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The Value of Pharmacogenetics to Reduce Drug-Related Toxicity in Cancer Patients

Doreen Z. Mhandire[1], **Andrew K. L. Goey**[1]

[1]Department of Pharmacology and Therapeutics, Roswell Park Comprehensive Cancer Center, Buffalo, NY 14263, USA

Abstract

Many anticancer drugs cause adverse drug reactions (ADRs) that negatively impact safety and reduce quality of life. The typical narrow therapeutic range and exposure-response relationships described for anticancer drugs make precision dosing critical to ensure safe and effective drug exposure. Germline mutations in pharmacogenes contribute to inter-patient variability in pharmacokinetics and pharmacodynamics of anticancer drugs. Patients carrying reduced-activity or loss-of-function alleles are at increased risk for ADRs. Pretreatment genotyping offers a proactive approach to identify these high-risk patients, administer an individualized dose, and minimize the risk of ADRs. In the field of oncology, the most well-studied gene-drug pairs for which pharmacogenetic dosing recommendations have been published to improve safety are *DPYD*-fluoropyrimidines, *TPMT/NUDT15*-thiopurines, and *UGT1A1*-irinotecan. Despite the presence of these guidelines, the scientific evidence showing the benefits of pharmacogenetic testing (e.g., improved safety and cost-effectiveness) and the development of efficient multi-gene genotyping panels, routine pretreatment testing for these gene-drug pairs has not been implemented widely in the clinic. Important considerations required for widespread clinical implementation include pharmacogenetic education of physicians, availability or allocation of institutional resources to build an efficient clinical infrastructure, international standardization of guidelines, uniform adoption of guidelines by regulatory agencies leading to genotyping requirements in drug labels, and development of cohesive reimbursement policies for pretreatment genotyping. Without clinical implementation, the potential of pharmacogenetics to improve patient safety remains unfulfilled.

1 Introduction

The use of many anticancer drugs (including targeted agents, anti-angiogenic drugs, and conventional cytotoxic chemotherapy) is associated with adverse drug reactions (ADRs) [1], which can negatively impact patient safety and quality of life (QOL). Moreover, ADRs also compromise drug efficacy due to treatment interruptions and/or discontinuation

✉Andrew K. L. Goey, andrew.goey@roswellpark.org.

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[2, 3], and result in increased healthcare costs associated with toxicity management and hospitalizations [4, 5]. The therapeutic range of anticancer drugs typically is narrow and exposure-response relationships for efficacy and/or safety have been established for many agents [6]. Therefore, precision dosing is of great importance to minimize the risk of toxicities while maximizing tumor response. However, precision dosing of many anti-cancer drugs is complicated by wide inter-patient variability in drug exposure (pharmacokinetics) and drug response (pharmacodynamics) [7], with outcomes that range from subtherapeutic treatment to life-threatening toxicities [8, 9]. The cause of these heterogenous responses often is multifactorial [10, 11], and includes physiological factors (e.g., age, gender, body weight), lifestyle and behavioral factors (e.g., smoking, alcohol use, drug adherence), drug-drug interactions [12], and genetic factors, which are the focus of this article. The effects of genes on drug response are studied in the field of pharmacogenetics (focusing on a single or a limited number of genes) and pharmacogenomics (considering many genes or the whole genome); both areas are part of precision medicine and the terms often are used interchangeably.

Pharmacogenetic research in oncology typically focuses on two types of genetic changes [13]: (1) somatic (tumor) mutations that largely determine tumor response to targeted agents and influence drug selection (e.g., HER2 testing for trastuzumab [14]); and (2) germline mutations in genes encoding for drug-metabolizing enzymes and drug transporters (pharmacogenes) that affect drug exposure and dose selection. In routine care of cancer patients, pretreatment genotyping for somatic mutations is currently applied more widely than germline testing for pharmacogenetic mutations. However, complementary to selection of the right drug, selecting the right dose is also essential to achieve safe and therapeutic drug exposure. To emphasize the value of germline pharmacogenetic testing for precision dosing, the current article focuses only on germline mutations in pharmacogenes.

Exposure-response relationships have been established for many anticancer drugs, so germline mutations in pharmacogenes could serve as safety biomarkers and warrant inclusion in precision dosing strategies. Germline pharmacogenetics classifies patients according to their ability to metabolize or transport drugs into metabolic or transporter phenotypes [15, 16]:

- (Ultra) rapid metabolizers or individuals with increased transporter function: possess multiple copies of the functional gene that results in overexpression of functional protein and increased protein activity.
- Normal metabolizers or individuals with normal transporter function: carry two normal/functional or “wildtype” alleles that results in normal gene and protein activity.
- Intermediate metabolizers or individuals with decreased transporter function: carry one normal and one reduced-activity “variant” allele that results in reduced protein activity.
- Poor metabolizers or individuals with poor transporter function: have two reduced-activity alleles that results in little or lost protein activity.

Reduced-activity single nucleotide polymorphisms (SNPs) could inhibit drug absorption, distribution, metabolism, and excretion (ADME) processes that increase plasma concentrations of drug substrates and risks of ADRs. Patients carrying these SNPs should be prescribed a lower drug dose to avoid supratherapeutic drug concentrations, which may lead to ADRs. The opposite is true for prodrugs, such as tamoxifen. Reduced-activity variant carriers are at risk of treatment failure due to decreased exposure to active metabolites. In this case, a higher starting dose is recommended.

This *Current Opinion* article summarizes the value of pharmacogenetics to reduce toxicities related to the use of anticancer drugs, the progress of clinical implementation, the challenges that remain in this field, and suggestions for future efforts to move this field forward.

