecitabine, carboplatin)	CL[L/h]=46, <i>Caucasian</i> : 3.36, V_{max} [mg/L/h]=4.19, <i>BSA</i> : 2.29, Q_{IF-TIS} =1190, <i>Caucasian</i> : 2.26, $B_{max-TIS}$ =9.42, <i>Caucasian</i> : 0.70	Covariates	(Zandvliet et al., 2006)
	Mixed cancer	Pop-PK	V_{max} : <i>CYP2C9</i> *3/2, <i>CYP2C19</i> *3	Metabolic genotype (CYP2C9/19), Toxicity, Dose, Covariates	(Zandvliet et al., 2007)
Interferone-Alpha, interferone-Gamma	Healthy volunteers	Pop-PK/PD		Response	(Garcia-Garcia et al., 2016)
Iodine, ^{131}I	Post-surgical thyroid carcinoma	PK		Renal impairment, Dose	(Pahlka and Sonnad, 2006)
Ipilimumab	Advanced melanoma	Pop-PK	$\theta_i = \theta \cdot (\text{COV} / \text{COV}_{\text{reference}})^{\text{BCOV}}$ CL[L/h]=0.015, BW: 0.642, LactateDehydrogenase: 1.13, V[L]=4.15, BW: 0.708	Covariates	(Feng et al., 2014)
Irinotecan	Bile-duct cancer, other cancer	PBPK		Physiology	(Yoshida et al., 2013)
	Malignant solid tumors	Pop-PK/PD	<i>Supports flat dosing (w/o BSA)</i>	Toxicity, Dose	(de Jong et al., 2004)
	Malignant solid tumors	Pop-PK		Investigational	(Xie et al., 2002)
	Cancer (N/S)	PBPK		Toxicity, Metabolic genotype (UGT1A1), Transporter genotype (OATP1B1)	(Toshimoto et al., 2017)
	Gastric cancer	Pop-PK	$CL_4 - AGE$, $V_5 - BSA$, $V_6 - AGE$, $V_7 - CL_{CR}$	Covariates	(Ahn et al., 2010)
	Malignant solid tumors	Bayesian pop-PK		Limited sampling	(Nakashima et al., 1995)
	Metastatic digestive cancer	Bayesian pop-PK		Limited sampling, Metabolite, Covariates	(Poujol et al., 2007)
	Refractory solid tumors	Pop-PK	CL, Q – BW: 0.75 (exponent), V_c, V_p – BW: 1 (exponent), CL_{APC} – BW: 0.75 (exponent), V_{APC} – BW: 1 (exponent), CL_{SN38} – Bilirubin, BW: 0.75 (exponent), Age, $V_{c,SN38}, V_{p,SN38}$ – BW: (exponent), Q_{SN38} – BW: 0.75 (exponent), CL_{SN38G} – BW: 0.75 (exponent), V_{SN38G} – BW: 1 (exponent)	Pediatrics, Metabolite, Covariates	(Thompson et al., 2008)

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	Cancer (N/S)	PBPK		Renal impairment, Metabolite	(Fujita et al., 2016)
	Glioblastoma, recurrent glioma	Pop-PK		DDIs, Metabolite	(Berg et al., 2015)
Irofulven	Malignant cancer	Pop-PK		Covariates	(Urien et al., 2003a)
Irosustat	Breast cancer	Pop-PK		Other special populations (postmenopausal women)	(Parra-Guillen et al., 2015)
Ixazomib	Cancer (N/S)	Pop-PK/PD		Toxicity	(Gupta et al., 2015)
Kahalalide F	Malignant solid tumors	Pop-PK		Covariates	(Miguel-Lillo et al., 2015)
Lapatinib	Healthy volunteers	PBPK		Inter-species extrapolation	(Hudachek and Gustafson, 2013)
	HER2-positive locally advanced or metastatic breast cancer	Pop-PK		Dose, Covariates	(Rezai et al., 2011)
Lenvatinib	Healthy volunteers, thyroid cancer	Pop-PK		Hepatic impairment, Dose	(Gupta et al., 2016b)
Letrozole	Healthy volunteers (postmenopausal women)	Pop-PK	$CL/F[L/h]=1.03 \cdot (2CYP2A6alleles+1CYP2A6allele \cdot 0.843+0CYP2A6alleles \cdot 0.448) \cdot (S_{CR}/0.70) - 1.27 \cdot (AST/17.5)^{-0.793}$, $V/F[L]=94.2 \cdot (BW/51.1)^{1.12}$	Metabolic genotype (CYP2A6), Covariates	(Tanii et al., 2011)
Leuprolide	Prostate cancer	Semi-mech. Pop-PK/PD		Efficacy, Covariates	(Lim and Salem, 2015)
Linifanib	Mixed cancer	Pop-PK	$CL/F[L/h]=2.82$, <i>ColoRectalCancer</i> : 1.41, Sex: 0.75, $V_e/F[L]=50.75$, <i>BW</i> : 0.52, <i>HepatocellularCancer</i> : 1.63, <i>RenalCellCancer</i> : 1.86, $V_p/F[L]=10.36$, <i>BW</i> : 0.52, <i>HepatocellularCancer</i> : 1.63, <i>RenalCellCancer</i> : 1.86, $k_a[L/h]=0.46$, <i>OralSolution</i> : 1.97, $F - TimeOfDose$: 0.73, <i>FoodCondition</i> : 0.86, <i>AcuteMyelogenousLeukemia/MyelodysplasticSyndrome</i> : 0.57	Food effects, Covariates	(Salem et al., 2014)
