



## SPECIAL ARTICLE

## Update on pharmacogenetics in pediatrics



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**Abstract** The implementation of pharmacogenetics in Spain has experienced a significant boost in the last year, driven by the update of the genetic services portfolio of the National Health System, the national Summary of Product Characteristics (SmPC) biomarker database and the development and update of clinical guidelines by scientific societies and expert groups. However, the scope of this implementation is quite limited in the pediatric population because most studies do not include children, which in turn means that, in many cases, guidelines do not specify what to do in this population. This article reviews the tests included in the Common Portfolio of Genetic Services, drugs with pharmacogenetic recommendations in technical data sheets, and the main global and national pharmacogenetic guidelines, extracting and analyzing the existing information for the pediatric population. Drug-gene pairs with greater use in pediatrics are presented in more detail, such as proton pump inhibitors and *CYP2C19*, Abacavir, allopurinol, carbamazepine, oxcarbazepine, and phenytoin with *HLA-A* and *HLA-B* genes, voriconazole and *CYP2C19*, tacrolimus and *CYP3A5*, aminoglycosides and *MT-RNR1*, thiopurines and *TMPT/NUDT15*, or atomoxetine and *CYP2D6*. Despite current limitations, the use of pharmacogenetics in pediatrics can and should be implemented in those cases where regulatory agencies and/or scientific societies recommend it.

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**PALABRAS CLAVE**

Farmacogenética;  
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Medicina de  
precisión;  
Pediatría

**Actualización de Farmacogenética en Pediatría**

**Resumen** La implementación de la farmacogenética en España ha sufrido un extraordinario impulso en el último año con la actualización de la cartera de servicios de genética del Sistema Nacional de Salud, la publicación de la base de datos nacional de biomarcadores farmacogenéticos en las fichas técnicas de los medicamentos y la generación y actualización de guías clínicas por parte de sociedades científicas y consorcios de expertos. Sin embargo, el alcance de esta

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implementación está bastante limitada en la población pediátrica debido a que la mayoría de los estudios que se hacen no incluyen a niños, lo que a su vez hace que, en muchas ocasiones, las guías no especifiquen qué hacer en esta población. En este artículo se revisan las pruebas incluidas en la Cartera Común de Servicios de genética, los fármacos con recomendación farmacogenética en ficha técnica y las principales guías mundiales y nacionales de recomendaciones farmacogenéticas y se extrae y analiza la información existente para la población pediátrica. Se presentan en mayor detalle aquellos pares fármaco/gen con un mayor uso en pediatría, como inhibidores de la bomba de protones y *CYP2C19*, abacavir, alopurinol, carbamazepina, oxcarbazepina y fenitoína con los genes *HLA-A* y *HLA-B*, voriconazol y *CYP2C19*, tacrolimus y *CYP3A5*, aminoglucósidos y *MT-RNR1*, tiopurinas y *TMPT/NUDT15*, y atomoxetina y *CYP2D6*. A pesar de las limitaciones, el uso de la farmacogenética en pediatría puede y debe implementarse en aquellos casos en que las agencias reguladoras, y/o las sociedades científicas así lo recomiendan.

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## Introduction

Pharmacogenetics studies how genetic variation impacts pharmacological treatment both in terms of efficacy and drug-induced toxicity. In recent years, there have been substantial advances in the field thanks to the performance of clinical trials and observational studies. However, specific data for the pediatric population is scarce. If we specifically focus on pharmacogenetics, a search in PubMed using the terms ((*pharmacogenetics*) OR (*pharmacogenomics*)) AND ((*children*) OR (*pediatrics*) OR (*pediatry*)) yielded a total of 4732 records as of July 19, 2024. In contrast, the search strategy ((*pharmacogenetics*) OR (*pharmacogenomics*)) NOT ((*children*) OR (*pediatrics*) OR (*pediatry*)) yielded 34 180 records. This reflects the extent to which the pediatric population is underrepresented in pharmacogenetic trials and, in consequence, the dearth of information currently available to apply pharmacogenetics to pediatric care.

In Spain, two recent milestones have promoted rapid advances in the availability and use of pharmacogenetic tests in the National Health System (NHS). The first one was the approval on June 23, 2023 by the Interterritorial Council of the NHS of the update to the genetic test catalog of the nationwide service portfolio of the public health care system, subsequently ratified by Order SND/606/2024 of June 13, 2024, which includes tests for 672 gene-disease associations or target regions that would be covered for any patient in the NHS, 33 of them in the field of pharmacogenomics. The second was the launch of the pharmacogenomic biomarker database of the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS, Spanish Agency of Medicines and Medical Devices) on July 29, 2024. The aim of this database is to facilitate access to the information contained in summaries of product characteristics (SmPCs) to promote the application of pharmacogenetics to clinical practice.<sup>1</sup>

It is important to note that none of these initiatives distinguish between adult and pediatric patients, so all

drugs and indications included that affect the pediatric population are likely to be applicable to this population. Nevertheless, there are important limitations in this regard. As noted above, the limited evidence from specific studies supporting their clinical utility in the pediatric populations is one of the chief limitations. Another significant limitation involves the impact of the maturation of drug-metabolizing enzymes and transporters on drug response.<sup>2</sup> For example, cytochromes *CYP2D6* and *CYP2C19*, which are involved in the metabolism of a large number of drugs, undergo a prolonged maturation process that starts in the fetal period.<sup>3</sup> Their enzymatic activity at birth is not equivalent to their activity in adulthood, so the clinical impact of variants in the *CYP2C19* and *CYP2D6* in the first months of life remains unknown.

The aim of this article is to guide the implementation of pharmacogenetics in pediatric care and contribute to updating the knowledge of pediatric care providers on the relevant pharmacogenetic data currently available for drugs used in the pediatric population. To this end, we conducted an exhaustive review of the pharmacogenomic test catalog of the Ministry of Health and of the AEMPS database, highlighting the frequent indications and uses in the pediatric population. We also reviewed and summarized the recommendations for the implementation of clinical pharmacogenomics in pediatric care included in the main pharmacogenetics guidelines that are currently available, such as those of the Clinical Pharmacogenomics Implementation Consortium (CPIC), the Dutch Pharmacogenetics Working Group and the Spanish Society of Pharmacogenetics and Pharmacogenomics, with particular emphasis on the most useful dosage adjustment recommendations based on the available evidence and the frequency the drugs are used in the pediatric population.

Knowledge of these associations and its appropriate application to the prescribing/contraindication or dosage of these drugs is key in order to improve the safety and

effectiveness of treatments in the pediatric population. We hope that this information will be useful and facilitate the implementation of pharmacogenetics in pediatric care.

### Pharmacogenetics in the Spanish NHS: nationwide portfolio of genetics services and drugs with pharmacogenetic indications in summaries of product characteristics

The pharmacogenomic biomarker database of the AEMPS includes 78 gene-drug pairs for 68 active ingredients involving 18 different genes. According to the website of the AEMPS, the information contained in this database is based on the gene-drug pairs supported by level 1A evidence documented in the database [pharmgkb.org](http://pharmgkb.org) as of June 2024 and pairs for whom information is not available in the SmPC but are included in the nationwide genetic and genomic test portfolio of the Spanish Ministry of Health. [Table 1](#) summarizes the information for the 19 drugs or drug families and the 12 genes for which the pharmacogenomic test catalog notes the indications for the test.

