Pharmacogenetics: From Bench to Byte—An Update of Guidelines

JJ Swen[1], M Nijenhuis[2], A de Boer[3], L Grandia[2], AH Maitland-van der Zee[3], H Mulder[3,4], GAPJM Rongen[5,6,7], RHN van Schaik[8], T Schalekamp[3], DJ Touw[9], J van der Weide[10], B Wilffert[11], VHM Deneer[12] and H-J Guchelaar[1]

Currently, there are very few guidelines linking the results of pharmacogenetic tests to specific therapeutic recommendations. Therefore, the Royal Dutch Association for the Advancement of Pharmacy established the Pharmacogenetics Working Group with the objective of developing pharmacogenetics-based therapeutic (dose) recommendations. After systematic review of the literature, recommendations were developed for 53 drugs associated with genes coding for *CYP2D6*, *CYP2C19*, *CYP2C9*, thiopurine-*S*-methyltransferase (*TPMT*), dihydropyrimidine dehydrogenase (*DPD*), vitamin K epoxide reductase (*VKORC1*), uridine diphosphate glucuronosyltransferase 1A1 (*UGT1A1*), *HLA-B44*, *HLA-B*5701*, *CYP3A5*, and factor V Leiden (*FVL*).

In recent years, there has been substantial progress in the field of pharmacogenetics. The number of publications on the subject has risen sharply, and the results of the first randomized clinical trial showing that pharmacogenetics can be used to prevent adverse drug events have been published.[1] Meanwhile, an increasing number of pharmacogenetic tests are becoming available.[2] However, despite US Food and Drug Administration–approved modifications to more than 30 drug labels to include pharmacogenetic information,[3] guidelines that link the result of a pharmacogenetic test to specific dose recommendations are sparse. Therefore, the Royal Dutch Association for the Advancement of Pharmacy established the Pharmacogenetics Working Group with the objectives of developing pharmacogenetics-based therapeutic (dose) recommendations based on systematic review of the literature and assisting physicians and pharmacists by integrating the recommendations into computerized systems for drug prescription, dispensing, and automated medication surveillance. The initial results for 85 genotype/phenotype–drug combinations, comprising 26 drugs, were published in this journal.[4] Here we present recommendations for 27 newly assessed drugs and updates of the existing monographs.

RESULTS

To date, we have compiled therapeutic (dose) recommendations for 163 genotype/phenotype–drug combinations comprising 53 drugs and 11 genes (**Table 1**; the table's references are provided in the **Supplementary References** online). The drugs were associated with genes coding for *CYP2D6* ($n = 25$), *CYP2C19* ($n = 11$), *CYP2C9* ($n = 7$), thiopurine-*S*-methyltransferase (*TPMT*) ($n = 3$), dihydropyrimidine dehydrogenase (*DPD*) ($n = 3$), vitamin K epoxide reductase (*VKORC1*) ($n = 2$), uridine diphosphate glucuronosyltransferase-1A1 (*UGT1A1*), *HLA-B44*, *HLA-B*5701*, *CYP3A5*, and factor V Leiden (*FVL*) (all $n = 1$). Therapeutic (dose) recommendations were formulated for 39 (73.6%) of the drugs. For clozapine, flupenthixol, and olanzapine, a gene–drug interaction with *CYP2D6* was considered, but no evidence was found in the literature, and hence no recommendations were required. For 11 of the drugs (20.8%), a gene–drug interaction was present, but no therapeutic (dose) recommendation was deemed necessary.

The quality of the retrieved data was scored as category 4 (published controlled studies of "good" quality; see **Supplementary Table S1** online for quality criteria) for 49.1% of the data and category 3 (published controlled studies of "moderate" quality) for 37.4%. For 59 (36.2%) of the genotype/phenotype–drug combinations, the clinical relevance of the interaction was

[1]Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, The Netherlands; [2]Division Drug Information Centre, KNMP, The Hague, The Netherlands; [3]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, Utrecht, The Netherlands; [4]Department of Clinical Pharmacy, Wilhelmina Hospital Assen, Assen, The Netherlands; [5]Department of Pharmacology - Toxicology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; [6]Department of General Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; [7]Nijmegen Centre for Evidence Based Practice, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; [8]Department of Clinical Chemistry, Erasmus University Medical Centre, Rotterdam, The Netherlands; [9]Central Hospital Pharmacy, The Hague, The Netherlands; [10]Department of Clinical Chemistry, St Jansdal Hospital, Harderwijk, The Netherlands; [11]Department of Quality and Patient Safety, Zorggroep Noorderbreedte, Leeuwarden, The Netherlands; [12]Department of Clinical Pharmacy, St Antonius Hospital, Nieuwegein, The Netherlands. Correspondence: H-J Guchelaar (h.j.guchelaar@lumc.nl)

Received 7 December 2010; accepted 31 January 2011; advance online publication 16 March 2011. doi:10.1038/clpt.2011.34

Table 1 Results for *CYP2D6, CYP2C9, CYP2C19, UGT1A1, TPMT, HLA-B44, HLA-B*5701, CYP3A5, VKORC1,* factor V Leiden, and *DPYD*

