



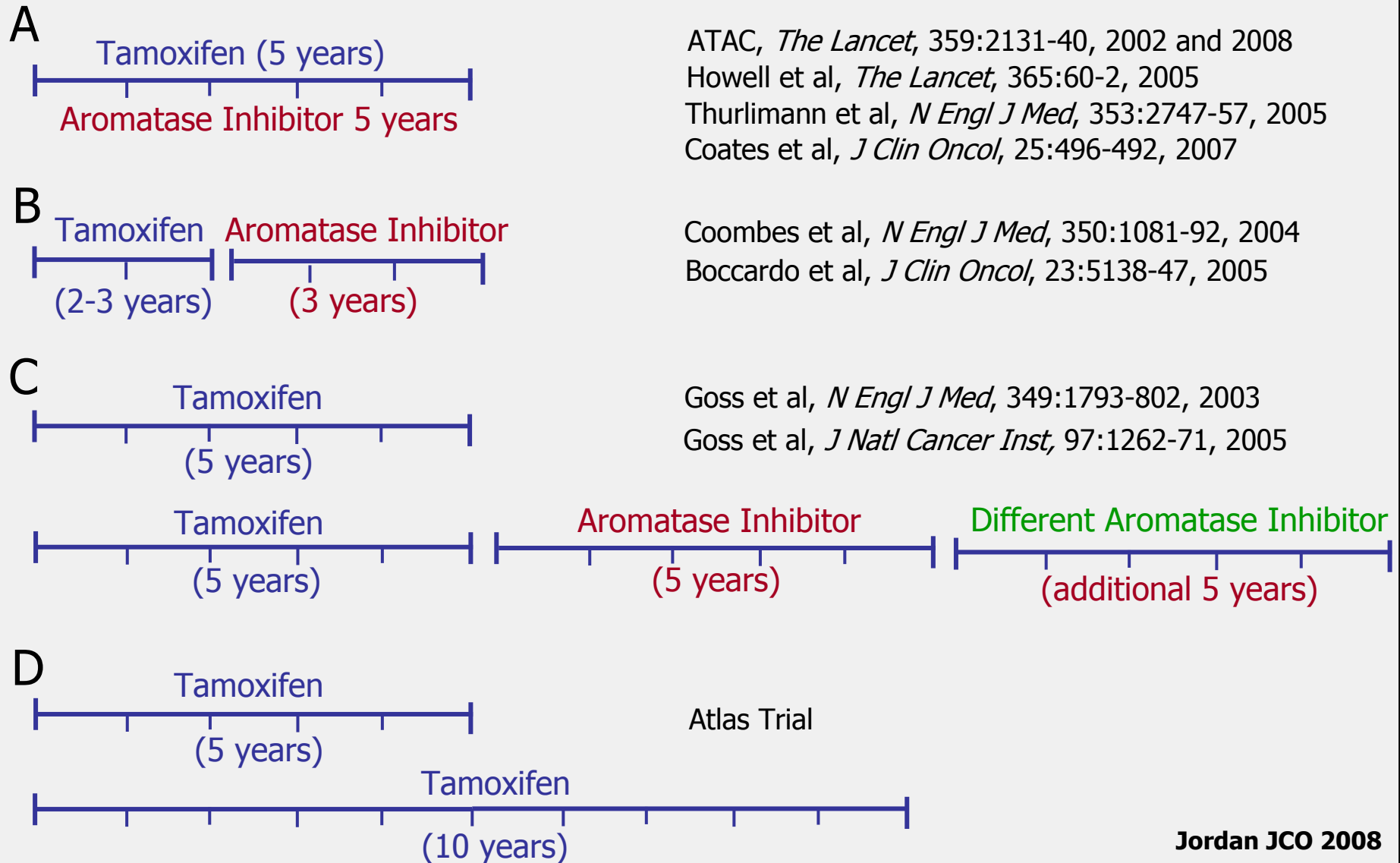
Endokrine Therapie: Translationale Forschungsansätze im Rahmen klinischer Studien

Hiltrud Brauch, Werner Schroth, Liza Bacchus, Wolfgang
Simon, Michel Eichelbaum und Matthias Schwab

COMBATING Breast Cancer
21-22 November 2008, Frankfurt

Treatment Practice 2008

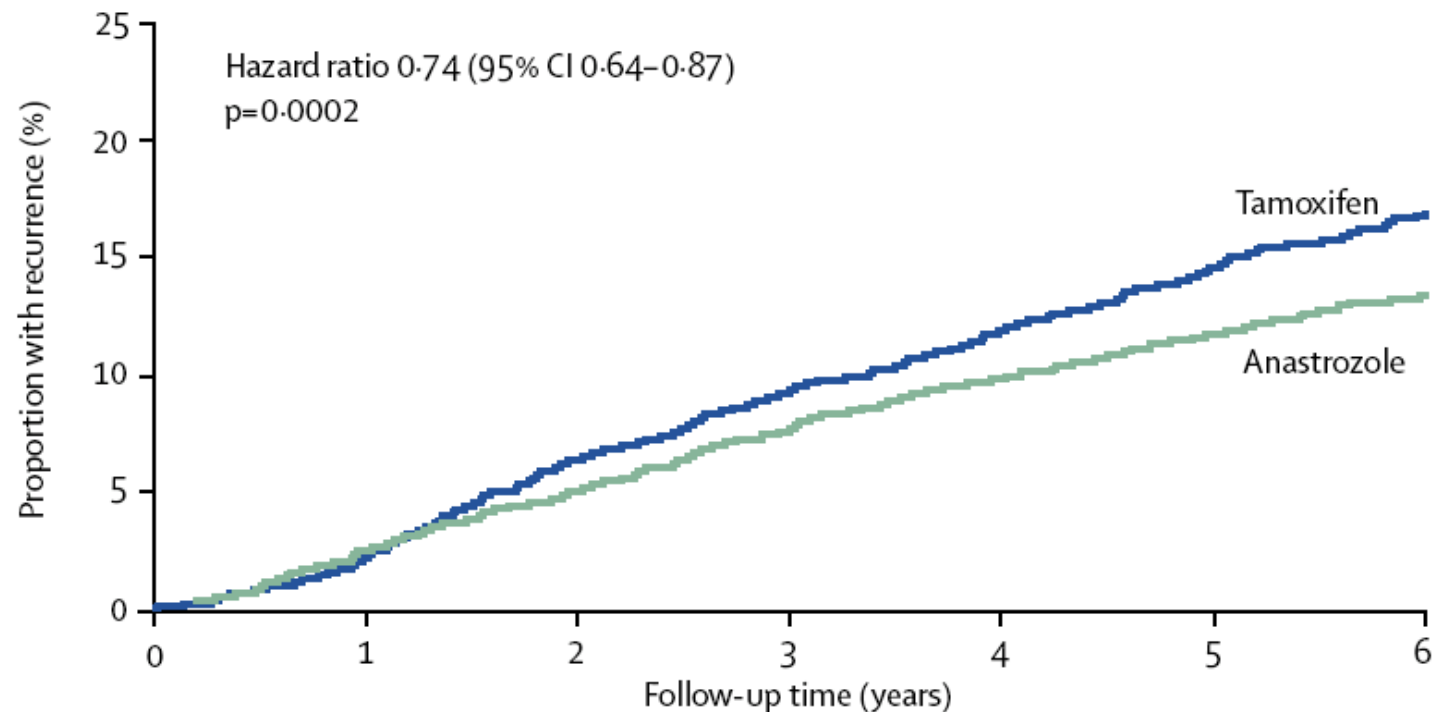
Long Term Estrogen Deprivation Treatment



The Current Million Dollar Question

Treatment Predictors for Upfront Testing Are in Demand

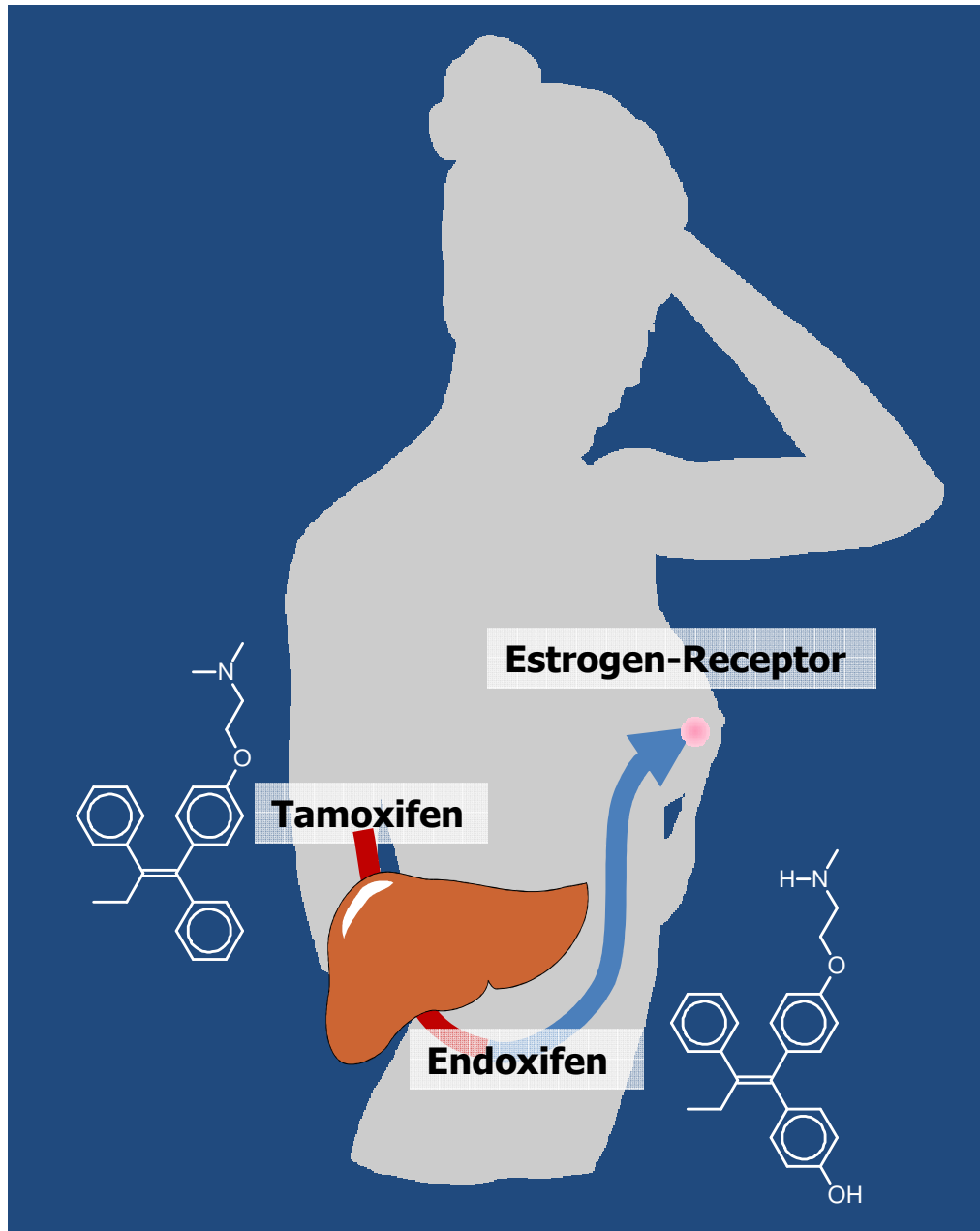
ATAC Trialists' Group, The Lancet 365:60-2, 2005



