Application of PGx in PK in Medical Practice: How Does PGx Inform Decisions?

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Aztreonam SmPC

Estimated creatinine clearance (ml/min)	Maintenance dose
10-30	Half the initial dose
Less than 10	Quarter of the initial dose

The normal dose interval should not be altered.

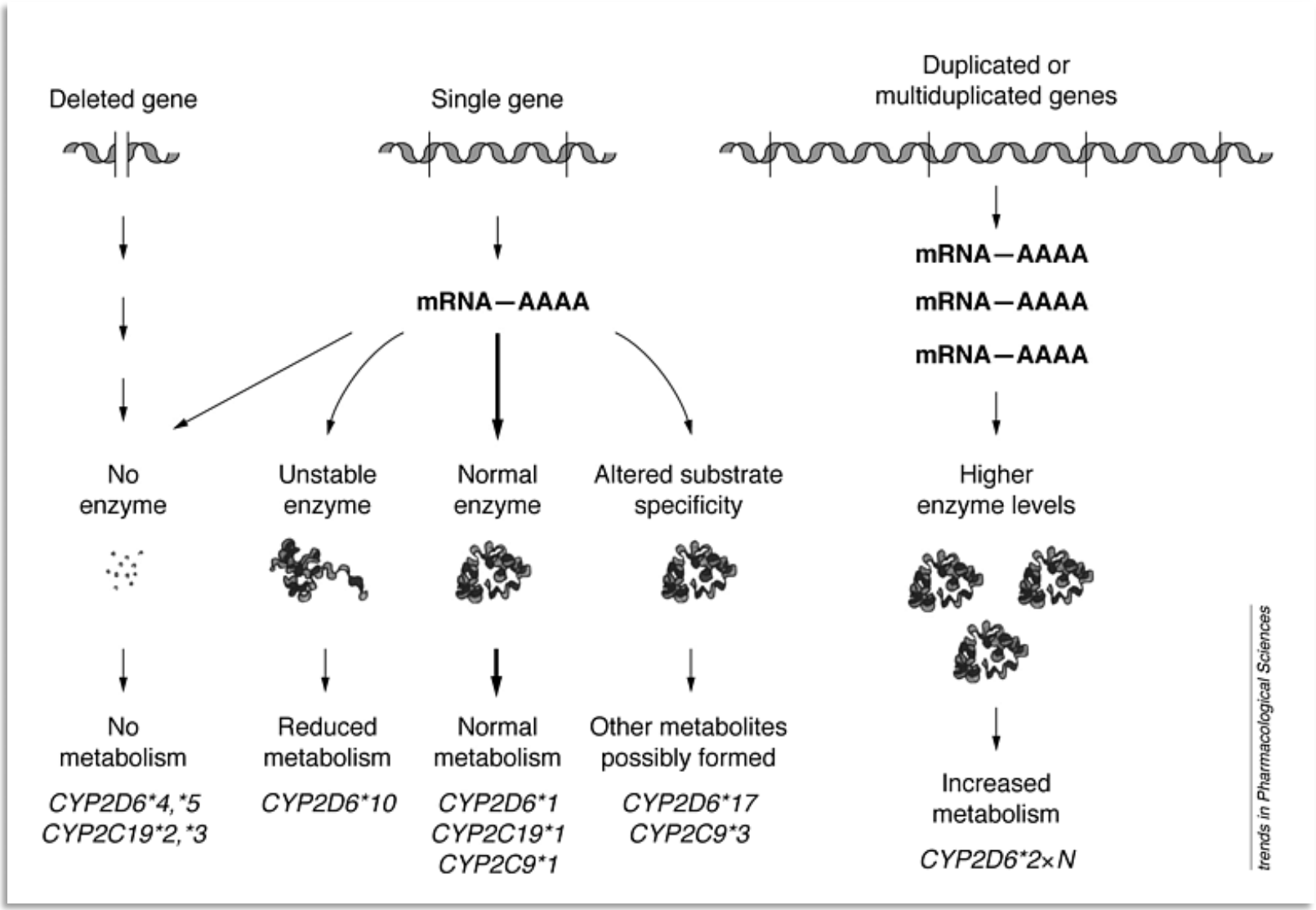
In patients on haemodialysis, a supplementary one eighth of the initial dose should be given after each dialysis

