Pharmacogenetics: From Bench to Byte

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Despite initial enthusiasm,[1–3] the use of pharmacogenetics has remained limited to investigation in only a few clinical fields such as oncology and psychiatry.[4–8] The main reason is the paucity of scientific evidence to show that pharmacogenetic testing leads to improved clinical outcomes.[9,10] Moreover, for most pharmacogenetic tests (such as tests for genetic variants of cytochrome P450 enzymes) a detailed knowledge of pharmacology is a prerequisite for application in clinical practice, and both physicians and pharmacists might find it difficult to interpret the clinical value of pharmacogenetic test results. Guidelines that link the result of a pharmacogenetic test to therapeutic recommendations might help to overcome these problems, but such guidelines are only sparsely available. In 2001, an early step was taken to develop such guidelines for the therapeutic use of antidepressants, and these included CYP2D6-related dose recommendations drawn from pharmacokinetic study data.[11] However, the use of such recommendations in routine clinical practice remains difficult, because they are currently outside the ambit of the clinical environment and are not accessible during the decision-making process by physicians and pharmacists, namely the prescription and dispensing of drugs.

It was for these reasons that the Royal Dutch Association for the Advancement of Pharmacy established the Pharmacogenetics Working Group (PWG) in 2005. In this 15-member multidisciplinary working group, clinical pharmacists, physicians, clinical pharmacologists, clinical chemists, epidemiologists, and toxicologists are represented. The objective of the PWG is to develop pharmacogenetics-based therapeutic (dose) recommendations on the basis of a systematic review of literature, and to assist the drug prescribers as well as the pharmacists by integrating the recommendations into computerized systems for drug prescription and automated medication surveillance. The recommendations do not indicate patients who are eligible for genotyping, but merely aim to optimize drug use in the small but ever-increasing group of patients whose genotypes are known.

In the Netherlands, computerized drug prescription and automated medication surveillance are well organized, and the majority of general practitioners as well as nearly all the community and hospital pharmacists use such a system.[12] Most of these automated medication systems use the G-standard, an extensive electronic drug database.[13] The therapeutic (dose) recommendations composed by the PWG are incorporated into the G-standard, thereby directly linking the pharmacogenetics-based therapeutic (dose) recommendations to the decision-making process. The first recommendations were released with the October 2006 edition of the G-standard. To our knowledge, the PWG initiative is the first to integrate pharmacogenetic test results and therapeutic (dose) recommendations into automated medication surveillance systems to be applied nationwide. In this article, we describe the procedures followed by the PWG for structured pharmacogenetic data collection, assessment, and subsequent synthesis of therapeutic (dose) recommendations. Furthermore, we report the first 26 defined recommendations included in the G-standard.

STRUCTURED ASSESSMENT OF GENE–DRUG INTERACTIONS

Scope

The scope of the PWG comprises the compilation of therapeutic (dose) recommendations on the basis of gene–drug interactions. It was decided to commence with the polymorphisms that affect pharmacokinetics. A list of polymorphic enzymes involved in

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Received 30 October 2007; accepted 13 December 2007; advance online publication 6 February 2008. doi:10.1038/sj.clpt.6100507

phases I and II of the metabolic process, including an overview of drug substrates, was compiled. The criteria for inclusion were: (i) that the enzyme is known to play an important role in the metabolic process *in vivo*, and (ii) that data relating to the gene–drug interaction are available in the published literature. The following sources were used for assessing whether these criteria were fulfilled:

- PubMed (http://www.ncbi.nlm.nih.gov)
- Website (http://medicine.iupui.edu/flockhart/table.htm, http://www.genemedrx.com, http://www.druginteractioninfo.org, http://www.themedicalletter.com)
- Drug interaction textbook[14]
- Pharmacogenetics textbook[15]

Data collection

For each drug, a systematic search of PubMed and Frisbee (a bibliography of Dutch medical literature)[16] was carried out. The articles included in the reference lists were individually screened for additional material or papers. Wherever information relating to gene–drug interaction was present in the European Public Assessment Report, the manufacturer was asked to provide further details. Review articles, studies involving non-human subjects and *in vitro* experiments were excluded.

Data assessment

For data assessment, a method earlier described was adapted.[13] Two core parameters were defined:

- Level of evidence of the gene–drug interaction. This indicates the quality of the evidence found in literature for the gene–drug interaction, and was scored on a five-point scale with a range from 0 (lowest evidence) to 4 (highest evidence) (**Table 1**).[17]
- Clinical relevance of the potential adverse drug event, decreased therapeutic response, or other clinical effect resulting from the gene–drug interaction.