Numbers at risk:

Anastrozole:	2618	2540	2448	2355	2268	2014	830
Tamoxifen:	2598	2516	2398	2304	2189	1932	774
Absolute difference:				1.7%	2.4%	2.8%	3.7%

Tamoxifen Pharmacogenetics / -genomics



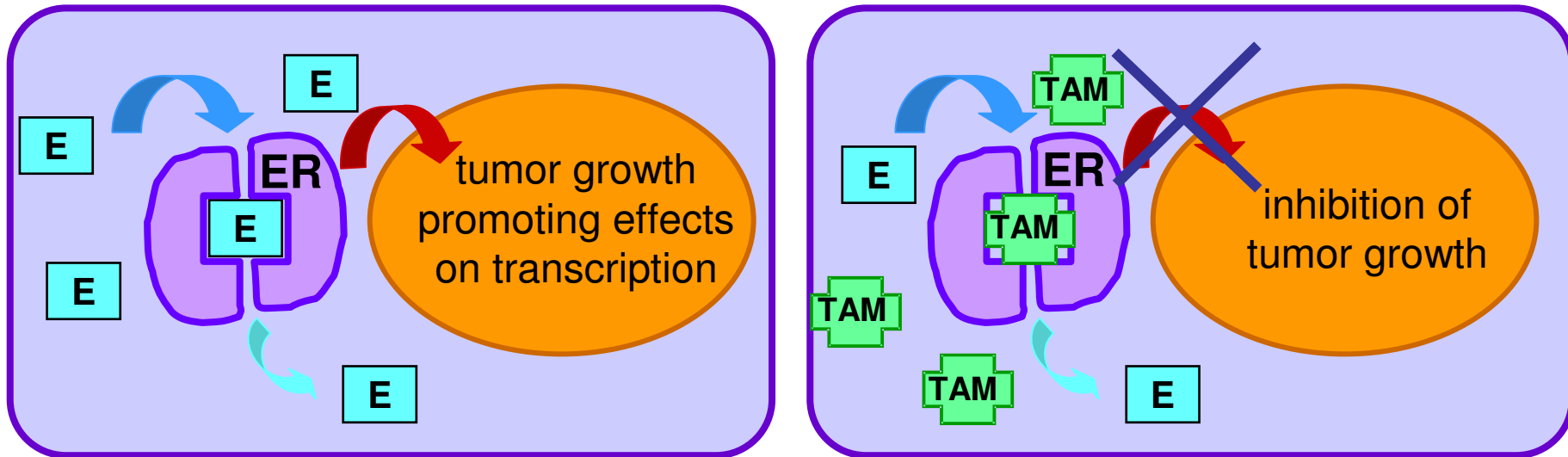
Inter-individual
variability in efficacy

Personalized Medicine

Optimize drugs and
drug combinations
according to the individuals
unique genetic makeup

Targeted Treatment with Tamoxifen

Competitive Inhibition of Estrogen Binding to ER



Estrogen receptor (ER)

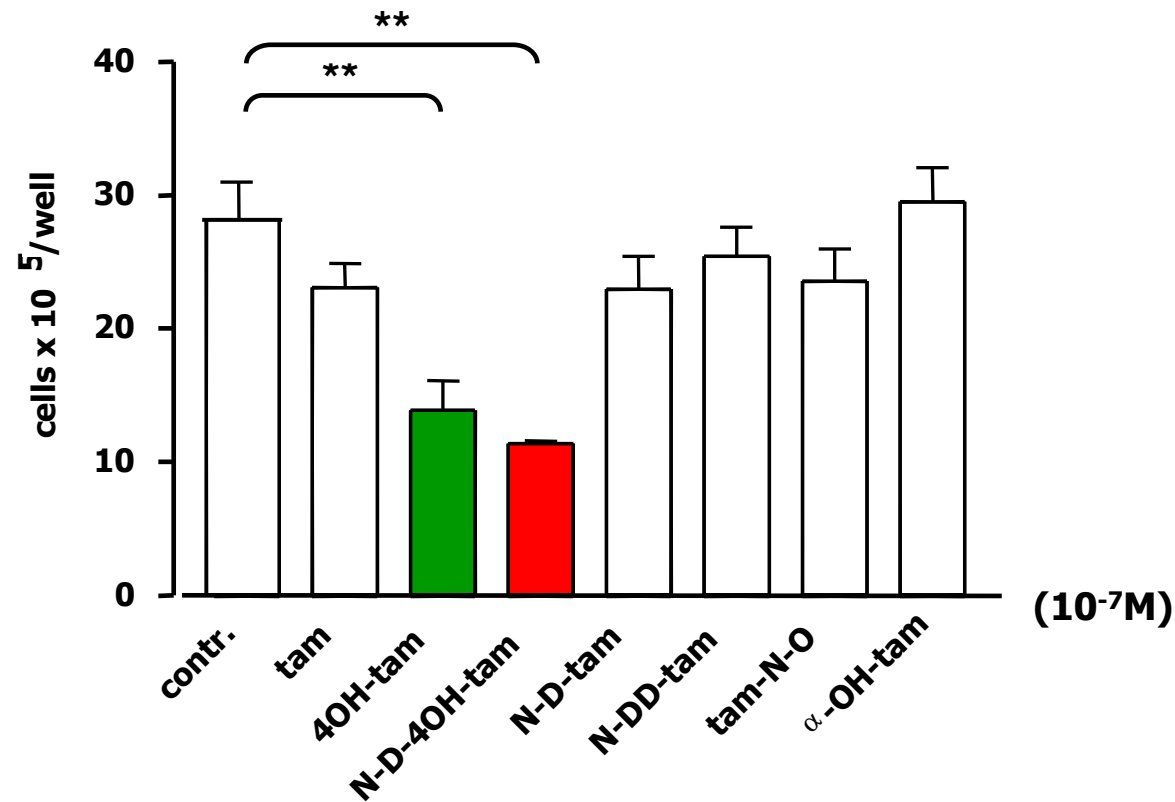
expressed in 60% to 70% of breast carcinomas

Affinity relative to estradiol

0.01 for tamoxifen

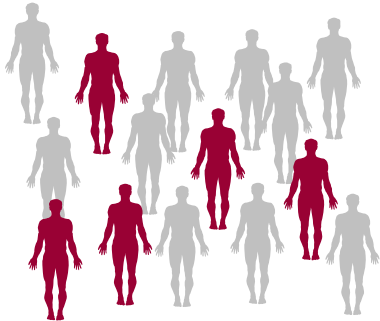
1.00 for metabolites 4-OH TAM and endoxifen

