Comparison of the Guidelines of the Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group

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Both the Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group provide therapeutic recommendations for well-known gene-drug pairs. Published recommendations show a high rate of concordance. However, as a result of different guideline development methods used by these two consortia, differences between the published guidelines exist. The aim of this paper is to compare both initiatives and explore these differences, with the objective to achieve harmonization.

An important barrier for the implementation of pharmacogenetics in clinical practice is the translation of the results of a genetic test into clinical action.[1–3] Kirchheiner *et al.*[4] were among the first to extract dosing recommendations based on pharmacokinetic (PK) data of patients with known *CYP2D6* and *CYP2C19* genotypes. Anticipating a proximate future in which both pharmacists and physicians would be confronted with patients with a known genotype, two consortia, the Dutch Pharmacogenetics Working Group (DPWG) and the Clinical Pharmacogenetics Implementation Consortium (CPIC), provide widely recognized therapeutic recommendations for specific gene-drug pairs.[5–32]

The DPWG was founded by the Royal Dutch Pharmacists Association (KNMP) in 2005 and in the last decade has reviewed 86 potential gene-drug pairs of which 47 guidelines provide therapeutic recommendations for one or more aberrant phenotypes (see **Table 1** and **Box 1** for additional information).[7]

The CPIC, established in 2009 as a joint project between the Pharmacogenomics Research Network and the Pharmacogenomics Knowledgebase (PharmGKB), has a similar goal to provide actionable, genotype-based prescribing recommendations for known gene-drug pairs (see **Table 1**).[3] To date, the CPIC has published 19 guidelines (eight that have been updated since the original publication) covering 40 gene-drug pairs, which are publicly available through both the PharmGKB (https://www.pharmgkb.org/) and CPIC websites (https://cpicpgx.org/).[8–17,19–32]

The aim of this paper is to compare both initiatives and explore differences in the methodology and therapeutic recommendations of both consortia.

METHODOLOGY OF CPIC

To select relevant gene-drug pairs, the CPIC uses a survey-based approach supplemented with nominations from members and external experts and is informed by actions such as the US Food and Drug Administration labeling.[3] The CPIC also takes into account the actionability of a gene-drug pair (i.e., genetic information should/could be used to change prescribing of affected drug) and the degree of testing for variations in the gene. For each new gene-drug pair, the CPIC coordinator forms a multidisciplinary writing committee consisting of experts with a relevant track record of related publications and/or other expertise. To assist in the literature search, compiling, and evaluation of identified evidence, a scientific curator from the PharmGKB is added to the team. The curator and coordinator are responsible for drafting the gene background information, phenotype assignments, and compilation of the tabular materials necessary for clinical implementation of the guideline.[34,35] Clinical studies, case studies, preclinical studies, and *in vitro* information of the drug(s) of interest with a genetic variant are evaluated and are systematically rated as weak, moderate, or high. Based on this body of evidence, as well as the evidence for the alternative therapy

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Table 1 Characteristics of the two consortia

	CPIC	DPWG
Founded	2009	2005
Type of membership	Open for application of new members with a clinical interest in pharmacogenetics, $N = 206$ as of March 2017	By invitation, $N = 14$
Composition	Multidisciplinary	Multidisciplinary
Objectives	1) To address the barriers to implementation of pharmacogenetic tests into clinical practice 2) To provide guidelines that enable the translation of genetic laboratory test results into actionable prescribing decisions for specific drugs	1) To develop pharmacogenetics-based therapeutic (dose) recommendations 2) To assist drug prescribers and pharmacists by integrating the recommendations into computerized systems for drug prescription and automated medication surveillance
No. of gene-drug pairs covered	40	86
No. of gene-drug pairs with therapeutic recommendation	40	47
Frequency of scheduled updates	As needed, reviewed at least every 2 years	If needed, max 4 years
Funding	National Institutes of Health	Royal Dutch Pharmacist's Association and H2020 contract number 668353-I

CPIC, Clinical Pharmacogenetics Implementation Consortium; DPWG, Dutch Pharmacogenomics Working Group.

being recommended, the writing committee derives clinical recommendations stratified by phenotype. Each recommendation is scored using a system based on that by Valdes *et al.*[36] as strong, moderate, optional, or no recommendation. A draft of the guideline is written by the committee and reviewed by other CPIC members. Feedback from this process is incorporated into the guideline before it is subjected to external peer review.[34,35] The guideline is considered for update whenever new evidence impacts prescribing recommendations (see **Figure 1**).

METHODOLOGY OF DPWG

To select relevant gene-drug pairs, curators from the DPWG perform systematic searches in PubMed on known gene variants that affect drug PKs and pharmacodynamics. For each gene-drug pair identified, papers are rated by two independent DPWG members based on a scoring system.[37] Based on the scores, the DPWG assesses whether a gene-drug pair is indeed present and whether a therapeutic (dose) recommendation is required. Recommendations can include a dose adjustment or a therapeutic strategy (i.e., therapeutic drug monitoring or stricter clinical monitoring of patients). Dose-adjustments are calculated using PK-data from available papers with evidence rated 3 or 4 on a 0–4 point scale. All evidence is condensed into a final report containing the DPWG conclusion whether a gene-drug pair is indeed present, whether action is required, and, if so, the therapeutic recommendation. These reports are then integrated into a database for electronic medication surveillance, the G-standard, which feeds all available electronic drug prescribing and dispensing systems in the Netherlands (see **Box 1**).[5,6] Gene-drug pairs are updated if needed but at least every 4 years (see **Figure 1**).

Differences in methodology

An overview of the characteristics and objectives of both consortia is presented in **Table 1**, and the methodology of both consortia in selection of relevant gene-drug interactions, literature review, and guideline synthesis are in **Figure 1**. Although the initial selection of the relevant gene-drug pairs was different, the general process of guideline synthesis by the DPWG and the CPIC is highly similar. Both consortia use professional curators to systematically search and evaluate scientific evidence.[36,37] However, there are some minor differences. The DPWG reviews the level of evidence and the level of clinical relevance on separate scales using a five-point (0–4) and seven-point (AA–F) scale,

BOX 1: INTEGRATION OF THERAPEUTIC RECOMMENDATIONS OF THE DPWG INTO CLINICAL CARE

The DPWG guidelines are available at point of care in the Netherlands through all electronic prescribing and medication surveillance systems and continuously updated and distributed through the G-standard. The G-standard is the Dutch national drug database, which contains information used in medication surveillance. The information of the G-standard supports the prescribing, dispensing, ordering, and reimbursement of drugs and is used by physicians, pharmacists, health insurers, and government and drug wholesalers in the Netherlands (https://www.knmp.nl/producten-en-diensten/gebruiksrecht-g-standaard/informatie-over-de-g-standaard/the-g-standaard-the-medicines-standard-in-healthcare). English versions of the DPWG guidelines have been published in 2008 and 2011 in the international literature, and a subset is currently available at the PharmGKB website: https://www.pharmgkb.org/.[5,6,33]

