Review

Pharmacogenetics in Neuroblastoma: What Can Already Be Clinically Implemented and What Is Coming Next?

Gladys G. Olivera [1,2], Andrea Urtasun [3,4], Luis Sendra [1,2,*], Salvador F. Aliño [1,2,*], Yania Yáñez [3], Vanessa Segura [3], Pablo Gargallo [3], Pablo Berlanga [5], Victoria Castel [3], Adela Cañete [3] and María José Herrero [1,2]

1   Pharmacogenetics and Gene Therapy Platform, IIS La Fe, Hospital La Fe, Torre A-Lab 4.03, Av. Fernando Abril Martorell 106, 46026 Valencia, Spain; gladys_guadalupe@iislafe.es (G.G.O.); maria.jose.herrero@uv.es (M.J.H.)
2   Department of Pharmacology, Faculty of Medicine, University of Valencia, Av. Blasco Ibáñez 15, 46010 Valencia, Spain
3   Pediatric Oncology Unit, Hospital Universitario y Politécnico La Fe, Av. Fernando Abril Martorell 106, 46026 Valencia, Spain; andrea.urtasun@sjd.es (A.U.); yanyez_yan@gva.es (Y.Y.); segura_van@gva.es (V.S.); pablogt28@gmail.com (P.G.); castel_vic@gva.es (V.C.); canyete_ade@gva.es (A.C.)
4   Oncohematology Department, Hospital Sant Joan de Deu, Passeig Sant Joan de Déu 2, Esplugues de Llobregat, 08950 Barcelona, Spain
5   Department of Pediatric and Adolescent Oncology, Institute Gustave Roussy Center, Rue Edouard Vaillant 114, 94800 Villejuif, France; pablo.berlanga@gustaveroussy.fr
*   Correspondence: luis.sendra@uv.es (L.S.); alino@uv.es (S.F.A.)

Abstract: Pharmacogenetics is one of the cornerstones of Personalized Precision Medicine that needs to be implemented in the routine of our patients' clinical management in order to tailor their therapies as much as possible, with the aim of maximizing efficacy and minimizing toxicity. This is of great importance, especially in pediatric cancer and even more in complex malignancies such as neuroblastoma, where the rates of therapeutic success are still below those of many other types of tumors. The studies are mainly focused on germline genetic variants and in the present review, state of the art is presented: which are the variants that have a level of evidence high enough to be implemented in the clinic, and how to distinguish them from the ones that still need validation to confirm their utility. Further aspects as relevant characteristics regarding ontogeny and future directions in the research will also be discussed.

Keywords: SNP (single nucleotide polymorphism); chemotherapy; drug label; clinical implementation guidelines

1. Introduction

Neuroblastoma (NB), the most common solid extracranial malignancy during childhood, has its origin in the adrenal medulla or paraspinal ganglia (sympathetic nervous system) during the period of development [1] and shows great phenotypic heterogeneity: some infants have spontaneous regression of the tumor while others present disease progression event after intensive multimodal treatment [2].

Although translational and clinical research has evolved considerably in recent years, in the cases requiring treatment, the prognosis of children with High-Risk Neuroblastoma (HR-NB) remains very poor. Despite the fact that it only represents around 8% of all pediatric cancers, it causes 15% of all deaths due to cancer in children. Barely 40% of the children diagnosed survive longer than 5 years [3,4]. Indeed, when metastatic relapse occurs, there is no curative treatment, and the overall survival rate after relapse is around 12 months. Thus, the lack of effective treatment continues to be a major concern for pediatric oncologists. Another relevant aspect to take into account is that >50% of survivor children

face sequelae derived from chemotherapy toxicity along with their life, reinforcing the idea that chemotherapy needs to be optimized [5].

At this point, doctors need tools to apply the best available treatment to each patient in terms of maximizing efficacy and minimizing toxicity. Pharmacogenetics (PGx), one of the cornerstones of Precision Personalized Medicine, is the study of variants in the patient's germline (constitutive) DNA related to the efficacy and safety of drugs. Tumor (somatic) genetic variants can also be considered, but they are out of the scope of this review. The most abundant genetic variants influencing PGx are the Single Nucleotide Polymorphisms (SNPs), accounting for approximately 90% of human genome variability [6,7]. However, key variants influencing PGx also include genomic insertions, deletions, and repeats, as well as genetic copy number variations (CNVs).

The state of the art in PGx is divided into two categories: there is an already well-defined group of relevant associated drug-SNP pairs whose level of scientific-clinical evidence offers the highest quality, robust enough to be implemented in routine clinical practice. On the other side, drug-SNP pairs with less core evidence require further translational research to validate their usefulness in the real clinical setting.

In this review, the current situation of both categories is presented. The first part describes the genetic variants that can already be implemented in the clinical setting, and doctors can use them to adjust the NB chemotherapeutic treatment. After that, a view of the main variants that are currently under investigation to validate or discard their utility in NB treatment is presented. The last part of the review describes further considerations under a translational research perspective. The drugs included are those employed for (1) Induction treatments: cisplatin, vincristine, carboplatin, etoposide, cyclophosphamide, topotecan, doxorubicin; (2) Consolidation: busulfan, melphalan; and finally (3) Maintenance therapy and others: 13-cis-retinoic acid (isotretinoin), dinutuximab beta, interleukin 2, granulocyte and macrophage-colonies stimulating factor (GM-CSF) and radiotherapy.

2. Pharmacogenetic Variants for Clinical Implementation

Relevant institutions and scientific societies worldwide agree on the use of three main pillars as the references to identify those genetic variants with the highest level of evidence to be implemented in the clinic. These three cornerstones are the indications of drug regulatory agencies, PharmGKB (Pharmacogenomics Knowledge Base) [8], and relevant international consortia of experts developing clinical guidelines for PGx implementation.

2.1. Drug Regulatory Agencies

Regulatory agencies as the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Pharmaceuticals and Medical Devices Agency from Japan (PMDA), and Health Canada Santé Canada (HCSC), amongst others [9–12], recommend in the Drug Labels a genetic test prior to the use of many drugs they approve. The Drug Label indicates if the test is required, recommendable, actionable, or simply informative [8]. At this point, it must be remarked that any requirement of a specific action in the drug label must be considered a legal requirement, with consequences in the case of disregard.

2.2. PharmGKB Clinical Annotations

PharmGKB, is a free access database created, curated, and managed by the University of Stanford and funded by US National Institutes of Health (NIH) and National Institute of General Medicine Science (NIGMS) [8]. It compiles most of the existing PGx information, from many different databases, including PubMed, under a Creative Commons license. It counts with a group of experts working on the dissemination of knowledge about the impact of human genetic variation on drug responses and on the translation of PGx into clinical practice. In fact, the website (www.pharmgkb.org, accessed on 25 June 2021) includes not only the information of its own curation from published data, the 'Clinical Annotations', but also that of the Drug Labels and the reports by Experts Consortia.

Clinical Annotations are the curated results obtained by PharmGKB's experts after publications review for assigning different levels of evidence in the association of a genetic variant with efficacy, toxicity, metabolism/pharmacokinetics, and dosage of a drug. This 'Level of Evidence' ranks from 1 to 4, being 1 the one meeting the highest criteria. Level 2 is tagged as "moderate", while 3 and 4 are "low" and "unsupported," respectively. Very recently, these criteria have incorporated a new scoring system.

