

**Erasmus MC**

Universitair Medisch Centrum Rotterdam



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*European Clinical Chemist*

**Clinical Applications of PGx**

**AACC – Washington 2007, February 26-27**



**Reporting  
PGX results**

Pharmacogenetics Core Laboratory

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# PGX-test report

Based on Swiss guidelines for reporting genetic tests

- Who did you test
  - Why did you test
  - How did you test
- 
- What are the laboratory (raw) results
  - What is the interpretation
  - What is the specific advice
- 
- What are the reference values (for specific groups)
  - What are the limitations of the test

Should be complete, AND easy to understand

Should fit one A4 paper

# PGX-report

Based on Swiss guidelines for reporting genetic tests

NAME  
DEPARTMENT  
HOSPITAL  
ADDRESS  
CITY

Doorkiesnummer 0 10-463 3 119 463 3302  
Faxnummer 010-436 7894  
Kamernummer L-184  
Email r.vanschak@erasmusmc.nl  
Onze referentie M01234  
Datum 1-1-2007

Erasmus MC



## Patient ID

Patient: Name, initials Requesting physician: Dr. A. Ate  
Date of birth: 01-01-2001 Department: ABC  
Your ref: 1234567 Hospital: XYZ  
Patient ID.: 1234567 Blood drawn on: 01-01-2001

Postadres  
Postbus 2040  
3000 CA Rotterdam Postbus 2040  
Bezoekadres  
Erasmusplein 1230  
3015 C E Rotterdam Dr

Bereikbaar met tram 8,  
bus 44 of metro Calandlijn  
(halte Dijkzigt).

KLINISCH CHEMIE

Afdelingshoofd  
Prof dr. J. Lindemans

Coördinator  
Dr. F. de Jonge  
Dr. A.W. van Toorenbergen  
Dr. R.H.N. van Schak

Sophia Kinderziekenhuis  
Dr. Y.B. de Fijze

Deugden Hoed Kliniek  
Dr. J.G. Bronsht

APOTHEEK

Dr. T. van Gelder  
Dr. R.A.A. Mathôt

V2007-07

Requested test TPMT genotyping  
Problem/request: screening TPMT deficiency  
Material: EDTA blood  
Analysis for: 238G>C, 460G>A, 719A>G (TPMT\*2, \*3A, \*3B, \*3C)  
Results: 238GG, 460GG, 719AA  
Conclusion: TPMT\*1/\*1  
Interpretation: Predicts normal metabolism.  
Advice: Base on genotype, no dose adjustments recommended.

Background interpretation: risk on side effects a priori is 10% (6-mercaptopurine); after testing 7% (normal), 35% (intermediary) and 100% (slow metabolizer). For azathioprine a priori risk 3.2%; after testing 2.3% (normal), 6.4% (intermediary) and 100% (slow metabolizer). Suggested dose slow metabolizers: 5-10% of standard (Levens ME 2004 TDM 26:186-91; Winter J et al 2004 Al Pharmaco Ther. 20:503-99).

Background of the test: duplicate test (PCR-RFLP and TaqMan) on the most prevalent gene polymorphisms causing low TPMT activity: TPMT\*2 (238G>C), \*3A (460G>A, 719A>G), \*3B (460G>A) and \*3C (719A>G). Detects >95% of genetically caused slow metabolizers. The test cannot differentiate between \*3B/\*3C (slow) and \*1/\*3A (intermediary); \*1/\*3A is then reported because chances on this are 18.000x more likely than for \*3B/\*3C. Allel frequencies: Caucasians 0.5% (\*2), 4.5% (\*3A), <0.05% (\*3B), 0.5% (\*3C); Africans 0% (\*2), 0% (\*3A), 0% (\*3B), 7.6% (\*3C); Asians 0% (\*2), 0% (\*3A), 0% (\*3B), 2.3% (\*3C).

Sincerely yours,

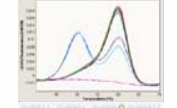
Dr. R.H.N. van Schak Clinical Chemist  
Dr. P.W. Schenk Clinical Chemist  
Dr. T. van Gelder Clinical Pharmacologist  
Dr. R.A.A. Mathôt Hospital Pharmacist

## Request Results Interpretation Advice

## Background interpretation

## Background of the test

## Authorisation



Cytochromes P450, Drugs, and Diseases



## Requested test TPMT genotyping

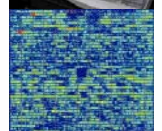
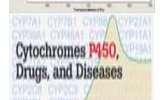
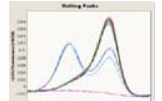
Problem/request: screening TPMT deficiency  
 Material: EDTA blood  
 Analysis for: 238G>C, 460G>A, 719A>G (TPMT\*2, \*3A, \*3B, \*3C)

Results: 238GG, 460GG, 719AA  
 Conclusion: TPMT\*1/\*1  
 Interpretation: **Predicts normal metabolism.**  
 Advice: Base on genotype, no dose adjustments recommended.