Inhibition of MCF-7 Cell Growth by Tamoxifen and its Major Metabolites



Buck and Knabbe *NY Acad Sci* 1089:119-26, 2006

Tamoxifen Efficacy and Resistance

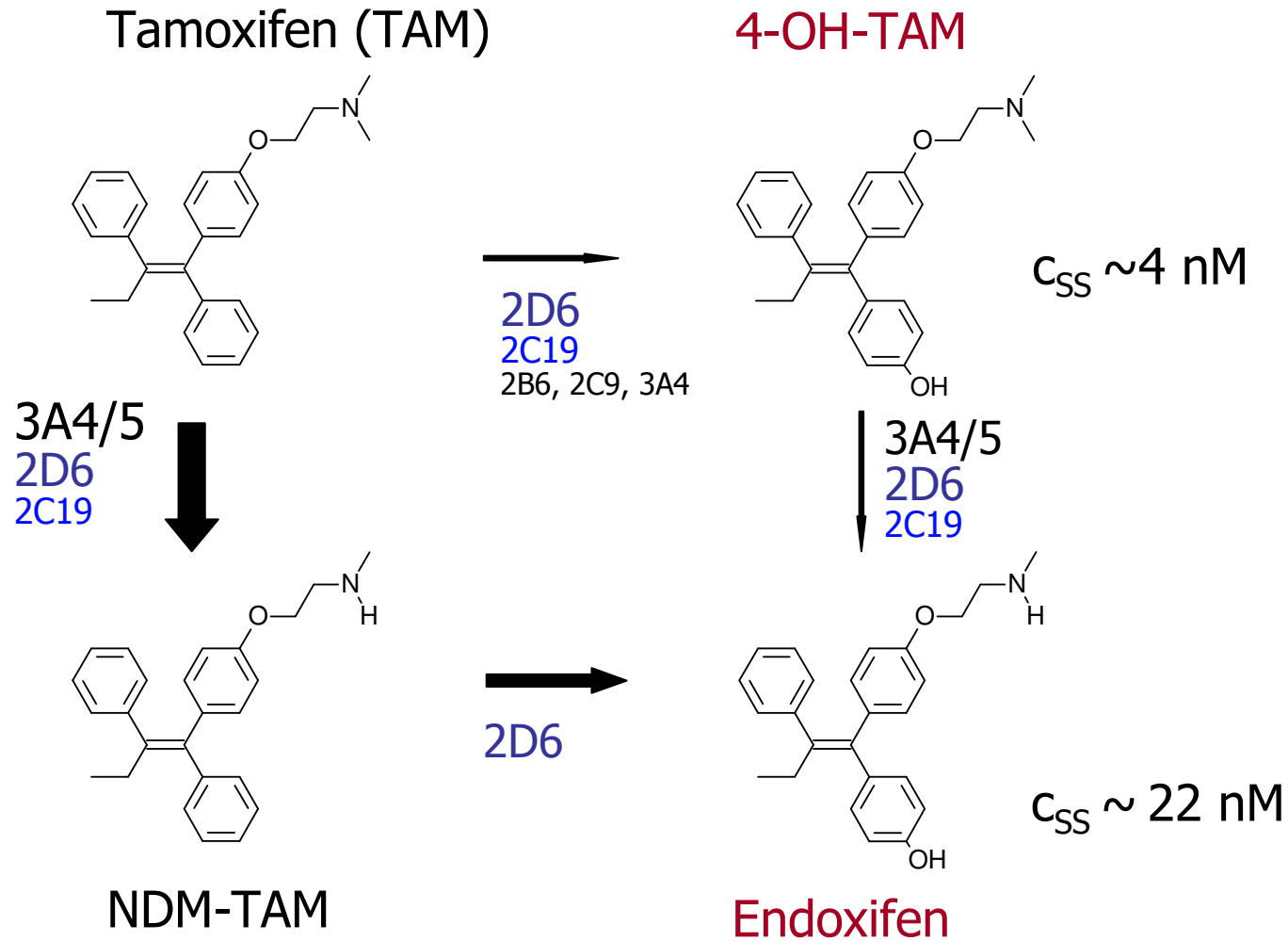


30% to 50% of patients receiving adjuvant tamoxifen relapse or die

Responders / **Non-responders**

- Efficacy depends on the availability of active metabolites 4-OH TAM and endoxifen
- Major enzymes are CYP2D6 and CYP2C19 (and others)
- Enzyme polymorphisms
 - genotype – phenotype relationships
 - inter-individual variability in metabolic capacity
 - variable clinical outcome

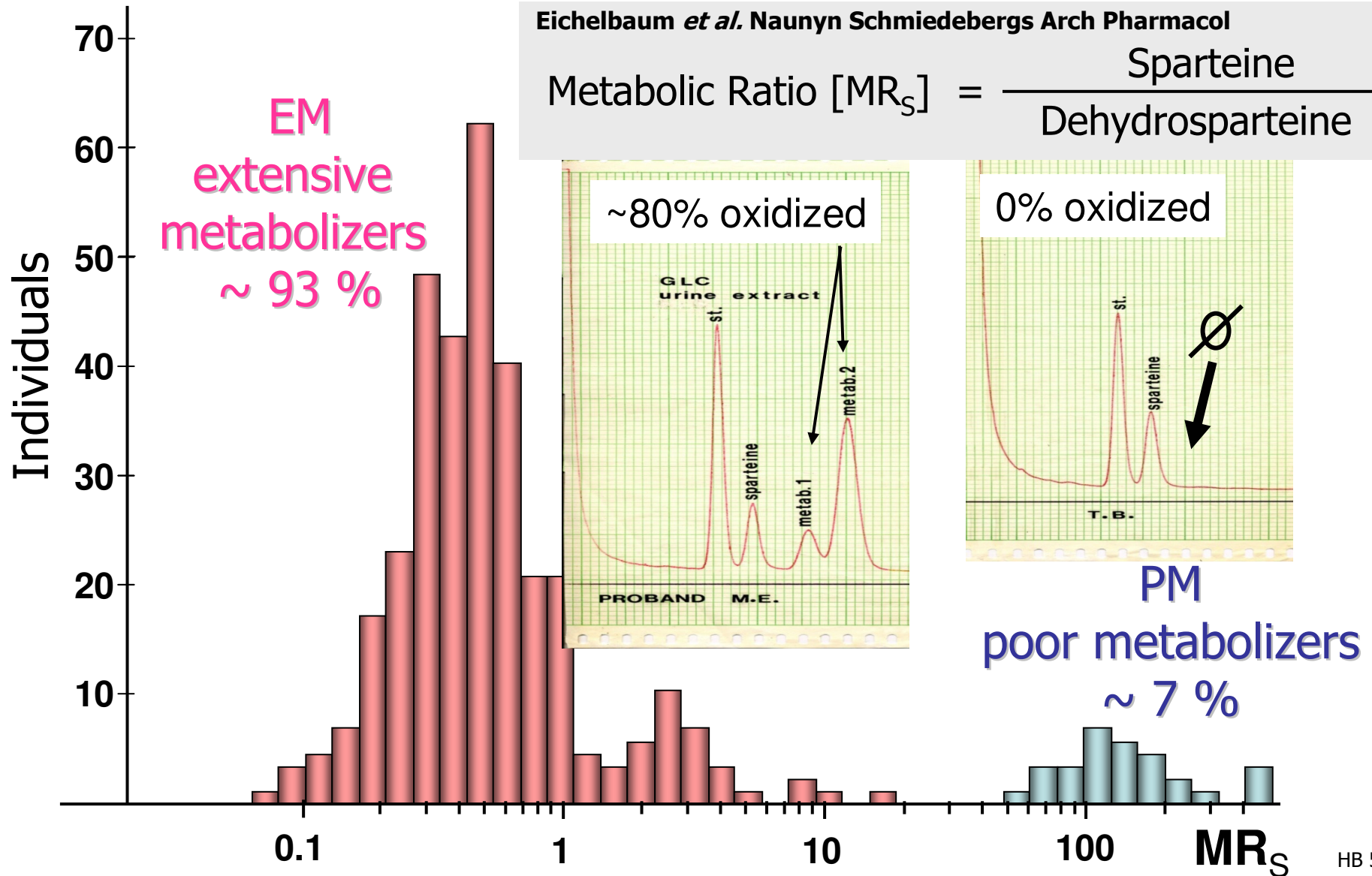
Biotransformation Tamoxifen and its Metabolites



100x more effective than prodrug

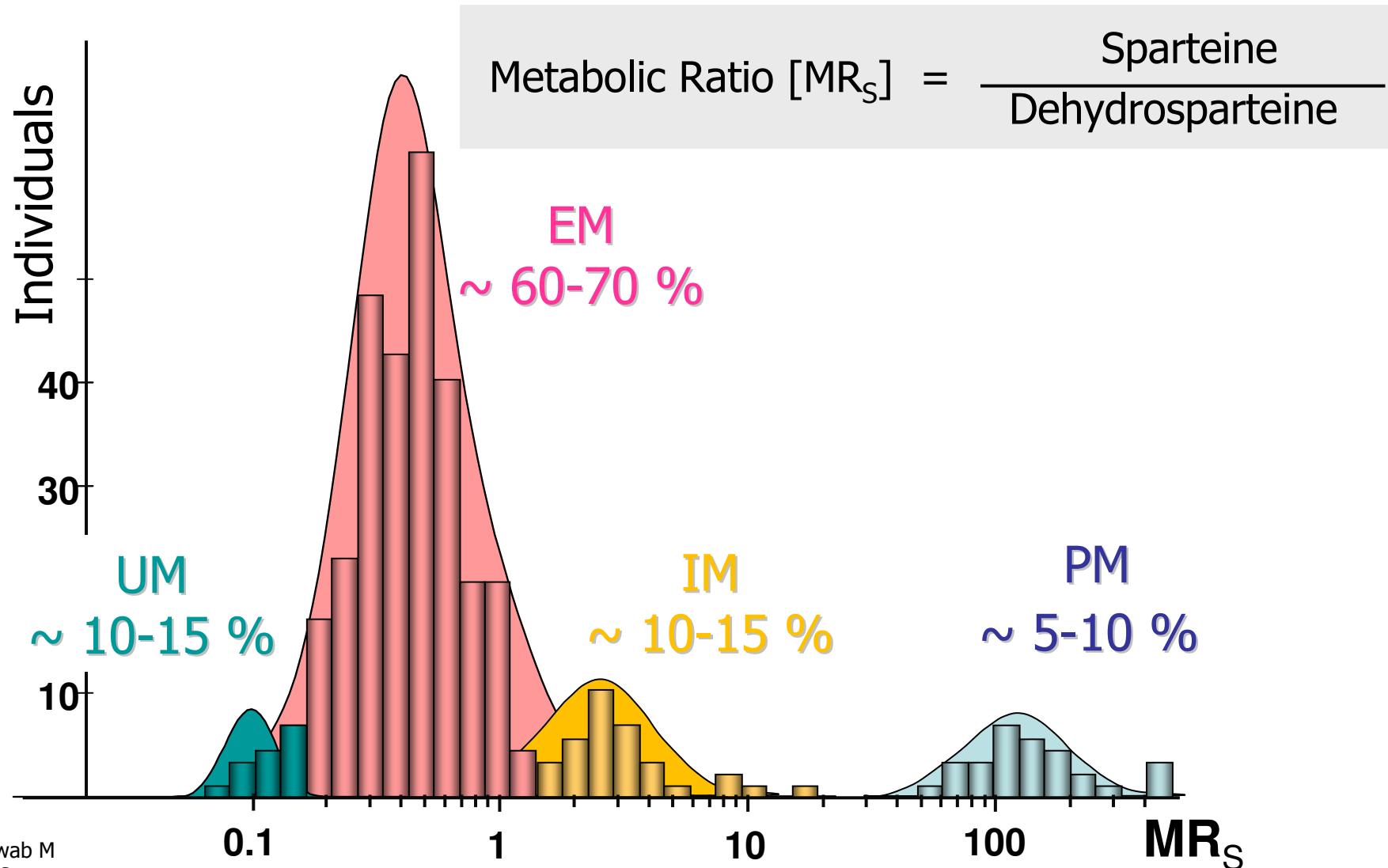
1975: Cytochrome P450 (CYP) 2D6 Phenotypes

