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Review article

Pediatric physiologically based pharmacokinetic models mediated by drug-metabolizing enzymes: Predictions, applications, and challenges

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ABSTRACT

Children, as a special population, exhibit significant age-specific characteristics and inter-individual variability in drug metabolism due to the influences of physiological development and genetic factors, bringing challenges to the efficacy and safety of clinical medication. Traditional pharmacokinetic studies are difficult to conduct in children and are constrained by numerous ethical limitations. Physiologically based pharmacokinetic (PBPK) modeling, as a mechanistic modeling tool, can integrate pediatric developmental physiological parameters, enzyme kinetic characteristics, and genetic polymorphism data. It has gradually become an important tool for predicting pediatric drug metabolism and optimizing dosing regimens. This review summarizes the key enzymatic characteristics of pediatric drug metabolism and the technological pathways and current application status of PBPK models in assessing pediatric drug metabolism. It discusses the major challenges, such as uncertainties in parameter extrapolation and the lack of pediatric-specific data. It further elaborates on the practical value of PBPK models in optimizing dosing regimens, supporting pediatric clinical trial design, and aiding regulatory decision-making. Finally, it proposes future directions for development by integrating artificial intelligence and multi-omics data. This review aims to provide a theoretical basis and practical reference for precision dosing in children and to promote the broader application of PBPK models in the pediatric pharmaceutical field.

1. Introduction

In the pediatric population, drug metabolism is a dynamic process fundamentally shaped by the forces of both physiological development and genetic inheritance, leading to significant variability in therapeutic outcomes. The liver, as the core organ of drug metabolism, features an enzyme system whose ontogeny displays significant isoform specificity and non-linear dynamic characteristics [1–4]. The content of the cytochrome P450 (CYP450) enzyme family reaches only 50% of adult levels by 6–12 months after birth, and the capacity for phase II conjugation reactions is also significantly delayed.[5] Concurrently, neonatal hepatic blood flow is relatively low and may not reach adult levels until infancy or early school age. These characteristics result in unique pharmacokinetic profiles for hepatically metabolized drugs across different developmental stages in children.

Genetic polymorphism represents another critical factor influencing pediatric drug metabolism. By modulating CYP450 enzyme activity, it classifies individuals into ultra-rapid metabolizers (UMs), extensive metabolizers (EMs), intermediate metabolizers (IMs), and poor metabolizers (PMs), leading to significant variability in drug metabolic rates. This variability can potentially result in accumulation toxicity, therapeutic failure, or excessive generation of toxic metabolites.[6] The immature development of the hepatic enzyme system in children confers a weaker compensatory capacity for fluctuations in enzyme activity, making the genetic determinism of metabolic phenotypes particularly pronounced. Therefore, accurate prediction of drug metabolism is essential to optimize dosing, enable personalized medicine, and reduce adverse effects in children.

The PBPK model is a mechanism-driven modeling approach grounded in physiological, anatomical, and physicochemical principles. By designating each tissue or organ as a distinct compartment, it quantifies hemodynamics, tissue characteristics, and drug-enzyme interactions,

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thereby enabling dynamic simulation of the entire absorption, distribution, metabolism, and excretion (ADME) process of drugs.[7,8] In the context of predicting pediatric drug metabolism, PBPK models can integrate developmental physiological parameters, enzyme kinetic data, and genetic information to accurately simulate metabolic differences from neonates to adolescents, offering dose optimization strategies for diverse patient populations and identifying potential safety risks. Currently, PBPK models have been widely applied throughout the entire process of pediatric drug development.[9,10]

This review aims to systematically summarize the core technologies and clinical applications of PBPK models in assessing pediatric drug metabolism. It will focus on elucidating how these models achieve accurate predictions by integrating pediatric developmental physiological parameters with genetic polymorphism data. The review will also explore current challenges in model application, such as uncertainties in parameter extrapolation and the lack of pediatric-specific data. Furthermore, it will discuss the practical value of PBPK models in optimizing individualized dosing regimens, improving pediatric clinical trial design, and supporting regulatory decision-making, ultimately providing a theoretical basis and practical reference for precision dosing research in children.

2. Drug-metabolizing enzymes in pediatric drug metabolism

2.1. CYP450 enzymes

2.1.1. CYP1A2

CYP1A2 accounts for approximately 13% of the total human hepatic CYP450 protein content and is primarily expressed in the liver, with distribution also observed in tissues such as the intestine.[11] This enzyme is involved in the metabolic conversion of various clinically commonly used drugs, including theophylline and caffeine.[12,13]

The expression of CYP1A2 exhibits significant age-dependent characteristics. During the fetal period, CYP1A2 is virtually absent. By postnatal day 7, its expression reaches approximately 5% of adult levels. Expression becomes active between 1 and 3 months of age, attains 50% of adult levels by 1 year, and approaches adult levels by approximately 3 years of age.[14]

The *CYP1A2* gene is highly polymorphic. The most extensively studied functional variants includes *CYP1A2*1C*, **1D*, **1E*, and **1F*.[15] Additionally, the *-3113A > G* polymorphism has a distribution frequency of approximately 10% in the Chinese population and is associated with decreased enzyme activity.[16]

