**Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart**

IKP STUTTGART

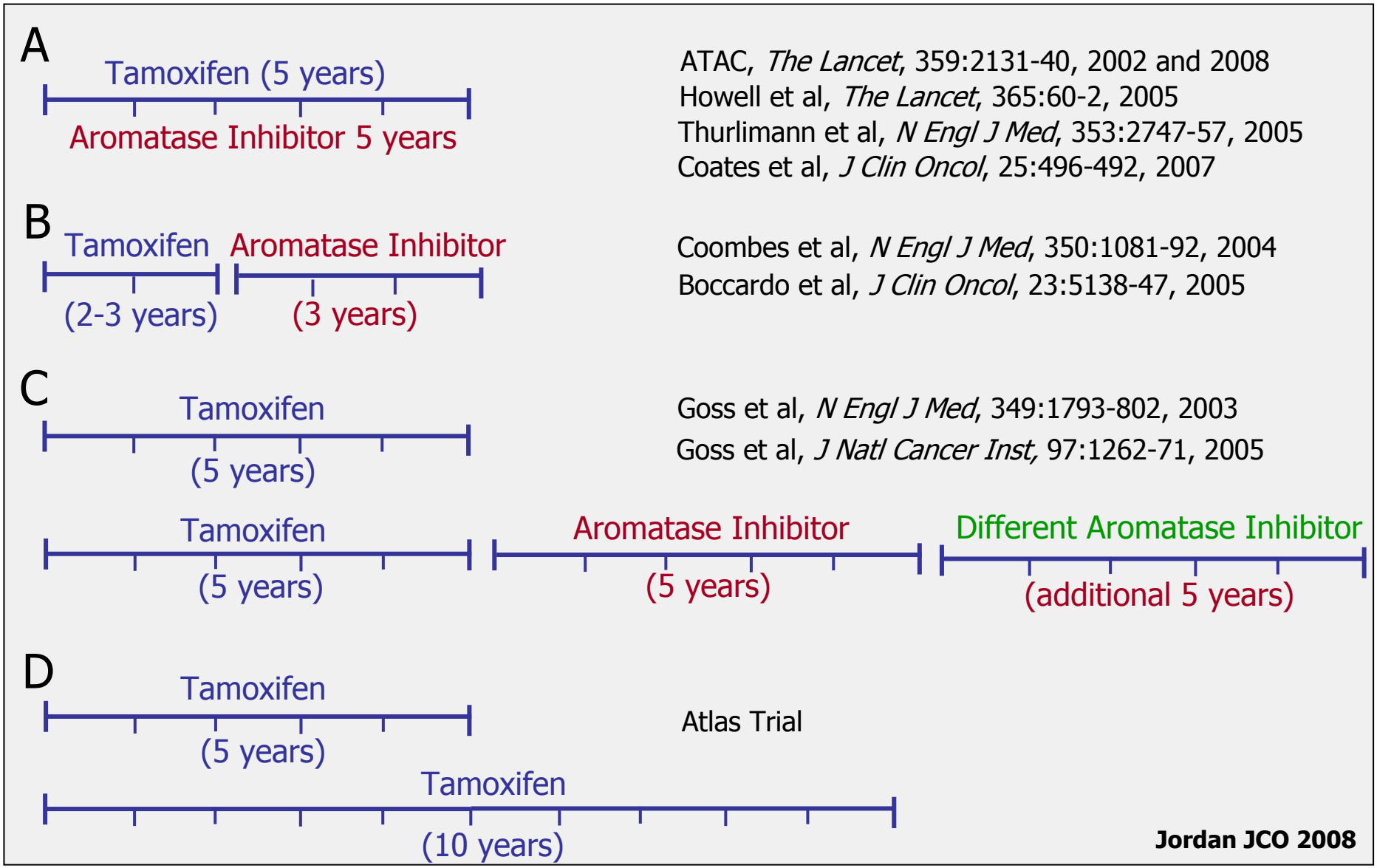
# Endokrine Therapie: Translationale Forschungsansätze im Rahmen klinischer Studien