2 Clinical Implementation of Pharmacogenetics: Progress Thus Far

Implementation of clinical pharmacogenetics has the potential to personalize therapy to maximize treatment efficacy and minimize ADRs [17]. Important initiatives towards clinical implementation of genotype-based dosing have been made by various consortia including the Clinical Pharmacogenetics Implementation Consortium (CPIC) [18], the Royal Dutch Association for the Advancement of Pharmacy-Pharmacogenetics Working Group (DPWG) [19], the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) [20], and the French National Network of Pharmacogenetics (RNPGx) [21]. Clinical guidelines developed by these consortia and other clinically relevant pharmacogenetic information is available in the NIH-funded Pharmacogenomics Knowledgebase (PharmGKB) [22]. Both PharmGKB and CPIC interact closely with the Pharmacogene Variation Consortium that catalogues allelic variation of pharmacogenes and standardizes pharmacogenetic nomenclature [23]. Other relevant archives include the NIH-based ClinVar (includes reports of relationships between human variations and phenotypes [24]) and ClinGen (defines the clinical relevance of genes and variants for use in precision medicine and research [25]).

As of December 2021, the various consortia have published pharmacogenetic guidelines (CPIC = 94, DPWG = 95, CPNDS = 8, Other societies = 20) that cover 31 genes and 141 drugs across various therapeutic areas [26]. From these guidelines, the following gene-drug pairs were selected with the most well-validated associations with toxicity: dihydropyrimidine dehydrogenase (*DPYD*)-fluoropyrimidines, thiopurine methyltransferase (*TPMT*) and nudix hydrolase 15 (*NUDT15*)-thiopurines, and *UGT1A1*-irinotecan (Table 1). In agreement with the guidelines for *TPMT*/NUDT15-thiopurines, the National Comprehensive Cancer Network (NCCN) Guideline for pediatric acute lymphoblastic leukemia recommends considering pretreatment *TPMT* and *NUDT15* genotyping [35]. With regard to *DPYD*-fluoropyrimidines and *UGT1A1*-irinotecan, the NCCN Guideline for colon cancer acknowledges the increased risk for toxicities in variant carriers, but no recommendations for pretreatment genotyping are given [36].

The establishment of pharmacogenetic dosing guidelines is important, but adoption of these guidelines by regulatory authorities is an important next step towards widespread clinical implementation of pharmacogenetics. When clinicians are recommended or mandated to order genotyping tests prior to starting treatment, the adoption of genotype-guided

dosing is expected to increase. Regulatory bodies, which include the US Food and Drug Administration (FDA), European Medicines Agency (EMA), Health Canada (Santé Canada) (HCSC), the Swiss Agency of Therapeutic Products (Swissmedic), and the Pharmaceuticals and Medical Devices Agency Japan (PMDA), have incorporated mandates or recommendations for pharmacogenetic testing in the drug labels of the anticancer drugs listed in Table 1. This section discusses to what extent the existence of pharmacogenetic guidelines and drug label recommendations have led to routine pretreatment genotyping of patients who are indicated for therapy with fluoropyrimidines, thiopurines, or irinotecan.

2.1 Genotyping Approaches: Pre-emptive Versus Reactive Genotyping

Pharmacogenetic implementation initiatives have taken place mostly in Europe, North America, and Asia [37]. The typical workflow applied in many initiatives is shown in Fig. 1. Two genotyping approaches can be distinguished at the time of ordering a pharmacogenetic test: pre-emptive or reactive testing [38]. Reactive genotyping describes the situation in which a genetic test is ordered during or after a pharmacogenetically high-risk drug is prescribed. The order often includes a limited number of genetic variants that are relevant to the prescribed drug. In contrast, pre-emptive genotyping usually includes multi-gene panels and is performed before a drug is indicated. Pre-emptive genotyping has the advantage of having genotyping results available at the time of prescription, thereby avoiding delays in initiation of therapy. The term “pretreatment genotyping/testing” used in this article refers to both pre-emptive and reactive genotyping.

2.2 *DPYD* Genotyping for Fluoropyrimidines

Fluoropyrimidines are antimetabolite drugs that are approved for treatment of colorectal, breast, pancreatic, and gastric cancers [39, 40]. The three fluoropyrimidine drugs are fluorouracil (5-FU), its oral prodrug capecitabine, and tegafur. The rate-limiting step in fluoropyrimidine metabolism is conversion of 5-FU to dihydrofluorouracil by dihydropyrimidine dehydrogenase (DPD), which is a polymorphic enzyme encoded for by the *DPYD* gene [41]. Carriers of *DPYD* polymorphisms that lead to reduced DPD activity (approximately 7% of Europeans; Table 1) are at increased risk of potentially lethal toxicities, such as neutropenia and severe diarrhea [27, 42]. Since 30 April 2020 the EMA has recommended *DPYD* testing prior to treatment with fluoropyrimidines [43]. The Swiss even require evaluation of DPD enzyme activity prior to starting therapy with 5-FU in patients who recently were treated with brivudine or other nucleoside analogs [44]. The Swiss label for capecitabine recommends pretreatment DPD phenotype or *DPYD* genotype assessment and contraindicates capecitabine in patients with complete DPD deficiency [45]. In recent years, the number of European countries that have adopted routine upfront *DPYD* genotyping is increasing, and include the Netherlands [46], France [29], and Finland [47]. In addition, pre-emptive *DPYD* genotyping in seven European countries is evaluated by the PREPARE trial led by the Ubiquitous Pharmacogenomics Consortium, which is funded by the European Commission’s Horizon-2020 program [48]. In the USA, the FDA does not recommend reactive or pre-emptive *DPYD* testing, which hampers wide adoption in routine clinical care of American cancer patients [49]. A few US centers (e.g., Mayo Clinic [50], Mount Sinai Medical Center [51], St. Jude Children’s Research Hospital [52], UF Health Shands Hospital [53], and Vanderbilt University Medical Center [54]) are