The regulation of enzyme activity by different genotypes is complex in children. A study involving 104 Korean preterm infants found that CYP1A2 activity was significantly correlated with theophylline clearance rate ($P < 0.001$), but was primarily influenced by postnatal age and postmenstrual age, with no significant differences observed in the effects of *CYP1A2*1C* and **1F* genotypes on enzyme activity.[17] Another study in preterm infants similarly confirmed that these genotypes did not significantly affect theophylline clearance.[18] This suggests that developmental factors dominate CYP1A2 regulation during the neonatal period, whereas the influence of genetic polymorphisms gradually emerges in older children. A study in Serbian pediatric patients with epilepsy demonstrated that children carrying the *CYP1A2* -163A/A genotype exhibited significantly increased clearance of carbamazepine.[19] Berel et al.[20] reported two pediatric patients receiving clozapine therapy who presented with persistently low plasma drug concentrations. Both were confirmed to be CYP1A2 UMs. This issue was subsequently corrected by the adjunctive administration of fluvoxamine, a potent CYP1A2 inhibitor. Furthermore, as CYP1A2 serves as the primary metabolic enzyme for atypical antipsychotics such as olanzapine and clozapine, its ontogeny and genetic polymorphisms may significantly impact pediatric pharmacokinetics. However, relevant research remains limited.[21] Currently, drug labeling information pertaining to CYP1A2-related considerations is also scarce.[22]

2.1.2. CYP2C9

CYP2C9 constitutes approximately 20% of total hepatic CYP protein content and mediates the metabolism of over 100 drugs.[23,24] Its substrates include phenytoin, warfarin, tolbutamide, and various non-steroidal anti-inflammatory drugs (NSAIDs), and it is also involved in the activation of prodrugs such as cyclophosphamide and ifosfamide. Given that many of these drugs possess narrow therapeutic windows, the ontogeny and genetic polymorphisms of CYP2C9 have critical implications for medication safety in pediatric populations.

The expression of CYP2C9 exhibits marked age dependence. During early gestation, expression levels are only 1%–2% of mature values. By mid-to-late gestation, they increase to approximately 27%, with substantial interindividual variability.[25,26] Postnatally, CYP2C9 expression increases significantly. Between the neonatal period and 5 months of age, 51% of samples have achieved mature expression levels, yet considerable variability remains. Notably, CYP2C9 activity in children aged 3–10 years significantly exceeds adult levels and does not decline to adult values until the end of puberty.[25]

The most clinically significant alleles of *CYP2C9* are the wild-type (*CYP2C9*1*) and two major variants: the R144C mutation (*CYP2C9*2*) and the I359L mutation (*CYP2C9*3*), with the latter being the primary cause of reduced enzyme activity. Based on metabolic phenotype, individuals carrying *CYP2C9*1/*1*、**1/*2 and *2/*2* are classified as EMs. Those with **1/*3*、**2/*3* are classified as IMs, and **3/*3* as PMs.[26]

The impact of *CYP2C9* genetic polymorphisms on pediatric pharmacotherapy has been substantiated in multiple clinical studies. A meta-analysis encompassing 8 clinical studies involving 507 pediatric patients demonstrated that children carrying *CYP2C9*1/*2*、**1/*3*, or at least one variant allele (**2* or **3*) required 15% to 41% lower warfarin maintenance doses compared to wild-type carriers ($P < 0.05$).[27] Another meta-analysis comprising 6 studies with 847 pediatric epilepsy patients revealed a significant association between *CYP2C9* polymorphisms and valproic acid plasma concentrations ($P = 0.02$). The impact of the **1/*3* phenotype was more pronounced in children than in mixed-age populations ($P = 0.04$).[28] A study involving 89 Indian children with epilepsy found that serum phenytoin levels were significantly higher in the *CYP2C9*3* genotype group compared to the wild-type group ($P = 0.009$), although no significant difference in adverse reaction incidence was observed ($P = 0.597$).[29]

As a key metabolic enzyme for numerous drugs with narrow therapeutic windows, CYP2C9 exhibits both developmental overshoot in activity and genetic polymorphisms, collectively contributing to the complexity of pediatric pharmacotherapy. However, dose optimization studies specifically targeting children at different developmental stages and with distinct genotypes remain relatively limited. Prospective clinical investigations are urgently needed to provide more robust evidence-based guidance.

2.1.3. CYP2C19

CYP2C19 is primarily localized in hepatic microsomes and shares 92% sequence homology with CYP2C9. It predominantly mediates hydroxylation reactions of drugs. Common substrates include proton pump inhibitors (e.g., omeprazole, lansoprazole), tricyclic antidepressants (e.g., imipramine, amitriptyline), selective serotonin reuptake inhibitors (e.g., fluoxetine and sertraline), benzodiazepines (e.g., diazepam), phenobarbital, phenytoin, voriconazole, and selegiline.[30]

CYP2C19 protein and catalytic activity are detectable as early as the first trimester of gestation, reaching approximately 12%–15% of adult levels by 8 weeks of gestation[31] and remaining relatively stable throughout the fetal period. Postnatally, the expression pattern of CYP2C19 shows no abrupt changes.[32] Activity gradually increases between 0 and 5 months of age. From 5 months to 10 years of age, substantial interindividual variability is observed, which may be attributable to genetic factors. During the period of 10 to 18 years of age, expression continues to increase, approaching adult levels. Some studies

have also reported that CYP2C19 activity in children aged 2–8 years exceeds that observed in adults.[33]

CYP2C19 exhibits highly genetic polymorphisms. Among the most common variant alleles are *CYP2C19*2* (G681A in exon 5) and *CYP2C19*3* (G636A in exon 4), both of which are loss-of-function alleles resulting in reduced enzyme activity. Based on genotype, individuals can be classified as EMs (**1/*1*), IMs (**1/*2 or *1/*3*), and PMs (**2/*2, *3/*3*). Additionally, *CYP2C19*17* has been demonstrated to be associated with increased enzyme activity.[34]