For the purpose of this review, we summarized the information contained in the AEMPS database as well as the indications authorized in the pediatric population and some of the frequent off-label uses of the included active ingredients (information obtained from SmPCs<sup>4</sup> in addition to consultation of the [Pediamecum](#) database of active ingredients authorized for use in pediatrics)<sup>5</sup> ([Table 2](#)). Based on the results of this analysis, there are recommendations for 78 gene-drug pairs, of which nearly 80% (62) correspond to biomarkers included in the nationwide testing portfolio, and another 13% (10) have been proposed for inclusion in it. On the other hand, focusing on the 68 active ingredients in this database, 65% (44) have one or more pediatric indications, and the vast majority are used off-label in this age group.

The table shows whether the drug is authorized for any pediatric indication, and whether the SmPC includes recommendations for dose adjustment or, otherwise, precautions or use based on the pharmacogenomic results.

Of the 19 drugs specifically included in the nationwide catalog, 13 (68%) have authorized pediatric indications: the anti-infectives abacavir, atazanavir, and voriconazole; the anticonvulsants carbamazepine, phenytoin, and oxcarbazepine; the thiopurines (azathioprine and mercaptopurine); omeprazole; ivacaftor; allopurinol; pimozide; and rasburicase. In the case of abacavir, atazanavir combined with voriconazole and ritonavir, ivacaftor, and rasburicase, testing is required prior to treatment, as it determines the indication of the drug (ivacaftor) or a clear contraindication for its use (all others). However, for the rest of the drugs included in the nationwide catalog and most of the drugs in the AEMPS database, the SmPC does not specify whether testing should be performed nor include specific recommendations for dose adjustment. That is why the main scientific societies and expert working groups in pharmacogenetics develop guidelines and consensus recommendations based on the current evidence. These guidelines are essential to guide the implementation of pharmacogenetics in clinical practice.

### Pediatric information in pharmacogenetic guidelines

At present, the CPIC is the pharmacogenetics association with the greatest number of guidelines for dosage adjustment. The article describing its guideline development process specifies that each recommendation includes an assessment of its usefulness in pediatric patients.<sup>6</sup> At the time of this writing, the CPIC has published a total of 27 guidelines, of which 24 include at least one section with recommendations adapted to the pediatric population ([Table 3](#)). Specifically, there are four drugs for which there are specific dosing recommendations for children: atomoxetine, efavirenz, voriconazole and warfarin. In the rest of the CPIC guidelines, recommendations based on the genotype and phenotype are extrapolated from the adult population, with certain limitations due to the scarcity of the evidence or the immaturity of drug metabolizing pathways in young children.<sup>2</sup>

Guidelines and consensus documents published by other groups and organizations, such as the Dutch Pharmacogenetics Working Group and the Spanish Society of Pharmacogenetics and Pharmacogenomics do not systematically include an assessment of the usefulness in the pediatric population. At present, they only include specific pediatric dosing information for atomoxetine due to the specific use of this drug in the treatment of attention-deficit/hyperactivity disorder.<sup>7,8</sup>

### Recommendations for drugs commonly used in pediatric care

We now proceed to a more detailed description of the drug-gene pairs for which CPIC guidelines are available and which are considered most relevant in pediatrics based on the current evidence and the frequent use of the corresponding drug in the pediatric population, following consultation with a group of experts that included pediatricians and hospital-based pediatric pharmacists.

#### Proton pump inhibitors-CYP2C19 gene

Proton pump inhibitors (PPIs) are frequently used in the pediatric population for conditions such as reflux esophagitis, gastroesophageal reflux disease, and duodenal ulcer caused by *Helicobacter pylori*. In addition, its use is increasingly widespread in this population for other indications that are not authorized in the SmPC.<sup>9</sup> Most PPIs are mainly metabolized by CYP2C19.<sup>4</sup> The activity of CYP2C19 is very low in the early months of life, so the clearance of PPIs in preterm infants and term infants aged less than 2 or 3 months is lower compared to the adult population.<sup>10</sup> In children aged more than 1 year, there is growing evidence that certain CYP2C19 variants affect the pharmacokinetics and response to PPIs,<sup>11,12</sup> as is the case in the adult population. The CYP2C19 ultrarapid metabolizer (UM) and rapid metabolizer (RM) phenotypes are associated with lower plasma concentrations and a poorer response to treatment compared to the normal metabolizer (NM) phenotype. On the other hand, the poor metabolizer (PM) phenotype is asso-

**Table 1** Summary of the pharmacogenomic tests included in the genetics service portfolio of the Spanish National Health System.

Drug	Biomarker/ gene	Indication for pharmacogenomic testing
Abacavir	<i>HLA-B*57:01</i>	Candidates for treatment with abacavir (testing required per SmPC)
Voriconazole	<i>CYP2C19</i>	Prophylaxis of invasive fungal infections in high-risk allogeneic hematopoietic stem cell transplant recipients. Limited to cases of suspected lack of response to treatment and/or suspected adverse drug reaction
Atazanavir	<i>CYP2C19, UGT1A1</i>	Candidates for treatment with atazanavir concurrent with voriconazole and ritonavir (testing required per SmPC)
Fluoropyrimidines	<i>DPYD</i>	Candidates for treatment with fluoropyrimidines (testing required per SmPC)
Irinotecan	<i>UGT1A1</i>	Candidates for treatment with irinotecan
Thiopurines	<i>TPMT, NUDT15</i>	Candidates for treatment with thiopurines
Carbamazepine	<i>HLA-A*31:01, HLA-B*15:02</i>	Candidates for treatment with carbamazepine and at risk of a serious adverse event: 1) Asian ancestry; 2) personal or family history of skin toxicity induced by other drugs; 3) previous severe cutaneous adverse reaction induced by carbamazepine.
Phenytoin	<i>HLA-B*15:02</i>	Candidates for treatment with carbamazepine and at risk of a serious adverse event: 1) Asian ancestry; 2) personal or family history of skin toxicity induced by other drugs; 3) previous severe cutaneous adverse reaction induced by phenytoin
Oxcarbazepine	<i>HLA-B*15:02</i>	Candidates for treatment with carbamazepine and at risk of a serious adverse event: 1) Asian ancestry; 2) personal or family history of skin toxicity induced by other drugs; 3) previous severe cutaneous adverse reaction induced by oxcarbazepine
Siponimod	<i>CYP2C9</i>	Candidates for treatment with siponimod (testing required per SmPC)
Clopidogrel	<i>CYP2C19</i>	Limited to suspected nonresponse to treatment and/or suspected serious adverse event
Statins	<i>SLCO1B1</i>	Previous serious adverse drug reaction (rhabdomyolysis) to simvastatin
Ivacaftor	<i>CFTR</i>	Candidates for treatment with ivacaftor (testing required per SmPC)
Allopurinol	<i>HLA-B*58:01</i>	Candidates for treatment with allopurinol and at risk of a serious adverse drug reaction, especially patients of African or Asian ancestry
Proton pump inhibitors	<i>CYP2C19</i>	In the context of treatment of <i>Helicobacter pylori</i> , limited to cases of failure of second-line treatment and treatments following omeprazole
Eliglustat	<i>CYP2D6</i>	Candidates for treatment with eliglustat (testing required per SmPC)
Pimozide	<i>CYP2D6</i>	Candidates for treatment with pimozide
Tetrabenazine	<i>CYP2D6</i>	Candidates for treatment with tetrabenazine
Rasburicase	<i>G6PD</i>	Candidates for treatment with rasburicase and at high risk of glucose-6-phosphate dehydrogenase deficiency (testing required per SmPC)

Source: Nationwide catalog of genetic and genomic tests of the Spanish National Health System (<https://cgen.sanidad.gob.es/>).

ciated with higher plasma concentrations compared the NM phenotype, in addition to an increased risk of drug toxicity. It is recommended that treatment be optimized based on the pharmacogenetic profile in patients aged more than 1 year, increasing the dose for treating ulcers in UMs and RMs, and considering a reduction in prolonged regimens for PMs from age 2 to 3 months<sup>13</sup> (Table 3).