The clinical relevance was scored on a seven-point scale derived from the National Cancer Institute's Common Toxicity Criteria.[18] A clinical or pharmacokinetic effect that was not statistically significant was classified as AA (lowest impact), whereas death, for example, was classified as F (highest impact) (**Table 2**). At every level of this point scale, new events are added after assessment by the PWG.

Status report and therapeutic (dose) recommendation

For each of the assessed gene–drug interactions, a status report was prepared that presented an overview of key findings from selected articles from the published literature, along with the scores representing level of evidence and clinical relevance. Based on these scores, each gene–drug interaction was coded with the highest scored level of evidence and clinical relevance. After a final assessment of the information presented in the status report, a decision was made whether or not a therapeutic(dose) recommendation was required. These recommendations could include (i) a dose adjustment, (ii) advice on therapeutic strategy (e.g., the advice for therapeutic drug monitoring or a warning for increased risk of adverse drug event or diminished therapeutic efficacy), or (iii) the recommendation to select an alternative drug. In order to clarify how the PWG had arrived at the final therapeutic (dose) recommendation, a concise rationale was provided.

A specific procedure was followed in the preparation of the status report . After data collection, the level of evidence and clinical relevance of each article were independently scored by two

Table 1 Assigned levels of evidence

Criteria for assigning levels of evidence	
4	Published controlled studies of good quality[a] relating to phenotyped and/or genotyped patients or healthy volunteers, and having relevant pharmacokinetic or clinical endpoints
3	Published controlled studies of moderate quality[b] relating to phenotyped and/or genotyped patients or healthy volunteers, and having relevant pharmacokinetic or clinical endpoints
2	Published case reports, well documented, and having relevant pharmacokinetic or clinical endpoints. Well documented case series
1	Published incomplete case reports Product information
0	Data on file
—	No evidence

[a]The study is deemed to be of "good quality" if:
(i) the use of concomitant medication with a possible influence on the phenotype is reported in the manuscript.
(ii) other confounders are reported (e.g., smoking status).
(iii) the reported data are based on steady-state kinetics.
(iv) the results are corrected for dose variability.

[b]Wherever one or more of these "good quality" criteria were missing, the quality of the study was considered to be "moderate."

Table 2 Classification of clinical relevance

Classification of clinical relevance	
AA	Clinical effect (NS) Kinetic effect (NS)
A	Minor clinical effect (S): QTc prolongation (<450 ms ♀, <470 ms ♂), INR increase <4.5 Kinetic effect (S)
B	Clinical effect (S): short-lived discomfort (<48 h) without permanent injury, for example, reduced decrease in resting heart rate, reduction in exercise tachycardia, diminished pain relief from oxycodone and ADE resulting from increased bioavailability of atomoxetine (decreased appetite, insomnia, sleep disturbance, etc.)
C	Clinical effect (S): long-standing discomfort (48–168 h) without permanent injury, for example, increase risk of failure of therapy with tricyclic antidepressants or atypical antipsychotic drugs: extrapyramidal side effects, parkinsonism: ADE resulting from increased bioavailability of tricyclic antidepressants, metoprolol, propafenone (central effects, e.g., dizziness).
D	Clinical effect (S): long-standing effect (>168 h), permanent symptom or invalidating injury, for example, failure of prophylaxis of atrial fibrillation; deep vein thrombosis
E	Clinical effect (S): Increased risk of failure of lifesaving therapy; expected bone marrow depression
F	Clinical effect (S): death; arrhythmia; unexpected bone marrow depression

ADE, adverse drug event; INR, international normalized ratio; NS, not statistically significant difference; S, statistically significant difference.

PWG members. In order to prevent interobserver variation, a seven-member subgroup of the PWG discussed the scores of each selected paper and composed a preliminary status report. This preliminary report was then evaluated by the complete PWG during one of its three-monthly meetings, resulting in the final consensus-based status report and inclusion into the G-standard.

