Pharmacokinetics and population pharmacokinetics in pediatric oncology

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Abstract
Pharmacokinetic research has become increasingly important in pediatric oncology as it can have direct clinical implications and is a crucial component in individualized medicine. Population pharmacokinetics has become a popular method especially in children, due to the potential for sparse sampling, flexible sampling times, computing of heterogeneous data, and identification of variability sources. However, population pharmacokinetic reports can be complex and difficult to interpret. The aim of this article is to provide a basic explanation of population pharmacokinetics, using clinical examples from the field of pediatric oncology, to facilitate the translation of pharmacokinetic research into the daily clinic.

KEYWORDS
cancer pharmacology, chemotherapy, pediatric oncology, pharmacokinetics, pharmacology, prediction modeling in cancer

1 INTRODUCTION

Despite cure rates approximating 80%, cancer is the leading cause of death due to disease in children.1,2 The treatment of pediatric cancer consists predominantly of combinations of chemotherapeutic agents. The level of exposure to these agents is an important determinant for the therapeutic efficacy and the toxicity. Whether a drug is safe and effective depends on the drug exposure in the body. Drug exposure should be within the therapeutic window, which means sufficiently high to produce the intended effect (the minimal effective concentration [MEC]) and below the level resulting in (unacceptable) toxicity or unwanted side effects (the minimum toxic concentration [MTC] or maximum tolerated dose [MTD]). Oncolytic drugs often have a narrow therapeutic window, and combined with a large variability between drug plasma concentrations observed in pediatric oncology patients, this can result in suboptimal therapy or increased toxicity.

Pharmacokinetics (PK) studies the relationship between dose and concentration within the body, whereas pharmacodynamics (PD) studies the effects of the drug. Knowledge of the relationships between dose concentration and concentration effect is fundamental in establishing the right dose and dose adjustments. Unfortunately, pediatric PK and PD data of anticancer drugs are often lacking, and dose regimens have been established empirically. In general, most drugs in pediatric oncology are dosed based on body weight or body surface area (BSA) if no specific pediatric dosing information is available. This is done by extrapolating the adult dose per kg body weight or m² BSA to the pediatric situation. However, this extrapolation is valid only on two conditions; first, the processes of distribution, metabolism, and elimination of the drug are proportional over the weight or BSA range. Second, the relationship between concentration and effect of the drug is similar between adults and children. In many cases, drug dosing for adults and children is correlated and extrapolation is possible.
However, due to developmental changes in children, especially in infants and children below two years of age, these conditions might not be met.\textsuperscript{4,5} The lack of pediatric PK/PD data is because pediatric oncology patients generally form a small population, and it is not ethical to administer therapeutic dosages of chemotherapeutic agents to healthy children. Traditional PK sampling is invasive, requiring multiple blood samples (e.g., \( n \geq 10 \)) at fixed time intervals. Additionally, the amount of blood which can be withdrawn from infants is limited.\textsuperscript{6} Population PK (PopPK)/PD modeling has many advantages; it allows time flexible and limited sampling (e.g., 2-3 samples per patient), quantify variability in concentrations and identify variability sources, as well as extrapolation based on statistical models and simulations with virtual patients to expand population scenarios and further individualize dosing.\textsuperscript{7,8}

In conclusion, knowledge of PK and its variability in the pediatric oncologic population is important in the optimization of (individualized) drug dosing in this population, with the final aim of improving prognosis. However, population PK studies can be complex and difficult to interpret due to their technical nature. The aim of this article is to provide a basic explanation of PK and PopPK, through the use of examples from the field of pediatric oncology, in order to facilitate the implementation of PK research into the daily clinic.

