Abstract: The liver plays a pivotal role in drug handling due to its contribution to the processes of
detoxification (phases 0 to 3). In addition, the liver is also an essential organ for the mechanism of
action of many families of drugs, such as cholesterol-lowering, antidiabetic, antiviral, anticoagulant,
and anticancer agents. Accordingly, the presence of genetic variants affecting a high number of
genomes expressed in hepatocytes has a critical clinical impact. The present review is not an exhaustive
list but a general overview of the most relevant variants affecting genes involved in detoxification phases.
The available information highlights the importance of defining the genomic profile responsible
for the hepatic handling of drugs in many ways, such as (i) impaired uptake, (ii) enhanced export,
(iii) altered metabolism due to decreased activation of prodrugs or enhanced inactivation of active
compounds, and (iv) altered molecular targets located in the liver due to genetic changes or
activation/downregulation of alternative/compensatory pathways. In conclusion, the advance in this
field of modern pharmacology, which allows one to predict the outcome of the treatments and to
develop more effective and selective agents able to overcome the lack of effect associated with the
existence of some genetic variants, is required to step forward toward a more personalized medicine.

Keywords: detoxification; haplotype; isoform; metabolism; mutation; pharmacogenomics; polymorphism;
SNP; transport; variant

1. Introduction

A better understanding of the genetic and molecular bases accounting for the interindividual
variability in response to pharmacological treatment requires the knowledge of the role of genetic
variants in genes expressed in hepatocytes and involved in the mechanisms affecting hepatic drug
handling. These include detoxification mechanisms that are classified into four groups: (i) phase
0, transporters determining the uptake of the drug by hepatocytes; (ii) phase 1, small changes in
the molecule induced by oxidation-reduction (redox) reactions; (iii) phase 2, conjugation of drugs
with a polyatomic group; and (iv) phase 3, which for some drugs involves the export across the
canicular membrane toward the biliary lumen and, in other cases, involves the transfer across
the hepatocyte sinusoidal membrane back to the blood for the elimination by the kidney of the
usually more hydrophilic derivatives generated by phases 1/2 in liver cells. The present review is not
an exhaustive list but a general overview of the most relevant variants affecting genes involved in
detoxification phases because they affect drug activity or induce higher toxicity, in most cases, owing
to accumulation in this organ, promoting drug-induced liver injury (DILI) (Table 1). To elaborate
this review, we have also taken into account that the liver is the target of many drugs, and hence the existence of genetic variants can affect the efficacy and toxicity of these drugs (Table 2). Additional information to that provided in the present review regarding the clinical relevance of genetic variants, i.e., demonstrated effects on pharmacokinetics, drug response and/or toxicity and their potential clinical impact can be found at databases such as the Pharmacogene Variation Consortium website (https://www.pharmvar.org/gene/), the Clinical Genome (ClinGen) resource (https://clinicalgenome.org/) and the PharmGKB database (http://www.pharmgkb.org/). Minor allele frequency (MAF) data were obtained from the Allele Frequency Aggregator (ALFA) project (version 27 February 2020) (https://www.ncbi.nlm.nih.gov/snp/docs/gsr/alfa/) included in the NCBI database of single nucleotide polymorphisms (dbSNP).

2. Phase 0: Uptake of Drugs

During phase 0 of hepatic detoxification, drugs are taken up by the hepatocytes from the blood mainly via carrier-mediated processes that involve members of the solute carrier (SLC) superfamily of proteins. The existence of single nucleotide polymorphisms (SNPs) in these genes, together with the variability of their expression levels in liver cells, are important factors contributing to the interindividual variability in the response of drugs that either act on hepatocytes or whose metabolism and elimination depends on liver function. In many cases, the consequence of genetic variants is the alteration of drug uptake, resulting in a significant impact on its efficacy, safety, and the appearance of adverse reactions. It should be noted that many carriers share overlapping substrate specificity. For this reason, even if the variant reduces the activity of a transporter, this is not always accompanied by essential differences in the clinical response, because it can be compensated by the activity of other transporters.

Databases, such as PharmGKB [1] and the ClinGen resource [2], have included more than 25,000 associations between genetic polymorphisms in SLC genes and drug response. Moreover, the International Transporter Consortium (ITC), which is comprised of scientists from academia, industry and regulatory agencies around the world, has documented a high degree of interindividual variability in SLC transporter activities due to the presence of these genetic variants [3].

2.1. Organic Anion-Transporting Polypeptides (OATPs)

Some members of the OATP family, such as OATP1B1, OATP1B3, and OATP2B1 (SLCO1B1, SLCO1B3, SLCO2B1 genes, respectively) are highly expressed at the basolateral membrane of hepatocytes, where they play an important role in the uptake of many different substrates [4]. Because of their role in drug uptake and disposition, OATP1B1 and OATP1B3 are considered among the most clinically relevant carriers by ITC guidelines [5,6].

OATP1B1 is expressed exclusively in the sinusoidal membrane of hepatocytes. This transporter has a broad substrate specificity that includes anionic, but also zwitterionic and neutral lipophilic compounds. Among them are drugs widely used to reduce the risk of cardiovascular diseases, such as statins, the antihypertensives enalapril, temocapril, olmesartan, and valsartan, and antidiabetics such as repaglinide [7]. OATP1B1 can also transport thiazolidinediones (troglitazone), anticancer drugs (SN-38, methotrexate, and taxanes), antibiotics (rifampicin, benzylpenicillin), antifungals (caspofungin) and immunosuppressants (tacrolimus) [8]. To date, almost 200 SNPs in the SLCO1B1 gene have been described, some of them very frequent, such as c.388A>G (p.Asn130Asp, rs2306283), whose minor allele frequency (MAF) is 42.8%. This variant has less capacity to transport certain drugs, for instance, repaglinide [9,10]. However, this does not result in an important impact on the pharmacokinetics, response and toxicity of these drugs. In contrast, other SLCO1B1 variants have considerable clinical importance. This is the case of c.521T>C (p.Val174Ala, rs4149056), which has MAF of 14.7%. When expressed in cells in vitro, this carrier has decreased transport activity, due to diminished expression at the plasma membrane [11] and a higher degree of protein phosphorylation [12]. There are four common haplotypes bearing these two SNPs: SLCO1B1*1A, consisting of wild-type sequences (c.388A/c.521T),
SLCO1B1*1B (c.388G/c.521T), SLCO1B1*5 (c.388A/c.521C) and SLCO1B1*15 (c.388G/c.521C). Among them, SLCO1B1*5 and SLCO1B1*15 haplotypes have been associated with higher serum concentrations of certain drugs, which may be due to a slower hepatic uptake. Although low clinical impact of these SNPs for many drugs that are substrates of OATP1B1 has been found, they markedly affect the pharmacokinetics of statins [13]. As compared with patients carrying the wild-type SLCO1B1*1A haplotype, serum concentrations of statins are higher in patients harboring the c.521T>C variant, which is accompanied by lower drug efficacy together with higher risk of suffering myopathy and rhabdomyolysis [14,15]. The impact of this variant is such that the clinical guidelines released by the ITC and the Dutch Pharmacogenetics Working Group recommend for patients harboring the c.521T>C variant to halve the dose of simvastatin or to replace atorvastatin with fluvastatin, which is a worse OATP1B1 substrate (http://www.pharmgkb.org) [1]. Moreover, patients carrying this variant have higher plasma levels of the anti-HIV drug atazanavir [16], and it has been proposed to reduce the drug dose when these patients also harbor the variants rs2472677 of NR1I2 and rs1045642 of ABCB1 to avoid adverse effects (http://www.pharmgkb.org) [1].

The substrate specificity of OATP1B3, also highly expressed in hepatocytes, markedly overlaps that of OATP1B1. Like other SLCO genes, SLCO1B3 is polymorphic, and many genetic variants have been associated with reduced transport activity or expression of OATP1B3 in vitro [17]. Among them, the most clinically relevant SNPs are c.334T>G (p.Ser112Ala, rs4149117) and c.699G>A (p.Met233Ile, rs7311358). These two very common SNPs have a frequency of 84.2% and 85.3%, respectively. The presence in the OATP1B3 protein of these two amino acid substitutions, but not when they appear separately, reduces the activity of this transporter expressed in a cellular model [18]. In addition, the presence of both SNPs in patients results in elevated plasma levels of tacrolimus, an immunosuppressant used in patients with renal transplantation [19].

The clinical significance of the presence of genetic variants in other members of the OATP family is not well understood, because only weak evidence or contradictory results have been obtained and, therefore, no recommendations have been made for clinical implementation. Thus, the ITC guidelines do not specifically recommend OATP2B1 research in drug development and personalized medicine. However, OATP2B1 is a drug transporter with a broad substrate specificity expressed in the liver and many other tissues, suggesting that it may have an important, but not yet fully elucidated, role in drug bioavailability. OATP2B1 mediates the uptake of statins, antihistamines (fexofenadine), antidiabetics (glibenclamide, glyburide), antiarrhythmics (amiodarone), and some antitumor drugs (antifolate drugs). Although in vitro studies have shown that SLCO2B1 SNPs affect the uptake of some of these drugs [20], in vivo confirmation is still required.

**Table 1.** Genetic variants affecting genes involved in mechanisms of liver drug handling.

| Phase | Gene | Variant | Drugs Affected | Consequences | References |
|-------|------|---------|----------------|--------------|------------|
| 0     | SLCO1B1 | rs4149056 | Statins, Atazanavir | Lower liver uptake. Enhanced toxicity | [13,16] |
|       |       |         | Pravastatin, Rosuvastatin | Lower liver uptake. Reduced efficacy | [14,15] |
| 1     | CYP2B6 | rs3745274, rs8192719, rs28399499 | Efavirenz | Decreased plasma concentrations | [21,22] |
|       | CYP2C19 | rs4986893, rs4244285 | Clopidogrel | Lower activity | [23] |
|       |       |         | Omeprazole, Lansoprazole | Higher plasma concentrations | [24,25] |
| 1     | CYP2C8 | rs1050968 | Paclitaxel, Rosiglitazone, Pioglitazone | Lower response | [26–30] |
### Table 1. Cont.

| Phase | Gene | Variant | Drugs Affected | Consequences | References |
|-------|------|---------|----------------|--------------|------------|
| 1     | CYP2C9 | rs1799853, rs1057910, rs7089580, rs28371686, rs6165452, rs4917639, rs7900194 | Warfarin, Phenytoin, Glipizide, Tolbutamide | Higher response. Enhanced toxicity | [31–34] |
| 1     | CYP2D6 | rs3892097, rs28371706 | Tamoxifen, Codeine | Lower response. Enhanced toxicity | [35–37] |
| 1     | CYP3A5 | rs776746 | Tacrolimus | Lower response | [38,39] |
| 1     | CYP4F2 | rs2108622 | Warfarin, Atenocoumarol | Lower response | [40] |
| 2     | COMT | rs4680 | Catechol-related drugs | Enhanced toxicity | [41] |
| 2     | GSTP1 | rs1695 | Oxaliplatin | Enhanced toxicity | [42] |
| 2     | NAT1 | rs13253389 | Cotoxine | Lower response. Enhanced toxicity | [43] |
| 2     | NAT2 | Several * | Isoniazid, Pyrazinamide, Rifampicin | Lower response. Enhanced toxicity | [44] |
| 2     | SULT1A1 | rs9282861, rs1801030 | SN-38, Flavopiridol, Raloxifene, Ezetimibe | Lower response | [45] |
| 2     | TPMT | rs1800462, rs1142345, rs1805584 | Thiopurine drugs (6-Mercaptopurine, 6-Thioguanine, Azathioprine) | Enhanced toxicity | [46] |
| 2     | UGT1A1 | rs4148323, rs817347 | Indinavir, Irinotecan | Enhanced toxicity | [47] |
|       |       | rs2032582 | Simvastatin, Ondasetron | Higher hepatic clearance. Reduced efficacy | [48,49] |
|       |       | rs1045642 | Ondasetron, Fentanyl | Higher hepatic clearance. Reduced efficacy | [49,50] |
| 3     | ABCB1 | rs2231142 | Allopurinol | Increased plasma urate. Higher dose recommended | [51,52] |
| 3     | ABCG2 | rs1751034 | Tenofovir | Lower plasma levels. Reduced efficacy | [53] |
| 3     | ABCC4 | rs1751034 | Tenofovir | Lower plasma levels. Reduced efficacy | [54] |

Only variants for which there is evidence of high or moderate clinical relevance (levels 1 to 2 in the PharmGKB database classification) have been included. *, See https://www.pharmgkb.org/mutation/PA18/clinicalAnnotation.

### 2.2. Organic Cation Transporters (OCTs)

OCT1 (SLC22A1) is the primary hepatic transporter of organic cations. This carrier is highly expressed at the sinusoidal membrane of the hepatocytes, where it mediates the uptake from the blood of a wide variety of cationic drugs [21]. Recent clinical evidence supports the results obtained from in vitro studies regarding the functional impact of genetic variants on OCT1 transport activity and the significant pharmacokinetic changes that accompany these variants.

