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Review

Pharmacogenetics in oncology: Unveiling its potential in treatment personalization and beyond

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Summary

The effectiveness and tolerability of medicines can vary considerably from person to person, even at the same dose. This variation is influenced by many factors, including constitutional genetic characteristics. In fact, some people have genetic variations that are common and neutral in the population, known as polymorphisms, which can affect drug metabolism or make them more susceptible to certain adverse effects. These variations can lead to dose-dependent toxicity in the case of genetic polymorphisms of metabolic enzymes or hypersensitivity to drugs. Pharmacogenetics therefore examines the specific genetic factors of each patient to understand their sensitivity to treatment and their risk of developing side effects. By enabling proactive adjustment of dosage and/or treatment, pharmacogenetics minimizes the risk of adverse effects and offers promising prospects for a more personalized approach to tumour management. This review will focus on the potential of pharmacogenetics in cancer care, from cancer treatment to supportive care. It will provide an overview of pharmacogenetic recommendations from national and international scientific and professional societies that are currently used in clinical practice. In addition, we will discuss the challenges and perspectives associated with integrating pharmacogenetics into clinical practice for more personalized management of cancer patients.

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Introduction

The effectiveness and tolerability of medicines can vary considerably from person to person, even at the same dose. This variability is influenced by many factors, including genetic characteristics. In fact, some people have genetic variations that are common and neutral in the population, known as polymorphisms, which can affect drug metabolism or make them more susceptible to certain adverse effects.

Genetic variations in enzymes involved in drug metabolism can lead to dose-dependent toxicities. For most compounds where the parent molecule is active, reduced metabolism can cause the buildup of the active and toxic molecule, resulting in adverse effects. Conversely, increased metabolism can render the standard dosage ineffective by not providing enough of the active molecule. The opposite applies to prodrugs, where increased metabolism is beneficial. Additionally, certain polymorphisms can lead to drug hypersensitivity, causing unpredictable and non-dose-dependent idiosyncratic toxicity, often associated with genetic variations affecting immune sensitivity.

Pharmacogenetics is defined as "the study of the link between some germline characteristics of an individual and the response of the organism to drugs". It is important to distinguish pharmacogenetics from pharmacogenomics. According to the U.S. Food and Drug Administration (FDA), pharmacogenomics is "the study of how genetic variations influence an individual's response to drugs". It encompasses the analysis of both germline and somatic genetic variations to optimize drug prescriptions across various medical fields. In oncology, pharmacogenomics enables the molecular profiling of tumors to guide targeted therapies, while pharmacogenetics focuses on inherited genetic variations to predict treatment responses and minimize adverse effects. Although tumor genetic alterations are central to therapeutic decisions, the complementary role of pharmacogenetics in personalized tumor management is essential. By preemptively analyzing pharmacogenetic polymorphisms, it is possible to adjust the dosage from the treatment initiation to optimize efficacy and limit the risk of adverse effects.

This literature review will highlight the potential of pharmacogenetics in anticancer therapies and their associated supportive treatments. It will review pharmacogenetic recommendations issued by national and international scientific societies. Additionally, we will address the challenges and prospects associated with integrating pharmacogenetics into clinical practice for even more personalized patient management.

Pharmacogenetics of anticancer drugs

Cytotoxic chemotherapies often require dosage adjustment based on physiological parameters and rigorous clinical and biological monitoring to prevent toxic effects while maintaining optimal efficacy. Furthermore, the importance of controlling pharmacological exposure is widely recognized for most conventional chemotherapy agents due to their narrow therapeutic window. Pharmacokinetics is now well established in clinical care but few molecules have pharmacogenetic factors clearly demonstrated enough clinical impact to be considered "actionable," meaning therapeutic modification are only recommended but not mandatory. Genetic polymorphisms modulate detoxification functions (as glutathione S-transferases), drug-metabolizing enzymes (as CYP450 family) or drug transport (as ATP-binding cassettes).

In this section, main pharmacogenes impacting cancer treatment for which national and international recommendations have been issued will be described.

Irinotecan

Irinotecan is a commonly used antineoplastic agent in the treatment of advanced colorectal cancers, administered via intravenous infusion, either as monotherapy or in combination. This prodrug, which exerts its cytotoxic action by the inhibition of DNA topoisomerase type I, is responsible for the formation of transient single-strand breaks. The toxic metabolite of irinotecan called SN-38 (7-ethyl-10-hydroxycamptothecin) exhibits toxicity 100 to 1000 times greater than the parent molecule. The toxicity of irinotecan is inversely proportional to the activity of UGT1A1, which detoxifies SN-38 by conjugation to form an inactive compound, SN-38G, more easily eliminated by the liver and kidneys. Irinotecan metabolism also involves cytochrome P450 enzymes, mainly CYP3A4 and, to a lesser extent, CYP3A5, giving rise to two inactive metabolites, 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]carbonyloxycamptothecin (APC), and 7-ethyl-10-(4-amino-1-piperidino) carbonyloxycamptothecin (NPC)

The main adverse effects include neutropenia (up to 34% grade 3–4), late-onset diarrhea (up to 20% grade 3–4), and nausea-vomiting (up to 13% grade 3–4). A high pre-treatment bilirubin level (greater than 0.7 or 1 mg/dL depending on studies), reflecting a deficiency in glucuronidation, is a predictive factor for severe neutropenia. A bilirubin level exceeding three times the upper limit of normal is a contraindication to treatment.

UGT1A1 has over sixty genetic variants, particularly in the promoter and coding regions of the gene. Among these variants, UGT1A1*28 (NC_000002.12 (Homo sapiens chromosome 2, GRCh38.p2) g.233760235TA[6], c.-39_-40insTA $(TA)_7TA$) is a major pharmacogenetic marker associated with hematological and digestive toxicity of irinotecan. Its frequency varies among ethnic groups (about 40% in Caucasians, 45% in African Americans, and 10% in Japanese). The number of "TA" repeats in the $(TA)_7TAA$ sequence of this allele is proportional to the enzymatic deficiency, which affects tolerance to irinotecan.

While few studies have shown an association between the UGT1A1*28 allele and treatment efficacy, the *28 variant has clearly been correlated with irinotecan toxicity (particularly

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neutropenia and late-onset diarrhea). Several meta-analyses have confirmed that individuals carrying at least one *28 allele have a significantly higher incidence of grade 3/4 febrile neutropenia and, to a lesser extent, grade 3/4 diarrhea compared to *1/*1 genotype patients [1]. The maximum tolerated dose in *28/*28 individuals (130 mg/m^2) is significantly lower than in *1/*28 (310–340 mg/m^2) and *1/*1 (370–390 mg/m^2) subjects under the FOLFIRI regimen (5FU – folinic acid – irinotecan). Preemptive genotyping of UGT1A1 is therefore beneficial to anticipate and reduce severe toxicities associated with irinotecan. The National Pharmacogenetics Network (RNPGx) has developed recommendations to guide irinotecan prescription, summarized in *table I*. Although recommendations only concern the *28 allele due to its high frequency, the UGT1A1*6 (NG_002601.2:g.175755G > A–NM_000463.2:c.211G > A-p.(Gly71Arg)), UGT1A1*27 (NC_000002.12 (Homo sapiens chromosome 2, GRCh38.p2 g.233760973C > A–c.868C > A–p.(Pro229Gln)) UGT1A1*36 defined as $TA_{(5)}$ (NG_002601.2:g.175492TA[6] -), UGT1A1*37 defined as $TA_{(8)}$ (NG_002601.2:g.175492TA[9]) allele are also associated with altered UGT1A1 metabolism. Note that in case of *6/*6 homozygosity, as with *28/*28, the FDA also recommends reducing the initial dose by 30% in the first cycle and adjusting according to tolerance.

Although the *CYP3A5* polymorphism plays a minor role in irinotecan metabolism and expressed only in some populations (not in the Caucasian population), it is not considered to have a significant impact.

In addition to drug-metabolizing genes, polymorphisms in transcription factors like PXR, CAR and VDR have also emerged in the literature but are not yet included in recommendations [2].

Irinotecan is also administered in other indications, especially in pediatrics at lower dosage but few studies highlighted the impact of pharmacogenetics with toxicities. This should be evaluated to achieve to pharmacogenetic recommandations if necessary in other cancer types.