**Background interpretation:** risk on side effects a priori is 10% (6-mercaptopurine); after testing 7% (normal), 35% (intermediar) and 100% (slow metabolizer). For azathioprine a priori risk 3.2%; after testing 2.3% (normal), 6.4% (intermediary) and 100% (slow metabolizer). Suggested dose slow metabolizers: 5-10% of standard (Evans WE 2004 TDM 26:186-91; Winter J et al 2004 AI Pharmacol Ther 20:593-99).

**Background of the test:** duplicate test (PCR-RFLP and TaqMan) on the most prevalent genetic polymorphisms causing low TPMT activity: TPMT\*2 (238G>C), \*3A (460G>A, 719A>G), \*3B (460G>A) and \*3C (719A>G). Detects >95% of genetically casued slow metabolizers. The test cannot differentiate between \*3B/\*3C (slow) and \*1/\*3A (intermediar): \*1/\*3A is then reported because chances on this are 18.000x more likely than for \*3B/\*3C.

**Allelfrequencies:** Caucasians 0.5% (\*2), 4.5% (\*3A), <0.05% (\*3B), 0.5% (\*3C); Africans 0% (\*2), 0% (\*3A), 0% (\*3B), 7.6% (\*3C); Asians: 0% (\*2), 0% (\*3A), 0% (\*3B), 2.3% (\*3C).



## Requested test CYP2D6 genotyping (limited set)

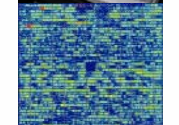
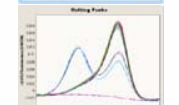
Problem/request: Side effects on Strattera caused by CYP2D6 PM status?  
 Material: EDTA blood  
 Analyses for: CYP2D6\*3, \*4, \*5, \*6 and gene duplication

Conclusion/interpretation: CYP2D6\*1/\*1 (2 active alleles) **normal metabolism**  
 Gene duplication negative

Answer/advice: We did not find evidence for a genetic cause for the reported side effects on Strattera.

**Background interpretation:** 5-10% of Caucasians is a CYP2D6 slow metabolizer (PM), and 2-3% is an ultra-rapid metabolizer (UM). PMs and UMs potentially need dose adjustments. Intermediate metabolizers (CYP2D6: 1 inactive + 1 decreased activity, or 2 decreased activity alleles) need possibly a minor dose adjustment. With 1 active and 1 inactive CYP2D6 allele, a normal metabolism is expected, although use of CYP2D6 co-medication side effects may occur more frequently compared to patients with two active alleles.. Please note that the amount of dose reduction very much depends on the drug used. Please contact your pharmacist or clinical pharmacologist.

**Background of the test:** XL-PCR, PCR-RFLP and TaqMan (duplicate analysis) on \*3 (249delA), \*4 (1846G>A), \*5 (deletion) and \*6 (1707delT): allelfrequencies in Caucasians 2%, 20%, 5%, 1%, resp. and gene duplication (2-3% of North Europeans). The test detectst 95% of genetic slow metabolizers in the Caucasian population. This percentage may differ for other ethnic groups (Gaedigk et al 1999 Pharmacogenetics 9, 269-82).



# Additional Info CYP2D6 - limited set (1)

## Clinical validity

Interindividual variations in drug metabolism affect the expected relationship between dose and bloodconcentration, and thereby clinical effect. Genetic polymorphisms in CYP2D6 leading to profound changes in CYP2D6 activity affect metabolic clearance of drugs, potentially resulting in adverse drug effects in poor metabolizers or suboptimal treatment in ultra rapid metabolizers when prescribing normal dosages. Adjusting dosages based on CYP2D6 genotype is recommended in these cases.

**Tabel 1. Clinical relevant CYP2D6 substrates**

Beta blockers	Antidepressives	Antipsychotics	Other
Carvedilol	Amityptiline	Haloperidol	Aripiprazol
Metoprolol	Clomipramine	Risperidon	Atomoxetine
Propafenon	Desipramine	Thioridazine	Codeïne
Timolol	Fluoxetine		Dextromethorphan
	Fluvoxamine		Flecainide
	Imipramine		Metoclopramide
	Paroxetine		Mexiletine
			Ondansetron
			Oxycodon
			Tamoxifen
			Tramadol
			Venlafaxine

For additional substrates, also see: <http://medicine.iupui.edu/flockhart/table.htm>