Drug	Subjects (*N*)	Genotype or phenotype	Level of evidence	Clinical relevance	Gene–drug interaction	Therapeutic (dose) recommendation	References
CYP2D6							
Amitriptyline	459	PM	3	A	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g., citalopram, sertraline) or monitor amitriptyline and nortriptyline plasma concentration	1–3
		IM	3	C	Yes	Reduce dose by 25% and monitor plasma concentration or select alternative drug (e.g., citalopram, sertraline)	1–6
		UM	3	C	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g., citalopram, sertraline) or monitor (E-10-hydroxy)amitriptyline plasma concentration	3, 7, 8
Aripiprazole	124	PM	4	C	Yes	Reduce maximum dose to 10 mg/day (67% of the maximum recommended daily dose)	9–12
		IM	4	A	Yes	No	10, 13–15
		UM	—	—	Yes	No	—
Atomoxetine	10,081	PM	3	B	Yes	Standard dose. Dose increase probably not necessary; be alert to ADEs	16–21
		IM	4	A	Yes	No	22
		UM	—	—	Yes	Insufficient data to allow calculation of dose adjustment. Be alert to reduced efficacy or select alternative drug (e.g., methylphenidate, clonidine)	—
Carvedilol	135	PM	4	B	Yes	No	23, 24
		IM	4	A	Yes	No	25–29
		UM	—	—	Yes	No	—
Clomipramine	272	PM	4	C	Yes	Reduce dose by 50% and monitor (desmethyl) clomipramine plasma concentration	30–35
		IM	4	C	Yes	Insufficient data to allow calculation of dose adjustment. Monitor (desmethyl)clomipramine plasma concentration	32, 36, 37
		UM	2	C	Yes	Select alternative drug (e.g., citalopram, sertralin) or monitor (desmethyl)clomipramine plasma concentration	38, 39
Clozapine	297	PM	4	AA	No	No	40–44
		IM	4	AA	No	No	41, 44
		UM	4	AA	No	No	43, 44
Codeine	453	PM	4	B	Yes	Analgesia: select alternative drug (e.g., acetaminophen, NSAID, morphine—not tramadol or oxycodone) or be alert to symptoms of insufficient pain relief Cough: no	45–55
		IM	3	A	Yes	Analgesia: select alternative drug (e.g., acetaminophen, NSAID, morphine—not tramadol or oxycodone) or be alert to symptoms of insufficient pain relief Cough: no	46, 56
		UM	3	F	Yes	Analgesia: select alternative drug (e.g., acetaminophen, NSAID, morphine—not tramadol or oxycodone) or be alert to ADE Cough: be extra alert to ADEs due to increased morphine plasma concentration	45, 57–60
Doxepin	76	PM	3	F	Yes	Reduce dose by 60%. Adjust maintenance dose in response to (nor)doxepin plasma concentration	7, 61–64
		IM	3	A	Yes	Reduce dose by 20%. Adjust maintenance dose in response to (nor)doxepin plasma concentration	63
		UM	3	A	Yes	Select alternative drug (citalopram, sertraline) or increase dose by 100%. Adjust maintenance dose in response to (nor)doxepin plasma concentration	62

Table 1 Continued on next page

Table 1 (Continued)

Drug	Subjects (*N*)	Genotype or phenotype	Level of evidence	Clinical relevance	Gene–drug interaction	Therapeutic (dose) recommendation	References
Duloxetine	0[b]	PM	0	AA	Yes	No	65
		IM	—	—	Yes	No	—
		UM	—	—	Yes	No	—
Flecainide	145	PM	4	A	Yes	Reduce dose by 50%, record ECG, monitor plasma concentration	66–70
		IM	3	A	Yes	Reduce dose by 25%, record ECG, monitor plasma concentration	71, 72
		UM	—	—	Yes	Record ECG and monitor plasma concentration or select alternative drug (e.g., sotalol, disopyramide, quinidine, amiodarone)	—
Flupenthixol	0	PM	—	—	No	No	—
		IM	—	—	No	No	—
		UM	—	—	No	No	—
Haloperidol	1,411	PM	4	C	Yes	Reduce dose by 50% or select alternative drug (e.g., pimozide, flupenthixol, fluphenazine, quetiapine, olanzapine, clozapine)	73–80
		IM	4	A	Yes	No	73–77, 81–89
		UM	4	C	Yes	Insufficient data to allow calculation of dose adjustment. Be alert to decreased haloperidol plasma concentration and adjust maintenance dose in response to haloperidol plasma concentration or select alternative drug (e.g., pimozide, flupenthixol, fluphenazine, quetiapine, olanzapine, clozapine)	73, 74
Imipramine	268	PM	4	C	Yes	Reduce dose by 70% and monitor imipramine and desipramine plasma concentrations	32, 90–94
		IM	4	A	Yes	Reduce dose by 30% and monitor imipramine and desipramine plasma concentrations	90, 92, 94
		UM	4	A	Yes	Select alternative drug (e.g., citalopram, sertraline) or increase dose by 70% and monitor imipramine and desipramine plasma concentration	92, 94
Metoprolol	1,966	PM	4	C	Yes	Heart failure: select alternative drug (e.g., bisoprolol, carvedilol) or reduce dose by 75% Other indications: be alert to ADEs (e.g., bradycardia, cold extremities) or select alternative drug (e.g., atenolol, bisoprolol)	95–110
		IM	4	B	Yes	Heart failure: select alternative drug (e.g., bisoprolol, carvedilol) or reduce dose by 50% Other indications: be alert to ADEs (e.g., bradycardia, cold extremities) or select alternative drug (e.g., atenolol, bisoprolol)	96–100,102, 107, 108, 110–115
		UM	4	D	Yes	Heart failure: select alternative drug (e.g., bisoprolol, carvedilol) or titrate dose to a maximum of 250% of the normal dose in response to efficacy and ADE Other indications: select alternative drug (e.g., atenolol, bisoprolol) or titrate dose to a maximum of 250% of the normal dose in response to efficacy and ADE	98, 100–103
Mirtazapine	333	PM	3	B	Yes	No	7, 30, 116–120
		IM	3	A	Yes	No	119, 121
		UM	3	A	Yes	No	7, 116, 118