2.3. Clinical Implementation Guidelines

These are drug adjustment guidelines published by experts' consortia to provide recommendations about what actions the prescriber should consider according to patient genotype. The main consortia are the Clinical Pharmacogenetics Implementation Consortium (CPIC) [13], the Royal Dutch Association for the Advancement of Pharmacy—Pharmacogenetics Working Group (DPWG) [14], but also other professional and scientific societies [15]. PharmGKB also compiles this information on the website and provides links to the complete articles under the section 'Prescribing Info-Clinical Guideline Annotations'.

According to these three pillars, Table 1 shows the revised drugs that meet at least one criterion of the three pillars: PGx information in the drug label according to Drug Regulatory Agencies, PharmGKB Clinical Annotations with Level of Evidence 1 or 2, Clinical Implementation Guideline elaborated by an international expert Consortium. It must be underlined that, as previously stated, PharmGKB has just performed relevant modifications, beginning approximately on 25 March 2021. For caution, in this table, we have considered the immediate previous information regarding Clinical Annotations, but the current modifications have been marked.

Three drugs have genetic recommendations in Drug Labels according to different regulatory agencies, but these recommendations are not strictly PGx. They are mainly related to the use for which the drug is intended, its clinical indication, and the genes to be analyzed are not in the constitutive DNA of the patient but in the tumor. These drugs are Busulfan (FDA: *ABL1* and *BCR* genes), 13-cis-retinoic acid (not isotretinoin, but tretinoin has required testing for *PML* and *RARA* genes in the FDA Drug Label, the same in Health Canada Santé Canada Label, and also, but at an informative level, in the Japanese regulatory agency). The same situation applies to vincristine but, apart from Drug Label, it has a Clinical Annotation.

Dinutuximab contains information in the FDA label regarding *MYCN* in the clinical trials performed.

In this sense, only the indications for *TPMT* regarding Cisplatin are really related to germline variants and a toxic event that could be prevented: ototoxicity.

Regarding Clinical Implementation Guidelines, we have this kind of source for two of the revised drugs: cisplatin and doxorubicin [16,17]. The recommendations of the CPNDS for the PGx-guided use of these drugs are summarized in Table 2.

Table 1. Drugs included in NB treatment with clinically valuable PGx recommendations. The drugs included meet at least one of the clinical implementations three pillars-criteria: PGx included in Drug Label, PharmGKB Clinical Annotations Levels of Evidence 1 and 2, the existence of Clinical Implementation Guidelines published by relevant consortia. ALL: Acute Lymphoblastic Leukemia CPNDS: Canadian Pharmacogenomics Network for Drug safety, Cycloph: Cyclophosphamide, FDA: US Food and Drug Administration. Symbol − for guideline and drug label: lack of information.

Drug	Gene	SNP	Reference Genotype	Risk Genotype	ClinAnnot: Level	Recommendation for the Risk Genotype	Guideline/ Drug Label
Busulfan							−/FDA: Actionable *ABL1*, *BCR* (in ALL)
Carboplatin	*ERCC1*	rs11615	GG	AA, AG	2B: E,T	Moderate risk of inefficacy and toxicity	−/−
	GSTP1	rs1695	GG	AA, AG	2A: T	Moderate risk of toxicity	
	MTHFR	rs1801133	AA	AG, GG	2A: E	Moderate risk of inefficacy	
	XRCC1	rs25487	CC	CT, TT	2B: E	Moderate risk of inefficacy	
	ERCC1	rs3212986	AA	AC, CC	2B: T	Moderate risk of toxicity	
	NQO1	rs1800566	GG	AA, AG	2A: E	Moderate risk of inefficacy	
Cycloph.	*TP53*	rs1042522	CC	CG, GG	2B: E,T	Moderate risk of inefficacy and toxicity	−/−
	SOD2	rs4880	AA	AG, GG	2B: E	Moderate risk of inefficacy	
	GSTP1	rs1695	AA,AG	GG	2A: E,T	Moderate risk of inefficacy and toxicity	
Cisplatin	*TP53*	rs1042522	CC	CG, GG	2B: E,T	Moderate risk of inefficacy and toxicity	CPNDS: *TPMT*/ FDA: Informative *TPMT*
	MTHFR	rs1801133	AA	AG, GG	2A: E	Moderate risk of inefficacy	
	GSTP1	rs1695	AA	AG, GG	2B: T	Moderate risk of toxicity	
	GSTP1	rs1695	GG	AG, AA	2A: E	Moderate risk of inefficacy	
	XPC	rs2228001	TT	GT, GG	1B: T	High risk of toxicity	
	XRCC1	rs25487	CC	CT, TT	2B: E	Moderate risk of inefficacy	
	ERCC1	rs3212986	AA	AC, CC	2B: T	Moderate risk of toxicity	
	ERCC1	rs11615	GG	AA, AG	2B: E,T	Moderate risk of inefficacy and toxicity	
Doxorubicin	*NQO1*	rs1800566	GG	AA, AG	2A: E	Moderate risk of inefficacy	CPNDS: *RARG*, *SLC28A3*, *UGT1A6*/−
Etoposide	*DYNC2H1*	rs716274	AA	AG, GG	2B: T	Moderate risk of toxicity	−/−
Vincristine	*CEP72*	rs924607	CC,CT	TT	2B: T	Moderate risk of toxicity	−/FDA: Required *ABL1*, *BCR* (in ALL)

Note: the Clinical Annotations included in this table have been changed to Level 3 after new updates at www.pharmgkb.org from 25 March 2021.

Table 2. Summary of recommendations provided in the CPNDS guidelines for cisplatin and doxorubicin.

Gene	SNP	Reference Genotype	Risk Genotype	CPNDS Recommendations
CISPLATIN				
TPMT	rs1800462	CC	CG, GG	The consortium recommends testing these variants due to their relation with ototoxicity.
	rs1800460	CC	CT, TT	[+++] Physicians are encouraged to consider the use of otoprotectors if the patient's tumor type is one for which otoprotectors can be effective without adversely affecting antitumor activity.
	rs1142345	TT	CT, CC	Alternative treatments may be prescribed when they have demonstrated equal efficacy, manageable and acceptable toxicity, less ototoxicity, and are considered options within the current standards of care. Increase monitoring in high-risk patients. Should be encouraged to receive more frequent follow-up audiometric hearing tests after treatment has ended.
DOXORUBICIN				
RARG	rs2229774	GG	AG, AA	The consortium recommends testing of these variants due to their relation with cardiotoxicity.
SLC28A3	rs7853758	AA, AG	GG	[+] Increase frequency of monitoring, even with serial yearly echocardiographic monitoring and follow-up as recommended by COG guidelines; aggressive screening and management of cardiovascular risk factors, if the patient is considered at high risk.
				[++] Prescribe dexrazoxane.
UGT1A6	rs17863783	GG	GT, TT	[+++] Use liposomal encapsulated anthracycline preparations; use of continuous inclusion or slower inclusion rates; use of less cardiotoxic types of anthracyclines; use of other cardioprotective agents; prescribe alternative chemotherapy regiments for certain tumor types where alternative regiments have been shown to be equally effective.

CPNDS: Canadian Pharmacogenomics Network for Drug Safety. Grading scheme used for clinical practice guidelines: [+] Level A corresponds to a high level of evidence (benefits clearly overcome the risks); [++] level B is a recommendation with lower scientific evidence level based on expert opinion; and [+++] level C is mainly based in expert's opinion to be used in research context. SNP: single nucleotide polymorphisms, COG: Children's Oncology Group.