Many SNPs and SLC22A1 haplotypes have been linked to clinical effects. Nevertheless, the results are not robust enough for clinical guidelines to include recommendations regarding changes in drug dosage for patients carrying these variants. The five non-synonymous SNPs of SLC22A1 with clinical consequences that have been most extensively studied are c.181C>T (p.Arg61Cys, rs12208357, MAF 6.9%), c.262T>C/A (p.Cys88Ser/Arg, rs55918055, MAF 0.3%), c.1201G>A (p.Gly401Ser, rs34130495,
MAF 2.5%), c.1260_1262del (p.Met420del, rs72552763, MAF 10.4%), and c.1393G>A (p.Gly465Arg, rs34059508, MAF 2.2%). The six haplotypes resulting from these SNPs are SLC22A1(*1 to *6) [21]. The Arg61Cys, Cys88Ser/Arg and Gly465Arg variants have a deleterious effect on OCT1 transport capacity, while others like Gly401Ser and Met420del result in a slight reduction in OCT1 function [56]. Patients carrying any of these OCT1 variants showed higher plasma concentrations of metformin [57] together with a lower hypoglycemic response to this drug [58]. In addition, these variants also affect the pharmacokinetics of imatinib, tropisetron, sumatriptan, morphine, tramadol, and sorafenib [56,59]. Other deleterious SLC22A1 variants have been associated with increased risk of metformin-induced side effects [60]. Although many SNPs have been described in other organic cation transporters, such as OCTN1 (SLC22A4) and OCTN2 (SLC22A5), these have not been linked to relevant clinical consequences [21].

2.3. Organic Anion Transporters (OATs)

Most members of the OAT family have low expression in the liver, except for OAT2 (SLC22A7), which is highly expressed in hepatocytes and has broad substrate specificity. Accordingly, the presence of SNPs in SLC22A7 could be expected to be clinically relevant. However, no robust results have been reported. Patients with colorectal cancer carrying the frequent synonymous variant c.1269C>T (p.Ser423Ser, rs2270860, MAF 33.6%) and the intronic polymorphism g.43272188A>G (rs4149178, MAF 17.3%) have been reported to have a higher risk of capecitabine-induced toxicity [61]. Although several SNPs in the SLC22A9 gene encoding OAT7 have been described, and some of them reduce pravastatin uptake in vitro, the clinical consequences of these variants are not yet well known [62].

3. Phase 1: Drug Oxidoreduction

Several enzymes of the superfamily of cytochrome P450 (CYPs) are involved in the hepatic oxidative metabolism of numerous drugs. Although CYP2C and CYP3A (20%–30% of liver CYPs) are the most important subfamilies, many other CYPs, such as CYP1A2, CYP2B, CYP2D, CYP2E1, CYP2J2, and CYP4F2, are also expressed in the liver and have a clinical impact on drug oxidoreduction [63]. Genetic variants in CYP genes play an important role in liver pharmacogenomics. Thus, the presence of multiallelic polymorphisms has been the rationale for classifying individuals as poor (PM), intermediate (IM), extensive (EM) and ultrafast (UM) drug metabolizers, which is closely related to suffering from adverse drug reactions (ADR) and, in some patients, dosage adjustment is required to obtain the desired drug effect.

3.1. CYP2B6

This enzyme accounts for the oxidation of ≈3% of drugs metabolized by CYPs, such as efavirenz, bupropion, and cyclophosphamide [64]. This gene is highly polymorphic, with variants affecting efavirenz metabolism and pharmacokinetics, which have become relevant for the treatment of HIV [65]. Patients carrying variants c.516G>T (p.Gln172Gln, rs3745274, MAF 25.9%) and g.21563C>T (rs8192719, MAF 26.3%) suffering from HIV infection may have decreased plasma concentrations and increased clearance of efavirenz as compared to patients with the GT or TT and CT or TT genotype, respectively. Moreover, patients with variants c.516G>T (p.Gln172Gln, rs3745274), c.983T>C (p.Ile328Thr, rs28399499, MAF 0.4%), or both 516G>T/983T>C, as well as haplotypes CYP2B6*4 and CYP2B6*6, have been associated with adverse effects of efavirenz treatment [22].

3.2. CYP2C19

There are 30 CYP2C19 variants, some of which have been widely studied due to their clinical relevance in the treatment of gastric ulcers, depression, thromboembolic disease, and epilepsy. Dosing guidelines for patient management [66] and genotyping platforms have been approved by the Food and Drug Administration (FDA) to detect CYP2C19 alleles [67]. Thus, variants c.636G>A (p.Trp212Ter, rs4986893, MAF 1.2%) and c.681G>A (p.Pro227Pro, rs4244285, MAF 14.8%), and loss-of-function alleles
haplotypes, c.482-2313A
and
with NSAIDs. However, further studies are needed to confirm this point [68].

(3 to
*8
(VKORC1), influence warfarin clearance.

CYP2C8*3
and the pharmacokinetics of ibuprofen. This may be due in part to the fact that ibuprofen is
(PPAR) is reduced, but also the risk of developing edema, as compared with individuals carrying
individuals [31]. Lower blood sugar levels during glipizide and tolbutamide therapy have also been
that binds to the receptor more efficiently than tamoxifen. Thus, cancer patients carrying
allele variants *10, *3, *4 (variant c.1846G>A, rs3892097, MAF 18.4%) *4I, *5 and *6 with a PM phenotype
showed a greater risk of relapse [35]. The variants mentioned above also have a role in reducing the effect and increasing the risk of secondary effects of some antidepressants such as amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline and trimipramine. A relationship between the presence of CYP2D6*10, *17 (variant c.1023C>T, p.Thr107Ile/Asn, rs28371706, MAF 2.9%), *1xN, *2, *2aN, *3, *4, *40, *41, *5 and *6 variants and the alteration in the metabolism of codeine to morphine has been reported [37]. Several studies have shown a decrease in morphine levels and in analgesia in PMs that receive codeine compared to IMs, and IMs compared with UMs, which have a higher conversion rate of codeine into morphine, which can lead to toxic systemic concentrations of the later [74]. Other CYP2D6 variants, such as *3, *4, *5 and *10, are involved in ADR events during treatment with fluvoxamine, paroxetine, risperidone, flecainide, propafenone, and metoprolol.

3.6. CYP3A5

Several members of the CYP3A subfamily, such as CYP3A4, CYP3A5, CYP3A7, and CYP3A43, are responsible for the biotransformation of 40%-50% of the 200 most frequently prescribed drugs [75]. CYP3A5 includes 25 allelic variants, of which CYP3A5*3 (g.6986A>G, rs776746, MAF 88.2%) is the most studied one, followed by alleles *6 and *7 [76], whereas *3*3 phenotype implies the absence of expression of this enzyme. Despite the confirmed role of CYP3A5 in the clearance of tacrolimus [38], it has not been consistently associated with the risk of acute rejection after organ transplantation in patients treated with this immunosuppressant. However, there is a dosing equation for the use of tacrolimus in adult kidney transplant recipients, which, together with days post-transplant and other individual factors, includes the CYP3A5 genotype [39]. Thus, EM and IM individuals generally have decreased dosage adjustment as compared with those who are PMs, possibly due to a delay in achieving optimal blood tacrolimus concentrations. Therefore, EMs and IMs would require a higher recommended starting dose [77].

3.7. CYP4F2

This enzyme affects vitamins E and K metabolism. Genetic variants in CYP4F2 gene altering the bioavailability of vitamin K (e.g., c.1297G>A, p.Val433Met, rs2108622, MAF 28.5%) also have an impact on the dosing of several vitamin K antagonists, such as warfarin and acenocoumarol [40].

4. Phase 2: Drug Conjugation

Several enzymes involved in the conjugation with polyatomic moieties play an essential role in drug inactivation by the liver. Moreover, these biotransformations usually result in more polar and hence more water-soluble derivatives, which are more easily secreted into bile or eliminated by the kidney after being extruded from the hepatocyte across the sinusoidal membrane.

4.1. Catechol O-methyl Transferases (COMTs)

This group of enzymes is responsible for the transfer of methyl groups from S-adenosyl methionine to catecholamines. The substrates of COMT include endogenous neurotransmitters but also drugs with catechol structures used in the treatment of hypertension, asthma, and Parkinson’s disease [46]. For the soluble form of COMT, there is a polymorphism affecting the amino acid 108 (c.322G>A, p.Val108Met, rs4680) while for the membrane-associated form (with 50 additional N-terminal amino acids), this identical polymorphism (c.472G>A) is at position 158 (p.Val158Met, rs4680). The Met allele (A) is known as the low activity or “L” variant, whereas the Val (G) or “H” allele is the high activity one [46]. Interindividual differences in the cognitive responses to several drugs used in psychiatric illness are related to COMT genetic variants [78]. Moreover, the effect of diuretics, calcium channel blockers, and angiotensin receptors blockers on systolic or diastolic blood pressure is strongly associated with COMT variants. [79]. In addition, before starting the pharmacological treatment of Parkinson’s disease, it is important to consider the gender and the presence of genetic variants in MAO-B and COMT genes.
(MAO-B-rs1799836 and COMT-rs4680), since the outcome is affected by sexual dimorphism in genes related to dopamine metabolism [80].

4.2. Glutathione S-Transferases (GSTs)

GSTs are a family of enzymes able to catalyze the formation of thioether conjugates between glutathione and xenobiotic compounds. Several anticancer drugs, such as platinum derivatives, anthracyclines, Vinca alkaloids, cyclophosphamide, and phycotoxins are substrates of GSTs [81]. The family of soluble GST enzymes is divided into eight classes designated Alpha, Kappa, Mu, Pi, Sigma, Theta, Zeta and Omega, among which the most critical genes in liver drug metabolism are GSTM1, GSTT1, GSTP1, and GSTA1. Common polymorphisms for GSTP1 have been described, which are associated with the toxicity and response to several anticancer drugs and, in particular, platinum-related agents [82]. Thus, the non-synonymous polymorphism of GSTP1 Ile105Val (c.313A>G in exon 5, rs1695), sometimes referred to as GSTP1*B, is considered as a risk factor in the early onset of neurotoxicity during the treatment of colorectal cancer with oxaliplatin [42].

4.3. N-acetyl Transferases (NATs)

These are cytosolic enzymes found in numerous tissues of different species [46]. In the adult human liver, arylamine-N-acetyltransferases are involved in the biotransformation of aromatic amines and hydrazines [46]. NAT1 and NAT2 are polymorphic enzymes (28 alleles for NAT1 and 88 alleles for NAT2) [83]), and such polymorphisms determine the acetylator phenotype. NAT1 activity may have implications in the response to anticancer drugs. Thus, NAT1 polymorphisms that produce changes in the enzymatic activity may affect the response of these individuals to chemotherapy. NAT1*4 and NAT2*4 are the reference or wild type alleles for the respective genes [84,85]. In contrast to NAT1, NAT2 has a high frequency of functional variation and diversity of haplotypes that differ among ethnic groups. NAT2 genotypes can be grouped into three different phenotypes “slow acetylator” (two slow alleles), “intermediate acetylator” (one slow and one fast one) and “fast acetylator” (two fast alleles) [84].

4.4. Sulfotransferases (SULTs)

These enzymes catalyze the conjugation of 3′-phosphoadenosine 5′-phosphosulfate (PAPS) with an acceptor group (N-, O- or S) in SULT substrates [46]. Sulfonation has an essential role in the biotransformation of many endogenous and xenobiotic compounds. Four families of SULTs (SULT1, SULT2, SULT4, and SULT6) with at least 13 different members have been described. SULTs are divided into membrane-linked and cytosolic enzymes [46]. The best known genetic polymorphisms are those of the hepatic isoform SULT1A1 [46]. The most common allelic variant of SULT1A1 gene in different populations is c.638G>A (p.Arg213His, rs9282861), known as SULT1A1*2, which is associated with higher thermolability and lower enzymatic activity as compared to the wild-type variant [45]. SULT1A1*3, SNP 667A>G (p. Met223Val, rs1801030), is the second most frequent polymorphism, which generates an enzyme with a higher affinity for PAPS and SULT substrates [86].