Calculation of dose adjustments

The calculation of dose adjustments was based on four rules:

- Pharmacokinetic data only from papers with a level of evidence of 3 or 4 were used.
- Data from selected papers reporting both statistically significant and not statistically significant differences were used. Results showing differences that were not statistically significant were considered as having been caused by limited sample size per genotype. Dose recommendations were calculated only if statistically significant data were available, so as to rule out the possibility of making dosage calculations from data generated purely by chance.
- Dose calculations were based on the sum of parent drug and active metabolites for atomoxetine (4-hydroxyatomoxetine), clomipramine (desmethylclomipramine), imipramine (desipramine), nortriptyline (10-hydroxynortriptyline), propafenone (5-hydroxypropafenone), risperidone (9-hydroxy-risperidone), and venlafaxine (O-desmethylvenlafaxine).
- For prodrugs, pharmacokinetics of the active metabolite were used (e.g., morphine when codeine is used for analgesia).

We assumed that currently used standard doses are representative for extensive metabolizers. For calculating dose adjustments for the CYP2D6 PM phenotype (D_{PM}), we started by making a dose adjustment calculation from each selected paper from the published literature, using the formula below:

$$D_{PM}(\%) = \frac{AUC_{EM}}{AUC_{PM}} \times 100\%$$

After calculating dose adjustments from the data in each individual paper, a final dose recommendation was calculated as the population size-weighted mean of the individual dose adjustments:

$$D_{PM}(\%) = \frac{(N_{(a)} \times D_{PM(a)}) + (N_{(b)} \times D_{PM(b)}) + (N_{(c)} \times D_{PM(c)}) + \cdots + (N_{(x)} \times D_{PM(x)})}{N_{(a)} + N_{(b)} + N_{(c)} + \cdots + N_{(x)}}$$

N = number of subjects with corresponding phenotype in article a, b, c, … x.

Dose recommendations of drugs for other genotypes and phenotypes were calculated using analogous equations, except in the case of prodrugs (e.g., codeine for analgesia) and drugs with metabolites whose contribution to the clinical effect is unknown (e.g., tamoxifen).

Consequences for automated medication systems

On the basis of the information collated in the status report, the PWG classified the gene–drug combination according to whether or not there was interaction between gene and drug (interaction: yes/no) and whether or not any alerts that were generated had to be tagged for action (action: yes/no). Wherever action is required, the alert with the therapeutic(dose) recommendation appears on the screen during prescription and dispensing (Figure 1). Where no action is required, the alert is only logged in the system.

Alerts will be generated only if a certain gene–drug combination occurs. Therefore, the recording of a patient's genotype in the computerized drug prescription or automated medication surveillance system is a prerequisite for the generation of an alert. The classifications and their consequences for the computerized drug prescription and automated medication surveillance system have been described earlier.[13] Four different types of alerts, each with its own text, are provided by the PWG; a prescriber text, a pharmacy counter text, a hospital text, and a background text. Each of these is specifically designed to meet the requirements of its user. After a prescription has been issued by a physician (prescriber text), the prescription is transferred to the pharmacy either electronically or physically (by the patient). In the Netherlands, the prescription is then processed electronically by a pharmacy assistant (pharmacy counter text in a pharmacy, hospital text in a hospital setting), and the prescribed drug is dispensed. Prescriptions are checked for medication errors by the pharmacist (background text in community pharmacy, hospital text in hospital).

Composed therapeutic (dose) recommendations

To date, we have used this method of assessment for 85 genotype/phenotype–drug combinations comprising 26 drugs (Table 3). The assessed drugs were substrates for CYP2D6 (n = 21), CYP2C19 (n = 1), CYP2C9 (n = 3), and UGT1A1 (n = 1). After assessment of the literature, therapeutic (dose) recommendations were composed for 17 of the 26 drugs. It was decided that for four of the drugs (clozapine, duloxetine, flupenthixol, and olanzapine) no gene–drug interaction was present and therefore no therapeutic (dose) recommendation was required. For aripiprazole, tamoxifen, acenocoumarol, phenprocoumon,

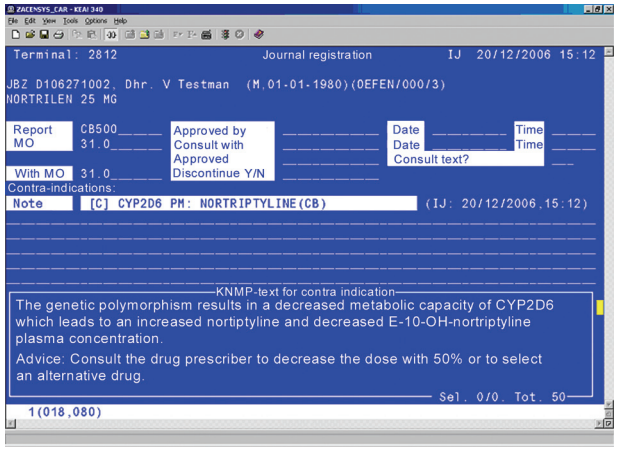

Figure 1 Typical alert generated by automated medication surveillance after prescription of nortriptyline to a patient known to be a poor metabolizer of CYP2D6 (translated from Dutch).