Table 1 Continued on next page

Table 1 (Continued)

Drug	Subjects (*N*)	Genotype or phenotype	Level of evidence	Clinical relevance	Gene–drug interaction	Therapeutic (dose) recommendation	References
Nortriptyline	270	PM	3	C	Yes	Reduce dose by 60% and monitor nortriptyline + 10-hydroxynortriptyline plasma concentrations	122–127
		IM	4	C	Yes	Reduce dose by 40% and monitor nortriptyline + 10-hydroxynortriptyline plasma concentrations	122–124, 126, 128–132
		UM	3	C	Yes	Select alternative drug (e.g., citalopram, sertraline) or increase dose by 60% and monitor nortriptyline + 10-hydroxynortriptyline plasma concentrations	39, 123, 124, 128
Olanzapine	201	PM	3	AA	No	No	133–135
		IM	3	AA	No	No	134, 136, 137
		UM	—	—	No	No	—
Oxycodone	78	PM	3	B	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug—not tramadol or codeine—or be alert to symptoms of insufficient pain relief	138–142
		IM	3	AA	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug—not tramadol or codeine—or be alert to symptoms of insufficient pain relief	140
		UM	1	A	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug (NOT tramadol or codeine) or be alert to ADEs (e.g., nausea, vomiting, constipation, respiratory depression, confusion, urinary retention)	143
Paroxetine	633	PM	4	A	Yes	No	119, 144–151
		IM	4	A	Yes	No	119, 145, 148–154
		UM	4	C	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g., citalopram, sertraline)	144,148, 150, 151, 155
Propafenone	257	PM	4	C	Yes	Reduce dose by 70%, record ECG, monitor plasma concentration	156–165
		IM	3	A	Yes	Insufficient data to allow calculation of dose adjustment. Adjust dose in response to plasma concentration and record ECG or select alternative drug (e.g., sotalol, disopyramide, quinidine, amiodarone)	165–168
		UM	3	D	Yes	Insufficient data to allow calculation of dose adjustment. Adjust dose in response to plasma concentration and record ECG or select alternative drug (e.g., sotalol, disopyramide, quinidine, amiodarone)	159, 165
Risperidone	1,721	PM	4	D	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g., quetiapine, olanzapine, clozapine) or be extra alert to ADEs and adjust dose to clinical response	169–175
		IM	4	C	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g., quetiapine, olanzapine, clozapine) or be extra alert to ADEs and adjust dose to clinical response	173, 174, 176–184
		UM	4	C	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g., quetiapine, olanzapine, clozapine) or be extra alert to decreased response and titrate dose in response to clinical effect and ADE	173–175, 185
Tamoxifen	5,020	PM	4	E	Yes	Increased risk for relapse of breast cancer. Consider aromatase inhibitor for postmenopausal women	186–196
		IM	4	E	Yes	Increased risk for relapse of breast cancer. Avoid concomitant use of CYP2D6 inhibitors. Consider aromatase inhibitor for postmenopausal women	187, 189–197
		UM	4	A	Yes	No	192, 197

Table 1 Continued on next page

Table 1 (Continued)

Drug	Subjects (*N*)	Genotype or phenotype	Level of evidence	Clinical relevance	Gene–drug interaction	Therapeutic (dose) recommendation	References
Tramadol	968	PM	4	B	Yes	Select alternative drug—not oxycodone or codeine—or be alert to symptoms of insufficient pain relief	198–211
		IM	4	B	Yes	Be alert to decreased efficacy. Consider dose increase. If response is still inadequate, select alternative drug—not oxycodone or codeine—or be alert to symptoms of insufficient pain relief	198–200, 208, 211–213
		UM	3	C	Yes	Reduce dose by 30% and be alert to ADEs (e.g., nausea, vomiting, constipation, respiratory depression, confusion, urinary retention) or select alternative drug (e.g., acetaminophen, NSAID, morphine—not oxycodone or codeine)	199, 206, 211, 214, 215
Venlafaxine	251	PM	4	C	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g., citalopram, sertraline) or adjust dose to clinical response and monitor (*O*-desmethyl)venlafaxine plasma concentration	216–222
		IM	4	C	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g., citalopram, sertraline) or adjust dose to clinical response and monitor (*O*-desmethyl)venlafaxine plasma concentration	218–221, 223–225
		UM	4	A	Yes	Be alert to decreased venlafaxine and increased (*O*-desmethyl)venlafaxine plasma concentration. Titrate dose to a maximum of 150% of the normal dose or select alternative drug (e.g., citalopram, sertraline)	218, 220
Zuclopenthixol	231	PM	4	A	Yes	Reduce dose by 50% or select alternative drug (e.g., flupenthixol, quetiapine, olanzapine, clozapine)	226–230
		IM	4	A	Yes	Reduce dose by 25% or select alternative drug (flupenthixol, quetiapine, olanzapine, clozapine)	227–229
		UM	—	—	Yes	Insufficient data to allow calculation of dose adjustment. Be alert to low zuclopenthixol plasma concentrations or select alternative drug (flupenthixol, quetiapine, olanzapine, clozapine)	—
CYP2C9							
Acenocoumarol[a]	6,811	*1/*2	4	F	Yes	Check INR more frequently after initiating or discontinuing NSAIDs	231–249
		*2/*2	4	F	Yes	Check INR more frequently after initiating or discontinuing NSAIDs	231–236, 238–249
		*1/*3	4	F	Yes	Check INR more frequently after initiating or discontinuing NSAIDs	231–250
		*2/*3	4	F	Yes	Check INR more frequently after initiating or discontinuing NSAIDs	232–250
		*3/*3	4	F	Yes	Check INR more frequently during dose titration and after initiating or discontinuing NSAIDs	231–234, 238, 242–245, 247, 250, 251
Glibenclamide	86	*1/*2	3	AA	Yes	No	252–254
		*2/*2	3	AA	Yes	No	252, 254
		*1/*3	3	B	Yes	No	252–255
		*2/*3	3	AA	Yes	No	252, 254, 256
		*3/*3	3	A	Yes	No	254, 256
Gliclazide	912	*1/*2	3	AA#	Yes	No	257–259
		*2/*2	3	AA#	Yes	No	257, 259
		*1/*3	3	AA#	Yes	No	257–260
		*2/*3	3	AA#	Yes	No	257
		*3/*3	3	AA#	Yes	No	257