SmPC Changes Based on Renal or Hepatic Impairment

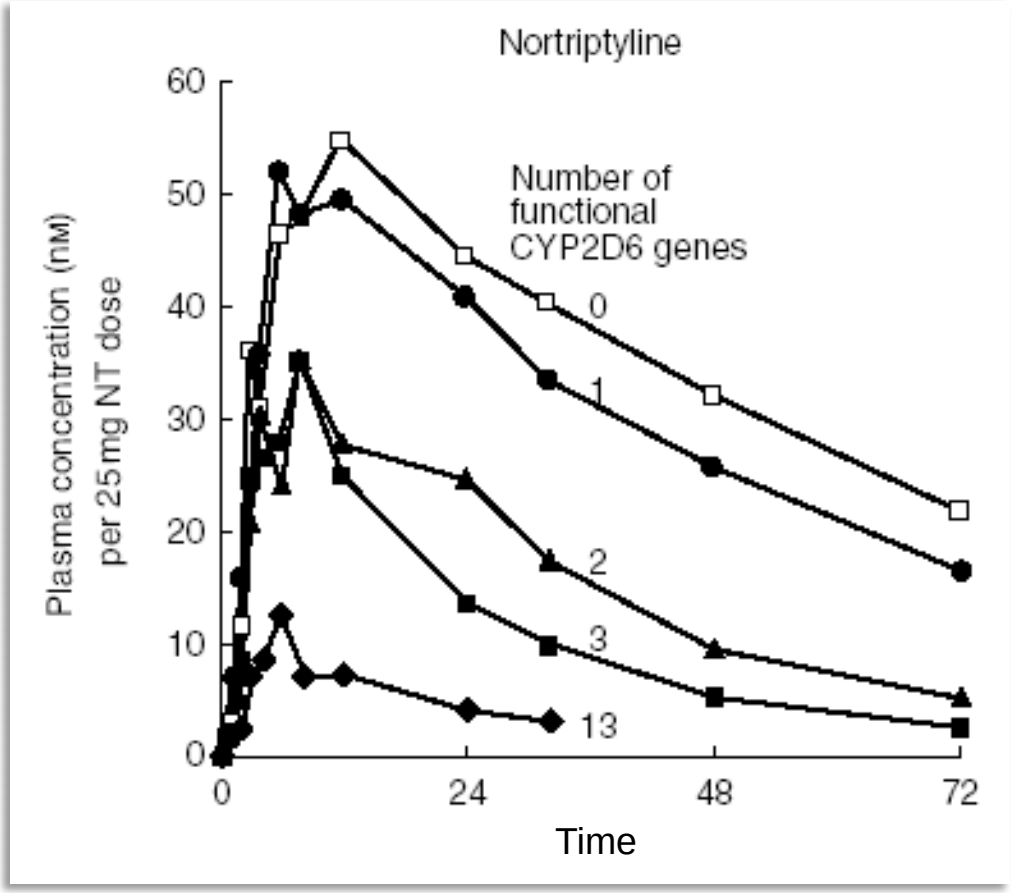
- Many drug labels have been changed based on renal or hepatic impairment
- Specific dose recommendations are provided
- These are based on PK studies
- These PK studies are rarely validated by clinical outcome

- For PGx determined changes in pharmacokinetics, the standard necessary for dose alteration is more stringent

CYP2D6 Polymorphisms



CYP2D6 Polymorphisms and Nortriptyline Metabolism



Many antidepressants (tricyclic antidepressants, including nortriptyline, selective serotonin re-uptake inhibitors and others) are metabolised by the hepatic cytochrome P450 isoenzyme P450IID6. Three to ten per cent of the population have reduced isoenzyme activity ('poor metabolisers') and may have higher than expected plasma concentrations at usual doses.

Dalen et al, 1998

Report on CYP2D6 in Antidepressant Drug Response

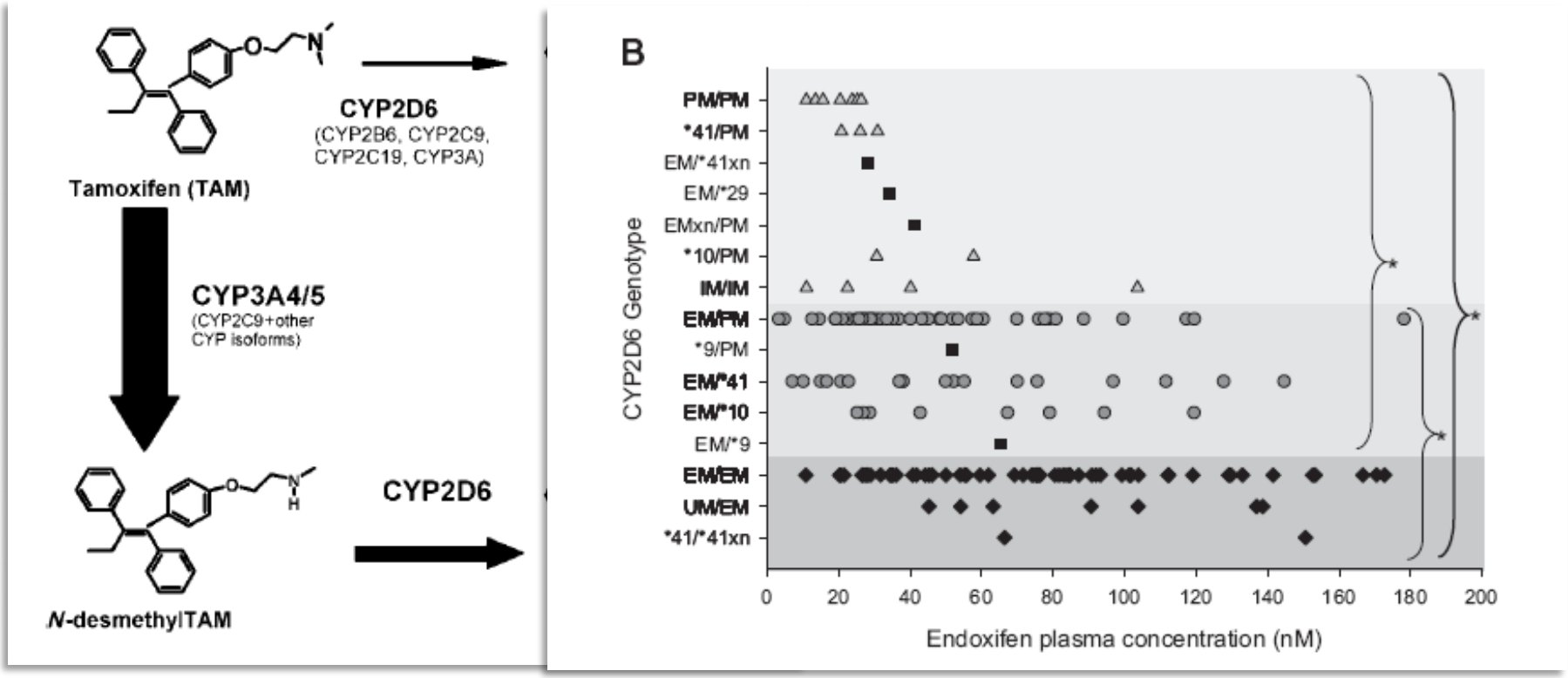
Evidence Report/Technology Assessment
Number 146