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

COMBATING Breast Cancer
21-22 November 2008, Frankfurt

# Treatment Practice 2008

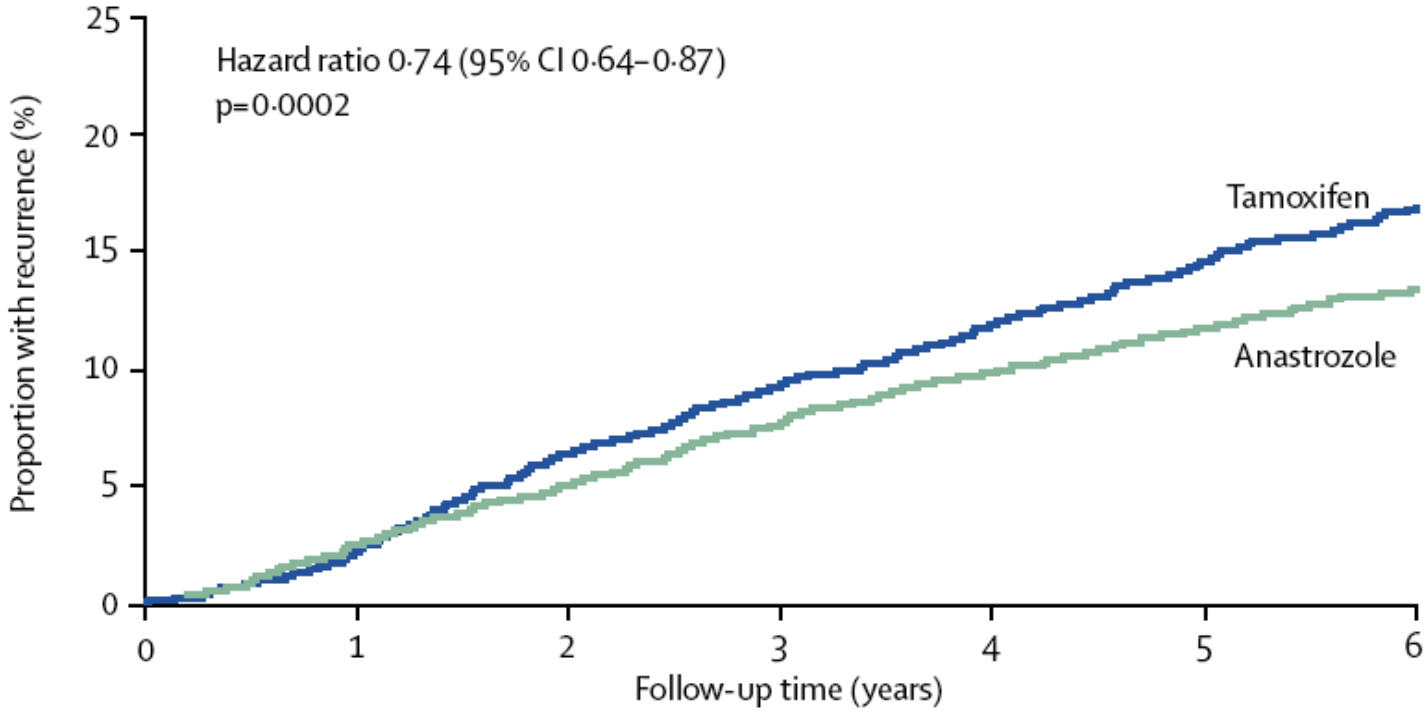
## Long Term Estrogen Deprivation Treatment



# The Current Million Dollar Question

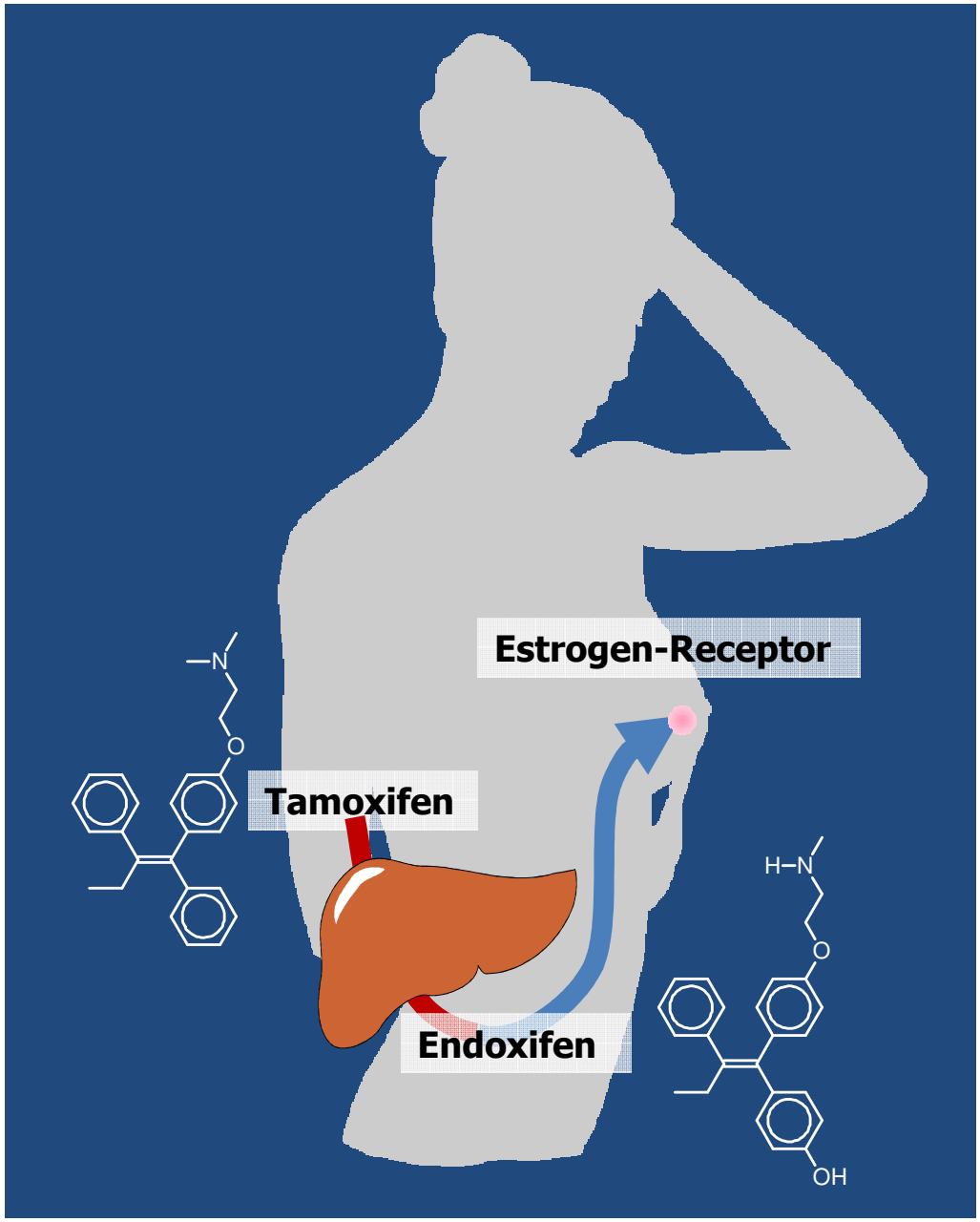
## Treatment Predictors for Upfront Testing Are in Demand