	Hepatocellular cancer	Pop-PK	$CL/F [L/h] - Males$: 3.65, <i>Females</i> : 2.81, $V/F[L] - Males$: 96.8, <i>Females</i> : 71.5	Dose, Covariates	(Chiu et al., 2013)
Lym-1, ¹²³ I	B-cell lymphoma	Semi-mech. PK		Investigational	(Koizumi et al., 1986)
Matizumab	Advanced cancer	Pop-PK	$\theta_i = \theta \cdot (1 + \beta COV_i \cdot (COV_i - COV_{median}))$ $CL_t[mL/h]=15.3$, <i>FatFreeMass</i> : 0.0138, $V_i[L]=3.79$, <i>FatFreeMass</i> : 0.0077	Dose, Covariates	(Kuester et al., 2009)
	Advanced cancer	Pop-PK	$\theta_i = \theta \cdot (1 + \beta COV_i \cdot (COV_i - COV_{median}))$ $CL_t[mL/h]=14.6$, <i>BW</i> : 0.0087, $V_i[L]=3.73$, <i>BW</i> : 0.0044	Covariates	(Kuester et al., 2008)
Melphalan	Advanced malignancy	Bayesian pop-PK	$CL[L/h]=1.37 \cdot CL_{CR} - 18.9 \cdot (Sex-1) + 7.01$	Covariates	(Mougenot et al., 2004)

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	Advanced prostate cancer	Pop-PK/PD	$\theta_i = \theta \cdot (\text{COV}_i / \text{COV}_{\text{reference}})^{\beta_{\text{COV}}}$ $\text{CL}[\text{L/h/70kg}] = 10.9$, BW : 0.0831, S_{CR} : 0.0831, $\text{Q}[\text{L/h/70kg}] = 0.110$, BW : 0.693	Toxicity, Covariates	(Smith et al., 1993)
	Mixed cancer	Bayesian pop-PK	$\text{CL}[\text{L/h}] = 0 + 0.34 \cdot BW - 3.17 \cdot \text{PriorCarboplatinTherapy} + 0.0377 \cdot \text{GFR}$, $\text{V}[\text{L}] = 1.12 + 0.178 \cdot BW$	Pediatrics, Dose, Covariates	(Nath et al., 2007)
		Bayesian pop-PK	$\text{CL}_{\text{Non-renal}}[\text{L/h}] = 79.7 \cdot (\text{Hematocrit}/34)^{0.679} \cdot (\text{FatFreeMass}/50)^{0.75}$ $\text{CL}_{\text{Renal}}[\text{L/h}] = 50.7 \cdot (\text{CL}_{\text{CR}}/88)$, $\text{V}[\text{L}] = 63.8 \cdot (\text{FatFreeMass}/50)$	Efficacy, Toxicity, Covariates	(Nath et al., 2010)
	Bone marrow transplant	PK	$\text{CL}[\text{L/h}] = 4.77 + 0.37 \cdot BW - 3.99 \cdot \text{PriorCarboplatinTreatment} - 2.84 \cdot \text{GFR} + 2.10 \cdot \text{PriorTotalBodyIrradiation}$	Pediatrics, Dose, Covariates	(Nath et al., 2005)
Menogaril	Metastatic tumors	PK		Investigational	(Piergies and Benson, 1995)
Methotrexate	Osteosarcoma	Pop-PK/PD	$\theta_i = \theta \cdot (\text{COV}_i / \text{COV}_{\text{reference}})^{\beta_{\text{COV}}}$ $\text{CL}[\text{L/h}] = 15.7$, Hematocrit : 0.85, $\text{Vc}[\text{L}] = 79.2$, BW : 1.29	Toxicity, Covariates	(Johansson et al., 2011)
	Hematologic malignancy	Pop-PK		Investigational	(Nader et al., 2017)
	Cancer (N/S)	PK/PD		Efficacy, Dose	(Gardner, 2002)
	Breast cancer	Bayesian pop-PK		Dose	(Monjanel-Mouterde et al., 2002)
	Cancer (N/S)	Bayesian pop-PK		Dose, Pediatrics	(Barrett et al., 2008)
	Osteosarcoma	Pop-PK	$\text{CL} - \text{CL}_{\text{CR}} > 89 \mu\text{mol/L}$, $\text{AlanineAminotransferase}$, $\text{V} - \text{Height}$, BSA , Hemoglobin	Limited sampling, Covariates	(Dupuis et al., 2008)
	Cancer (N/S)	Pop-PK		Covariates	(Nagulu et al., 2010)
	Cancer (N/S)	Pop-PK	$\text{CL}_{\text{MTX}}[\text{mL/min}] = 8.84 + 0.0423 \cdot (87 - \text{CL}_{\text{CR}}) - 2.45 \cdot \text{Benzimidazoles} - 1.46 \cdot \text{NSAID}$, $\text{CL}_{7\text{-OH-MTX}}[\text{mL/min}] = 2 + 0.0423 \cdot (87 - \text{CL}_{\text{CR}}) - 2.45 \cdot \text{Benzimidazoles} - 0.369 \cdot \text{NSAID}$	Metabolite, Covariates	(Joergers et al., 2006a)
	Mixed cancer	Bayesian pop-PK		Evaluation/validation, Dose , Pediatrics	(Dombrowsky et al., 2011)
	Osteosarcoma	Bayesian pop-PK		Dose, Toxicity	(Pignon et al., 1994)