Testing for Cytochrome P450 Polymorphisms in Adults With Non-Psychotic Depression Treated With Selective Serotonin Reuptake Inhibitors (SSRIs)

Conclusions: There is a paucity of good-quality data addressing the questions of whether testing for CYP450 polymorphisms in adults entering SSRI treatment for non-psychotic depression leads to improvement in outcomes, or whether testing results are useful in medical, personal, or public health decisionmaking.

http://www.ahrq.gov/downloads/pub/evidence/pdf/cyp450/cyp450.pdf

Tamoxifen and CYP2D6



Endoxifen – active metabolite

Borges et al, CPT, 2006

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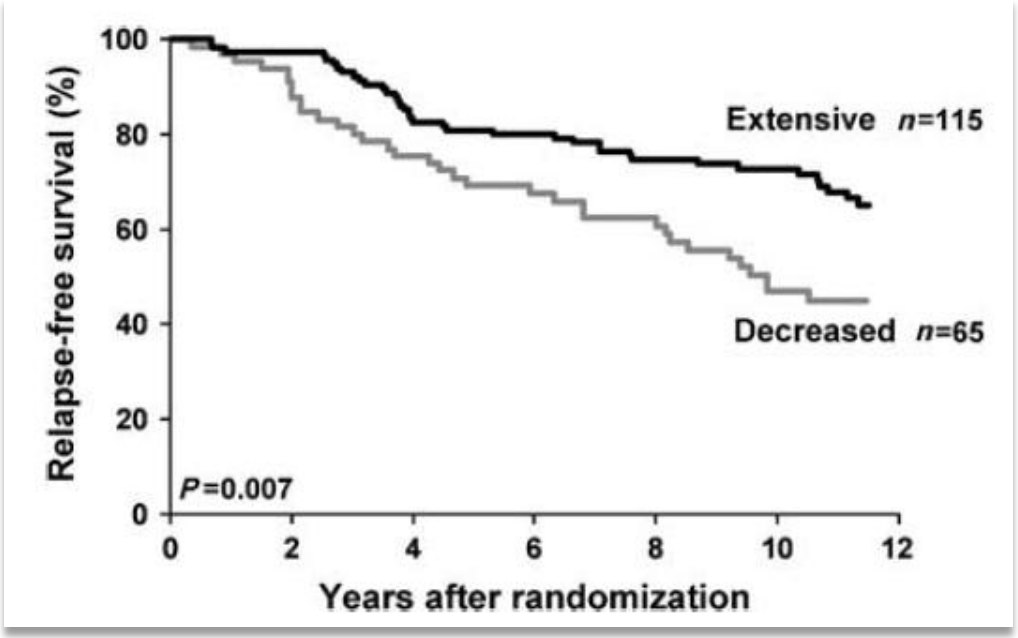
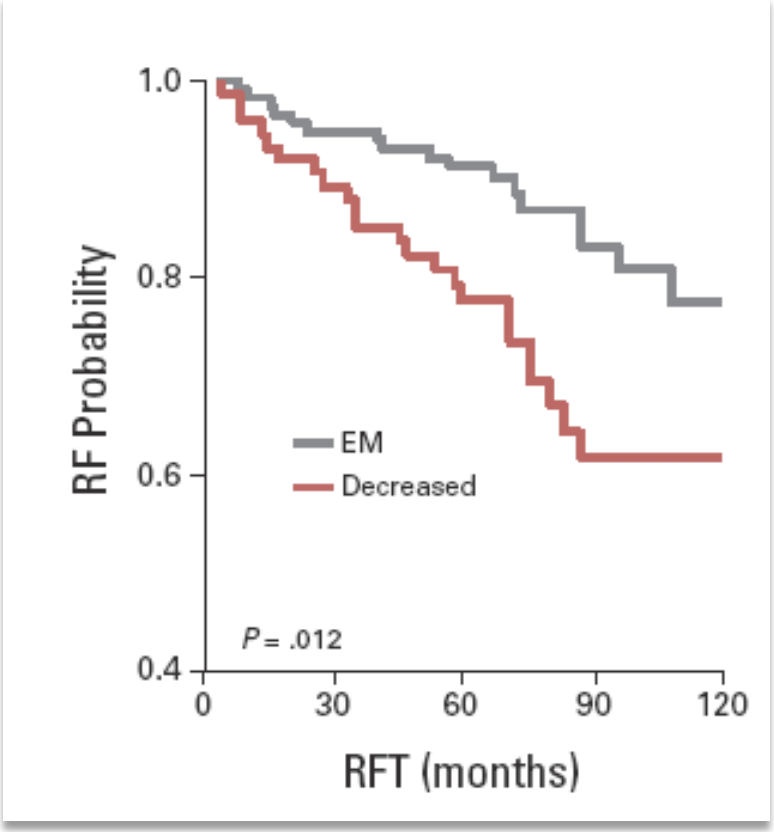
CYP2D6 Genotype and Tamoxifen Efficacy