3. Pharmacogenetic Variants under Investigation Regarding NB Therapy

Regarding research, there is still a lot of work to conduct. There are multitudes of SNPs whose influence on drug response was proposed but is not yet sufficiently tested, and, therefore, validation is needed. As shown in Table 1, only a few drugs from the group included in this review have one pillar (at least) supporting their implementation in the clinical setting. However, for the rest of the drugs, many of the genes coding the transporters, metabolizing enzymes, and targets of these drugs are already known, and

research should be addressed to identify the implications of the SNPs in those genes on the safety and efficacy of those drugs.

Table 3 shows a compilation of the most promising SNPs that are under research, according to the literature search. In most of the manuscripts, the studies have been performed with the combinations of drugs that are currently used in chemotherapy regimens. For clarity, we have searched for literature with results attributable to single drugs and not to combinations of them. Another criterion for the selection, in most cases, has been the known relationship between the gene and the drug in terms of transport, metabolism, and/or mechanism of action.

Our knowledge about the genes involved in the mechanism of action, transport, and metabolism of the drugs is in many cases much more limited than expected. This happens not only with the newest drugs, but also with the classic chemotherapy that has been employed for decades. Therefore, focusing our attention on the SNPs contained in the genes responsible for the fate of the drug in our organism is not always easy. In addition, interactions exist, and these can happen immediately or with mid-long term effects, difficult to predict. All these together lead to "difficult to explain findings," except for a much-reduced group of genes directly related to specific events. For example, SNPs in genes such as *MTHFR*, *TP53*, or *VDR* have been correlated with overall survival and event-free survival in PGx studies of NB patients, whereas these genes are not directly involved in the body routes of the chemotherapeutic drugs employed. In our group's experience, rs1801133 in *MTHFR* ($p = 0.02$) and rs1544410 in *VDR* ($p = 0.006$) added an important predictive value for overall survival to the *MYCN* status, with a more accurate patients sub stratification than using *MYCN* alone [58–60].

If we check the bibliography, the most robust results should be reported from clinical trials, but these are obtained in predesigned and very much controlled situations different from the real clinical setting. For this reason, studies should be performed respecting the clinical reality, including concomitant treatments, especially considering that in pediatric oncology, many of the children participate in clinical trials evaluating their treatment and impeding them to participate in another specific for pharmacogenetics [61,62].

Table 3. Candidate SNPs and genes to evaluate regarding the efficacy and toxicity of the drugs in Neuroblastoma (based in PharmGKB and the included references).

Drug.	Gene	SNP	Hypothetic Effect	References
Busulfan	CTH	rs1021737	Pediatric patients with the TT genotype (receiving hematopoietic stem cell transplantation) may have an increased risk for sinusoidal obstruction syndrome (SOS) when treated with cyclophosphamide and busulfan as compared to patients with the GG or GT genotypes.	Huezo-Diaz Curtis P., 2018 (Ref. [18])
	CYP2C9	rs1799853	Pediatric patients with the CT and TT genotypes (undergoing hematopoietic stem cell transplant) may have decreased metabolism of busulfan as compared to patients with the CC genotype.	Uppugunduri CR., 2014 (Ref. [19])
	CYP2C19	rs12248560	Pediatric patients with the CC genotype (undergoing transplantation) may have decreased metabolism of busulfan as compared to patients with the CT or TT genotypes.	
	GSTA1	rs3957357	Pediatric patients with the AG and GG genotypes (who are undergoing hematopoietic stem cell transplantation) may have decreased clearance of busulfan as compared to patients with the AA genotype.	Ten Brink MH., 2013 (Ref. [20])
	GSTM1	rs3754446	Patients with the AA and AC genotypes (and acute myeloid leukemia) may have decreased clearance of busulfan as compared to patients with the CC genotype.	Yee SW., 2013 (Ref. [21])
Carboplatin Cisplatin	AKT1	rs2494752	Patients with the GG and AA genotypes who are treated with carboplatin or cisplatin may have decreased risk of progression of the disease as compared to patients with the AG genotype.	Xu X., 2012 (Ref. [22])
		rs1130214	Patients with the CC genotype (and lung cancer) who are treated with carboplatin or cisplatin may have a higher risk of distant disease progression as compared to patients with the AC or AA genotype.	Xu JL., 2012; (Ref. [23])
	EIF3A	rs3740556	Patients with the GG genotype (and lung cancer) may have a poorer response when treated with platinum-based chemotherapy as compared to patients with the AA or AG genotype.	Xu X., 2013 (Ref. [24])
	MTR	rs1805087	Pediatric patients with the GG genotype and cancer may have an increased risk for drug toxicity and an increased response to treatment with cisplatin or carboplatin as compared to patients with the AA or AG genotypes.	Patiño A., 2009 (Ref. [25])
	PIK3CA	rs2699887	Patients with the CC genotype (and non-small-cell lung cancer) may have an increased risk for toxicity when treated with platinum-based chemotherapy as compared to patients with the TT genotype.	Pu X., 2011 (Ref. [26])

Table 3. *Cont.*

Drug.	Gene	SNP	Hypothetic Effect	References
	PTEN	rs2299939	Patients with the AA genotype (and non-small-cell lung cancer) may have an increased risk for toxicity when treated with platinum-based chemotherapy as compared to patients with the AC or CC genotype.	
	SLC31A1	rs7851395	Patients with the AA genotype may have increased overall survival when treated with carboplatin or cisplatin (in people with Non-Small-Cell Lung Carcinoma) as compared to patients with genotypes AG or GG.	Xu X., 2012 (Ref. [22])
	Unknown (Intronic)	rs2498804	Patients with the CC genotype (and non-small-cell lung cancer) may have an increased risk of distant disease progression when treated with platinum-based chemotherapy as compared to patients with the AA or AC genotypes.	Pu X., 2011 (Ref. [26])
	ABCB1	rs1045642	Allele G is associated with an increased risk of death when treated with cyclophosphamide in combination with other drugs, (in patients with osteosarcoma) as compared to allele A.	Caronia D., 2011 (Ref. [27])
	ABCC4	rs9561778	Patients with the TT or GT genotypes (and breast cancer) who are treated with cyclophosphamide may have an increased risk of neutropenia/leukopenia and gastrointestinal toxicity, as compared to patients with the GG genotype.	Low SK., 2009 (Ref. [28])
Cyclophosph.	*CYP2B6*	rs7254579	Patients (with lupus) and the CC or CT genotypes may have decreased metabolism of cyclophosphamide, resulting in decreased concentrations of active cyclophosphamide metabolite as compared to patients with TT genotype.	Su W., 2016 (Ref. [29])
		rs4802101	Patients with the CC genotype may have decreased metabolism of cyclophosphamide, resulting in decreased concentrations of active cyclophosphamide metabolites and decreased risk of gastrointestinal toxicity, or leukopenia, as compared to patients with the CT or TT genotypes.	
		rs8192709	(Recipients of HLA-identical hematopoietic stem cell transplantation) with the TT or CT genotypes (and leukemia) may have an increased risk for hemorrhagic cystitis when treated with cyclophosphamide compared to patients with the CC genotype.	Rocha V., 2009 (Ref. [30])