	Solid tumors	Bayesian pop-PK		Dose, Evaluation/validation	(Pignon et al., 1995)
Mitomycin C	Liver cancer	PK		Investigational	(Rump et al., 1996)
Mitoxantrone	Metastatic breast cancer, inflammatory breast cancer	PK		Investigational	(Richard et al., 1992)
MNRP1685A	Advanced solid tumor	Pop-PK/PD		Efficacy	(Xin et al., 2012)
Motesanib	Thyroid cancer	Pop-PK/PD		Efficacy, Dose	(Claret et al., 2010)
	Thyroid cancer	Pop-PK/PD		Efficacy, Dose	(Lu et al., 2010)

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	Cancer (N/S)	Pop-PK		Metabolite, Investigational	(2010) (Gosselin et al., 2015)
Nab-paclitaxel	Cancer (N/S)	Pop-PK		Investigational	(Chen et al., 2015)
	Cancer (N/S)	Pop-PK/PD	VM _{EL} [μg/L]=40.2, <i>Albumin</i> : 0.341	Toxicity, Hepatic impairment, Covariates	(Chen et al., 2014)
Navitoclax	Cancer (N/S)	Semi-mech. Pop-PK/PD		Toxicity	(Kaefer et al., 2014)
Nimotuzumab	Advanced breast cancer	Semi-mech. Pop-PK		Covariates	(Rodriguez-Vera et al., 2015)
Nivolumab	Solid tumors	Pop-PK	CL: <i>BW</i> , <i>eGFR</i> , <i>BaselinePerformanceStatus</i> , <i>Sex</i> , <i>Asian</i> , V _c : <i>BW</i> , <i>Sex</i>	Covariates	(Bajaj et al., 2017)
O(6)-benzylguanine	Central nervous system tumors	PK		Pediatrics	(Neville et al., 2004)
Onartuzumab	Advanced solid tumors	Pop-PK		DDIs (erlotinib), Dose, Covariates	(Xin et al., 2013)
Orteronel	Healthy volunteers	PBPK		Renal impairment, DDIs	(Lu et al., 2014a)
Osimertinib	Non-small cell lung cancer	Pop-PK		Dose	(Brown et al., 2017)
Oxaliplatin	Peritoneal cancer	Pop-PK	V _{IP} [L]=3.73·(<i>BSA</i> /1.69) ^{1.24} , k _{EL-B} [h ⁻¹]=4.58·(<i>TotalProtein</i> /42) ^{-0.75}	Surgery, Covariates	(Chalret du Rieu et al., 2014b)
	Metastatic cancer	Pop-PK	CL[L/h]=14.1·(<i>BW</i> /71) ^{1.10} ·(<i>SCR</i> /87) ^{-0.57} ·(0.60 if <i>Female</i>), V ₁ [L]=24.9·(<i>BW</i> /71) ^{1.29} , Q[L/h]=34.8·(<i>BW</i> /71) ^{1.01}	Covariates	(Bastian et al., 2003)
	Cancer (N/S)	Pop-PK	CL[L/h]=0.67· <i>BW</i> ^{0.75} ·(0.6/ <i>SCR</i>) ^{0.67} , Q ₂ [L/h]=2.94· <i>BW</i> ^{0.75} +Q ₃ , Q ₃ [L/h]=0.22· <i>BW</i> ^{0.75} , V ₁ [L]=0.39· <i>BW</i> ·(<i>Age</i> /21) ^{0.16} , V ₂ [L]=6.23· <i>BW</i> , V ₃ [L]=17.1· <i>BW</i>	Pediatrics, Renal impairment, Hepatic impairment, Covariates	(Nikanjam et al., 2015)
	Advanced colorectal cancer	Pop-PK	CL[L/h]= 0.28· <i>BSA</i> ·(1-0.058· <i>Hematocrit</i>)	Covariates	(Delord et al., 2003)
	Peritoneal carcinomatosis	Semi-mech. Pop-PK/PD		Toxicity, Covariates	(Valenzuela et al., 2011)
	Advanced colorectal cancer	Pop-PK (w. 5-fluorouracil)		Investigational, Covariates	(Kho et al., 2006)
	Cancer (N/S)	Pop-PK/PD		Efficacy, Formulation, Dose	(Lim et al., 2015a)
Paclitaxel	Cancer (N/S)	Pop-PK	CL[L/h]=4.71, <i>GestationalEffects</i> : 1.92, V _c [L]=12.8, <i>GestationalEffects</i> : 4.21, V _{p1} [L]=17.1, <i>GestationalEffects</i> : 3.16,	Other special populations (pregnancy), Covariates	(van Hasselt et al., 2014)

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			Vp2[L]=2640, <i>GestationalEffects</i> : 2.57		
Ovarian cancer, small-cell lung cancer, solid tumors	Semi-mech. Pop-PK/PD			Dose, Toxicity	(Joerger, 2012)
Ovarian cancer	Pop-PK	CL[L/h] – <i>CYP2C8-PerformanceStatus0-1</i> : 396, CL[L/h] – <i>CYP2C8-PerformanceStatus2</i> : 304, CL – <i>BSA</i> : 0.62, <i>Age</i> : -0.006, $V_1[L]=296, BSA: 1.11,$ $V_2[L]=793, BSA: 0.48$ Using Henningsson model: $CL[L/h]=396 \cdot (1+0.62 \cdot (BSA-1.71)) \cdot (1-0.012 \cdot (Bilirubin-5)) \cdot (1-0.006 \cdot (Age-60.7))$		Metabolic genotype (CYP2C8), Covariates	(Bergmann et al., 2011)