### **Abacavir, allopurinol, carbamazepine, oxcarbazepine and phenytoin-*HLA-A* and *HLA-B* genes**

*HLA-A* and *HLA-B* are genes that are part of the human major histocompatibility complex (human leukocyte antigen [HLA]) of the immune system and are highly polymorphic due

**Table 2** Drugs whose summary of product characteristics includes pharmacogenetic information according to the AEMPS and their use in pediatric care.

Drug	Biomarker/ gene	Involved subgroup	Type	Recommendations in SmPC	Nationwide NHS portfolio	Authorized pediatric indications	Other uses (off-label)
Abacavir	<i>HLA-B</i>	HLA-B*57:01 positive allele	Safety	Contraindication	Yes	HIV (>3 months)	Preterm infants, newborns, and infants aged less than 3 months
Acenocoumarol	<i>VKORC1</i>	c.1639G >A	Safety/effectiveness	Dose adjustment	No	Treatment and prevention of thromboembolic disorders	
Allopurinol	<i>HLA-B</i>	HLA-B*58:01 positive allele	Safety	Contraindication	Yes	Malignancies (especially leukemia), inborn errors of metabolism (eg, Lesch-Nyhan syndrome)	Leishmaniasis, prenatal asphyxia, hyperuricemia in chronic kidney disease
Amikacin	<i>MT-RNR1</i>	c.1555A >G	Safety	Consider alternative treatment	No	Severe infections by gram-negative bacteria	Infection by <i>Mycobacterium tuberculosis</i> in HIV-positive patient, other mycobacterial infections
Amitriptyline	<i>CYP2C19</i>	Poor metabolizers	Safety/effectiveness	Dose adjustment	Yes	Nocturnal enuresis, neuropathic pain	Depression, prophylaxis of migraine
Aripiprazole	<i>CYP2D6</i> <i>CYP2D6</i>	Poor metabolizers Poor metabolizers	Safety/effectiveness Safety/effectiveness	Dose adjustment Dose adjustment	Yes Yes	Schizophrenia (>15 years, oral route), manic episode in patient with bipolar disorder (>13 years)	Irritability in autism, attention-deficit/hyperactivity disorder, tics in Tourette syndrome, irritability in Asperger syndrome
Atazanavir	<i>CYP2C19</i>	Intermediate or poor metabolizers with concurrent treatment with voriconazole and ritonavir	Safety/effectiveness	Precautions for use	Yes	HIV (≥6 years)	
Atomoxetine	<i>CYP2D6</i>	Poor metabolizers	Safety/effectiveness	Dose adjustment	Proposed	Attention-deficit/hyperactivity disorder (≥6 years)	Narcolepsy with cataplexy
Atorvastatin	<i>SLCO1B1</i>	c.521T >C	Safety	Precautions for use	Yes	Primary hypercholesterolemia (>10 years)	Prevention of cardiovascular disease in children at high risk
Azathioprine	<i>TPMT</i>	Intermediate or poor metabolizers	Safety	Dose adjustment	Yes	Solid organ transplantation, inflammatory bowel disease, and other immune diseases (rheumatoid arthritis, lupus, dermatomyositis, etc)	Myasthenia gravis, polyarteritis nodosa, Duchenne muscular dystrophy, autoimmune thrombocytopenia, atopic dermatitis, or uveitis
Capecitabine	<i>NUDT15</i>	Intermediate or poor metabolizers	Safety	Dose adjustment	Yes		
	<i>DPYD</i>	Intermediate or poor metabolizers	Safety	Contraindication/ dose adjustment	Yes	No	

Table 2 (Continued)

Drug	Biomarker/ gene	Involved subgroup	Type	Recommendations in SmPC	Nationwide NHS portfolio	Authorized pediatric indications	Other uses (off-label)
Carbamazepine	<i>HLA-A</i>	HLA-A*31:01 positive allele	Safety	Contraindication	Yes	Epilepsy	Mood and conduct/disruptive behavior disorders
	<i>HLA-B</i>	HLA-B*15:02 positive allele	Safety	Contraindication	Yes		
Celecoxib	<i>CYP2C9</i>	Poor metabolizers or <i>CYP2C9</i> *3 carriers	Safety	Precautions for use/dose adjustment	Yes	No	Juvenile idiopathic arthritis ( $\geq 2$ years)
Citalopram	<i>CYP2C19</i>	Poor metabolizers	Safety/effectiveness	Dose adjustment	Yes	No	Prevention of atherothrombotic and thromboembolic events in atrial fibrillation. Secondary prevention of atherothrombotic events.
Clomipramine	<i>CYP2D6</i>	N/A	N/A	N/A	Yes	Obsessive-compulsive disorder, nocturnal enuresis	
Clopidogrel	<i>CYP2C19</i>	N/A	N/A	N/A	Yes	No	
	<i>CYP2C19</i>	Poor metabolizers	Effectiveness	Precautions for use	Yes		
Codeine	<i>CYP2D6</i>	Ultrarapid metabolizers	Safety	Precautions for use	Yes	Nonproductive cough, pain (>12 years of age without respiratory impairment). Restricted use in pediatric population (source: MUH [FV], 3/2015)	
Doxepin	<i>CYP2D6</i>	N/A	N/A	N/A	Yes	No	HIV (>3 months and weight > 3 kg)
Efavirenz	<i>CYP2B6</i>	Homozygous for c.516G >T	Safety	Precautions for use	No		
Elexacaftor/ lumacaftor/ivacaftor	<i>CFTR</i>	F508del (c.1521_1523delCTT), (c.350G >A), (c.532G >A), (c.1645A >C), (c.1646G >A), (c.1651G >A), (c.1652G >A), (c.3731G >A), (c.4046G >A), (c.3752G >A), (c.3763T >C)	Effectiveness	Indication	Proposed	Treatment of cystic fibrosis (> 6 years) with at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator gene ( <i>CFTR</i> )	
Eliglustat	<i>CYP2D6</i>	Indeterminate or ultrarapid metabolizers	Effectiveness/safety	Contraindication/ dose adjustment	Yes	No	Atrial and ventricular arrhythmias, especially those secondary to digoxin toxicity
Escitalopram	<i>CYP2C19</i>	Poor metabolizers	Effectiveness/safety	Dose adjustment	Yes	No	
Phenytoin	<i>CYP2C9</i>	Intermediate or poor metabolizers	Effectiveness/safety	Precautions for use	Yes	Status epilepticus, generalized tonic-clonic seizures, and partial seizures. Treatment and prevention of seizures in neurosurgery.	