Table 3. *Cont.*

Drug.	Gene	SNP	Hypothetic Effect	References
		rs2279343	Patients with the GG or AG genotypes (who have received a hematopoietic stem cell transplant) and are treated with cyclophosphamide may have an increased risk for oral mucositis as compared to patients with the AA genotype.	
		rs3745274	(Leukemia patients who are) recipients (of HLA-identical hematopoietic stem cell transplantation) from donors with the GG genotype may have an increased risk of developing veno-occlusive disease of the liver when treated with cyclophosphamide as compared to donor cells with the GT or TT genotype.Patients with the GG or GT genotypes (and Breast Cancer) who are treated with cyclophosphamide and doxorubicin may be more likely to require a reduction in dose as compared to patients with the TT genotype.	Bray J., 2010 (Ref. [31])
	CYP2C19	rs4244285	Patients with the GG genotype (and Systemic Lupus Erythematosus) who are treated with cyclophosphamide may have increased metabolism of cyclophosphamide, leading to higher concentrations of the active metabolite and an increased risk of toxicity (ovarian, gastrointestinal, or hematological) as compared to patients with the AA and AG genotype.	Su W., 2016 (Ref. [29])
	CYP3A4	rs2740574	Premenopausal patients with the TT genotype (and breast cancer) who are treated with cyclophosphamide may have a shorter period before chemotherapy-induced ovarian failure compared to patients with the CC or CT genotype.	Su HI., 2010 (Ref. [32])
Dinutuximab			SNPs reducing or impairing the expression of *GD2* could impede Dinutuximab efficacy.	Chen RL., 2000 Greenwood KL., 2018 (Refs. [33,34])
Doxorubicin	*ABCB1*	rs1045642 rs2032582 rs1128503	Patients harboring the CC-GG-CC genotypes had significantly lower peak plasma concentrations of doxorubicinol compared to patients who had TT-TT-TT genotypes.	Lal S., 2008 (Ref. [35])
	ABCC1	rs45511401	Patients with the TT or GT genotypes (and non-Hodgkin lymphoma) who are treated with doxorubicin may have an increased risk for cardiotoxicity as compared to patients with the GG genotype.	Wojnowski L., 2005 (Ref. [36])
	ABCC2	rs8187710	Patients with the AA or AG genotypes (and non-Hodgkin lymphoma) who are treated with doxorubicin may have an increased risk of cardiotoxicity as compared to patients with the GG genotype.	
		rs17222723	Patients with the AA or AT genotypes (and non-Hodgkin lymphoma) who are treated with doxorubicin may have an increased risk of cardiotoxicity as compared to patients with the TT genotype.	

Table 3. *Cont.*

Drug.	Gene	SNP	Hypothetic Effect	References
	CBR1	rs9024	Patients with the GG genotype may have increased clearance of doxorubicin and decreased exposure to doxorubicin compared to patients with the AG genotype.	Lal S., 2008 (Ref. [37])
	CBR3	rs8133052	Patients with the AA genotype (and breast cancer) who are treated with doxorubicin may have decreased metabolism of doxorubicin and may have greater tumor reduction, but may also have increased severity of neutropenia as compared to patients with the GG genotype.	Fan L., 2008 (Ref. [38])
	CYBA	rs4673	Cancer patients with the AA or AG genotypes who are treated with doxorubicin may have an increased risk for cardiotoxicity as compared to patients with the GG genotype.	Megías-Vericat JE., 2018 and Wojnowski L., 2005 (Refs. [36,39])
	GSTA1	rs3957357	Patients with the GG and AG genotypes (and soft tissue sarcoma) may have a shorter progression-free survival time when treated with doxorubicin as compared to patients with the AA genotype.	Gelderblom H., 2014 (Ref. [40])
	GSTP1	rs1695	Patients with osteosarcoma and the GG or AG genotypes may be at an increased risk of developing leukopenia when treated with doxorubicin as compared to patients with the AA genotype.	Windsor RE., 2012 (Ref. [41])
	RAC2	rs13058338	Cancer patients with the TT or AT genotypes who are treated with doxorubicin or idarubicin may have an increased risk for drug toxicity as compared to patients with the AA genotype.	Megías-Vericat JE., 2018 and Wojnowski L., 2005 (Refs. [36,39])
Etoposide			All these relevant pharmacogenes *ABCB1*, *ABCC3*, *CYP3A4*, *CYP3A5*, *GSTP1*, *UGT1A1*, are known to be relevant in etoposide pharmacokinetics, thus studies validating their main SNPs regarding the drug's toxicity and efficacy are needed.	Relling M.V., 1994; Zelcer N., 2001; Huang RS.,2007 (Refs. [42–44])
GM-CSF			Human GM-CSF receptor beta chain gene could be a good candidate to investigate the role of SNPs that could interfere the activation of the receptor by the drug.	Shen Y., 1992 (Ref. [45])
Interleukin2			SNPs in the gene coding for IL2 receptor could be very informative to assess the response to this treatment.	Ladenstein R., 2018; YamaneB.H., 2009; Shusterman S., 2019 (Refs. [46–48])

Table 3. *Cont.*

Drug.	Gene	SNP	Hypothetic Effect	References
Melphalan			*ABCB1* and *GSTP1* are relevant pharmacogenes that seem to be involved in melphalan pharmacokinetics. Exploring their main SNPs could be of interest.	Karkey M.A., 2005 and Hodges L.M., 2011 (Refs. [49,50])
Radiotherapy	*CDK1*	rs10711	Patients with the GG or GT genotypes may have increased risk of pneumonitis when treated with radiotherapy (lung cancer) as compared to patients with genotype TT.	Pu X., 2014 (Ref. [51])
	PRKCE	rs11125035	Patients with the AA genotype may have increased risk of esophagitis when treated with radiotherapy as compared to patients with genotype TT or AT.	Pu X., 2014 (Ref. [51])
	TANC1	rs10497203 rs264631 rs264651 rs6432512 rs264588 rs264663 rs7582141	Patients with the CC or AC/CG or GG/GG/CT or TT/AA or AC/CT or TT/GT or TT genotypes, respectively in the referred SNPs (left column) (and prostate cancer) who are treated with radiotherapy may have an increased risk of late stage toxicity as compared to patients with the other possible genotypes.	Fachal L., 2014 (Ref. [52])
Topotecan	*ABCG2*	rs4148157	Pediatric patients with the GG genotype (and brain tumors) may have decreased absorption and lower concentrations of topotecan compared to patients with the AA and AG genotypes.	Roberts J.K.,2016 (Ref. [53])
Vincristine	*ABCB1*	rs1045642	Pediatric patients with the AA or AG genotypes (and acute lymphoblastic leukemia) who are treated with vincristine may have a decreased likelihood of event-free survival as compared to patients with the GG genotype.	Ceppi F.,2014 (Ref. [54])
		rs4728709	Pediatric patients with the GG genotype (and acute lymphoblastic leukemia) who are treated with vincristine may have an increased risk of grade 1–2 neurotoxicity as compared to patients with the AA or AG genotypes.	Ceppi F.,2014 (Ref. [54])
			CYP3A5 seems to be the main metabolizing enzyme for vincristine, thus analyzing its main SNPs could be of interest	Egbelakin A.,2011 (Ref. [55])
Isotretinoin	*LEP*	rs7799039	These SNPs seem to correlate with the lipid disorders caused by the drug.	Khabour O.F.,2018 (Ref. [56])
			Other SNPs in relevant genes related to the mechanism of action of the drug could shed light for decreasing adverse side effects and increasing efficacy: *RXRA, JAK2, CDC25C*	Lee J.J,2011 (Ref. [57])