Antimetabolite medication

Nucleotide analogues: fluoropyrimidines

Fluorouracil (5-FU) is a widely used antimetabolite medication for treating various solid tumors, including colorectal, breast, ovarian, and upper aerodigestive tract cancers. Capecitabine, on the other hand, is an oral prodrug of 5-FU. When administered intravenously (IV), over 80% of the 5-FU dose is metabolized in the liver into inactive metabolites by an enzyme called dihydropyrimidine dehydrogenase (DPD). DPD enzymatic deficiencies can lead to severe grade 3 to 4 toxicities in 10% to 30% of patients, and in some cases, these toxicities can be fatal (0.3% to 2%). These adverse effects include hematological, digestive, and mucosal issues [3,4]. The interindividual variability in DPD activity can partly be explained by genetic variations in the *DPYD* gene, which encodes for this enzyme. Although complete deficiencies in DPD are rare (0.1% to 0.5% in the general population), partial deficiencies are more common (3% to 10% of Caucasian patients). Several mutations (see *table II*) are recognized as significantly associated with an increased risk of toxicity under fluoropyrimidines: the presence of one of these mutations is predictive of 5-FU-related toxicity [3].

However, only 4% to 5% of Caucasian patients carry one of these four commonly screened mutations ("DPYD*2A": Chr1(GRCh37):g.97915614C > T–NM_000110.4(DPYD):c.1905 + 1G > A–p.?//Chr1(GRCh37):g.97547947T > A–NM_000110.4(DPYD):c.2846A > T- p.(Asp949Val)//"HapB3'': Chr1(GRCh37):g.98045449G > C+ g.98039419C > T–NM_000110.4(DPYD):c.1129-5923C > G+ c.1236G > A)//"DPYD*13'': Chr1(GRCh37):g.97981343A > C–NM_000110.4(DPYD):c.1679T > G–p.(Ile560Ser)). Consequently, screening based solely on these four

Table I

Irinotecan and UGT1A1: recommendations from the RNPGx

UGT1A1 genotype	Genotype?	*1/*1	Patients carrying *6, *27 or *28 in heterozygous state	Patients carrying *6, *27 or *28 in heterozygous state
Irinotecan < 180 mg/m^2 (FOLFIRI–FOLFIRINOX)	Non applicable	Risk of toxicity not increased: initially planned dose appropriate	Risk of toxicity not increased: initially planned dose appropriate	Risk of toxicity not increased: initially planned dose appropriate
Irinotecan 180–230 mg/m^2 (FOLFIRI standard)	Recommended	Risk of toxicity not increased: initially planned dose appropriate	Moderately increased risk of toxicity: monitoring recommanded	Significant risk of toxicity: 30% dose reduction in the first cycle
Irinotecan ≥ 240 mg/m^2 (FOLFIRI FORT)	Mandatory	Risk of toxicity not increased: initially planned dose appropriate	Moderately increased risk of toxicity: monitoring recommanded	Significant risk of toxicity: dose escalation contraindicated–30% dose reduction in the first cycle

UGT1A1*6 (NG_002601.2:g.175755G > A–NM_000463.2:c.211G > A- p.(Gly71Arg)); UGT1A1*27 (NC_000002.12 (Homo sapiens chromosome 2, GRCh38.p2 g.233760973C > A); UGT1A1*28 (NC_000002.12 (Homo sapiens chromosome 2, GRCh38.p2) g.233760235TA [6]).

TABLE II

Fluoropyrimidines and DPYD: recommendations from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

Nomenclature HGVS (NM_000110.4)	Metabolic score	Frequency in the Caucasian population	Allèle 1-Allèle 2	DPYD*1 Activity score = 1	« D949V » c.2846A > T Activity score = 0,5	HapB3 c.1129-5923C > G/ c.1236G > A Activity score = 0,5	DPYD*2A c.1905 + 1G > A Activity score = 0	DPYD*13 c.1679T > G Activity score = 0
/	100%	/	DPYD*1 Activity score =1	Total activity score = 2 → initiate at 100% of the standard dose	Total activity score = 1,5 → initiate at 75% of the standard dose	Total activity score = 1,5 → 75% of the standard dose	Total activity score = 1 → initiate at 50% of the standard dose	Total activity score = 1 → initiate at 50% of the standard dose
c.2846A > T	60%	0,7%	« D949V » c.2846A > T Activity score = 0,5	Total activity score = 1,5 → initiate at 75% of the standard dose	Total activity score = 1 → initiate at 50% of the standard dose	Total activity score = 1 → initiate at 50% of the standard dose	Total activity score = 0,5 → initiate at 25% of the standard dose	Total activity score = 0,5 → initiate at 25% of the standard dose
c.1129-5923C > G in total linkage disequilibrium with c.1236G > A	decreased	2,4%	HapB3 c.1129-5923C > G/ c.1236G > A Activity score = 0,5	Total activity score = 1,5 → initiate at 75% of the standard dose	Total activity score = 1 → initiate at 50% of the standard dose	Total activity score = 1 → initiate at 50% of the standard dose	Total activity score = 0,5 → initiate at 25% of the standard dose	Total activity score = 0,5 → initiate at 25% of the standard dose
c.1905 + 1G > A	0%	0,5%	DPYD*2A (c.1905 + 1G > A) Activity score = 0	Total activity score = 1 → initiate at 50% of the standard dose	Total activity score = 0,5 → initiate at 25% of the standard dose	Total activity score = 0,5 → initiate at 25% of the standard dose	Total activity score = 0 → Avoid 5-FU and capecitabine	Total activity score = 0 → Avoid 5-FU and capecitabine
c.1679T > G	25%	0,1%	DPYD*13 c.1679T > G Activity score = 0	Total activity score = 1 → initiate at 50% of the standard dose	Total activity score = 0,5 → initiate at 25% of the standard dose	Total activity score = 0,5 → initiate at 25% of the standard dose	Total activity score = 0 → Avoid 5-FU and capecitabine	Total activity score = 0 → Avoid 5-FU and capecitabine

DPYD*2A": Chr1(GRCh37):g.97915614C > T–NM_000110.4(DPYD):c.1905 + 1G > A–p.? Chr1(GRCh37):g.97547947T > A–NM_000110.4(DPYD):c.2846A > T- p.(Asp949Val); "HapB3": Chr1(GRCh37):g.98045449G > C+ g.98039419C > T–NM_000110.4(DPYD):c.1129-5923C > G+ c.1236G > A); "DPYD*13": Chr1(GRCh37):g.97981343A > C–NM_000110.4(DPYD):c.1679T > G–p.(Ile560Ser)).

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mutations has relatively low sensitivity: only 5% to 40% of patients with grade 3–4 toxicity carry one of these four mutations. Thus, the absence of a detected mutation does not necessarily guarantee good treatment tolerance. Although genotyping has a very high specificity, exceeding 90%, the correlation between genotyping and phenotyping is not absolute. Some patients heterozygous for variations c.1905 + 1G > A or c.2846A > T may have normal enzymatic activity, potentially due to allelic regulation of the *DPYD* gene with overexpression of the wild-type allele. Conversely, some patients with deficient phenotypes show no functional variants of the *DPYD* gene [1]. Recommendations for reducing fluoropyrimidine doses based on *DPYD* genotype, covering the three variants *2A, D949 V, and *13 have also been formulated by international consortia – the Dutch Pharmacogenetics Working Group (DWPG) in 2011, as well as the Clinical Pharmacogenetics Implementation Consortium (CPIC) in 2013.

An DPD activity score based on genotyping of DPYD*2A alleles (score = 0), *13 (score = 0), c.2846A > T (score = 0.5), and HapB3 (score = 0.5) has been developed, resulting in five recommendation levels based on diplotype score (100% of the dose, 75% of the dose, 50% of the dose, 25% of the dose, contraindication). However, this score, although established from in vitro and in vivo data, has not yet been clinically validated, and assigning the score 0.5 to HapB3 is subject to debate [4].

Currently in France, only phenotyping by measuring uracil levels is mandatory. The GPCO-Unicancer-RNPGx consortium has defined a threshold value of 16 ng/mL beyond which the presence of a DPD deficiency may be suspected, and a threshold value of 150 ng/mL for which a total DPD deficiency can be confirmed. *DPYD* genotyping is not systematically performed and mostly targets only the four mentioned variants. The FUSAFE meta-analysis emphasizes the crucial role of integrating DPYD *2A/p.D949 V/*13 genotyping with clinical variables to effectively identify patients at high risk for severe fluoropyrimidine-related toxicity [5]. The limited sensitivity of targeted genotyping and the frequent discordances between DPD phenotyping and genotyping underscore the necessity of using both methods to comprehensively screen for all DPD deficiencies.