N-Oxidation of Sparteine in Man and Interindividual Differences



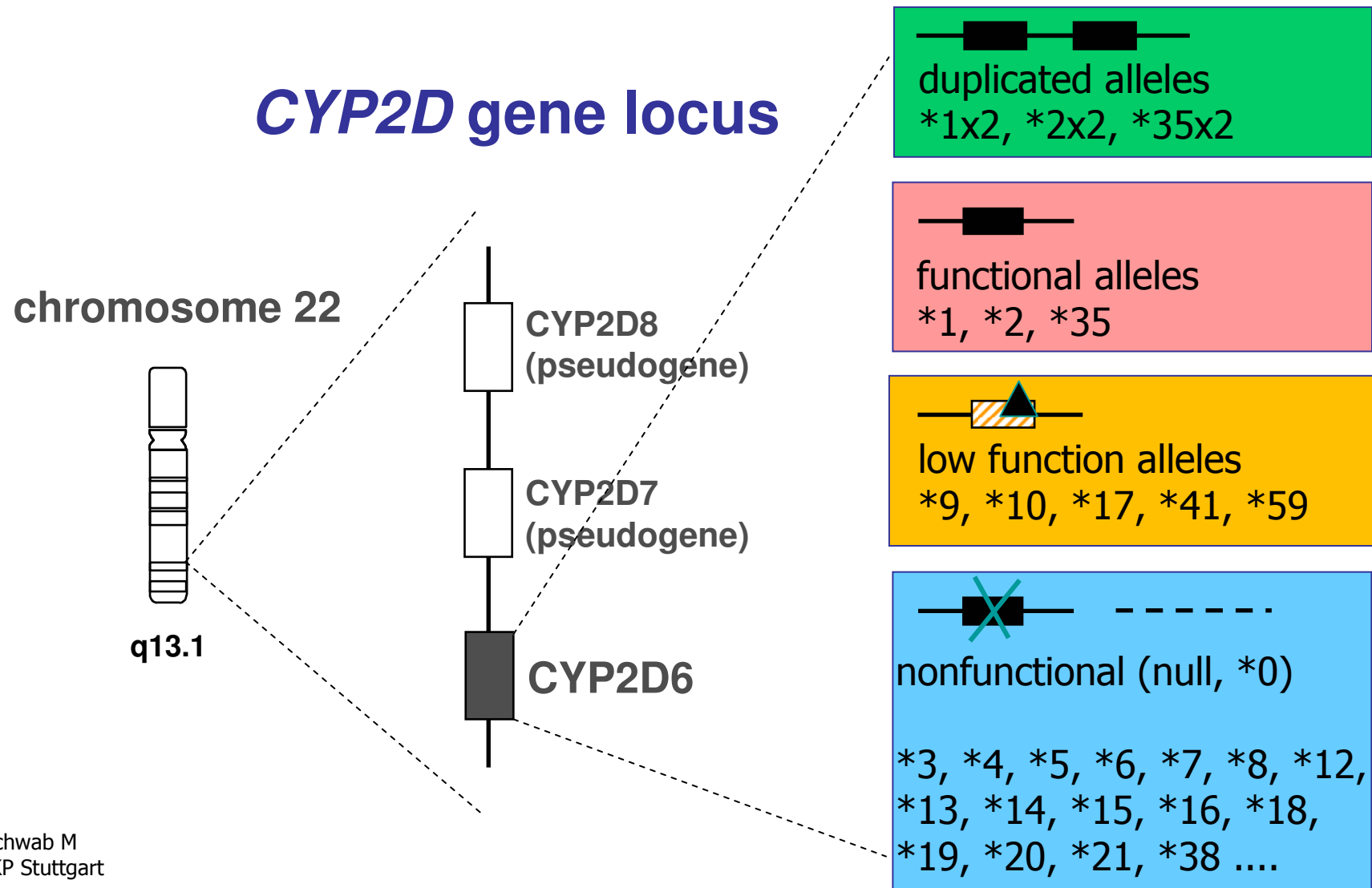
2008: CYP2D6 Polymorphisms in Caucasians