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



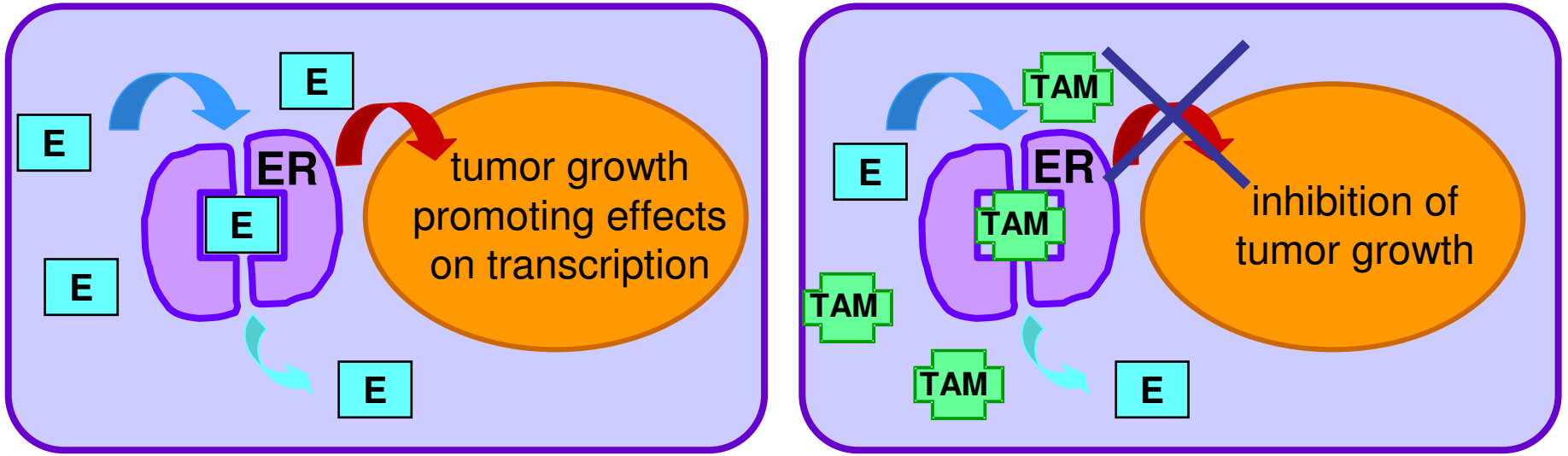

Inter-individual
variability in efficacy

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)

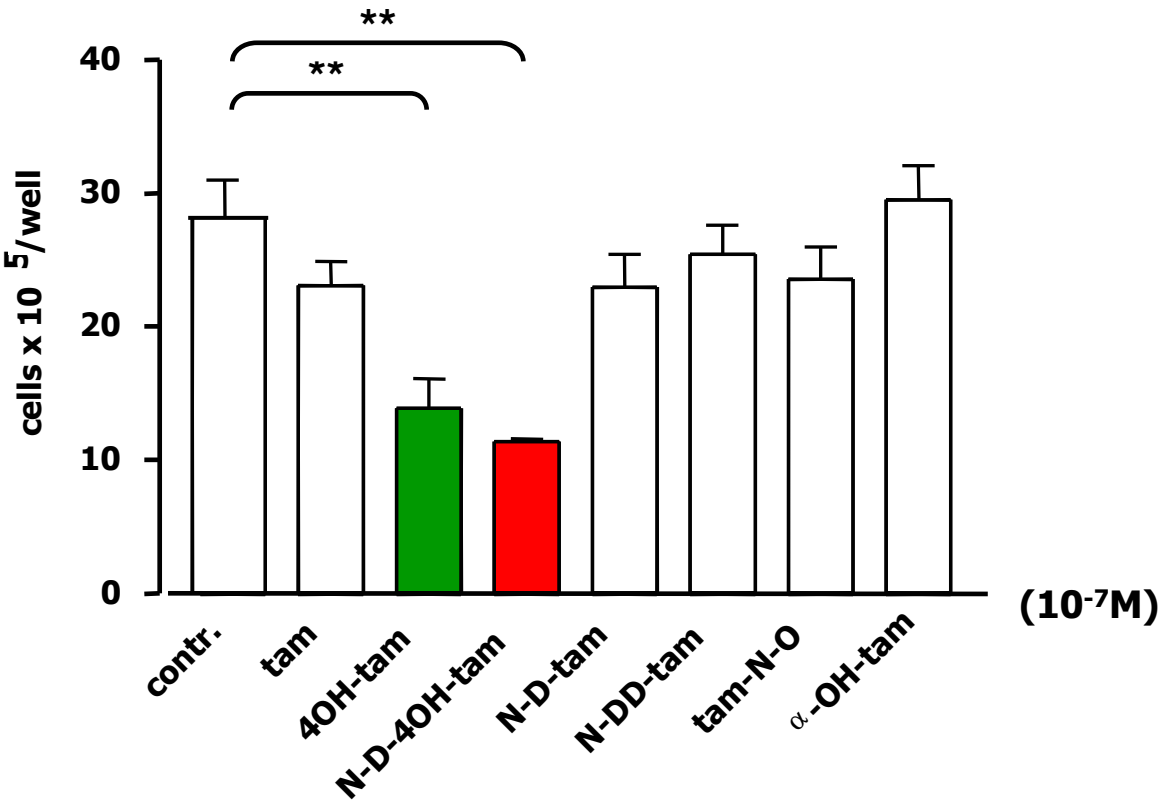
expressed in 60% to 70% of breast carcinomas