CYP2C19 genetic polymorphisms significantly influence the disposition of various drugs in pediatric populations. A pharmacokinetic study conducted in 40 children demonstrated that pantoprazole AUC was significantly lower in individuals carrying the *CYP2C19*17/*17* genotype compared to those with **1/*1* and **1/*17* genotypes, with significant associations observed between genotype and dose-normalized AUC ($P < 0.0001$) as well as apparent elimination rate constant ($P = 0.0012$).[35] Another clinical study involving 207 pediatric patients with *Helicobacter pylori* infection reported that although the eradication rate was slightly higher in PMs (96.4%) than in EMs (78.3%) and IMs (83.3%), the differences did not reach statistical significance.[36] Regarding adverse effects, a retrospective analysis of 259 children undergoing allogeneic hematopoietic stem cell transplantation revealed that those carrying *CYP2C19*2* mutations had a significantly increased risk of hemorrhagic cystitis ($P = 0.021$), potentially associated with altered cyclophosphamide metabolism leading to elevated urinary acrolein exposure.[37] Multiple studies have also confirmed that *CYP2C19* genotype is a key determinant of voriconazole plasma concentrations in children, with PMs exhibiting significantly higher trough concentrations and requiring lower maintenance doses to achieve therapeutic targets.[38,39] A retrospective study in Japanese patients with epilepsy ($n = 1901$) demonstrated that *CYP2C19* genotype significantly influenced lacosamide plasma concentrations and treatment persistence, with three-year treatment retention rates being significantly higher in non-PMs than in PMs ($P < 0.05$), suggesting that poor metabolizer status may compromise long-term medication adherence due to excessively high drug concentrations.[40]

2.1.4. CYP2D6

Although CYP2D6 constitutes less than 2% of the total hepatic CYP enzyme content, it is involved in the metabolism of approximately 25% of commonly used clinical drugs, primarily exerting its effects through first-pass metabolism in the liver.[41] This enzyme is also expressed at low levels in the kidney, intestine, lung, placenta, and brain. Substrates metabolized by CYP2D6 include dextromethorphan, tricyclic antidepressants (e.g., imipramine, nortriptyline), selective serotonin reuptake inhibitors (e.g., fluoxetine, paroxetine), non-tricyclic antidepressants (e.g., atomoxetine, venlafaxine), antipsychotics (e.g., olanzapine, risperidone, haloperidol), and β-blockers (e.g., metoprolol, propranolol).[42]

Studies have demonstrated that CYP2D6 enzyme activity stabilizes after 42 weeks of postmenstrual age. Consequently, genetic variation serves as the primary determinant of CYP2D6-mediated substrate disposition capacity in infants, children, and adolescents.[43]

CYP2D6 exhibits over 100 allelic variants.[44] Based on functional activity, these can be categorized into normal-function groups (e.g., *CYP2D6*1* and **2*), reduced-function groups (e.g., *CYP2D6*9*, **10*, **17*, and **41*), and non-functional groups (e.g., *CYP2D6*3*, **4*, **5*, and **6*).[45,46] Corresponding phenotypes include UMs, EMs, IMs, and PMs.[47]

CYP2D6 genetic polymorphism is a key genetic determinant of interindividual variability in drug metabolism. A prospective observational study involving 63 psychiatric patients aged 10–18 years demonstrated that EMs exhibited better therapeutic responses to antipsychotic medications, with significant improvements in clinical symptoms and social functioning, whereas IMs showed poorer efficacy, delayed treatment response, and a higher prevalence of abnormal brain imaging findings.[48] In a study of aripiprazole for the treatment of tic disorders in children, significant differences in metabolic ratios and clearance rates were observed among UM, EM, and IM groups, with UMs showing significantly lower clinical response rates compared to EM and IM patients.[49] Another study involving 56 adolescents with psychiatric disorders receiving risperidone, aripiprazole, or olanzapine reported that *CYP2D6* genotype influenced treatment efficacy and quality of life. EMs demonstrated significantly greater reductions in Positive and Negative Syndrome Scale (PANSS) scores at 3, 6, and 12 months of treatment compared to IMs ($P < 0.05$), PMs exhibited the highest PANSS scores, and EMs had the lowest incidence of adverse reactions.[50] Furthermore, a pharmacokinetic model developed using intravenous administration data in neonates revealed that *CYP2D6* genotype significantly affected the clearance of tramadol and its active metabolite, underscoring the necessity of genotype-guided dosing.[51]

2.1.5. CYP3A

CYP3A represents one of the most critical subfamilies of drug-metabolizing enzymes in humans, involved in the metabolism of approximately 50% of drugs. CYP3A4 and CYP3A5 are the primary functional isoforms. CYP3A enzymes are highly expressed in the liver and small intestine, with additional distribution in tissues such as the kidney, lung, brain, duodenum, and lymphocytes.[52]

CYP3A4 is the predominant (approximately 30%) CYP enzyme expressed in the liver after birth. Significant interindividual variability has been observed in the hepatic expression and functional activity of CYP3A4. Its expression is extremely low during the fetal and early neonatal periods, then transcriptional activation occurs within the first week after birth. Protein levels then increase gradually over the first 6 months and approach adult levels by around 4 years of age.[53] The clearance of CYP3A4 substrates appears to follow an age-dependent pattern. Activity may be higher in toddlers and children than in adults, showing an inverted U-shaped trajectory.[54,55]

The *CYP3A4* gene exhibits polymorphisms, but coding region variants have low allele frequencies. Their impact on enzyme expression or function appears limited. These variants may partially explain interindividual differences in drug clearance, but they may not the major cause.[56] However, many drugs can induce (e.g., carbamazepine, phenytoin, rifampicin) or inhibit (e.g., erythromycin, itraconazole, cyclosporine) CYP3A4 activity. Developmental changes in enzyme function may amplify the clinical effects of these drug interactions, especially in children.