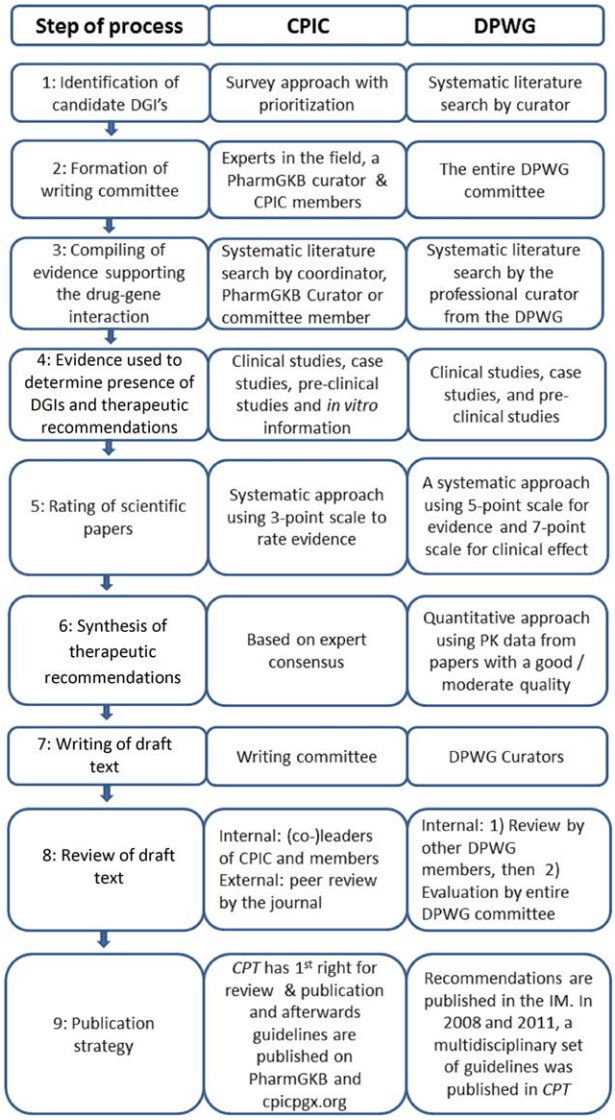

Figure 1 A comparison of the methodology for guideline synthesis of the two consortia. DGI, drug-gene interaction. *IM, Informatorium Medicamentorum*. A handbook published by the KNMP containing the DPWG recommendations in addition to other drug-related information. [Color figure can be viewed at cpt-journal.com]

respectively, whereas the CPIC rates the level of evidence on a three-point (weak–moderate–high) scale.[36,37]

A second difference is the sources of information considered for guideline development. The DPWG only provides a recommendation if data from at least one clinical study of good or moderate quality are available, whereas the CPIC also considers data from preclinical studies and case reports. A third difference is the process used to synthesize a dose recommendation. The DPWG applies a quantitative method, whereas the CPIC applies an approach based on expert consensus.

Differences in terminology for allele function and phenotype assignment

Differences in the terminology used to describe allele function also exist. An example is the difference in the word used to describe an allele that has a "greater than normal function." The CPIC uses the term "increased function," whereas the DPWG uses "gain-of-function." A similar difference in terminology is seen for alleles with decreased function (see **Table 2**).

With the publication of the first therapeutic guideline of *CYP2D6*, the CPIC opted for the historical term extensive metabolizer to describe individuals who carry one or two alleles that encode for a fully functional enzyme.[9,16] However, based on the results from the recent CPIC term standardization project, normal metabolizer (NM) will replace extensive metabolizer in all new and updated CPIC guidelines.[38] The term extensive metabolizer is also used by the DPWG in the published guidelines and is currently still used in clinical practice.[5–7] In this comparison, the term normal metabolizer will be used to describe individuals who were previously (CPIC) or are currently (DWPG) categorized as extensive metabolizers (see **Table 3**).

The CPIC term standardization project also resulted in the addition of phenotypes, such as CYP2C19 rapid metabolizer with a functional definition of "increased enzyme activity compared to normal metabolizers, but less than ultra-rapid metabolizers" and the SLCO1B1 increased function with a functional definition of "increased transporter function compared to normal function."[38]

Differences in allele classification and genotype to phenotype conversion

Both the CPIC and the DPWG provide therapeutic recommendations at the phenotype level. As a result, a genotype-predicted phenotype (gPhenotype) needs to be inferred from the results of the genetic test. This process requires translation tables provided by both consortia. For the genes *CYP2C9*, *CYP2C19*, *CYP2D6*, and *DPYD*, differences in both the classification of alleles (category I) and the translation of genotype to phenotype (category II) can be observed (see **Table 3**).

CYP2C9

Based on a publication from 2004, the DPWG guideline categorizes the *CYP2C9*8* allele as a "gain-of-function" allele.[39] The CPIC categorizes the same allele as a "possible decreased function" allele based on two more recent reports by Liu *et al.*[40] and Allabi *et al.*[41] The allele frequency of *CYP2C9*8* is ~0% in white patients and 4.70% in African American patients.[42,43] As a result of the low allele frequency, this difference in allele classification does not seem to have clinical consequences for white patients. However, in African American patients, this difference could result in different therapeutic recommendations.

CYP2C19

Both consortia recognize the *CYP2C19*17* allele as an allele with a function greater than normal and categorize the genotypes *17/*17 as ultra-rapid metabolizers (UM) and *2/*17 and *3/*17 as intermediate metabolizers (IM), respectively. However, a difference exists between the genotype to phenotype translation of the *1/*17 genotype. In guidelines of CPIC published before July 2016 the diplotype *1/*17 is categorized as the phenotype ultra-rapid metabolizer,[24,26,44–50] whereas the DPWG classifies this

Table 2 Discordances in terminology for allele function and phenotypes

Category	Functional definition	Consortium	Term
Allele	Greater than normal function	CPIC	Increased function
		DPWG	Gain-of-function[a]
Allele	Less than normal function	CPIC	Decreased function
		DPWG	Decreased activity[a]
Phenotype	Individuals who carry two alleles which encode for a fully functional enzyme or individuals with a combination of an allele which encodes for a fully functional enzyme and an allele that encodes for an enzyme with decreased function	CPIC	Normal metabolizer
		DPWG	Extensive metabolizer[a]
Phenotype	An individual carrying one normal function allele and one increased function allele	CPIC	Rapid metabolizer
		DPWG	-

CPIC, Clinical Pharmacogenetics Implementation Consortium; DPWG, Dutch Pharmacogenomics Working Group.
[a]In this article the terminology of the CPIC will be used.

diplotype as a normal metabolizer based on the same literature[5,6,44–50] (see **Table 2**). As of July 2016, the CPIC introduced the additional phenotype rapid metabolizer to fill the need to distinguish between individuals with a *1/*17 and *17/*17 on a phenotype level (see **Table 3**). This new phenotype was introduced in the CPIC guideline providing information and therapeutic recommendations on the gene-drug interaction of *CYP2C19* and voriconazole.[32,38]

Based on the *17 allele frequency of 18% among African populations and 18–24% among white populations, this difference in genotype to phenotype translation can result in a difference in treatment recommendations for many individuals.[6,24] For example, a prescription with amitriptyline for a patient with a *CYP2C19*1/*17* genotype results in a recommendation to switch to an alternate therapy based on the CPIC guideline, whereas the DPWG guidelines advise the normal starting dose for the same genotype.[6,24]

DPYD

The CPIC provides fluoropyrimidine dosing recommendations for normal/high, intermediate, and deficient dihydropyrimidine dehydrogenase activity phenotypes based on *DPYD* genotypes.[14] In contrast, the DPWG uses an activity-score (AS) to accommodate the increasing number of *DPYD* allelic variants and their difference in function (See **Table 3**).[7,51] Further differences can be seen in the amount of variants that are discussed in the guidelines. For example, the 496A>G, 1156G>T, 1651G>A, and 1845G>T variants are not mentioned in the CPIC guideline, whereas the IVS10-15TC variant is mentioned without a classification of the status. In contrast, the DPWG indicates that the variant alleles 496A>G and IVS10-15TC are only associated with toxicity in a single study and the 1156G>T, 1651G>A, and 1845G>T variant alleles are mentioned as cause of toxicity in case reports.