2 | PART I: WHAT IS PHARMACOKINETICS?
PK is the study of the kinetics of pharmacological substances within the body and describes the processes of drug absorption, distribution, metabolism, and excretion. It focuses predominantly on the relation between the administered dose and the concentration-time profile of the drug in a body compartment (e.g., plasma). The PD describes the dose-response relationship, for example, tumor response or side effects.\textsuperscript{9,10} PK and PD are often studied together in PK/PD models in order to determine the relationship between dose, concentration, and effect. PK studies are performed in different areas, such as preclinical drug development, phase I, II, and III trials, to provide and establish dosing guidelines for registration.\textsuperscript{11–13} PK analyses may also be performed clinically in individual patients for individualized dosing, i.e., therapeutic drug monitoring (TDM).\textsuperscript{14–16}

Example 1: Clinical relevance of PK: Individualizing the dose and treatment with the use of PK parameters can improve outcome and avoid unnecessary toxicities. Evans et al. showed that individualized-based dosing of high-dose methotrexate in pediatric B-lineage ALL patients, based on their clearance and AUC, resulted in a significantly higher percentage of patients remaining in continuous complete remission compared with conventional fixed dosing based on BSA.\textsuperscript{17} PK modeling can help predict the individual clearance and AUC, and hence improve outcome.

2.1 Linear versus nonlinear PK
The concept of linearity in drug elimination is of great clinical importance (assuming a strong correlation between concentration and effect), as it determines how the drug concentration in the body changes in relation to dose adjustments. A drug is considered to have linear PK if there is a linear relation between the administered dose and the exposure (AUC). Thus, increasing the dose by a factor two results in a factor two increase in exposure. Most drugs follow linear PK within the clinically applied concentration range. A drug is considered to have nonlinear PK when increasing the dose produces a nonproportional increase in exposure (Figure 1). Nonlinearity often occurs when certain PK processes become saturated, e.g., (re)absorption pathways (limiting the uptake and availability of the drug from the gut) or from saturation of metabolic and excretion pathways (limiting elimination and producing accumulation of the drug). Drugs with linear PK are generally preferable in the clinic due to their predictable dose-concentration relation. Nonlinearity is clinically not ideal, as increasing doses might result in disproportional shifts in the concentration. With nonlinear elimination TDM is recommended, especially if the drug has a small therapeutic window.

Example 2: Nonlinearity: Asparaginase concentration should remain above a threshold for complete asparagine depletion; hence, TDM is important to ensure sufficient levels throughout treatment and to detect immune-mediated inactivation.\textsuperscript{18,19} Several forms of asparaginase are available, e.g., native \textit{E. coli}–derived asparaginase, PEGylated asparaginase and Erwinia asparaginase, which have different PK profiles. Native \textit{E. coli} asparaginase and Erwinia asparaginase exhibit linear PK, whereas PEGylated asparaginase has a time-dependent elimination.\textsuperscript{20–23} PEGylated asparaginase is conjugated with polyethylene glycol (PEG), to reduce the clearance, therefore increasing the dose interval from every two or three days to every two weeks. However, PopPK studies by Hempel et al. and Würthwein et al. show that the PEGylation results time-dependent elimination, where clearance increases with time after dose. This can result in lower than expected (subtherapeutic) trough levels and should be accounted for.\textsuperscript{21,24} PK models can help predict these trough levels. Asparaginase concentrations might also affect the clearance of other drugs such as dexamethasone, which could lead to a lower exposure of both asparaginase and dexamethasone. This could result in a worse outcome concerning an increased risk of relapse.\textsuperscript{21,24,25}

3 | ADME
PK can be divided into four main processes: drug absorption, distribution, metabolism, and excretion (ADME). Knowledge of the processes that determine the PK is important, as it can have major clinical implications. This is especially true for chemotherapeutic drugs, which often have a small therapeutic window. The ADME processes can differ between patients, within patients and affected by external factors such as comedication. In children, these differences are even more pronounced. The human body does not develop isometrically but allometrically, meaning different organs and processes develop at different rates in terms of growth and maturation. Therefore, in pediatric PK modeling, allometric scaling is often used to adjust for growth and maturation. Especially in the first two years of life, using a linear approach
or even a corrected approach (like allometric scaling) to describe PK parameters might not suffice. Several changes during the development of a child complicate dosing linearity, and affect how drugs are absorbed, distributed, and eliminated from the body.