Evolution of 4 Distinct Phenotypes

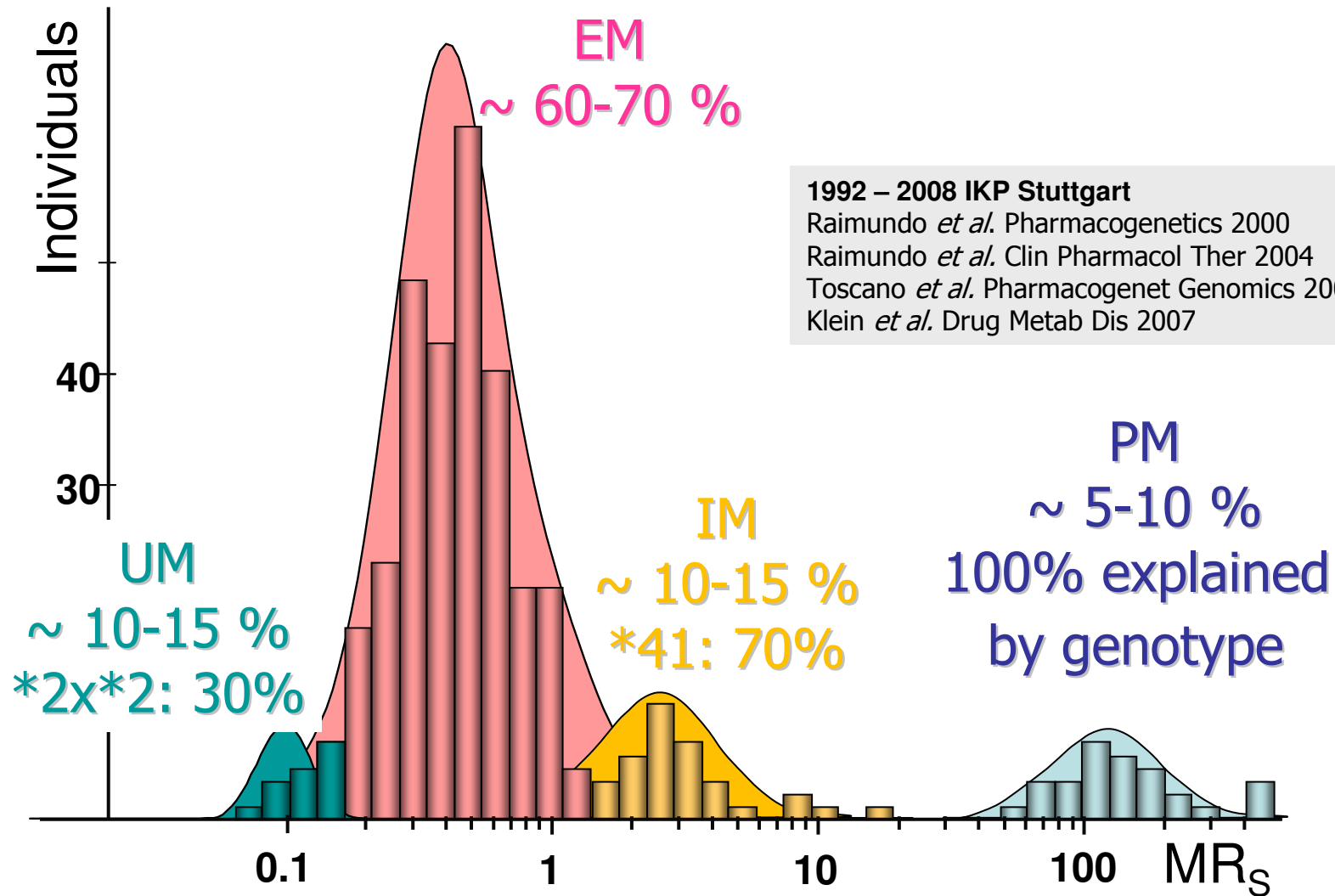


Molecular Basis of the *CYP2D6* Polymorphism

> 80 Genetic Variants



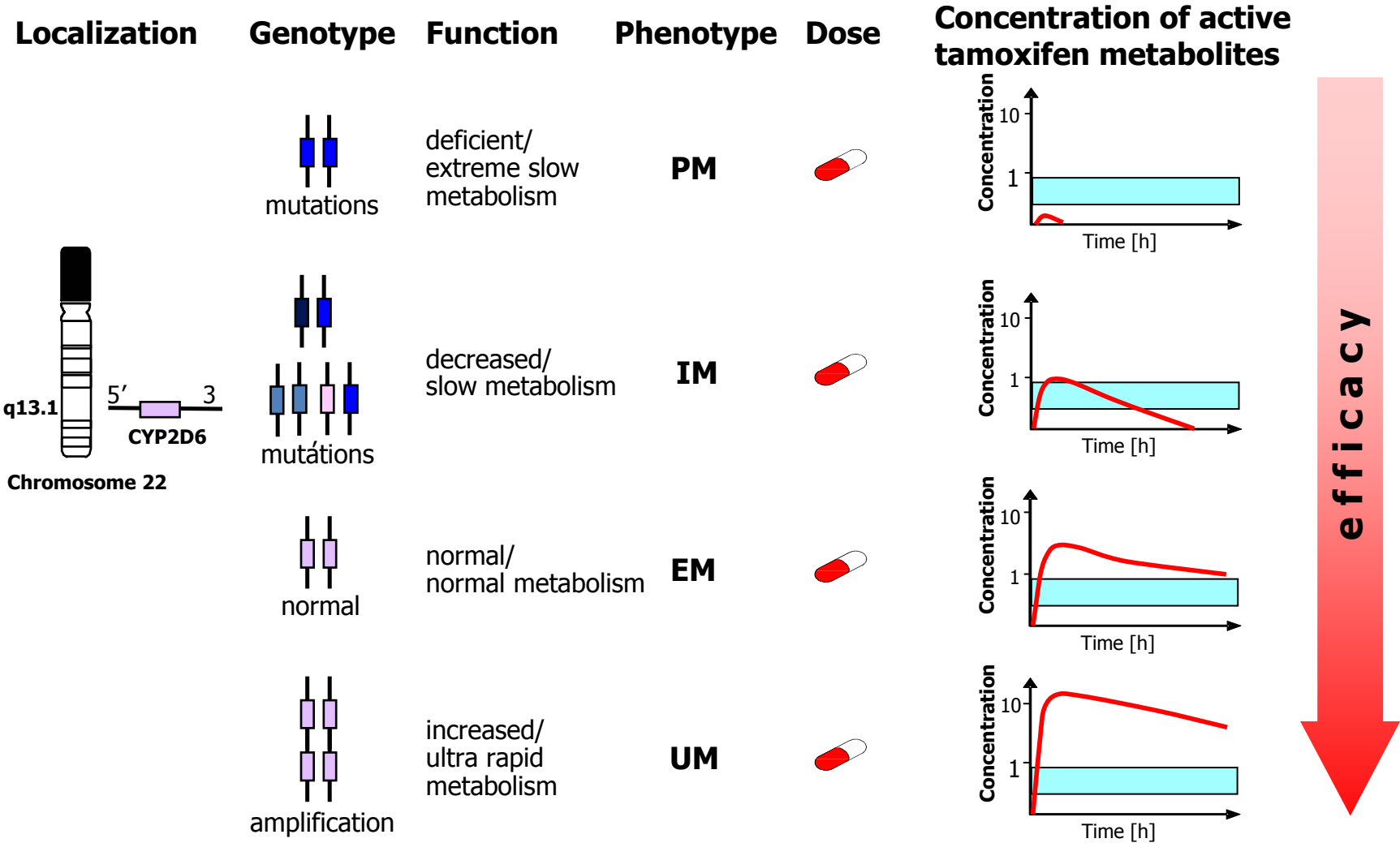
CYP2D6 Metabolizer Phenotypes and Corresponding Genotypes



1992 – 2008 IKP Stuttgart
 Raimundo *et al.* Pharmacogenetics 2000
 Raimundo *et al.* Clin Pharmacol Ther 2004
 Toscano *et al.* Pharmacogenet Genomics 2006
 Klein *et al.* Drug Metab Dis 2007

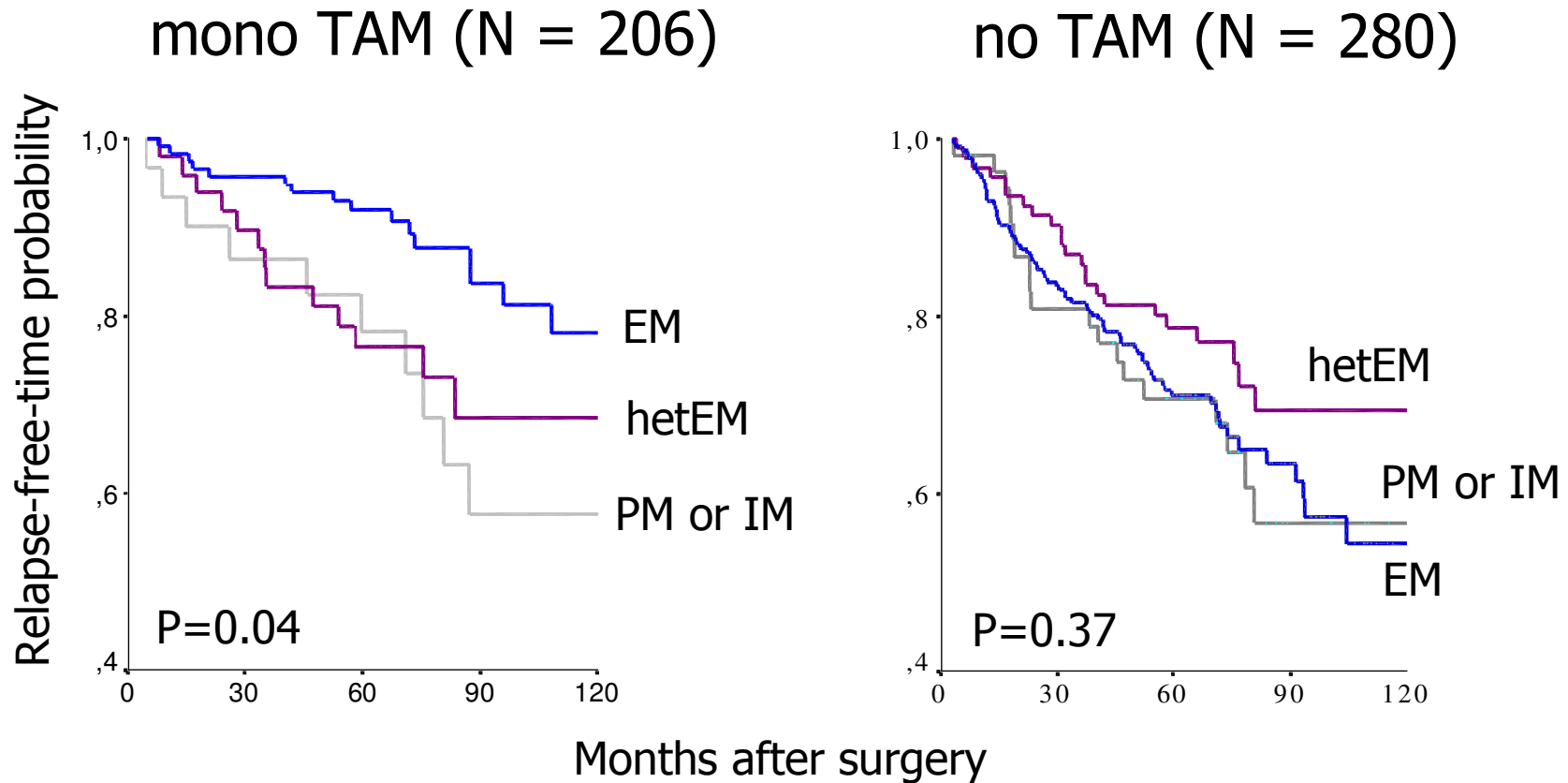
Human CYP Allele Nomenclature Home Page: <http://www.cypalleles.ki.se/>

Predicted Consequences of *CYP2D6* Genotypes on Tamoxifen Therapy



CYP2D6 Polymorphisms and Relapse-Free-Time Probabilities upon Tamoxifen Treatment