CYP3A5 is the major extrahepatic CYP3A isoform. Its activity varies markedly among individuals but shows no clear age-related pattern. The substrate profile of CYP3A5 overlaps with that of CYP3A4, with minor differences in kinetic properties. Genetic polymorphisms of *CYP3A5* are closely linked to enzyme activity. However, its overall contribution to drug metabolism remains to be further clarified.[57]

In clinical studies, one investigation in children with nephrotic range proteinuria showed that co-administration of diltiazem increased the dose-adjusted trough concentration of tacrolimus by approximately 2-fold. The increase was more pronounced in *CYP3A5*3* expressers (1.8-fold) than in non-expressers (1.3-fold).[58] Another retrospective study involving 135 pediatric patients found that age under 4 years and co-administration of enzyme inducers significantly reduced the concentration - dose ratio of perampanel. In contrast, co-administration of valproic acid or carrying the *CYP3A5*3/*3* genotype significantly increased this ratio.[59] Among 60 pediatric heart transplant recipients, children carrying *CYP3A4*22* or meeting the *CYP3A* PM phenotype (*CYP3A5*3/*3* and *CYP3A4*22*) required significantly lower doses to achieve target tacrolimus trough concentrations and exhibited higher dose-adjusted trough concentrations.[60]

2.2. UDP-glucuronosyltransferase

UDP-glucuronosyltransferase (UGT) catalyzes glucuronidation, a major phase II metabolic pathway in drug disposition. Based on amino acid sequence homology, the UGT superfamily is primarily divided into

two families, UGT1 and UGT2. Members of the UGT1A subfamily play a key role in drug metabolism and the clearance of endogenous substances.

2.2.1. UGT1A1

UGT1A1 encodes the UGT enzyme responsible for bilirubin glucuronidation. This isoform is primarily expressed in the liver. It catalyzes the glucuronidation of bilirubin and other hydrophobic endogenous and exogenous compounds. As a specific substrate of UGT1A1, the metabolic clearance efficiency of bilirubin directly reflects the *in vivo* functional status of this enzyme.[61] The *UGT1A1* gene is highly polymorphic. Among these variants, *UGT1A1*6* and *UGT1A1*28* are the two most common loss-of-function alleles in Asian populations. Both mutations can lead to a significant reduction (up to 70%) in enzyme activity.[62]

Several clinical studies have investigated the impact of *UGT1A1* polymorphisms on drug metabolism and treatment safety in children. In a study of 44 pediatric oncology patients receiving irinotecan, no significant association was found between *UGT1A1*6* or *UGT1A1*28* genotypes and the incidence of severe (grade III-IV) toxicity. However, carrying a mutant allele (*UGT1A1*6* or *UGT1A1*28*) appeared to be linked to lower overall survival rates. Further analysis revealed that children with the *UGT1A1*6* mutation had a significantly higher risk of grade I–IV irinotecan-related diarrhea ($P = 0.043$) and anemia ($P = 0.002$). However, this conclusion requires validation in large-scale prospective studies.[63] In antiepileptic therapy, a population pharmacokinetic study analyzed 236 topiramate plasma concentrations from 181 children with epilepsy. The results identified *UGT1A1* rs4148324 as a significant covariate affecting topiramate clearance.[64] Another cohort study of 163 children with epilepsy further confirmed that *UGT1A1* rs4148324 was significantly associated with topiramate plasma concentrations. Patients with the *TG* or *GG* genotypes exhibited significantly higher standardized topiramate concentrations than those with the wild-type *TT* genotype. This phenomenon may be explained by the high linkage disequilibrium between rs4148324 and rs34983651 (*UGT1A1*28*). These two variants may synergistically affect *UGT1A1* transcriptional activity and metabolic capacity, thereby altering the glucuronidation clearance of topiramate.[65]

2.2.2. UGT1A6

UGT1A6 is another important member of the UGT1A family. It primarily catalyzes the glucuronidation of phenolic compounds in the liver. It is also expressed to varying degrees in extrahepatic tissues, including the kidney, stomach, small intestine, colon, and lung.[61] UGT1A6 conjugates numerous drugs and xenobiotics. It also exhibits high conjugation efficiency for serotonin, an important neurotransmitter.[66]

Valproic acid is a first-line treatment for childhood epilepsy, and its *in vivo* clearance is primarily achieved through UGT-mediated glucuronidation. A study of 98 epilepsy patients receiving valproic acid monotherapy showed that patients with double heterozygous mutations at the *T19G*, *A541G*, and *A552C* loci of the *UGT1A6* gene required higher valproic acid doses than those with wild-type or single heterozygous mutations ($P = 0.010$). Dose-adjusted plasma concentrations were significantly lower than those in single heterozygous mutation patients ($P = 0.027$).[67] However, other studies reported no significant association between *UGT1A6* polymorphisms (*T19G*, *A541G*, *A552C*) and valproic acid plasma concentrations or clinical outcomes in children.[68,69] Therefore, larger, multicenter, prospective studies will help clarify the clinical value of *UGT1A6* in personalized pediatric therapy.

3. Application of PBPK models in pediatric drug development and precision dosing

3.1. Development of pediatric PBPK models

PBPK modeling offers distinct theoretical advantages and broad application prospects in pediatric drug research compared to traditional population pharmacokinetic approaches. Its core strength lies in integrating key physiological characteristics (e.g., developmental stage, disease status, and genetic factors) into a mechanistic framework through organ-specific parameterization. This enables mechanistic insights into drug disposition in special populations, particularly in children. Consequently, relatively abundant data from adults or healthy subjects can be extrapolated to pediatric populations with limited clinical data, thereby supporting initial pediatric dosing regimen design.[70] For pediatric populations, the key value of PBPK modeling is its capacity to incorporate individualization equations based on physiological developmental trajectories. These equations integrate developmental changes, including organ volume and blood perfusion, renal function maturation, and age-dependent expression of drug-metabolizing enzymes and transporters, into the prediction framework. Unlike conventional models relying on statistical fitting, PBPK modeling provides more detailed mechanistic insights. This facilitates a deeper understanding of how age-related factors influence the ADME of drugs, leading to more reliable predictions of pediatric drug safety and efficacy. Following decades of methodological development and validation, pediatric PBPK modeling has become an essential tool in drug development and clinical individualized therapy.