3.1 | Absorption

The absorption phase describes the uptake of the drug into the bloodstream, for example, from the gastrointestinal tract. In PK, the rate of absorption is referred to by the first-order rate constant “ka.” Most drugs are not completely absorbed when administered orally. The percentage of absorbed drug available to the body is referred to as the bioavailability (F). The absorption phase can be preceded by a dissolution phase in the gut (e.g., dissolution of a tablet). Different pharmaceutical formulations can result in different absorption profiles. In children, the absorption rate and bioavailability can differ from adults due to anatomical and developmental differences. These factors, predominantly in the first two years of life, include reduced gut transit time, increased intestinal permeability, and altered passive and active drug transporters. A drug can also bind to food or other medication in the stomach, hence inactivating or inhibit absorption of the drug, such as ciprofloxacin and milk or tube-feeding.

Example 3: Absorption: Topotecan is used for pediatric brain tumors. It can be administered both intravenously and orally. However, topotecan shows extensive variability between and within patients, especially in very young children. Roberts et al. studied the PopPK of oral topotecan in infants and young children focusing on the effects of age and drug efflux transporters on absorption. Polymorphism of the efflux transporter ABCG2 showed to have a significant effect on absorption, resulting in an almost twofold difference in maximum concentration. Additionally, Thompson et al. showed how PopPK models are used to include the linear and nonlinear binding in order to improve the prediction of free concentrations that can establish the drug effects.

3.2 | Distribution

After absorption, the drug is distributed throughout the body based on its physicochemical properties. Distribution is expressed as an apparent volume (V). This is a proportional factor defined as the volume into which the drug appears to be distributed with a concentration equal to the plasma concentration, as if the body was “one well-stirred compartment.” For some drugs, plasma concentrations decrease rapidly after administration due to distribution to body tissues. In this case, one compartment does not suffice to describe the concentration-time profile of distribution and multiple compartments may be required to adequately describe the profile. On a more advanced level, the intracellular distribution can be taken into account. Distribution in children is affected by altering body composition, for example, changes in water/fat ratio, muscle ratio, and extracellular water. Plasma protein concentration and binding can differ as well, which is important for highly protein-bound drugs. If 98% of a drug is bound to proteins, a decrease to 96% results in twice the concentration of the available drug.

Example 4: Plasma protein binding: The corticosteroid prednisolone used in acute lymphoblastic leukemia has both linear and nonlinear binding to plasma proteins. The binding to albumin is linear in contrast to the saturable binding to corticosteroid binding globulin (CBG). The concentration of free unbound prednisolone depends on CBG, albumin, and free prednisolone. With higher dosages, relatively higher concentrations of free prednisolone will be present and could potentially increase the risk of negative side effects.Ionita et al. and Petersen et al. showed how PopPK models are used to include the linear and nonlinear binding in order to improve the prediction of free concentrations that can establish the drug effects.

Example 5: Body composition: Like most chemotherapeutics, doxorubicin has severe side effects. Krischke et al. showed in a PopPK model that children <3 years of age had a significantly lower clearance compared with older children even after correction for BSA, resulting in higher exposure in younger children. Additionally, Thompson et al. showed that doxorubicinol, an active metabolite of doxorubicin, was dependent on body composition: children with >30% body fat showed a significantly lower clearance of doxorubicinol, with a mean of 37 L/h/m² compared with 64 L/h/m² for <30% body fat; however, the groups were small. The metabolite doxorubicinol may contribute to the cardiotoxicity after doxorubicin administration.

3.3 | Metabolism

Metabolism describes the processes involving conversion of the drug into metabolites. Most anticancer drugs are excreted from the body after being metabolized into active (pro-drug), less active, or inactive
metabolizes. Metabolization occurs predominantly in the liver and gut through the cytochrome P450 enzyme system. Differences or changes in the enzyme system can result in increased or decreased clearance of the drug, thereby decreasing or increasing the exposure. This can occur due to inherited genetic differences in the metabolic pathway, e.g., polymorphism of CYP450 subfamilies (isoenzymes). Another common cause of altered metabolism is drug-drug interactions, where a drug inhibits or induces the metabolic pathway of other drugs or itself. In adults, metabolism is often the cause of large PK variability. However, developmental changes in children superimposes on this variability, due to relative high liver mass, increased hepatic blood flow, liver enzyme synthesis and concentration, and differences in gut wall enzymes including bacterial enzymes.

