

Erasmus MC

Universitair Medisch Centrum Rotterdam



Ron van Schaik

European Clinical Chemist

Clinical Applications of PGx

AACC – Washington 2007, February 26-27



**Reporting
PGX results**

Pharmacogenetics Core Laboratory

Dept. Clinical Chemistry

Erasmus MC Rotterdam

The Netherlands

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www.erasmusmc.nl/pharmacogenetics

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,

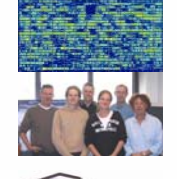
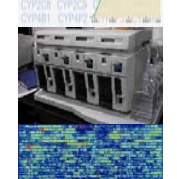
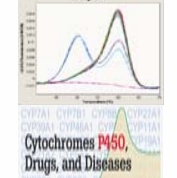
Dr. R.H.N. van Schak Clinical Chemist
Dr. P.W. Schenk Clinical Chemist
Dr. T. van Gelder Clinical Pharmacologist
Dr. R.A.A. Mathôt Hospital Pharmacist

Request Results Interpretation Advice

Background interpretation

Background of the test

Authorisation



Requested test TPMT genotyping

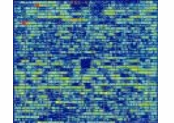
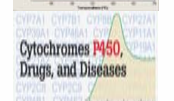
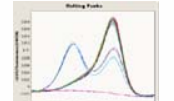
Problem/request: screening TPMT deficiency
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Results: 238GG, 460GG, 719AA
 Conclusion: TPMT*1/*1
 Interpretation: **Predicts normal metabolism.**
 Advice: Base on genotype, no dose adjustments recommended.

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Allelfrequenties: 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)

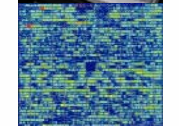
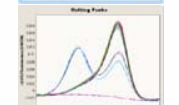
Problem/request: Side effects on Strattera caused by CYP2D6 PM status?
 Material: EDTA blood
 Analyses for: CYP2D6*3, *4, *5, *6 and gene duplication

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)

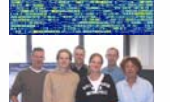
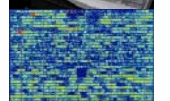
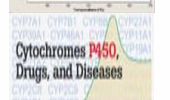
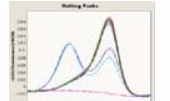
Clinical validity

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 substates, also see: <http://medicine.iupui.edu/flockhart/table.htm>



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