**Table 2** (Continued)

Drug	Biomarker/ gene	Involved subgroup	Type	Recommendations in SmPC	Nationwide NHS portfolio	Authorized pediatric indications	Other uses (off-label)
Flecainide	<i>HLA-B</i>	HLA-B*15:02 positive allele	Safety	Contraindication	Yes		
	<i>CYP2D6</i>	N/A	N/A	N/A	Yes	(>12 years) Life-threatening ventricular arrhythmias. Prevention of symptomatic supraventricular arrhythmias in absence of structural heart disease. Patients with supraventricular tachycardia without underlying heart disease.	
Fluorouracil	<i>DPYD</i>	Intermediate or poor metabolizers	Safety	Contraindication/ dose adjustment	Yes	No	
Fluvastatin	<i>CYP2C9</i>	N/A	N/A	N/A	Yes	Heterozygous familial hypercholesterolemia (>9 years)	
Fluvoxamine	<i>CYP2D6</i>	N/A	N/A	N/A	Yes	Obsessive-compulsive disorder (>8 years)	
Gefitinib	<i>EGFR</i>	c.2573T >G	Effectiveness	Indication	No	No	
Haloperidol	<i>CYP2D6</i>	Poor metabolizers	Safety	Precautions for use	Yes	Schizophrenia (> 13 years). Aggressive behavior (>6 years) in autism or pervasive developmental disorders. Tourette syndrome (> 10 years).	Behavioral disorders associated with refractory aggression and hyperactivity, nausea and vomiting that do not respond to treatment or in palliative care patients
Ibuprofen	<i>CYP2C9</i>	N/A	N/A	N/A	Yes	Fever, pain, and inflammation (>6 years and weight >20 kg), inflammatory diseases, and rheumatic diseases such as juvenile idiopathic arthritis (> 6 months), ankylosing spondylitis, osteoarthritis, or arthritis. Children aged $\geq$ 12 years or with weight $\geq$ 40 kg. IV: patent ductus arteriosus in preterm infants born before 34 weeks.	Pancreatitis in cystic fibrosis

Table 2 (Continued)

Drug	Biomarker/ gene	Involved subgroup	Type	Recommendations in SmPC	Nationwide NHS portfolio	Authorized pediatric indications	Other uses (off-label)
Imipramine	<i>CYP2D6</i>	N/A	N/A	N/A	Yes	Nocturnal enuresis (>5 years)	Depression, hyperactivity associated with tics, behavioral disorders, pain/adjuvant therapy in cancer treatment
Irinotecan	<i>CYP2C19</i> <i>UGT1A1</i>	N/A Poor metabolizers	N/A Safety	N/A Dose adjustment	Yes Yes	No	Refractory solid and central nervous system tumors, relapsed or refractory neuroblastoma (in combination with temozolomide)
Ivacaftor	<i>CFTR</i>	F508del (c.1521_1523delCTT), (c.350G >A), (c.532G >A), (c.1645A >C), (c.1646G >A), (c.1651G >A), (c.1652G >A), (c.3731G >A), (c.4046G >A), (c.3752G >A), (c.3763T >C)	Effectiveness	Indication	Yes	Cystic fibrosis and with one of the following gating (class III) mutations in the <i>CFTR</i> gene: G551D, G1244E, G1349D, G178R, G551S, S1251 N, S1255 P, S549 N or S549R (> 6 months)	
Ivacaftor/lumacaftor	<i>CFTR</i>	F508del (c.1521_1523delCTT), (c.350G >A), (c.532G >A), (c.1645A >C), (c.1646G >A), (c.1651G >A), (c.1652G >A), (c.3731 G >A), (c.4046G >A), (c.3752G >A), (c.3763T >C)	Effectiveness	Indication	Proposed	Cystic fibrosis, homozygous for F508del (> 6 years)	
Ivacaftor/tezacaftor	<i>CFTR</i>	F508del (c.1521_1523delCTT), (c.350G >A), (c.532G >A), (c.1645A >C), (c.1646G >A), (c.1651G >A), (c.1652G >A), (c.3731G >A), (c.4046G >A), (c.3752G >A), (c.3763T >C)	Effectiveness	Indication	Proposed	Cystic fibrosis: homozygous for F508del or heterozygous for F508del with one of the following residual-function mutations: P67L, R117C, L206W, R352Q, A455E, D579G, 711 + 3A → G, S945L, S977F, R1070W, D1152H, 2789 + 5G → A, 3272-26A → G y 3849 + 10kbc → T (≥ 12 years)	

Table 2 (Continued)

Drug	Biomarker/ gene	Involved subgroup	Type	Recommendations in SmPC	Nationwide NHS portfolio	Authorized pediatric indications	Other uses (off-label)
Lamotrigine	<i>HLA-B</i>	HLA-B*15:02 positive	Safety	Contraindication	Yes	Partial and generalized seizures, including tonic-clonic seizures ( $\geq 13$ years). Seizures associated with Lennox-Gastaut syndrome (>2 years)	Bipolar disorder
Lansoprazole	<i>CYP2C19</i>	Poor metabolizers	Effectiveness/safety	Precautions for use	Yes	No	Prevention and treatment of reflux esophagitis. Treatment of duodenal and gastric ulcers. Eradication of <i>Helicobacter pylori</i> . Zollinger-Ellison syndrome
Lornoxicam	<i>CYP2C9</i>	Poor metabolizers	Effectiveness/safety	Precautions for use	Yes	No	
Mavacamten	<i>CYP2C19</i>	Poor, intermediate, normal, rapid and ultrarapid metabolizers	Effectiveness/safety	Dose adjustment	Proposed	No	
Meloxicam	<i>CYP2C9</i>	N/A	N/A	N/A	Yes	Exacerbations of osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis (>16 years)	Relief of signs and symptoms of juvenile idiopathic arthritis
Mercaptopurine	<i>NUDT15</i>	Intermediate or poor metabolizers	Safety	Dose adjustment	Yes	Acute lymphoblastic leukemia	Crohn disease in adolescents. Non-Hodgkin lymphoma
	<i>TPMT</i>	Intermediate or poor metabolizers	Safety	Dose adjustment	Yes		
Metoprolol	<i>CYP2D6</i>	N/A	N/A	N/A	Yes	No	High blood pressure, acute myocardial infarction, angina pectoris, and supraventricular tachycardia. Migraine prophylaxis. Congestive heart failure. Hypertrophic cardiomyopathy, control of aortic disease in Marfan syndrome, long QT syndrome
Omeprazole	<i>CYP2C19</i>	Poor metabolizers	Effectiveness/safety	Precautions for use	Yes	Reflux esophagitis and symptomatic treatment of heartburn and acid reflux (>1 year)	Severe erosive esophagitis, gastric ulcers, gastric hypersecretion, stress ulcer prophylaxis, IV route

Table 2 (Continued)

Drug	Biomarker/ gene	Involved subgroup	Type	Recommendations in SmPC	Nationwide NHS portfolio	Authorized pediatric indications	Other uses (off-label)
Ondansetron	<i>CYP2D6</i>	N/A	N/A	N/A	Yes	Treatment of duodenal ulcer caused by <i>Helicobacter pylori</i> (>4 years) Chemotherapy-induced nausea and vomiting ( $\geq 6$ months) Postoperative nausea and vomiting (>1 month)	Cyclic vomiting syndrome, recurrent vomiting associated with acute gastroenteritis
Oxcarbazepine	<i>HLA-B</i>	HLA-B*15:02 positive allele	Safety	Contraindication	Yes	Partial epileptic seizures with or without secondary generalization ( $\geq 6$ years)	
Pantoprazole	<i>CYP2C19</i>	Poor metabolizers	Effectiveness/safety	Precautions for use	Yes	Symptomatic gastroesophageal reflux disease ( $\geq 12$ years)	Erosive esophagitis and gastroesophageal reflux disease ( $\geq 5$ years)
Paroxetine	<i>CYP2D6</i>	N/A	N/A	N/A	Yes	No	
Pimozide	<i>CYP2D6</i>	Poor metabolizers	Effectiveness/safety	Precautions for use	Yes	Acute and chronic psychosis and anxiety disorders (very limited evidence in >3 years)	Tourette syndrome
Piroxicam	<i>CYP2C9</i>	Poor metabolizers	Effectiveness/safety	Precautions for use	Yes	Topical and symptomatic local relief of painful or inflammatory conditions (>12 years)	Pain and inflammation in inflammatory and rheumatic diseases
Pitavastatin	<i>SLCO1B1</i>	N/A	N/A	N/A	Proposed	Heterozygous familial hypercholesterolemia (>6 years)	
Propafenone	<i>CYP2D6</i>	N/A	N/A	N/A	Yes	Paroxysmal supraventricular tachycardia (atrial fibrillation, paroxysmal atrial flutter, Wolff-Parkinson-White syndrome), ventricular arrhythmias	IV route
Quetiapine	<i>CYP3A4</i>	N/A	N/A	N/A	Yes	No	
Rasburicase	<i>G6PD</i>	Patients with G6PDH deficiency	Safety	Contraindication	Yes	Acute hyperuricemia in malignant blood tumors with a high tumor burden and risk of rapid tumor lysis syndrome or rapid tumor reduction at the start of chemotherapy	