Example 6: Of polymorphism: Pharmacogenetic variation can affect the treatment. Polymorphisms of thiopurine methyltransferase (TMPT) can result in lower activity of the enzyme that competes with 6-thioguanine nucleotides. This increases the effect of 6-thioguanines such as 6-mercaptopurine and 6-thioguanine, affecting the relapse risk in pediatric ALL. Hawwa et al. used PopPK to examine the effects of genetic polymorphism and developed a PK model to improve dosing of 6-mercaptopurine, which showed a large effect of TMPT on the metabolism.

Example 7: Drug-drug interactions: Azole antifungals are used as anti-fungal prophylaxis in pediatric cancer, especially during high-risk periods. Azoles are strong inhibitors of a number of CYP450 subfamilies and P-glycoprotein (transporter protein; P-gp). Toxicities of azoles with concomitant Vinca alkaloids and calcineurin inhibitors due to increasing their exposure have been reported. TDM is recommended. The PK of azoles, such as voriconazole, is complex. Many PK models and simulations have been performed to determine variability, dosing schedule, and to study the drug interactions.

Example 8: Drug interaction and genetic polymorphism: Etoposide is a substrate of P-gp, CYP3A4, and CYP3A5. Glucocorticoids, such as dexamethasone and prednisolone, can inhibit or induce CYP3A and P-gp. Kishi et al. showed in a PK study an almost twofold increase in dexamethasone and prednisolone, can inhibit or induce CYP3A4 and CYP3A5. Glucocorticoids, such as dexamethasone and prednisolone, can inhibit or induce CYP3A and P-gp. Kishi et al. showed in a PK study an almost twofold increase in dexamethasone and prednisolone, affecting the relapse risk in pediatric ALL. Hawwa et al. used PopPK to examine the effects of genetic polymorphism and developed a PK model to improve dosing of 6-mercaptopurine, which showed a large effect of TMPT on the metabolism.

3.4 | Excretion and elimination

Excretion and elimination describe the removal of the drug from the body. Drug and metabolites can be excreted by the kidneys in the urine and/or by the liver through biliary excretion into feces based on their physicochemical properties. Other routes of excretion, such as sweat or breath, are in most cases negligible. Metabolism and excretion are quantitatively described by the clearance (CL), which is the overall ability to eliminate a compound from the body. It is expressed as the volume that is cleared of the compound per unit of time (e.g., L/h).

Elimination can be linear (first-order kinetics) or nonlinear (zero-order, Michaelis-Menten, and nonlinear elimination kinetics). In first-order PK, the amount of drug eliminated per time period is proportional to the concentration in blood. The time to clear the body of 50% of the drug (half-life: $t_{1/2}$) remains constant and is independent of the concentration. CL and $t_{1/2}$ are inversely correlated, assuming unaltered distribution. In “zero-order pharmacokinetics,” a constant amount of drug is removed from the bloodstream per unit of time regardless of the concentration. Therefore, high concentrations have a relatively low clearance and long elimination half-life compared with relatively high clearance and short half-life at low concentrations. The nonlinear Michaelis-Menten (enzyme) kinetics is due to saturation of the elimination pathway. When saturation occurs, the body cannot increase the clearance with increasing concentrations, as it lacks the capacity, and will therefore continue to eliminate the drug at the maximum (fixed) rate. Other types of nonlinearity are, for example, time-dependent kinetics. Decreased clearance and prolonged half-life can result in unwanted accumulation of the drug. Clearance in children can differ from adults due to altered renal excretion rate (relatively large kidney size), active, and passive tubular transporter mechanisms and urinary pH.