Solid tumors	Pop-PK/PD		<i>Suggests dose adaptation for hepatic impairment</i>	Hepatic impairment, Toxicity, Covariates	(Joerger et al., 2007a)
Solid tumors	Pop-PK	$VM_{EL}[\mu\text{mol/h}]=37.4 \cdot 1.2^{Sex} \cdot (BSA/1.8)^{0.842},$ $VM_{TR}[\mu\text{mol/h}]=169 \cdot 1.2^{Sex} \cdot (BSA/1.8) \cdot 0.911,$ $KM_{TR}[\mu\text{mol/L}]=0.826 \cdot 2.11^{Sex},$ $V_3[L]=252 \cdot (BSA/1.8) \cdot 1.17,$ $k_{12}[h^{-1}]=1.15 \cdot 0.893^{Sex},$ $Q[L/h]=20.1 \cdot (BSA/1.8)^{0.724}$		Covariates	(Joerger et al., 2006b)
Cancer (N/S)	Pop-PK			Metabolic genotype (CYP2C8, CYP3A4/5), Transporter genotype (ABCB1), Covariates	(Henningsson et al., 2005)
Solid tumors	Pop-PK	$CL[L/h]=343 \cdot (1+0.65 \cdot (BSA-1.76)) \cdot (1-0.012 \cdot (Bilirubin-6)),$ $V_1[L]=418 \cdot (1+1.45 \cdot (BSA-1.76)),$ $V_2[L]=1010 \cdot (1+0.868 \cdot (BSA-1.76)),$ $B_{max}=0.212 \cdot (1+1.09 \cdot (AAG-1.35))$		Evaluation/validation, Covariates	(Henningsson et al., 2003)
Malignant solid tumors	Pop-PK			Formulation	(van Zuylen et al., 2001)
Metastatic breast cancer, metastatic ovarian cancer	Pop-PK			Investigational	(Karlsson et al., 1999)
Cancer (N/S)	Pop-PK/PD			Toxicity	(Karlsson et al., 1998)
Metastatic cancer	PK			Investigational	(Mross et al., 2000)
Ovarian cancer	PK			Investigational	(Ye et al., 2000)
Mixed cancer	Semi-mech. Pop-PK/PD			Toxicity, Covariates	(Kloft et al., 2006)
Advanced non-hematologic malignancy	Pop-PK			Formulation	(Bulitta et al., 2009)
Metastatic cancer	Pop-PK/PD			Toxicity	(Fetterly et al., 2008a)
Ovarian cancer	Pop-PK/PD (w.			Toxicity	(Joerger et al., 2007b)

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		carboplatin)			
	Mixed cancer	Semi-mech. Pop-PK/PD		Toxicity	(Henningsson et al., 2001)
	Relapsed or refractory ovarian cancer, relapsed or refractory breast cancer	Pop-PK/PD		Toxicity, Efficacy	(Gianni et al., 1995)
Palbociclib	Advanced solid tumors, non-Hodgkin lymphoma, mantle cell lymphoma, metastatic breast cancer	Pop-PK/PD		Toxicity, Dose, Covariates	(Sun et al., 2017)
Panitumumab	Advanced solid tumors	Pop-PK	$CL[L/day]=0.273 \cdot (BW/80)^{0.411} \cdot 0.769^{Female} \cdot 0.861^{NonSmallCellLungCancer} \cdot 0.957^{RenalCancer} \cdot 0.870^{OtherCancer}$, $V_i[L]=3.95 \cdot (BW/80)^{0.526} \cdot 0.831^{Female}$, $V_{max}[mg/day]=12.1 \cdot (BW/80)^{0.621} \cdot (Age/60)^{-0.495}$	Covariates	(Ma et al., 2009)
Patritumab	Non-small cell lung cancer	Pop-PK		Hepatic impairment, Renal impairment	(Yoshida et al., 2016)
Patupilone	N/A	PBPK		Inter-species extrapolation	(Xia et al., 2012)
Pazopanib	Cancer (N/S)	Bayesian pop-PK/PD		Toxicity	(Suttle et al., 2013)
	Cancer (N/S)			Investigational	(Yu et al., 2017a)
Pembrolizumab	Advanced solid tumors	Pop-PK	$CL[L/day]=0.202 \cdot (BW/76.8)^{0.578} \cdot (Albumin/39.6)^{0.854} \cdot BaselineTumorBurden/89.6^{0.0926} \cdot (eGFR/88.47)^{0.139} \cdot ((1-0.152) \text{ if Female}) \cdot (1+0.145) \text{ if Non-small cell lung cancer}) \cdot ((1+0.0739) \text{ if Eastern Cooperative Oncology Group}) \cdot ((1+0.140) \text{ if prior pilimumab})$, $V[L]=3.48 \cdot (BW/76.8)^{0.492} \cdot (Albumin/39.6)^{-0.178} \cdot ((1-0.134) \text{ if Female}) \cdot (1+0.0736) \text{ if prior pilimumab})$	Dose, Covariates	(Ahamadi et al., 2017)
	Mixed cancer	Semi-mech. Pop-PK/PD		Toxicity, Covariates	(Latz et al., 2006b)
	Mixed cancer	Pop-PK	$CL[mL/min]=43.0+47.2 \cdot CL_{CR}/92.6$, $V_i[L]=6.13 \cdot BSA^{1.32}$	Covariates	(Latz et al., 2006a)