Table 3 Discordances in genotype to phenotype translation

Gene	Genotype / AS	Classification[a]	References
CYP2C19	*1/*17	CPIC: rapid metabolizer	24,26,44–50
		DPWG: normal metabolizer	5,6,44–50
CYP2D6	AS 1.0	CPIC: normal metabolizer	15,16
		DPWG: intermediate metabolizer	57
CYP2D6	AS 2.5	CPIC: ultra-rapid metabolizer	15,16
		DPWG: normal metabolizer	7
DPYD	2846AT / 1236GA	CPIC: normal metabolizer	14
		DPWG: AS 1.5 / intermediate metabolizer	7,14,51
DPYD	e.g., (*2A + (2846AT or 1236GA))	CPIC: intermediate metabolizer	14
		DPWG: AS 0.5 / intermediate metabolizer	7,14,51

AS, activity score; CPIC, Clinical Pharmacogenetics Implementation Consortium; DPWG, Dutch Pharmacogenomics Working Group.
[a]As a result of a consensus in a CPIC project to standardize terms for pharmacogenetic test results, the CPIC has adopted the term normal metabolizer to replace the historical term extensive metabolizer as experts participating in the CPIC project found it less confusing for clinicians. In this comparison, the term normal metabolizer is used (see **Table 2**).[38]

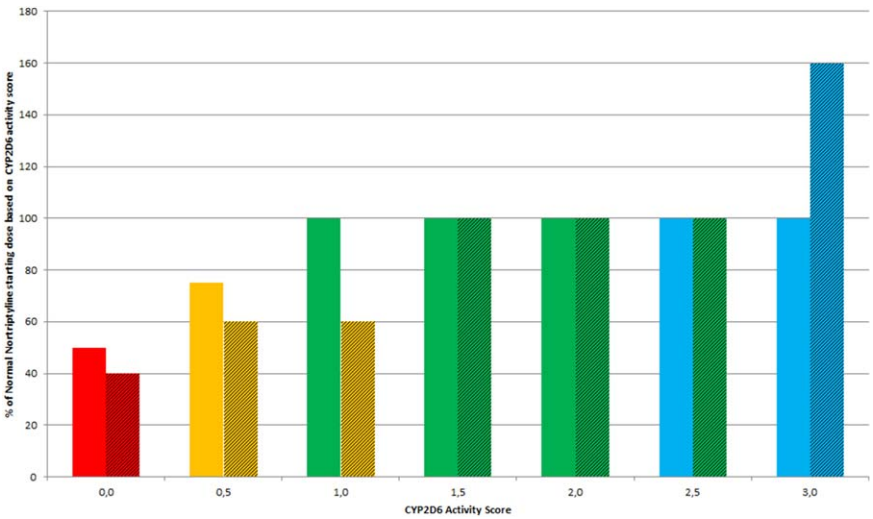

Figure 2 Phenotype translation and nortriptyline dose recommendations of the Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenomics Working Group (DPWG) based on CYP2D6 activity scores. Solid bars: The CPIC interpretation of phenotype and dosing recommendation. Hatched bars: The DPWG interpretation of phenotype and dosing recommendation. Red = poor metabolizer; orange = intermediate metabolizer; green = normal metabolizer; and blue = ultra-rapid metabolizer. Note: The CPIC provides no specific dose adjustment for amitriptyline but recommends considering increasing the dose and using therapeutic drug monitoring to guide dose adjustments. [Color figure can be viewed at cpt-journal.com]

Inversely, the 1129-5923C>G is mentioned by the CPIC, but not by the DPWG.

Finally, a difference between the two guidelines exists in the evidence supporting the allele classification of the *13 and the 1236G>A/haplotype B3 variant. The CPIC reports that there is a clear association of the *13 allele with reduced clearance of capecitabine and 5-fluorouracil in addition to evidence from case reports.[14] In contrast, the DPWG concludes that the evidence supporting a decreased activity of the *13 allele is limited and only described in case reports.[7] Inversely, the DPWG categorizes the 1236G>A/haplotype B3 as a reduced function variant with a body of evidence similar to the 2846A>T variant.[7] In contrast, the CPIC mentions this variant without assigned status, similar to the IVS10-15TC variant.[14]

CYP2D6

Both consortia classify the *CYP2D6*36* allele as a variant allele; however, there is a difference in the interpretation of the functionality of this allele between the two consortia. The DPWG classifies the activity of the *36 allele as reduced,[52–57] while the CPIC classifies the allele as nonfunctional based on four articles published after 2002.[58–61] The difference in allele classification of functionality can potentially be explained by the distinction between the single variant, which has no residual CYP2D6 activity, and the *36 +*10 tandem allele with residual activity (of the *10 allele). In contrast, the DPWG still uses the old classification of the *36 and has not yet made a difference between the single and tandem variants. Due to the low allele frequency of the *36 and the *36+*10 tandem in African Americans and Europeans (0.00–0.98%), this difference in allele status will not have much clinical consequences for these populations. However, in patients from Asian descent, the frequency of these two variant alleles of *CYP2D6* is much higher, 1.52% (0.00–16.40) and 26.41% (22.45–32.65) for the single and tandem variant of the *36, respectively, and this could have implications for the therapy of Asian individuals carrying the single variant of *CYP2D6*.[6,26]

A second more important difference between the DPWG and the CPIC guidelines concerns the translation of the genotype to the CYP2D6 phenotype. Both consortia use the AS of CYP2D6 proposed by Gaedigk *et al.*[62,63] to attribute the scores of 0, 0.5, 1.0, and N to alleles with no function, decreased function, normal function, and alleles with normal function and a duplication of N times, respectively, to calculate a gene-activity score for *CYP2D6*. Although the DPWG and the CPIC agree on the diplotype score of 0 for poor metabolizers (PM), they use a different conversion of the AS to the intermediate metabolizer gPhenotype.[62,63] The DPWG has assigned the scores of 1.0 (combination of a functional and a nonfunctional allele or a combination of two alleles with reduced function) and 0.5 to intermediate metabolizer phenotype and the scores of 1.5 and 2.0 to the normal metabolizer phenotype,[57] whereas the CPIC assigned the scores of 1.0–2.0 to the normal metabolizer phenotype and the score of 0.5 to the intermediate metabolizer phenotype, respectively (see **Figure 2**).[15,16]

Due to the relatively high frequency of null alleles as the *3, *4, and *5 among African, American, and European populations, and the high occurrence of the *10 allele among Asian individuals, a large group of patients will have an AS of 1.0. These patients will be classified as either normal metabolizers or intermediate metabolizers and may receive different treatment recommendations. The different translation of *CYP2D6* genotype to phenotype between the DPWG and the CPIC guidelines has a potentially significant impact on the treatment with drugs of individuals with an AS of 1.0 (see **Figure 2**).

Therapeutic recommendations

A total of 40 and 86 gene-drug pairs were reviewed by the CPIC and the DPWG, respectively. For 27 gene-drug pairs, both the CPIC and the DPWG provide guidelines, which were included in the comparison. For five gene-drug pairs, the rating of the evidence and the therapeutic recommendations were equal. For eight gene-drug pairs, differences in the rating of the body of evidence supporting the same therapeutic recommendation were observed, but no clinically relevant differences in the therapeutic recommendations were identified (see **Table 4**). An example of this difference is the therapeutic recommendation for the CYP2C19 intermediate metabolizer and clopidogrel. Both consortia recommend to switch to a different platelet inhibitor for the CYP2C19 intermediate metabolizer phenotype but the rating of the available evidence by the CPIC and the DPWG are moderate and strong, respectively.[6,21] For 16 of the 27 gene-drug pairs with a total of 31 individual gene-drug-phenotype combinations, relevant differences (see definition) were observed in the therapeutic recommendations. In the case of six gene-drug pairs, relevant differences in therapeutic recommendations were seen for only one aberrant phenotype, whereas for eight gene-drug pairs differences were seen for two aberrant phenotypes and for two gene-drug pairs differences were seen in more than two aberrant phenotypes. All discordant therapeutic recommendations can be found in **Table 4**. Some of the discordances will be highlighted below.