The general workflow for developing pediatric PBPK models is illustrated in Fig. 1. To ensure reliable model structure and accurate parameter estimation, a widely recommended modeling strategy involves first establishing a well-validated adult PBPK model before constructing a pediatric version. Adult model development helps identify key pharmacokinetic processes of the drug *in vivo* (e.g., major clearance pathways, tissue distribution characteristics) and determine drug-specific parameters independent of age (e.g., lipophilicity, plasma protein binding, membrane permeability). Subsequently, the adult model is extrapolated to pediatric populations by substituting age-specific physiological parameters (e.g., organ volume, tissue blood perfusion rate, plasma protein concentrations, and glomerular filtration rate).

It should be noted that pediatric PBPK modeling still faces data gaps for several key parameters. Although anatomical and physiological parameters such as organ volume and blood flow are well-characterized across age groups, systematic and quantitative age-related data on the expression and activity of drug-metabolizing enzymes and transporters during childhood development remain limited. These information gaps directly impact the predictive accuracy of models for critical parameters such as drug clearance. However, if age-related expression patterns of metabolic enzymes and transporters can be obtained through literature integration or *in vitro* experiments, and model predictions are adequately validated in independent clinical datasets, pediatric PBPK models can still be considered suitable for their intended use. Such models can support initial pediatric dose selection and optimization of clinical trial protocols.[71]

3.2. PBPK modeling in characterizing pediatric drug metabolism

PBPK modeling leverages *in vitro* data to enable *in vitro-in vivo* extrapolation (IVIVE), providing an important approach for predicting drug clearance in pediatric populations. For example, based on *in vitro* activity assays using recombinant drug-metabolizing enzymes, drug clearance per unit of enzyme protein can be calculated. This value can then be extrapolated to whole-liver clearance for different age groups by incorporating age-specific liver weight and target enzyme expression per gram of liver tissue. This approach is particularly valuable for innovative drugs lacking pediatric clinical data, offering critical references for first-in-pediatric dose design.[72] Complementarily, when adult *in vivo* pharmacokinetic data are available, adult clearance can be scaled to pediatric populations using physiological knowledge of age-related differences in metabolic enzyme expression. This can further improve prediction reliability. If data from *in vitro* experiments (e.g., recombinant enzymes, human liver S9 fractions, human liver microsomes, or human hepatocytes) have been used to estimate hepatic clearance in

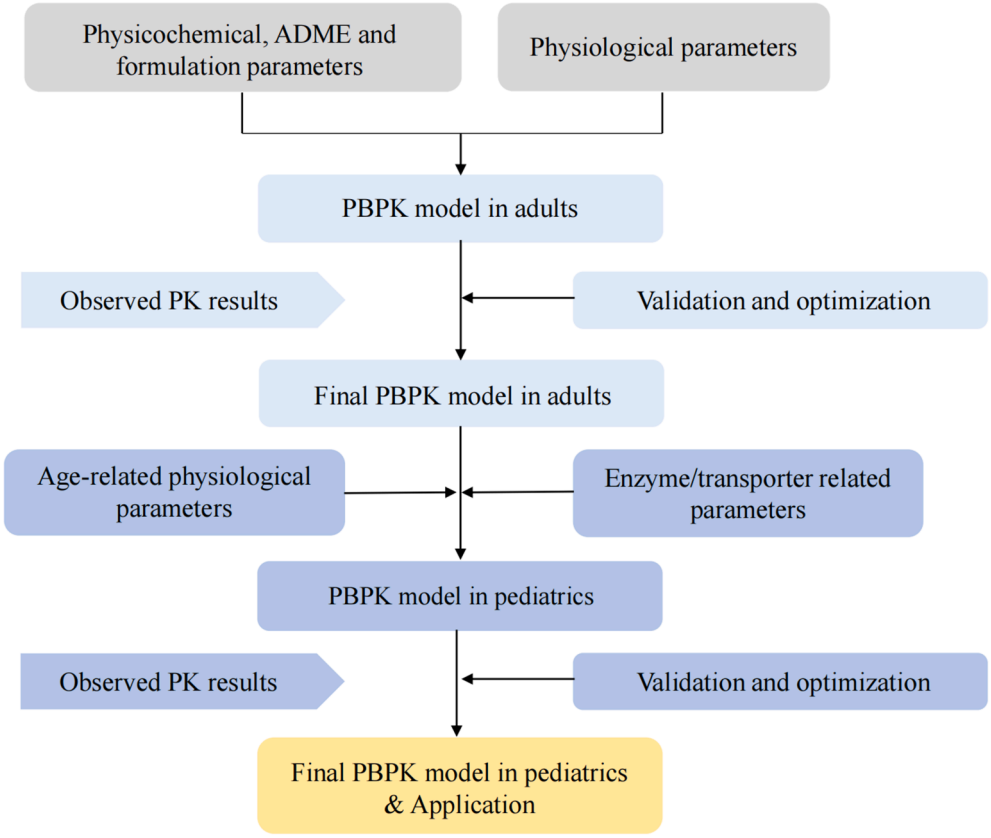


Fig. 1. Flowchart of PBPK model building of pediatrics.

adult models, these data can also be extrapolated to pediatric models by accounting for reported differences in enzyme expression and activity. Currently, for drug metabolism mediated by enzymes such as CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, ontogeny models have been further refined through validation against clinically observed clearance values. These models may enable accurate predictions in children as young as 1 month of age.[73]