Example 9: Michaelis-Menten kinetics: Voriconazole is an antifungal used in immunocompromised children such as hematological malignancies. Karlsson et al. showed with a PopPK model that voriconazole follows nonlinear Michaelis-Menten kinetics. They also showed important PK differences between children and adults. The concentration at which half of the maximum enzyme activity is achieved (Michaelis-Menten constant) is higher in children. Therefore, the nonlinearity is less pronounced and occurs at higher concentrations and doses compared with adults. Additionally, with covariate analysis, CYP2C19 genotype and alanine aminotransferase levels were identified as significant factors affecting the clearance. Gastine et al. also used PopPK and simulations to evaluate target voriconazole dose and interval using a nonlinear model with allometric scaling.

In summary, alterations in eliminating organs, genetic polymorphisms, and growth and development cause significant PK variability. Consequently, when this variability is not accounted for, variability in drug exposure will affect treatment outcome in case of a concentration and effect correlation. Hence, studying the PK of drugs and providing insight in the characteristics of the drugs and possible dependency of demographic and pathophysiological factors is important for optimal treatment and enables tailoring the treatment to the individual patient.
study in adults. However, this method is impractical and inconvenient in children as blood sampling in pediatric patients, especially infants, is limited by the total blood volume that can be withdrawn to remain within safe limits, and strict sampling times might hamper the treatment schedule or interfere with daily activities.6,73 Chemotherapeutic agents cannot ethically be tested on healthy volunteers, therefore limiting the available population. Fortunately, these problems can be easily circumvented through the use of population PK modeling. Due to their flexibility and possibilities, PK/PD modeling is useful throughout different phases of drug development. For example in the translation of preclinical trials to clinical trials, simulating exposure effect relationship and assessment of variability.74–76 Two common PK modeling approaches are noncompartmental and compartmental analyses. The former does not rely on the assumptions of body composition, whereas the latter assumes “well-stirred” interconnected compartments. Noncompartmental analyses are useful, for example, within a single study with a homogeneous population. However, with heterogeneous data (e.g., across trials) and high variability (e.g., due to patient characteristics and different occasions), compartmental analysis is useful. Comparison of different methods is described by Ette and Williams 2014 and Kiang et al. 2012.14,77,78

4.1 | Compartmental PK analysis

A “top-down” approach (PopPK) starts with clinical data such as blood samples and patient demographics. Subsequently mathematical and statistical models are developed and fitted to the data in order to determine which model best describes the data. For practical reasons, the body is often considered as “one well-stirred compartment.” However, drugs do not distribute evenly among tissues outside the bloodstream; therefore, additional compartments can be used to describe the data. These compartments do not necessarily reflect a physiological volume, but are empirically derived on the basis of mathematical equations. On the contrary, physiologically based PK (PBPK) models do reflect physiologic compartments, which are connected through vascular transport systems. These systems are built on mechanistic insights from in vitro and ex vivo experiments.79 This is a “bottom-up” approach that starts with mathematical models/systems and is validated and optimized using clinical data. Ideally, it would also encompass the PK in tumor tissue, e.g., the cellular uptake and excretion from malignant cells. The disadvantage can be the limited available models/systems.80–84 More information on PBPK can be found for example in studies by Jones and Rowland85 and Khalil and Läer.86

Most PopPK models contain one or two compartments, although they may comprise more compartments. A one-compartment model uses one central compartment (e.g., plasma). A two-compartment model generally has a central compartment (Vc) reflecting blood and highly perfused tissues with rapid distribution, and a peripheral compartment (Vp) with poorly perfused tissues such as adipose tissue. After administration, the drug is quickly transported from the central to the peripheral compartment until an equilibrium situation occurs (steady state). This distribution is commonly referred to as the distribution phase. The second phase, where the drug is eliminated from the central compartment and slowly redistributed from the peripheral, is referred to as the elimination phase. The movement between the compartments is described by intercompartmental clearance (Q). A two-compartment model has two t1/2 values, one for the distribution and one for the elimination phase. If only one value is presented, it is usually the t1/2 of the elimination phase or a combined (hybrid) value calculated from the distribution and elimination phase (Figure 2).87,88