Table 3 Composed therapeutic (dose) recommendations

Drug	Genotype or phenotype	Level of evidence	Clinical relevance	Interaction	Action (i.e., therapeutic (dose) recommendation)	References
CYP2D6						
Aripiprazole	PM	0	AA	Yes	No	26,27
	IM	3	A	Yes	No	28
	UM	—	—	Yes	No	
Atomoxetine	PM	3	B	Yes	Select alternative if possible; or be aware of adverse drug events; or reduce dose by 50%	29–31
	IM	—	—	Yes	Be aware of adverse drug events	
	UM	—	—	Yes	Be aware of diminished efficacy	
Clomipramine	PM	4	C	Yes	Reduce dose by 50% and monitor (desmethyl)clomipramine plasma concentration	32–35
	IM	4	C	Yes	Monitor (desmethyl)clomipramine plasma concentration	36,37
	UM	—	—	Yes	Select alternative drug or monitor (desmethyl)clomipramine plasma concentration	
Clozapine	PM	4	AA	No	No	38–41
	IM	3	AA	No	No	41
	UM	4	AA	No	No	40,41
Codeine	PM	4	B	Yes	Analgesia: Select alternative if possible or be aware of symptoms of diminished pain relief Cough: No	42–52
	IM	3	A	Yes	Analgesia: Select alternative if possible or be aware of symptoms of diminished pain relief Cough: No	43,53
	UM	3	F	Yes	Analgesia: Select alternative if possible or be aware of ADE Cough: Be extra alert for ADE caused by increased morphine concentration in plasma	42,54–56
Duloxetine	PM	0	AA	Yes	No	57
	IM	—	—	Yes	No	
	UM	—	—	Yes	No	
Flecainide	PM	4	A	Yes	Reduce dose by 50% reduction, record ECG , monitor plasma concentration	58–62
	IM	—	—	Yes	Record ECG, monitor plasma concentration	
	UM	—	—	Yes	Record ECG, monitor plasma concentration	
Flupentixol	PM	—	—	No	No	
	IM	—	—	No	No	
	UM	—	—	No	No	
Haloperidol	PM	4	C	Yes	Reduce dose by 50% or select alternative drug	63–68
	IM	4	A	Yes	No	63,64,69–77
	UM	4	C	Yes	Be extra alert to diminished haloperidol plasma concentration or select alternative drug	63
Imipramine	PM	4	C	Yes	Reduce dose by 50%, monitor imipramine and desipramine plasma concentration	37,78–80
	IM	3	AA	Yes	Monitor imipramine and desipramine plasma concentration	78
	UM	—	—	Yes	Select alternative drug or monitor imipramine and desipramine plasma concentration	
Metoprolol	PM	4	C	Yes	Heart failure: Select alternative drug or reduce dose by 50% Other indications: Be extra alert to side effects such as bradycardia and cold extremities or select alternative drug	81–90
	IM	4	B	Yes	Be extra alert to side effects such as bradycardia and cold extremities or select alternative drug	82,87,88,90–94

Table 3 continued on next page

Table 3 (continued)