conducting pre-emptive panel testing that includes *DPYD*. Dartmouth-Hitchcock Medical Center [55] and M Health Fairview [56] are examples of healthcare providers in the USA that perform reactive *DPYD* genotyping. In Canada, where HCSC does not mandate pretreatment *DPYD* genotyping, *DPYD* testing is not adopted widely [57], although the test has been implemented in the province of Quebec [58]. In Japan, PMDA does not require or recommend pretreatment *DPYD* testing, and the PMDA labels of 5-FU [59] and capecitabine [60] only list *DPYD* as an actionable variant.

2.3 *TPMT* and *NUDT15* Genotyping for Thiopurines

The thiopurines 6-mercaptopurine (6-MP) and 6-thioguanine (6-TG) are purine antimetabolites that are approved for the treatment of acute lymphoblastic leukemia and acute myeloid leukemia, respectively. Thiopurine metabolism is complex and involves several enzymatic steps for the formation of active, cytotoxic metabolites [61]. TPMT, a key polymorphic enzyme in this process, catabolizes 6-MP to an inactive metabolite, thereby lowering the amount of 6-MP that is available for conversion into cytotoxic thioguanine nucleotides (TGNs) [30]. Patients carrying loss-of-function *TPMT* alleles will have higher TGN levels that increase risk of severe myelosuppression [62]. TPMT also metabolizes 6-TG into an inactive metabolite, thereby reducing the amount of 6-TG that can be transformed into active TGNs. In TPMT-deficient patients treated with 6-TG, TGNs will accumulate and a lower starting dose is recommended to minimize the risk of toxicities [30]. Another important polymorphic enzyme in thiopurine metabolism is NUDT15, which metabolizes the cytotoxic metabolites 6-thioguanosine triphosphate (TGTP) and 6-thio-deoxy-guanosine triphosphate (TdGTP) into inactive metabolites. Carriers of loss-of-function variants of *NUDT15* have a greater risk of myelosuppression due to accumulation of TdGTP and TGTP [63], and should receive a reduced thiopurine starting dose [30].

The EMA label states that *TPMT* and *NUDT15* genotyping may be considered before initiating 6-MP therapy [64], but no recommendation has been established for 6-TG. Swissmedic lists *NUDT15* and *TPMT* as actionable pharmacogenetic variants for genotype-guided dosing of both 6-MP [65, 66] and 6-TG [67]. *TPMT* and *NUDT15* testing is not required in the EMA and Swissmedic drug labels, but *TPMT* testing prior to prescription of thiopurine drugs has become routine clinical practice in Europe [68]. The FDA drug labels of 6-MP oral suspension and tablets recommend reactive testing for *TPMT* and *NUDT15* variants in the event of severe myelosuppression or repeated episodes of myelosuppression [69, 70]. Cincinnati Children's Hospital Medical Center [71], Duke University Hospital [72], and Boston Children's Hospital (also offers pre-emptive testing) [73] are examples of US hospitals that perform reactive *TPMT* testing. Several other US hospitals have implemented pre-emptive *TPMT* genotyping [50, 74, 75].

2.4 *UGT1A1* Genotyping for Irinotecan

Irinotecan is a cytotoxic agent used for the treatment of metastatic colorectal cancer [76]. As a prodrug, irinotecan needs to be metabolized by hepatic carboxylesterases to SN-38, the active metabolite. SN-38 inhibits topoisomerase I, ultimately causing irreversible double strand breaks in DNA and cell death. SN-38 is glucuronidated by polymorphic UGT1A1 to inactive SN-38 glucuronide, which is excreted via the biliary route [77]. Carriers of

UGT1A1-mutant alleles (e.g., *UGT1A1*28*) that reduce enzymatic activity are exposed to higher intestinal SN-38 levels and are predisposed to dose-limiting neutropenia and diarrhea [78, 79].

None of the regulatory agencies require *UGT1A1* genetic testing in their irinotecan drug labels despite well-established associations between *UGT1A1* variants and irinotecan-induced toxicities (e.g., severe neutropenia) [80]. The PMDA appears to be the most strict, and recommends *UGT1A1* testing and genotype-guided dosing of irinotecan in pancreatic cancer patients [81]. The FDA, EMA, Swiss-medic, and HCSC do not mandate pretreatment *UGT1A1* genotyping, but recommend starting dose reductions for patients homozygous for *UGT1A1*28* [76, 82–84]. Routine pretreatment *UGT1A1* genotyping is yet to be applied in most clinics, but certain hospitals in France [85] and in the USA have implemented [86] or are investigating the feasibility of implementation [87, 88].

3 Benefits and Challenges of Pharmacogenetics Implementation

3.1 Benefits

As mentioned in the Introduction, testing for germline pharmacogenetic mutations can be a valuable tool for precision dosing. Precision dosing is expected to enhance various aspects of treatment outcomes, including safety, efficacy, and cost-effectiveness.