Table 1 Continued on next page

Table 1 (Continued)

Drug	Subjects (*N*)	Genotype or phenotype	Level of evidence	Clinical relevance	Gene–drug interaction	Therapeutic (dose) recommendation	References
Glimepiride	442	*1/*2	3	AA	Yes	No	252, 253, 256, 258
		*2/*2	4	AA	Yes	No	252
		*1/*3	4	AA#	Yes	No	252, 253, 256, 258, 261, 262
		*2/*3	3	D	Yes	No	252, 253, 256
		*3/*3	3	D	Yes	No	256, 262
Phenprocoumon[a]	1,802	*1/*2	4	F	Yes	No	239–242, 263–271
		*2/*2	4	F	Yes	Check INR more frequently	239–242, 264–269, 271
		*1/*3	4	F	Yes	No	239–242, 263–269, 271
		*2/*3	4	F	Yes	Check INR more frequently	239–242, 263–267, 269, 271
		*3/*3	4	D	Yes	Check INR more frequently	264–267, 269
Phenytoin	1,354	*1/*2	4	A	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, sedation)	272–278
		*2/*2	4	A	Yes	Standard loading dose. Reduce maintenance dose by 50%. Evaluate response and serum concentration after 7–10 days. Be alert to ADEs (e.g., ataxia, nystagmus, dysarthria, sedation)	272–274, 276–278
		*1/*3	4	D	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, sedation)	272–275, 278–286
		*2/*3	4	A	Yes	Standard loading dose. Reduce maintenance dose by 50%. Evaluate response and serum concentration after 7–10 days. Be alert to ADEs (e.g., ataxia, nystagmus, dysarthria, sedation)	273, 277
		*3/*3	4	D	Yes	Standard loading dose. Reduce maintenance dose by 50%. Evaluate response and serum concentration after 7–10 days. Be alert to ADEs (e.g., ataxia, nystagmus, dysarthria, sedation)	272, 274–276, 286–290
Tolbutamide	544	*1/*2	3	A	Yes	No	252, 291–295
		*2/*2	3	A	Yes	No	252, 291, 293, 294
		*1/*3	3	B	Yes	No	252, 291–297
		*2/*3	3	A	Yes	No	252, 294, 295
		*3/*3	3	A	Yes	No	294–296
CYP2C19							
Citalopram/ Escitalopram	2,396	PM	4	A	Yes	No	298–305
		IM	4	A	Yes	No	298–300, 302, 305, 306
		UM	4	A	Yes	Monitor plasma concentration and titrate dose to a maximum of 150% in response to efficacy and ADE or select alternative drug (e.g., fluoxetine, paroxetine)	299, 307

Table 1 Continued on next page

Table 1 (Continued)

Drug	Subjects (*N*)	Genotype or phenotype	Level of evidence	Clinical relevance	Gene–drug interaction	Therapeutic (dose) recommendation	References
Clopidogrel	11,785	PM	4	F	Yes	Increased risk for reduced response to clopidogrel. Consider alternative drug. Prasugrel is not or to a much smaller extent metabolized by CYP2C19 but is associated with an increased bleeding risk compared to clopidogrel	308–326
		IM	4	F	Yes	Increased risk for reduced response to clopidogrel. Consider alternative drug. Prasugrel is not or to a much smaller extent metabolized by CYP2C19 but is associated with an increased bleeding risk compared to clopidogrel	308–328
		UM	3	A	Yes	No	308, 315–317, 329
Esomeprazole	975	PM	4	AA#	Yes	No	330, 330–339
		IM	4	AA#	Yes	No	330–338, 340
		UM	—	—	Yes	*Helicobacter pylori* eradication: increase dose by 50–100%. Be extra alert to insufficient response Other: be extra alert to insufficient response. Consider dose increase by 50–100%	—
Imipramine	541	PM	3	A	Yes	Reduce dose by 30% and monitor plasma concentration of imipramine and desipramine or select alternative drug (e.g., fluvoxamine, mirtazapine)	93, 341–346
		IM	3	A	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g., fluvoxamine, mirtazapine)	93, 342–345
		UM	—	—	Yes	No	—
Lansoprazole	2,304	PM	4	AA#	Yes	No	347–369
		IM	4	AA#	Yes	No	347–368, 370, 371
		UM	—	—	Yes	*H. pylori* eradication: increase dose by 200%. Be extra alert to insufficient response Other: be extra alert to insufficient response. Consider dose increase by 200%	—
Moclobemide	31	PM	3	A	Yes	No	372–374
		IM	—	—	Yes	No	—
		UM	—	—	Yes	No	—
Omeprazole	2,522	PM	4	AA#	Yes	No	331, 353, 355, 358, 359, 361, 364, 375–389
		IM	4	AA#	Yes	No	331, 353, 355, 358, 359, 361, 364, 371, 375–379, 381–385, 387–390
		UM	3	A	Yes	*H. pylori* eradication: increase dose by 100–200%. Be extra alert to insufficient response Other: be extra alert to insufficient response. Consider dose increase by 100–200%	391–393
Pantoprazole	829	PM	3	AA#	Yes	No	336, 394–398
		IM	3	AA#	Yes	No	336, 340, 390, 395–398
		UM	3	AA	Yes	*H. pylori* eradication: increase dose by 400%. Be extra alert to insufficient response Other: be extra alert to insufficient response. Consider dose increase by 400%	398