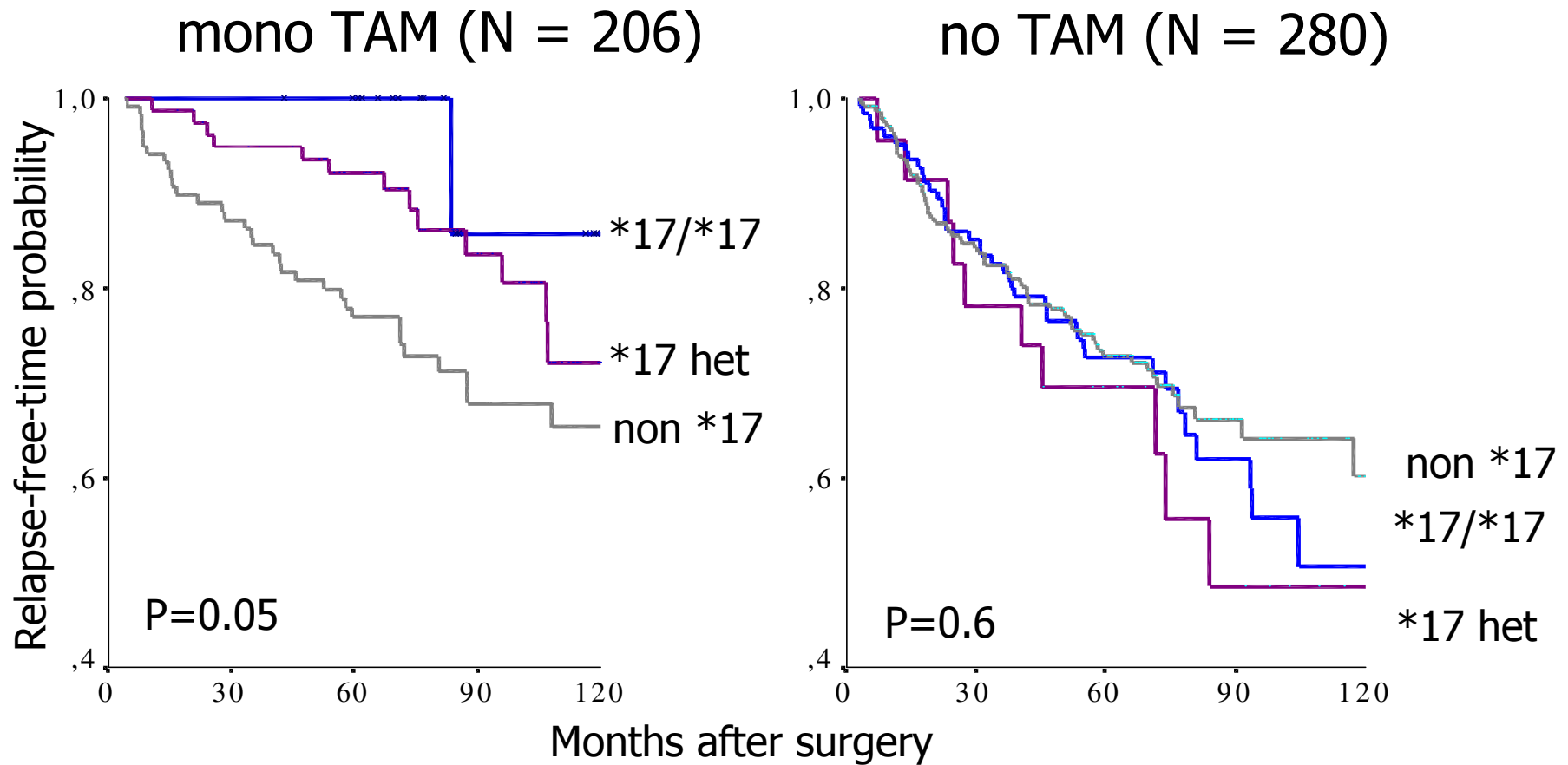
Schroth et al. JCO 33:5187-5193, 2007



HR 2.24 (95% CI 1.16-4.33; $P = 0.02$)

CYP2C19 Tamoxifen Metabolizer Phenotypes

Schroth et al. JCO 33:5187-5193, 2007

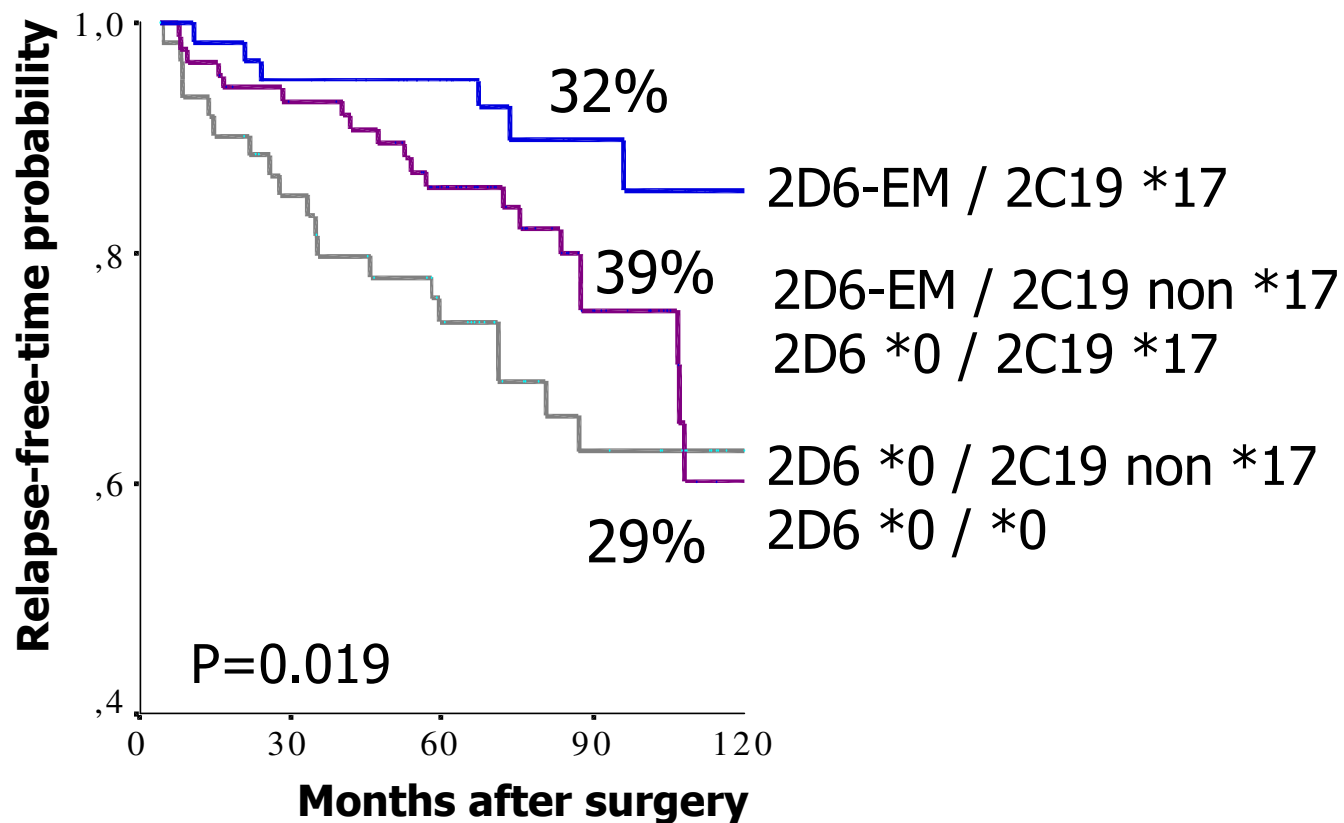


HR 0.45 (95% CI 0.21-0.92; $P = .03$)

Tamoxifen Treatment Response

Influence of Combined CYP2D6 and CYP2C19 Polymorphisms

Schroth et al. JCO 33:5187-5193, 2007



Published Evidence for a Relevance of CYP2D6 Genetics

Publication	Pharmacological and Clinical Findings
Stearns <i>et al.</i> J Natl Cancer Inst 2003	Endoxifen: high ER affinity of and growth suppression, SSRI affect tamoxifen metabolites
Desta <i>et al.</i> J Pharmacol Exp Ther 2004	Tam Sequential Biotransformation
Jin <i>et al.</i> J Natl Cancer Inst 2005	Endoxifen levels lower in patients with CYP2D6 hom variants
Borghes <i>et al.</i> Clin Pharmacol Ther 2006	Quantitative effect of CYP2D6 and inhibitors
Lim <i>et al.</i> J Pharmacol Exp Ther 2006	4-OH Tam and endoxifen: similar changes in global gene expression (MCF7 cells)
Goetz <i>et al.</i> J Clin Oncol 2005 Breast Cancer Res Treat 2007	Clinical outcome of efficacy and hot flashes Combined effect of genetic variation and inhibition
Schroth <i>et al.</i> J Clin Oncol 2007	Clinical outcome, PM and IM, no effect in control group, CYP2C19 potentially relevant
Lim <i>et al.</i> J Clin Oncol 2007	Genotypes predictive of tamoxifen pharmacokinetics Clinical Outcome
Xu <i>et al.</i> Annals of Oncology 2008	Clinical outcome: genotype and survival
Kiyotani <i>et al.</i> Cancer Sci 2008	Clinical outcome: genotype and recurrence
Mortimer <i>et al.</i> Breast Cancer Res Treat 2008	WHEL trial: Hot flashes predict breast cancer outcome
Punglia <i>RS et al.</i> J Natl Cancer Inst 2008	Mathematical Modeling predicts comparable treatment results for tamoxifen and AI

Published Evidence against a Relevance of *CYP2D6* Genetics

Publication	Findings from Patients
Wegman <i>et al.</i> Breast Cancer Res Treat 2005	CYP2D6*4 and decrease in number of recurrences
Nowell <i>et al.</i> Breast Cancer Res Treat 2005	No association between CYP2D6 *4 and overall survival
Wegman <i>et al.</i> Breast Cancer Res Treat 2007	CYP2D6*4: better disease free survival

Possible reasons for conflicting data

- Small sample size
- Variation in tamoxifen dose and length of treatment
- Additional chemotherapy
- Lack of consistent ER testing

IKP Studies: Tamoxifen – Pharmacogenomics

Retrospective and Prospective Patient Collections

Validation study with > 1200 cases

- | ER+, postmenopausal, Tam only
- 4 German breast cancer collections
- 1 US breast cancer collection

GENICA study population > 1100 cases

- 400 ER+ cases with tamoxifen
- 5 year follow-up to be completed

International Tamoxifen <http://www.pharmgkb.org/views/project.jsp?pld=63>

Pharmacogenetics Consortium (ITPC)

data pooling and joint analysis

IKP Studies: Tamoxifen – Pharmacogenomics

Proof-of-Principle

IKP 211 (all in one)

Genotype

CYP2D6
others

Phenotype

Tamoxifen
metabolite levels
in plasma

Outcome

Time-to-Relapse
5-year disease-free
survival

The diagram illustrates the influence of co-medication on the relationship between genotype, phenotype, and outcome. It features three columns: Genotype, Phenotype, and Outcome. The Genotype column lists *CYP2D6* and others. The Phenotype column lists Tamoxifen metabolite levels in plasma. The Outcome column lists Time-to-Relapse and 5-year disease-free survival. Two blue arrows point from the Genotype column to the Phenotype column, and another blue arrow points from the Phenotype column to the Outcome column. A large blue arrow at the bottom points from left to right, indicating the overall influence of co-medication on the entire process.