4. Further Consideration for a Perspective on NB PGx Translational Research

4.1. The Role of Ontogeny in NB Pharmacogenetics

The statement that children are not small adults is valid, particularly in pediatric clinical PGx. In order to offer children the optimal treatment, it is important not only to know the characteristics of the particular disease but also to integrate the changes of normal growth and development with their impact on the ontogeny of pharmacokinetic and pharmacogenomic factors. There are several age-related anatomic and physiological changes that have been found to influence drug ADME (Absorption, Distribution, Metabolism and Excretion) processes, such as differences in fat proportion in the body, gastric pH evolution, renal development, etc., but some of them are directly linked to the expression and role of relevant pharmacogenes. For instance, the activity of ABCB1 (P glycoprotein) and ABCG2, two of the most extensively studied ATP-binding cassette (ABC) transporters are decreased in the neonatal period [63,64]. Regarding metabolism, CYP3A7 shows the highest activity in the liver during embryonic, fetal, and newborn stages. After that, its activity declines, and other CYPs take the main roles. CYP3A4 appears during the first week after birth, reaching approximately 30–40% of adult activity by the first month and full adult activity by the 6th month of life. Its activity increases so much that it reaches 120% of the adults between 1 and 4 years of age, decreasing to normal adult levels after puberty [65–67]. In the case of CYP1A2, its expression is delayed until 3 months after birth. Regarding Phase II enzymes, as UGT1A family, it is remarkable that UGT1A1 starts to increase at birth and does not reach adult levels since 3–6 months later; and that UGT1A6 and UGT1A9 activity levels are smaller in people younger than 10 years old in comparison with adults [67].

4.2. What Else Do We Need to Take into Account? Research Integrating Epigenomics and Metabolomics

The next goal is complementing PGx with two other relevant technologies that must undoubtedly be integrated: Epigenomics and Metabolomics. Explained in a very simple way, Epigenetics will deal with the study of the methylation status of the promoters of certain pharmacogenes as a mechanism of higher regulation that, above the nucleotide sequence of DNA, will determine whether a gene is really being expressed or not [68,69]. Metabolomics, also in a simplistic manner for this context, could characterize the plasma presence of metabolites corresponding to the drugs administered to the patients to check if the drugs have been effectively metabolized or not [70]. Complementing pharmacogenetics with the other two Omics techniques must help understand relevant questions: phenomena occurring in the patients that represent an upper layer of complexity for understanding the patients' real response to drugs. For instance, metabolic pathways that are switched on when the main metabolic route is "off" or hyper/hypomethylation phenomena that regulate the expression of genes, masking potential effects of the nucleotide sequence. In order to understand the real characteristics of each patient, integration of all this information by means of very advanced Biostatistics, Systems Biology, Pharmacology, and Artificial Intelligence will be required.

5. Conclusions

PGx knowledge needs to be implemented in the clinical routine of NB patients to support a more personalized approach regarding chemotherapy. The field is divided, with drug-genetic variants with a high level of scientific and clinical evidence and many more drug-SNP pairs needing further research in real patient contexts in order to validate their effects. The available literature regarding those associations is in many cases scarce and old, and the results have not been confirmed or updated. Thus, we need to put our efforts into this type of research. Meanwhile, those associations with high levels of evidence should be assessed in all our patients with the aim of providing the clinician with an additional tool to modify the treatment, if possible, and/or to be alert to increased risks of immediate or late toxicities. The current scenario provides data on relationships between SNP-drugs, but the reality is different most of the time due to the use of a combination of drugs. Thus,

we need to validate the proposed "one-to-one" relationships in the real clinical context because interactions do exist, and the expected effects of concrete SNPs could not be the same in the context of polytherapy.

Author Contributions: Conceptualization, S.F.A., L.S. and M.J.H.; methodology, M.J.H., P.B., P.G.; investigation, G.G.O., A.U., Y.Y.; resources, V.S., G.G.O.; data curation, M.J.H., A.C., V.C.; writing—original draft preparation, G.G.O., L.S., M.J.H.; writing—review and editing, S.F.A., M.J.H.; visualization; funding acquisition, A.C., S.F.A., M.J.H. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement: The data reported is contained in the referenced papers as well as in PharmGKB website (www.pharmgkb.org).

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Tolbert, V.P.; Coggins, G.E.; Maris, J.M. Genetic susceptibility to neuroblastoma. *Curr. Opin. Genet. Dev.* **2017**, *42*, 81–90. [CrossRef] [PubMed]
2. Hero, B.; Simon, T.; Spitz, R.; Ernestus, K.; Gnekow, A.K.; Scheel-Walter, H.G.; Schwabe, D.; Schilling, F.H.; Benz-Bohm, G.; Berthold, F. Localized infant neuroblastomas often show spontaneous regression: Results of the prospective trials NB95-S and NB97. *J. Clin. Oncol.* **2008**, *26*, 1504–1510. [CrossRef] [PubMed]
3. Park, J.R.; Bagatell, R.; Cohn, S.L.; Pearson, A.D.; Villablanca, J.G.; Berthold, F.; Burchill, S.; Boubaker, A.; McHugh, K.; Nuchtern, J.G.; et al. Revisions to the international neuroblastoma response criteria: A consensus statement from the National Cancer Institute clinical trials planning meeting. *J. Clin. Oncol.* **2017**, *35*, 2580–2587. [CrossRef]
4. Morgenstern, D.A.; Pötschger, U.; Moreno, L.; Papadakis, V.; Owens, C.; Ash, S.; Pasqualini, C.; Luksch, R.; Garaventa, A.; Canete, A.; et al. Risk stratification of high-risk metastatic neuroblastoma: A report from the HR-NBL-1/SIOPEN study. *Pediatr. Blood Cancer* **2018**, *65*, e27363. [CrossRef] [PubMed]
5. Clemens, E.; van der Kooi, A.L.F.; Broer, L.; van Dulmen-den Broeder, E.; Visscher, H.; Kremer, L.; Tissing, W.; Loonen, J.; Ronckers, C.M.; Pluijm, S.M.F.; et al. The influence of genetic variation on late toxicities in childhood cancer survivors: A review. *Crit. Rev. Oncol. Hematol.* **2018**, *126*, 154–167. [CrossRef]
6. Ross, C.J.D.; Visscher, H.; Rod Rassekh, S.; Castro-Pastrana, L.I.; Shereck, E.; Carleton, B.; Hayden, M.R. Pharmacogenomics of serious adverse drug reactions in pediatric oncology. *J. Popul. Ther. Clin. Pharmacol.* **2011**, *18*, 134–151.
7. Conyers, R.; Devaraja, S.; Elliott, D. Systematic review of pharmacogenomics and adverse drug reactions in paediatric oncology patients. *Pediatr. Blood Cancer* **2018**, *65*, e26937. [CrossRef]
8. Whirl-Carrillo, M.; McDonagh, E.M.; Hebert, J.M.; Gong, L.; Sangkuhl, K.; Thorn, C.F.; Altman, R.B.; Klein, T.E. Pharmacogenomics knowledge for personalized medicine. *Clin. Pharmacol. Ther.* **2012**, *92*, 414–417. [CrossRef]
9. U S Food and Drug Administration Home Page. Available online: https://www.fda.gov/ (accessed on 25 June 2021).
10. European Medicines Agency. Available online: https://www.ema.europa.eu/ (accessed on 25 June 2021).
11. Pharmaceuticals and Medical Devices Agency. Available online: http://www.pmda.go.jp/english/ (accessed on 25 June 2021).
12. Drugs and Health Products—Canada. Available online: https://www.canada.ca/en/health-canada/services/drugs-health-products.html (accessed on 25 June 2021).
13. Clinical Phramacogenetics Implementation Consortium. Available online: https://cpicpgx.org (accessed on 25 June 2021).
14. Dutch Pharmacogenetics Working Group. Available online: https://knmp.nl (accessed on 25 June 2021).
15. García-Alfonso, P.; Saiz-Rodríguez, M.; Mondéjar, R.; Salazar Blanco, J.; Páez, D.; Borobia Pérez, A.; Safont Aguilera, M.J.; García García, I.; Colomer, R.; García González, X.; et al. Consensus of experts from the Spanish Pharmacogenetics and Pharmacogenomics Society and the Spanish Society of Medical Oncology for the genotyping of *DPYD* in cancer patients who are candidates for treatment with fluoropyrimidines. *Clin. Transl. Oncol.* **2021**. (submitted, under review).
16. Lee, J.W.; Pussegoda, K.; Rassekh, S.R.; Monzon, J.G.; Liu, G.; Hwang, S.; Bhavsar, A.P.; Pritchard, S.; Ross, C.J.; Amstutz, U.; et al. Clinical Practice Recommendations for the Management and Prevention of Cisplatin-Induced Hearing Loss Using Pharmacogenetic Markers. *Ther. Drug Monit.* **2016**, *38*, 423–431. [CrossRef]
17. Aminkeng, F.; Ross, C.J.; Rassekh, S.R.; Hwang, S.; Rieder, M.J.; Bhavsar, A.P.; Smith, A.; Sanatani, S.; Gelmon, K.A.; Bernstein, D.; et al. Recommendations for genetic testing to reduce the incidence of anthracycline-induced cardiotoxicity. *Br. J. Clin. Pharmacol.* **2016**, *82*, 683–695. [CrossRef]