CYP2C19 and CYP2D6 + tricyclic antidepressants

The DPWG has provided individual therapeutic recommendations for *CYP2D6* and the tricyclic antidepressants (TCAs) amitriptyline, clomipramine, doxepin, nortriptyline, and imipramine, as well as *CYP2C19* and imipramine based on area under the curve (AUC) and steady-state concentrations.[7] The CPIC additionally provides recommendations for *CYP2C19* and amitriptyline, clomipramine, doxepin, and trimipramine, as well as *CYP2D6* and desipramine, whereas the DPWG has not (yet) provided therapeutic recommendations because the consortium has categorized these gene-drug pairs as low clinical impact based on the scientific literature.[7] As a result of the used methodology, the CPIC has provided equal therapeutic recommendations for the TCAs amitriptyline, clomipramine, doxepin, imipramine, and trimipramine to avoid these drugs in CYP2C19 ultra-rapid, rapid, and poor metabolizers. In addition, the same therapeutic recommendation of a 25% dose reduction is provided for CYP2D6 intermediate metabolizers and a recommendation to avoid TCAs in CYP2D6 ultra-rapid and poor metabolizers (**Table 4**).

Other differences in the therapeutic recommendations for TCAs can be seen in the dosing recommendations for CYP2D6 ultra-rapid metabolizers. In this case, the CPIC recommends to avoid using a TCA due to the potential lack of efficacy and to consider an alternative drug not metabolized by CYP2D6. If a TCA is warranted, the CPIC recommends considering titrating to a higher target dose and using therapeutic drug monitoring guiding dose adjustments. In contrast, the DPWG provides specific, PK-based dosing advice. If a TCA is warranted, the DPWG recommends starting dosages for amitriptyline, clomipramine, doxepin, imipramine, and nortriptyline (see **Figure 2**) of 125%, 150%, 200%, 170%, and 160% of the normal starting doses, respectively, followed by a recommendation to utilize therapeutic drug monitoring[6,7,24] (**Table 4**).

DPYD + fluoropyrimidines

As mentioned previously, the DPWG uses an AS for *DPYD* whereas the CPIC uses phenotypes of normal/high, intermediate, and deficient activity (soon to be changed to normal, intermediate, and poor metabolizers, respectively, in the next *DPYD* guideline update based on the results of the CPIC term standardization project).[14,51] The gene activity model scores alleles with a reduced function as 0.5, whereas fully dysfunctional alleles are classified as 0. The AS model allows scores of 1.5 and 0.5 in addition to the scores of 2.0 (EM), 1.0 (IM), and 0.0 (PM). Both guidelines include an initial 50% dose-reduction for intermediate metabolizers (AS = 1) and a recommendation to switch to an alternative drug for poor metabolizers (AS = 0). The DPWG also contains a recommendation for 25% and 75% dose reduction of the starting dose for the AS of 1.5 and 0.5, respectively[7,14] (**Table 4**).

Thiopurine methyltransferase + thiopurines

In the guidelines of the DPWG, the dosing advice for azathioprine and 6-mercaptopurine are a 50% dose-reduction and 90% dose-reduction for thiopurine methyltransferase (TPMT) intermediate metabolizers and poor metabolizers, respectively. The CPIC recommends a mean starting dose of 50% (range 30–70%) and 10% of the conventional dose for TPMT intermediate metabolizers and poor metabolizers, respectively. Thrice weekly dosing instead of the normal daily dosing is also recommended for poor metabolizers. In the case of thioguanine, the DPWG recommends a slightly (15%) smaller dose reduction for intermediate metabolizers compared to the 30–50% dose reduction and thrice weekly dosing advised in the CPIC guideline (**Table 4**).

Analysis of differences

From the 19 guidelines published by the CPIC (covering 40 gene-drug pairs) and 86 guidelines by the DPWG, 27 guidelines cover the same gene-drug pairs. Based upon the comparison of the guidelines, there is substantial agreement between the recommendations given by the two consortia. However, for 13 gene-drug pairs there are differences (≥20%) in therapeutic recommendations for one or more aberrant phenotypes. Most of the observed differences in therapeutic recommendations probably result from differences in applied methodologies. In some cases, this results in a situation in which the CPIC provides a recommendation for a gene-drug combination based on an expert consensus formed for a group of drugs (e.g., TCAs), whereas the DPWG finds the evidence for certain individual gene-drug combinations insufficient and is unable to calculate a dosing recommendation (e.g., *CYP2C19* and amitriptyline). In other cases, both consortia recognize a gene-drug interaction, but come to a different dosing recommendation for a certain phenotype as a result of the used methodology (e.g., the CYP2C19 poor metabolizer and imipramine). A second explanation of the differences

Table 4 Gene-drug pairs and dose recommendations by the CPIC and the DPWG (differences in dosing recommendations of ≥20% are marked bold)

Gene	Drug	Gene-drug interaction	Phenotype	Action required?	Therapeutic recommendations + classification of evidence.		Cat.	Ref.
CYP2C9	Phenytoin	CPIC: Yes	IM	Yes	Consider 25% reduction of recommended starting maintenance dose. Subsequent doses should be adjusted according to therapeutic drug monitoring and response.	M		19
			PM	Yes	Consider 50% reduction of recommended starting maintenance dose. Subsequent doses should be adjusted according to therapeutic drug monitoring and response.	S		19
		DPWG: Yes	IM	Yes	Standard loading dose. Reduce maintenance dose by 25%. Evaluate response and serum concentration after 7–10 days. Be alert to ADEs (e.g., ataxia, nystagmus, dysarthria, and sedation).	4D		5
			PM	Yes	Standard loading dose. Reduce maintenance dose by 50–60%. Evaluate response and serum concentration after 7–10 days. Be alert to ADEs (e.g., ataxia, nystagmus, dysarthria, and sedation).	4D		5
CYP2C9	Warfarin	CPIC: Yes	*1/*2	Yes	**Calculate dose based on validated published pharmacogenetic algorithm.**	S	V	17,18
			*1/*3	Yes	**Calculate dose based on validated published pharmacogenetic algorithm.**	S	V	17,18
			*2/*2	Yes	**Calculate dose based on validated published pharmacogenetic algorithm.**	S	V	17,18
			*2/*3	Yes	**Calculate dose based on validated published pharmacogenetic algorithm.**	S	V	17,18
			*3/*3	Yes	**Calculate dose based on validated published pharmacogenetic algorithm.**	S	V	17,18
		DPWG: Yes	*1/*2	Yes	**Initiate therapy with recommended starting dose.**	4A	V	7
			*1/*3	Yes	**Consider a reduction to 65% of the normal starting dose.**	4D	V	7
			*2/*2	Yes	**Consider a reduction to 65% of the normal starting dose.**	4A	V	7
			*2/*3	Yes	**Consider a reduction to 45% of the normal starting dose.**	4A	V	7
			*3/*3	Yes	**Consider a reduction to 45% of the normal starting dose.**	4C	V	7
CYP2C19	Amitriptyline	CPIC: Yes	IM	No	Initiate therapy with recommended starting dose.	S		24,25
			PM	Yes	**1) Avoid amitriptyline use due to potential for suboptimal response. Consider alternative drug not metabolized by CYP2C19. TCAs without major CYP2C19 metabolism include nortriptyline and desipramine. 2) Consider 50% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.**	M	III	24,25
			UM or RM	Yes	**1) Avoid amitriptyline use due to potential for suboptimal response. Consider alternative drug not metabolized by CYP2C19. TCAs without major CYP2C19 metabolism include nortriptyline and desipramine. 2) If amitriptyline is warranted, utilize therapeutic drug monitoring to guide dose adjustments.**	O	III	24,25
		DPWG: Yes	IM	No	Initiate therapy with recommended starting dose.	IN		7
			PM	No	**Initiate therapy with recommended starting dose.**	IN	III	7