3.1.1 Improved Safety—A pharmacogenetic-guided dose is intended to lower the risk of ADRs and the need for dose reductions, treatment interruptions, or even hospitalizations, thereby improving patient safety. ADRs are potentially fatal for anticancer drugs, such as fluoropyrimidines and thiopurines, and pretreatment pharmacogenetic testing can therefore save lives. *DPYD* genotyping prior to initiating fluoropyrimidine therapy and genotype-guided dosing were shown to reduce the risk of grade ≥ 3 toxicities and drug-induced death when compared with patients with *DPYD*2A* variant alleles who received the standard dose [89]. A more recent prospective safety study confirmed that clinical implementation of pretreatment genotyping of four *DPYD* variants (**2A, *13*, c.2846A > T and c.1236G > A) was feasible and reduced the risk for fluoropyrimidine-related toxicities [90]. As for *UGT1A1*-irinotecan, several prospective dose-finding studies showed that irinotecan was tolerated better at lower doses in patients carrying variants of *UGT1A1*28* alone [91–94] or combined with *UGT1A1*93* [95]. For example, the maximum tolerated dose (MTD) of irinotecan was lower in cancer patients homozygous for *UGT1A1*28* (400 mg every 3 weeks) compared with *UGT1A1*1/*28* heterozygous patients (700 mg every 3 weeks) or *UGT1A1* wildtype patients (850 mg every 3 weeks) [92]. Also for *TPMT*-thiopurines, a reduced risk for toxicities (i.e., grade 3–4 infections and grade 3–4 febrile neutropenia) was shown prospectively in children with acute lymphoblastic leukemia who received *TPMT*-guided dosing compared with patients whose 6-MP dose was not adjusted based on *TPMT* genotype [96].

3.1.2 Improved Efficacy—Pharmacogenetic testing is expected to enhance drug efficacy in addition to improving patient safety. More patients are expected to complete the intended duration of treatment by reducing the incidence of ADRs. Anticancer treatment interruptions can negatively impact therapeutic outcome (e.g., molecular response, disease-

free survival, risk of recurrence) as has been reported for capecitabine [97] and tyrosine kinase inhibitors [98]. Genotype-guided dosing may also improve efficacy by administering higher doses to patients whose genotypes indicate decreased sensitivity to drug-related toxicities. For instance, colorectal cancer patients without the *UGT1A1*28/*28* genotype tolerated higher irinotecan doses than the recommended labeled dose, which suggests that these patients are likely being under-dosed under standard non-genotype-based dosing regimens [91–93]. Of note, whether increased doses of irinotecan improve drug efficacy in patients with certain genotypes requires confirmation in prospective clinical studies.

3.1.3 Improved Cost-Effectiveness—From a societal and economical point of view, reducing the risk of drug-induced toxicities lowers pressure on healthcare systems and expenses related to toxicity management and hospitalizations. For the anticancer drugs listed in Table 1, several cost-effectiveness studies have shown that once in a lifetime genetic testing coupled with dose adjustments is more effective (i.e., quality-adjusted life-years gained) at an acceptable additional cost than standard-of-care procedures without pretreatment testing or genotype-based dose adjustments. For example, *UGT1A1* genotyping followed by reduction of the starting dose of irinotecan has been shown to be cost-effective [99–101] or even cost-saving, as has been shown in Chinese colorectal cancer patients: *UGT1A1*6/*28* genotyping and dose adjustments resulted in an increase of quality-adjusted life-years and a cost reduction of at least US$651 per patient when compared with patients who received the non-genotype-adjusted standard dose of irinotecan [102]. Also, pretreatment *DPYD* genotyping followed by dose adjustments for fluoropyrimidines was shown to be cost-saving [89, 103–105]. For example, upfront screening for four *DPYD* variants combined with genotype-guided dosing resulted in a net cost saving of 51 € per patient compared with the costs of a non-screening approach [105]. In addition to irinotecan and fluoropyrimidines, thiopurines can induce life-threatening myelosuppression. Pretreatment *TPMT* testing was shown to be a cost-effective strategy in patients treated with thiopurines for Crohn's disease [106], rheumatological conditions [107], and inflammatory bowel disease (IBD) [108]. Combined screening for *TPMT* and *NUDT15* risk alleles was cost-effective in Asian patients with IBD [109]. However, few cost-effectiveness studies have been performed in cancer patients. In children with ALL, one study concluded that *TPMT* testing had a favorable cost-effectiveness ratio when taking into account genotyping costs, estimates for frequency of TPMT deficiency, rates of thiopurine-mediated myelosuppression in *TPMT*-deficient patients, and myelosuppression-related hospitalization costs in Germany, Ireland, the Netherlands, and the UK [110]. The cost-effectiveness ratio was 2100 € per life-year gained, which was considered as a favorable outcome. In contrast, a second cost-effectiveness study in pediatric ALL patients concluded that *TPMT* genotyping prior to 6-MP administration was not cost-effective: compared with weight-based dosing of 6-MP, the incremental costs for genotype-based dosing were US$277 and no difference in survival was shown [111].

3.2 Challenges

Despite the presence of pharmacogenetic dosing guidelines and recommendations in drug labels, clinical adoption of these recommendations in routine patient care is lagging [37, 112, 113]. For instance, among Medicaid and Medicare beneficiaries in

the state of Mississippi (N = 72,208) who were taking medications that contained pharmacogenetic labeling information, less than 11% underwent genetic testing [114]. In the following sections, we discuss some barriers that preclude widespread pharmacogenetic implementation in routine clinical care and potential solutions to overcome these barriers (Table 2).