18. Huezo-Diaz Curtis, P.; Uppugunduri, C.R.S.; Muthukumaran, J.; Rezgui, M.A.; Peters, C.; Bader, P.; Duval, M.; Bittencourt, H.; Krajinovic, M.; Ansari, M. Association of CTH variant with sinusoidal obstruction syndrome in children receiving intravenous busulfan and cyclophosphamide before hematopoietic stem cell transplantation. *Pharm. J.* **2018**, *18*, 64–69. [CrossRef]

19. Uppugunduri, C.R.; Rezgui, M.A.; Diaz, P.H.; Tyagi, A.K.; Rousseau, J.; Daali, Y.; Duval, M.; Bittencourt, H.; Krajinovic, M.; Ansari, M. The association of cytochrome P450 genetic polymorphisms with sulfolane formation and the efficacy of a busulfan-based conditioning regimen in pediatric patients undergoing hematopoietic stem cell transplantation. *Pharm. J.* **2014**, *14*, 263–271. [CrossRef]

20. Ten Brink, M.H.; van Bavel, T.; Swen, J.J.; van der Straaten, T.; Bredius, R.G.; Lankester, A.C.; Zwaveling, J.; Guchelaar, H.J. Effect of genetic variants GSTA1 and CYP39A1 and age on busulfan clearance in pediatric patients undergoing hematopoietic stem cell transplantation. *Pharmacogenomics* **2013**, *14*, 1683–1690. [CrossRef]

21. Yee, S.W.; Mefford, J.A.; Singh, N.; Percival, M.E.; Stecula, A.; Yang, K.; Witte, J.S.; Takahashi, A.; Kubo, M.; Matsuda, K.; et al. Impact of polymorphisms in drug pathway genes on disease-free survival in adults with acute myeloid leukemia. *J. Hum. Genet.* **2013**, *58*, 353–361. [CrossRef]

22. Xu, X.; Duan, L.; Zhou, B.; Ma, R.; Zhou, H.; Liu, Z. Genetic polymorphism of copper transporter protein 1 is related to platinum resistance in Chinese non-small cell lung carcinoma patients. *Clin. Exp. Pharmacol. Physiol.* **2012**, *39*, 786–792. [CrossRef]

23. Xu, J.L.; Wang, Z.W.; Hu, L.M.; Yin, Z.Q.; Huang, M.D.; Hu, Z.B.; Shen, H.B.; Shu, Y.Q. Genetic variants in the PI3K/PTEN/AKT/mTOR pathway predict platinum-based chemotherapy response of advanced non-small cell lung cancers in a Chinese population. *Asian Pac. J. Cancer Prev.* **2012**, *13*, 2157–2162. [CrossRef] [PubMed]

24. Xu, X.; Han, L.; Yang, H.; Duan, L.; Zhou, B.; Zhao, Y.; Qu, J.; Ma, R.; Zhou, H.; Liu, Z. The A/G allele of eIF3a rs3740556 predicts platinum-based chemotherapy resistance in lung cancer patients. *Lung Cancer* **2013**, *79*, 65–72. [CrossRef] [PubMed]

25. Patiño-García, A.; Zalacaín, M.; Marrodán, L.; San-Julián, M.; Sierrasesúmaga, L. Methotrexate in pediatric osteosarcoma: Response and toxicity in relation to genetic polymorphisms and dihydrofolate reductase and reduced folate carrier 1 expression. *J. Pediatr.* **2009**, *154*, 688–693. [CrossRef] [PubMed]

26. Pu, X.; Hildebrandt, M.A.; Lu, C.; Lin, J.; Stewart, D.J.; Ye, Y.; Gu, J.; Spitz, M.R.; Wu, X. PI3K/PTEN/AKT/mTOR pathway genetic variation predicts toxicity and distant progression in lung cancer patients receiving platinum-based chemotherapy. *Lung Cancer* **2011**, *71*, 82–88. [CrossRef]

27. Caronia, D.; Patiño-Garcia, A.; Peréz-Martínez, A.; Pita, G.; Moreno, L.T.; Zalacain-Díez, M.; Molina, B.; Colmenero, I.; Sierrasesúmaga, L.; Benítez, J.; et al. Effect of ABCB1 and ABCC3 polymorphisms on osteosarcoma survival after chemotherapy: A pharmacogenetic study. *PLoS ONE* **2011**, *6*, e26091. [CrossRef]

28. Low, S.K.; Kiyotani, K.; Mushiroda, T.; Daigo, Y.; Nakamura, Y.; Zembutsu, H. Association study of genetic polymorphism in ABCC4 with cyclophosphamide-induced adverse drug reactions in breast cancer patients. *J. Hum. Genet.* **2009**, *54*, 564–571. [CrossRef]

29. Shu, W.; Guan, S.; Yang, X.; Liang, L.; Li, J.; Chen, Z.; Zhang, Y.; Chen, L.; Wang, X.; Huang, M. Genetic markers in CYP2C19 and CYP2B6 for prediction of cyclophosphamide's 4-hydroxylation, efficacy and side effects in Chinese patients with systemic lupus erythematosus. *Br. J. Clin. Pharmacol.* **2016**, *81*, 327–340. [CrossRef]

30. Rocha, V.; Porcher, R.; Fernandes, J.F.; Filion, A.; Bittencourt, H.; Silva, W., Jr.; Vilela, G.; Zanette, D.L.; Ferry, C.; Larghero, J.; et al. Association of drug metabolism gene polymorphisms with toxicities, graft-versus-host disease and survival after HLA-identical sibling hematopoietic stem cell transplantation for patients with leukemia. *Leukemia* **2009**, *23*, 545–556. [CrossRef]