4.2 | Population PK approach

The PopPK-based approach has been developed since the seventies, which facilitated the derivation of PK parameters from only a few samples per patient (sparse sampling). Additionally, the approach provided more flexibility both in number of samples and time at which samples were taken, as long as the exact collection times were registered. The population approach enables the use of heterogeneous data; e.g., using data from different trials, across different populations, a combination of dense and sparse data and flexible sampling times. These advantages are particularly useful in pediatric oncology as the population is small, for example, with rare forms of cancer. Therefore, the ability to combine data from different trials, countries, and groups allows increasing the population. Sparse sampling is particularly useful to the decreased burden due to invasive sampling, for example, in
Population data pooling. The sparse individual data might not be sufficient for individual PK analyses; however, the pooled population data are. The calculated PK parameters from the pooled data (e.g., CL and V) are population means. Individual information is retained as individual variability from the mean.

Types of variability. Concentration-time curves depicting the three forms of variability. ID1 has two concentration-time curves from two subsequent dose administrations (solid line); ID2 has a single concentration-time curve after a single administration. 1. Between-subject variability (BSV), differences (e.g., in peak concentration) between the two patients; 2. Interoccasion variability (IOV), difference between dose administration time points; 3. Residual variability, due to model misspecification.

4.3 Covariate analysis

Estimation of variability is important. For instance, if large interpatient variability is present in CL, unexpected high or low drug concentrations can be found within individual patients, which might result in subtherapeutic or toxic levels. Hence, quantification of the variability is important to determine the expected range between patients. After population analysis, the derived model may be used to perform TDM of the drug. By Bayesian combination of PopPK parameters with the individual concentration estimates, the individual PK parameters can be obtained. These estimates may be used to adjust the dose (Bayesian forecasting). The statistical model quantifies variability; however, it does not provide the source of variability. The identification of variability sources can be achieved through the evaluation of covariates. Covariates include patient or group characteristics such as age, weight, kidney function, disease state, comedication, or any other variable that could reasonably account for the variability in patients. A covariate can be correlated to one or more PK parameters. The identification of covariates can be used in children to identify variability related to developmental changes. Additionally, the covariate analysis can also study the PK differences with different comedication, disease groups,
FIGURE 5  Correlation clearance and distribution versus body weight. The curvilinear relation between clearance CL(L/h) and body weight (solid line) and linear relation volume of distribution V(L) and body weight (dashed line). The clearance is normalized using the exponent for allometric scaling (0.75)

4.4 | Allometric scaling

In pediatrics, a wide array of body sizes is found. Body size is considered the most important predictor of CL and V.\textsuperscript{4,30,99} V generally increases linearly with body weight, whereas clearance generally increases nonlinearly (Figure 5). This explains why children in the age range 2 to 4 years have higher clearances and dose on basis of kg body weight than older children or adults. To better describe this nonlinearity of CL in children, allometric scaling is used. The ¾ power model is the most common approach, where CL is multiplied by normalized weight (individual weight / standard weight) raised to the power of 0.75. CL and V are often normalized for a body weight of 70 kg, which facilitates comparison between different studies.\textsuperscript{29,30,73,100} Details and comparison of allometric approaches can be found in, e.g., Wang et al.\textsuperscript{30} and Anderson and Holford 2012.\textsuperscript{73}

Example 10. Development and maturation: Busulfan exhibits substantial interpatient variability, especially in children.\textsuperscript{101–105} High concentrations result in severe toxicities, whereas subtherapeutic levels put the patient at risk of graft failure. Therefore, TDM-adjusted individualized dosing is indicated.\textsuperscript{106} McCune et al. showed low and fluctuating clearances of busulfan below the age of 3 where it peaked and plateaued until the age of 17.\textsuperscript{107} Paci et al. showed a higher increase in clearance per body weight for infants <9 kg (2.4-fold) compared with children >9 kg (1.7-fold). PK studies with busulfan showed a vast improvement with the implementation of allometrically scaled body weight to describe this nonlinear correlation between body weight and clearance. In some studies, it was superimposed with age to better describe the changes with age. Paci et al. showed a reduction of 63% to 27% in interpatient variability in busulfan concentrations after implementation of allometric scaling in their PK model.\textsuperscript{102,103,105,108} Bartelink et al. developed a PK model that could be used with good precision as basis of individualized busulfan dosing, including the nonlinear body weight clearance relation.\textsuperscript{102,109}