Goetz, CPT, 2008



Schroth et al, JCO, 2007

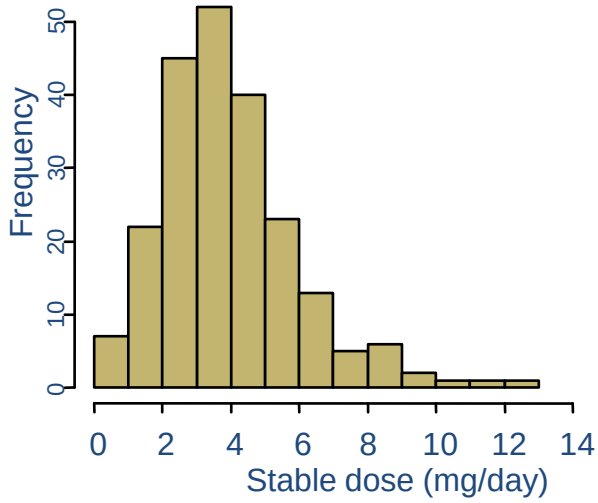
Blue Cross and Blue Shield Association (2008)

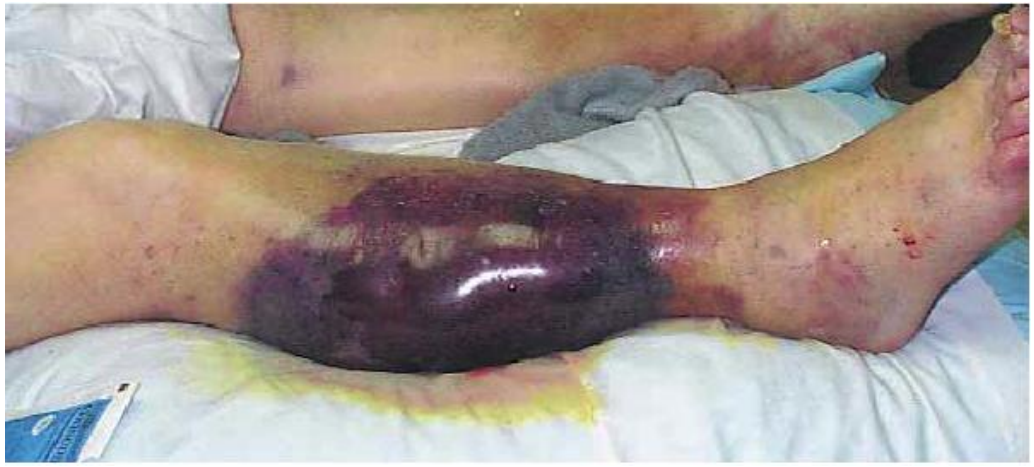
"insufficient evidence to permit conclusions regarding the use of CYP2D6 genotyping for directing endocrine therapy regimen selection for women at high risk for or with breast cancer"

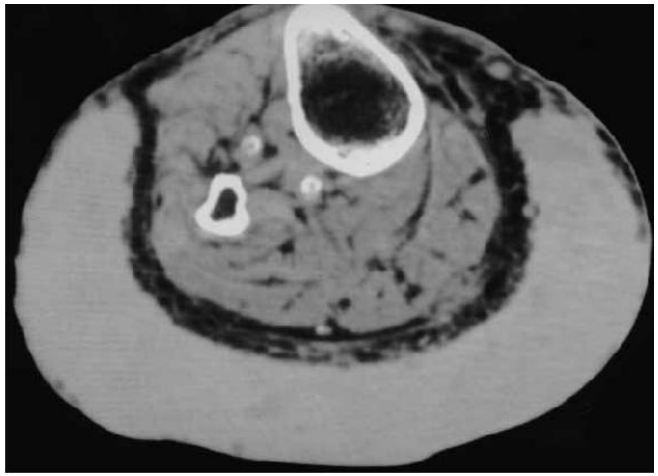
http://www.bcbs.com/blueresources/tec/vols/23/cyp2d6-pharmacogenomics-of.html