Pemetrexed	Metastatic colorectal cancer, pancreatic cancer, recurrent/metastatic breast cancer, esophageal cancer	Pop-PK	$CL[L/h]=(2.82+0.0292 \cdot CL_{CR}+0.0475 \cdot (BW-70)+0.0041 \cdot (ALT-30.5)) \cdot (1-0.344 \cdot FOL)$, $V_c[L]=(11.3+0.105 \cdot (BW-70)) \cdot (1-0.325 \cdot Sex)$, $V_p[L]=9.78+4.28 \cdot (BSA-1.8)-1.25 \cdot (Albumin-3.67)$	Covariates	(Ouellet et al., 2000)
	Cancer (N/S)	PBPK		DDIs	(Posada et al., 2015)
Pertuzumab	Advanced solid malignancies, advanced ovarian cancer, metastatic breast cancer	Pop-PK	$CL[L/day]=0.214 \cdot (BW/69)^{0.587} \cdot (Albumin/39.2)^{-1.01} \cdot (ALKP/107)^{0.169}$, $V_c[L]=2.74 \cdot (BSA/1.72)^{1.160}$	Covariates	(Ng et al., 2006)
	Neoadjuvant early breast	Pop-PK		DDIs	(Quartino et

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	cancer				al., 2017
Phenylacetate	Refractory cancer	PK		Pediatrics	(Thompson et al., 2003)
PI-88	Solid tumors	Pop-PK	$CL[mL/h]=3440+(1800 \cdot (BSA-1.9))-(867 \cdot \text{Cancer})$, $V[mL]=16900+(14400 \cdot (BSA-1.9))$, $k_a[h^{-1}]=1.07-(0.0401 \cdot (BMI-25.7))$	Covariates	(Hudachek et al., 2010)
Plitidepsin	Advanced solid tumors, advanced renal and colorectal tumors, advanced medullary thyroid carcinoma, advanced metastatic melanoma	Pop-PK		Covariates	(Nalda-Molina et al., 2009)
PM00104	Malignant tumors	Pop-PK/PD		Toxicity, Covariates	(Gonzalez-Sales et al., 2012)
Polyestradiol phosphate	Prostate cancer	PK		Dose	(Henriksson et al., 1999)
Porfimer Sodium, 2-[1-Hexyloxyethyl]-2-devinyl pyropheophorbide-a (Photochlor), 5-ALA-induced protoporphyrin IX	Cancer (N/S)	PK		Investigational	(Bellnier et al., 2006)
Pozitotinib	Advanced solid tumors	Pop-PK	$k_a[h^{-1}]=0.921$, $k_{a,Food}=0.359$, $V_d/F[L]=147 \cdot (BW/70)^{1.23}$	Food effects, Covariates	(Noh et al., 2015)
PRO95780	Cancer (N/S)	PK/PD		Inter-species extrapolation	(Xiang et al., 2013)
Pyrazine diazohydroxide	Solid tumor, lymphoma	PK		Investigational	(Vogelzang et al., 1994)
Raltitrexed	Advanced solid tumors	Pop-PK	$CL[L/h]=0.54+0.02 \cdot CL_{CR}$, $V[L]=6.64+0.08 \cdot BW-0.16 \cdot Albumin$	Covariates	(Blair et al., 2004)
	Recurrent or refractory leukemia	PK		Pediatrics	(Horton et al., 2005)
RG7160	Advanced EGFR-positive solid tumors	Pop-PK		Dose	(Paz-Ares et al., 2011)
Rilotumumab	Mixed cancer	Pop-PK	$CL[L/day/70kg/60years]=0.184$, $BW: 0.625$ (power), $Age: 0.268$ (power), $V_c[L/70kg/60years]=3.56$, $BW: 0.611$ (power), $Age: 0.229$ (power)	Covariates	(Zhu et al., 2014)
Rituximab	Diffuse large B-cell lymphoma	Pop-PK		Covariates	(Tout et al., 2017)
RO5323441	Advanced solid tumors, metastatic treatment refractory colorectal or ovarian cancer, metastatic	Pop-PK		DDIs	(Wang et al., 2017)

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	and/or unresectable hepatocellular carcinoma				
Selumetinib	Advanced solid tumors, low-grade gliomas	Pop-PK	F: <i>FedState</i> : 0.117 (linear coefficient), D1[nmol/h]=0.622, <i>FedState</i> : 4.09 (linear coefficient for duration of zero order input), $t_{lag}[h]=0.319$, <i>FedState</i> : 0.348 (linear coefficient), CL/F[L/h]=13.5, <i>BSA</i> : 0.923 (power), <i>ALT</i> : 0.187 (power), $V_2/F[L]=32.6$, <i>BSA</i> : 1.24 (power), <i>Age</i> : 0.327 (power)	Pediatrics, Dose, Covariates	(Patel et al., 2017)
Sepantropium bromide	Advanced solid tumors, low-grade glioma	Pop-PK	$CL[L/h]=42.1 \cdot (CL_{CR}/79.22)^{0.425} \cdot (ALT/19)^{0.124} \cdot 0.995^{HormoneRefractoryProstateCancer} \cdot 1.24^{UnresectableMelanoma}$	Covariates	(Aoyama et al., 2013)