While reduced DPD activity is the main cause of toxicity, the metabolism of fluoropyrimidines involves multiple factors. Comprehensive DPYD sequencing may reveal additional genetic variants and identify more patients at risk, but it is not sufficient on its own to explain the full spectrum of toxicity risks. In addition to the gene polymorphisms in DPYD, the toxicity and efficacy ratio of capecitabine is also influenced by polymorphisms in cytidine deaminase (CDA), as well as promoter deletions in the CDA gene, which lead to an ultra-rapid metabolizer phenotype. Furthermore, polymorphisms in CES, TYMS and MTHFR genes also play a role in increasing the risk of severe toxicity with both capecitabine and 5-FU [6]. However, as of now, there are no formal clinical guidelines recommending routine testing for these genetic variations.

Nucleoside analogue: thiopurines

6-Mercaptopurine (6MP) is an essential molecule in pediatric hematology for the maintenance treatment of acute lymphoblastic leukemia. This prodrug must be metabolized to exert its cytotoxic action. A first metabolism pathway corresponding to the purinergic nucleotide synthesis pathway leads to the formation of thionucleotides called 6-TGN (6-ThioGuanine Nucleotides) which are the most active metabolites. The 6-TGN are sulfur analogues of endogenous nucleotides. They are incorporated into nucleic acids leading to disrupt the multiplication of rapid renewing cells. A second metabolism pathway is under the control of ThioPurine S-Methyl Transferase (TPMT) catalyzing the S-methylation of 6-MP into methylated derivatives, called 6-MMPN (6-Methyl MercaptoPurine Nucleotides). The latter exert an inhibition at the level of the de novo synthesis of purine bases. TPMT thus regulates the balance between cytotoxic nucleotides (6-TGN) and methylated derivatives into hematopoietic cells. Many studies have demonstrated that the concentrations of 6-TGN and 6-MMPN influence effectiveness but also the occurrence of adverse effects. Indeed, low 6-TGN concentrations are associated with therapeutic failure and high 6-TGN concentrations are at risk of severe or even fatal myelotoxicity. High levels of 6-MMPN are at risk of hepatotoxicity. It is widely recognized that *TPMT* polymorphism is a major source of variation in response to 6-MP. Three mutations of this gene present at exon 5 (Chr6(GRCh37):g.18143955C > G–NM_000367.5(*TPMT*): c.238G > C; p.(Ala80Pro)–"TPMT*2"), exon 7 (Chr6(GRCh37): g.18139228C > T–NM_000367.5(*TPMT*):c.460G > A–p.(Ala154Thr)–TPMT*3B'') and exon 10 (Chr6(GRCh37): g.18130918T > C–NM_000367.5(*TPMT*):c.719A > G; p.(Tyr240Cys)- "TPMT*3C") lead to accelerated degradation of the enzyme. Notably, the TPMT*3A variant results from the combination of TPMT*3B and TPMT*3 C mutations. The latter are important because they alone represent 95% of patients deficient in TPMT. In terms of frequency, 89% of Caucasian patients carry a normal homozygous genotype and have high TPMT activity, 11% carry a heterozygous genotype and have intermediate activity and finally the mutated homozygous patients have a complete deficiency of TPMT activity. The genotype-phenotype relationship is well established to date.

Furthermore, the pharmacogenetic impact of the enzyme NUDT15, a nucleotide phosphatase which converts cytotoxic 6-TGN triphosphate into 6-TGN monophosphate, has recently been described. To date, the most studied variant is *NUDT15*3* (Chr13(GRCh37):g.48619855C > T–NM_018283.4(*NUDT15*): c.415C > T- p.(Arg139Cys)) but recent publications on this gene are increasing. The allele frequency of the *TPMT* and *NUDT15* variants varies greatly depending on ethnic groups. The CPIC® recommends dosage reductions for patients carrying at least

Table III

Thiopurines indicated for malignancies and TPMT: recommendations from the Clinical Pharmacogenetics Implementation Consortium (CPIC)–*if normal starting mercaptopurine dose is ≥ 75 mg/m²/day or ≥ 1.5 mg/kg/day or if normal azathioprine starting dosea is 2–3 mg/kg/day or ≥ 40–60 mg/m²/day or if thioguanine starting dose is ≥ 40–60 mg/m²/day

			NUDT15 not genotyped	*NUDT15**1/*1	*NUDT15**1/*2 ou * *NUDT15**1/*3	*NUDT15**2/*2 *NUDT15**2/*3 *NUDT15**3/*3		
	Phenotype		NUDT15 metabolizer status unknown	NUDT15 Normal metabolizer	NUDT15 Intermediate metabolizer	NUDT15 poor metabolizer		
		Phenotype frequency in the Caucasian population	/	98,6%	0,76%	0.001% (East Asian: 0,9%)		
TPMT *1/*1	TPMT Normal metabolizer	90,9%	Start with normal starting dose	Start with normal starting dose	Start with reduced starting strong doses (30–80% of normal mercaptopurine or azathioprine dose–or 50–80% of normal thioguanine dose)*	Mercaptopurine: Initiate dose at 10 mg/m²/day and adjust dose based on myelosuppression and disease-specific guidelines.	Azathioprine: start with drastically reduced normal daily dosesa (reduce daily dose by 10-fold)	Thioguanine: Reduce doses to 25% of normal dosea and adjust doses of thioguanine based on degree of myelosuppression
*TPMT**1/*2 *TPMT* *1/*3A *TPMT* *1/*3B *TPMT* *1/*3C *TPMT* *1/*4	TPMT Intermediate metabolizer	8,4%	Start with reduced starting strong doses (30–80% of normal mercaptopurine or azathioprine dose–or 50–80% of normal thioguanine dose)*	Start with reduced starting strong doses (30–80% of normal mercaptopurine or azathioprine dose–or 50–80% of normal thioguanine dose)*	Start with reduced starting strong doses (30–80% of normal mercaptopurine or azathioprine dose–or 50–80% of normal thioguanine dose)*	Start with reduced starting strong doses (30–80% of normal mercaptopurine or azathioprine dose–or 50–80% of normal thioguanine dose)*		
TPMT *3A/*3A TPMT *2/*3A TPMT *3A/*3 C TPMT *3 C/*4 TPMT *2/*3 C TPMT *3A/*4	TPMT poor metabolizer	0,19%	Start with drastically reduced doses (reduce daily dose by 10-fold and reduce frequency to ce:br/>thrice weekly instead of daily	Start with drastically reduced doses (reduce daily dose by 10-fold and reduce frequency to ce:br/>thrice weekly instead of daily	Start with drastically reduced doses (reduce daily dose by 10-fold and reduce frequency to thrice weekly instead of daily	Start with drastically reduced doses (reduce daily dose by 10-fold and reduce frequency to thrice weekly instead of daily		

"TPMT*2": Chr6(GRCh37):g.18143955C > G–NM_000367.5(TPMT):c.238G > C; p.(Ala80Pro); "TPMT*3B": Chr6(GRCh37):g.18139228C > T–NM_000367.5(TPMT):c.460G > A–p.(Ala154Thr); "TPMT*3C": Chr6(GRCh37):g.18130918T > C–NM_000367.5(TPMT):c.719A > G; p.(Tyr240Cys); "TPMT*3A": TPMT*3B + TPMT*3.

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one pathogenic variant of these two genes corresponding to an initial dose between 10 to 70% of the protocol dose of 6-MP (*table III*) [7]. Furthermore, *ITPA* variants could play a role in explaining certain non-hematological toxicities, highlighting the need for further investigation in this area [8]. Since phenotyping provides complementary insights to pharmacogenetics, integrating both approaches could refine risk assessment and optimize treatment strategies: regular hematological monitoring and concentrations measurements of 6-TGN and 6-MMPN in red blood cells are also necessary.

