



# Pharmacogenetic dose recommendations in clinical practice



Jesse J Swen, PharmD; Professor Henk-Jan Guchelaar, PharmD, PhD

## Introduction

Pharmacogenetics (PGt) is the study of variations in DNA sequence related to drug response. The ultimate goal of PGt is to predict and thereby improve the drug response in the individual patient. After the completion of the Human Genome Project, it was often predicted that PGt would be one of the first clinical applications of the new knowledge. Indeed, the number of publications in this field listed on PubMed increased steadily until levelling out in 2009 at 1,100–1,200 publications per year.

## Support for clinical use

However, the clinical use of PGt testing has lagged considerably behind [1]. Many factors may have hindered the uptake of pharmacogenetic testing into clinical practice. The main reason is the limited scientific evidence to show that PGt testing leads to improved clinical outcomes [1, 2]. Moreover, for most PGt 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 PGt test results.

Guidelines that link the result of a PGt test to therapeutic recommendations might help to overcome these problems, but they are not readily available [3]. Therefore, the Royal Dutch Association for the Advancement of Pharmacy established a Pharmacogenetics Working Group (PWG) in 2005 [4]. Clinical pharmacists, physicians, clinical pharmacologists, clinical chemists, epidemiologists and toxicologists are represented in this 15-member multidisciplinary working group.

The objective of the PWG is to develop PGt-based therapeutic (dose) recommendations based on systematic literature reviews and to assist drug prescribers as well as pharmacists by incorporating the recommendations into computerised systems for drug prescription and automated medication surveillance. The recommendations do not indicate patients who are eligible for genotyping,

but merely aim to optimise drug use in the small but ever-increasing group of patients whose genotypes are known.

The recommendations issued since October 2006 are available through most automated drug systems in The Netherlands making them accessible to physicians and pharmacists. To date, therapeutic (dose) recommendations for 163 genotype/phenotype-drug combinations comprising 53 drugs and 11 genes have been written [5]. The drugs have been associated with genes coding for CYP2D6 (n = 25), CYP2C19 (n = 11), CYP2C9 (n = 7), thiopurine-S-methyltransferase (TPMT) (n = 3), dihydropyrimidine-dehydrogenase (n = 3), vitamin-K-epoxide-reductase (n = 2), uridine-diphosphateglucuronosyltransferase-1A1, HLA-B44, HLA-B\*5701, CYP3A5, and Factor V Leiden (all n = 1).

## Some recommendations in detail

Therapeutic (dose) recommendations have been formulated for 39 (73.6%) of the drugs. Recommendations for mercaptopurine and tamoxifen are discussed in more detail, see Table 1. TPMT catalyses the S-

Table 1: Examples of guidelines provided by the PWG of the Royal Dutch Association for the Advancement of Pharmacy\*

Drug (gene)	Phenotype	Level of evidence	Clinical relevance	Therapeutic (dose) recommendation
Azathioprine/ Mercaptopurine (TPMT)	PM	4	F	Select alternative drug or reduce dose by 90%. Increase dose in response to haematologic monitoring and efficacy
	IM	4	E	Select alternative drug or reduce dose by 50%. Increase dose in response to haematologic monitoring and efficacy
Tamoxifen (CYP2D6)	PM	4	E	Increased risk of relapse of breast cancer. Consider aromatase inhibitor for postmenopausal women
	IM	4	E	Increased risk of relapse of breast cancer. Avoid concomitant use of CYP2D6 inhibitors. Consider aromatase inhibitor for postmenopausal women
	UM	4	A	None required

\* Adapted from [4, 5]. Gene–drug interactions were scored on two parameters. First, the quality of evidence for the gene–drug interaction was scored on a 5-point scale ranging from 0 (lowest evidence) to 4 (highest evidence). Secondly, the clinical relevance of the potential gene–drug interaction was scored on a 7-point scale ranging from AA (lowest impact) to F (highest impact). PM: poor metaboliser; IM: intermediate metaboliser; UM: ultra-extensive metaboliser; PWG: Pharmacogenetics Working Group.

methylation of the thiopurine drugs 6-mercaptopurine and its prodrug azathioprine to inactive metabolites. The TPMT \*2, \*3A, \*3B, and \*3C alleles account for > 90% of inactivating alleles. At conventional thiopurine doses, homozygous (poor metabolisers, PMs) and heterozygous (intermediate metabolisers, IMs) carriers of these alleles are at increased risk of severe myelosuppression. The PWG's recommendation is to select an alternative drug for IMs and PMs. If this is not possible, the dose should be reduced by 50% and 90%, respectively.