Table 2 (Continued)

Drug	Biomarker/ gene	Involved subgroup	Type	Recommendations in SmPC	Nationwide NHS portfolio	Authorized pediatric indications	Other uses (off-label)
Risperidone	<i>CYP2D6</i>	Poor and ultrarapid metabolizers	Effectiveness/safety	Precautions for use	Yes	Persistent aggression in behavioral disorders in children with below-average intellectual functioning or with diagnosed intellectual disability (>5 years)	Bipolar disorder (>10 years), schizophrenia (>13 years), Tourette syndrome, behavioral changes in autism spectrum disorders (>5 years)
Rosuvastatin	<i>SLCO1B1</i> <i>ABCG2</i>	c.521T > C c.421C >A	Safety Safety	Dose adjustment Dose adjustment	Proposed	Heterozygous familial hypercholesterolemia (>6 years)	
Sertraline	<i>CYP2C19</i>	Poor metabolizers	Effectiveness/safety	Precautions for use	Yes	Obsessive-compulsive disorder (>6 years)	
Simvastatin	<i>CYP2B6</i> <i>SLCO1B1</i>	N/A c.521 T >C	N/A Safety	N/A Precautions for use	Proposed Yes	Heterozygous familial hypercholesterolemia (male adolescents in Tanner stage II or above of pubertal development, and female adolescents at least one year after menarche, aged 10 to 17 years)	
Siponimod	<i>CYP2C9</i>	Intermediate or poor metabolizers	Effectiveness/safety	Dose adjustment	Yes	No	
Tamoxifen	<i>CYP2D6</i>	Poor metabolizers	Effectiveness/safety	Precautions for use	Yes	No	Pubertal, idiopathic, and drug-induced gynecomastia. Polyostotic fibrous dysplasia (McCune-Albright syndrome). Retinoblastoma
Tegafur	<i>DPYD</i>	Intermediate or poor metabolizers	Safety	Contraindication/ dose adjustment	Yes	No	
Tetrabenazine	<i>CYP2D6</i>	Ultrarapid, intermediate, or poor metabolizers	Effectiveness/safety	Dose adjustment	Yes	No	Choreic movement disorders, post-hypoxic chorea, postencephalitic hyperkinesia, Lesch-Nyhan syndrome, Tourette syndrome, generalized dystonia, dystonic cerebral palsy

**Table 2** (Continued)

Drug	Biomarker/ gene	Involved subgroup	Type	Recommendations in SmPC	Nationwide NHS portfolio	Authorized pediatric indications	Other uses (off-label)
Tioguanine	<i>NUDT15</i>	Intermediate or poor metabolizers	Safety	Dose adjustment	Yes	Acute lymphoblastic leukemia. Acute myeloid leukemia.	Lymphoblastic lymphoma
	<i>TPMT</i>	Intermediate or poor metabolizers	Safety	Dose adjustment	Yes		
Tobramycin	<i>MT-RNR1</i>	c.1555A >G	Safety	Consider alternative treatment	No	Serious infections caused by susceptible aerobic gram-positive bacteria or gram-negative bacilli, including <i>Pseudomonas aeruginosa</i> , and enterobacteria Pain (>3 years)	
Tramadol	<i>CYP2D6</i>	Poor and ultrarapid metabolizers	Effectiveness/safety	Precautions for use	Yes		
Venlafaxine	<i>CYP2D6</i>	N/A	N/A	N/A	Yes	No	Depression, generalized anxiety and social phobia, panic disorder, cataplexy and other abnormal manifestations of REM sleep. Attention- deficit/hyperactivity disorder and autism spectrum disorder.
Voriconazole	<i>CYP2C19</i>	Intermediate or poor metabolizers	Effectiveness/safety	Precautions for use	Yes	Treatment and prevention of fungal infections ( $\geq 2$ years)	
Vortioxetine	<i>CYP2D6</i>	Poor metabolizers	Effectiveness/safety	Precautions for use	Proposed	No	
Zuclopenthixol	<i>CYP2D6</i>	N/A	N/A	N/A	Yes	No	

Abbreviation: HIV, human immunodeficiency virus.

to the need to present a broad range of peptides for immune recognition.<sup>14</sup> Some alleles of these genes have been associated with T-cell-mediated hypersensitivity reactions and serious adverse skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug-induced hypersensitivity reaction with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis following administration of certain drugs, especially in certain ethnic groups.<sup>15,16</sup> Among them, the HLA-B\*57:01 allele is associated with hypersensitivity reactions following administration of abacavir, a nucleoside reverse transcriptase inhibitor, so testing of all candidates for treatment with this drug is recommended before treatment initiation, in addition to the use of alternative drugs if the test is positive.

Other examples of HLA risk alleles include HLA-B\*58:01 (associated with allopurinol-induced Stevens-Johnson syndrome/toxic epidermal necrolysis in Han Chinese, Malays, Thais, Europeans, and Koreans), HLA-B\*15:02 (phenytoin-induced Stevens-Johnson syndrome/toxic epidermal necrolysis in Han Chinese and Thais), and HLAB\*15:02 (toxicity induced by carbamazepine and oxcarbazepine in Han Chinese, Thais, Koreans, and Malays). In addition, the HLA-A\*31:01 allele may increase the risk of carbamazepine-induced skin reactions, with a stronger association in the European and Japanese populations. In all these cases, the presence of one or two copies of the risk allele is a contraindication for the drug, and testing is recommended in subgroups of patients considered at risk, as well as in patients with a family history of hypersensitivity reactions associated with these drugs. All available guidelines extrapolate the adult recommendation to the pediatric population on the basis that this risk association is independent of age, with the exception of phenytoin, for which there is mention that the information is derived from studies that included children.

In the case of phenytoin, the guideline also includes dose adjustment recommendations based on the CYP2C9 phenotype assignment, as this is the enzyme chiefly responsible for metabolizing this drug. Since CYP2C9 activity in children approximates adult levels starting from age 5 months to 2 years, it is recommended that dose adjustments be applied from age 2 years.<sup>17</sup> However, one of the most common uses of phenytoin in the pediatric population is the management of neonatal seizures, and the genotype-enzyme activity correlation is not well established in the neonatal population, so the practical utility of testing is limited in this case.