Influence of Co-medication (CYP2D6-Inhibitors)

IKP211 Observational Study

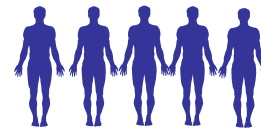
BMBF Funding Period: 07/05 - 12/10



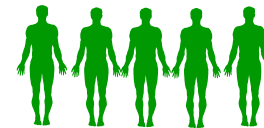
TRAFO
Gütesiegel (05/07)

Study population

Newly diagnosed breast cancers
postmenopausal, ER⁺



600 TAM



600 AI

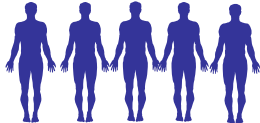
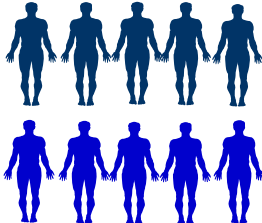
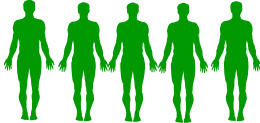
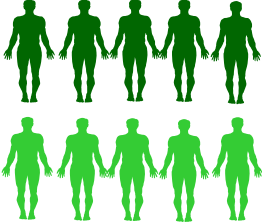
Participating Centers in Germany

Contacted	> 100
With contract	45
Actively recruiting centers	30

International Centers (UK, Australia)

IKP 211 Recruitment Status October 2008

Newly diagnosed breast cancer cases: 540

Treatment ER ⁺ , postmeno	IKP 211, CYP2D6 genetics (mEH), TAM Metabolite, TGFβ2
Tamoxifen 600	 329 (55%) 
Aromatase Inhibitor 600	 211 (35%) 



Bundesministerium
für Bildung
und Forschung

Improvement of Breast Cancer Diagnosis and Treatment Tübingen - Stuttgart

IKP211

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Universitätsklinikum Tübingen
Frauenklinik



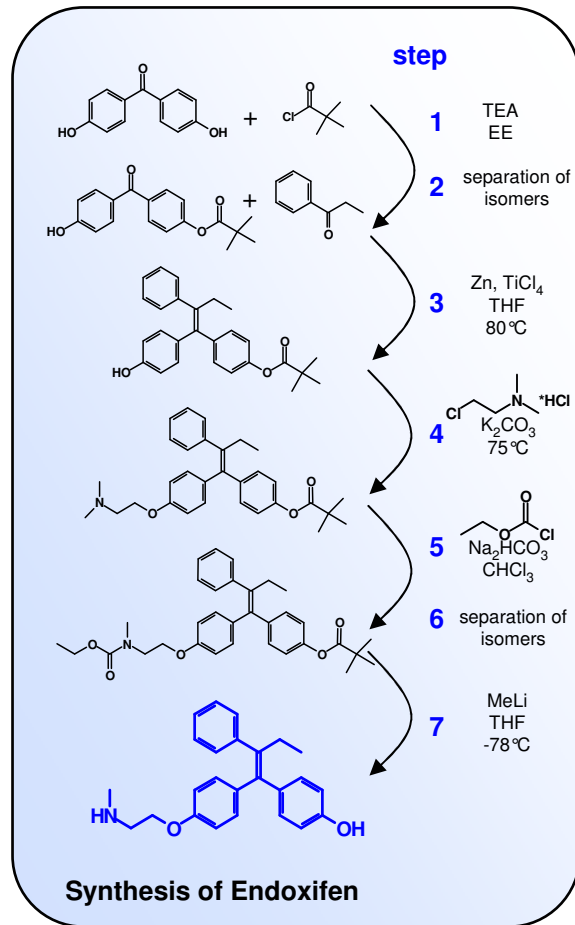
Robert Bosch Krankenhaus
Stuttgart



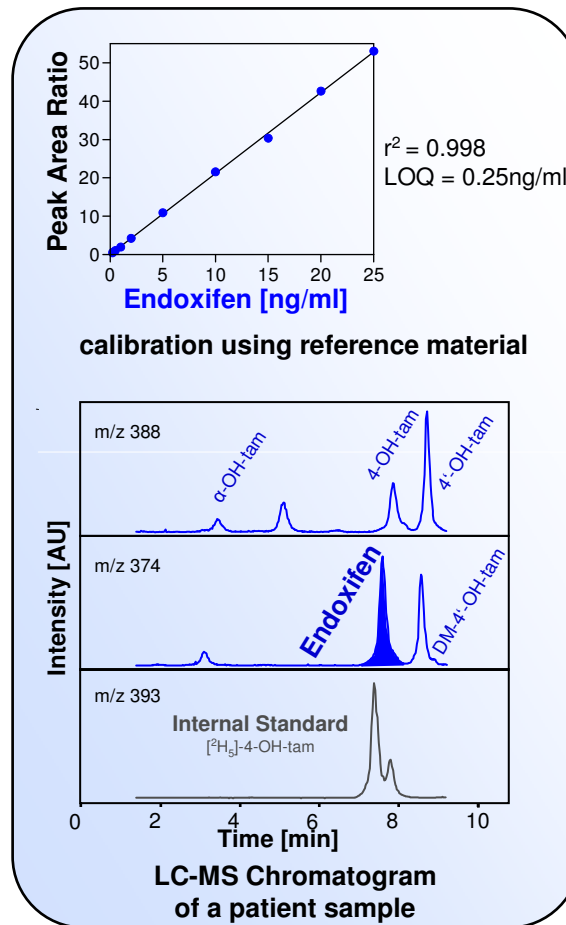
Koordinierungszentrum Klinische
Studien am Universitätsklinikum
Tübingen