31. Bray, J.; Sludden, J.; Griffin, M.J.; Cole, M.; Verrill, M.; Jamieson, D.; Boddy, A.V. Influence of pharmacogenetics on response and toxicity in breast cancer patients treated with doxorubicin and cyclophosphamide. *Br. J. Cancer* **2010**, *102*, 1003–1009. [CrossRef] [PubMed]

32. Su, H.I.; Sammel, M.D.; Velders, L.; Horn, M.; Stankiewicz, C.; Matro, J.; Gracia, C.R.; Green, J.; DeMichele, A. Association of cyclophosphamide drug-metabolizing enzyme polymorphisms and chemotherapy-related ovarian failure in breast cancer survivors. *Fertil. Steril.* **2010**, *94*, 645–654. [CrossRef]

33. Chen, R.L.; Reynolds, C.P.; Seeger, R.C. Neutrophils are cytotoxic and growth-inhibiting for neuroblastoma cells with an anti-GD2 antibody but, without cytotoxicity, can be growth-stimulating. *Cancer Immunol. Immunother.* **2000**, *48*, 603–612. [CrossRef] [PubMed]

34. Greenwood, K.L.; Foster, J.H. The safety of dinutuximab for the treatment of pediatric patients with high-risk neuroblastoma. *Expert Opin. Drug Saf.* **2018**, *17*, 1257–1262. [CrossRef] [PubMed]

35. Lal, S.; Wong, Z.W.; Sandanaraj, E.; Xiang, X.; Siang Ang, P.C.; Lee, E.J.D.; Chowbay, B. Influence of ABCB1 and ABCG2 polymorphisms on doxorubicin disposition in Asian breast cancer patients. *Cancer Sci.* **2008**, *99*, 816–823. [CrossRef] [PubMed]

36. Wojnowski, L.; Kulle, B.; Schirmer, M.; Schlüter, G.; Schmidt, A.; Rosenberger, A.; Vonhof, S.; Bickeböller, H.; Toliat, M.R.; Suk, E.K.; et al. NAD(P)H oxidase and multidrug resistance protein genetic polymorphisms are associated with doxorubicin-induced cardiotoxicity. *Circulation* **2005**, *112*, 3754–3762. [CrossRef]

37. Lal, S.; Sandanaraj, E.; Wong, Z.W.; Ang, P.C.; Wong, N.S.; Lee, E.J.; Chowbay, B. CBR1 and CBR3 pharmacogenetics and their influence on doxorubicin disposition in Asian breast cancer patients. *Cancer Sci.* **2008**, *99*, 2045–2054. [CrossRef]

38. Fan, L.; Goh, B.C.; Wong, C.I.; Sukri, N.; Lim, S.E.; Tan, S.H.; Guo, J.Y.; Lim, R.; Yap, H.L.; Khoo, Y.M.; et al. Genotype of human carbonyl reductase CBR3 correlates with doxorubicin disposition and toxicity. *Pharmacogenet. Genom.* **2008**, *18*, 621–631. [CrossRef]

39. Megías-Vericat, J.E.; Montesinos, P.; Herrero, M.J.; Moscardó, F.; Bosó, V.; Rojas, L.; Martínez-Cuadrón, D.; Rodríguez-Veiga, R.; Sendra, L.; Cervera, J.; et al. Impact of NADPH oxidase functional polymorphisms in acute myeloid leukemia induction chemotherapy. *Pharm. J.* **2018**, *18*, 301–307. [CrossRef]

40. Gelderblom, H.; Blay, J.Y.; Seddon, B.M.; Leahy, M.; Ray-Coquard, I.; Sleijfer, S.; Kerst, J.M.; Rutkowski, P.; Bauer, S.; Ouali, M.; et al. Brostallicin versus doxorubicin as first-line chemotherapy in patients with advanced or metastatic soft tissue sarcoma: An European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group randomised phase II and pharmacogenetic study. *Eur. J. Cancer* **2014**, *50*, 388–396. [CrossRef]

41. Windsor, R.E.; Strauss, S.J.; Kallis, C.; Wood, N.E.; Whelan, J.S. Germline genetic polymorphisms may influence chemotherapy response and disease outcome in osteosarcoma: A pilot study. *Cancer* **2012**, *118*, 1856–1867. [CrossRef] [PubMed]

42. Relling, M.V.; Nemec, J.; Schuetz, E.G.; Schuetz, J.D.; Gonzalez, F.J.; Korzekwa, K.R. O-demethylation of epipodophyllotoxins is catalyzed by human cytochrome P450 3A4. *Mol. Pharmacol.* **1994**, *45*, 352–358. [PubMed]

43. Zelcer, N.; Saeki, T.; Reid, G.; Beijnen, J.H.; Borst, P. Characterization of drug transport by the human multidrug resistance protein 3 (ABCC3). *J. Biol. Chem.* **2001**, *276*, 46400–46407. [CrossRef] [PubMed]

44. Huang, R.S.; Duan, S.; Bleibel, W.K.; Kistner, E.O.; Zhang, W.; Clark, T.A.; Chen, T.X.; Schweitzer, A.C.; Blume, J.E.; Cox, N.J.; et al. A genome-wide approach to identify genetic variants that contribute to etoposide-induced cytotoxicity. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 9758–9763. [CrossRef]

45. Shen, Y.; Baker, E.; Callen, D.F.; Sutherland, G.R.; Willson, T.A.; Rakar, S.; Gough, N.M. Localization of the human GM-CSF receptor beta chain gene (CSF2RB) to chromosome 22q12.2–>q13.1. *Cytogenet. Cell Genet.* **1992**, *61*, 175–177. [CrossRef]

46. Ladenstein, R.; Pötschger, U.; Valteau-Couanet, D.; Luksch, R.; Castel, V.; Yaniv, I.; Laureys, G.; Brock, P.; Michon, J.M.; Owens, C.; et al. Interleukin 2 with anti-GD2 antibody ch14.18/CHO (dinutuximab beta) in patients with high-risk neuroblastoma (HR-NBL1/SIOPEN): A multicentre, randomised, phase 3 trial. *Lancet Oncol.* **2018**, *19*, 1617–1629. [CrossRef]

47. Yamane, B.H.; Hank, J.A.; Albertini, M.R.; Sondel, P.M. The development of antibody-IL-2 based immunotherapy with hu14.18-IL2 (EMD-273063) in melanoma and neuroblastoma. *Expert Opin. Investig. Drugs* **2009**, *18*, 991–1000. [CrossRef]

48. Shusterman, S.; Naranjo, A.; van Ryn, C.; Hank, J.A.; Parisi, M.T.; Shulkin, B.L.; Servaes, S.; London, W.B.; Shimada, H.; Gan, J.; et al. Antitumor Activity and Tolerability of hu14.18-IL2 with GMCSF and Isotretinoin in Recurrent or Refractory Neuroblastoma: A Children's Oncology Group phase II study. *Clin. Cancer Res.* **2019**, *25*, 6044–6051. [CrossRef]

49. Harkey, M.A.; Czerwinski, M.; Slattery, J.; Kiem, H.P. Overexpression of glutathione-S-transferase, MGSTII, confers resistance to busulfan and melphalan. *Cancer Investig.* **2005**, *23*, 19–25. [CrossRef]

50. Hodges, L.M.; Markova, S.M.; Chinn, L.W.; Gow, J.M.; Kroetz, D.L.; Klein, T.E.; Altman, R.B. Very important pharmacogene summary: ABCB1 (MDR1, P-glycoprotein). *Pharmacogenet. Genom.* **2011**, *21*, 152–161. [CrossRef]