Table 4 Continued on next page

Table 4 Continued

Gene	Drug	Gene-drug interaction	Phenotype	Action required?	Therapeutic recommendations + classification of evidence.		Cat.	Ref.
			UM	No	**Initiate therapy with recommended starting dose.**	IN	III	7
CYP2C19	Citalopram / escitalopram	CPIC: Yes	IM	No	**Initiate therapy with recommended starting dose.**	S	III	26
			PM	Yes	1) Consider a 50% reduction of recommended starting dose and titrate to response. 2) Select alternative drug not predominantly metabolized by CYP2C19.	M		26
			UM	Yes	**Consider an alternative drug not predominantly metabolized by CYP2C19.**	M	III	26
		DPWG: Yes	IM	Yes	**1) Consider a maximum daily dose of 20 mg for age <65 or 10 mg for ≥65 years. 2) Consider a 50% reduction in starting dose and rise to normal dose under monitoring of ECG to 40 mg for age <65 or 20 mg for ≥65 years.**	4A	III	6,7
			PM	Yes	Consider a maximum daily dose of 20 mg for age <65 or 10 mg for ≥65 years.	4A		6,7
			UM	No	**Initiate therapy with recommended starting dose.**	3AA	III	6,7
CYP2C19	Clopidogrel	CPIC: Yes	IM	Yes	Consider alternative drug not metabolized by CYP2C19.	M		20,21
			PM	Yes	Consider alternative drug not metabolized by CYP2C19.	S		20,21
			UM	No	Initiate therapy with recommended starting dose.	S		20,21
		DPWG: Yes	IM	Yes	Consider alternative drug not metabolized by CYP2C19.	4F		6,7
			PM	Yes	Consider alternative drug not metabolized by CYP2C19.	4F		6,7
			UM	No	Initiate therapy with recommended starting dose.	4A		6,7
CYP2C19	Clomipramine	CPIC: Yes	IM	No	Initiate therapy with recommended starting dose.	O		24,25
			PM	Yes	**1) Avoid clomipramine use due to potential for suboptimal response. Consider alternative drug not metabolized by CYP2C19. TCAs without major CYP2C19 metabolism include nortriptyline and desipramine. 2) Consider 50% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.**	O	III	24,25
			UM or RM	Yes	**1) Avoid clomipramine use due to potential for suboptimal response. Consider alternative drug not metabolized by CYP2C19. TCAs without major CYP2C19 metabolism include nortriptyline and desipramine. 2) If clomipramine is warranted, utilize therapeutic drug monitoring to guide dose adjustments.**	O	III	24,25
		DPWG: Yes	IM	No	Initiate therapy with recommended starting dose.	IN		7
			PM	No	**Initiate therapy with recommended starting dose.**	IN	III	7
			UM	No	**Initiate therapy with recommended starting dose.**	IN	III	7
CYP2C19	Doxepin	CPIC: Yes	IM	No	Initiate therapy with recommended starting dose.	O		24,25

Table 4 Continued on next page

Table 4 Continued

Gene	Drug	Gene-drug interaction	Phenotype	Action required?	Therapeutic recommendations + classification of evidence.		Cat.	Ref.
			PM	Yes	**1) Avoid doxepin use due to potential for suboptimal response. Consider alternative drug not metabolized by CYP2C19. TCAs without major CYP2C19 metabolism include nortriptyline and desipramine. 2) Consider 50% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.**	O	III	24,25
			UM or RM	Yes	**1) Avoid doxepin use due to potential for suboptimal response. Consider alternative drug not metabolized by CYP2C19. TCAs without major CYP2C19 metabolism include nortriptyline and desipramine. 2) If doxepin is warranted, utilize therapeutic drug monitoring to guide dose adjustments.**	O	III	24,25
		DPWG: No	IM	No	Initiate therapy with recommended starting dose.	IN		7
			PM	No	**Initiate therapy with recommended starting dose.**	IN	III	7
			UM	No	**Initiate therapy with recommended starting dose.**	IN	III	7
CYP2C19	Imipramine	CPIC: Yes	IM	No	Initiate therapy with recommended starting dose.	O		24,25
			PM	Yes	**1) Avoid imipramine use due to potential for suboptimal response. Consider alternative drug not metabolized by CYP2C19. TCAs without major CYP2C19 metabolism include nortriptyline and desipramine. 2) Consider 50% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.**	O	III	24,25
			UM or RM	Yes	**1) Avoid imipramine use due to potential for suboptimal response. Consider alternative drug not metabolized by CYP2C19. TCAs without major CYP2C19 metabolism include nortriptyline and desipramine. 2) If imipramine is warranted, utilize therapeutic drug monitoring to guide dose adjustments.**	O	III	24,25
		DPWG: Yes	IM	No	Initiate therapy with recommended starting dose.	4A		6,7
			PM	Yes	**1) Consider a 30% reduction of recommended starting dose and utilize therapeutic drug monitoring of imipramine and desipramine. 2) Consider alternative drug not metabolized by CYP2C19.**	4A	III	6,7
			UM	No	**Initiate therapy with recommended starting dose.**	4A	III	6,7
CYP2C19	Sertraline	CPIC: Yes	IM	No	**Initiate therapy with recommended starting dose.**	S	III	26
			PM	Yes	**1) Consider a 50% reduction of recommended starting dose and titrate to response. 2) Select alternative drug not predominantly metabolized by CYP2C19.**	O	III	26
			UM	Yes	Initiate therapy with recommended starting dose. If patient does not respond to recommended maintenance dosing, consider alternative drug not predominantly metabolized by CYP2C19.	O		26

Table 4 Continued on next page

Table 4 Continued

Gene	Drug	Gene-drug interaction	Phenotype	Action required?	Therapeutic recommendations + classification of evidence.		Cat.	Ref.
		DPWG: Yes	IM	Yes	**Consider a maximum daily dose of 100 mg and utilize clinical monitoring on response/side effects or therapeutic drug monitoring of sertraline + desmethylsertraline to guide dose adjustments.**	4A	III	6,7
			PM	Yes	**Consider a maximum daily dose of 50 mg and utilize clinical monitoring on response/side effects or therapeutic drug monitoring of sertraline + desmethylsertraline to guide dose adjustments.**	4C	III	6,7
			UM	No	Initiate therapy with recommended starting dose.	4AA		6,7
CYP2C19	Voriconazole	CPIC: Yes	IM	No	**Initiate therapy with recommended starting dose.**	M	V	32
			PM	Yes	**Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole.**	M	V	32
			RM	Yes	**Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole.**	M	II	32
			UM	Yes	**Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole.**	M	V	32
		DPWG: Yes	IM	Yes	**Monitor serum concentration.**	4A	V	5–7
			PM	Yes	**Monitor serum concentration.**	4A	V	5–7
			UM	Yes	**Consider a 50% increase of the recommended starting dose & monitor serum concentration.**	4A	V	5–7
CYP2D6	Amitriptyline	CPIC: Yes	IM	Yes	**Consider 25% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.**	M	III	24,25
			PM	Yes	1) Avoid amitriptyline use due to potential for side effects. Consider alternative drug not metabolized by CYP2D6. 2) If amitriptyline is warranted, consider 50% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.	S		24,25
			UM	Yes	1) Avoid amitriptyline use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. 2) If amitriptyline is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Utilize therapeutic drug monitoring to guide dose adjustments.	S		24,25
		DPWG: Yes	IM	Yes	**1) Consider alternative drug not metabolized by CYP2D6. 2) If an alternative is not possible, consider a decrease of up to 60% of the recommended dose under therapeutic drug monitoring of amitriptyline and nortriptyline.**	3C	III	6,7
			PM	Yes	1) Consider alternative drug not metabolized by CYP2D6. 2) If an alternative is not possible, consider a decrease of up to 50% of the recommended dose under therapeutic drug monitoring of amitriptyline and nortriptyline.	3A		6,7