Chemical Synthesis, Analytics and Bedside

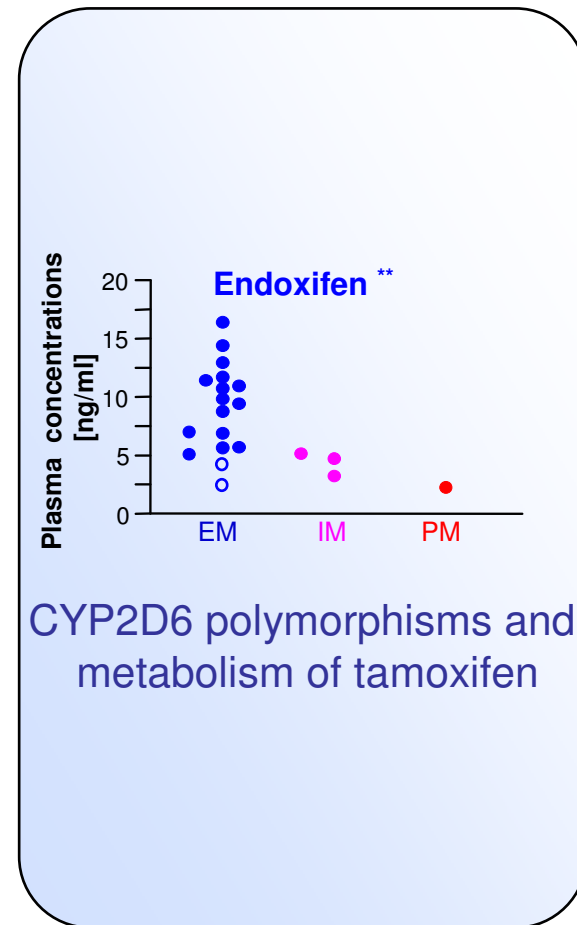
Synthesis of reference materials



Development of a sensitive analytical method

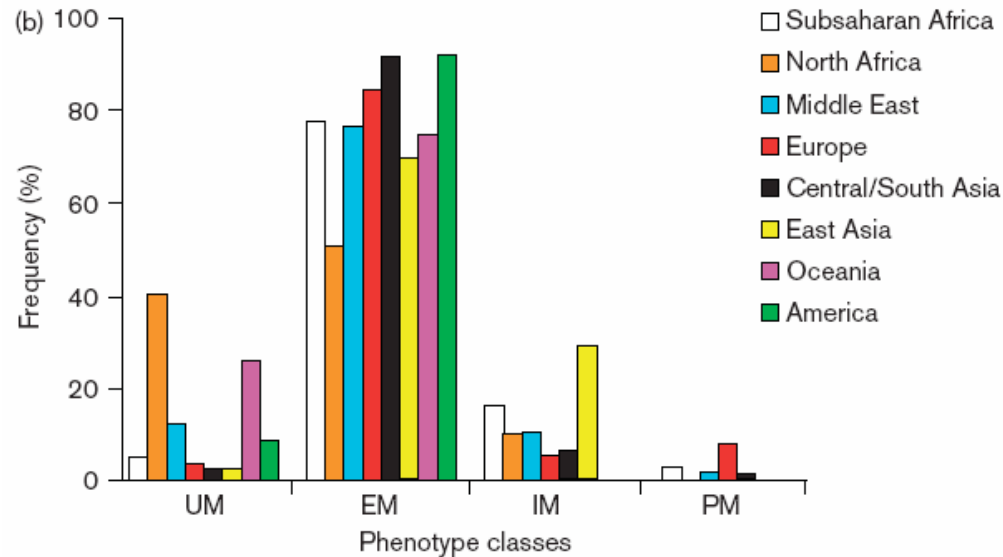


Clinical trial



CYP2D6 Genotype – Phenotypes Correlation

Global Distribution

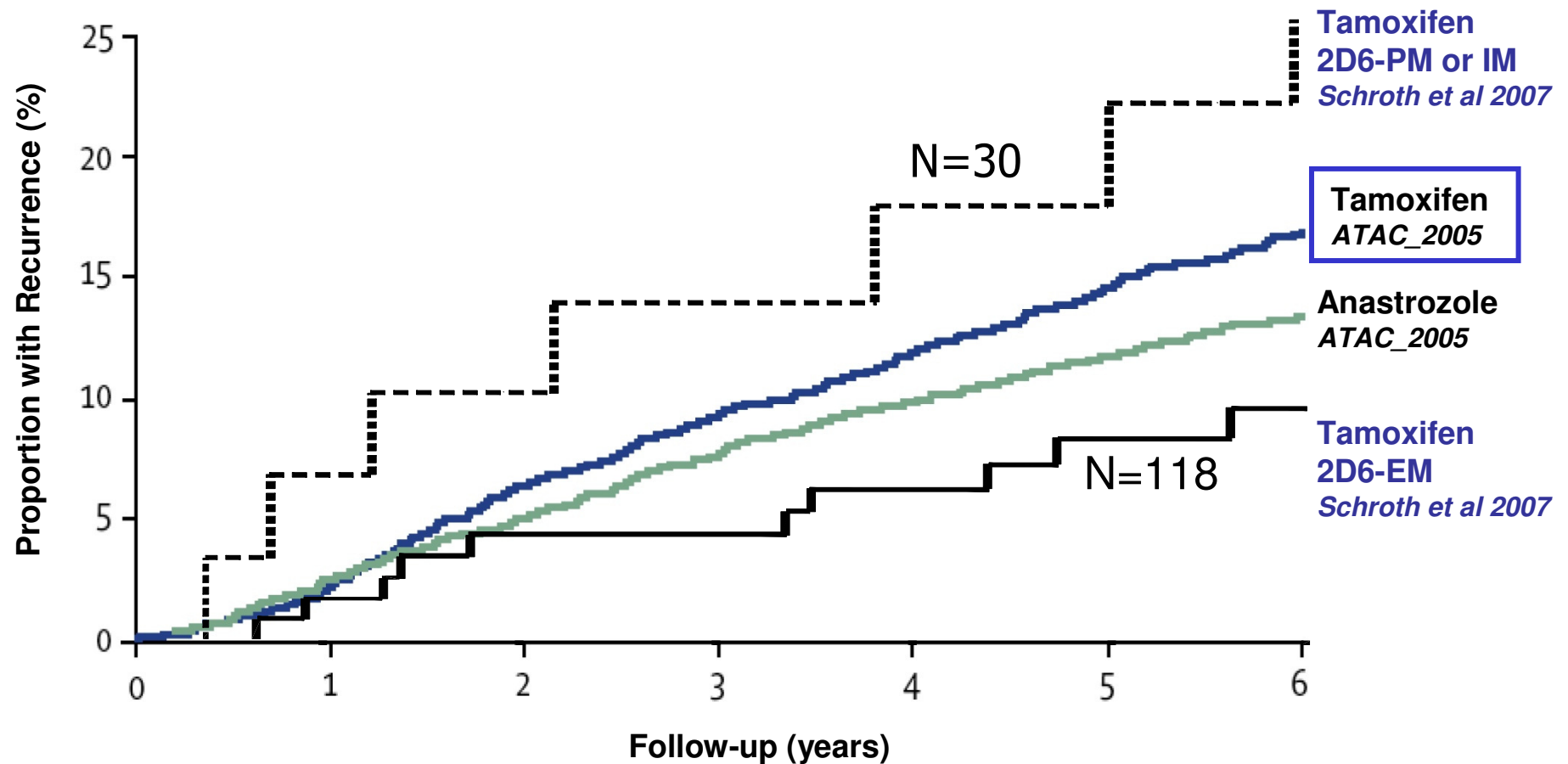


Metabolizer	Frequency	Alleles
Poor (PM)	5-10%	*3, *4, *5, *6, *7, *8
Intermediate (IM)	10-15%	*9, *10, *41, others
Extensive (EM)	70-85%	*1 (wild type), *2
Ultra rapid (UM)	~2%	gene duplication

*4 and *5 cover 90% of PM in Europeans ■

*10 most common variant in East Asians ■

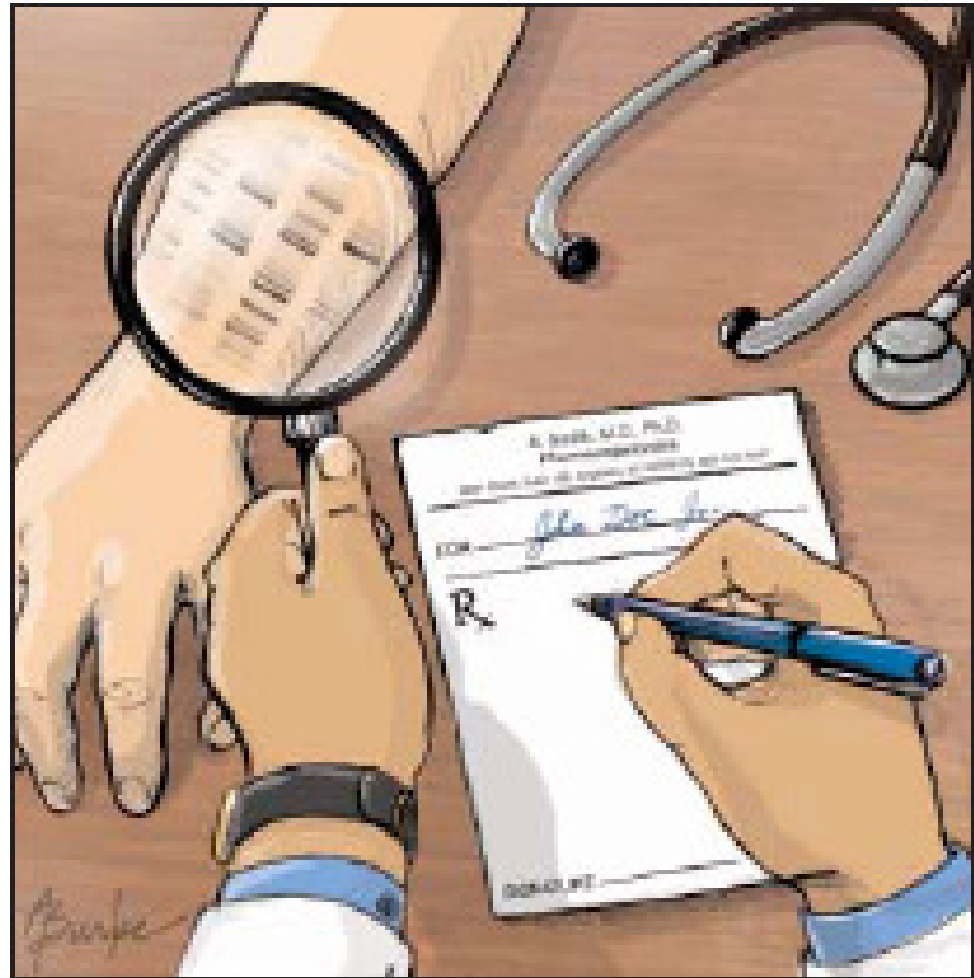
Hypothesis: Stratification by *2D6* Genotype Will Improve Tamoxifen Treatment Benefits



Breast Cancer Pharmacogenomics

Individualization of Drug Therapy

The right drug -
to the right patient -
at the right time -
in the right dose



Acknowledgement



Robert-Bosch-Krankenhaus



Universitätsklinikum Tübingen
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Wolfgang Janni



Robert-Bosch-Krankenhaus

Breast Cancer Symposium 2009 Stuttgart



New Developments in the Endocrine Treatment of Breast Cancer

February 5, 2009 13:00 h – 19:00 h

Robert Bosch-Haus Heidehof, Stuttgart

Chair persons

Prof. Dr. Matthias Schwab and Prof. Dr. Hiltrud Brauch
Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology
and Robert-Bosch-Hospital

In Cooperation with Prof. Dr. Diethelm Wallwiener
Comprehensive Cancer Center (CCC)
University of Tübingen

Breast Cancer Symposium 2009 Stuttgart



Lectures

Defeating drug resistance to SERMs: Building on the success of tamoxifen and raloxifene

Professor V Craig Jordan, OBE, PhD, DSc

Vice President and Research Director for Medical Sciences
Alfred G. Knudson Chair of Cancer Research
Fox Chase Cancer Center, Philadelphia, PA, USA



Robert-Bosch-Krankenhaus

From OncoGenome analysis to novel cancer therapies

Professor Axel Ullrich, PhD

Director at the Max Planck Institute of Biochemistry
Department of Molecular Biology
Martinsried, Germany



Clinical aspects of endocrine treatment

Professor Manfred Kaufmann, MD

Director, Hospital of Gynaecology and Obstetrics
University of Frankfurt

The relevance of tamoxifen pharmacogenetics for clinical outcome

Professor Hiltrud Brauch, PhD

Deputy Head, Dr. Margarete Fischer Bosch Institute of Clinical Pharmacology, Stuttgart
and University of Tübingen