Sibrotuzumab	Advanced metastatic cancer	Pop-PK	$\theta_i = \theta \cdot (1 + \beta COV_i \cdot (COV_i - COV_{median}))$ $CL_t[mL/h]=22.1$, <i>BW</i> : 0.0182, $V_1[L]=4.13$, <i>BW</i> : 0.0125, $V_2[L]=3.19$, <i>BW</i> : 0.0105, $V_{max}[mL/h]=0.0338$, <i>BW</i> : 0.00934	Covariates	(Kloft et al., 2004)
Sirolimus	Healthy volunteers	PBPK		Hepatic impairment, DDIs	(Emoto et al., 2013)
	Advanced cancer	Pop-PK	$CL1/F[L/h]=12.9 \cdot (Hematocrit_{Median}/Hematocrit_i)^{0.14}$	Covariates	(Wu et al., 2012b)
Sonidegib	Healthy volunteers	PBPK		DDIs	(Einolf et al., 2017)
Sulindac	Healthy volunteers	Pop-PK	$k_{a-Tablet}[h-1]=0.67$, $k_{a-Capsule}[h-1]=1.09$, $N_{Tablet}=9.11$, $N_{Capsule}=15.5$, $MTT_{Tablet}[h]=0.845$, $MTT_{Capsule}[h]=0.427$, $BIO_{Capsule}=1.12$	Formulation, Covariates	(Berg et al., 2013)
Sunitinib	Advanced gastrointestinal stromal tumor, advanced renal cell carcinoma	Pop-PK/PD		Efficacy, Toxicity, Covariates	(Houk et al., 2010)
	Cancer (N/S)	Semi-mech. Pop-PK		Metabolite, Dose	(Yu et al., 2015)
	Acute myeloid leukemia	Pop-PK (sunitinib malate)	Continuous: $\theta_i = \theta \cdot (COV_i / COV_{reference})^{\beta_{COV}}$ Categorical: $\theta_i = \theta \cdot (1 + \beta_{COV} \cdot COV_i)$ $CL/F[L/h]=51.8$, <i>Sex</i> : -0.0876, <i>Asian</i> : -0.130, <i>GIST</i> : -0.285, <i>SolidTumor</i> : -0.269, <i>mRCC</i> : -0.258, $V/F[L]=2030$, <i>BW</i> : 0.459	Covariates	(Houk et al., 2009)
	Healthy volunteers, Cancer (N/S)	Pop-PK/PD		Response, Covariates	(Lindauer et al., 2010a)
Suramin	Malignant cancer	Bayesian pop-PK		Dose, Evaluation/validation	(van Rijswijk et al., 1992)
	Prostate cancer	Bayesian pop-PK		Dose, Evaluation/validation	(Jodrell et al., 1994)
Tamoxifen	Cancer (N/S)	PK/PD		Efficacy, Dose	(Gardner, 2002)
	Breast cancer	Pop-PK	$\theta_{2D6,1}: 0.262$, $\theta_{3A4,1}: 0.157$	Metabolic phenotype (CYP3A,	(ter Heine et al., 2014)

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				CYP2D6), Metabolite, Covariates	
	Healthy volunteers	PBPK		Metabolite, Metabolic genotype (CYP2D6), Adherence	(Dickschen et al., 2017)
	Breast cancer	PBPK		Metabolic phenotype (CYP2D6)	(Dickschen et al., 2012)
Tegafur	Gastric cancer	Pop-PK		Surgery	(Lim et al., 2015b)
	Mixed cancer	Bayesian pop-PK (tegafur-potassium oxonate-gimeracil)	$V_{FT}[L]=16.0 \cdot BSA$, $V_{5-FU}[L]=11.5 \cdot BSA$, $k_{i-Women}[\mu g/mL]=0.037$, $k_{i-Men}[\mu g/mL]=0.042$	Ethnicity, Covariates	(Comets et al., 2003)
	Metastatic or recurrent solid malignancy	Pop-PK (tegafur-5-fluorouracil)	CDHP: $CL/F[L/h]=(5.86+0.025 \cdot S_{CR}) \cdot BSA$, $V/F[L]=42.7 \cdot BSA$, FT: $k_a[h^{-1}]=1.39$, $k_{a-GastricResection}[h^{-1}]=1.62 \cdot 1.39$, $CL/F_{CYP2A6-No/oneVariantAllele}[L/h]=2.02 \cdot BSA$, $CL/F_{CYP2A6-TwoVariantAlleles}[L/h]=0.58 \cdot 2.02 \cdot BSA$	Metabolic genotype (CYP2A6), Toxicity, Surgery, Covariates	(Hirose et al., 2010)
Temozolomide	Advanced cancer	Pop-PK	CL: <i>Sex, BSA, CancerType</i>	Toxicity, Covariates	(Jen et al., 2000)
	Primary central nervous system tumors	Pop-PK	CL/F, V/F: <i>BSA, Age</i>	Pediatrics, Metabolite, Covariates	(Panetta et al., 2003)
Temsirrolimus	Advanced renal cancer	Bayesian pop-PK	CL[L/h]=1.39, <i>BSA: 1.28, Dose: 0.551</i>	Metabolite (sirolimus), Toxicity, Efficacy, Covariates	(Boni et al., 2005)
	Recurrent solid tumors	Pop-PK	CL[L/h/70kg]: 3.71, <i>Dose: 0.878</i>	Pediatrics, Metabolite, Covariates	(Mizuno et al., 2014)
Teniposide	Acute leukemia	PK		Pediatrics	(Evans et al., 1982b)