Table 4 Continued on next page

Table 4 Continued

Gene	Drug	Gene-drug interaction	Phenotype	Action required?	Therapeutic recommendations + classification of evidence.		Cat.	Ref.
			UM	Yes	1) Consider alternative drug not metabolized by CYP2D6. 2) If an alternative is not possible, consider an increase of up to 125% of the recommended dose under therapeutic drug monitoring of amitriptyline and nortriptyline. Be alert of a possible decrease in therapeutic levels and an increase of active cardiotoxic hydroxymetabolites.	3C		6,7
CYP2D6	Clomipramine	CPIC: Yes	IM	Yes	Consider 25% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.	O		24,25
			PM	Yes	1) Avoid clomipramine use due to potential for side effects. Consider alternative drug not metabolized by CYP2D6. 2) If clomipramine is warranted, consider 50% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.	O	III	24,25
			UM	Yes	1) Avoid clomipramine use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. 2) If clomipramine is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Utilize therapeutic drug monitoring to guide dose adjustments.	O		24,25
		DPWG: Yes	IM	Yes	1) Consider 30% reduction of recommended starting dose. 2) Utilize therapeutic drug monitoring of clomipramine and desmethylclomipramine.	4C		5–7
			PM	Yes	Depression: 1) Consider 60% reduction of recommended starting dose. 2) Utilize therapeutic drug monitoring of clomipramine and desmethylclomipramine. Anxiety: 1) Consider alternative drug not metabolized by CYP2D6. 2) If an alternative is not possible, consider a decrease of up to 50% of the recommended dose under therapeutic drug monitoring of clomipramine and desmethylclomipramine.	4C	III	5–7
			UM	Yes	1) Consider alternative drug not metabolized by CYP2D6. 2) If an alternative is not possible, consider an increase of up to 150% of the recommended dose under therapeutic drug monitoring of amitriptyline and nortriptyline. Be alert of a possible decrease in therapeutic levels and an increase of cardiotoxic active hydroxymetabolites.	3C		5–7
CYP2D6	Codeine	CPIC: Yes	IM	Yes	Use label-recommended age-specific or weight-specific dosing. If no response, consider alternative analgesics, such as morphine or a nonopioid.	M		15,16
			PM	Yes	Avoid codeine use due to lack of efficacy.	S		15,16
			UM	Yes	Avoid codeine use due to potential for toxicity.	S		15,16
		DPWG: Yes	IM	Yes	Cough: no action required. Pain: Be on alert for a lack of clinical effect. In case of a lack of clinical effect, consider a raise in daily dose or consider an alternative drug.	3A		5–7

Table 4 Continued on next page

Table 4 Continued

Gene	Drug	Gene-drug interaction	Phenotype	Action required?	Therapeutic recommendations + classification of evidence.		Cat.	Ref.
			PM	Yes	Cough: no action required. Pain: Consider an alternative drug	4B		5–7
			UM	Yes	Contraindicated.	3F		5–7
CYP2D6	Doxepin	CPIC: Yes	IM	Yes	Consider 25% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.	O		24,25
			PM	Yes	1) Avoid doxepin use due to potential for side effects. Consider alternative drug not metabolized by CYP2D6. 2) If doxepin is warranted, consider 50% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.	O		24,25
			UM	Yes	1) Avoid doxepin use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. 2) If doxepin is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Utilize therapeutic drug monitoring to guide dose adjustments.	O		24,25
		DPWG: Yes	IM	Yes	Consider a 20% reduction of recommended starting dose. Utilize therapeutic drug monitoring to monitor doxepin and nordoxepin to guide dose adjustments.	3A		6,7
			PM	Yes	Consider a 60% reduction of recommended starting dose. Utilize therapeutic drug monitoring to monitor doxepin and nordoxepin to guide dose adjustments.	3F		6,7
			UM	Yes	1) Consider alternative drug not metabolized by CYP2D6. 2) If an alternative is not possible, consider an increase of up to 200% of the recommended dose under therapeutic drug monitoring of doxepin and nordoxepin.	3A		6,7
CYP2D6	Fluvoxamine	CPIC: Yes	IM	No	Initiate therapy with recommended starting dose.	M		(26)
			PM	No	**1) Consider a 25-50% reduction of recommended starting dose and titrate to response.** **2) Use an alternative drug not metabolized by CYP2D6.**	O	IV	(26)
			UM	No	No recommendation due to lack of evidence.	O		(26)
		DPWG: No	IM	No	Initiate therapy with recommended starting dose.>	IN		7
			PM	No	**Initiate therapy with recommended starting dose.**	3AA	IV	7
			UM	No	Initiate therapy with recommended starting dose.	IN		7
CYP2D6	Imipramine	CPIC: Yes	IM	Yes	Consider 25% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.	O		24,25
			PM	Yes	**1) Avoid imipramine use due to potential for side effects. Consider alternative drug not metabolized by CYP2D6.** **2) If imipramine is warranted, consider 50% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.**	O	III	24,25

Table 4 Continued on next page

Table 4 Continued

Gene	Drug	Gene-drug interaction	Phenotype	Action required?	Therapeutic recommendations + classification of evidence.		Cat.	Ref.
			UM	Yes	1) Avoid imipramine use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. 2) If imipramine is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Utilize therapeutic drug monitoring to guide dose adjustments.	O		24,25
		DPWG: Yes	IM	Yes	Consider 30% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.	4A		5–7
			PM	Yes	**Consider 70% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.**	4C	III	5–7
			UM	Yes	1) Consider alternative drug not metabolized by CYP2D6. 2) If an alternative is not possible, consider an increase of up to 170% of the recommended dose under therapeutic drug monitoring of imipramine and desipramine.	4A		5–7
CYP2D6	Nortriptyline	CPIC: Yes	IM	Yes	Consider 25% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.	M		24,25
			PM	Yes	1) Avoid nortriptyline use due to potential for side effects. Consider alternative drug not metabolized by CYP2D6. 2) If nortriptyline is warranted, consider 50% reduction of recommended starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.	S		24,25
			UM	Yes	1) Avoid nortriptyline use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. 2) If nortriptyline is warranted, consider titrating to a higher target dose (compared to normal metabolizers). Utilize therapeutic drug monitoring to guide dose adjustments.	S		24,25
		DPWG: Yes	IM	Yes	Consider a 40% reduction of recommended starting dose. Utilize therapeutic drug monitoring of nortriptyline and 10-hydroxytriptyline to guide dose adjustments.	4C		5–7
			PM	Yes	Consider a 60% reduction of recommended starting dose. Utilize therapeutic drug monitoring of nortriptyline and 10-hydroxytriptyline to guide dose adjustments.	3C		5–7
			UM	Yes	1) Consider alternative drug not metabolized by CYP2D6. 2) If an alternative is not possible, consider an increase of up to 60% of the recommended dose. Utilize therapeutic drug monitoring of nortriptyline and 10-hydroxytriptyline to guide dose adjustments.	3C		5–7
CYP2D6	Paroxetine	CPIC: Yes	IM	No	Initiate therapy with recommended starting dose.	M		26
			PM	Yes	**1) Consider alternative drug not predominantly metabolized by CYP2D6. 2) If paroxetine use warranted, consider a 50% reduction of recommended starting dose and titrate to response.**	O	III	26
			UM	Yes	Consider alternative drug not predominantly metabolized by CYP2D6.	S		26