Drug	Genotype or phenotype	Level of evidence	Clinical relevance	Interaction	Action (i.e., therapeutic (dose) recommendation)	References
	UM	4	B	Yes	Dose adaptation seems not necessary. Be extra alert to diminished therapeutic response or select alternative drug	82,83
Nortriptyline	PM	3	C	Yes	Reduce dose by 50%and monitor (E-10-OH)nortriptyline plasma concentration, or select alternative drug	95–99
	IM	4	C	Yes	Reduce dose by 50% and monitor (E-10-OH)nortriptyline plasma concentration, or select alternative drug	95–97,99–103
	UM	3	A	Yes	Select alternative drug or monitor (E-10-OH)nortriptyline plasma concentration	96,97
Olanzapine	PM	3	AA	No	No	104,105
	IM	1	A	No	No	105
	UM	—	—	No	No	
Oxycodone	PM	2	B	Yes	Select alternative drug or be aware of symptoms of diminished pain relief	106,107
	IM	—	—	Yes	Select alternative drug if possible or be aware of symptoms of diminished pain relief	
	UM	2	A	Yes	Select alternative drug or be aware of symptoms of diminished pain relief	108
Paroxetine	PM	4	A	Yes	No	109–113
	IM	4	A	Yes	No	110,111,114
	UM	4	AA	Yes	Be extra alert to low paroxetine plasma concentrations or select alternative drug	109
Propafenone	PM	4	C	Yes	Reduce dose by 70%, record ECG, and monitor plasma concentration	115–123
	IM	3	A	Yes	Reduce dose by 50%, record ECG, and monitor plasma concentration	124–126
	UM	3	D	Yes	Record ECG and monitor plasma concentration	118
Risperidone	PM	4	C	Yes	Select alternative drug or be extra alert to ADE and adjust dose based on clinical response	127–131
	IM	4	A	Yes	Select alternative drug or be extra alert to ADE and adjust dose based on clinical response	130–135
	UM	4	C	Yes	Select alternative drug or be extra alert to diminished therapeutic response and adjust the dose in response to clinical effect and ADE	130,131,136
Tamoxifen	PM	4	E	Yes	No	137–142
	IM	4	A	Yes	No	138,140–142
	UM	—	—	Yes	No	
Tramadol	PM	3	B	Yes	Select alternative drug if possible or be aware of symptoms of diminished pain relief	143–148
	IM	3	A	Yes	Select alternative drug if possible or be aware of symptoms of diminished pain relief	143,144,149
	UM	1	B	Yes	Select alternative drug or be aware of symptoms or be extra alert to ADE	150
Venlafaxine	PM	4	C	Yes	Select alternative drug or reduce dose by 50%	151–153
	IM	4	A	No	No	153–155
	UM	4	AA	Yes	Select alternative drug or be extra alert to diminished venlafaxine plasma concentration and increased O-desmethylvenlafaxine plasma concentration	153
Zuclopenthixol	PM	4	A	Yes	Reduce dose by 50% or select alternative drug	156–159
	IM	4	A	Yes	Reduce dose by 25% or select alternative drug	157,158
	UM	—	—	Yes	Be extra alert to low zuclopenthixol plasma concentrations or select alternative drug	

Table 3 continued on next page

Table 3 (continued)

Drug	Genotype or phenotype	Level of evidence	Clinical relevance	Interaction	Action (i.e., therapeutic (dose) recommendation)	References
CYP2C9						
Acenocoumarol[a]	*1/*2	4	F	Yes	No	160–170
	*2/*2	4	F	Yes	No	160–165,167–170
	*1/*3	4	F	Yes	No	160–171
	*2/*3	4	F	Yes	No	160–170
	*3/*3	4	D	Yes	No	160–163,167,172
Phenprocoumon[a]	*1/*2	4	F	Yes	No	168–170,173–176
	*2/*2	4	F	Yes	No	168–170,174–176
	*1/*3	4	F	Yes	No	168–170,174–176
	*2/*3	4	F	Yes	No	168–170,173–176
	*3/*3	3	D	Yes	No	174–176
Phenytoin	*1/*2	4	A	Yes	Reduce dose by 25%. Evaluate clinical effect and serum concentration after at least 7–10 days. Advise the patient to contact the prescriber in case of ADE	177–182
	*2/*2	4	A	Yes	Reduce dose by 50%. Evaluate clinical effect and serum concentration after at least 7–10 days. Advise the patient to contact the prescriber in case of ADE	177–179,181,182
	*1/*3	4	D	Yes	Reduce dose by 25%. Evaluate clinical effect and serum concentration after at least 7–10 days. Advise the patient to contact the prescriber in case of ADE	177–180,183–188
	*2/*3	4	A	Yes	Reduce dose by 50%. Evaluate clinical effect and serum concentration after at least 7–10 days. Advise the patient to contact the prescriber in case of ADE	178,182
	*3/*3	4	D	Yes	Reduce dose by 50%. Evaluate clinical effect and serum concentration after at least 7–10 days. Advise the patient to contact the prescriber in case of ADE	177,179–181, 189,190
CYP2C19						
Voriconazole	*1/*2	3	A	Yes	No	191–194
	*2/*2	3	A	Yes	No	191–194
	*1/*3	3	A	Yes	No	191–193
	*2/*3	3	A	Yes	No	191–193
	*3/*3	3	A	Yes	No	191–193
UGT1A1						
Irinotecan	*1/*28	3	F	Yes	No	195–211
	*28/*28	3	E	Yes	No	195,196,198–207, 209,211–213