Table 1 Continued on next page

Table 1 (Continued)

Drug	Subjects (*N*)	Genotype or phenotype	Level of evidence	Clinical relevance	Gene–drug interaction	Therapeutic (dose) recommendation	References
Rabeprazole	2,239	PM	4	AA#	Yes	No	334, 352, 357, 359, 361, 364, 376, 380, 381, 385, 388, 394, 399–410
		IM	4	AA	Yes	No	334, 352, 357, 359, 361, 364, 376, 381, 385, 388, 399–403, 405–409
		UM	—	—	Yes	No	—
Sertraline	26	PM	3	C	Yes	Reduce dose by 50%	7, 411
		IM	3	A	Yes	Insufficient data to allow calculation of dose adjustment. Be extra alert to ADEs (e.g., nausea, vomiting, diarrhea)	411
		UM	—	—	Yes	No	—
Voriconazole	314	PM	3	A	Yes	Monitor serum concentration	412–421
		IM	3	A	Yes	Monitor serum concentration	412, 413, 416, 419–421
		UM	3	A	Yes	No	418, 420
UGT1A1							
Irinotecan	3,883	*1/*28	3	F	Yes	No	422–448
		*28/*28	3	E	Yes	Dose >250 mg/m^2: reduce initial dose by 30%. Increase dose in response to neutrophil count Dose ≤250 mg/m^2: no dose adjustment	422, 423, 425–435, 437, 439–445, 447–454
TPMT							
Azathioprine/ Mercaptopurine	2,853	PM	4	F	Yes	Select alternative drug or reduce dose by 90%. Increase dose in response of hematologic monitoring and efficacy	455–467
		IM	4	E	Yes	Select alternative drug or reduce dose by 50%. Increase dose in response of hematologic monitoring and efficacy	455, 456, 458, 459, 461, 462, 464–466, 468–477
Thioguanine	792	PM	2	F	Yes	Select alternative drug. Insufficient data to allow calculation of dose adjustment	478, 479
		IM	3	D	Yes	Select alternative drug. Insufficient data to allow calculation of dose adjustment	480–483
HLA-B44							
Ribavirine	130	HLA-B44 negative	4	C	Yes	No	484
*HLA-B*5701*							
Abacavir	3,791	HLA-B*5701 positive	4	E	Yes	Select alternative drug	485–498
CYP3A5							
Tacrolimus	1,302	*1/*1	4	B	Yes	No	499–511
		*1/*3	4	D	Yes	No	499–512
VKORC1							
Acenocoumarol[a]	776	CT	4	A	Yes	No	233, 250, 513–515
		TT	4	A	Yes	Check INR more frequently	233, 250, 513–515

Table 1 Continued on next page

Table 1 (Continued)

Drug	Subjects (*N*)	Genotype or phenotype	Level of evidence	Clinical relevance	Gene–drug interaction	Therapeutic (dose) recommendation	References
Phenprocoumon[a]	391	CT	4	D	Yes	No	269, 514
		TT	4	D	Yes	Check INR more frequently	269, 514
Factor V Leiden							
Estrogen-containing OC	7,441	FVL homozygous	3	D	Yes	Positive (family) history of thrombotic events: avoid estrogen-containing OC and select alternative (e.g., copper intrauterine device, progestin-only contraceptive) Negative (family) history of thrombotic events: avoid additional risk factors (e.g., obesity, smoking)	516–523
		FVL heterozygous	4	D	Yes	Positive (family) history of thrombotic events: avoid estrogen-containing OC and select alternative (e.g., copper intrauterine device, progestin-only contraceptive) Negative (family) history of thrombotic events: avoid additional risk factors (e.g., obesity, smoking)	516–520, 522–535
DPYD							
Fluorouracil/ Capecitabine	3,733	PM	3	F	Yes	Select alternative drug. Tegafur is not a suitable alternative because this drug is also metabolized by DPD	536–544
		IM	3	F	Yes	Reduce dose by 50% or select alternative drug. Tegafur is not a suitable alternative because this drug is also a substrate for DPD. Increase dose in response to toxicity and efficacy	536–542, 544–555
Tegafur/uracil Combination	0[b]	PM	3	AA	Yes	Select alternative drug. Fluorouracil or capecitabine are not suitable alternatives because both are also metabolized by DPD	556
		IM	3	AA	Yes	No	556

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. Positive clinical effects were scored as AA#.