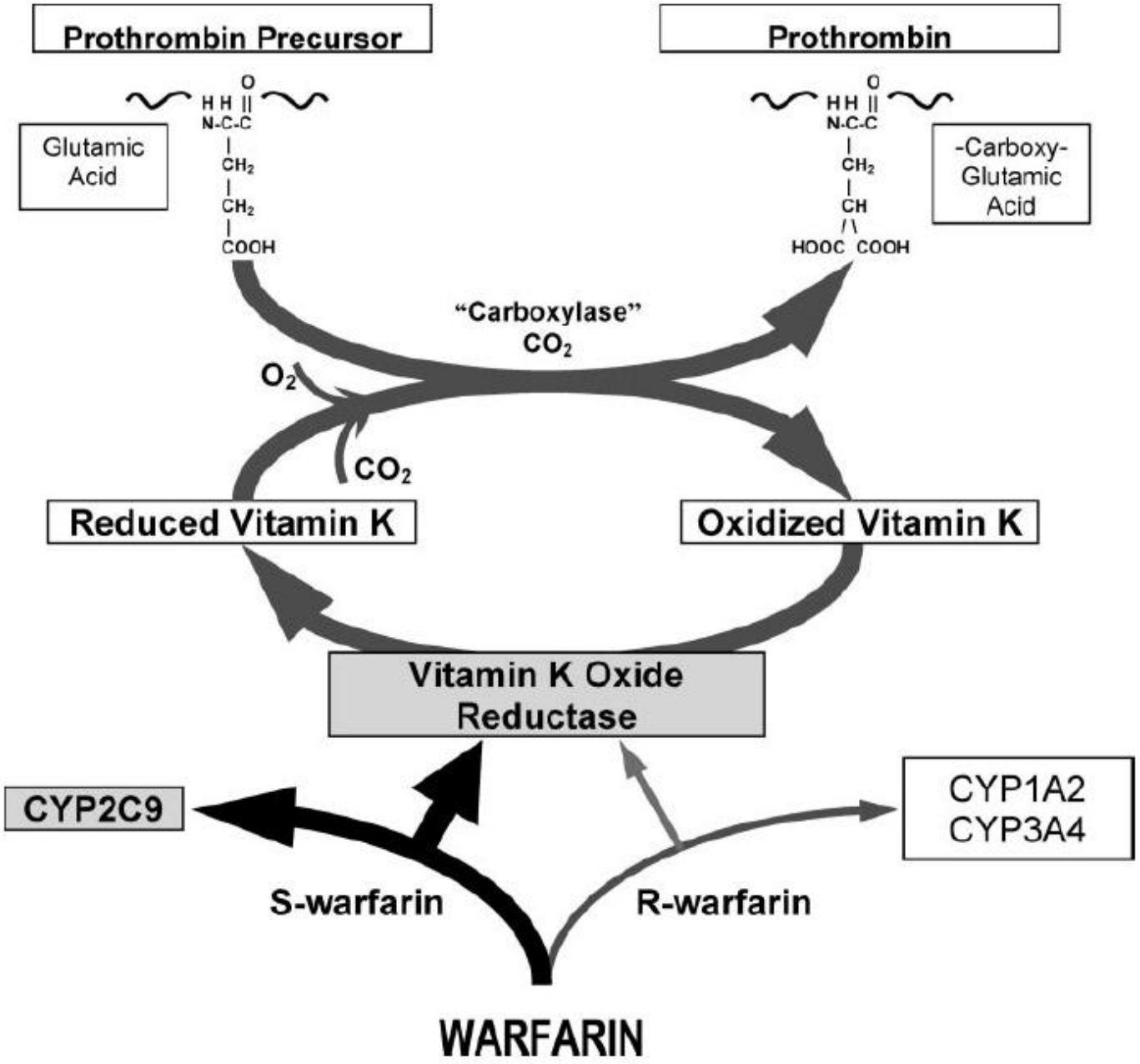
Warfarin

- 600,000 users in the UK (1% of the UK population)
- 6% over 80 years on warfarin
- Within INR range only 50% of time








Prothrombin Precursor
Prothrombin
Glutamic Acid
-Carboxy-Glutamic Acid
"Carboxylase"
CO_2
O_2
CO_2
Reduced Vitamin K
Oxidized Vitamin K
Vitamin K Oxide Reductase
CYP2C9
CYP1A2
CYP3A4
S-warfarin
R-warfarin
WARFARIN