Similarly to nucleotide analogs, some nucleoside one such as gemcitabine are influenced by gene polymorphisms affecting *CDA*, which can result in increased toxicity. Conversely, ultrarapid metabolizers treated with gemcitabine are at a higher risk of treatment failure. The same considerations apply to cytarabine and azacytidine, where CDA activity can affect both toxicity and efficacy, with variations leading to either increased toxicity or lack of therapeutic efficacy [9]. To date, no formal recommendations have been established regarding the systematic implementation of these *CDA* genetic tests in clinical practice.

Tamoxifen

The importance of pharmacogenetics has been clearly established for tamoxifen among the hormone therapy options, a selective estrogen receptor modulator (SERM) used in the treatment of breast cancer. Taking tamoxifen for 5 years after surgery is aimed at reducing the annual recurrence rate by almost half and the breast cancer mortality rate by one-third in women with ER-positive breast cancer. Inter- and intraindividual variations in the concentrations of tamoxifen and its active metabolites, 4-hydroxytamoxifen (4HT) and endoxifen, have been observed. Tamoxifen undergoes significant metabolism in the liver, primarily through two major metabolic pathways involving cytochrome P450 enzymes. The main pathway, accounting for over 90% of tamoxifen metabolism, begins with the demethylation of tamoxifen to N-desmethyltamoxifen, primarily mediated by CYP3A4. This step is followed by oxidation by CYP2D6, producing hydroxy-N-desmethyltamoxifen, also known as endoxifen. A minor pathway involves the hydroxylation of tamoxifen, mainly by CYP2D6 but also partially by CYP3A4 and CYP2C19, leading to the formation of 4HT, which can then be metabolized into endoxifen [10].

The consequences of interindividual variability for 4HT are not yet fully understood, but those of endoxifen variability have been studied. Patients with low activity of the CYP2D6 enzyme, and thus significantly lower endoxifen concentrations when treated with tamoxifen, have an increased risk of breast cancer recurrence [10]. This has led to the hypothesis that *CYP2D6* polymorphisms could serve as predictive biomarkers for tamoxifen efficacy. However, this remains controversial due to conflicting clinical evidence. The CYPTAM study failed to show a clear association between *CYP2D6* genotypes, endoxifen levels, and clinical outcomes in tamoxifen-treated patients, raising doubts about the clinical utility of *CYP2D6* genotyping [11]. However, this study has been subject to criticism particularly regarding methodological limitations such as the uncontrolled use of CYP2D6 inhibitors. Similarly, earlier studies from JNCI in the early 2010s also failed to establish a strong correlation between *CYP2D6* genotype and clinical response, but these studies were criticized for using tumor DNA instead of germline DNA for *CYP2D6* genotyping, which may not accurately reflect the patient's constitutional metabolizing capacity. This discrepancy can arise due to somatic mutations that alter CYP2D6 expression or function, as well as loss of heterozygosity (LOH), that may lead to the deletion of one allele. LOH could then result in misclassification of a patient's metabolizer status [11].

Before these controversies arose, the Clinical Pharmacogenetics Implementation Consortium (CPIC) had already issued high-level recommendations for prescribing tamoxifen as adjuvant therapy based on *CYP2D6* genotype. These recommendations integrate both haplotypes, which include major SNPs, and structural variations such as copy number variations and hybrid genes between *CYP2D6* and its pseudogene *CYP2D7* (*table IV*). However, the clinical relevance of *CYP2D6* genotyping remains debated. In contrast to CPIC, the European Society for Medical Oncology (ESMO) discouraged *CYP2D6* genotyping for tamoxifen therapy in 2019, arguing that the current body of evidence does not support its routine clinical implementation. More recent studies continue to show conflicting results, with some supporting the predictive value of *CYP2D6* for tamoxifen response, while others suggest that therapeutic drug monitoring (TDM) of endoxifen levels may be a more reliable approach [11].

Given these uncertainties, a personalized approach incorporating *CYP2D6* genotyping, TDM, and clinical factors may be necessary to optimize tamoxifen therapy in ER-positive breast cancer patients [10].

Concerning other hormone therapy, further investigations are needed. The impact of genetic polymorphisms of *CYP2A6* is potentially associated with letrozole. Although some genome-wide association studies have identified new genes or pathways associated with adverse events related to aromatase inhibitors, the underlying mechanisms require further investigation [10].

New Therapies and Pharmacogenetics

Targeted Therapies

Toxicities of tyrosine kinase inhibitors (TKIs) are generally attributed to excessively high pharmacological concentrations. Interindividual variability in exposure to these molecules can be explained by various factors, including genetic polymorphisms that modulate metabolism. Most TKIs are primarily metabolized by CYP3A4, for which certain polymorphisms are associated with reduced enzymatic activity. Among these, CYP3A4*22 ((Chr7(GRCh37):g.99366316G > A–NM_017460.6(*CYP3A4*):

TABLE IV
CYP2D6 phenotype and oncology drug recommendations: Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines

		Tamoxifen			Codeine/Tramado3		Setrons		Amitriptyline	
CYP2D6 phenotype	Metabolic score	CYP2C6 frequency	Implications for tamoxifen pharmacologic measures	Therapeutic recommendations	Implications for codein/tramadol pharmacologic measures	Therapeutic recommendations	Implications for setron pharmacologic measures	Therapeutic recommendations	Implications for amitiptyline pharmacologic measures	Therapeutic recommendations
CYP2D6 ultrarapid metabolizer	> 2,0 (for opiods therapies: 2,25)	1-10%	Therapeutic endoxifen concentrations	Standard dose (20 mg/day) (tamoxifen 20 mg/day).	Increased formation of morphine leading to higher risk of toxicity	Avoid codeine use If opioid use is warranted, consider a non-tramadol opioid.	Increased metabolism Reduced efficacy of ondansetron and tropisetron	Select alternative drug not predominantly metabolized by CYP2D6 (i.e., granisetron)	Increased metabolism of TCAs to less active compounds compared to normal Risk of inefficacy	Avoid tricyclic use If a TCA is warranted, utilize therapeutic drug monitoring to guide dose adjustments.
CYP2D6 rapid metabolizer	1,5-2,0	65-80%	Normal metabolism	Standard dose (20 mg/day) (tamoxifen 20 mg/day)	Normal metabolism	Standard dose	Normal metabolism	Standard dose	Normal metabolism	Standard dose
CYP2D6 normal metabolizer	1,0									
CYP2D6 intermediate metabolize	0.5	10-15%	Lower endoxifen concentrations Probable higher risk of breast cancer recurrence	Consider hormonal therapy such as an aromatase inhibitor If contraindicated, consider higher tamoxifen dose (40 mg/day)	Reduced morphine formation	Use codeine label recommended age-specific or weight-specific dosing. If no response and opioid use is warranted, consider a non-tramadol opioid.	Very limited data available for CYP2D6 IMs	No recommendation	Reduced metabolism Increased side effects risk	No recommendation for amitriptyline as analgesic
CYP2D6 poor metabolizer	0	5-10%	Lower endoxifen concentrations Probable higher risk of breast cancer recurrence	Prefer an aromatase inhibitor	Greatly reduced morphine formation leading to diminished analgesia.	Avoid codeine use because of possibility of diminished analgesia. If opioid use is warranted, consider a non-tramadol opioid	Very limited data available for CYP2D6 PMs	No recommendation	Greatly reduced metabolism of TCAs to less active compounds compared to normal metabolizers Higher plasma concentrations of active drug will increase the probability of side effects	No recommendation for amitriptyline as analgesic

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c.522-191C > T)) appears to be a relevant polymorphism, with a frequency of 4% to 8%, known to cause a reduction of up to 50% in mRNA expression and thus enzymatic activity. Higher pharmacological exposure in patients heterozygous for the CYP3A4*22 genotype could be compensated by administering lower doses, as suggested by a prospective study conducted by Van Eerden et al. on 207 patients. However, dose adjustment based on the CYP3A4*22 genotype does not seem appropriate for all TKIs metabolized by CYP3A4: a significant decrease in pharmacological exposure to imatinib has been reported. This could be due to the self-inhibition of CYP3A4 by imatinib itself, indicating that imatinib metabolism depends not only on CYP3A4 [12]. While polymorphisms such as CYP3A4*22 can contribute to variability in drug exposure, clinical evidence regarding their direct impact on the efficacy of TKIs remains limited. Many TKIs exhibit broad therapeutic tolerance, meaning that variations in metabolism may not always result in clinically significant differences in treatment outcomes. Further studies are needed to better define the clinical relevance of *CYP3A4* polymorphisms in TKI therapy and to optimize personalized treatment strategies.