A complete list of references can be found in the **Supplementary References** online.

ADE, adverse drug event; ECG, electrocardiogram; FVL, factor V Leiden; IM, intermediate metabolizer; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; OC, oral contraceptive; PM, poor metabolizer; UM, ultrarapid metabolizer.

CYP2C19 IM, *1/*2, *1/*3, *17/*2, *17/*3; CYP2C19 PM, *2/*2, *2/*3, *3/*3; CYP2C19 UM, *17/*17; CYP2D6 IM, patients carrying two decreased-activity (*9, *10, *17, *29, *36, *41) alleles or carrying one active (*1, *2, *33, *35) and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele, or carrying one decreased-activity (*9, *10, *17, *29, *36, *41) allele and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele; CYP2D6 PM, patients carrying two inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) alleles; CYP2D6 UM, patients carrying a gene duplication in absence of inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) or decreased-activity (*9, *10, *17, *29, *36, *41) alleles; DPD PM, patients carrying two inactive (*2A, *3, *7, *8, *10, *11, *12, *13, 496A>G, IVS10-15T>C, 1156G>T, 1845G>T) alleles, two decreased-activity (*9B, *10) alleles, or one inactive (*2A, *3, *7, *8, *10, *11, *12, *13, 496A>G, IVS10-15T>C, 1156G>T, 1845G>T) and one decreased-activity (*9B, *10) allele; DPD IM, patients carrying one active (*1, *4, *5, *6, *9A) allele and one inactive (*2A, *3, *7, *8, *10, *11, *12, *13, 496A>G, IVS10-15T>C, 1156G>T, 1845G>T) or decreased-activity (*9B, *10) allele. For the inactive DPYD alleles *3, *7, *8, *11, *12, *13, 1156G>T, 1845G>T and decreased-activity DPYD alleles *9B, *10, toxicity has been described in case reports but has not been confirmed in independent studies or pharmacokinetic analyses. TPMT IM, patients carrying one active (*1, *1S, *1A) and one inactive (*2, *3A-*3D, *4-*18) allele; TPMT PM, patients carrying two inactive (*2, *3A-*3D, *4-*18) alleles.

[a]Therapeutic (dose) recommendations for acenocoumarol and phenprocoumon solely based on CYP2C9 genotype without knowledge of VKORC1 status. Advice based on situation in the Netherlands. [b]Therapeutic (dose) recommendation based on information from the Summary of Product Characteristics.

classified as category C (long-standing discomfort (48–168 h) without permanent injury) or higher (see **Supplementary Table S2** online for details).

CYP2D6

For CYP2D6 poor metabolizers (PMs), defined as patients carrying two defective alleles, dose reductions are recommended for clomipramine, flecainide, haloperidol, zuclopenthixol (all 50%); doxepin, nortriptyline (both 60%); imipramine, propafenone (both 70%); and metoprolol (75%). There were insufficient data to calculate dose adjustments for amitriptyline, oxycodone, risperidone, and venlafaxine. With respect to tamoxifen, an increased risk for breast cancer relapse is present, and it is advised that an aromatase inhibitor be considered for treating postmenopausal women with breast cancer. Other recommendations included the selection of an alternative drug, therapeutic drug monitoring, increased alertness to adverse drug events and to reduced efficacy, and the recording of an electrocardiogram.

For CYP2D6 intermediate metabolizers (IMs), defined as patients carrying two decreased-activity alleles or one active/decreased-activity allele and one inactive allele, dose reductions ranging from 20 to 50% are advised for doxepin, amitriptyline, zuclopenthixol, imipramine, nortriptyline, and metoprolol. There were insufficient data to calculate dose adjustments for clomipramine, oxycodone, propafenone, risperidone, and venlafaxine. For tamoxifen, the use of an aromatase inhibitor for treating

postmenopausal women with breast cancer and the avoidance of concomitant use of a CYP2D6 inhibitor are advised. Other recommendations are comparable to the recommendations for PMs.

For CYP2D6 ultrarapid metabolizers (UMs), defined as patients carrying a gene duplication in the absence of inactive or decreased-activity alleles, dose adjustments ranging from 30 to 150% are recommended for doxepin, imipramine, metoprolol, nortriptyline, tramadol, and venlafaxine. For eight of the assessed gene–drug combinations, there were insufficient data to calculate dose adjustments. The metabolic capacity of UMs shows a considerable variability due to the range of gene copy numbers possible within the definition of UM. Also, the impact of the increased concentrations of drug metabolites to which UMs are exposed is often unknown. Therefore, the selection of an alternative drug is frequently advised.

CYP2C9

Seven CYP2C9 substrates were assessed. For phenytoin, dose reductions of 25% (*1/*2, *1/*3) and 50% (*2/*2, *2/*3, *3/*3) are recommended. For acenocoumarol and phenprocoumon, although clinically relevant gene–drug interactions are present, no dose adjustment is recommended because of strict international normalized ratio monitoring by the Dutch Thrombosis Service.[5] The need for adjustment of the initial dose is currently under investigation.[6] In addition to the *CYP2C9* genotype, the *VKORC1* genotype is an important determinant of coumarin response. Therefore, the status of both *CYP2C9* and *VKORC1* should be considered when identifying candidates for intensified international normalized ratio monitoring. Despite a clear pharmacokinetic effect of the gene–drug interaction, no recommendations were formulated for any of the sulfonylureas; the absolute risk for hypoglycemia is low, and the dose is titrated in response to plasma levels of glucose/glycosylated hemoglobin.