### Voriconazol-CYP2C19

Voriconazole is a broad-spectrum triazole antifungal agent indicated in adults and children aged 2 years and older for the treatment and prophylaxis of fungal infections.<sup>18</sup>

Its metabolism is complex and depends mainly on the CYP3A4, CYP2C19, and CYP2C9 enzymes, which metabolize approximately 70% to 75% of the drug, while the remaining 25% to 30% is metabolized by enzymes from the flavin-containing monooxygenase (FMO) family.<sup>4</sup> Although the expression of CYP2C19 and FMO3 is similar in children and adults, their contribution to the clearance of voriconazole seems to be higher in children, while CYP3A4 would play a larger role in adults.<sup>19</sup>

Different studies suggest that CYP2C19 variants account for 50% to 55% of the variation in voriconazole metabolism.<sup>20</sup> The presence of these variants may give rise to the phenotypes mentioned above (UM, RM, intermediate metabolizer [IM], PM), which have an impact on voriconazole exposure.

In the pediatric age group, PMs and IMs exhibit higher plasma concentrations of voriconazole compared to NMs, while RMs do not have significantly different concentrations compared to NMs. In contrast, UMs have decreased voriconazole concentrations. There is evidence that voriconazole exposure is greater in IM or PMs, which may require dose adjustments to minimize the risk of toxicity. It is important to monitor concentrations in these patients and adjust the dose as needed.<sup>21</sup>

Dosing recommendations for children and adolescents are extrapolated from adults, except for RMs, for whom it is recommended to initiate treatment with the standard dose and monitor plasma concentrations.

### Tacrolimus-CYP3A5

Tacrolimus is an immunosuppressant in the calcineurin inhibitor group widely used in pediatrics, chiefly for graft-versus-host disease prophylaxis in solid-organ transplant recipients (kidney, liver, heart).<sup>5</sup>

Tacrolimus is largely metabolized in the liver and the intestinal wall by CYP3A5 and CYP3A4. CYP3A5 variants may affect the pharmacokinetics of tacrolimus, explaining 50% of interindividual variability.<sup>22</sup> Nearly 80% of individuals of European ancestry are PMs, so they require lower doses than NMs or IMs. For this reason, the standard dose of tacrolimus is adjusted for PMs.

The effect of the CYP3A5 genotype in the pharmacokinetics of tacrolimus in pediatric populations has been studied in different clinical contexts,<sup>23</sup> and most studies have been conducted in kidney transplant recipients.<sup>24,25</sup> In patients with NM (CYP3A5\*1/\*1) or IM (CYP3A5\*1/\*3) phenotypes, tacrolimus trough concentrations tend to be 1.5 to 2 times lower compared to PMs starting from the first weeks of treatment to up to one year post transplantation.<sup>25-27</sup> This has led to recommendation of a higher initial dose compared to the dose recommended for PMs.

It should be noted that other factors, such as age or concomitant treatment, may contribute to the interindividual variability in tacrolimus exposure in children. Regardless of the genotype, therapeutic drug monitoring is recommended to ensure concentrations within the therapeutic range established for immunosuppression.

### Aminoglycosides-MT-RNR1

Aminoglycosides are authorized for pediatric use for treatment of serious infections caused by gram-negative bacteria. These drugs have notable side effects, such as nephrotoxicity, vestibulotoxicity, and sensorineural hearing loss (cochleotoxicity)

MT-RNR1 is a gene that encodes the 12 s rRNA subunit and is the mitochondrial homologue of the prokaryotic 16S rRNA. Some MT-RNR1 variants (m.1095T >C; m.1494C >T; m.1555A >G) more closely resemble the bacterial 16 s rRNA subunit and result in increased risk of aminoglycoside-induced

**Table 3** Drugs used in the pediatric population for which a Clinical Pharmacogenomics Implementation Consortium guideline is available.

CPIC	Gene	Type	Pediatric recommendation in guideline	Specific pediatric recommendation	Summary of recommendation	Date of initial publication	Date of last update
Abacavir <sup>43</sup>	<i>HLA-B</i>	Safety	No	No Pediatric extrapolation of adult recommendation	Contraindicated in <i>HLA-B*57:01</i> carriers	Apr-12	May-14
Nonsteroidal anti-inflammatory drugs <sup>44</sup> (celecoxib, ibuprofen, flurbiprofen, lornoxicam and meloxicam)	<i>CYP2C9</i>	Safety	Yes (adolescents)	No  Pediatric extrapolation of adult recommendation. Enzyme activity maturity from 3 years	<i>CYP2C9</i> IM (activity = 1): start treatment at minimum effective dose <i>CYP2C9</i> PM: start treatment at 25%-50% of minimum effective dose. If titration is necessary, wait until steady state is achieved <i>Meloxicam</i> : <i>CYP2C9</i> IM (activity = 1): initiate treatment with 50% minimum effective dose <i>CYP2C9</i> PM: consider alternative NSAID that is not metabolized via <i>CYP2C9</i> or has a shorter half-life	Mar-20	Mar-20
Allopurinol <sup>45</sup>	<i>HLA-B</i>	Safety	No	No Pediatric extrapolation of adult recommendation	Contraindicated in <i>HLA-B*58:01</i> carriers	Feb-13	Jun-15
Aminoglycosides <sup>28</sup>	<i>MT-RNR1</i>	Safety	Yes	No	Contraindicated in carriers of risk variants in <i>MT-RNR1</i> gene (m.1095T >C; m.1494C >T; m.1555A >G)	May-21	May-21
Inhalational anesthetics Succinylcholine <sup>46</sup>	<i>RYR1</i> <i>CACNA1S</i>	Safety	Yes	Recommendations independent of patient age, applicable to adult and pediatric patients from birth No	Contraindicated in patients carrying risk variants of <i>RYR1</i> and <i>CACNA1S</i> genes	Sep-19	Dec-23

**Table 3** (Continued)

CPIC	Gene	Type	Pediatric recommendation in guideline	Specific pediatric recommendation	Summary of recommendation	Date of initial publication	Date of last update
SSRI antidepressants <sup>38</sup>	<i>CYP2D6</i> <i>CYP2C19</i>	Efficacy and safety	Yes (children and adolescents)	No	<i>Citalopram and escitalopram</i> : <i>CYP2C19</i> UM and PM: contemplate the use of another SSRI not metabolized via <i>CYP2C19</i> RM: if the desired effect is not achieved with the standard dose, contemplate the use of another SSRI not metabolized via <i>CYP2C19</i> IM: initiate standard dose with slower titration	Apr-23	Apr-23
	<i>CYP2B6</i>						
	<i>SLC6S4</i>						
	<i>HTR2A</i>						
Tricyclic antidepressants <sup>41</sup>	<i>CYP2D6</i>	Efficacy and safety	Yes (children and adolescents)	No	CYP2C19 UM, RM and PM: avoid use, consider alternative drug not metabolized via <i>CYP2C19</i> CYP2D6 UM and PM: avoid use, consider alternative drug not metabolized by <i>CYP2D6</i> CYP2D6 IM: reduce dose by 25%	May-13	Oct-19
	<i>CYP2C19</i>						
Atazanavir <sup>48</sup>	<i>UGT1A1</i>	Safety	Yes	No Pediatric extrapolation of adult recommendation	UGT1A1 PM: consider alternative treatment due to high probability of developing jaundice	Sep-15	Nov-17