4.5. Thiopurine-S-Methyltransferase (TPMT)

TPMT activity depends on S-adenosyl methionine to catalyze the S-methylation of aromatic and heterocyclic sulfhydryl compounds that include anticancer and immunosuppressive thiopurines, such as 6-mercaptopurine (6-MP), 6 thioguanine (6-TG) and azathioprine, used for the treatment of acute lymphoblastic leukemia, autoimmune disorders, inflammatory bowel disease, and recipients of solid organ transplantation. The altered enzymatic activity of TPMT causes the accumulation of thiopurine nucleotides and the cytotoxic symptoms leading to hematopoiesis failure [46]. TPMT is a cytosolic enzyme with high expression in the liver and kidney, where its overall activity is determined by the existence of genetic polymorphisms [46]. Up to 28 different alleles of the TPMT gene have been identified [87] and associated with great interindividual variability in the therapeutic efficacy and
toxicity of thiopurines. Among them, the molecular and clinical implications of TPMT*2, TPMT*3A, TPMT*3B, and TPMT*3C have been well studied. The variant TPMT*2 is p.Ala80Pro (c.G238>C, rs1800462) [88], which leads to a protein with 100 times reduced catalytic activity. When patients carrying this allele are treated with standard doses of thiopurines, excessively high levels of these drugs may be reached and hence they have a higher risk of side-effects due to myelosuppression [88]. The variant TPMT*3C, p.Tyr240Cys (c.719A>G, rs1142345) is the most common allele in African-American and East Asian populations. TPMT*3C is associated with decreased TPMT enzymatic activity due to enhanced protein degradation [89]. TPMT*4 (rs1800584) includes a transition from G>A in the final splice acceptor nucleotide in intron 9 of the TPMT gene. The presence of this variant results in deficient TPMT activity in carrier subjects [90].

The TPMT*3A haplotype contains two non-synonymous SNPs, *3B and *3C and is the most common haplotype in the Caucasian population. The TPMT*3A variant results in a significant decrease in TPMT enzymatic activity leading to a higher risk of toxicity when a thiopurine-based therapy is administered [90].

4.6. UDP-Glucuronyltransferases (UGTs)

This is a superfamily of membrane-bound enzymes that catalyze the formation of chemical bonds between nucleophilic O, N, S, or C atoms with uridin-5′-diphosphate-β-D-glucuronic acid [46]. Among the 22 human UGT proteins, UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B7, and 2B15 isoforms are considered the most important in drug metabolism [46]. Liver UGT1A1 is the only enzyme responsible for bilirubin metabolism [91]. The high number of UGT1A1 variants includes enzymes with reduced or increased activity, which results in an altered phenotype [91]. Thus, the UGT1A1*6 allele p.Gly71Arg (c.211G>A, rs4148323) has been associated with hyperbilirubinemia during the treatment with the anti-HIV drug indinavir [92]. The UGT1A1*28 allele (rs3064744) consists of seven TA repeats in the promoter region, which leads to ≈70% decrease in its transcriptional activity and hence diminished gene expression [93,94]. Both UGT1A1*6 and UGT1A1*28 alleles have been extensively studied with regard to drug toxicity in particular to irinotecan, which can produce harmful side effects such as neutropenia and diarrhea [47]. Although the UGT1*28 allele has also been associated with a higher risk of irinotecan-induced side effects, other studies have failed to confirm these noxious effects of irinotecan in carriers of either *28 or *6 genotypes [95–97]. Thus, validation trials to elucidate the usefulness of genotyping these alleles as a convenient practice before treating colorectal cancer patients with irinotecan are still needed.

5. Phase 3: Drug Export

Among detoxification processes, phase 3 consists of the extrusion of xenobiotics from the hepatocytes mainly through ATP-binding cassette (ABC) export pumps [8]. Most genes of this superfamily are highly polymorphic, which has an impact on the functionality of these transporters, resulting in increased or decreased drug concentrations in hepatocytes. These changes can alter the pharmacokinetics of their substrates, affecting the efficacy and/or toxicity of these drugs [98]. Thus, according to data available at the PharmGKB database [1], the presence of SNPs in ABC genes, such as ABCA1, ABCB1, ABCB5, ABCC1-7, ABCC10, ABCG1, and ABCG2, has been associated with altered drug response and toxicity. However, high or moderate clinical relevance (levels 1 to 2 in the PharmGKB database classification) [1] of genetic variants has been reported only in the case of ABCB1, ABCC4, ABCC7, and ABCG2 [98].

5.1. Multidrug Resistance Protein 1 (MDR1)

MDR1, also called P-glycoprotein (P-gp, gene ABCB1), is expressed in many epithelial cells, where it accounts for the transport of a wide variety of drugs [99]. MDR1 is highly expressed at the canalicular membrane of hepatocytes, where this pump mediates the secretion into bile of endogenous and xenobiotic compounds. There is significant interindividual variability in the function of this drug export pump, which may be due to the presence of numerous genetic variants, whose effect on the
transport of hundreds of drugs has been studied in vitro. However, according to the PharmGKB classification, only two SNPs in the \textit{ABCB1} gene have clinical relevance (level 2): c.2677T\textgreater G/A (p.Ser893Ala, rs2032582, MAF 61.7\% and 4.9\% for G and A alleles, respectively) and c.3435T\textgreater C (p.Ile1145Ile, rs1045642, MAF 48.8\%) \[100\]. The presence of both variants is accompanied by high MDR1 expression \[101\]. In addition, rs2032582 variant has been associated with decreased simvastatin concentrations in hepatocytes, probably due to an increase in MDR1-mediated simvastatin secretion into the bile. Patients carrying this variant experience lower simvastatin-induced cholesterol reduction compared to patients with the wild-type genotype \[48\]. Similar MDR1-mediated enhanced hepatic clearance accompanying these SNPs has also been reported to affect the efficacy of other drugs, such as ondansetron \[49\] and fentanyl \[50\]. Moreover, individuals carrying the variant rs1045642 are less likely to suffer from methotrexate-induced liver toxicity than those with the wild-type variant \[51\]. The presence of the rs1045642 variant also decreases the risk of hepatic toxicity induced by other drugs such as digoxin \[52\]. In contrast, in children with acute lymphoblastic leukemia carrying this variant, a relationship between lower plasma levels of methotrexate and a higher risk of neutropenia and thrombocytopenia has been found \[102\].

5.2. Breast Cancer Resistance Protein (BCRP)

BCRP (gene \textit{ABCG2}) is also expressed in the canalicular membrane of hepatocytes, where this pump participates in the extrusion into bile of a wide variety of drugs, with a substrate specificity that partially overlaps that of MDR1 \[103\]. Besides more than 100 intronic variants that lead to reduced mRNA expression, many SNPs have been identified in the coding region of the \textit{ABCG2} gene \[104\]. Two common polymorphisms are c.34G\textgreater A (p.Val12Met, rs2231137, MAF 7.0\%) and c.421C\textgreater A (p.Gln141Lys, rs2231142, MAF 10.1\%). When the variant Val12Met was expressed in K562 cells, this mutation reduced the capacity of BCRP to transport tyrosine kinase inhibitors \[105\]. However, clinical studies have not found any relationship between the presence of this variant and the pharmacokinetics of BCRP substrates \[103\]. The variant rs2231142 affects the nucleotide-binding domain of the transporter and decreases protein levels because it promotes its degradation. It has been recommended that patients with gout carrying the rs223114 variant in \textit{ABCG2} take a higher dose of allopurinol than patients with the wild-type genotype \[53\]. However, this recommendation should be reviewed, because the dosage of the drug is based on urate plasma levels, which as a BCRP substrate can be influenced by changes in the expression and activity of this pump. It has also been shown that patients taking rosuvastatin who carry the allele rs2231142 in \textit{ABCG2} have higher plasma drug concentrations, probably due to lower secretion of this drug into bile \[54\]. Higher accumulation of rosuvastatin in the liver enhances its pharmacological effect, resulting in a more marked reduction in cholesterol levels, but also a higher risk of toxicity \[106\]. When this variant is present together with rs4149056 in the \textit{SLCO1B1} gene, a limitation of the dose of rosuvastatin and atorvastatin is recommended to prevent side effects \[107\]. It has been suggested that individuals carrying this variant could also have increased risk of suffering from drug-induced toxicity during treatment with sulfasalazine, sunitinib, gefitinib, and other statins (simvastatin and fluvastatin) \[108\]. Accordingly, the ITC considers this polymorphism as clinically relevant \[108\].

5.3. Multidrug-Resistance Associated Protein 4 (MRP4)

MRP4 (gene \textit{ABCC4}) is expressed at the basolateral membrane of the hepatocytes, where it plays an important role in preventing the accumulation of bile acids by exporting them to the blood under cholestatic conditions \[109\]. MRP4 has broad substrate specificity, including among its substrates, nucleoside analogs and antiviral drugs. Some SNPs of this highly polymorphic gene have clinical impact \[109\]. For instance, when treated against HIV with tenofovir, patients carrying the very frequent SNP c.3348G\textgreater A (p.Lys1116Asn, rs1751034, frequency of 80.2\%) in the \textit{ABCC4} gene have lower plasma levels of this drug, due to its enhanced MRP4-mediated liver and kidney clearance \[55\].
5.4. Other ABC Genes

The presence of the variants c.656G>A (p.Arg219Lys, rs2230806) and g.49960C>G (rs12003906) in ABCA1 gene results in a decreased function and expression, respectively, of the ABCA1 transporter, which leads to an increased hepatic accumulation of hypolipemic drugs, such as pravastatin and fenofibrate, and hence an enhanced response to these drugs [110]. However, the ability of ABCA1 to transport these drugs has not been demonstrated. Even though more than 100 SNPs have been described in other ABC genes, especially in those of the subfamily ABCC, and for many of them in vitro studies have shown an impact on the expression and function of these transporters, conflicting results have been obtained in clinical studies regarding the relationship between the presence of these SNPs and changes in drug response or induced toxicity [111].

Table 2. Genetic variants affecting genes involved in the liver response to drugs.

| Group                | Gene    | Variants                     | Drugs Affected  | Consequences       | References |
|----------------------|---------|------------------------------|-----------------|--------------------|------------|
| Cholesterol lowering drugs | HMGCR   | rs17244841, rs17238540       | Pravastatin     | Reduced response   | [112]      |
|                      |         | rs17671591                   | Atorvastatin    | Increased response | [113]      |
|                      | APOE    | rs7412                       | Simvastatin, Pravastatin, Atorvastatin | Increased response | [114–116] |
|                      |         | rs449647                     | Lovastatin, Bezafibrate | Altered response | [117]      |
|                      | LDLR    | rs2738466, rs1433099         | Pravastatin     | Increased response | [118]      |
|                      | CETP    | rs1532624                    | Statins         | Reduced response   | [119]      |
| Antidiabetic drugs   | ATM     | rs11212617                   | Sulfonylureas, Metformin | Reduced response | [120,121] |
|                      | IRS1    | rs1801278                    | Metformin       | Reduced response   | [122]      |
|                      | PPARG   | rs1801282                    | Pioglitazone    | Increased response | [123]      |
| Anticoagulant drugs  | VKORC1  | rs99223231, rs9934438, rs8050894, rs2884737 | Warfarin | Increased response Toxicity | [124,125] |
|                      |         | rs7294                       | Warfarin        | Reduced response   | [126,127] |
|                      | KDR     | rs1870377                    | Sorafenib       | Reduced response   | [128,129] |
|                      |         | rs2305948                    | Sorafenib       | Increased response | [128]      |
|                      |         | rs2071559                    | Sorafenib       | Reduced response   | [128]      |
|                      | VEGFA   | rs2010963                    | Sorafenib       | Reduced response   | [130]      |
|                      | VEGFC   | rs4604006                    | Sorafenib       | Reduced response   | [130]      |
|                      | eNOS3   | rs2070744                    | Sorafenib       | Reduced response   | [131]      |
|                      | ANGPT2  | rs55633437                   | Sorafenib       | Reduced response   | [131]      |
|                      | HIF1A   | rs12434438                   | Sorafenib       | Increased response | [132]      |
|                      | ERCCI   | rs11615                      | Gemcitabine, Cisplatin | Increased response | [133]      |
|                      | SLC31A1 | rs12686377                   | Platinum derivatives | Impaired response | [133]      |
|                      | IDH1    | rs121913499, rs121913500     | Ivosidenib      | Increased response | [134]      |
6. The Liver as the Target Organ for Drugs

To carry out their therapeutic effect, several important families of drugs act upon targets located in liver cells and the existence of genetic variants affecting the genes encoding these targets may, therefore, alter the individual response to these drugs.

6.1. Cholesterol-Lowering Drugs

Statins are the most widely used lipid-lowering drugs due to their efficacy in the management of dyslipidemias. Among the genes involved in their mechanism of action are: HMGCR, which encodes 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase); APOE, which encodes apolipoprotein E involved in the transport of cholesterol through the bloodstream; LDLR, which encodes the LDL receptor, and some others. The existence of genetic variants in these genes has important clinical implications on the effects of statins [135,136].