CYP2C19

The number of CYP2C19 substrates assessed increased from 1 to 12, and the *CYP2C19*17* allele (resulting in UMs) was added. Recommendations have been made with respect to all drugs except moclobemide and rabeprazole. Several articles have reported that the use of proton pump inhibitors results in better clinical efficacy in PMs and IMs as compared to extensive metabolizers. These results were scored as clinical relevance category AA# (AA: no statistically significant kinetic or clinical effect; "#" indicates a positive effect). Because of the risk of undertreatment, dose increases ranging from 50 to 400% are advised for UMs who are receiving treatment with proton pump inhibitors. In the case of voriconazole, because of its nonlinear pharmacokinetics, no dose adjustment is recommended.

UGT1A1

The *UGT1A1*28* allele is associated with irinotecan toxicity. Although results are not consistent, there is sufficient evidence that a reduction in the initial dose by 30% is required for regimens containing >250 mg/m^2 of irinotecan prescribed to homozygous carriers of the *UGT1A1*28* allele. This is in agreement with the Food and Drug Administration–mandated label change. No dose reduction is recommended for heterozygous carriers of the *UGT1A1*28* allele because dose reduction might result in undertreatment.

TPMT

TPMT catalyzes the *S*-methylation of the thiopurine drugs 6-mercaptopurine, azathioprine, and thioguanine. Selection of an alternative drug is advised for IMs and PMs. If this is not possible, the dose should be reduced by 50 and 90%, respectively. The data for thioguanine were insufficient for calculating dose adjustments.

HLA-B44

There was some evidence that HLA-B44-negative patients show less response to treatment with ribavirine. However, given that ~90% of the population is HLA-B44-negative and that no alternative treatment is available, no action is advised.

*HLA-B*5701*

To date, the association between *HLA-B*5701* genotype and the hypersensitivity reaction to abacavir remains the only example of a randomized clinical trial of pharmacogenetics. The advice regarding selection of an alternative drug for treating *HLA-B*5701*-positive patients is in agreement with the recommendations of the Food and Drug Administration and the European Medicines Agency.

CYP3A5

Because of the large number of publications, studies limited to healthy volunteers, pharmacokinetic end points, or liver transplantations were excluded. Although an interaction between *CYP3A5* genotype and tacrolimus metabolism exists, no action is advised because in Dutch transplantation hospitals the tacrolimus dose is titrated in response to therapeutic drug monitoring.

VKORC1

The *VKORC1* genotype appears to contribute more to the variability in coumarin dose requirements than the *CYP2C9* genotype does. The presence of the *VKORC1* C1173T polymorphism results in a decrease in dose requirements of acenocoumarol and phenprocoumon. However, for reasons identical to those related to the coumarin–CYP2C9 interaction, it was decided not to advise a dose reduction.

FVL

Patients with a positive (family) history of thrombotic events, and who are also carriers of the FVL allele, are advised to avoid the use of estrogen-containing oral contraceptives.

DPYD

Three DPD substrates were evaluated: 5-fluorouracil, its oral prodrug capecitabine, and tegafur. Selection of an alternative drug is advised for PMs, defined as homozygous carriers of a nonfunctional allele. For IMs, defined as heterozygous carriers of a nonfunctional allele, a dose reduction of 50% is advised for 5-fluorouracil and capecitabine.

DISCUSSION

We have developed pharmacogenetics-based therapeutic (dose) recommendations for 163 genotype/phenotype–drug combinations comprising 53 drugs and 11 genes. These recommendations include updates on the 26 existing therapeutic (dose) recommendations as well as recommendations for 27 new gene–drug combinations. The recommendations issued since October 2006 are available through most automated drug prescription, dispensing, and medication surveillance systems in the Netherlands.

The Pharmacogenetics Working Group initiative is not the first to develop guidelines with pharmacogenetics-based dose recommendations. A 2001 paper on CYP2D6 phenotype–based dose recommendations for antidepressants represents an early step.[7] A more recent example is the inclusion of pharmacogenetic information in coumarin dosing algorithms.[6,8] Furthermore, several groups have developed databases that are devoted to disseminating knowledge in the area of pharmacogenetics, e.g., PharmGKB (http://www.pharmgkb.org/). However, our recommendations are the first to be available nationwide during the process of drug prescribing and dispensing.

Our approach has some limitations, though. First, pharmacogenetics was not the primary objective for most of the studies we assessed; therefore, many of the studies were underpowered, with insufficient sample size per genotype or phenotype. Second, the end points assessed were often pharmacokinetic ones and the result of single-dose experiments in healthy volunteers—not representative of the conditions in daily clinical practice. However, since our previous report, the number of studies with pharmacogenetics as the primary objective has increased significantly.[4]

In our opinion, there is currently only limited evidence to justify population-wide prospective pharmacogenetic screening. A pharmacogenetic test prior to drug prescription is obligatory only for trastuzumab. Yet there are indications that patients with a non-wild-type genotype may be at increased risk for an aberrant drug response. Therefore, we formulated recommendations for patients with a previously determined genotype. In current clinical practice, the number of such patients is limited and consists mainly of subjects who were genotyped after unexplained adverse drug events or lack of response to "normal" drug dose. However, with the continuous decline in the costs of pharmacogenetic tests and the increasing number of laboratories with genotyping infrastructure, this number is bound to increase.