It is also worthwhile to discuss CYP3A5 expression in other populations, as the substrates are quite similar. However, current literature suggests that CYP3A5 may have a less significant impact on TKI metabolism compared to CYP3A4. While *CYP3A5* polymorphisms influence drug metabolism in some individuals, their overall effect on TKI pharmacokinetics and clinical outcomes appears to be more limited.

Although polymorphisms in genes encoding drug-metabolizing enzymes and transporters can contribute to variability in the pharmacokinetics of tyrosine kinase inhibitors (TKIs), the direct influence of such genetic variations on clinical outcomes remains an area of ongoing investigation. For sunitinib, a well-established targeted therapy for metastatic renal cell carcinoma (mRCC), studies have explored genetic polymorphisms in transporters such as *ABCB1* and metabolic enzymes like *CYP3A4* and *CYP3A5*. However, their direct impact on sunitinib's efficacy and toxicity remains inconclusive. Recent studies have suggested that certain polymorphisms, such as *ABCB1* rs2032582, may be associated with an increased risk of specific adverse events, including hypertension and hand–foot syndrome, in some patients. This highlights the potential role of genetic factors in predicting treatment-related toxicity, even though further research is needed to establish definitive clinical markers [13].

Furthermore, some TKIs can cause idiosyncratic iatrogenic reactions, unrelated to dose. For example, in the case of lapatinib, a HER2 inhibitor used in the treatment of HER2-amplified breast cancer, immune-mediated hepatotoxicity has been described, associated with HLA-DRB107:01/DQA102:01 alleles. However, no systematic analysis of HLA typing is required when using lapatinib in the treatment of metastatic breast cancer [14].

Therapeutics monoclonal antibodies

Excluding polymorphisms associated with specific immunotherapy toxicities, no study has yet examined the association between individual genetic variations and the development of hypersensitivity to monoclonal antibody (mAb) treatments. However, certain polymorphisms may influence the pharmacokinetics of these mAbs.

The metabolism of monoclonal antibodies (mAbs) does not involve the cytochrome P450 enzymatic system. Their elimination primarily occurs through endocytosis and pinocytosis, followed by catabolism. Elimination can be specific or nonspecific: it depends on the interaction of the mAb with its antigen and may vary depending on tumor-specific characteristics, including the quantity of expressed antigens. Absorption of mAbs generally occurs through receptor-mediated endocytosis in response to the binding of the Fc domain of the antibody to FcγR receptors expressed on immune cells such as monocytes, macrophages, and dendritic cells. Musolino et al. identified a polymorphism in the *FCGR3A* gene (rs396991 T/G–Chr1(GRCh37): g.161514542A > C–NM_000569.8(*FCGR3A*):c.526T > G–p.(Phe176Val)) leading to increased binding affinity, thereby enhancing antibody-dependent cell cytotoxicity. This is due to a change from phenylalanine (F) to valine (V) at position 158. Patients with HER2-positive breast cancer who were homozygous for the F158 V polymorphism showed a higher response rate to trastuzumab [15]. The neonatal Fc receptor (FcRn) plays a crucial role in extending the half-life of mAbs by recycling them instead of directing them to lysosomal degradation. Through FcRn-mediated recycling, mAbs are protected from degradation and returned to the circulation, thereby prolonging their systemic exposure. However, despite its importance in antibody homeostasis, some studies have reported no significant association between polymorphisms in the *FCGRT* gene (which encodes FcRn) and clinically relevant changes in pharmacokinetics or treatment outcomes [16].

Antibody drug conjugate

Sacituzumab govitecan is indicated as second-line treatment for metastatic and locally advanced breast cancer with triple-negative receptors, and as third-line and beyond treatment for ER+ receptor-positive diseases resistant to hormone therapy. This therapeutic agent is an anti-Trop2 antibody coupled with SN38, an active and toxic metabolite of irinotecan. The half-life of the linker hydrolysis is only 18 hours at neutral pH, suggesting that some amount of SN38 is already free in the chemotherapy pocket [17]. During administration, this active and toxic metabolite enters the systemic circulation and is metabolized by UGT1A1. Wang et al. observed that patients carrying the UGT1A1*28 allele were more likely to discontinue treatment due to significant toxicities. Although these findings are based on a limited cohort, they are consistent with the pharmacological rationale of sacituzumab govitecan and irinotecan [18].

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Pharmacogenetics of supportive care treatments

The enzymes CYP2C19 and CYP2D6 are essential for metabolizing many drugs, and genetic variations can significantly influence their activity. Individuals classified as "slow metabolizers'' often carry variants that reduce enzymatic activity, leading to potential drug accumulation and an increased risk of side effects. "Normal metabolizers,'' with functional alleles, metabolize drugs at standard rates. "Rapid metabolizers,'' carrying variants that enhance enzymatic activity, may require higher doses to achieve the desired therapeutic effect due to their faster drug metabolism. Finally, "ultra-rapid metabolizers,'' who possess gene duplications or certain variants, exhibit very high enzymatic activity and may need significant dose adjustments to avoid subtherapeutic effects. It is important to note that there are numerous CYP2D6 variants that result in no enzymatic function, and these variants are comprehensively cataloged in the PharmVar database.

Analgesic Treatments

Opioid Analgesics

Among the possible therapeutic options, tramadol and opioids such as codeine, hydrocodone, oxycodone, and methadone stand out – all metabolized by the polymorphic enzyme CYP2D6. High-level evidence-based recommendations exist regarding tramadol and codeine (*table IV*). However, recommendations regarding hydrocodone and oxycodone are less conclusive and will not be discussed further here.

Codeine is metabolized into morphine primarily by the enzyme CYP2D6. In individuals classified as ultrarapid metabolizers, certain genetic variations in CYP2D6 lead to a significantly faster and more extensive conversion of codeine into morphine compared to normal metabolizers. This accelerated metabolism can result in higher-than-expected morphine concentrations in the bloodstream, which may increase the risk of opioid toxicity and other adverse effects. Conversely, in individuals with hypometabolism, certain genetic variations in *CYP2D6* result in slower conversion of codeine into morphine compared to normal metabolizers. This reduced metabolism can lead to lower-than-expected morphine levels in the bloodstream, potentially resulting in diminished analgesic efficacy and inadequate pain relief. Pharmacokinetic studies have revealed an increased conversion of codeine to morphine in ultra-rapid metabolizers of CYP2D6 compared to normal metabolizers. This heightened metabolism can lead to potentially toxic systemic concentrations of morphine, even with low doses of codeine administered to healthy volunteers. In these ultra-rapid metabolizers, the median area under the morphine plasma curve is 45% higher, and plasma concentrations of morphine and its glucuronides are approximately 50% higher compared to normal metabolizers when codeine is administered. Nevertheless, it's important to note a considerable variability among patients genotyped as normal metabolizers: some of them may exhibit symptoms like those of ultra-rapid metabolizers. The underlying mechanisms for this significant variation among individuals with the same diplotype remain unknown in terms of genetics and environment [19].

Conversely, slow metabolizers exhibit a significantly lower mean morphine area under the curve in serum by 96% and a lower mean maximum plasma concentration (Cmax) of morphine by 95% compared to normal and intermediate metabolizers. During a pain test involving immersing a hand in cold water in healthy volunteers, normal and intermediate metabolizers (by phenotyping) experienced analgesia with codeine administration, while poor metabolizers showed no difference in analgesia with codeine administration compared to a placebo. Therefore, tramadol and codeine are contraindicated in ultra-rapid metabolizers and discouraged in ultra-slow metabolizers [19]. To note, Codein use is contre-indicated in France, for children under 12 years old, after tonsillectomy or adenoidectomy because the risk of toxicity is to high due to pharmacogenetics. A genetic screening for children could have been useful to maintain this drug for pain management.

Tricyclic antidepressants

The impact of *CYP2D6* and *CYP2C19* polymorphisms on drug metabolism varies depending on the specific medication, as different drugs may be metabolized at different rates and may require different dosing considerations.

Amitriptyline, a tricyclic antidepressant, is also used for the treatment of neuropathic pain, typically at lower doses than those prescribed for depression (0.1 mg/kg/day in pediatric patients; starting from 25 mg per day in adults).