Statins are competitive inhibitors of HMG-CoA reductase, the rate-limiting enzyme of the biosynthesis of cholesterol by hepatocytes. There are two frequent and tightly linked intronic SNPs in the HMGCR gene: SNP12 g.74642855A>T (rs17244841) and SNP29 g.74655498T>G (rs17238540). Although their effects on the expression and activity of this enzyme are unknown, they have been associated with a lower efficacy of pravastatin therapy regarding the decrease in both total cholesterol and LDL-cholesterol [112]. Genotypes CT and TT of the g.74615021C>T (rs17671591) variant have been associated with increased response to atorvastatin (greater reduction in LDL-cholesterol) in patients with hypercholesterolemia, as compared to genotype CC [113].

Conflicting results have been reported by studies assessing the effect of APOE variants on the lipid-lowering efficacy of statins [136]. This gene is expressed as one of the three alleles, which, in order of increasing affinity for the LDL receptor are: E2, E3 (wild-type) and E4. Carriers of the APOE E2 allele (c.526C>T, p.Arg176Cys, rs7412) have a greater reduction of total cholesterol, LDL-cholesterol and triglycerides levels when treated with simvastatin [114], pravastatin [115] or atorvastatin [116]. Some studies have reported that lovastatin therapy was less effective in people carrying the APOE E4 allele (c.388T>C, p.Cys130Arg, rs429358) [137]. However, other authors have not found any impact of these variants on the response to this drug [138]. The c.-491A>T (rs449647) polymorphism produces a significant decrease in APOE promotar activity as the result of altered interactions with transcription factors. This can also influence the response to statin treatment, as carriers of the T allele treated with atorvastatin showed a significantly higher reduction in LDL-cholesterol levels than carriers of the wild-type allele [117]. On the contrary, T carriers present a less satisfactory response to the lipid-lowering drug bezafibrate [117].

Genetic variants in the LDLR locus can affect lipid homeostasis, cardiovascular disease risk, and drug response to statin treatment. Thus, patients with vascular diseases carrying the GG genotype of the genetic variant g.11242765A>G (rs2738466) or the TT genotype of the genetic variant g.11242658T>C (rs1433099) have a better response to pravastatin as compared with those carrying the more frequent AA and CC genotypes, respectively [118].

Cholesteryl ester transfer protein (CETP) is involved in the transport of cholesteryl esters to the liver. The g.57005479C>A (rs1532624) polymorphism on the CETP gene has been associated with the response to statin therapy in a cohort of elderly patients. Thus, individuals with hyperlipidemia and AA and AC genotypes had a poorer response to HMG-CoA reductase inhibitors than patients with CC genotype [119].

The CYTP7A1 gene encodes cholesterol 7-hydroxylase, the rate-limiting enzyme in the neutral pathway of bile acids synthesis from cholesterol. Patients with the GG and GT genotypes of the SNP c.-267C>A (rs3808607) have a decreased response to atorvastatin as compared to patients with the TT genotype. However, contradictory findings have been reported, which prevents these genetic data from this gene from influencing clinical decisions on statin administration [116,139].
6.2. Antidiabetic Drugs

Oral antidiabetic drugs used for the treatment of type 2 diabetes mellitus belong to different families of compounds (biguanides, sulfonylureas, thiazolidinediones, meglitinides, and others). There is a considerable amount of information on the role of genetic variants in the response to diabetic medications [140–142]. Although the main targets of many oral antidiabetic drugs are located in the pancreas and adipose tissue, to fully accomplish their therapeutic effect, the mechanisms of action of some of these drugs also involve targets located in hepatocytes.

Ataxia-telangiectasia mutated (ATM) serine/threonine kinase, known to be involved in DNA repair and cell cycle control, plays a role in the effect of metformin upstream of AMP-activated protein kinase. The C allele of the frequent (57%) variant g.108283161C>A (rs11212617) has been associated with a better response to metformin of type 2 diabetes mellitus patients as compared with individuals carrying the A allele [120,121].

In the liver, insulin receptor substrate 1 (IRS1) and IRS2 are essential in insulin-dependent regulation of glucose and lipid metabolism. When the role of IRS1 variants in the failure of treatment with oral antidiabetic drugs (mostly sulfonylureas and metformin) was investigated, a significant association with the loss-of-function SNP c.2911G>A (p.Gly971Arg, rs1801278) was found [122]. Thus, treatment with oral antidiabetic drugs has >80% higher risk of failing in homozygous individuals for the A allele than in homozygous G carriers [122].

Thiazolidinediones are a therapeutic option for patients with type 2 diabetes mellitus by improving their sensitivity to insulin and β-cell secretory function. The target of thiazolidinediones is PPAR gamma (PPARG gene), a nuclear receptor acting as a lipid sensor. The most frequent variant of PPARG is c.34C>G (p.Pro12Ala, rs1801282, MAF 9.9%), which has been associated with a better response to pioglitazone and has been proposed as a biomarker for identifying patients more likely to respond to this drug [123].

6.3. Antiviral Drugs

Most drugs used to treat viral hepatitis act on the replicative machinery of the virus. However, SNPs in IMPDH2 gene encoding the enzyme inosine 5′-monophosphate dehydrogenase type II have been found to affect the response of patients receiving antiviral hepatitis drugs, such as ribavirin, taribavirin, merimepodib, and mycophenolate mofetil [143,144]. This gene has low genetic diversity, but the non-synonymous variant c.787C>T (p.Leu263Phe, rs121434586) has a significant impact on IMPDH2 activity, which can hence contribute to the interindividual variability regarding the antiviral efficacy of ribavirin [145].

6.4. Anticoagulant Drugs

Oral anticoagulants, such as warfarin, acenocoumarol, phenprocoumon, and phenindione are structurally similar to vitamin K and act as competitive inhibitors of the enzyme VKORC1. However, many patients do not satisfactorily respond to these drugs. In the case of warfarin, differences in the genotype contribute to the interindividual variability in the dose required to reach therapeutic anticoagulant effects [146,147]. The presence of four frequent and tightly linked SNPs located at the VKORC1 gene regulatory regions, i.e., c.-1639C>T (rs9923231), at the promoter, and c.173+1000G>A (rs9934438), c.173+1369C>G (rs8050894) and c.173+324A>C (rs2884737), at intron 1 [124,148], increases the expression of the enzyme and thus the response to warfarin. These SNPs are very frequent, with MAF ranging from 21% to 38%, although this varies according to ethnic factors [149]. Homozygous and heterozygous genotypes of these SNPs have been associated with high or intermediate sensitivity to warfarin, respectively. Accordingly, in c.-1639C>T carriers, it has been recommended to adjust warfarin dosage. Thus, to effectively inhibit clotting factor activation, a higher warfarin dose is needed in patients with CC genotype than in TC genotype carriers, whereas a lower dose is needed in individuals
with TT genotype. In support of this concept, patients carrying this SNP have increased risk of bleeding when treated with warfarin [125].

Other VKORC1 SNPs, such as c.106G>T (p.As36Tyr, rs61742245), c.173+525G>A (rs17708472, at intron 1), c.174-1133A>G (rs2359612, at intron 2), and c.*134C>T (rs7294, at 3′-UTR), are associated with lower sensitivity to coumarin derivatives due to decreased expression of this enzyme. Accordingly, to achieve therapeutic effects in patients carrying these SNPs, an increase in the dose of these drugs has been recommended [126,127].

Non-synonymous variants in the VKORC1 coding region such as c.85G>T (p.Val29Leu, rs104894539), c.134T>C (p.Val45Ala, rs104894540), c.172A>G (p.Arg58Gly, rs104894541) and c.383T>G (p.Leu128Arg, rs104894542) also contribute to the differential response to warfarin and coumarin derivatives [150,151].

6.5. Anticancer Drugs

Although a few patients with hepatocellular carcinoma (HCC) can benefit from chemotherapy, many others do not respond. In that respect, several SNPs in a variety of genes belonging to target pathways of anticancer drugs can predict the lack of response to pharmacological treatment of HCC. For instance, SNPs in genes of the vascular endothelial growth factor (VEGF) signaling pathway have clinical relevance in patients receiving sorafenib. Thus, the missense variant c.1416A>T (p.Gln472His, rs1870377, MAF 22.1%) in the KDR gene (also known as VEGFR2) affects the fifth NH2-terminal Ig-like domain within the extracellular region of the receptor and has been reported to decrease the ability of KDR to bind VEGF [152]. In a Chinese HCC cohort, homozygous patients for the wild-type allele (AA) of this variant showed better response to sorafenib and longer time to progression than patients with heterozygous (TA) or homozygous (TT) genotype [128]. This SNP has also been associated with a higher risk of adverse reactions to sorafenib, which include hypertension and hand-foot skin reaction [129]. The c.889G>A (p.Val297Ile, rs2305948) variant, which affects the third NH2-terminal Ig-like domain within the extracellular region of the VEGFR-2 receptor, also has an impact on the ligand binding efficiency [152]. The AA genotype of this variant was associated with a longer time to progression [128]. The promoter variant c.-604T>C (rs2071559) alters the binding site for the transcription factor E2F, resulting in a decreased KDR expression [152]. A homozygous genotype for the C allele has been associated with shorter overall survival in HCC patients treated with sorafenib [128].

A relationship between the response of HCC patients to sorafenib and the presence of SNPs in VEGF genes, which encode ligands of VEGF receptors, has been reported. Thus, the combination of GG genotype of the SNP c.-94C>G (rs2010963) at the 5′-UTR region of the VEGFA and CC genotype of the intronic SNP c.1422+200T>C (g.176687621T>C, rs4604006) in VEGFC was associated with worse outcomes in HCC patients receiving sorafenib. However, it remains unclear whether those SNPs are associated with changes in circulating levels of VEGF [130]. Although there is no information on the relationship between the presence of VEGF variants and the response of HCC to other targeted therapies, these variants have been related to sorafenib response in patients with metastatic colorectal cancer [153]. The results from genotyping angiogenesis-related genes show that only VEGFA variant rs2010963 maintains an independent correlation with progression-free and overall survival in these patients [153], which has led researchers to propose VEGFA rs2010963 genotyping as a useful tool for a more accurate selection of optimal candidates for sorafenib therapy among metastatic colorectal cancer patients [153].

Polymorphisms in other genes directly related to the VEGF-dependent angiogenesis pathway, such as c.-813C>T (g.150992991C>T, rs2070744) in eNOS3, c.714G>T (p.Thr238Thr, rs55633437) in ANGPT2 and c.1065+2924G>A (g.61730580G>A, rs12434438) in HIF1A have also been linked to sorafenib efficacy in HCC patients [131,154]. In these studies, homozygous for the eNOS3 SNP and patients carrying at least one T allele of the ANGPT2 SNP had worse overall and progression-free survival [131,154]. Another element that plays a key role in angiogenesis is the hypoxia-inducible factor 1-alpha, a transcription factor encoded by the HIF1A gene and involved in VEGF expression.
The presence of the A allele of the HIF1A rs12434438 variant has been related to a better outcome in patients receiving sorafenib. Accordingly, this variant has been proposed as an independent predictor for a favorable response of HCC to sorafenib [131,154].

Regarding cholangiocarcinoma (CCA), several variants have been associated with the efficacy of drugs commonly used in the treatment of this cancer. The combination of two single polymorphisms, c.354T>C (p.Asn118Asn, rs11615) in ERCC1, a DNA repair gene, and c.136-14361C>T (g.113241753C>T, rs12686377) in SLC31A1, encoding CTR1, one of the main transporters of platinum derivatives, has been proposed as a potential biomarker to predict the response to the combined treatment of gemcitabine with cisplatin, which is the first-line chemotherapeutic regimen for CCA patients [133]. In addition, a higher expression of the truncated \(\Delta N\) isoform \(\Delta 133p53\) of the TP53 gene detected in tumor tissues has been associated with worse outcomes in CCA patients [155], but no clinical correlation with drug response has been reported. A relationship between high levels of that p53 variant and the resistance to 5-fluorouracil, the second-line therapy for CCA, has been confirmed by an in vitro study [156].

Since conventional therapy for CCA has limited effectiveness, new strategies based on the tumor mutational profile are being studied. The investigation of targeted therapies to treat this cancer has been focused on somatic mutations frequently occurring in CCAs, such as the gain-of-function mutations c.394C>T/A/G (p.Arg132Cys/Ser/Gly, rs121913499) and c.395G>T (p.Arg132Leu, rs121913500) in the IDH1 gene and several FGFR2 fusions or translocations [157]. A recent phase III study with ivosidenib, an inhibitor of the mutant IDH1 protein, has shown improved progression-free survival in CCA patients with mutated IDH1 [158]. The results of a phase II trial for pemigatinib, an FGFR inhibitor, in CCA patients harboring FGFR2 fusions or rearrangements are also promising [159].

In addition to the alterations in its intracellular targets, sorafenib requires crossing the plasma membrane to reach them. This is hampered by the reduced function of OCT1, which frequently occurs in HCC and CCA cells. Among the reasons accounting for this loss-of-function, which have recently been elucidated [160,161], is the existence of up to seven inactivating somatic mutations identified both in HCC and CCA [56]. In a series of 23 HCC and 15 CCA, the probability of containing at least one of these mutations was 48% in HCC and 40% in CCA [56].