Thioguanine	Mixed cancer	PK		Pediatrics	(Kitchen et al., 1997)
Topotecan	Recurrent solid tumors, recurrent acute leukemia, medulloblastoma, high-risk neuroblastoma, recurrent Wilms tumor	Pop-PK	$CL[L/h/m^2]=15.9+0.184 \cdot GFR+13.5 \cdot MissingGFR+13.5 \cdot TrialNo4+6.49 \cdot InvestigationFormulation-7.3 \cdot Age+9.9 \cdot Phenytoin$, $V[L/m^2]=32.7+6.0 \cdot TrialNo1+15.3 \cdot TrialNo4$	Pediatrics, Covariates	(Schaiquevich et al., 2007)
	Metastatic epithelial ovarian cancer	Bayesian pop-PK	$CL[L/h]=5.47 \cdot CL_{CR}$, $Vc[L]=0.584 \cdot BW$	Limited sampling, Covariates	(Montazeri et al., 2000)
	Refractory solid tumors	Pop-PK/PD		Toxicity, Pediatrics	(Zamboni et al., 2001)
	Solid tumors	Pop-PK	$CL[L/h]=(5.77+12.8 \cdot CL_{CR}/70) \cdot (BW/70)^{0.75} \cdot \exp(-0.120 \cdot (ECOGperformanceStatus-1))$, $V1[L]=19.3 \cdot (BW/70)^{0.75}$,	Toxicity, Covariates	(Mould et al., 2002)

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			$V_2[L]=45.7 \cdot (BW/70)$		
	Myelodysplastic syndromes	Pop-PK/PD	$V_c/F[L]=395, Age$	Dose, Covariates	(Klein et al., 2006)
	Mixed cancer	Semi-mech. Pop-PK/PD		Toxicity, Covariates	(Kloft et al., 2006)
	Metastatic epithelial ovarian cancer	Bayesian pop-PK		Limited sampling	(Boucaud et al., 2003)
	Metastatic epithelial ovarian cancer	PK		Evaluation/validation, Dose	(Montazeri et al., 2002)
Trabectedin	Malignant tumors	Semi-mech. Pop-PK/PD		Toxicity	(Hing et al., 2008)
	Advanced solid tumors, breast cancer, melanoma, soft tissue sarcoma, renal cancer, colorectal cancer, ovarian cancer	Bayesian pop-PK (w. dexamethasone)	$CL[L/h]=31.5$, <i>Dexamethasone</i> : 6.05 (additive), <i>MissingDexamethasone</i> : 4.60 (additive), $V_1[L]=13.9$, <i>Males</i> : 2.22 (additive)	Covariates	(Perez-Ruixo et al., 2007)
	Advanced solid tumors, breast cancer, melanoma, soft tissue sarcoma, renal cancer, colorectal cancer, ovarian cancer	Semi-mech. Pop-PK/PD		Dose, Toxicity, Covariates	(Fetterly et al., 2008b)
Trastuzumab	HER2-positive early breast cancer	Pop-PK	$CL[L/day]=0.111 \cdot (BW/68)^{1.04} \cdot (AlanineTransaminase/19)^{0.144}$, $V_c[L]=2.91 \cdot (BW/68)^{0.443}$, $V_p[L]=3.06 \cdot (BW/68)^{0.500}$	Covariates	(Quartino et al., 2016)
	HER2-positive inoperable cancer	Pop-PK		DDIs	(Eppler et al., 2015)
	HER2-positive breast cancer	Pop-PK/PD		Toxicity, Covariates	(van Hasselt et al., 2011)
	HER2-positive metastatic breast cancer	Pop-PK	$CL[L/day]=0.225 \cdot (\min(EDC,200)/8.23) \cdot 0.041$, $CL \cdot (1+(0.221 \cdot MET))$, $V_1[L]=2.95 \cdot (BW/65) \cdot 0.556 \cdot (\min(EDC,200)/8.23) \cdot 0.105$	Dose, Covariates	(Bruno et al., 2005)
Trastuzumab emtansine	HER2-positive metastatic breast cancer	Semi-mech. Pop-PK/PD		Toxicity, Dose, Covariates	(Bender et al., 2012)
	HER2-positive breast cancer	Pop-PK	$CL[L/day]=\exp(0.676+0.49 \cdot (BW/70)+0.035 \cdot \log(BaselineEpidermalGrowthFactor/25)-0.423 \cdot \log(Albumin/41)+0.052 \cdot \log(BaselineSumLongestLesions/9)-0.002 \cdot BaselineTrastuzumab+0.071 \cdot (AspartateAminotransferase/25))$, $V_c[L]=\exp(3.127+0.596 \cdot \log(BW/70))$	Renal impairment, Ethnicity, Covariates	(Lu et al., 2014b)
	HER2-positive metastatic breast cancer	Semi-mech. Pop-PK		Covariates	(Chudasama et al., 2012)
	HER2-positive locally	Pop-PK		Ethnicity	(Li et al., 2016)

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	advanced/metastatic breast cancer				
	HER2-positive breast cancer	Pop-PK/PD		Efficacy, Dose	(Singh and Shah, 2017)