While pharmacogenetic guidelines support genotyping for *CYP2D6* and *CYP2C19* in the context of antidepressant use, their relevance at analgesic doses remains uncertain.

At low doses, the risk of adverse effects from supra-therapeutic plasma levels appears limited, particularly for *CYP2D6* and *CYP2C19* slow or intermediate metabolizers. Consequently, no dose adjustments are currently recommended for these phenotypes in the context of pain management – including for CYP2C19*17 carriers (*table IV*) [20].

While there is limited data describing the use of amitriptyline in neuropathic pain among ultrarapid metabolizers of CYP2D6, it can be expected that these ultrarapid metabolizers are at increased risk of therapeutic failure due to lower than expected drug concentrations: alternative agents may thus be considered. Although there is little information on how to adjust initial doses of amitriptyline based on combined genetic results of *CYP2D6* and *CYP2C19* during neuropathic pain treatment, knowledge of patients with a combination of slow or ultrarapid phenotypes for CYP2D6 may allow for closer monitoring (e.g., a slow metabolizer of CYP2D6 also having either ultrarapid or slow metabolism of CYP2C19) [20].

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Selective serotonin reuptake inhibitors (SSRIs)

Antidepressants that inhibit serotonin reuptake, such as selective serotonin reuptake inhibitors (like citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), serotonin-norepinephrine reuptake inhibitors (such as venlafaxine, duloxetine, and milnacipran), and serotonin modulators with similar properties to SSRIs (such as vortioxetine), are the primary pharmacological treatments for major depressive disorders and anxiety disorders. Genetic variations in enzymes like CYP2D6, CYP2C19, and CYP2B6 influence how these medications are metabolized, impacting their effectiveness and tolerability. While we won't delve into recommendations for all antidepressants in this class, we'll focus on duloxetine, which is specifically indicated for neuropathic pain.

Duloxetine is metabolized by enzymes like CYP1A2 and CYP2D6. However, existing data suggests that genetic variations in CYP2D6 have little clinical significance for duloxetine. Unlike many other drugs in the same class, duloxetine does not have specific pharmacogenetic recommendations [21].

Non-steroidal anti-inflammatory drug (NSAIDS)

The pharmacogenetic recommendations of the Clinical Pharmacogenetics Implementation Consortium (CPIC) for nonsteroidal anti-inflammatory drugs (NSAIDs) highlight the impact of *CYP2C9* gene polymorphisms(CYP2C9*2: Chr10(GRCh37):g.96702047C > T–NM_000771.4(*CYP2C9*):c.430C > T–p.(Arg144Cys)/CYP2C9*3: Chr10(GRCh37):g.96741053A > C–NM_000771.4(*CYP2C9*):c.1075A > C–p.(Ile359Leu)) on the metabolism and clearance of these medications. Genetic variability influences NSAID exposure and safety, particularly in intermediate metabolizers (IM, CYP2C9*1/*3, *2/2) and poor metabolizers (PM, CYP2C93/*3, *2/*3), who exhibit reduced drug elimination and an increased risk of gastrointestinal, renal, and cardiovascular adverse effects. For ibuprofen, intermediate metabolizers (AS = 1) should start with the lowest recommended dose, with close monitoring for adverse effects. In poor metabolizers (AS = 0.5 or 0), the CPIC recommends a 25–50% dose reduction or the use of an alternative such as naproxen or aspirin, as ibuprofen elimination is significantly prolonged [22].

Antiemetic Treatments

5-HT3 receptor antagonists–"setrons"

5-Hydroxytryptamine type 3 (5-HT3) receptor antagonists, commonly known as "setrons," are used to prevent nausea and vomiting induced by chemotherapy, radiation therapy, and surgery. *CYP2D6* polymorphisms can affect the metabolism of certain drugs in this class (such as ondansetron and tropisetron), potentially altering their efficacy (*table IV*).

A decrease in the antiemetic efficacy of ondansetron and tropisetron has been observed in ultra-rapid metabolizers (UMs) of CYP2D6, leading to vomiting when used to treat postoperative or chemotherapy-induced nausea and vomiting. It has been shown that ultra-rapid metabolizers had the highest vomiting rate compared to normal metabolizers in patients receiving tropisetron or ondansetron for chemotherapy-induced nausea and vomiting. Although no study has shown a major impact of the slow metabolizer (PM) status of CYP2D6 on the side effects of ondansetron, one study indicated that PM patients treated with ondansetron had fewer vomiting episodes [23].

For ultra-rapid metabolizers, due to the risk of effective underexposure linked to ultra-rapid metabolism, it is preferable to opt for another setron such as granisetron, which is metabolized by CYP3A4. No therapeutic adjustment has been recommended for intermediate or slow metabolizers [23].

Proton pump inhibitors

Proton pump inhibitors are drugs that inhibit gastric acid production by covalently binding to a specific enzyme in gastric cells. This action results in a reduction in gastric acid secretion for 24 to 48 hours. However, this inhibition is irreversible and can only be overcome by the synthesis of new enzymes, a process that takes approximately 54 hours.

While PPIs have been widely prescribed due to their effectiveness, emerging data suggests that long-term use is associated with adverse effects such as electrolyte imbalances, infections, kidney issues, and bone fractures.

Patients with genotypes predisposing to higher plasma exposure may consider dose reduction to minimize the risks associated with long-term PPI use, especially at higher plasma concentrations [24].

First generation (Omeprazole, lansoprazole, pantoprazole)

CYP2C19 is a major metabolic pathway for the elimination of first-generation PPIs (~80%), with a lesser contribution from CYP3A4. Following the administration of standard doses of first-generation PPIs, intermediate metabolizers (IMs) and poor metabolizers (PMs) of CYP2C19 exhibit a higher area under the curve (AUC) for PPIs (3 to 14 times) and a higher maximum plasma concentration of the drug (2 to 6 times) compared to normal metabolizers (NMs) of CYP2C19 due to reduced clearance of PPIs via the CYP2C19 pathway. Increased exposure to PPIs in CYP2C19 IMs and PMs has been associated with improved acid suppression (i.e., higher intragastric pH and longer duration with pH > 4.0). However, prolonged acid suppression in CYP2C19 intermediate or poor metabolizers chronically using PPIs may carry a higher risk of PPI-related adverse events compared to individuals with other metabolic profiles. Given the emerging associations between CYP2C19 activity and the incidence of adverse events (e.g., infections), it is recommended to initiate standard daily dosing to maximize the likelihood of efficacy and, once efficacy is achieved, consider a 50% reduction in the daily dose as part of chronic PPI therapy (beyond 12 weeks) to minimize the risk of adverse events related to prolonged acid suppression in CYP2C19 IMs and PMs (*table V*) [24].

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Table V
CYP2C19 phenotype and oncology drug recommendations: Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines

		Voriconazole		IPP: omeprazole, lansoprazole, pantoprazole	
CYP2C19 phenotype	*CYP2C19* frequency	Implications for voriconazole pharmacologic measures	Therapeutic recommendations	Implications for IPP pharmacologic measures	Therapeutic recommendations
CYP2C19 ultrarapid metabolizer (*17/*17)	2–5%	The probability of attainment of therapeutic voriconazole concentrations is small with standard dosing	Avoid voriconazole–prefer isavuconazole, liposomal amphotericin B, and posaconazole	Decreased plasma concentrations of PPIs compared with CYP2C19 NMs; increased risk of therapeutic failure	Increase starting daily dose by 100%. Daily dose may be given in divided doses. Monitor for efficacy
CYP2C19 rapid metabolizer (*1/*17)	2–30%	The probability of attainment of therapeutic concentrations is modest with standard dosing	If possible, prefer isavuconazole, liposomal amphotericin B, and posaconazole	Decreased plasma concentrations of PPIs compared with CYP2C19 NMs; increased risk of therapeutic failure	Initiate standard starting daily dose. Consider increasing dose by 50–100% for the treatment of Helicobacter pylori infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy.
CYP2C19 normal metabolizer	5–50%	Normal voriconazole metabolism	Standard dose	Normal PPI metabolism; may be at increased risk of therapeutic failure compared with CYP2C19 IMs and PMs	Initiate standard starting daily dose. Consider increasing dose by 50–100% for the treatment of H. pylori infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy
CYP2C19 intermediate metabolize	18–45%	Higher dose-adjusted trough concentrations of voriconazole compared with normal metabolizers	Standard dose	Increased plasma concentration of PPI compared with CYP2C19 NMs; increased chance of efficacy and potentially toxicity	Initiate standard starting daily dose. For chronic therapy (> 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy
CYP2C19 poor metabolizer	2–15%	Higher dose-adjusted trough concentrations of voriconazole and may increase probability of adverse events	Prefer alternative (prefer isavuconazole, liposomal amphotericin B, and posaconazole) Iif used, lower dose and monitor closely	Increased plasma concentration of PPI compared with CYP2C19 NMs; increased chance of efficacy and potentially toxicity	Initiate standard starting daily dose. For chronic therapy (> 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy

CYP2C19*17 (Chr10(GRCh37): g.96521657C > T–NM_000769.4(*CYP2C19*):c.-806C > T).