7. Conclusions and Perspectives

The existence of genetic variants affecting a high number of genes expressed in liver cells or mutations generated in liver tumors has important clinical repercussions due to the role of this organ in drug handling but also because, for many drugs, the liver is the target for their mechanism of action. The present review has highlighted the importance of defining the genomic profile concerning drug-related genes to predict the outcome of treatments based on these drugs as well as to develop more efficient and selective agents able to overcome the lack of effect associated with the existence of genetic variants, which may affect the hepatic handling of drugs in many ways, such as (i) impaired uptake, (ii) enhanced export, (iii) altered metabolism due to decreased activation of prodrugs or enhanced inactivation of active compounds, and (iv) altered molecular targets located in the liver due to genetic changes or activation/downregulation of alternative/compensatory pathways. In conclusion, the advancement in this field of modern pharmacology, which allows one to predict the outcome of the treatments and to develop more effective and selective agents able to overcome the lack of effect associated with the existence of some genetic variants, is required to bring forward a more personalized medicine.

Author Contributions: J.J.G.M., M.A.S., M.J.M., A.S.-M., A.G.T., O.B. and M.R.R. have contributed substantially to the elaboration of the manuscript. Moreover, O.B. and M.R.R. contributed equally to the coordination of this review article. All authors have read and agreed to the published version of the manuscript.

Funding: This study was funded by the CIBERehd (EHD15PI05/2016) and “Fondo de Investigaciones Sanitarias, Instituto de Salud Carlos III”, Spain (PI16/00598 and PI19/00819, co-funded by European Regional Development Fund/European Social Fund, “Investing in your future”); Spanish Ministry of Economy, Industry and Competitiveness (SAF2016-75197-R); “Junta de Castilla y Leon” (SA063P17); AECC Scientific Foundation (2017/2020), Spain; and “Centro Internacional sobre el Envejecimiento” (OLD-HEPAMARKER, 0348_CIE_6_E),
Spain; Fundación University of Salamanca, Spain (PC-TCUE18-20_051). ASM was supported by a predoctoral scholarship (FPU) funded by the Ministry of Science, Innovation and Universities, Spain. AGT was supported by a predoctoral scholarship funded by the University of Salamanca (Program III) and Santander Bank, Spain.

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

**References**

1. 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] [PubMed]

2. Rehm, H.L.; Berg, J.S.; Brooks, L.D.; Bustamante, C.D.; Evans, J.P.; Landrum, M.J.; Ledbetter, D.H.; Maglott, D.R.; Martin, C.L.; Nussbaum, R.L.; et al. ClinGen—The Clinical Genome Resource. *N. Engl. J. Med.* 2015, 372, 2235–2242. [CrossRef] [PubMed]

3. Giacomini, K.M.; Huang, S.M.; Tweedie, D.J.; Benet, L.Z.; Brouwer, K.L.; Chu, X.; Dahlin, A.; Evers, R.; Fischer, V.; Hillgren, K.M.; et al. Membrane transporters in drug development. *Nat. Rev. Drug Discov.* 2010, 9, 215–236. [CrossRef] [PubMed]

4. Hagenbuch, B.; Meier, P.J. Organic anion transporting polypeptides of the OATP/SLC21 family: Phylogenetic classification as OATP/SLCO superfamily, new nomenclature and molecular/functional properties. *Pflug. Arch. Eur. J. Physiol.* 2004, 447, 653–665. [CrossRef]

5. Zamek-Gliszczynski, M.J.; Taub, M.E.; Chothe, P.P.; Chu, X.; Giacomini, K.M.; Kim, R.B.; Ray, A.S.; Stocker, S.L.; Unadkat, J.D.; Wittwer, M.B.; et al. Transports in Drug Development: 2018 ITC Recommendations for Transporters of Emerging Clinical Importance. *Clin. Pharmacol. Ther.* 2018, 104, 890–899. [CrossRef]

6. Giacomini, K.M.; Balimane, P.V.; Cho, S.K.; Eadon, M.; Edeki, T.; Hillgren, K.M.; Huang, S.M.; Sugiyama, Y.; Weitz, D.; Wen, Y.; et al. International Transporter Consortium commentary on clinically important transporter polymorphisms. *Clin. Pharmacol. Ther.* 2013, 94, 23–26. [CrossRef]

7. Maeda, K. Organic anion transporting polypeptide (OATP)1B1 and OATP1B3 as important regulators of the pharmacokinetics of substrate drugs. *Biol. Pharm. Bull.* 2015, 38, 155–168. [CrossRef]

8. Marin, J.J. Plasma membrane transporters in modern liver pharmacology. *Scientifica* 2012, 2012, 428139. [CrossRef]

9. Kalliokoski, A.; Neuvonen, M.; Neuvonen, P.J.; Niemi, M. Different effects of SLCO1B1 polymorphism on the pharmacokinetics and pharmacodynamics of repaglinide and nateglinide. *J. Clin. Pharmacol.* 2008, 48, 311–321. [CrossRef]

10. Lee, H.H.; Ho, R.H. Interindividual and interethnic variability in drug disposition: Polymorphisms in organic anion transporting polypeptide 1B1 (OATP1B1; SLCO1B1). *Br. J. Clin. Pharmacol.* 2017, 83, 1176–1184. [CrossRef]

11. Nozawa, T.; Minami, H.; Sugiura, S.; Tsuij, A.; Tamai, I. Role of organic anion transporter OATP1B1 (OATP-C) in hepatic uptake of irinotecan and its active metabolite, 7-ethyl-10-hydroxycamptothecin: In vitro evidence and effect of single nucleotide polymorphisms. *Drug Metab. Dispos. Biol. Fate Chem.* 2005, 33, 434–439. [CrossRef]

12. Crowe, A.; Zheng, W.; Miller, J.; Pahwa, S.; Alam, K.; Fung, K.M.; Rubin, E.; Yin, F.; Ding, K.; Yue, W. Characterization of Plasma Membrane Localization and Phosphorylation Status of Organic Anion Transporting Polypeptide (OATP) 1B1 c.521 T>C Nonsynonymous Single-Nucleotide Polymorphism. *Pharm. Res.* 2019, 36, 101. [CrossRef] [PubMed]

13. Link, E.; Parish, S.; Armitage, J.; Bowman, L.; Heath, S.; Matsuda, F.; Gut, I.; Lathrop, M.; Collins, R. SLCO1B1 variants and statin-induced myopathy—A genomewide study. *N. Engl. J. Med.* 2008, 359, 789–799. [CrossRef] [PubMed]

14. Niemi, M.; Neuvonen, P.J.; Hofmann, U.; Backman, J.T.; Schwab, M.; Lutjohann, D.; von Bergmann, K.; Eichelbaum, M.; Kivisto, K.T. Acute effects of pravastatin on cholesterol synthesis are associated with SLCO1B1 (encoding OATP1B1) haplotype *17. Pharm. Genom.* 2005, 15, 303–309. [CrossRef] [PubMed]

15. Pasanen, M.K.; Fredrikson, H.; Neuvonen, P.J.; Niemi, M. Different effects of SLCO1B1 polymorphism on the pharmacokinetics of atorvastatin and rosvastatin. *Clin. Pharmacol. Ther.* 2007, 82, 726–733. [CrossRef] [PubMed]
16. Bonora, S.; Rusconi, S.; Calcagno, A.; Bracchi, M.; Vigano, O.; Cusato, J.; Lanza, M.; Trentalange, A.; Marinaro, L.; Siccardi, M.; et al. Successful pharmacogenetics-based optimization of unboosted atazanavir plasma exposure in HIV-positive patients: A randomized, controlled, pilot study (the REYAGEN study). J. Antimicrob. Chemother. 2015, 70, 3096–3099. [CrossRef] [PubMed]

17. Letschert, K.; Keppler, D.; Konig, J. Mutations in the SLCO1B3 gene affecting the substrate specificity of the hepatocellular uptake transporter OATP1B3 (OATP8). Pharmacogenetics 2004, 14, 441–452. [CrossRef]

18. Picard, N.; Yee, S.W.; Woillard, J.B.; Lebranchu, Y.; Le Meur, Y.; Giacomini, K.M.; Marquet, P. The role of organic anion-transporting polypeptides and their common genetic variants in mycophenolic acid pharmacokinetics. Clin. Pharmacol. Ther. 2010, 87, 100–108. [CrossRef]

19. Boivin, A.A.; Cardinal, H.; Barama, A.; Naud, J.; Pichette, V.; Hebert, M.J.; Roger, M. Influence of SLCO1B3 genetic variations on tacrolimus pharmacokinetics in renal transplant recipients. Drug Metab. Pharmacokinet. 2013, 28, 274–277. [CrossRef] [PubMed]

20. Nozawa, T.; Nakajima, M.; Tamai, I.; Noda, K.; Nezu, Y.; Sai, Y.; Tsuji, A.; Yokoi, T. Genetic polymorphisms of human organic anion transporters OATP-C (SLC21A6) and OATP-B (SLC21A9): Allele frequencies in the Japanese population and functional analysis. J. Pharmacol. Exp. Ther. 2002, 302, 804–813. [CrossRef]

21. Lozano, E.; Briz, O.; Macias, R.I.R.; Serrano, M.A.; Marin, J.J.G.; Herraez, E. Genetic Heterogeneity of SLC22 Family of Transporters in Drug Disposition. J. Pers. Med. 2018, 8. [CrossRef] [PubMed]

22. Sukasem, C.; Cressy, T.R.; Prapaithong, P.; Tawon, Y.; Pasomsub, E.; Srichunrusami, C.; Jantararoungtong, T.; Lallemand, M.; Chantarattia, W. Pharmacogenetic markers of CYP2B6 associated with efavirenz plasma concentrations in HIV-1 infected Thai adults. Br. J. Clin. Pharmacol. 2012, 74, 1005–1012. [CrossRef] [PubMed]

23. Collet, J.P.; Hulot, J.S.; Anzaha, G.; Pena, A.; Chastre, T.; Caron, C.; Silvain, J.; Cayla, G.; Bellemain-Appaix, A.; Vignalou, J.B.; et al. High doses of clopidogrel to overcome genetic resistance: The randomized crossover CLOVIS-2 (Clopidogrel and Response Variability Investigation Study 2). JACC Cardiovasc. Interv. 2011, 4, 392–402. [CrossRef] [PubMed]

24. Furuta, T.; Shirai, N.; Takashima, M.; Xiao, F.; Hanai, H.; Sugimura, H.; Ohashi, K.; Ishizaki, T.; Kaneko, E. Effect of genotypic differences in CYP2C19 on cure rates for Helicobacter pylori infection by triple therapy with a proton pump inhibitor, amoxicillin, and clarithromycin. Clin. Pharmacol. Ther. 2001, 69, 158–168. [CrossRef] [PubMed]

25. Baldwin, R.M.; Ohlsson, S.; Pedersen, R.S.; Mwinyi, J.; Ingelman-Sundberg, M.; Eliasson, E.; Bertilsson, L. Increased omeprazole metabolism in carriers of the CYP2C19*17 allele: a pharmacokinetic study in healthy volunteers. Br. J. Clin. Pharmacol. 2008, 65, 767–774. [CrossRef] [PubMed]

26. Aquilante, C.L.; Niemi, M.; Gong, L.; Altman, R.B.; Klein, T.E. PharmGKB summary: Very important pharmacogene information for cytochrome P450, family 2, subfamily C, polypeptide 8. Pharm. Genom. 2013, 23, 721–728. [CrossRef]

27. Stage, T.B.; Christensen, M.M.; Feddersen, S.; Beck-Nielsen, H.; Brosen, K. The role of genetic variants in CYP2C8, LPIN1, PPARC1A and PPARgamma on the trough steady-state plasma concentrations of rosiglitazone and on glycosylated haemoglobin A1c in type 2 diabetes. Pharm. Genom. 2013, 23, 219–227. [CrossRef]

28. Marcath, L.A.; Kidwell, K.M.; Robinson, A.C.; Vangipuram, K.; Burness, M.L.; Griggs, J.J.; Poznack, C.V.; Schott, A.F.; Hayes, D.F.; Henry, N.L.; et al. Patients carrying CYP2C8*3 have shorter systemic paclitaxel exposure. Pharmacogenomics 2019, 20, 95–104. [CrossRef]

29. Dawed, A.Y.; Donnelly, L.; Tavendale, R.; Carr, F.; Leese, G.; Palmer, C.N.; Pearson, E.R.; Zhou, K. CYP2C8 and SLCO1B1 Variants and Therapeutic Response to Thiazolidinediones in Patients With Type 2 Diabetes. Diabetes Care 2016, 39, 1902–1908. [CrossRef]