3.2.1 Lack of Pharmacogenetic Education—Physicians are the gatekeepers for the ordering of pharmacogenetic tests. Therefore, they need to understand the concepts, and be convinced of the importance, of pharmacogenetics. Hence, pharmacogenetic knowledge of physicians is a key determinant for the success of pharmacogenetic implementation in routine clinical care [115]. Several studies have shown that clinicians have pharmacogenetic knowledge deficits, lacked pharmacogenetic education, and find it challenging to keep up with the rapid generation of novel gene-drug pairs without educational support [116–119]. Pharmacogenetic education could tackle these issues and address concerns that physicians may have towards pharmacogenetic testing, such as the fear of causing unnecessary delays of therapy initiation or the belief that dose reductions in variant carriers may lead to inferior tumor response. Therefore, pharmacogenetic training should be offered during medical programs and throughout the clinicians' professional careers to keep up with the ongoing advancements in the field of pharmacogenetics. An important role in these educational activities could be fulfilled by clinical pharmacists and genetic counselors [71, 120], of which a critical shortage exists in the USA [121]. In addition, alerts generated by clinical decision support (CDS) systems should be clear, concise, and provide educational links to background information. In contrast to pharmacogenetic testing, the uptake of somatic testing does not seem to be affected by a lack of education among clinicians. First, testing for actionable somatic mutations often is mandatory as stated in guidelines and drug labels. For example, a somatic BRAF V600E or V600K mutation needs to be confirmed before melanoma patients are permitted to start with BRAF inhibitor therapy [122, 123]. Second, compared with pharmacogenetic testing, interpretation of somatic test results is usually more straight-forward: the presence or absence of the mutation of interest directly indicates whether a patient is eligible for treatment with a targeted drug.

3.2.2 Lack of Adoption of Pharmacogenetic Guidelines by Regulatory Agencies—Pharmacogenetic dosing guidelines produced by consortia, such as CPIC or DPWG, must be adopted by regulatory agencies for pharmacogenetic testing to be implemented in routine clinical care. At the time of drug approval, inclusion of pharmacogenetic recommendations in drug labels typically relies on proprietary data from the pharmaceutical companies. During the submission process, regulatory agencies, such as the FDA, provide guidances on the submission of pharmacogenetic data [124]. In contrast to new drug applications, adoption of guidelines published by pharmacogenetic consortia are usually related to drugs that have already been approved. Revision of product labels of these drugs is a challenging process [125]. Potential hurdles towards inclusion of pharmacogenetic information in labels of approved drugs include: (1) the quantity, quality, and nature of publicly available data that form the basis of the guidelines; (2) alignment of a multidisciplinary team, the members of which may have differing perspectives; and (3) logistical concerns towards clinical implementation (e.g., rapid turnaround time,

availability of a validated analytical assay). Nevertheless, successful incorporation of pharmacogenetic recommendations into drug labels is expected to increase pharmacogenetic testing uptake rates, analogous to pretreatment testing requirements for somatic mutations in the case of targeted therapies. The extent to which regulatory agencies have implemented pharmacogenetic recommendations in their drug labels differ. For instance, the EMA recommends *DPYD* genotyping prior to starting treatment with fluoropyrimidines [43], whereas the FDA does not mandate pretreatment *DPYD* testing although the FDA drug labels of 5-FU and capecitabine warn for increased risk of severe toxicities in DPD-deficient patients [39, 40].

3.2.3 Lack of Standardization of Guidelines, Genotyping Panels, Genotype–Phenotype Translation—Discrepancies exist between pharmacogenetic guidelines of international consortia and drug labels for certain gene-drug pairs. When genetic tests are ordered, consensus between institutions and laboratories should be reached on which variants to include for a specific gene. For example, the FDA drug label of irinotecan only considers the *UGT1A1*28* polymorphism for genotype-adjusted dosing adjustments [76]. Among East-Asian patients, however, the *UGT1A1*6* variant is more prevalent and, therefore, in addition to *UGT1A1*28*, testing for this SNP is recommended in the Japanese PMDA drug label for irinotecan [81]. The ongoing globalization requires the inclusion of actionable SNPs that are prevalent in non-Caucasian populations in multicultural societies. Heterogeneity in pharmacogenetic recommendations has not only been identified between regulatory agencies [126], but also between pharmacogenetic consortia, such as CPIC and the DPWG [127]. Inconsistent dose recommendations could confuse prescribers and hinder adoption of pharmacogenetic guidelines. For example, CPIC and the DPWG recommend 50% dose reduction of fluoropyrimidines in patients with a DPD activity score of 1.5 [27, 28], whereas RNPGx recommends a 25% dose reduction in these patients [29] (Table 1). To achieve standardization of their guidelines, pharmacogenetic consortia need to collaborate, which has been done successfully by CPIC and DWPG for the gene-drug pair *DPYD*-fluoropyrimidines. This has led to updates of their *DPYD* genotyping guidelines for fluoropyrimidines, thereby minimizing discrepancies between these guidelines [127]. For certain genes, such as *CYP2D6*, lack of international agreement on genotype to phenotype translation could also hamper the development of universal genotype-guided dosing recommendations. Recent harmonization efforts by CPIC and DPWG have resulted in a standardized *CYP2D6* genotype to phenotype translation method [33].

3.2.4 Resources and Infrastructure—Successful implementation of pharmacogenetic testing relies on the presence of skilled and dedicated personnel, and an efficient infrastructure. During the initiation phase, the presence of a physician champion and advocates of pharmacogenetics are beneficial to accelerate the implementation process and gain support from hospital leadership to provide initial funding [71]. Launching pharmacogenetic implementation requires a multidisciplinary team effort from staff that includes physicians, clinical pharmacists, geneticists, nurses, laboratory staff, and informaticians [71, 128].