Table 4 Continued on next page

Table 4 Continued

Gene	Drug	Gene-drug interaction	Phenotype	Action required?	Therapeutic recommendations + classification of evidence.		Cat.	Ref.
		DPWG: Yes	IM	No	Initiate therapy with recommended starting dose.	4A		5–7
			PM	No	**Initiate therapy with recommended starting dose.**	4A	III	5–7
			UM	Yes	Consider alternative drug not metabolized by CYP2D6.	4C		5–7
CYP3A5	Tacrolimus	CPIC: Yes	IM (heterozygous expressor)	Yes	Increase starting dose 1.5–2 times recommended starting dose. Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	S		30
			NM (homozygous expressor)	Yes	**Increase starting dose 1.5–2 times recommended starting dose. Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.**	S	III	30
		DPWG: Yes	Heterozygous expressor	Yes	Increase starting dose 1.75 times recommended starting dose. Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.	4E		6,7
			Homozygous expressor	Yes	**Increase starting dose 2.5 times recommended starting dose. Total starting dose should not exceed 0.3 mg/kg/day. Use therapeutic drug monitoring to guide dose adjustments.**	4E	III	6,7
DPYD	Capecitabine/ 5-FU	CPIC: Yes	IM	Yes	Start with at least a 50% reduction in starting dose followed by titration of dose based on toxicity or PK test (if available).	M		14
			PM	Yes	Select alternate drug.	S		14
		DPWG: Yes	1.5	Yes	**Start with at least a 25% reduction in star ting dose followed by titration of dose based on toxicity and efficacy.**	4F	II	6,7,51
			1.0	Yes	Start with at least a 50% reduction in starting dose followed by titration of dose based on toxicity and efficacy.	4F		6,7,51
			0.5	Yes	**Start with at least a 75% reduction in starting dose followed by titration of dose based on toxicity and efficacy.**	4F	II	6,7,51
			0.0	Yes	Select alternate drug.	4F		6,7,51
DPYD	Tegafur	CPIC: Yes	IM	Yes	**Start with at least a 50% reduction in starting dose followed by titration of dose based on toxicity or pharmacokinetic test (if available).**	M	III	14
			PM	Yes	Select alternate drug.	S		14
		DPWG: Yes	1.5	Yes	Select alternate drug.	2E		6,7,51
			1.0	Yes	**Select alternate drug.**	2D	III	6,7,51
			0.5	Yes	Select alternate drug.	0E		6,7,51
			0.0	Yes	Select alternate drug.	0E		6,7,51
HLA-B	Abacavir	CPIC: Yes	*57:01/*X;*57:01/; *57:01	Yes	Abacavir is not recommended.	S		12,13

Table 4 Continued on next page

Table 4 Continued

Gene	Drug	Gene-drug interaction	Phenotype	Action required?	Therapeutic recommendations + classification of evidence.		Cat.	Ref.
		DPWG: Yes	*57:01/*X;* 57:01/; *57:01	Yes	Abacavir is contraindicated.	4E		6,7
HLA-B	Carbamazepine	CPIC: Yes	*15:02/*X; *15:02/; *15:02	Yes	A. If patient is carbamazepine-naive, do not use carbamazepine. B. If patient has previously used carbamazepine for longer than 3 months without incidence of cutaneous adverse reactions, cautiously consider use of carbamazepine.	S(A) O(B)		11
		DPWG: Yes	*15:02/*X; *15:02/; *15:02 *15:11/*X; *15:11/; *15:11 *31:01/*X; *31:01/; *31:01	Yes	For HLA-B*1502, the recommendation is to choose an alternative. If an alternative is possible, choosing an alternative is also recommended for HLA-A*3101 and HLA-B*151.	4E (ALL)		7
SLCO1B1	Simvastatin	CPIC: Yes	Decreased function (521TC)	Yes	1) Prescribe a lower dose. 2) Consider an alternative statin (e.g., pravastatin or rosuvastatin). 3) Consider routine CK surveillance.	S		22,23
			Poor function (521CC)	Yes	1) Prescribe a lower dose. 2) Consider an alternative statin (e.g., pravastatin or rosuvastatin). 3) Consider routine CK surveillance.	S		22,23
		DPWG: Yes	521TC	Yes	1) Consider alternative drug. 2) If simvastatin is warranted, prescribe a maximum dose of 40 mg/day.	4D		7
			521CC	Yes	Select alternative drug.	4D		7
TPMT	Azathioprine/ mercaptopurine	CPIC: Yes	IM	Yes	If disease treatment normally starts at the "full dose," consider starting at 30–70% of target dose (e.g., 1–1.5 mg/kg/d), and titrate based on tolerance. Allow 2–4 weeks to reach steady state after each dose adjustment.	S		8,9
			PM	Yes	1) Consider alternative agents. 2) If using azathioprine start with drastically reduced doses (reduce daily dose by 10-fold and dose thrice weekly instead of daily) and adjust doses of azathioprine based on degree of myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady state after each dose adjustment. Azathioprine is the likely cause of myelosuppression.	S		8,9
		DPWG: Yes	IM	Yes	1) Select alternative drug. 2) Reduce dose by 50%. Increase dose in response of hematologic monitoring and efficacy.	4E		6,7
			PM	Yes	1) Select alternative drug. 2) Reduce dose by 90%. Increase dose in response of hematologic monitoring and efficacy.	4F		6,7

Table 4 Continued on next page

Table 4 Continued

Gene	Drug	Gene-drug interaction	Phenotype	Action required?	Therapeutic recommendations + classification of evidence.		Cat.	Ref.
TPMT	Thioguanine	CPIC: Yes	IM	Yes	Start with reduced doses (reduce by 30–50%) and adjust doses of thioguanine based on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, and depending on other therapy, emphasis should be on reducing thioguanine over other agents.	M	V	8,9
			PM	Yes	Start with drastically reduced doses (reduce daily dose by 10-fold and dose thrice weekly instead of daily) and adjust doses of thioguanine based on degree of myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, emphasis should be on reducing thioguanine over other agents. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy.	S		8,9
		DPWG: Yes	IM	Yes	1) Select alternative drug. 2) Reduce dose by 25%. Increase dose in response of hematologic monitoring and efficacy.	3E	V	6,7
			PM	Yes	1) Select alternative drug. 2) Reduce dose to 6–7% of starting dose. Increase dose in response of hematologic monitoring and efficacy.	2F		6,7
VKORC1	Warfarin	CPIC: Yes	-1639GA	Yes	**Calculate dose based on validated published pharmacogenetic algorithm.**	S	V	17,18
			-1639AA	Yes	**Calculate dose based on validated published pharmacogenetic algorithm.**	S	V	17,18
		DPWG: Yes	-1639GA	Yes	**Initiate therapy with recommended starting dose.**	4A	V	7
			-1639AA	Yes	**Consider a reduction to 60% of the normal starting dose.**	4A	V	7