51. Pu, X.; Wang, L.; Chang, J.Y.; Hildebrandt, M.A.T.; Ye, Y.; Lu, C.; Skinner, H.D.; Niu, N.; Jenkins, G.D.; Komaki, R.; et al. Inflammation-related genetic variants predict toxicity following definitive radiotherapy for lung cancer. *Clin. Pharmacol. Ther.* **2014**, *96*, 609–615. [CrossRef] [PubMed]

52. Fachal, L.; Gómez-Caamaño, A.; Barnett, G.C.; Peleteiro, P.; Carballo, A.M.; Calvo-Crespo, P.; Kerns, S.L.; Sánchez-García, M.; Lobato-Busto, R.; Dorling, L.; et al. A three-stage genome-wide association study identifies a susceptibility locus for late radiotherapy toxicity at 2q24.1. *Nat. Genet.* **2014**, *46*, 891–894. [CrossRef] [PubMed]

53. Roberts, J.K.; Birg, A.V.; Lin, T.; Daryani, V.M.; Panetta, J.C.; Broniscer, A.; Robinson, G.W.; Gajjar, A.J.; Stewart, C.F. Population pharmacokinetics of oral topotecan in infants and very young children with brain tumors demonstrates a role of ABCG2 rs4148157 on the absorption rate constant. *Drug Metab. Dispos.* **2016**, *44*, 1116–1122. [CrossRef] [PubMed]

54. Ceppi, F.; Langlois-Pelletier, C.; Gagné, V.; Rousseau, J.; Ciolino, C.; De Lorenzo, S.; Kevin, K.M.; Cijov, D.; Sallan, S.E.; Silverman, L.B.; et al. Polymorphisms of the vincristine pathway and response to treatment in children with childhood acute lymphoblastic leukemia. *Pharmacogenomics* **2014**, *15*, 1105–1116. [CrossRef]

55. Egbelakin, A.; Ferguson, M.J.; MacGill, E.A.; Lehmann, A.S.; Topletz, A.R.; Quinney, S.K.; Li, L.; McCammack, K.C.; Hall, S.D.; Renbarger, J.L. Increased risk of vincristine neurotoxicity associated with low CYP3A5 expression genotype in children with acute lymphoblastic leukemia. *Pediatr. Blood Cancer* **2011**, *56*, 361–367. [CrossRef]

56. Khabour, O.F.; Alzoubi, K.H.; Firoz, A.S.; Al-Awad, R.M.M. Association between leptin gene rs7799039 polymorphism and lipid profile changes induced by isotretinoin treatment in acne patients. *Ther. Clin. Risk Manag.* **2018**, *14*, 949–954. [CrossRef]

57. Lee, J.J.; Wu, X.; Hildebrandt, M.A.T.; Yang, H.; Khuri, F.R.; Kim, E.; Gu, J.; Ye, Y.; Lotan, R.; Spitz, M.R.; et al. Global assessment of genetic variation influencing response to retinoid chemoprevention in head and neck cancer patients. *Cancer Prev. Res.* **2011**, *4*, 185–193. [CrossRef] [PubMed]

58. Olivera, G.G.; Yáñez, Y.; Gargallo, P.; Sendra, L.; Aliño, S.F.; Segura, V.; Sanz, M.Á.; Cañete, A.; Castel, V.; De Mora, J.F.; et al. MTHFR and VDR polymorphisms improve the prognostic value of MYCN status on overall survival in neuroblastoma patients. *Int. J. Mol. Sci.* **2020**, *21*, 2714. [CrossRef]

59. Nordgard, S.H.; Alnæs, G.I.G.; Hihn, B.; Lingjærde, O.C.; Liestøl, K.; Tsalenko, A.; Sørlie, T.; Lønning, P.E.; Børresen-Dale, A.L.; Kristensen, V.N. Pathway based analysis of SNPs with relevance to 5-FU therapy: Relation to intratumoral mRNA expression and survival. *Int. J. Cancer* **2008**, *123*, 577–585. [CrossRef] [PubMed]

60. Findlay, J.M.; Middleton, M.R.; Tomlinson, I. A systematic review and meta-analysis of somatic and germline DNA sequence biomarkers of esophageal cancer survival, therapy response and stage. *Ann. Oncol.* **2015**, *26*, 624–644. [CrossRef] [PubMed]

61. Rubio-San-Simón, A.; Verdú-Amorós, J.; Hladun, R.; Juan-Ribelles, A.; Molero, M.; Guerra-García, P.; Pérez-Martínez, A.; Castañeda, A.; Cañete, A.; de Rojas, T.; et al. Challenges in early phase clinical trials for childhood cancer during the COVID-19 pandemic: A report from the new agents group of the Spanish Society of Paediatric Haematology and Oncology (SEHOP). *Clin. Transl. Oncol.* **2021**, *23*, 183–189. [CrossRef] [PubMed]

62. Pritchard-Jones, K.; Dixon-Woods, M.; Naafs-Wilstra, M.; Valsecchi, M.G. Improving recruitment to clinical trials for cancer in childhood. *Lancet Oncol.* **2008**, *9*, 392–399. [CrossRef]

63. Mlakar, V.; Curtis, P.H.D.; Uppugunduri, C.R.S.; Krajinovic, M.; Ansari, M. Pharmacogenomics in pediatric oncology: Review of gene—Drug associations for clinical use. *Int. J. Mol. Sci.* **2016**, *17*, 1502. [CrossRef]

64. Lin, J.H.; Yamazaki, M. Role of P-glycoprotein in pharmacokinetics: Clinical implications. *Clin. Pharmacokinet.* **2003**, *42*, 59–98. [CrossRef]

65. Haag, C.K.B. *Ontogeny and Pharmacogenetics: Determinants of Age-Associated Differences in Drng Clearance during Human Development*; Erasmus University Rotterdam: Rotterdam, The Netherlands, 2002; ISBN 9067340057.

66. Fernandez, E.; Perez, R.; Hernandez, A.; Tejada, P.; Arteta, M.; Ramos, J.T. Factors and mechanisms for pharmacokinetic differences between pediatrie population and adults. *Pharmaceutics* **2011**, *3*, 53–72. [CrossRef]

67. Rao, S.; Uppugunduri, C.; Ansari, M. Commentary: A Myriad Aberrations on Information of Ontogeny of Drug Metabolizing Enzymes in the Pediatric Population: An Obstacle for Personalizing Drug Therapy in the Pediatric Population. *Drug Metab. Lett.* **2016**, *10*, 72–74. [CrossRef]

68. Katsila, T.; Patrinos, G.P. The Implications of Metabotypes for Rationalizing Therapeutics in Infants and Children. *Front. Pediatr.* **2015**, *3*, 68. [CrossRef]

69. Kim, I.W.; Han, N.; Burckart, G.J.; Oh, J.M. Epigenetic changes in gene expression for drug-metabolizing enzymes and transporters. *Pharmacotherapy* **2014**, *34*, 140–150. [CrossRef] [PubMed]

70. Ingelman-Sundberg, M.; Zhong, X.B.; Hankinson, O.; Beedanagari, S.; Yu, A.M.; Peng, L.; Osawa, Y. Potential role of epigenetic mechanisms in the regulation of drug metabolism and transport. *Drug Metab. Dispos.* **2013**, *41*, 1725–1731. [CrossRef] [PubMed]