Affinity relative to estradiol

0.01 for tamoxifen

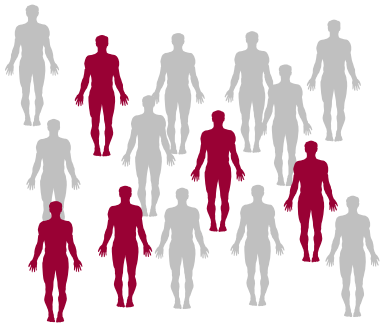
1.00 for metabolites 4-OH TAM and endoxifen

# 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**

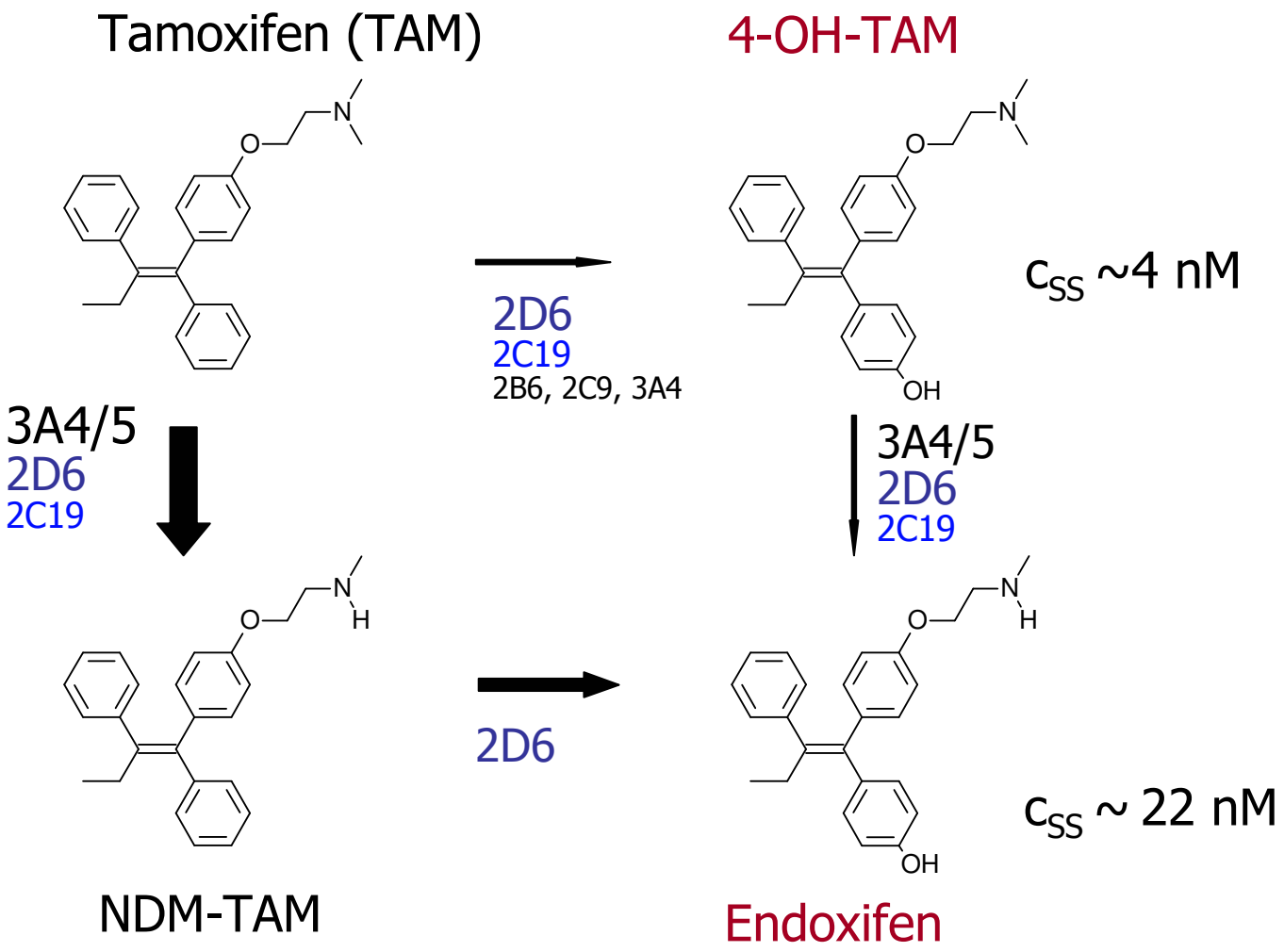
- Efficacy depends on the availability of active metabolites 4-OH TAM and endoxifen
- Major enzymes are CYP2D6 and CYP2C19 (and others)
- Enzyme polymorphisms