	HER2-positive metastatic breast cancer	Pop-PK		Limited sampling	(Lu et al., 2013)
Triptorelin	Healthy volunteers, Prostate cancer	Pop-PK/PD		Efficacy	(Tornøe et al., 2007)
	Healthy volunteers, Prostate cancer	Semi-mech. Pop-PK/PD		Efficacy, Formulation	(Romero et al., 2012)
Troxacitabine	Advanced solid tumors, Advanced leukemia	Pop-PK	Model based on mg/h dosing: $CL - CL_{CR}, BSA,$ $V_1 - BSA,$ $V_2 - BSA,$ $Q_3 - BSA,$ Model based on mg/h/BSA[m ²] dosing: $CL - CL_{CR}$	Covariates	(Lee et al., 2006)
	Solid tumors	Semi-mech. Pop-PK/PD		Toxicity	(Ng et al., 2011)
Veliparib	BRCA 1/2-mutated cancer, PARP-sensitive tumors	Pop-PK/PD	$CL_R/F[L/h]=17.3 \cdot 0.7 \cdot (CL_{CR}/95)^{0.903},$ $V_d/F[L]=99.2 \cdot (LeanBodyMass/48)^{1.21}$	Efficacy, Metabolite, Covariates	(Niu et al., 2017)
Venetoclax	Chronic lymphocytic leukemia and non-Hodgkin's lymphoma	Pop-PK	$CL/F[L/day]=413,$ <i>ModerateCYP3Ainhibitor</i> : 0.807, <i>StrongCYP3Ainhibitor</i> : 0.158, <i>Rituximab</i> : 1.21, $V_d/F[L]=113,$ <i>Female</i> : 0.683, <i>CLL/SLL/NHL</i> : 1.79, $F1=1.0$ (fixed), <i>Fasting</i> : 0.334, <i>Fed</i> : 1.24, <i>ModerateFat</i> : 1.26, <i>HighFat</i> : 1.42	Food effects, DDIs, Dose, Covariates	(Jones et al., 2016)
Vincristine	Cancer (N/S)	Pop-PK	$CL - BW,$ $V - BW$	Pediatrics, Metabolic phenotype (CYP3A), Limited sampling, Toxicity, Covariates	(Moore et al., 2011)
	Acute lymphoblastic leukemia	PK		Pediatrics	(de Graaf et al., 1995)
	Acute lymphoblastic leukemia, non-Hodgkin lymphoma, Wilms' tumor	Bayesian pop-PK		Pediatrics, Limited sampling	(Gidding et al., 1999)
	Lympholytic leukemia, histocytic lymphoma, multiple myeloma, idiopathic thrombocytopenic purpura, lymphoma, Hodgkin's disease	PK		Investigational	(Sethi et al., 1981)

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	Solid tumors	Bayesian pop-PK		Metabolic genotype (CYP3A4/5), Transporter genotype (ABCB1), Pediatrics, Covariates	(Guilhaumou et al., 2011)
Vinorelbine	Breast, prostate, lung, bladder, other cancer	Pop-PK		Toxicity, Dose, Covariates	(Wong et al., 2006)
	Metastatic breast cancer	Pop-PK	$CL[L/h]=74.2 \cdot (BSA_i/BSA_{median})^{1.25} \cdot (AlkalinePhosphate_i/AlkalinePhosphate_{median})^{-0.25}$	Dose, Covariates	(Deporte-Fety et al., 2004)
	Non-small cell lung cancer	Pop-PK		Other special populations (elderly)	(Puozzo and Gridelli, 2004)
	Advanced metastatic cancer	Bayesian pop-PK		Other special populations (elderly)	(Gauvin et al., 2000)
	Non-small cell lung cancer	Bayesian pop-PK		Dose	(Sabot et al., 1998)
	Advanced metastatic cancer	Bayesian pop-PK	CL – (Elderly)	Limited sampling	(Gauvin et al., 2002)
	HER2-positive locally advanced or metastatic breast cancer	Pop-PK (w. lapatinib)	$CL[L/h]=24.9 \cdot (PlateletCount_i/250000)^{-1.1} \cdot (BW/70)^{0.75}$, V1, V2, V3 – (BW/70), Q2, Q3 – (BW/70) ^{0.75}	Dose, Covariates	(Rezai et al., 2011)
Vinzolidine	Breast cancer, melanoma, Renal cancer	PK		Investigational	(Taylor et al., 1990)
Footnotes: AAG: α_1 -acid glycoprotein; BMI: body mass index; BSA: body surface area; BW: bodyweight; CL _{CR} : creatinine clearance; CNS: central nervous system; DDIs: drug-drug interactions; eGFR: estimated glomerular filtration rate; GFR: glomerular filtration rate; IBW: ideal bodyweight; N/A: not applicable; N/S: not stated; PBPk: physiologically-based pharmacokinetics; PD: pharmacodynamic; PK: pharmacokinetic; pop: population; S _{CR} : serum creatinine; w.: with.					

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