The selective oestrogen receptor modulator tamoxifen is used in the treatment and prevention of oestrogen receptor-positive breast cancers. Tamoxifen undergoes extensive metabolism and is considered a 'prodrug'. *CYP3A4* and *CYP3A5* are the major enzymes responsible for N-demethylation, whereas 4-hydroxylation is predominantly mediated by *CYP2D6*. Endoxifen, one of

the metabolites, is 30 to 100 times more potent than tamoxifen and is considered the most active metabolite. Endoxifen formation is dependent on *CYP2D6* activity and hence genetic variation in *CYP2D6* results in variation in endoxifen plasma concentrations and response to tamoxifen. The PWG's recommendation warns of an increased risk of relapse of breast cancer in PMs and IMs and advises considering an aromatase inhibitor instead of tamoxifen for postmenopausal women. For IMs, concomitant use of *CYP2D6* inhibitors should also be avoided.

### Conclusion

Bridging the gap from research to bedside seems within reach in the field of PGt. Many challenges remain but the availability of PGt-based therapeutic (dose) recommendations represents an important step towards the application of PGt information in daily patient care.

### Authors

Jesse J Swen, PharmD  
Professor Henk-Jan Guchelaar, PharmD, PhD  
Department of Clinical Pharmacy and Toxicology  
Leiden University Medical Center  
PO Box 9600  
NL-2300 RC Leiden, The Netherlands

### References

1. Swen JJ, Huizinga TW, Gelderblom H, et al. Translating pharmacogenomics: challenges on the road to the clinic. *PLoS Med.* 2007;4(8):e209.
2. Roden DM, Altman RB, Benowitz NL, et al. Pharmacogenomics: challenges and opportunities. *Ann Intern Med.* 2006;145(10):749-57.
3. Amstutz U, Carleton BC. Pharmacogenetic testing: time for clinical practice guidelines. *Clin Pharmacol Ther.* 2011;89(6):924-7.
4. Swen JJ, Wilting I, de Goede AL, et al. Pharmacogenetics: from bench to byte. *Clin Pharmacol Ther.* 2008;83(5):781-7.
5. Swen JJ, Nijenhuis M, de BA, et al. Pharmacogenetics: from bench to byte - an update of guidelines. *Clin Pharmacol Ther.* 2011;89(5):662-73.

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## Bar codes on all unit doses by 2015



Ronald van Lienden, MSc

Rinske Pauw, PharmD

**I**n March 2010, we organised a brainstorming conference with 50 Dutch hospital pharmacists to investigate major logistical problems in hospital pharmacies.

The most important subject to emerge was the lack of bar codes on unit doses (BUDs). A unit dose is the smallest dosage that can be administered to a patient and it must be identifiable via a scannable datamatrix bar code to validate the right drug to the right patient, in the right dose, at the right time and by the right route. Currently, 50% of medicines lack a BUD. This 50% mainly represents the more risky medicines, such as parenterally administered drugs and cytostatics.

Most attendees were convinced that adoption of BUDs would significantly increase patient safety. Besides improving patient safety, smart use of the scanned data leads to more efficient supply chains and hence to reduced distribution costs: reduced stock levels, less handling and spillage. The supply chain can be synchronised by sharing detailed patient data within the chain,

e.g. point of sale information with producers, wholesalers and packaging specialists.

Together with the Dutch Association of Hospital Pharmacists (NVZA) we arranged a follow-up symposium on BUDs. Stakeholders in the hospital pharmacy distribution chain were invited to share their thoughts on achieving 100% BUDs (hospital pharmacists, wholesalers, producers of generics and specialties, inspection, GS1 and packaging specialists). The NVZA presented the Dutch guidelines on BUDs, starting a dialogue with the participants.

One of the central themes of this discussion was the European context. At this moment, every European country has its own legislation about information on medicines. This results in country-specific packaging layouts for each medicine. There is a strong need for a common European standard on bar code identification on the various packaging levels.

During the symposium, the attendees came up with a list of 'quick wins'. Some goals

have already been achieved, such as identifying the 25 most risky medicines to be bar-coded in 2011, inventory pooling between wholesalers, a central website dealing with bar code problems and scanning issues. Manufacturers have strongly increased the number of bar-coded medicines in the last few months and are starting to adopt the GS1 bar code standard. Last but not least, hospital pharmacies have incorporated the NVZA guidelines on BUDs into their purchasing conditions.

We will continue our attempts to achieve 100% BUDs by 2015.

### Authors

Ronald van Lienden, MSc Logistics, MBA  
Director, Good to Great Consulting BV  
Hoogstedelaan 40  
NL-6812 DN Arnhem, The Netherlands

Rinske Pauw, PharmD  
Department of Hospital Pharmacy  
Midden-Brabant  
PO Box 90107  
NL-5000 LA Tilburg, The Netherlands