→ genotype – phenotype relationships

→ inter-individual variability in metabolic capacity

→ variable clinical outcome

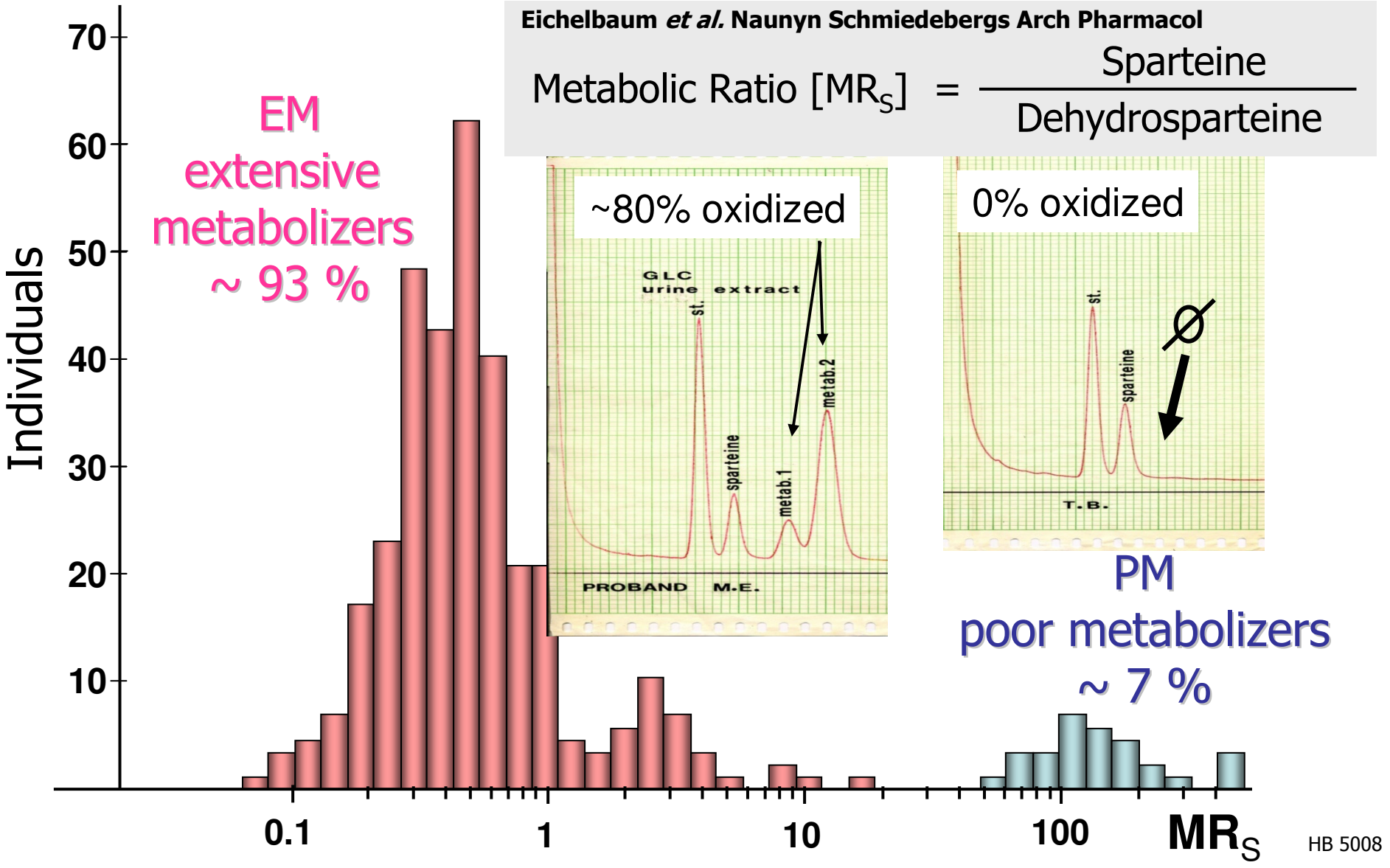
# Biotransformation Tamoxifen and its Metabolites