Integration of genotyping results in electronic health records (EHRs) and CDS systems is an important determinant for successful clinical implementation of pharmacogenetics [129]. Many active pharmacogenetic programs integrated pharmacogenetic CDS systems in their existing EHRs themselves [130]. However, not all institutes have the resources for this approach and need to rely on external vendors of pharmacogenetic support platforms [129]. Important considerations when selecting a genomic support platform include: (1) generation of active pharmacogenetic CDS pre-test and post-test alerts; (2) easy access to both internal and external pharmacogenetic test results to clinicians in the EHR; (3) regular updates of clinical recommendations based on the most recent guidelines; (4) return pharmacogenetic results to the patient portal; and (5) customization options based on institutional needs.

Pharmacogenetic testing should not delay the initiation of therapy, which can be a bottleneck for reactive genotyping orders [71]. Several clinical implementation initiatives use microarrays (e.g., DMET™, PharmacoScan™, Infinium™ Global Diversity Array with Enhanced PGx, or customized arrays) that can include more than 57,000 ADME genetic markers [53, 75, 131]. Turnaround time from sample preparation to the genotype results file can be as short as 3 days. Genotyping methods in clinical practice also include polymerase chain reaction (PCR)-based assays with turnaround times of up to 7 days [132–134], a combination of PCR and custom-target sequencing approaches [50], and primer-extension-based assays [135]. The analytical turnaround time of these methods may seem acceptable, but the actual turnaround time for integration of genotyping results in the EHRs can be several weeks, especially when genotyping is performed externally [136]. To ensure clinically acceptable turnaround times, implementers must build an efficient infrastructure from sample collection, sample shipment to a certified laboratory (in-house or external), sample analysis, interpretation of results, reporting of results, and integration of results into the EHRs that finally result in dose recommendations. The abovementioned steps require significant financial commitment (especially at the start of implementation) at both institutional and national levels. The financial burden is one of the reasons why implementation of pharmacogenetic testing is lagging in developing countries [137–139]. Of note, the logistic and financial challenges discussed in this section also apply to the integration of somatic testing into clinical cancer care [140, 141].

3.2.5 Limited Insurance Coverage—Another major barrier towards widespread adoption of pharmacogenetic testing is the limited insurance coverage of pharmacogenetic tests [142]. Genotyping costs vary widely internationally [143] with costs typically lower in Europe than in the USA [144, 145]. Also, insurance coverage is highly variable, even on a national level, as is the case in the USA where Medicare/Medicaid and many private insurance companies have their own policies [146, 147]. Overall, coverage rates for pharmacogenetic tests in the USA have been low (30–40%) [146, 148]. Recently, however, coverage of pharmacogenetic tests by Centers for Medicare and Medicaid Services (CMS) has expanded across most of the USA [149, 150]. CMS coverage now includes single gene and multi-gene tests for all clinically actionable gene-drug interactions as defined by the FDA and CPIC guidelines [149, 150]. With regard to pre-emptive testing, reimbursement of multi-gene panels is even more challenging than single-gene-drug pair tests [151]. Coverage or reimbursement by health insurers is affected by factors that include regulation, cost-

effectiveness data, strength of evidence, presence of guidelines from professional societies, and endorsement of these guidelines [152]. From a research perspective, an important step towards increasing coverage rates is to perform more cost-effectiveness studies of pharmacogenetic testing in cancer patients (e.g., *TPMT*-thiopurines) and its impact on costs for healthcare systems, health insurance companies, and out-of-pocket patient costs [153].

4 Future Perspectives

To overcome some of the challenges discussed in the previous section, we propose the following for future pharmacogenetic research or implementation initiatives.

The belief that dose reductions in patients with reduced-activity variants will adversely affect tumor response could be a reason for clinicians to not perform genotype-based dosing for the gene-drug pairs discussed in this paper. To address this concern, prospective randomized studies need to be carried out to demonstrate noninferior efficacy of genotype-based dosing in comparison with full-dose therapy in wildtype patients. These studies are now missing for *UGT1A1*-irinotecan and *DPYD*-fluoropyrimidines, although pharmacokinetic analyses showed similar exposure to SN-38 [92] and 5-FU [90] in patients who received a reduced genotype-guided dose versus fully dosed wildtype patients. In children with acute lymphoblastic leukemia, *TPMT*-guided dosing did not affect efficacy in terms of event-free survival [154].

In addition to including efficacy outcomes, another valuable endpoint in prospective pharmacogenetic studies would be patient-reported QOL outcomes by utilizing questionnaires, such as those from the European Organisation for Research and Treatment [155] or the Functional Assessment of Cancer Therapy [156], which are widely used metrics for QOL in oncology trials. To the best of our knowledge, QOL has not been included as an endpoint in randomized pharmacogenetic trials comparing QOL in patients receiving genotype-guided dosing versus patients receiving standard-of-care treatment. The case for pharmacogenetic testing would be strengthened if, in addition to improvement of safety with preservation of efficacy, improvement of QOL has also been confirmed.