CYP2C9 Allelic Variants

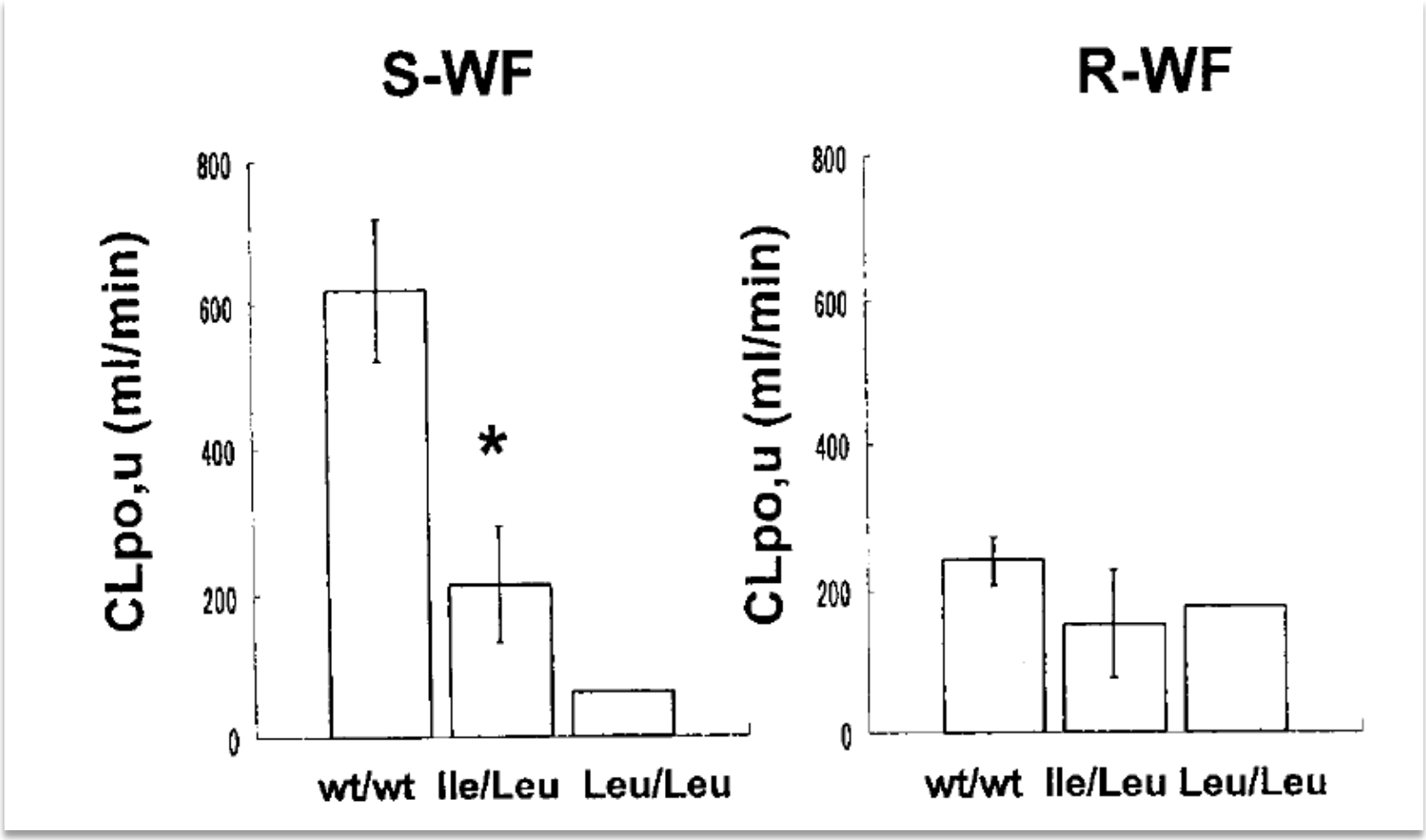
	Japanese patients (n = 90)	*Caucasian patients (n = 47)*
*CYP2C9*1* (wild type)	0.967	0.723†
*CYP2C9*2* (exon 3)	0	0.223†
*CYP2C9*3* (exon 7)	0.033	0.053
*CYP2C9*4* (exon 7)	0	0
*CYP2C9*5* (exon 7)	0	0
T/C transition (intron 2)	0.006	0.175†

According to the recommendation of the Human Cytochrome P450 Allele Nomenclature Committee,[14] we refer *CYP2C9*1*, *CYP2C9*2*, *CYP2C9*3*, *CYP2C9*4*, and *CYP2C9*5* to the Arg144/Ile359, Cys144/Ile359, Arg144/Leu359, Arg144/Thr359, and Asp/Glu360 alleles, respectively. The *T/C* transition allele is located 73 base pairs downstream from exon 2.

†$P < .01$, Japanese versus Caucasian patients.