100x more effective than prodrug

# 1975: Cytpchrome P450 (CYP) 2D6 Phenotypes

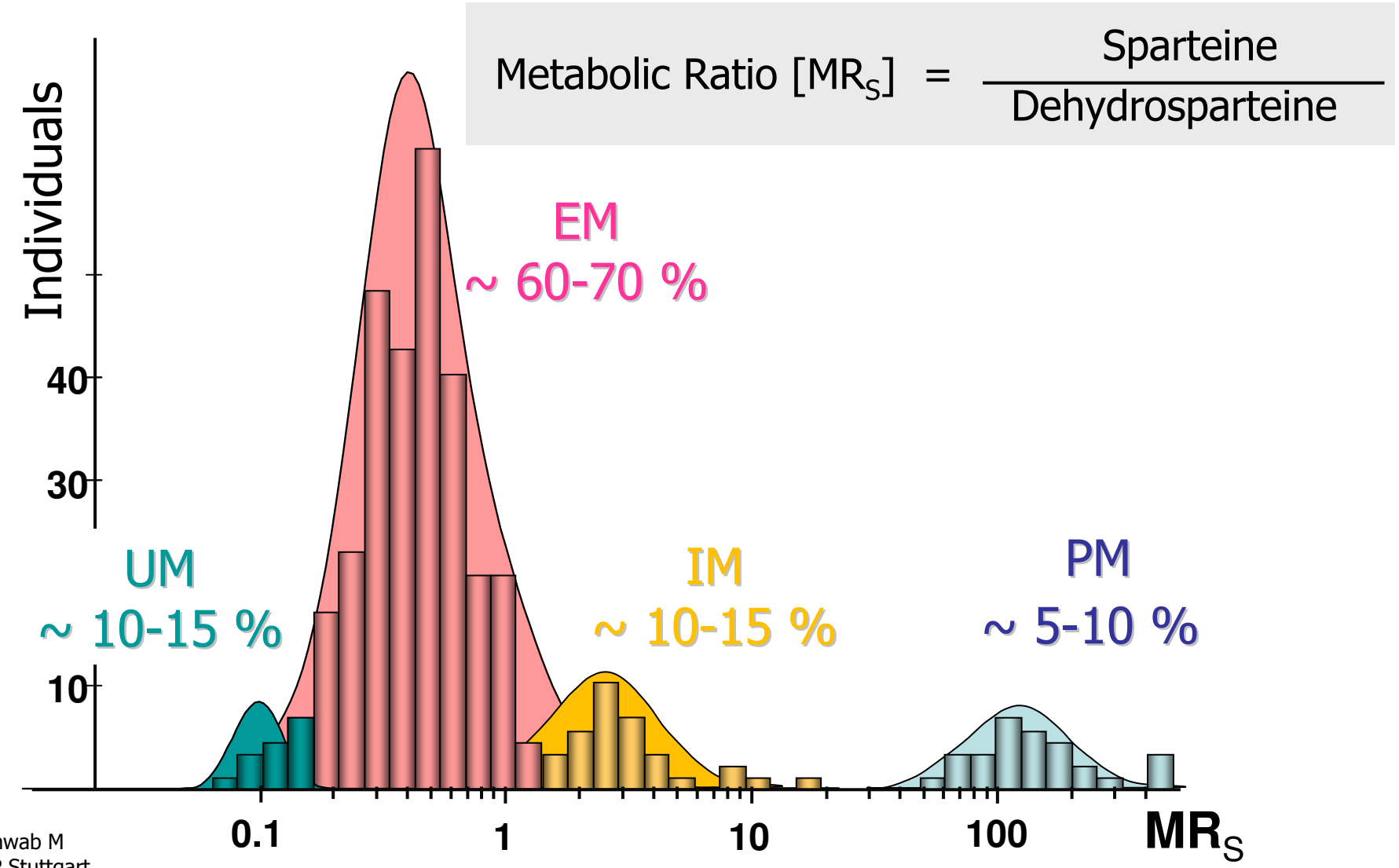
## N-Oxidation of Sparteine in Man and Interindividual Differences