**Table 3** (Continued)

CPIC	Gene	Type	Pediatric recommendation in guideline	Specific pediatric recommendation	Summary of recommendation	Date of initial publication	Date of last update
Atomoxetine <sup>49</sup>	CYP2D6	Efficacy and safety	Yes	Yes	CYP2D6 UM and NM (activity score $\geq 1$ ): dose may be increased after 3 days of treatment CYP2D6 PM: initiate standard starting dose with increase from day 14 if necessary	Feb-19	Oct-19
Beta-blockers <sup>42</sup> (metoprolol)	CYP2D6 ADRB1 ADRB2 ADRA2C	Safety	Yes	No	CYP2D6 PM: initiation at minimum effective dose with slow titration. In the case of adverse events, consider a different beta-blocker	Jul-24	Jul-24
Carbamazepine Oxcarbazepine <sup>50</sup>	GRK4 GRK5 HLA-A HLA-B	Safety	Yes	No Pediatric extrapolation of adult recommendation	Drugs contraindicated in HLA-B*15:02 and HLA-A*31:01 carriers	Sep-13	Dec-17
Clopidogrel <sup>51</sup>	CYP2C19	Efficacy	Yes	No Pediatric extrapolation of adult recommendation	CYP2C19 IM and PM: avoid use of clopidogrel, consider treatment with alternative antiplatelet medication	Aug-11	Jan-22
Efavirenz <sup>36</sup>	CYP2B6	Safety	Yes	Yes	<i>Patients aged <math>\geq 3</math> months and &lt; 3 years.</i> CYP2B6 PM: reduce dose based on patient weight 5 to < 7 kg: 50 mg 7 to < 14 kg: 100 mg 14 to < 17 kg: 150 mg $\geq 17$ kg: 150 mg <i>Patients &gt; 3 years with weight &lt; 40 kg:</i> no dosing recommendations based on pharmacogenetic profile. <i>Patients weighing <math>\geq 40</math> kg:</i> CYP2B6 IM: consider starting daily dose of 400 mg CYP2B6 PM: consider starting daily dose of 400-200 mg	Apr-19	Apr-19

Table 3 (Continued)

CPIC	Gene	Type	Pediatric recommendation in guideline	Specific pediatric recommendation	Summary of recommendation	Date of initial publication	Date of last update
Statins <sup>52</sup>	<i>SLCO1B1</i>	Safety	Yes	No	<p><i>All statins:</i>  <i>SLCO1B1</i> intermediate and poor function: specific recommendation for each indication and statin</p> <p><i>Rosuvastatin:</i>  <i>ABCG2</i> poor function: consider doses no greater than 20 mg or alternative treatment options</p> <p><i>Fluvastatin:</i>  <i>CYP2C9</i> IM: avoid doses greater than 40 mg or consider alternative treatment options  <i>CYP2C9</i> PM: avoid doses greater than 20 mg or consider alternative treatment options</p>	Jan-22	Jan-22
	<i>ABCG2</i>						
	<i>CYP2C9</i>						
Phenytoin <sup>53</sup>	<i>HLA-B</i>	Safety	Yes (recommendation based on <i>CYP2C9</i> in children aged > 2 years)	No	<p>Contraindicated in HLA-B*15:02 carriers</p> <p>In patients who do not carry HLA-B*15:02:  <i>CYP2C9</i> IM (activity score = 1): consider 25% reduction in initial dose + therapeutic drug monitoring  <i>CYP2C9</i> PM (activity score = 0): consider 50% reduction in initial dose + therapeutic drug monitoring</p>	Nov-14	Aug-20
	<i>CYP2C9</i>						
Fluoropyrimidines <sup>54</sup>	<i>DPYD</i>	Safety	Yes	No	<p>DPYD IM (activity score 1.5): consider 25% reduction in starting dose  DPYD IM (activity score 1): consider reducing starting dose by 25%  DPYD PM (activity score 0-0,5): avoid the use of fluoropyrimidines</p>	Dec-13	Oct-17

Table 3 (Continued)

CPIC	Gene	Type	Pediatric recommendation in guideline	Specific pediatric recommendation	Summary of recommendation	Date of initial publication	Date of last update
Proton pump inhibitors <sup>13</sup>	<i>CYP2C19</i>	Efficacy and safety	Yes (>1 year)	No	CYP2C19 UM: Increase starting daily dose by 100%. (Daily dose may be given in divided doses) CYP2C19 NM and RM: consider increasing dose by 50%-100% for the treatment of erosive esophagitis and duodenal ulcer caused by <i>Helicobacter pylori</i> infection CYP2C19 IM and PM: for chronic therapy lasting more than 12 weeks, consider 50% reduction in daily dose	Aug-20	Aug-20
Ivacaftor <sup>55</sup>	<i>CFTR</i>	Efficacy	Yes (>6 years)	No	Use in patients carrying described G551D- <i>CFTR</i> variants	Mar-14	May-19
Ondansetron Tropisetron <sup>56</sup>	<i>CYP2D6</i>	Efficacy	Yes (>1 month)	No	CYP2D6 PM: consider alternative antiemetic not chiefly metabolized via CYP2D6	Dec-16	Oct-19
Opioids <sup>57</sup> (codeine and tramadol)	<i>CYP2D6</i> <i>OPRM1</i> <i>COMT</i>	Efficacy and safety	Yes (>12 years)	No	CYP2D6 UM and PM: avoid use of codeine and tramadol	Feb-12	Dec-20

**Table 3** (Continued)

CPIC	Gene	Type	Pediatric recommendation in guideline	Specific pediatric recommendation	Summary of recommendation	Date of initial publication	Date of last update
Pegylated interferon alfa <sup>58</sup>	<i>IFNL3</i>	Efficacy	No	No	Patients with CT or TT genotype (rs12979860 variant) do not respond well to ribavirin + PEG-IFN- $\alpha$ -based regimens	Feb-14	Feb-14
Tacrolimus <sup>22</sup>	<i>CYP3A5</i>	Efficacy	Yes	No Pediatric extrapolation of adult recommendation	CYP3A5 NM and IM: Increase starting dose 1.5-2 times + therapeutic drug monitoring	Jul-15	Jul-15
Tamoxifen <sup>59</sup>	<i>CYP2D6</i>	Efficacy	No	No Pediatric extrapolation of adult recommendation	CYP2D6 IM and PM: consider alternative treatment; if not possible, consider dose increase	Jan-18	Jan-18
Thiopurines <sup>31</sup> (tioguanine, mercaptopurine, azathioprine)	<i>TPMT</i>	Safety	Yes	No	TPMT IM: start with reduced starting doses (30%–80% of normal dose) TPMT PM: start with drastically reduced doses (based on drug/ indication). Azathioprine: For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy	Mar-11	Nov-18
	<i>NUDT15</i>			Pediatric extrapolation of adult recommendation	NUDT15 IM: Start with reduced starting doses (30–80% of normal dose)		

**Table 3** (Continued)

CPIC	Gene	Type	Pediatric recommendation in guideline	Specific pediatric recommendation	Summary of recommendation	Date of initial publication	Date of last update
Various drugs <sup>60</sup>	<i>G6PD</i>	Safety	Yes	No Pediatric extrapolation of adult recommendation	NUDT15 PM: start with drastically reduced doses (based on drug/indication). Azathioprine: For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy G6PD deficiency: avoid contraindicated drugs	Aug-14	Aug-22
Voriconazole <sup>21</sup>	<i>CYP2C19</i>	Efficacy and safety	Yes	Yes	CYP2C19 UM: consider use of an alternative antifungal agent CYP2C19 RM, NM, IM: initiation with standard dose and therapeutic drug monitoring CYP2C19 PM: consider use of an alternative antifungal if reducing the initial dose is not an option	Dec-16	Dec-16
Warfarin <sup>61</sup>	<i>CYP2C9</i> <i>VKORC1</i> <i>CYP4F2</i>	Safety	Yes	Yes	For patients of European ancestry with CYP2C9*2, CYP2C9*3 or/and VKORC1-1639 genotypes, use validated algorithm	Oct-11	Dec-16

Abbreviations: CPIC, Clinical Pharmacogenomics Implementation Consortium; IM, intermediate metabolizer; NM, normal metabolizer; NSAID, nonsteroidal anti-inflammatory drug; PM, poor metabolizer; RM, rapid metabolizer; SSRI, selective serotonin reuptake inhibitor; UM, ultrarapid metabolizer.  
The additional references for [Table 3](#) can be found in Appendix B.

hearing loss. Therefore, use of aminoglycosides should be avoided in individuals with these *MT-RNR1* variants, unless the high risk of permanent hearing loss is outweighed by the severity of infection and safe or effective alternative therapies are not available.<sup>28</sup> The recommendations are independent of patient age and apply to adult and pediatric patients from birth.