30. Haraya, K.; Kato, M.; Chiba, K.; Sugiyama, Y. Prediction of inter-individual variability on the pharmacokinetics of CYP2C8 substrates in human. Drug Metab. Pharmacokinet. 2017, 32, 277–285. [CrossRef]

31. Aithal, G.P.; Day, C.P.; Kesteven, P.J.; Daly, A.K. Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. Lancet 1999, 353, 717–719. [CrossRef]

32. Kidd, R.S.; Straughn, A.B.; Meyer, M.C.; Blaisdell, J.; Goldstein, J.A.; Dalton, J.T. Pharmacokinetics of chlorpheniramine, phenytoin, glipizide and nifedipine in an individual homozygous for the CYP2C9*3 allele. Pharmacogenetics 1999, 9, 71–80. [CrossRef] [PubMed]
33. Ninomiya, H.; Mamiya, K.; Matsuo, S.; Ieiri, I.; Higuchi, S.; Tashiro, N. Genetic polymorphism of the CYP2C subfamily and excessive serum phenytoin concentration with central nervous system intoxication. *Ther. Drug Monit.* 2000, 22, 230–232. [CrossRef] [PubMed]

34. Kirchheiner, J.; Brockmoller, J. Clinical consequences of cytochrome P450 2C9 polymorphisms. *Clin. Pharmacol. Ther.* 2005, 77, 1–16. [CrossRef]

35. Cronin-Fenton, D.P.; Damkier, P. Tamoxifen and CYP2D6: A Controversy in Pharmacogenetics. *Adv. Pharmacol.* 2018, 83, 65–91. [CrossRef]

36. Goetz, M.P.; Sangkuhl, K.; Guchelaar, H.J.; Schwab, M.; Province, M.; whirl-Carrillo, M.; Symmans, W.F.; McLeod, H.L.; Ratain, M.J.; Zembutsu, H.; et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and Tamoxifen Therapy. *Clin. Pharmacol. Ther.* 2018, 103, 770–777. [CrossRef]

37. Oscarson, M.; Hidestrand, M.; Johansson, I.; Ingelman-Sundberg, M. A combination of mutations in the CYP2D6*17 (CYP2D6Z) allele causes alterations in enzyme function. *Mol. Pharmacol.* 1997, 52, 1034–1040. [CrossRef]

38. Vecchia Genvигir, F.D.; Campos-Salazar, A.B.; Felipe, C.R.; Tedesco-Silva, H., Jr.; Medina-Pestana, J.O.; Quateli, D.; Cerda, A.; Hirata, M.H.; Herrero, M.J.; Alino, S.F.; et al. CYP3A5*3 and CYP2C8*3 variants influence exposure and clinical outcomes of tacrolimus-based therapy. *Pharmacogenomics* 2020, 21, 7–21. [CrossRef]

39. Passey, C.; Birnbaum, A.K.; Brundage, R.C.; Oetting, W.S.; Israni, A.K.; Jacobson, P.A. Dosing equation for Patients with Chronic Kidney Disease. *Clin. Ther.* 2014, 36, 1242–1252.e2. [CrossRef]

40. Sak, K. The Val158Met polymorphism in COMT gene and cancer risk: Role of endogenous and exogenous catechols. *Drug Metab. Rev.* 2017, 49, 56–83. [CrossRef] [PubMed]

41. LeMasters, G.K.; Khurana Hershey, G.K.; Sivaprasad, U.; Martin, L.J.; Pilipenko, V.; Ericksen, M.B.; Burkle, J.W.; Lindsey, M.A.; Bernstein, D.I.; Lockey, J.E.; et al. N-acetylsulfotransferase 1 polymorphism increases cotinine levels in Caucasian children exposed to secondhand smoke: The CCAAPS birth cohort. *Pharm. J.* 2015, 15, 189–195. [CrossRef] [PubMed]

42. Cronin-Fenton, D.P.; Damkier, P. Tamoxifen and CYP2D6: A Controversy in Pharmacogenetics. *Clin. Pharmacol. Ther.* 2014, 93, 2884–2894. [CrossRef] [PubMed]

43. LeMasters, G.K.; Khurana Hershey, G.K.; Sivaprasad, U.; Martin, L.J.; Pilipenko, V.; Ericksen, M.B.; Burkle, J.W.; Lindsey, M.A.; Bernstein, D.I.; Lockey, J.E.; et al. N-acetylsulfotransferase 1 polymorphism increases cotinine levels in Caucasian children exposed to secondhand smoke: The CCAAPS birth cohort. *Pharm. J.* 2015, 15, 189–195. [CrossRef] [PubMed]

44. Dompreh, A.; Tang, X.; Zhou, J.; Yang, H.; Topletz, A.; Adu Ahwireng, E.; Antwi, S.; Enimil, A.; Langaeae, T.; Peloquin, C.A.; et al. Effect of Genetic Variation of NAT2 on Isoniazid and SLCO1B1 and CES2 on Rifampin Pharmacokinetics in Ghanaian Children with Tuberculosis. *Antimicrob Agents Chemother* 2018, 62. [CrossRef] [PubMed]

45. Sak, K. The Val158Met polymorphism in COMT gene and cancer risk: Role of endogenous and exogenous catechols. *Drug Metab. Rev.* 2017, 49, 56–83. [CrossRef] [PubMed]

46. Vecchia Genvигir, F.D.; Campos-Salazar, A.B.; Felipe, C.R.; Tedesco-Silva, H., Jr.; Medina-Pestana, J.O.; Quateli, D.; Cerda, A.; Hirata, M.H.; Herrero, M.J.; Alino, S.F.; et al. CYP3A5*3 and CYP2C8*3 variants influence exposure and clinical outcomes of tacrolimus-based therapy. *Pharmacogenomics* 2020, 21, 7–21. [CrossRef]

47. Passey, C.; Birnbaum, A.K.; Brundage, R.C.; Oetting, W.S.; Israni, A.K.; Jacobson, P.A. Dosing equation for Patients with Chronic Kidney Disease. *Clin. Ther.* 2014, 36, 1242–1252.e2. [CrossRef]

48. Becker, M.L.; Visser, L.E.; van Schaik, R.H.; Hofman, A.; Ingelman-Sundberg, M. A combination of mutations in the CYP2D6*17 (CYP2D6Z) allele causes alterations in enzyme function. *Mol. Pharmacol.* 1997, 52, 1034–1040. [CrossRef]

49. He, H.; Yin, J.Y.; Xu, Y.J.; Li, Y.; Liu, Z.G.; Zhou, F.; Zhai, M.; Li, Y.P.; et al. Association of ABCB1 polymorphisms with the eect of Genetic Variation of NAT2 on Isoniazid and SLCO1B1 and CES2 on Rifampin Pharmacokinetics in Ghanaian Children with Tuberculosis. *Antimicrob Agents Chemother* 2018, 62. [CrossRef] [PubMed]

50. Lotsch, J.; von Hentig, N.; Freynhagen, R.; Griesinger, N.; Zimmermann, M.; Doehring, A.; Rohrbacher, M.; Sittl, R.; Geisslinger, G. Cross-sectional analysis of the influence of currently known pharmacogenetic modulators on opioid therapy in outpatient pain centers. *Pharm. Genom.* 2009, 15, 2013–2020. [CrossRef] [PubMed]

51. Suthandiram, S.; Gan, G.G.; Zain, S.M.; Bee, P.C.; Lian, L.H.; Chang, K.M.; Ong, T.C.; Mohamed, Z. Effect of polymorphisms within methotrexate pathway genes on methotrexate toxicity and plasma levels in adults with hematological malignancies. *Pharmacogenomics* 2014, 15, 1479–1494. [CrossRef] [PubMed]
69. Van Booven, D.; Marsh, S.; McLeod, H.; Carrillo, M.W.; Sangkuhl, K.; Klein, T.E.; Altman, R.B. Cytochrome P450 2C9-CYP2C9. *Pharm. Genom.* 2010, 20, 277–281. [CrossRef]

70. Pinto, N.; Dolan, M.E. Clinically relevant genetic variations in drug metabolizing enzymes. *Curr. Drug Metab.* 2011, 12, 487–497. [CrossRef]

71. Lee, C.R.; Goldstein, J.A.; Pieper, J.A. Cytochrome P450 2C9 polymorphisms: A comprehensive review of the in-vitro and human data. *Pharmacogenomics* 2002, 12, 251–263. [CrossRef]

72. Owen, R.P.; Sangkuhl, K.; Klein, T.E.; Altman, R.B. Cytochrome P450 2D6. *Pharm. Genom.* 2009, 19, 559–562. [CrossRef]

73. Yang, Y.; Botton, M.R.; Scott, E.R.; Scott, S.A. Sequencing the CYP2D6 gene: From variant allele discovery to clinical pharmacogenetic testing. *Pharmacogenomics* 2017, 18, 673–685. [CrossRef] [PubMed]

74. Crews, K.R.; Gaedigk, A.; Dunnenberger, H.M.; Beijnen, J.H.; Huitema, A.D. An overview of the relations between polymorphisms in drug metabolising enzymes and drug transporters and survival after cancer drug treatment. *Cancer Treat. Rev.* 2011, 37, 487–497. [CrossRef] [PubMed]

75. Kuehl, P.; Zhang, J.; Lin, Y.; Lamba, J.; Assem, M.; Schuetz, J.; Watkins, P.B.; Daly, A.; Wrighton, S.A.; Hall, S.D.; et al. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. *Nat. Genet.* 2001, 27, 383–391. [CrossRef] [PubMed]

76. Lamba, J.; Decker, B.; Barbarino, J.M.; Peterson, J.F.; Stein, C.M.; Sadee, W.; Shen, D.D.; Callaghan, J.T.; Sadhasivam, S.; et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clin. Pharmacol. Ther.* 2014, 95, 376–382. [CrossRef] [PubMed]

77. Hein, D.W.; Boukouvala, S.; Grant, D.M.; Minchin, R.F.; Sim, E.; Crews, K.R.; Gaedigk, A.; Dunnenberger, H.M.; Beijnen, J.H.; Huitema, A.D.; et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. *Clin. Pharmacol. Ther.* 2015, 98, 19–24. [CrossRef] [PubMed]

78. Scheggia, D.; Sannino, S.; Scattoni, M.L.; Papaleo, F. COMT as a drug target for cognitive functions and dysfunctions. *CNS Neurol. Disord Drug Targets* 2012, 11, 209–221. [CrossRef]

79. Xu, J.; Bostrom, A.E.; Saved, M.; Dubey, R.K.; Waeger, G.; Vollenweider, P.; Marques-Vidal, P.; Mwinyi, J.; Schioth, H.B. A genetic variant in the catechol-O-methyl transferase (COMT) gene is related to age-dependent differences in the therapeutic effect of calcium-channel blockers. *Medicine* 2017, 96, e7029. [CrossRef]

80. Sampaio, T.E.; Dos Santos, E.U.D.; de Lima, G.D.C.; Dos Anjos, R.S.G.; da Silva, R.C.; Asano, A.G.C.; Asano, N.M.J.; Crovella, S.; de Souza, P.R.E. MAO-B and COMT Genetic Variations Associated With Levodopa Treatment Response in Patients With Parkinson’s Disease. *J. Clin. Pharmacol.* 2018, 58, 920–926. [CrossRef]

81. Wheeler, H.E.; Gamazon, E.R.; Stark, A.L.; O’Donnell, P.H.; Gorsic, L.K.; Huang, R.S.; Cox, N.J.; Dolan, M.E. Genome-wide meta-analysis identifies variants associated with platinating agent susceptibility across populations. *Pharm. J.* 2013, 3, 35–43. [CrossRef] [PubMed]

82. Ekhart, C.; Rodenhuis, S.; Smits, P.H.; Beijnen, J.H.; Huitema, A.D. An overview of the relations between polymorphisms in drug metabolising enzymes and drug transporters and survival after cancer drug treatment. *Cancer Treat. Rev.* 2009, 35, 18–31. [CrossRef] [PubMed]

83. Hein, D.W.; Boukouvala, S.; Grant, D.M.; Minchin, R.F.; Sim, E. Changes in consensus arylamine N-acetyltransferase gene nomenclature. *Pharm. Genom.* 2008, 18, 367–368. [CrossRef]

84. Sim, E.; Fakis, G.; Laurieri, N.; Boukouvala, S. Arylamine N-acetyltransferases—From drug metabolism and pharmacogenetics to identification of novel targets for pharmacological intervention. *Adv. Pharmacol.* 2012, 63, 169–205. [CrossRef]

85. Sim, E.; Abuhammad, A.; Ryan, A. Arylamine N-acetyltransferases: From drug metabolism and pharmacogenetics to drug discovery. *Br. J. Pharmacol.* 2014, 171, 2705–2725. [CrossRef] [PubMed]