Takahashi et al, 2003

Allelic Variants of CYP2C9 and Warfarin Clearance



Takahashi et al, 1998

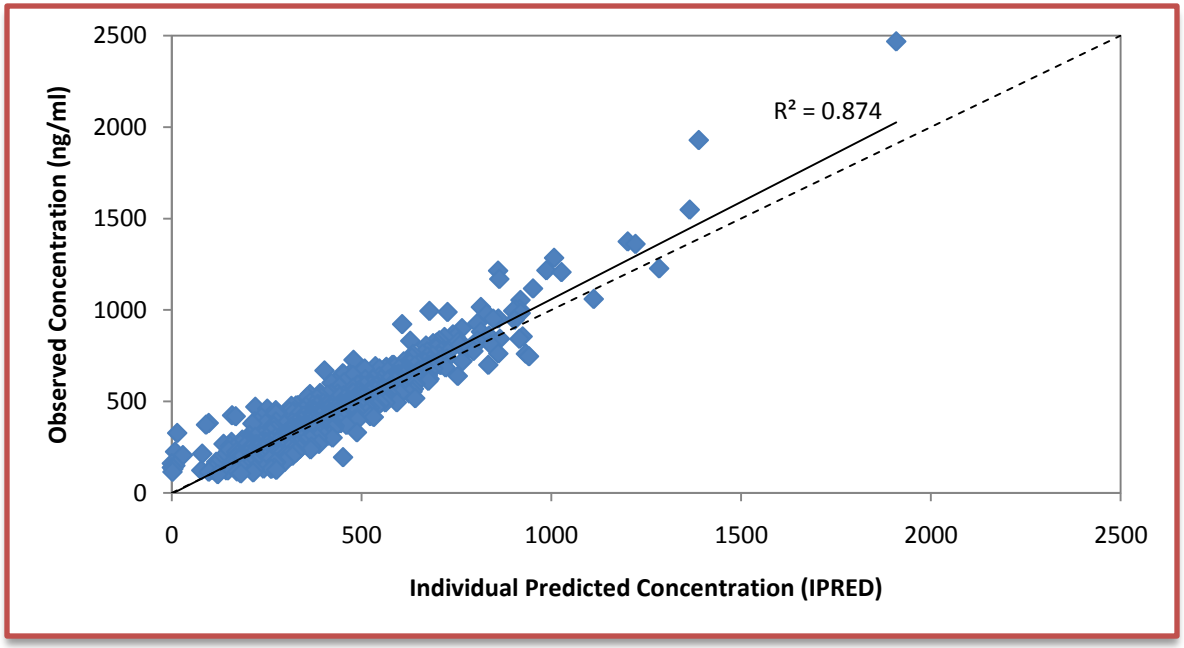
Population Pharmacokinetic Model

$$CL_{ji} = 0.331.\ \theta_{CYP2C9}.\ \theta_{Gender}.\ \theta_{COMED}.\ (wt/70)^{0.522}.e^{(BSVCL+BOVCL)}$$

$F_{CYP2C9} = 1$ *1*1
$F_{CYP2C9} = 0.759$ *1*2, *2*2
$F_{CYP2C9} = 0.525$ *1*3, *2*3
$F_{CYP2C9} = 0.182$ *3*3
$F_{CYP2C9} = 0.798$ Unknown

$\theta_{Gender} = 1$ Female
$\theta_{Gender} = 1.140$ Male

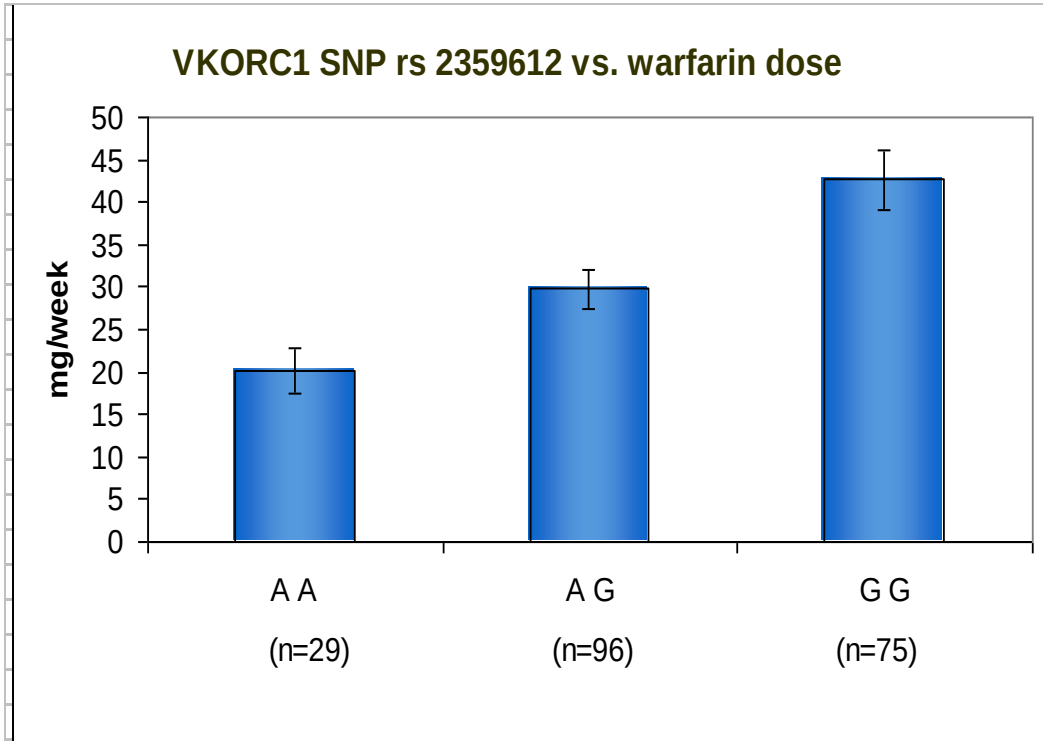
$\theta_{COMED} = 1$ (No co-medication)
$\theta_{COMED} = 0.956$ (CYP450 Inhibitor)
$\theta_{COMED} = 1.260$ (CYP450 Inducer)
$\theta_{COMED} = 0.725$ (Amiodarone)



CYP2C9 Polymorphisms and Warfarin Dose Requirements

CYP2C9 genotype	Number of patients	Aggregate mean dose (mg)
*CYP2C9*1*1*	639	5.5
*CYP2C9*1*2*	207	4.5
*CYP2C9*1*3*	109	3.4
*CYP2C9*2*2*	7	3.6
*CYP2C9*2*3*	11	2.7
*CYP2C9*3*3*	5	1.6