ADE: adverse drug event.
Level of evidence: Assigned level of evidence (0–4) for the gene–drug interaction. If scored "—" no data was retrieved with the literature search.
Clinical relevance: Assigned level of clinical relevance (AA-F) for the gene–drug interaction. If scored "—" no data were retrieved with the literature search.
Consequences for automated medication surveillance and prescribing systems were as follows:
Interaction yes, action yes: Automated medication surveillance/prescribing system automatically generates an "alert" text when the drug–gene combination is entered.
Interaction yes, action no: The gene–drug combination is logged into the system but the user is not automatically alerted. Local users of the system are able to generate an alert.
Interaction no, action no: The gene–drug combination will not generate an alert.
References 26–214 can be found in the on-line version of the manuscript.

[a]Therapeutic (dose) recommendations for acenocoumarol and phenprocoumon are based solely on CYP2C9 genotype without knowledge of VKORC1 status. It was decided not to provide therapeutic (dose) recommendations although a clinically relevant gene–drug interaction was present. The primary reason for this was that in the Netherlands coumarin treatment is strictly monitored.[214]

and voriconazole, although a gene–drug interaction was present, no therapeutic (dose) recommendation was made.

Overview and caveats

We have developed a method to interpret the results of structured assessment of gene–drug interactions, and translate them into therapeutic recommendations. These recommendations have been included in the G-standard since October 2006, and are applied in clinical practice for patients whose genotype is known. The availability of these guidelines as part of most computerized drug prescription and automated medication surveillance systems in the Netherlands will facilitate the use of pharmacogenetic

information in therapeutic decision-making. Recommendations relating to other drugs such as sulfonylurea, angiotensin II receptor blockers, and proton pump inhibitors, are currently under evaluation and will be released along with future three-monthly updates.

Many of the studies that were assessed did not have pharmacogenetics as their primary objective, and this resulted in underpowered studies. Even where pharmacogenetics was the primary study objective, the assessed endpoints were mostly pharmacokinetic; also, the results related to single-dose experiments in healthy volunteers and was therefore not representative of daily clinical practice. A third limitation was the frequent use of specific study populations such as Asians, involving the investigation of genotypes which occur only rarely in Caucasian populations. In particular, there is a dearth of data relating to intermediate and ultrarapid metabolizers. Because we did not allow extrapolation of dose recommendations if a phenotype was not present in the studied population, only a few dose recommendations could be calculated for ultrarapid and intermediate metabolizers. The number of research papers per gene–drug combination retrieved during our searches and eligible for assessment was lower than we had expected, varying from 0 to 21. For nortriptyline, a widely used example for demonstrating the possible impact of pharmacogenetics, only 10 original papers were found eligible for assessment. These findings demonstrate that there remains a need for more studies to provide data on the clinical consequences of pharmacogenetics. These studies should be adequately designed with regard to sample size and clinically relevant endpoints.[19] Also, initiatives such as the cataloging of pharmacogenetic information, introduced by the Pharmacogenomics and Pharmacogenetics Knowledge Base (http://www.pharmgkb.org/), are a valuable approach to providing research studies with adequate power to demonstrate the clinical relevance of pharmacogenetics.

Currently there is only limited evidence to justify prospective pharmacogenetic testing or population-wide screening. The justification for such testing and screening will depend upon the availability of sufficient data demonstrating that pharmacogenetic testing actually improves clinical outcome and is cost-effective.[20] Producing such evidence presents a significant challenge. Long-term monitoring of the clinical outcome of the PWG dose recommendations might provide such data. However, there are indications that patients with non-wild-type genotypes are more often prone to an aberrant drug response. Therefore, we chose to formulate therapeutic recommendations for the situation where the patient's genotype is known. Currently, the infrastructure for genotyping is available only in a limited number of centers and needs to be expanded or made accessible for other centers.[4,21]

Obviously, tests for single polymorphisms that affect pharmacokinetics may account for only part of the variability in drug response, and the pharmacogenetic tests that are currently available cannot replace other methods for dose individualization such as therapeutic drug monitoring.[22,23] We have described only genetic polymorphisms that affect the pharmacokinetics of a drug. The available literature on polymorphisms that affect pharmacodynamics, and the implications of these effects, is limited and sometimes contradictory.[24,25]

In summary, our initiative to develop pharmacogenetics-based therapeutic (dose) recommendations and to make them accessible during electronic drug prescription and automated medication surveillance represents an important step forward toward the application of pharmacogenetic information in daily patient care.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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