86. Raftogianis, R.B.; Wood, T.C.; Weinshilboum, R.M. Human phenol sulfotransferases SULT1A2 and SULT1A1: Genetic polymorphisms, allozyme properties, and human liver genotype-phenotype correlations. *Biochem. Pharmacol.* 1999, 58, 605–616. [CrossRef]

87. Garat, A.; Cauffiez, C.; Renault, N.; Lo-Guidice, J.M.; Allorge, D.; Chevalier, D.; Houdret, N.; Chavatte, P.; Loriot, M.A.; Gala, J.L.; et al. Characterisation of novel defective thiopurine S-methyltransferase allelic variants. *Biochem. Pharmacol.* 2008, 76, 404–415. [CrossRef]

88. Krynetski, E.Y.; Schuetz, J.D.; Galpin, A.J.; Pui, C.H.; Relling, M.V.; Evans, W.E. A single point mutation leading to loss of catalytic activity in human thiopurine S-methyltransferase. *Proc. Natl. Acad. Sci. USA* 1995, 92, 949–953. [CrossRef]
89. Salavaggione, O.E.; Wang, L.; Wiepert, M.; Yee, V.C.; Weinshilboum, R.M. Thiopurine S-methyltransferase pharmacogenetics: Variant allele functional and comparative genomics. Pharm. Genom. 2005, 15, 801–815. [CrossRef]

90. Otterness, D.M.; Szumlanski, C.L.; Wood, T.C.; Weinshilboum, R.M. Human thiopurine methyltransferase pharmacogenetics. Kindred with a terminal exon splice junction mutation that results in loss of activity. J. Clin. Investig. 1998, 101, 1036–1044. [CrossRef]

91. Strassburg, C.P. Pharmacogenetics of Gilbert’s syndrome. Pharmacogenomics 2008, 9, 703–715. [CrossRef] [PubMed]

92. Zucker, S.D.; Qin, X.; Rouster, S.D.; Yu, F.; Green, R.M.; Keshavan, P.; Feinberg, J.; Sherman, K.E. Mechanism of indinavir-induced hyperbilirubinemia. Proc. Natl. Acad. Sci. USA 2001, 98, 12671–12676. [CrossRef]

93. Bosma, P.J.; Chowdhury, J.R.; Bakker, C.; de Boer, A.; Oostra, B.A.; Lindhout, D.; Tytgat, G.N.; Jansen, P.L.; Oude Elferink, R.P.; et al. The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert’s syndrome. N. Engl. J. Med. 1995, 333, 1171–1175. [CrossRef]

94. Tukey, R.H.; Strassburg, C.P.; Mackenzie, P.I. Pharmacogenomics of human UDP-glucuronosyltransferases and irinotecan toxicity. Mol. Pharmacol. 2002, 62, 446–450. [CrossRef] [PubMed]

95. Marcuello, E.; Altes, A.; Menoyo, A.; Del Rio, E.; Gomez-Pardo, M.; Baiget, M. UGT1A1 and UGT1A9 polymorphisms predict response and toxicity in colorectal cancer patients treated with capecitabine/irinotecan. Clin. Cancer Res. 2005, 11, 1226–1236. [PubMed]

96. Innocenti, F.; Undevia, S.D.; Iyer, L.; Chen, P.X.; Das, S.; Kocherginsky, M.; Karrison, T.; Janisch, L.; Ramirez, J.; Rudin, C.M.; et al. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J. Clin. Oncol. 2004, 22, 1382–1388. [CrossRef]

97. Marcello, E.; Altes, A.; Menoyo, A.; Del Rio, E.; Gomez-Pardo, M.; Baiget, M. UGT1A1 gene variations and irinotecan treatment in patients with metastatic colorectal cancer. Br. J. Cancer 2004, 91, 678–682. [CrossRef]

98. Lopez-Fernandez, L.A. ATP-Binding Cassette Transporters in the Clinical Implementation of Pharmacogenetics. J. Pers. Med. 2018, 8. [CrossRef]

99. Briz, O.; Perez-Silva, L.; Al-Abdulla, R.; Abete, L.; Reviejo, M.; Romero, M.R.; Marin, J.J.G. What “The Cancer Genome Atlas” database tells us about the role of ATP-binding cassette (ABC) proteins in chemoresistance to anticancer drugs. Expert Opin. Drug Metab. Toxicol. 2019, 15, 577–593. [CrossRef]

100. Wolking, S.; Schaeffer, E.; Lerche, H.; Schwab, M.; Nies, A.T. Impact of Genetic Polymorphisms of ABCB1 (MDR1, P-Glycoprotein) on Drug Disposition and Potential Clinical Implications: Update of the Literature. Clin. Pharmacokinet. 2015, 54, 709–735. [CrossRef]

101. Pang, L.; Word, B.; Xu, J.; Wang, H.; Hammons, G.; Huang, S.M.; Lyn-Cook, B. ATP-Binding Cassette Genes Genotype and Expression: A Potential Association with Pancreatic Cancer Development and Chemoresistance? Gastroenterol. Res. Pract. 2014, 2014, 419391. [CrossRef] [PubMed]

102. Zgheib, N.K.; Akra-Ismail, M.; Aridi, C.; Mahfouz, R.; Abboud, M.R.; Solh, H.; Muwakkit, S.A. Genetic polymorphisms in candidate genes predict increased toxicity with methotrexate therapy in Lebanese children with acute lymphoblastic leukemia. Pharmac. Genom. 2014, 24, 387–396. [CrossRef]

103. Mao, Q.; Unadkat, J.D. Role of the breast cancer resistance protein (ABCG2) in drug transport. AAPS J. 2005, 7, E118–E133. [CrossRef] [PubMed]

104. Ishikawa, T.; Nakagawa, H. Human ABC transporter ABCG2 in cancer chemotherapy and pharmacogenomics. J. Exp. Ther. Oncol. 2009, 8, 5–24. [PubMed]

105. Skoglund, K.; Boiso Moreno, S.; Jonsson, J.I.; Vikingsson, S.; Carlsson, B.; Green, H. Single-nucleotide polymorphisms of ABCG2 increase the efficacy of tyrosine kinase inhibitors in the K562 chronic myeloid leukemia cell line. Pharm. Genom. 2014, 24, 52–61. [CrossRef]

106. Tomlinson, B.; Hu, M.; Lee, V.W.; Lui, S.S.; Chu, T.T.; Poon, E.W.; Ko, G.T.; Baum, L.; Tam, L.S.; Li, E.K. ABCG2 polymorphism is associated with the low-density lipoprotein cholesterol response to rosuvastatin. Circ. Cardiovasc. Genet. 2013, 6, 400–408. [CrossRef]

107. Fohner, A.E.; Brackman, D.J.; Giacomini, K.M.; Altman, R.B.; Klein, T.E. PharmGKB summary: Very important pharmacogene information for ABCG2. Pharm. Genom. 2017, 27, 420–427. [CrossRef]
109. Berthier, J.; Arnion, H.; Saint-Marcoux, F.; Picard, N. Multidrug resistance-associated protein 4 in pharmacology: Overview of its contribution to pharmacokinetics, pharmacodynamics and pharmacogenetics. Life Sci. 2019, 231, 116540. [CrossRef]

110. Voora, D.; Shah, S.H.; Reed, C.R.; Zhai, J.; Crosslin, D.R.; Messer, C.; Salisbury, B.A.; Ginsburg, G.S. Pharmacogenetic predictors of statin-mediated low-density lipoprotein cholesterol reduction and dose response. Circ. Cardiovasc. Genet. 2008, 1, 100–106. [CrossRef]

111. Silverton, L.; Dean, M.; Moitra, K. Variation and evolution of the ABC transporter genes ABCB1, ABCC1, ABCG2, ABCG5 and ABCG8: Implication for pharmacogenetics and disease. Drug Metab. Drug Interact. 2011, 26, 169–179. [CrossRef] [PubMed]

112. Chasman, D.I.; Posada, D.; Subrahmanyan, L.; Cook, N.R.; Stanton, V.P., Jr.; Ridker, P.M. Pharmacogenetic study of statin therapy and cholesterol reduction. JAMA 2004, 291, 2821–2827. [CrossRef] [PubMed]

113. Cuevas, A.; Fernandez, C.; Ferrada, L.; Zambrano, T.; Rosales, A.; Saavedra, N.; Salazar, L.A. HMGCR rs17671591 SNP Determines Lower Plasma LDL-C after Atorvastatin Therapy in Chilean Individuals. Basic Clin. Pharmacol. Toxicol. 2016, 118, 292–297. [CrossRef] [PubMed]

114. Nestel, P.; Simons, L.; Barter, P.; Clifton, P.; Hamilton-Craig, I.; Sikaris, K.; Sullivan, D. A comparative study of the efficacy of simvastatin and gemfibrozil in combined hyperlipoproteinemia: Prediction of response by baseline lipids, apo E genotype, lipoprotein(a) and insulin. Atherosclerosis 1997, 129, 231–239. [CrossRef]

115. Or dovas, J.M.; Lopez-Miranda, J.; Perez-Jimenez, F.; Rodriguez, C.; Park, J.S.; Cole, T.; Schaefer, E.J. Effect of apolipoprotein E and A-I V phenotypes on the low density lipoprotein response to HMG CoA reductase inhibitor therapy. Atherosclerosis 1995, 113, 157–166. [CrossRef]

116. Thompson, J.F.; Man, M.; Johnson, K.J.; Wood, L.S.; Lira, M.E.; Lloyd, D.B.; Banerjee, P.; Milos, P.M.; Myrand, S.P.; Paulauskis, J.; et al. An association study of 43 SNPs in 16 candidate genes with atorvastatin response. Pharm. J. 2005, 5, 352–358. [CrossRef]

117. Garcia-Otin, A.L.; Civeira, F.; Aristegui, R.; Diaz, C.; Recalde, D.; Sol, J.M.; Masramon, X.; Hernandez, G.; Pocovi, M. Allelic polymorphism -491A/T in apo E gene modulates the lipid-lowering response in combined hyperlipidemia treatment. Eur. J. Clin. Invest. 2002, 32, 421–428. [CrossRef]

118. Polisecchi, E.; Muallem, H.; Maeda, N.; Peter, I.; Robertson, M.; McMahon, A.D.; Ford, I.; Packard, C.; Shepherd, J.; Jukema, J.W.; et al. Genetic variation at the LDL receptor and HMG-CoA reductase gene loci, lipid levels, statin response, and cardiovascular disease incidence in PROSPER. Atherosclerosis 2008, 200, 109–114. [CrossRef]

119. de Keyser, C.E.; Eijgelsheim, M.; Hofman, A.; Sibbrands, E.J.; Maitland-van der Zee, A.H.; van Duijn, C.M.; Uitterlinden, A.G.; Witteman, J.C.; Ch Stricker, B.H. Single nucleotide polymorphisms in genes that are associated with a modified response to statin therapy: The Rotterdam Study. Pharm. J. 2011, 11, 72–80. [CrossRef]

120. Zhou, K.; Bellenguez, C.; Spencer, C.C.; Bennett, A.J.; Coleman, R.L.; Tavendale, R.; Hawley, S.A.; Donnelly, L.A.; Schofield, C.; Groves, C.J.; et al. Common variants near ATM are associated with glycemic response to metformin in type 2 diabetes. Nat. Genet. 2011, 43, 117–120. [CrossRef]

121. van Leeuwen, N.; Nijpels, G.; Becker, M.L.; Deshmukh, H.; Zhou, K.; Stricker, B.H.; Uitterlinden, A.G.; Hofman, A.; van ’t Riet, E.; Palmer, C.N.; et al. A gene variant near ATM is significantly associated with a modified response to statin treatment in type 2 diabetes: A replication and meta-analysis of five cohorts. Diabetologia 2012, 55, 1971–1977. [CrossRef]

122. Prudente, S.; Di Paola, R.; Pezzilli, S.; Garofolo, M.; Lamachia, O.; Filardi, T.; Mannino, G.C.; Mercuri, L.; Alberico, F.; Scarale, M.G.; et al. Pharmacogenetics of oral antidiabetes drugs: Evidence for diverse signals at the IRS1 locus. Pharm. J. 2018, 18, 431–435. [CrossRef]

123. Hsieh, M.C.; Lin, K.D.; Tien, K.J.; Tu, S.T.; Hsiao, J.Y.; Chang, S.J.; Lin, S.R.; Shing, S.J.; Chen, H.C. Common polymorphisms of the peroxisome proliferator-activated receptor-gamma (Pro12Ala) and peroxisome proliferator-activated receptor-gamma coactivator-1 (Gly482Ser) and the response to pioglitazone in Chinese patients with type 2 diabetes mellitus. Metabolism 2010, 59, 1139–1144. [CrossRef]