HB 5008

# 2008: CYP2D6 Polymorphisms in Caucasians

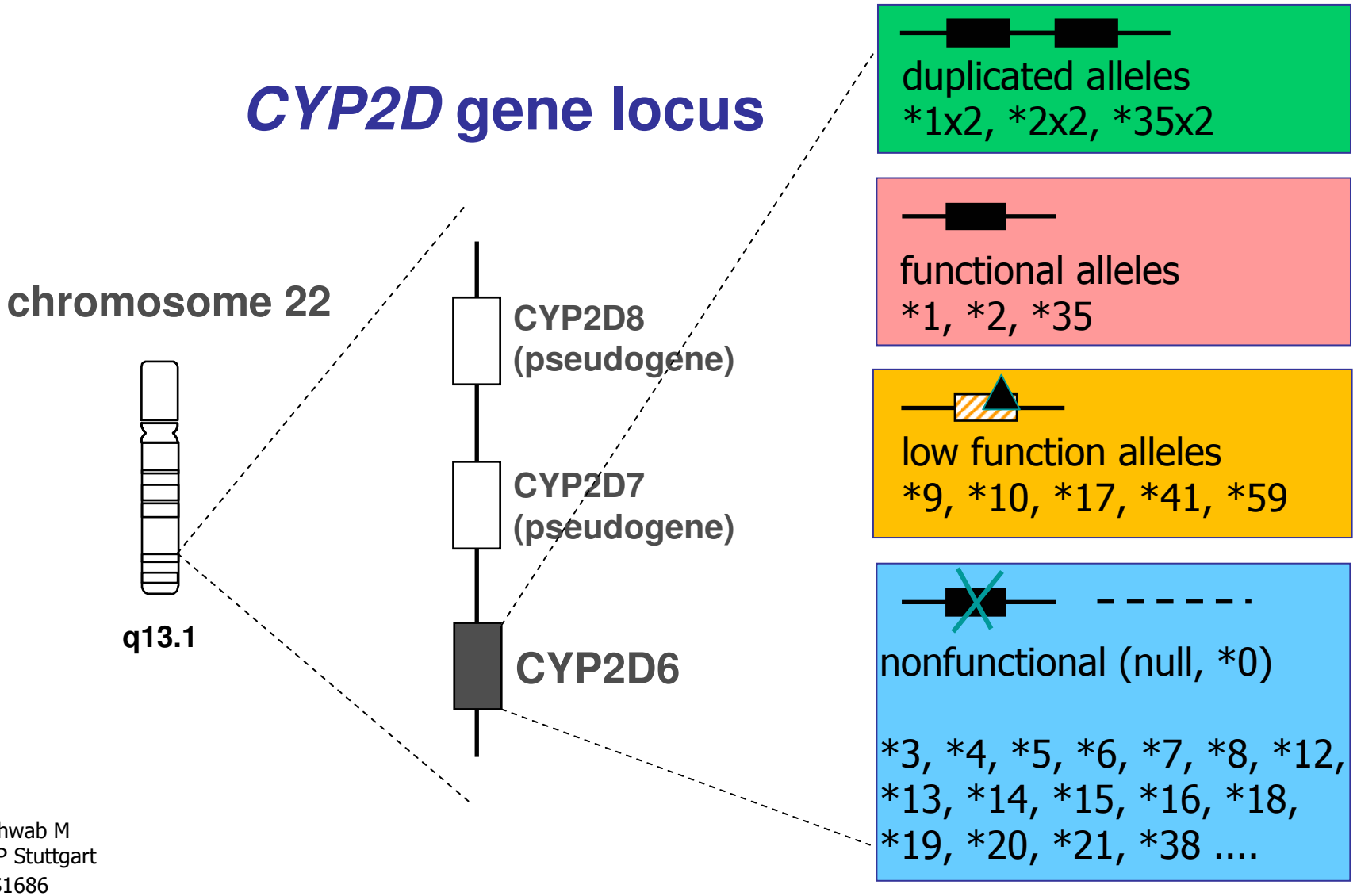
## Evolution of 4 Distinct Phenotypes




Schwab M
IKP Stuttgart
MS1685

# Molecular Basis of the *CYP2D6* Polymorphism

> 80 Genetic Variants




Schwab M
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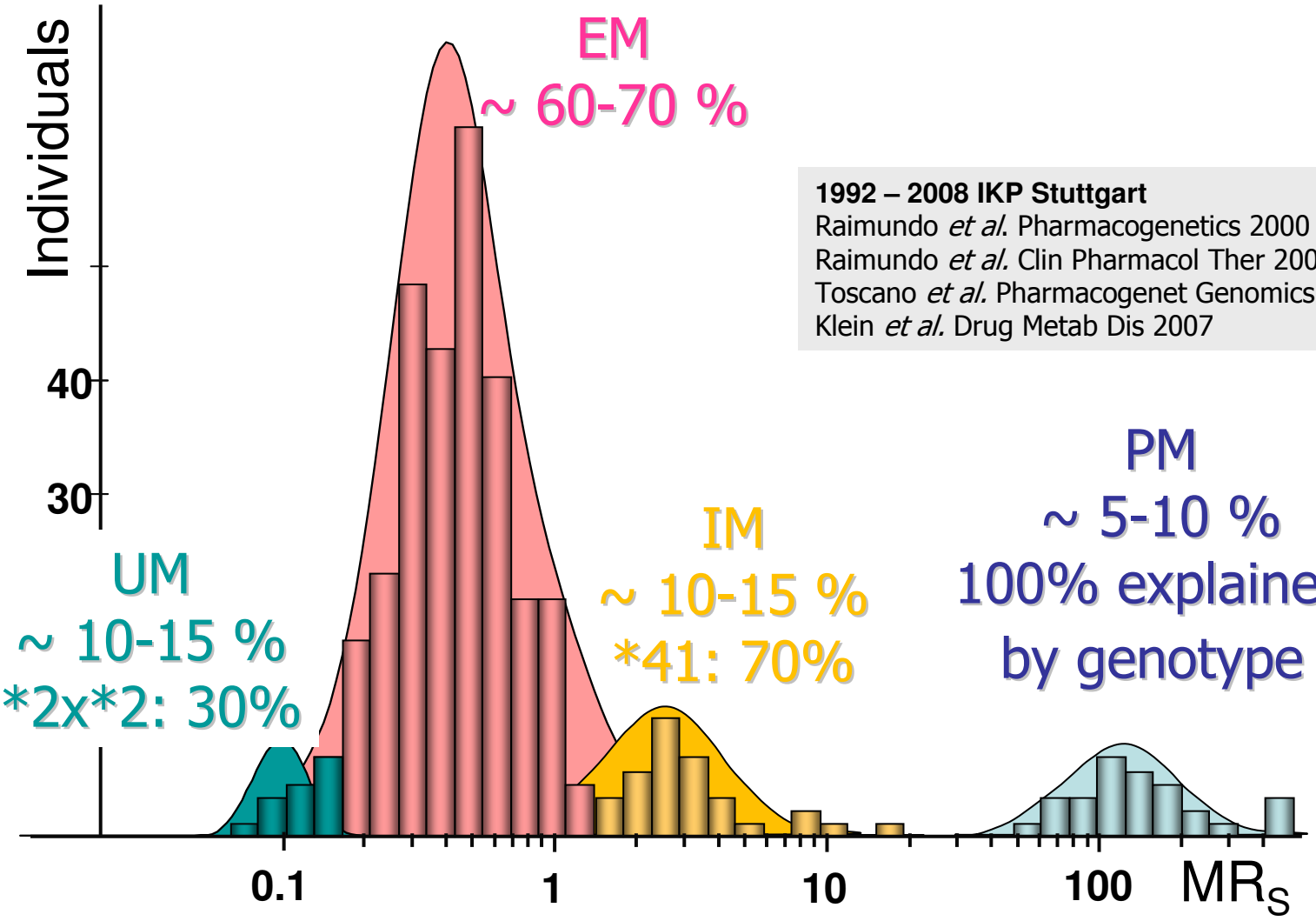
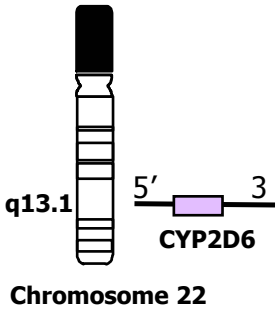
# CYP2D6 Metabolizer Phenotypes and Corresponding Genotypes