Genetic and Environmental Factors and Dose Requirements of Warfarin



Independent effects of VKORC1 and CYP2C9:

VKORC1:	$p<0.0001$, $r^2 = 0.29$
CYP2C9:	$p=0.0003$, $r^2 = 0.11$
Age:	$p<0.0001$, $r^2 = 0.10$
Body weight:	$p=0.0018$, $r^2 = 0.05$

55%

Wadelius et al. 2005

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Pharmacology and Management of the Vitamin K Antagonists*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

Jack Ansell, MD; Jack Hirsh, MD; Elaine Hylek, MD, MPH; Alan Jacobson, MD; Mark Crowther, MD; and Gualtiero Palareti, MD

(CHEST 2008; 133:160S–198S)

"… we suggest against pharmacogenetic-based dosing until randomized data indicate that it is beneficial (Grade 2C).."

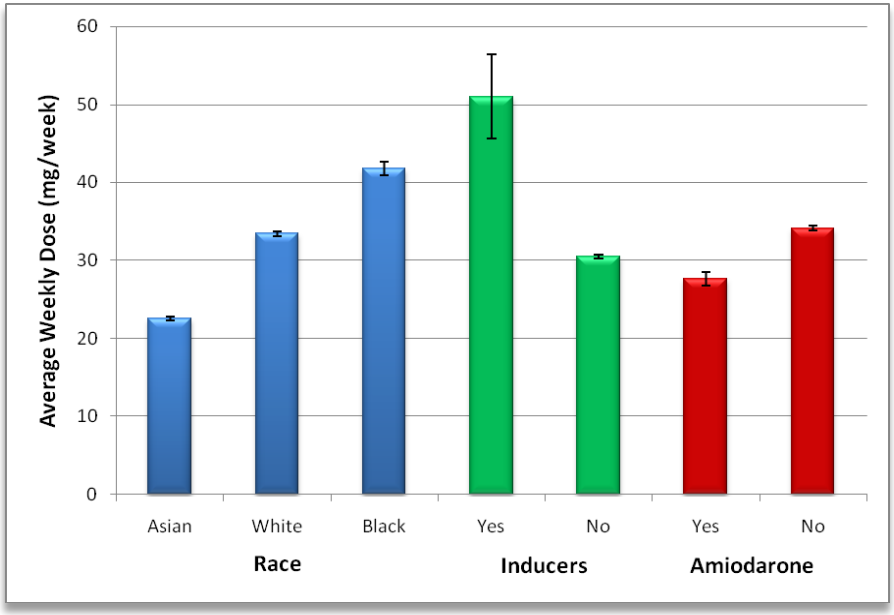
The Ideal Warfarin Dosing Algorithm

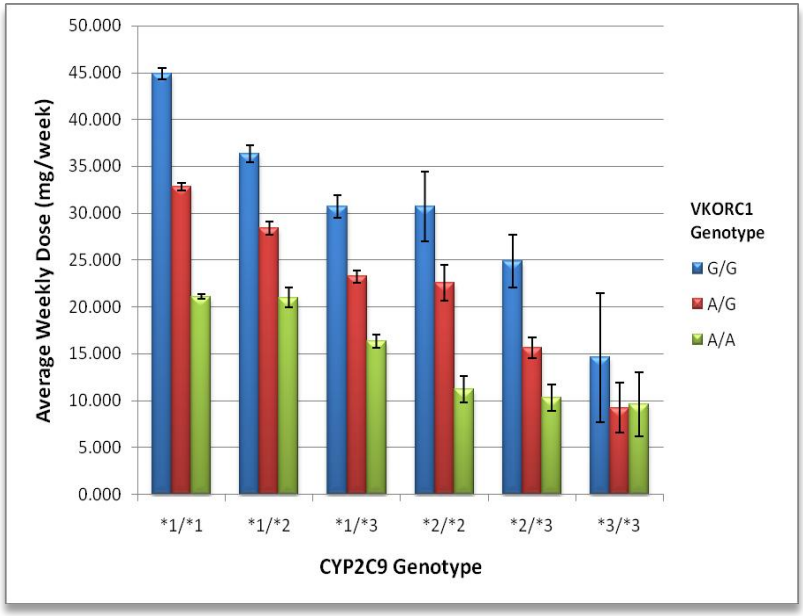
- Should predict both loading and maintenance doses
- Should allow the patient to reach therapeutic INR as soon as possible, without over-shooting (or being under-anticoagulated)
- Patients should reach the stable dose quickly and effectively
- Stable dose should provide relative stability within therapeutic INR range
- Should be simple to implement

The International Warfarin Pharmacogenetics Consortium

NEJM, 2009, in press

- Aim to develop a universally applicable algorithm for stable maintenance dose
- 5701 patient records, 21 research group





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Conclusions

- Patients with renal or hepatic impairment shows changes in drug PK – this is often present in the drug label
- PGx variation also leads to similar changes in PK characteristics of drugs
- Dose changes (or drug choice) are currently not governed by PGx variation
- A higher standard of evidence is demanded by clinicians (and guidelines) before implementing genetic testing for PK (and PD variation) in clinical practice