The recommendations of the Pharmacogenetics Working Group focus on the combination of a single gene with a single drug. However, the predictive value of a single genetic variant with regard to drug response is often limited, and combinations of multiple genetic variants may be involved. For example, only 5–18% and 15–37% of the variation in warfarin dose requirements are explained by *CYP2C9* and *VKORC1* genotypes, respectively.[9–13] Models that combine information on both genetic and nongenetic factors are able to explain up to 50% of the variation in warfarin dose requirements.[8] The formulation of recommendations that consider combinations of multiple genes presents a significant challenge for the future, given that very large study populations will be required to gather significant numbers of patients with combinations of rare genotypes. A second challenge is the integration of gene–drug and drug–drug interactions. To date, drug–drug interactions have been considered characteristic only of the drugs involved. However, in the light of current knowledge of pharmacogenetics, this might no longer be valid. For example, the interaction between a CYP2D6 inhibitor and a CYP2D6 substrate requires different management for CYP2D6 IMs than for CYP2D6 PMs. Therefore, the combination of gene–drug and drug–drug interactions may have major implications for drug prescribing and dispensing. Research in this field is only starting to evolve.[14]

In conclusion, we have developed pharmacogenetics-based therapeutic (dose) recommendations for 53 drugs. The recommendations are available nationwide during the process of drug prescribing and dispensing. We believe that the availability of the therapeutic (dose) recommendations during the process of therapeutic decision making represents an important step in the clinical use of pharmacogenetic information.

METHODS

A detailed description of the methods used for data collection, data assessment, and preparation of gene–drug monographs has previously been provided in this journal.[4] In brief, a list of genetic polymorphisms affecting pharmacokinetics and pharmacodynamics, including an overview of drug substrates, was compiled. For each drug, a systematic search of the literature was performed. Review articles and studies involving nonhuman subjects and *in vitro* experiments were excluded. Each gene–drug interaction was scored on two parameters. First, the quality of evidence for the gene–drug interaction was scored on a five-point scale ranging from 0 (lowest evidence) to 4 (highest evidence) (**Supplementary Table S1**). Population size was not included as a parameter for assessing the quality of evidence, but dose adjustments were calculated as the population size–weighted mean. Second, the clinical relevance of the potential gene–drug interaction was scored on a seven-point scale ranging from AA (lowest impact) to F (highest impact) (**Supplementary Table S2**). For each gene–drug interaction, a risk analysis containing a review of the selected articles, their assigned levels of evidence and clinical relevance, and a therapeutic (dose) recommendation were compiled. Recommendations included those related to dose adjustments as well as advice on therapeutic strategy (e.g., therapeutic drug monitoring, selection of alternative drugs, and warning for adverse drug events).

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/cpt

ACKNOWLEDGMENTS

No additional funding was received. We thank Jean Conemans and Ingeborg Wilting for their valuable contributions as former members of the Pharmacogenetics Working Group.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

1. Mallal, S. *et al*. HLA-B*5701 screening for hypersensitivity to abacavir. *N. Engl. J. Med.* **358**, 568–579 (2008).
2. Flockhart, D.A., Skaar, T., Berlin, D.S., Klein, T.E. & Nguyen, A.T. Clinically available pharmacogenomics tests. *Clin. Pharmacol. Ther.* **86**, 109–113 (2009).
3. US Food and Drug Administration. Table of Pharmacogenomic Biomarkers in Drug Labels <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm> Accessed 15 October 2010.
4. Swen, J.J. *et al*. Pharmacogenetics: from bench to byte. *Clin. Pharmacol. Ther.* **83**, 781–787 (2008).

5. van den Besselaar, A.M., van der Meer, F.J. & Gerrits-Drabbe, C.W. Therapeutic control of oral anticoagulant treatment in The Netherlands. *Am. J. Clin. Pathol.* **90**, 685–690 (1988).
6. van Schie, R.M. *et al*. Genotype-guided dosing of coumarin derivatives: the European pharmacogenetics of anticoagulant therapy (EU-PACT) trial design. *Pharmacogenomics* **10**, 1687–1695 (2009).
7. Kirchheiner, J. *et al*. CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages. *Acta Psychiatr. Scand.* **104**, 173–192 (2001).
8. Klein, T.E. *et al*. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N. Engl. J. Med.* **360**, 753–764 (2009).
9. Tan, G.M., Wu, E., Lam, Y.Y. & Yan, B.P. Role of warfarin pharmacogenetic testing in clinical practice. *Pharmacogenomics* **11**, 439–448 (2010).
10. D'Andrea, G. *et al*. A polymorphism in the VKORC1 gene is associated with an interindividual variability in the dose-anticoagulant effect of warfarin. *Blood* **105**, 645–649 (2005).
11. Li, T., Chang, C.Y., Jin, D.Y., Lin, P.J., Khvorova, A. & Stafford, D.W. Identification of the gene for vitamin K epoxide reductase. *Nature* **427**, 541–544 (2004).
12. Rieder, M.J. *et al*. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. *N. Engl. J. Med.* **352**, 2285–2293 (2005).
13. Rost, S. *et al*. Mutations in VKORC1 cause warfarin resistance and multiple coagulation factor deficiency type 2. *Nature* **427**, 537–541 (2004).
14. Vormfelde, S.V. *et al*. Relative impact of genotype and enzyme induction on the metabolic capacity of CYP2C9 in healthy volunteers. *Clin. Pharmacol. Ther.* **86**, 54–61 (2009).