### Thiopurines (azathioprine, mercaptopurine, tioguanine)-*TPMT*, *NUDT15*

Thiopurines (tioguanine, mercaptopurine and azathioprine) are drugs whose use in the pediatric population include treatment of acute lymphoblastic leukemia and inflammatory bowel disease. Their toxicity profile includes gastrointestinal adverse events, myelosuppression and hepatotoxicity. The two latter are most concerning and are dose-dependent.<sup>29</sup>

Thiopurine S-methyltransferase (*TPMT*) and *NUDT15* hydroxylase 15 (*NUDT15*) are essential enzymes in thiopurine metabolism. Thus, individuals with decreased *TPMT* or *NUDT15* activity are at high risk of serious adverse events. There is evidence of a strong correlation between the *TPMT* and *NUDT15* genotype and the metabolizer phenotype for these enzymes.<sup>30</sup>

None of the guidelines, save for the 2013 CPIC guideline, mentions the pediatric population in its recommendations.<sup>31</sup> The CPIC guideline addresses dose adjustments in pediatric patients, in spite of the scarcity of data for this population. Thus, since the dosing recommendations for thiopurines in adults are given in relation to kilograms of body weight or body surface area, the guideline states that it can be assumed (as is actually done in practice) that the recommended dose adjustments can be extrapolated to children.

### Atomoxetine-*CYP2D6*

Atomoxetine is a potent and highly selective inhibitor of the presynaptic norepinephrine transporter used in children aged 6 years and older to treat attention-deficit/hyperactivity disorder. It is also used off-label in narcolepsy with cataplexy.

Multiple factors affect the pharmacokinetics of atomoxetine. It is predominantly metabolized by *CYP2D6* and, to a much lesser extent, *CYP2C19*.<sup>32</sup> Plasma concentrations of atomoxetine in PMs have been found to be up to eight-fold higher compared to NMs.<sup>33</sup> This is consistent with the increased incidence of adverse events in PMs compared to RMs in the pediatric population, especially decreased appetite, combined insomnia and combined depression.<sup>34</sup>

In pediatric *CYP2D6* PMs, a lower starting dose is recommended, along with a slower escalation or even no escalation if the desired therapeutic effect is achieved. The combination of genotyping and therapeutic drug monitoring, if available, is the best approach to ensure safe use.<sup>35</sup> If monitoring is not possible, caution is particularly recommended in the case of concurrent treatment with *CYP2D6* inhibitors (fluoxetine, fluvoxamine, quinidine, terbinafine), as they can increase plasma concentrations of atomoxetine.

### Recommendations for other drugs used less frequently in pediatrics

Efavirenz is a nonnucleoside reverse transcriptase inhibitor. It is used to treat human immunodeficiency virus in combination with other drugs in children aged 3 months or older and weighing more than 3 kg. At present, its use in pediatric patients is limited, as there are alternatives with better tolerability. The SmPC notes that patients homozygous for the G516 T *CYP2B6* variant may have higher plasma concentrations of efavirenz. The guideline provides dosing recommendations based on the *CYP2B6* phenotype and the age and weight of the patient.<sup>36</sup>

In the case of drugs such as clopidogrel, ondansetron, tricyclic antidepressants, or serotonin reuptake inhibitors, the use of clinical guidelines for dose adjustment is well established in the adult population, but there are few specific pharmacogenetic studies (usually small) on which to base specific recommendations for the pediatric and adolescent population. In addition, the frequent off-label use of these drugs further hinders the availability of evidence specific for these diseases. In most cases, the guidelines mention the possibility of extrapolating adult recommendations based on the pharmacokinetics of drug-gene interaction and the maturation of the involved enzymatic pathways, if use of these drugs is necessary.

The only guidelines that refer to specific recommendations for the pediatric and adolescent populations are the selective serotonin reuptake inhibitors, tricyclic antidepressants, and the recently published beta-blocker guidelines.

In the case of selective serotonin reuptake inhibitors, the guideline indicates that citalopram, escitalopram, and sertraline are the drugs for which the most pharmacogenetic data are available to support gene-based prescribing in pediatric and adolescent populations, although these data are mainly derived from small pharmacokinetic studies.<sup>37,38</sup>

In respect of amitriptyline, the guideline notes that due to the lower dosage used for treatment of neuropathic pain in pediatric patients (eg, 0.1 mg/kg/day) it is less likely that PMs and IMs will experience adverse effects due to supratherapeutic plasma concentrations of amitriptyline, so dose adjustments are only recommended for indications requiring higher doses.

The beta-blocker guideline mentions two pharmacogenetic studies in the pediatric population, one on the association of *ADRB1* and *CYP2C9* variants with the efficacy of atenolol and losartan in Marfan syndrome, and another on the impact of *CYP2D6* polymorphisms on the efficacy of propranolol for treatment of hemangioma.<sup>39,40</sup> However, definite conclusions cannot be drawn based on the results of these studies. The guideline concludes that it may be appropriate, with caution, to extrapolate the recommendations given for the adult population to *CYP2D6* and metoprolol (in PMs, initiation with a lower dose and slower progressive titration, watching for the potential development of bradycardia), since the *CYP2D6* genotype seems to correlate to enzyme activity from 2 weeks post birth.

Other drugs such as statins, fluoropyrimidines, or tamoxifen are rarely used in the pediatric population, so there are no pharmacogenetic studies or specific recommendations for them. Pharmacogenetic tests are not routinely performed in

the pediatric population, but it should be noted that as genotyping techniques advance, prospective testing with broad gene panels is becoming increasingly common. In such cases, the information will be available for future use and will be helpful if the use of these drugs is contemplated.

## Implementation and limitations

In the pediatric population, the problems generally encountered in the implementation of pharmacogenetics (lack of training for health care staff, lack of experts in pharmacogenetics, the dispersion of tests among different services, limited interest on the part of hospital administrators, etc) are exacerbated by the dearth of pediatric research establishing differential characteristics in reference to the population normally included in clinical trials and observational studies. Despite these difficulties, the update of the genomic service portfolio, with the inclusion of pharmacogenomics, is a clear boost to its implementation. The creation of multidisciplinary groups to engage in the implementation of pharmacogenetics in each hospital is key, as is the inclusion of pediatric specialists in these groups to ensure the rapid and safe application of pharmacogenetics in the pediatric population.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.anpede.2025.503936>.

## Declaration of competing interest

The authors have no conflicts of interest to declare.

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