Parvez et al.[74] measured the expression levels of CYP enzymes involved in metronidazole metabolism using liver microsomes from 115 children and 35 adults. Results showed that CYP2A6, CYP2E1, and CYP3A4 expression increased with age, while CYP3A7 exhibited a postnatal decline. CYP2A6 and CYP3A5 expression were significantly associated with rs4803381 and rs776746 genotypes, respectively. A PBPK model developed based on the proteomics data successfully characterized the *in vivo* disposition of metronidazole and its active metabolite. The metabolite-to-parent drug ratio increased with age, and CYP2A6 expression showed a strong correlation with metabolite formation ($r^2 = 0.75$). Notably, CYP3A7 contributed approximately 75% to metronidazole clearance in neonates, suggesting that variability in CYP2A6 and CYP3A7 expression may lead to interindividual differences in metronidazole pharmacokinetics among young children. The large-scale developmental dataset of hepatic CYP enzymes established in this study provides a generalizable methodological framework for pediatric PBPK modeling of similar drugs. Yao et al.[75] systematically collected demographic and physiological parameters from children aged 0-18 years in the Chinese population. They established a virtual Chinese pediatric population model using the Simcyp platform. The model was validated using probe drugs with different elimination pathways, such as theophylline (CYP1A2 metabolism), fentanyl (CYP3A4 metabolism), and ceftazidime and vancomycin (renal clearance). The predicted peak concentration, area under the curve (AUC), and clearance values were all within 0.5–2.0-fold of the observed values. These results confirm that the model adequately characterizes the pharmacokinetics of drugs metabolized by CYP1A2 and CYP3A4 or eliminated renally in Chinese children. Southall et al.[76] further integrated physiological parameters specific to Chinese children to develop a PBPK model. They selected drugs with different metabolic pathways (fentanyl, midazolam, ruxolitinib, efavirenz, and theophylline) as well as renally cleared drugs for validation. The results showed that 79% of the predicted pharmacokinetic parameters fell within 0.8–1.25-fold of the observed values, and 100% fell within 0.67–1.5-fold, demonstrating good predictive accuracy of the model. Johnson et al.[77] developed a Japanese pediatric PBPK model by integrating Japanese children's physiological parameters into a Northern European pediatric model. The model was validated using 14 drugs with various clearance pathways. Results showed that 71% of predicted pharmacokinetic parameters fell within 0.8–1.25-fold of observed values, and 90% fell within 0.67–1.5-fold.

These studies collectively demonstrate the critical role of pediatric PBPK modeling in integrating race-specific physiological parameters, quantitatively characterizing drug exposure profiles across different metabolic pathways in diverse pediatric populations, and supporting pediatric dose extrapolation and regimen optimization. However, the application of PBPK models in young children, particularly neonates and preterm infants, still faces numerous challenges. Insufficient data on the maturation of certain metabolic enzymes lead to difficulties in model predictions. Additionally, system-specific parameters in this population can change rapidly over short periods, making PBPK model predictions of measured drug concentrations less accurate compared to those in older children and adults.[78] Nevertheless, with growing understanding of developmental physiological parameters in preterm infants and neonates, related research is providing a more solid theoretical basis for drug metabolism mechanisms in this age group. This is driving further optimization and application of PBPK models in pediatric drug development.

Michelet et al.[79] developed a PBPK model spanning from preterm infants to adults using propofol as a model drug for CYP3A4. This study

integrated CYP3A4 ontogeny data and successfully predicted drug clearance and concentration-time profiles across different age groups. The findings validated the reliability of PBPK models based on metabolic enzyme developmental characteristics for cross-age extrapolation. Kovar et al.[80] established a parent-metabolite PBPK model for buprenorphine covering adults, children (4.6–7.5 years), and preterm infants (gestational age 27–34 weeks). The model integrated developmental data for metabolic enzymes including CYP3A4 and UGT2B7. It demonstrated excellent predictive performance and provided important references for the safe use of opioids in preterm infants. Van Hoogdalem et al.[81] further employed PBPK modeling to investigate the impact of maturity on buprenorphine pharmacokinetics in neonates with neonatal opioid withdrawal syndrome. The study identified biliary clearance, buccal mucosal absorption, and CYP3A4 expression levels as key factors influencing pharmacokinetic variability in this population.

3.3. Application of pediatric PBPK models

3.3.1. Pediatric dose prediction and precision dosing strategies

By integrating ontogeny functions and genotype information of metabolic enzymes, PBPK models enable precise dose prediction and adjustment. For drugs with known metabolic enzyme polymorphisms, PBPK models can recommend individualized starting doses or adjustment regimens by incorporating pediatric-specific factors such as age, body weight, and genotype. These models can also integrate patient-specific factors, including organ function (e.g., hepatic or renal impairment), body composition (e.g., BMI or body fat percentage), and disease status. Furthermore, given the frequent need for combination medication in pediatric patients, PBPK models can predict changes in drug exposure with different genotypes when enzyme inhibitors or inducers are co-administered, thereby identifying potential high-risk subpopulations. This provides precision dosing adjustments for specific pediatric populations not included in clinical trials during drug development.