Rapid metabolizers (RMs) and ultrarapid metabolizers (UMs) are determined by the presence of the CYP2C19*17 (Chr10 (GRCh37): g.96521657C > T–NM_000769.4(*CYP2C19*):c.-806C > T) allele with increased function. Because the majority of studies describing associations between *CYP2C19* genotype, pharmacokinetics and pharmacodynamics of PPIs have been conducted in Asian populations where the CYP2C19*17 allele is less frequent, there is limited data on the relationship between CYP2C19*17. Additional studies with CYP2C19 RMs and UMs are needed. Nevertheless, the documented low exposure to PPIs in patients who are CYP2C19 UMs compared to NMs, IMs, and PMs suggests that these individuals may benefit from higher than normal daily doses of PPIs: doubling the initial daily dose may be considered in CYP2C19 UMs (*table V*) [24].

Second generation (Esomeprazole, rabeprazole)

Second-generation PPIs, such as esomeprazole and rabeprazole, have a metabolism less dependent on CYP2C19. Rabeprazole is primarily eliminated by non-enzymatic mechanisms. This suggests that they are less affected by the genetic variability of CYP2C19 compared to first-generation PPIs. Thus, there is

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currently no clear pharmacogenetic recommendation for their use UMs [24].

Antibiotic treatments

Voriconazole

The voriconazole is an antifungal medication belonging to the triazole class that acts by inhibiting ergosterol synthesis through blocking lanosterol 14α-demethylase. It is used to treat various fungal infections, including invasive aspergillosis, candidemia in non-neutropenic patients, disseminated Candida infections, esophageal candidiasis, as well as infections caused by Scedosporium apiospermum and Fusarium spp.

Voriconazole metabolism is primarily mediated by CYP2C19, with minor contributions from CYP3A4 and CYP2C9. Paradoxically, voriconazole itself inhibits these enzymes, leading to significant variability in blood concentrations among individuals. This variability is influenced by CYP2C19 variant alleles, age, hepatic function, concurrent medications and the patient's inflammatory status. To avoid complications associated with either too low or too high concentrations, therapeutic drug monitoring (TDM) of voriconazole is recommended, with a target residual concentration range between 1.0 and 4.0 µg/mL for most invasive infections.

In addition to therapeutic adjustments based on clinical factors such as drug interactions, hepatic function, fungal species, or comorbidities, genotyping of CYP2C19 is also highly useful in determining the optimal therapeutic strategy (*table V*). Ultrarapid metabolizers of CYP2C19 tend to metabolize voriconazole more rapidly, which can delay reaching therapeutic concentrations, while slow metabolizers may have higher concentrations, thereby increasing the risk of adverse effects. For those latters, dose reduction with careful monitoring may be considered to minimize dose-dependent adverse effects such as hepatotoxicity, visual disturbances, visual hallucinations, and other neurological disorders [25]. For ultrarapid/rapid metabolizers of CYP2C19, there is an increased risk of therapeutic failure due to insufficient concentrations, which may necessitate the use of an alternative antifungal medication. Achieving therapeutic levels of voriconazole in these ultrarapid metabolizers is challenging and may result in delayed effective treatment of invasive infections [25].

Aminoglycosides

Aminoglycosides are antibiotics used as first-line treatment via parenteral route to address severe infections caused by aerobic Gram-negative bacteria. Their mechanism of action relies on inhibiting bacterial ribosomes, thereby disrupting bacterial protein synthesis. However, these medications can lead to adverse effects, notably nephrotoxicity and ototoxicity, including vestibulotoxicity and sensorineural hearing loss (cochleotoxicity). These side effects are typically dose-dependent and occur in patients receiving high doses of aminoglycosides over a prolonged period.

Some individuals have a predisposition to aminoglycoside-induced hearing loss (AIHL), with single doses resulting in profound bilateral sensorineural hearing loss. This predisposition is linked to variants in the *MT-RNR1* gene, which encodes the 12s subunit of human rRNA. Some variants, such as m.1095T > C,m.1494C > T, and m.1555A > G, share homology with the 16s subunit of bacterial rRNA, explaining the increased risk of AIHL.

Currently, there is no demonstrated difference between various aminoglycosides regarding this risk of iatrogenic deafness. Therefore, it is recommended to avoid using aminoglycosides in individuals carrying these *MT-RNR1* variants, except in cases of severe infection and absence of safe or effective alternative therapies [26].

In the absence of an effective alternative, aminoglycoside use should be as brief as possible. It is advisable to consult an infectious disease specialist to consider alternative approaches, closely monitor medication dosage, and frequently assess hearing loss during and after treatment, in collaboration with an audiovestibular physician.

Anesthetic agents

Halogenated anesthetic agents and succinylcholine

In oncology, the pharmacogenetics of halogenated anesthetic agents used in general anesthesia before any surgery is also important to consider. These agents, such as halothane, enflurane, isoflurane, methoxyflurane, and sevoflurane, as well as succinylcholine, can trigger a malignant hyperthermia crisis in patients carrying a risk variant, referred to as "MHS" (malignant hyperthermia susceptible). Although rare, malignant hyperthermia can lead to fatal cardiac arrest. The prevalence of the MHS trait is estimated to be between 1/2000 and 1/3000, with an incidence of approximately 1/10,000 to 1/250,000 anesthetics [27].

Variants in the *RYR1* or *CACNA1S* genes, transmitted in an autosomal dominant manner, increase the risk of malignant hyperthermia. Patients carrying one of these variants are contraindicated for halogenated anesthetic agents. Unlike other variants discussed previously, the pharmacogenetics of these agents does not affect their pharmacokinetics.

The *RYR1* gene, altered in 70% of patients at risk of malignant hyperthermia, codes for the RYR1 protein, which plays a crucial role in the excitation-contraction coupling of skeletal muscle fibers. The *CACNA1S* gene, which codes for the α1S subunit of the dihydropyridine receptor, is also involved in this process, although less frequently. Individuals predisposed to malignant hyperthermia may develop uncontrolled muscle contractions and hypermetabolism when exposed to these agents. Early symptoms of malignant hyperthermia include tachycardia and an increase in expired CO2, followed by muscle rigidity, metabolic and respiratory acidosis, hyperkalemia, hyperthermia, and arrhythmia [27].

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Despite the complexity of the genetic variants associated with malignant hyperthermia, the identification of one of the fifty deleterious variants in the *RYR1* or *CACNA1S* genes indicates a contraindication to these halogenated agents: malignant hyperthermia crises, which can be lethal, with a morbidity rate of 35% and a mortality rate of 12% for a fulminant malignant hyperthermia reaction [27].

Current practice in pharmacogenetics

Collection and analysis procedures

Most pharmacogenetic tests are performed on whole blood samples collected in EDTA tubes by the majority of laboratories engaged in pharmacogenetic activities. In France, as in many other countries, informed consent is a legal and ethical prerequisite before conducting any pharmacogenetic testing. It does not differ from other constitutional genetic testing.

A discipline still not widely implemented

At present, very few pharmacogenetic tests are mandatory in France. Only two tests fall into this category: screening for the HLA-B57*01 allele before initiating abacavir-containing treatment in any HIV-infected patient, regardless of their ethnic origin, and genotyping of *CYP2D6* before starting eliglustat treatment for Gaucher's disease.