5 | MODEL TESTING AND VALIDATION

Throughout the development process of PK modeling, different mathematical models are fitted to the data to determine which model best describes the data. Visual tests (comparison of predicted and observed drug concentrations) and numerical tests (statistical tests, precision) are performed. For diagnostic purposes, several goodness-of-fit plots may be evaluated showing model predicted versus observed concentration (Supporting Information Figure SA). Two common diagnostic tools are the visual predictive check (VPC; simulation) and the bootstrap procedure (resampling). A VPC is used to assess how well the predictions made by the PK model describe the actual observed data, including the variability.\textsuperscript{110} The observed and simulated data are presented on top of each other. VPCs are created by simulating a large number of replicates of the original data set (Monte Carlo simulations). The VPC shows the dependent variable (e.g., concentration) versus independent (e.g., time) for both the simulated and observed data (Figure 6). The concentrations predicted by the model should be in line with the observed data. Detailed information on VPCs is described by Bertrand et al.\textsuperscript{110} Other simulation-based methods are available and include, for example, the posterior predictive check (PPC), numerical predictive check (NPC), and normalized predictive distribution error...
(NPDE), which are explained in more detail by Sherwin et al. and Karlsson and Savic.111–113

Bootstrapping is a computer-based resampling technique (creating new data sets utilizing the original data set) which can be used to assess the accuracy and stability of the model results.111,114–118 Bootstrap samples are generated by repeated independent random sampling with replacement of samples from the original data set.117,118 The results of the estimated PK parameters using the resampled data sets should be in line with the results of the original data set. If not, this might indicate that the model describes the data set rather than the population and might not be extrapolated outside of the studied population.

Due to technological progression, especially computational power, increasingly complex (mathematical) models can be developed. However, a major concern with these complicated models is overparameterization, where too many parameters are included in the model resulting in unreliable or unrealistic estimates. The model and parameter estimates describe the data set rather than the population. To reduce overparameterization, the number of parameter estimates can be reduced or fixed. Hence, validation of developed models is an important aspect of PK modeling. Different validation methods are described by Sherwin et al.77 Validation can be internal (within the data set) or external (using a different data set). The best technique depends on the available data and intended use.93 Validation using an external (new independent) data set is most stringent.118 However, an external data set might not always be available. Splitting the data is possible for large data sets, where one part is used for model development and the other for validation. Often available data are limited; hence, simulation and resampling techniques are used.117 Other resampling technique is cross-validation, using repeated data splitting.93,115,118

6 | CONCLUSION

Although the PopPK approach has been around for a while, the clinical implications of this approach are not always obvious and translation into the clinic can be difficult. This might be due to the mathematical complexity of the models and the analysis. This article describes the implications of PK in the clinic and how it is involved in the work of clinicians. As shown throughout the article the PK of an individual patient can be affected by many factors including the size (body weight, BSA and age), pharmacogenetics (e.g., enzyme polymorphism), disease state, drug-drug interactions, external factors (e.g., food; drug formulations), drug administration route, and development/maturation (e.g., of kidneys, liver, metabolism pathways). The nonlinearity of processes, such as growth development and saturated metabolic pathways, complicates the extrapolation from one group to the other. Pediatric oncology patients need specific attention due to the aspects of growth and development, the severity of illness, the different combinations of medication (including supportive care), and the small therapeutic window of most chemotherapeutics. Toxicities are a main concern; however, subtherapeutic treatment can also be fatal, due to disease progression, and should be avoided. Hence, pediatric oncology can greatly benefit from PK studies for individualized and optimized dosing. PopPK is the ideal method to study PK in children due to sparse and time flexible blood sampling, the use of heterogeneous data, the quantification, and identification of variability and simulations. Hopefully, an increasing number of PK studies will be performed in order to individualize dosing based on specific patient (and disease) characteristics to optimize treatment and limit side effects.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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