5-FU, 5-fluorouracil; ADEs, adverse drug events; CPIC, Clinical Pharmacogenetics Implementation Consortium; DPWG, Dutch Pharmacogenomics Working Group; ECG, electrocardiogram; IM, intermediate metabolizer; IN, insufficient evidence; M, moderate; NM, normal metabolizer; O, optional; PK, pharmacokinetic; PM, poor metabolizer; RM, rapid metabolizer; S, strong; TCA, tricyclic antidepressant; UM, ultra-rapid metabolizer.
0 = data on file; 1 = published incomplete case reports; 2 = well documented case reports / case series; 3 = published controlled studies of moderate quality; 4 = published controlled studies of good quality; A = minor clinical effect; B = clinical effect: short-lived discomfort (<48 hours) without permanent injury; C = clinical effect: long-standing discomfort (48–168 hours) without permanent injury; D = clinical effect: long-standing effect (>168) and permanent symptom or invalidating injury; E = increased risk of failure of lifesaving therapy / expected bone marrow depression; F = death, arrhythmia, unexpected bone marrow depression.
*Category of discordance: I = discordance in allele classification, II = discordance in genotype to phenotype translation, III = discordance in therapeutic recommendation attributed to a difference in methodology of the two consortia, IV = discordance in therapeutic recommendation attributed to a time-effect, V = discordance in therapeutic recommendation attributed to a difference in clinical practice.

between the CPIC and the DPWG are the result of a "time effect," as literature searches are performed at different time points by the two consortia and new articles are published continuously (category IV; see **Table 4**). For example, a difference exists in the therapeutic recommendation for fluvoxamine between the guideline for *CYP2D6* and *CYP2C19* genotypes and dosing of selective serotonin reuptake inhibitors of the CPIC from 2015 and the DPWG guideline for fluvoxamine. This difference can partially be explained by the article by Suzuki *et al*.,[64] which was not included in the DPWG guidelines because it was published after the literature search of the DPWG. This article showed a significant effect of *CYP2D6* genotype on fluvoxamine steady-state concentration. This example underscores the need to update existing recommendations.

Additionally, differences in therapeutic recommendations are sometimes the result of differences in clinical practices between countries (category V; see **Table 4**). An example of this difference can be seen in the recommendations for the gene-drug combination of *CYP2C19* and voriconazole.[6,7,32] The CPIC recommends to choose an alternative agent that is not dependent on CYP2C19 metabolism in poor and ultra-rapid metabolizers and a standard regimen in intermediate metabolizers. Therapeutic drug monitoring is mentioned as a factor that can warrant a change in dosing regimen or choice of drug similar to other clinical factors (e.g., drug-drug interactions or impaired renal/hepatic function) that can lead to change in selection of therapy or dose adjustments. Therapeutic drug monitoring is only mentioned specifically in the therapeutic recommendation for a poor metabolizer in the event that voriconazole is considered more appropriate than alternative agents. In contrast, the DPWG provides the recommendation to start with a standard of care dosing and always follow-up with therapeutic drug monitoring in case of poor and intermediate metabolizers. In case ultra-rapid metabolizers a 50% increase of the starting dose is recommended followed by therapeutic drug monitoring. These differences between the guidelines clearly show a difference in the place of therapeutic monitoring within voriconazole therapy between the different practice settings.

Another example of differences as a result of clinical practice can be seen in the recommendations for coumarins. The DPWG and the CPIC both provide recommendations for the gene-drug pairs of *CYP2C9* and *VKORC1* and warfarin. In addition, the DPWG also provides therapeutic recommendations for acenocoumarol and phenprocoumon, which are mainly used in the Netherlands.[6,7,17,18] The CPIC provides recommended daily maintenance dosing regimen for warfarin in mg/day based on specific algorithms, whereas the DPWG guidelines only provides a decrease in the loading dose. In the Netherlands, patients using coumarins are strictly monitored by anticoagulation clinics using the international normalized ratio. With this strict control of the international normalized ratio, the need for a predicted daily coumarin dose based on pharmacogenetic information is limited. Due to the large difference in the monitoring of patients, the added clinical value of pharmacogenetics is different in both settings, resulting in other therapeutic recommendations of the DPWG and the CPIC, respectively.

Specifically for *CYP2D6*, differences in the translation of genotypes to phenotypes that exist between the guidelines of the two consortia can be explained by the different interpretations of certain genotypes throughout literature. For the gene *CYP2D6*, some consider an AS of 1.0 an intermediate metabolizer, whereas the package insert of the Amplichip categorizes this score as a normal metabolizer.[56] In part, this is due to variability in how AS is translated into phenotype for different probe drugs. Studies using tramadol, dextromethorphan, and sparteine as the probe drug show no difference in the kinetic profile between individuals with an AS of 1.0 and individuals with an AS of 2.0.[54,55,65–69] In contrast, using trimipramine, doxepin, haloperidol, and debrisoquine as the probe drug shows a significant difference between individuals with an AS of 1.0 and 2.0.[54,70–75] Specifically for CYP2D6, it can be concluded that the use of different model substrates have led to mixed interpretations of genotypes, which in turn have led to different interpretations of the AS of 1.0 by the two consortia. In fact, an international team of CPIC and DPWG members has recently agreed to try to impose standards on how AS are interpreted into phenotypes for major CYP2D6 substrates.

As previously mentioned, the differences between guidelines can potentially lead to differences in dosages or choice of drugs for patients with the same genotype. In case of some discordances, a minor update (e.g., an update of the status of the *CYP2C9*8* and *CYP2D6*36* alleles in the DPWG guidelines; categories I and IV) can solve discrepancies, whereas, in some cases, harmonization is warranted to create uniform interpretations of genotypes into phenotypes (category II).

Finally, the difference in publication strategy should also be addressed. A current disadvantage of the DPWG guidelines is the limited availability in English. In addition, the available English versions date back to 2011 and do not contain the most recent information. Currently, as a part of the European Union granted Ubiquitous Pharmacogenomics project, the DPWG is working on the English translation of their therapeutic recommendations and it is anticipated that, in the near future, these documents will be made available to clinicians of other nations in the form of European guidelines, which further strengthens the need for harmonization with the CPIC (http://upgx.eu/).[76]

In conclusion, this comparison shows that the CPIC and the DPWG guidelines are generally similar in terms of allele classification, genotype to phenotype translations, and therapeutic recommendations for most gene-drug pairs. However, some differences between the guidelines of the two consortia exist and should be harmonized where possible, especially in the case of different allele classifications and genotype to phenotype translations.

Methodology of comparison

The process of guideline synthesis was compared based on the information provided in articles describing the two initiatives.[5,34] A list of gene-drug pairs evaluated by both the DPWG and the CPIC was created. The CPIC guidelines published up to March 2017 were extracted from https://cpicpgx.org/guidelines/. Information on the DPWG guidelines was extracted from the G-standard on the March 1, 2017. For each gene-drug pair,

guidelines were systematically compared for used terminology (used for the determination of allele function and phenotypes), allele classification/genotype, dose recommendations, evidence, and clinical relevance scores. Differences in allele classification were labeled as a category I difference and differences in genotype to phenotype translation were labeled as a category II difference. Relevant differences in therapeutic recommendations were defined as different therapeutic strategies (e.g., no adjustment vs. changes in dose vs. alternate therapy) or a ≥20% difference in the recommended dose between the two guidelines for a specific genotype. The found relevant differences were then subdivided based on the attributed explanation for the differences. Discordances in therapeutic recommendations presumably explained by differences in the methodologies of the two consortia were allocated to category III, discordances presumably explained by a time-effect were classified as category IV, and discordances in recommendations that were presumably explained by differences in clinical practice between nations were allocated to category V.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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AUTHOR CONTRIBUTIONS

P.B., J.S., and H.J.G. designed the research. P.B. performed the research. P.B., J.S., H.J.G., K.C., R.G., M.W., T.K., and M.R. analyzed the data. P.B., J.S., H.J.G., K.C., R.G., M.W., T.K., and M.R. wrote the manuscript.

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