124. Wang, D.; Chen, H.; Momary, K.M.; Cavallari, L.H.; Johnson, J.A.; Sadée, W. Regulatory polymorphism in vitamin K epoxide reductase complex subunit 1 (VKORC1) affects gene expression and warfarin dose requirement. Blood 2008, 112, 1013–1021. [CrossRef]
125. Mega, J.L.; Walker, J.R.; Ruff, C.T.; Vandell, A.G.; Nordio, F.; Deenadayalu, N.; Murphy, S.A.; Lee, J.; Mercuri, M.F.; Giugliano, R.P.; et al. Genetics and the clinical response to warfarin and edoxaban: Findings from the randomised, double-blind ENGAGE AF-TIMI 48 trial. *Lancet* 2015, 385, 2280–2287. [CrossRef]

126. Loebstein, R.; Dvoskin, I.; Halkin, H.; Vescelsky, M.; Lubetsky, A.; Rechavi, G.; Amariglio, N.; Cohen, Y.; Ken-Dror, G.; Almog, S.; et al. A coding VKORC1 Asp36Tyr polymorphism predisposes to warfarin resistance. *Blood* 2007, 109, 2477–2480. [CrossRef]

127. Li, T.; Lange, L.A.; Li, X.; Susswein, L.; Bryant, B.; Malone, R.; Lange, E.M.; Huang, T.Y.; Stafford, D.W.; Evans, J.P. Polymorphisms in the VKORC1 gene are strongly associated with warfarin dosage requirements in patients receiving anticoagulation. *J. Med. Genet.* 2006, 43, 740–744. [CrossRef] [PubMed]

128. Zheng, Y.B.; Zhan, M.X.; Zhao, W.; Liu, B.; Huang, J.W.; He, X.; Fu, S.R.; Zhao, Y.; Li, Y.; Hu, B.S.; et al. The relationship of kinase insert domain receptor gene polymorphisms and clinical outcome in advanced hepatocellular carcinoma patients treated with sorafenib. *Mol. Oncol.* 2014, 8, 21–39. [CrossRef] [PubMed]

129. Jain, L.; Sissung, T.M.; Danesi, R.; Kohn, E.C.; Dahut, W.L.; Kummar, S.; Venzon, D.; Liewehr, D.; English, B.C.; Baum, C.E.; et al. Hypertension and hand-foot skin reactions related to VEGFR2 genotype and improved clinical outcome following bevacizumab and sorafenib. *J. Exp. Clin. Cancer Res.* 2010, 29, 95. [CrossRef] [PubMed]

130. ScartoZZi, M.; Faloppi, L.; Svegliati Baroni, G.; Loretelli, C.; Piscaglia, F.; Iavarone, M.; Toniutto, P.; Fava, G.; De Minicis, S.; Mandolesi, A.; et al. VEGF and VEGFR genotyping in the prediction of clinical outcome for HCC patients receiving sorafenib: The ALICE-1 study. *Int. J. Cancer* 2014, 135, 1247–1256. [CrossRef] [PubMed]

131. Marisi, G.; Petracci, E.; Faloppi, L.; Foschi, F.G.; Lauletta, G.; Iavarone, M.; Canale, M.; Valijusti, M.; Neri, L.M.; et al. ANGPT2 and NOS3 Polymorphisms and Clinical Outcome in Advanced Hepatocellular Carcinoma Patients Receiving Sorafenib. *Cancers* 2019, 11. [CrossRef] [PubMed]

132. Faloppi, L.; Puzzoni, M.; Casadei Gardini, A.; Silvestris, N.; Masi, G.; Marisi, G.; Vivaldi, C.; Gadaleta, C.D.; Ziranu, P.; Bianconi, M.; et al. Angiogenesis Genotyping and Clinical Outcomes in Patients with Advanced Hepatocellular Carcinoma Receiving Sorafenib: The ALICE-2 Study. *Target. Oncol.* 2020, 15, 115–126. [CrossRef] [PubMed]

133. Pongmaneratanakul, S.; Tanasanvimon, S.; Pengsuparp, T.; Areepium, N. Prevalence of CTR1 and ERCC1 Polymorphisms and Response of Biliary Tract Cancer to Gemcitabine-Platinum Chemotherapy. *Asian Pac. J. Cancer Prev.* 2017, 18, 857–861. [CrossRef] [PubMed]

134. Lowery, M.A.; Burris, H.A.; 3rd; Janku, F.; Shroff, R.T.; Cleary, J.M.; Azad, N.S.; Goyal, L.; Maher, E.A.; Gore, L.; Hollebecque, A.; et al. Safety and activity of ivosidenib in patients with IDH1-mutant advanced cholangiocarcinoma: A phase 1 study. *Lancet Gastroenterol. Hepatol.* 2019, 4, 711–720. [CrossRef]

135. Maggo, S.D.; Kennedy, M.A.; Clark, D.W. Clinical implications of pharmacogenetic variation on the effects of statins. *Drug Saf.* 2011, 34, 1–19. [CrossRef] [PubMed]

136. Maxwell, W.D.; Ramsey, L.B.; Johnson, S.G.; Moore, K.G.; Shtutman, M.; Schoonover, J.H.; Kawaguchi-Suzuki, M. Impact of Pharmacogenetics on Efficacy and Safety of Statin Therapy for Dyslipidemia. *Drug Saf.* 2011, 34, 1–19. [CrossRef] [PubMed]

137. Carmena, R.; Roederer, G.; Mailloux, H.; Lussier-Cacan, S.; Davignon, J. The response to lovastatin treatment in patients with heterozygous familial hypercholesterolemia is modulated by apolipoprotein E polymorphism. *Metabolism* 1993, 42, 895–901. [CrossRef]

138. Sanllehy, C.; Casala, E.; Rodriguez-Villar, C.; Zambon, D.; Ojuel, J.; Ballesta, A.M.; Ros, E. Lack of interaction of apolipoprotein E phenotype with the lipoprotein response to lovastatin or gemfibrozil in patients with primary hypercholesterolemia. *Metabolism* 1998, 47, 560–565. [CrossRef]

139. Kajinami, K.; Brousseau, M.E.; Ordovas, J.M.; Schaefer, E.J. Interactions between common genetic polymorphisms in ABCG5/G8 and CYP7A1 on LDL cholesterol-lowering response to atorvastatin. *Atherosclerosis* 2004, 175, 287–293. [CrossRef]

140. Maruthur, N.M.; Gribble, M.O.; Bennett, W.L.; Bolen, S.; Wilson, L.M.; Balakrishnan, P.; Sahu, A.; Bass, E.; Kao, W.H.; Clark, J.M. The pharmacogenetics of type 2 diabetes: A systematic review. *Diabetes Care* 2014, 37, 876–886. [CrossRef] [PubMed]

141. Singh, S.; Usman, K.; Banerjee, M. Pharmacogenetic studies update in type 2 diabetes mellitus. *World J. Diabetes* 2016, 7, 302–315. [CrossRef] [PubMed]
142. Mannino, G.C.; Andreozzi, F.; Sesti, G. Pharmacogenetics of type 2 diabetes mellitus, the route toward tailored medicine. *Diabetes Metab Res. Rev.* 2019, 35, e3109. [CrossRef] [PubMed]

143. Shields, W.W.; Pockros, P.I. Ribavirin analogs. *Clin. Liver Dis.* 2009, 13, 419–427. [CrossRef] [PubMed]

144. Thomas, E.; Ghany, M.G.; Liang, T.J. The application and mechanism of action of ribavirin in therapy of hepatitis C. *Antivir. Chemother.* 2012, 23, 1–12. [CrossRef]

145. Wang, J.; Zeevi, A.; Webber, S.; Giriutta, D.M.; Addonizio, L.; Selby, R.; Hutchinson, I.V.; Burckart, G.J. A novel variant L263F in human inosine 5′-monophosphate dehydrogenase 2 is associated with diminished enzyme activity. *Pharm. Genom.* 2007, 17, 283–290. [CrossRef]

146. Cooper, G.M.; Johnson, J.A.; Langae, T.Y.; Feng, H.; Stanaway, I.B.; Schwarz, U.I.; Ritchie, M.D.; Stein, C.M.; Roden, D.M.; Smith, J.D.; et al. A genome-wide scan for common genetic variants with a large influence on warfarin maintenance dose. *Blood* 2008, 112, 1022–1027. [CrossRef] [PubMed]

147. Cha, P.C.; Mushiroda, T.; Takahashi, A.; Kubo, M.; Minami, S.; Kamatani, N.; Nakamura, Y. Genome-wide association study identifies genetic determinants of warfarin responsiveness for Japanese. *Hum. Mol. Genet.* 2010, 19, 4735–4744. [CrossRef]

148. Limd, N.A.; Wadelius, M.; Cavallari, L.; Eriksen, N.; Crawford, D.C.; Lee, M.T.; Chen, C.H.; Motsinger-Reif, A.; Sagreiya, H.; Liu, N.; et al. Warfarin pharmacogenetics: A single VKORC1 polymorphism is predictive of dose across 3 racial groups. *Blood* 2010, 115, 3827–3834. [CrossRef]

149. Johnson, J.A.; Cavallari, L.H. Pharmacogenetics and cardiovascular disease—Implications for personalized medicine. *Pharmacol. Rev.* 2015, 65, 987–1009. [CrossRef]

150. Rost, S.; Fregin, A.; Ivaskevicius, V.; Conzelmann, E.; Hortnagel, K.; LaPegeard, K.; Seifried, E.; Scharrer, I.; Tuddenham, E.G.; et al. Mutations in VKORC1 cause warfarin resistance and multiple coagulation factor deficiency type 2. *Nature 2004, 427, 537–541.* [CrossRef]

151. Ramirez, A.H.; Shi, Y.; Schildcruit, J.S.; Delaney, J.T.; Xu, H.; Oetjens, M.T.; Zuvich, R.L.; Basford, M.A.; Bowton, E.; Jiang, M.; et al. Predicting warfarin dosage in European-Americans and African-Americans using DNA samples linked to an electronic health record. *Pharmacogenomics 2012, 13, 407–418.* [CrossRef] [PubMed]

152. Wang, Y.; Zheng, Y.; Zhang, W.; Yu, H.; Lou, K.; Zhang, Y.; Zhao, B.; Yang, Y.; Hui, R. Polymorphisms of KDR gene are associated with coronary heart disease. *J. Am. Coll Cardiol.* 2007, 50, 760–767. [CrossRef] [PubMed]

153. Giampieri, R.; Salvatore, L.; Del Prete, M.; Prochilo, T.; D’Anzeo, M.; Loretelli, C.; Loupakis, F.; Aprile, G.; Maccaroni, E.; Andrikou, K.; et al. Angiogenesis genotyping and clinical outcome during regorafenib treatment in metastatic colorectal cancer patients. *Sci. Rep.* 2016, 6, 25195. [CrossRef]

154. Faloppi, L.; Casadei Gardini, A.; Masì, G.; Silvestris, N.; Loretelli, C.; Ulivi, P.; Vivaldi, C.; Bianconi, M.; Giampieri, R.; Bittoni, A.; et al. Angiogenesis polymorphisms profile in the prediction of clinical outcome of advanced HCC patients receiving sorafenib: Combined analysis of VEGF and HIF-1α—Final results of the ALICE-2 study. *J. Clin. Oncol.* 2016, 34, 280. [CrossRef]

155. Nutthasirikul, N.; Limpaiboon, T.; Leelayuwat, C.; Patrakitkomjorn, S.; Jearanaikoon, P. Ratio disruption with previously treated locally advanced or metastatic cholangiocarcinoma (CCA). *Ann. Oncol.* 2019, 30. [CrossRef]

156. Vogel, A.; Sahai, V.; Hollebecque, A.; Vaccaro, G.; Melisi, D.; Al-Rajabi, R.; Paulson, A.S.; Borad, M.J.; Gallinson, D.; Murphy, A.G.; et al. LBA40FIGHT-202: A phase II study of pemigatinib in patients (pts) with previously treated locally advanced or metastatic cholangiocarcinoma (CCA). *Ann. Oncol.* 2019, 30. [CrossRef]
160. Al-Abdulla, R.; Lozano, E.; Macias, R.I.R.; Monte, M.J.; Briz, O.; O’Rourke, C.J.; Serrano, M.A.; Banales, J.M.; Avila, M.A.; Martinez-Chantar, M.L.; et al. Epigenetic events involved in organic cation transporter 1-dependent impaired response of hepatocellular carcinoma to sorafenib. *Br. J. Pharmacol.* **2019**, *176*, 787–800. [CrossRef] 

161. Lozano, E.; Macias, R.I.R.; Monte, M.J.; Asensio, M.; Del Carmen, S.; Sanchez-Vicente, L.; Alonso-Pena, M.; Al-Abdulla, R.; Munoz-Garrrido, P.; Satriano, L.; et al. Causes of hOCT1-Dependent Cholangiocarcinoma Resistance to Sorafenib and Sensitization by Tumor-Selective Gene Therapy. *Hepatology* **2019**, *70*, 1246–1261. [CrossRef] [PubMed] 

© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).