Soliman et al.[82] successfully developed and validated PBPK models for omeprazole and its major metabolites in both adults and children. Simulations of a 0.7 mg/kg dosing regimen demonstrated that the duration with intragastric pH $>$ 4 within a 24-h period was significantly prolonged in infants under 1 year of age compared to older children and adults, suggesting an increased risk of infection and impaired calcium absorption in this age group. Drug-drug interaction (DDI) simulations further revealed that complete inhibition of CYP3A4 (and CYP3A7 during infancy) resulted in an approximately 4-fold increase in omeprazole exposure in children under 2 years, whereas no significant change was observed in adults. These findings indicate that infants and young children are particularly susceptible to CYP3A inhibitor-mediated DDI. In a pediatric PBPK modeling study of posaconazole,[83] the investigators incorporated age-specific anatomical and physiological parameters along with ontogeny data for the UGT1A4 to extrapolate to the pediatric population. Simulations revealed that the conventional oral suspension was unlikely to achieve effective exposure levels in children under 7 years of age due to solubility limitations. For the intravenous formulation, the optimal therapeutic dose was determined to be 11–13 mg/kg once daily, while the prophylactic dose was 8–9 mg/kg once daily. For the delayed-release oral suspension, the optimal therapeutic dose ranged from 12 to 14 mg/kg once daily, with a prophylactic dose of 8.5–10 mg/kg once daily. Eltanami et al.[84] developed and validated PBPK models for the commonly used combination regimen of clobazam (CLB) and stiripentol (STP) in children with Dravet syndrome. The models were used to evaluate the impact of age and *CYP2C19* genotype on DDI. CLB is metabolized primarily by CYP3A4 to form its active metabolite, N-desmethylclobazam (N-CLB), which is subsequently cleared via CYP2C19. STP inhibits multiple CYP enzymes. The investigators first constructed a model based on adult data to optimize the inhibitory parameters of STP on CYP2C19, and then extrapolated to children aged 2 years and older successfully by incorporating CYP enzyme ontogeny profiles. DDI risk assessment based on this model revealed that STP increased N-CLB exposure by 7- to 8-fold in CYP2C19 EMs, whereas no increase or even a decrease was observed in PMs. Further extrapolation to infants aged 6 months to 2 years predicted that exposures of CLB, N-CLB, and STP were comparable to those in older children and remained within therapeutic windows, supporting the safe use of STP in combination with CLB in infants older than 6 months.

3.3.2. Optimal design of pediatric clinical trials

PBPK modeling plays an important role in pediatric clinical trial design. By generating virtual subpopulations and simulating various scenarios, it enables the design of more efficient and targeted studies, thereby reducing trial costs and improving drug development success rates. Extrapolating data from adults or older children to infants and young children represents a typical application scenario for PBPK models. By integrating key physiological factors such as enzyme activity differences and organ function status, PBPK models can simulate drug metabolism processes across different pediatric age groups. This provides important references for first-in-pediatric dosing regimen design and reduces the need for large-scale trials in this vulnerable population.

Jo et al.[85] developed a PBPK model for dapagliflozin to support pediatric dosing regimen design. The model was initially constructed and validated using *in vitro* data and adult clinical parameters, then refined using data from adolescent patients with type 2 diabetes mellitus aged 11–17 years. Given that UGT1A9 ontogeny maturity is critical for predicting drug exposure in young children, the study compared the impact of two different UGT1A9 ontogeny models on dose recommendations. Based on the optimized model, the study predicted exposure levels following monotherapy in children and adolescents aged 1 month to 18 years. This was used to identify pediatric regimens matching the exposure of a single 10 mg adult dose, thereby guiding first-dose selection in young children lacking clinical data. Traver et al.[86] developed a PBPK model for liglitazone to guide pediatric starting dose selection. The investigators first constructed and validated an adult PBPK model using *in vitro* data along with single ascending dose and multiple ascending dose data from Phase I studies. This model characterized the drug's elimination pathways, including CYP2C8 metabolism (45%), CYP3A4 metabolism (24%), and biliary clearance (19.5%). When extrapolating to the pediatric population, CYP2C8 and CYP3A4 ontogeny profiles were integrated into the model. Pediatric starting doses were predicted based on the target steady-state exposure of the 150 mg once-daily oral dose in adults. Preliminary clinical data from five pediatric patients aged 5-12 years with cerebral adrenoleukodystrophy showed that observed drug concentrations fell within the 95% confidence intervals of model predictions. Bayesian predicted clearance values were consistent with PBPK model predictions, confirming the predictive performance of the model.

3.3.3. Regulatory submissions and considerations for review

Regulatory submissions utilizing PBPK modeling to predict pediatric pharmacokinetics are playing an increasingly important role in elucidating how metabolism influences drug disposition, safety, and efficacy. Regulatory agencies including the US FDA and European EMA have progressively accepted PBPK modeling as a supportive tool in pediatric drug development, particularly in the absence of clinical data. However, it is worth noting that current new drug applications submitted to the FDA remain predominantly focused on DDIs. Submissions involving models for susceptible subpopulations at different life stages (e.g., children), organ dysfunction, and genetic polymorphisms still account for a relatively small proportion. Among new drugs approved by the FDA between 2020 and 2024, only 2.6% of submissions employed PBPK modeling for pediatric dose prediction, highlighting ongoing challenges related to data scarcity and insufficient model validation in this field. During regulatory review, the FDA places particular emphasis on whether models adequately account for physiological changes associated with pediatric growth and development, such as enzyme expression and organ function maturation. The agency also stresses that models

must possess a reliable *in vitro*-to-clinical extrapolation chain and validation data specific to targeted age groups.[87]

For example, in the regulatory submission for ALYFTREK, the applicant developed PBPK models to predict drug exposure in children aged 6 to 11 years. These models aimed to evaluate CYP3A-mediated DDIs, establish pediatric dosing regimens, and predict potential risks to CYP2C9 substrates. Regulatory review concluded that while adult DDI predictions and dosing regimens were successfully validated, pediatric extrapolation proved inadequate, and the CYP2C9-mediated interaction risk remained incompletely characterized.[88] In another case, VORANIGO, the applicant developed PBPK models to predict DDIs for VORANIGO in two contexts, as a victim drug during co-administration with the CYP1A2 inhibitor fluvoxamine or inducers rifampin/phenytoin, and as a perpetrator drug affecting substrates of CYP3A4, CYP2C8, CYP2B6 enzymes and BCRP/P-gp transporters. Regulatory assessment concluded that the model was deemed adequate to support labeling for VORANIGO as a victim drug, accurately predicting a 10-fold increase in exposure when co-administered with the strong CYP1A2 inhibitor fluvoxamine and an approximately 40% decrease with moderate inducers (rifampin, phenytoin). Conversely, the model was considered inadequate for predicting VORANIGO as a perpetrator of CYP3A4 and CYP2C8 induction, leading to a conservative label statement that DDI potential cannot be excluded, thereby alerting clinicians to potential interaction risks.[89] These cases demonstrate that when reviewing pediatric PBPK models, the FDA carefully evaluates mechanistic completeness, reliability of parameter sources, and the ability to characterize age-related physiological changes. The agency emphasizes that limitations identified in pediatric model applications must be clearly stated in product labeling.