The uptake rate of pharmacogenetic testing could also be increased by integration of pharmacogenetics into routine germline testing or somatic testing that is being conducted otherwise in cancer patients [157]. In addition to somatic tumor genetic testing, cancer patients often undergo matched germline analysis for accurate identification and interpretation of genetic alterations [158] and/or to assess familial predisposition to cancer [159, 160]. Matched germline testing offers the opportunity to simultaneously screen for pharmacogenetic germline variants, which would save the inconvenience and costs associated with an additional pharmacogenetic test. In the absence of matched germline testing, pharmacogenetic analysis could be included in the somatic test panel followed by confirmatory germline testing [157].

5 Conclusions

In oncology, the value of pretreatment pharmacogenetic testing to reduce ADRs has been well established for the gene-drug pairs *DPYD*-fluoropyrimidines, *TPMT/NUDT15*-

thiopurines, and *UGT1A1*-irinotecan. International guidelines have been published and, to a varying extent, regulatory agencies have adopted these guidelines in the labels of these anticancer drugs. Implementation initiatives also showed that clinical implementation of pre-emptive, or at least pretreatment, genotyping is feasible in particular for the gene-drug pairs *DPYD*-fluoropyrimidines and *TPMT/NUDT15*-thiopurines. However, several obstacles preclude widespread adoption of pharmacogenetic testing in routine patient care. Areas that require attention include pharmacogenetic education of physicians, creating an efficient infrastructure at an institutional level, international consensus on guidelines and uniform adoption of these guidelines by regulatory agencies, and development of cohesive reimbursement policies for pretreatment genotyping.

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Key Points

Pretreatment genotyping for germline mutations in pharmacogenes can be applied to identify patients with an increased risk of adverse drug reactions.

The benefits of pharmacogenetic testing and genotype-guided dosing have been described in the literature and international guidelines, but these procedures have not been implemented on a wide scale in routine patient care. The most common clinical implementation for anti-cancer drugs has been for *DPYD* and *TPMT* genotyping prior to treatment with fluoropyrimidines and thiopurines, respectively.

Implementation challenges need to be overcome in the areas of education of physicians, harmonization of pharmacogenetic guidelines, adoption of these guidelines at a regulatory level, and reimbursement for genetic testing.

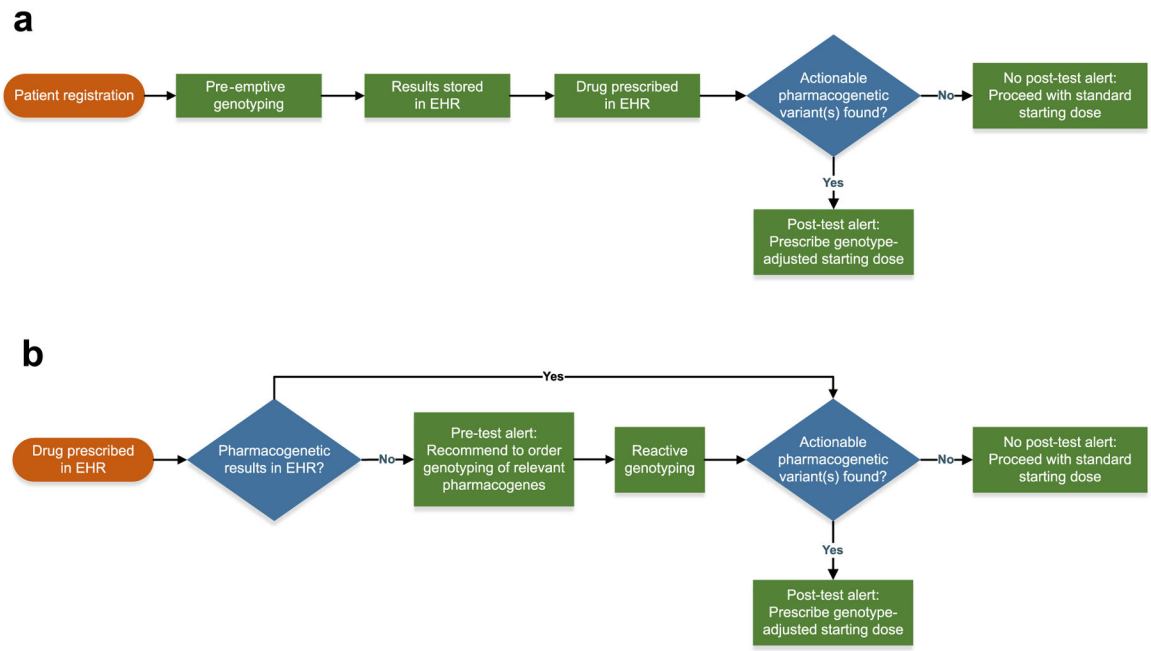

Fig. 1.

Typical workflow of a clinical decision support system for pre-emptive (**a**) and reactive (**b**) pharmacogenetic testing