In oncology, despite the existence of national and international expert recommendations, French health authorities have not yet issued official directives regarding pharmacogenetic genotyping. The development of pharmacogenetics in France is primarily driven by the Francophone Pharmacogenetics Network (RNPGx). Although the pharmacogenetics of some anticancer agents is well established, its prescription is not systematic. Consequently, the clinical integration of pharmacogenetics largely depends on oncologists in the absence of specific directives on this subject.

Analysis of the prescription rate across all specialties reveals that few clinicians have integrated pharmacogenetics into their routine practice. Only 25.4% (76/311) of respondents in the French study by Verdez reported having ever prescribed or recommended a pharmacogenetic test [28]. Among the obstacles to prescribing these tests is a lack of knowledge about the procedures, indications, and management in case of discovery of a variant at risk.

Furthermore, the specific regulatory constraints in France may contribute to the limited enthusiasm for implementing pharmacogenetic testing at the bedside.

In the framework of the France Genomic Medicine 2025 plan, 62.7% of surveyed clinicians believe that it would be relevant to communicate pharmacogenetic data following exome or genome analysis. Among French professionals surveyed, 86.8% consider pharmacogenetic tests as potential tools for therapeutic optimization. Pharmacogenetic guidance, particularly in dose adaptation based on pharmacogenetic results, enhances clinician adherence: nearly 70% of clinicians agreed to follow therapeutic adaptation based on preemptive pharmacogenetic results in the study by Swen et al. [29].

Furthermore, the use of genetic information can be complex and may not be straightforward for all clinicians. Integrating this data into patient care requires careful consideration of various factors that influence the phenotype, such as renal insufficiency, hepatic insufficiency, and drug interactions. Therefore, pharmacological expertise is often necessary to navigate these complexities.

Reimbursement of pharmacogenetics: a current issue

The lack of reimbursement for most pharmacogenetic tests by health insurance represents a significant obstacle to the implementation of pharmacogenetics. Apart from a few rare tests, most of these tests are not reimbursed and can only be prescribed to patients covered by public or private healthcare facilities. Only a few tests listed in the "complementary list" of the nomenclature or those performed under the Reference Framework for Innovative Acts Outside the Nomenclature (RIHN) allow these facilities to receive financial compensation under the "teaching, research, reference, and innovation missions" (MERRI) envelope. However, the actual reimbursement of MERRI does not cover the entirety of the costs – usually around 50% – representing a significant economic loss and leading to considerable hesitation in offering these tests by many private facilities.

The reimbursement of oncological pharmacogenetics is currently being evaluated by the French National Authority for Health (HAS)–which is expected to issue its conclusions during the second half of 2024 or 2025.

Perspectives of pharmacogenetics in oncology

Towards a "pharmacogenetic passport" in oncology?

The introduction of a preemptive pharmacogenetic approach was explored in the PREPARE study (Preemptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions), the results of which were published in February 2023 by Swen et al. This prospective multicenter study demonstrated the benefits of integrating a "pharmacogenetic passport" into the care pathway. This passport includes preemptive genotyping of 12 pharmacogenetic genes: *CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5, DPYD, F5, HLA-B, SLCO1B1, TPMT, UGT1A1, VKORC1*, thus involving the metabolism of 42 drugs belonging to 12 different therapeutic classes.

The intention-to-treat analysis revealed a 30% reduction in adverse effects in the intervention group (odds ratio [OR] of 0.7, 95% confidence interval [CI] of 0.61 to 0.79, $p < 0.0001$). Furthermore, it is noteworthy that 70% of treatment modification recommendations were followed by treating physicians.

This study represents the first multicenter study demonstrating the value of preemptive implementation of a pharmacogenetic panel [29]. The results emphasize the need to establish a standardized, validated, and harmonized pharmacogenetic testing system, thereby supporting pharmacogenetics-guided decision-making at the point of care. Additionally, training healthcare professionals in personalized medicine and pharmacogenetics is essential.

The relevance of a "pharmacogenetic passport" is particularly evident in oncology, where patients are often polypharmacy users – receiving both anticancer therapy and supportive care, along with potential treatment for other chronic conditions.

Tumor screening: A strategy to enhance the clinical application of pharmacogenetics?

The integration of pharmacogenomics has enabled oncologists to better understand molecular medicine. Nowadays, molecular analysis of tumors is a common practice to identify specific therapeutic targets in tumor cells and screen for alterations potentially of constitutional origin. Indeed, every tumor cell derives from a constitutional cell, thus possessing the same initial genetic heritage punctuated by somatic alterations. Studies such as that of Teraf et al. have shown that tumor sequencing is adequate for detecting pathogenic germline single nucleotide polymorphisms (SNPs) and small insertions/deletions (indels). However, tumor screening alone may not suffice, as the sensitivity of tumor sequencing alone for detecting pathogenic germline variants was 89.5% [30]. Additionally, while most pathogenic germline single nucleotide variants (SNVs) and small insertions/deletions (indels) at the exon level can be detected by tumor screening alone, variations in germline copy number, intronic variants, and those involving repetitive element insertions may be challenging to detect accurately.

Therefore, it can be hypothesized that this same approach of tumor screening could be applied to pharmacogenetics. Gillis et al. studied the genotype concordance between tumor DNA and genomic blood DNA of 21 pharmacogenes in 752 patients with solid tumors. Using a threshold difference of 10% between the allelic variant fraction (VAF) of tumor DNA and blood DNA, the concordance for heterogeneous genotype calls was 78% and increased to 97.5% using a VAF threshold of 30% [29].

Thus, this tumor screening approach could serve as an effective pre-screening tool for identifying pharmacogenetic variants of interest. While it does not replace the need for a definitive constitutional test – given the risk of false positives due to somatic variants–but it can help guide clinicians toward potentially relevant variants, assisting in decision-making without immediate need for additional genotyping. This pre-screening approach could provide valuable information, enabling clinicians to direct further, more definitive testing.

Thus, this tumor screening approach could serve as an effective pre-screening tool for identifying pharmacogenetic variants of interest. While it does not replace the need for definitive constitutional testing, it offers early insights that may support clinical decision-making without requiring immediate additional genotyping. However, the feasibility of detecting structural variants in pharmacogenomics using FFPE tissue remains debated. Although clinically relevant, such variants are difficult to identify with short-read NGS methods due to technical limitations, including common FFPE-related artifacts. Caution is therefore warranted when interpreting pharmacogenetic data from FFPE samples.

Pharmacogenetics: a missing component in early drug development?

A key challenge in integrating pharmacogenetics into early drug development and new treatment combinations is the limited availability of robust data supporting its implementation. One major constraint is the small sample size in Phase I/II studies, which makes it difficult to detect rare but clinically relevant homozygous polymorphisms. The lack of sufficiently powered genetic studies, whether candidate-gene approaches with replication or Genome-Wide Association Studies (GWAS), can result in findings that do not fully capture individual genetic variability. Additionally, existing recommendations may not be applicable to all patient populations due to insufficient study data. For instance, pediatric populations receiving irinotecan as part of specific protocols could potentially benefit from UGT1A1 genotyping, regardless of dosage. Conducting pharmacoeconomic studies is essential to justify the investment in preemptive pharmacogenetic testing, assessing not only financial implications but also the impact on patient outcomes and quality of life. However, the current scarcity of large-scale, well-powered pharmacogenetic and pharmacoeconomic studies hinders the broader adoption of pharmacogenetics in clinical trials and routine practice. Without appropriate follow-up and strong evidence showing that genetic-based drug therapy individualization improves clinical and economic outcomes, it remains difficult to fully justify these investments. As a result, the absence of sufficient supporting data contributes to maintaining the status quo in clinical practice. In this context, the FDA's OPTIMUS project, which seeks to refine dose-finding studies by incorporating larger patient cohorts in randomized trials, could provide a valuable framework for identifying relevant pharmacogenetic covariates in early-phase clinical development. By integrating pharmacogenetic markers into optimized dose-selection strategies, this initiative could enhance the robustness of PGx-informed dosing recommendations and pave the way for broader implementation in precision medicine.

Conclusion

Targeted therapies have emphasized the role of somatic pharmacogenomics, but constitutional pharmacogenetics also offers valuable insights for optimizing chemotherapy dosing and

reducing toxicity. Despite its potential, its clinical integration remains limited due to low awareness and reimbursement challenges. Future oncology care could benefit from combining pharmacogenomics for tumor-driven treatment selection with pharmacogenetics to mitigate adverse effects, requiring clearer strategies for routine implementation.

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