4. Challenges and future perspectives

Despite the promising applications of PBPK models incorporating drug-metabolizing enzymes in pediatric populations, numerous challenges currently limit their predictive performance and clinical translation. These challenges are primarily manifested in the following aspects.

First, the acquisition of pediatric physiological parameters is difficult, resulting in incomplete foundational data. Knowledge gaps persist regarding the ontogeny of drug-metabolizing enzymes and transporters in children, particularly in neonates and infants. Limited data exist on protein expression levels and activity of certain metabolic enzymes in preterm infants, full-term neonates, and infants. System-specific parameters such as organ volumes and tissue perfusion rates across different age groups remain incomplete. Additionally, substantial inter-ethnic variability in the distribution of metabolic enzyme genetic polymorphisms necessitates more detailed data to develop ethnically representative models.

Second, the scarcity of pediatric clinical trial data impedes model validation. Due to ethical and operational constraints, blood sample collection in children is limited, resulting in insufficient pharmacokinetic data. Sparse sampling designs often fail to comprehensively evaluate model predictive accuracy across different age subgroups and dosing regimens. This limitation undermines confidence in predicted results among regulatory agencies and clinicians, restricting model application in critical decision-making.

Third, the complex influence of non-genetic factors increases modeling difficulty. Beyond genetic factors, non-genetic variables including nutritional status, dietary components, and concomitant medications collectively influence pediatric drug metabolism, further complicating PBPK model development.

With advances in methodological approaches and deepening multidisciplinary collaboration, pediatric PBPK models are expected to overcome current limitations and play a central role in pediatric drug development and clinical pharmacotherapy. The integration of artificial intelligence and machine learning techniques will create new opportunities for pediatric PBPK modeling. These approaches can optimize model parameter identification, improving the efficiency and accuracy of parameter estimation. Big data analytics enables metabolic phenotype classification to identify metabolic capacity in children with different genotypes, while deep learning methods can capture complex nonlinear relationships to enhance model prediction accuracy for inter-individual variability. Together, these techniques facilitate the construction of hybrid modeling frameworks with greater predictive power.

The rapid development of omics technologies provides rich information for understanding inter-individual differences in drug metabolism. Integrating absolute quantitative data of metabolic enzymes from proteomic assays into PBPK models enhances the ability to predict age-related changes in drug clearance. Future systematic integration of multi-omics data, including genomics, transcriptomics, proteomics, and metabolomics, holds promise for constructing refined models of enzyme and transporter expression. This would reveal the complete regulatory cascade from genotype to phenotype, providing a mechanistic foundation for personalized dosing.

Clinical decision support systems based on PBPK modeling are gradually transitioning from research tools to clinical applications. Future development of clinical decision systems integrated with electronic health records could enable dynamic dose adjustment by incorporating patient genotype, real-time physiological monitoring data, and medication history. Such systems would directly translate model predictive capabilities into clinical practice, advancing the implementation of precision medicine in pediatric populations.

Promoting the standardization and shared platform development of pediatric PBPK models represents an important direction for sustainable advancement in this field. Establishing public databases of pediatric physiological parameters, model code repositories, and validation benchmarks can enhance model transparency and reusability. Concurrently, collaborative efforts among academia, industry, and regulatory agencies may lead to unified guidelines for model development and validation, providing technical specifications for regulatory acceptance of pediatric PBPK models. International collaborative research programs also contribute to integrating data resources from pediatric populations across different ethnicities, facilitating the construction of more representative population models.

5. Conclusions

PBPK models incorporating drug-metabolizing enzymes provide powerful mechanistic tools for understanding drug metabolism characteristics in pediatric populations. These models effectively integrate ontogeny data of metabolic enzymes, genetic polymorphism information, and physiological parameter variations to support decision-making across the entire continuum from early drug development to clinical pharmacotherapy. Compared with conventional empirical dose conversion approaches, PBPK modeling enables more accurate characterization of drug disposition patterns across pediatric age groups from neonates to adolescents, providing scientific rationale for first-in-pediatric dose selection, clinical trial design, and precision dosing guidance.

Despite current challenges, including critical data gaps, difficulties in model validation, and complex drug interactions, pediatric PBPK models are poised to play increasingly important roles in precision medicine practice. This progress is driven by the accumulating developmental data on metabolic enzymes and transporters, deep integration of artificial intelligence technologies, and systematic incorporation of multi-omics data. Moving forward, continued advancement in standardized platform development and multidisciplinary collaboration will progressively overcome existing limitations. Ultimately, PBPK modeling will make substantial contributions to improving the safety, efficacy, and accessibility of medications for pediatric populations.

CRediT authorship contribution statement

Juan Wu: Writing – original draft, Methodology, Investigation, Conceptualization. **Yawen Yuan:** Writing – review & editing, Conceptualization. **Haonan Li:** Investigation. **Junyu Li:** Writing – review & editing. **Cheng Jin:** Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Not applicable.

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