Table 1

Pharmacogenetic guidelines on anticancer drugs as of December 2021

Anticancer drug	Clinically relevant polymorphisms	Cancer type	Dosing recommendations
Fluorouracil (5-FU), Capecitabine, Tegafur	*DPYD*: *2A (c.1905 + 1G > A, IVS14 + 1G > A) *13 (c.1679T > G) c.2846A > T Haplotype B3 (c.1236G > A, c.1129 − 5923C > G)	Colorectal, breast, gastric, pancreatic	Gene AS ranges from 0 (no DPD activity) to 2 (normal DPD activity), based on presence of *DPYD* variants CPIC [27] and SEFF/SEOM [34]: NM (AS = 2): no dose change IM (AS = 1 or 1.5): reduce starting dose by 50%, followed by TDM[a] PM (AS = 0 or 0.5): avoid use of fluoropyrimidines DPWG [28]: AS = 2: no dose change AS = 1 or 1.5: reduce starting dose by 50% AS = 0: avoid use of fluoropyrimidines AS= 0.5: enzyme activity cannot be predicted correctly, perform additional phenotyping test and adjust starting dose accordingly or avoid fluoropyrimidines RNPGx [29]: AS determined by DPD phenotyping and/or *DPYD* genotyping NM (AS = 2): no dose change IM (AS = 1.5): reduce dose by 25% IM (AS = 1): reduce dose by 50% PM (AS = 0 or 0.5): avoid use of fluoropyrimidines
6-mercaptopurine (6-MP), 6-thioguanine (6-TG)	*TPMT*: *2 (c.238G > C) *3A (c.460G > A, c.719A > G) *3B (c.460G > A) *3C (c.719A > G) *4 (c.626 − 1G > A) *11 (c.395G > A) *14 (c.1A > G) *15 (IVS7–1G > A) *23 (c.500C > G) *29 (c.2T > C) *41 (c.719A > C) *NUDT15*: *2 (c.415C > T, c.38GAG TCG [4]) *3 (c.415C > T) *9[b] (c.38GAG TCG [2]) *TPMT* and *NUDT15* alleles with uncertain function are not listed	ALL, AML	CPIC [30]: TPMT or NUDT15 NM: no dose change TPMT or NUDT15 IM: start with 30–80% of normal 6-MP dose or 50–80% of normal 6-TG dose TPMT PM: reduce daily dose by tenfold and reduce frequency to thrice weekly instead of daily NUDT15 PM: start 6-MP at 10 mg/m^2/day. For 6-TG: reduce normal dose by 75% For detailed recommendations for TPMT and NUDT15 combined phenotypes, see CPIC guideline [30] DPWG [31]: TPMT or NUDT15 IM: start with 50% of standard 6-MP dose or start with standard 6-MP dose and reduce to 50% in the event of toxicity. For 6-TG, start with 75% of standard dose or start with standard dose and reduce to 75% in the event of toxicity TPMT or NUDT15 PM: avoid 6-MP or start with 10% of standard dose. For 6-TG, avoid 6-TG or start with 6–7% (for TPMT PMs) or 10% (for NUDT15 PMs) of standard dose RNPGx [32]: *TPMT* genotyping and/or phenotyping is essential. No dosing recommendations given
Irinotecan	*UGT1A1*28* (c.−53_−52insTA,A(TA)7TAA)	Colorectal	DPWG [31]: *UGT1A1*1/*28* (IM): no action needed *UGT1A1*28/*28* (PM): reduce starting dose by 30% RNPGx [32]: *UGT1A1*28/*28*: no action for low doses (< 180 mg/m2/week). Reduce standard starting dose by 25–30% for doses of 180–230 mg/m^2 every 2–3 weeks. Avoid irinotecan for doses > 240 mg/m^2 every 2–3 weeks

AS activity score, *ALL* acute lymphoid leukemia, *AML* acute myeloid leukemia, *CML* chronic myeloid leukemia, *CPIC* Clinical Pharmacogenetics Implementation Consortium, *CPNDS* Canadian Pharmacogenomics Network for Drug Safety, *DPWG* Royal Dutch Association for the Advancement of Pharmacy-Pharmacogenetics Working Group, *DPD* dihydropyrimidine dehydrogenase (enzyme), *DPYD* dihydropyrimidine dehydrogenase (gene), *IM* intermediate metabolizers, *NM* normal metabolizers, *NUDT15* nudix hydrolase 15, *PM* poor metabolizers, *RNPGx* French National Network of Pharmacogenetics, *SEFF* Spanish Pharmacogenetics and Pharmacogenomics Society, *SEOM* Spanish Society of Medical Oncology, *TDM* therapeutic drug monitoring, *TPMT* thiopurine methyltransferase, *UGT1A1* UDP glucuronosyltransferase 1A1

[a]Dosing recommendation updated in November 2018 (https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/)

[b] *NUDT15*9* function changed from "uncertain function" to "no function" in February 2019 (https://cpicpgx.org/guidelines/guideline-for-thiopurines-and-tpmt/)

Table 2

Challenges and potential solutions for implementation of pharmacogenetic testing

Challenge	Potential solution
Lack of pharmacogenetic education for physicians	Mandatory pharmacogenetic courses in medical school and periodically during professional careers
Concerns for reduced drug efficacy in variant carriers treated at lower doses	Conduct of prospective pharmacogenetic studies to demonstrate noninferior drug efficacy in variant carriers receiving reduced doses *vs* fully dosed wildtype patients
Lack of adoption of pharmacogenetic guidelines by regulatory agencies for approved drugs	Proactive pharmacogenetic guidance from regulatory agencies during the drug approval process could decrease the number of drugs that require label updates after approval. Adoption of pharmacogenetics testing could also be enhanced by prospectively demonstrating improvement in quality of life and integration of pharmacogenetics into routine germline or somatic testing
Lack of standardization of guidelines, genotyping panels, genotype-phenotype translation	Collaboration between pharmacogenetic consortia to achieve harmonization of guidelines
Need for resources and an efficient institutional infrastructure	Assembly of a multidisciplinary team of pharmacogenetic advocates (including a physician champion) and seek for initial funding from local or institutional sources. Initial testing could be launched on a small scale (e.g., reactive testing for a limited number of gene-drug pairs)
Limited insurance coverage	Recognition by insurance companies of clinically actionable gene-drug interactions as defined by regulatory agencies or consortia (e.g., CPIC level A and B)

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