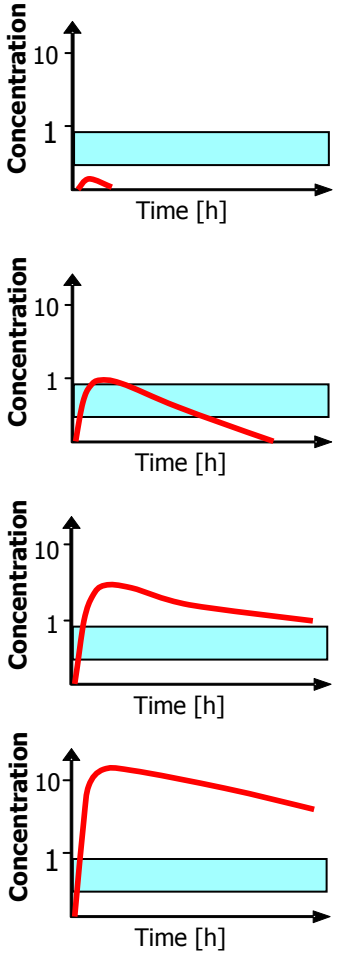

**1992 – 2008 IKP Stuttgart**
Raimundo *et al*. Pharmacogenetics 2000
Raimundo *et al.* Clin Pharmacol Ther 2004
Toscano *et al.* Pharmacogenet Genomics 2006
Klein *et al.* Drug Metab Dis 2007

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

# Predicted Consequences of *CYP2D6* Genotypes on Tamoxifen Therapy

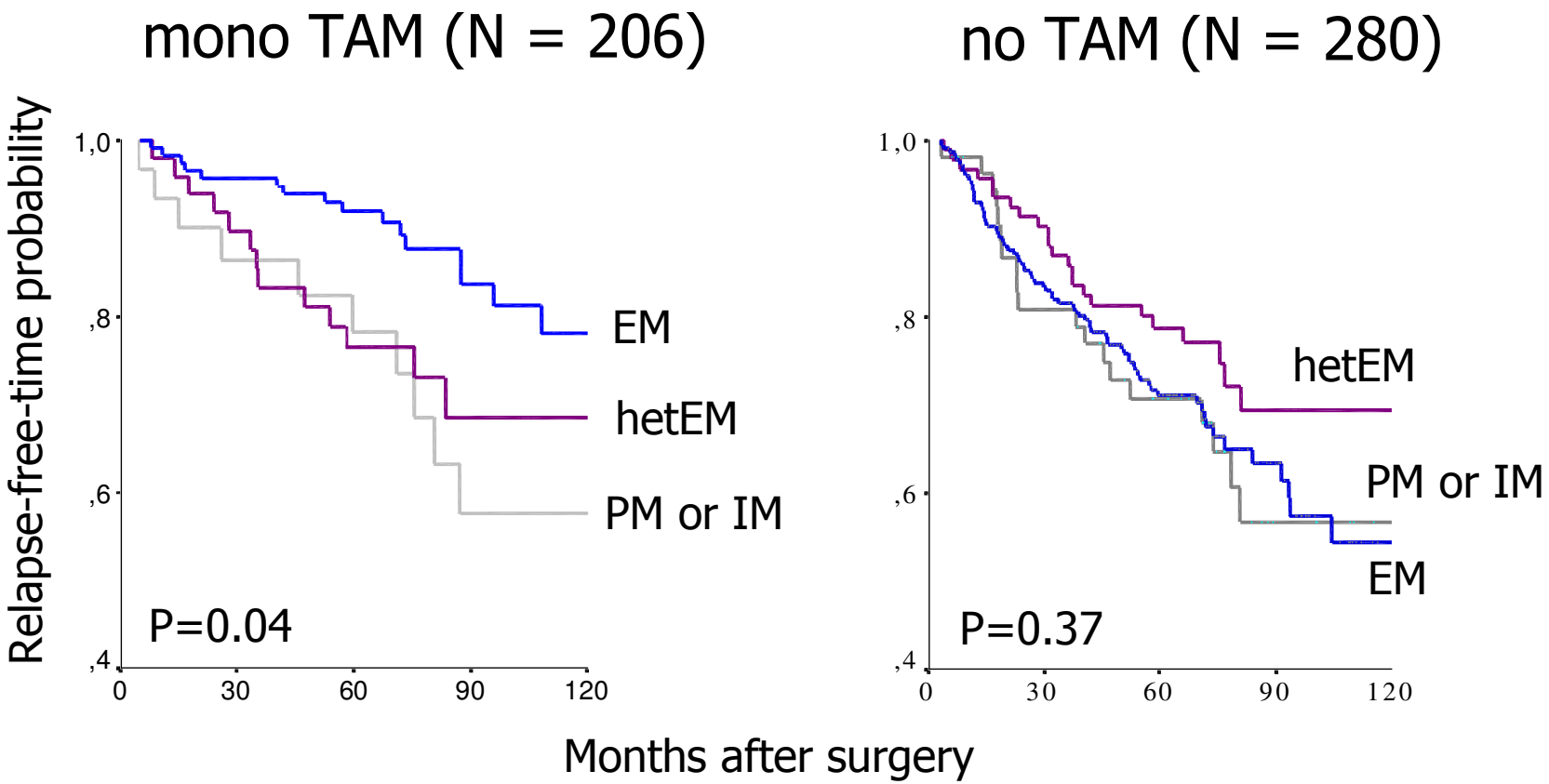



| Localization | Genotype | Function | Phenotype | Dose | Concentration of active tamoxifen metabolites |
|---|---|---|---|---|---|
| | mutations | deficient/ extreme slow metabolism | **PM** | | |
| | mutátions | decreased/ slow metabolism | **IM** | | |
| | normal | normal/ normal metabolism | **EM** | | |
| | amplification | increased/ ultra rapid metabolism | **UM** | | |




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

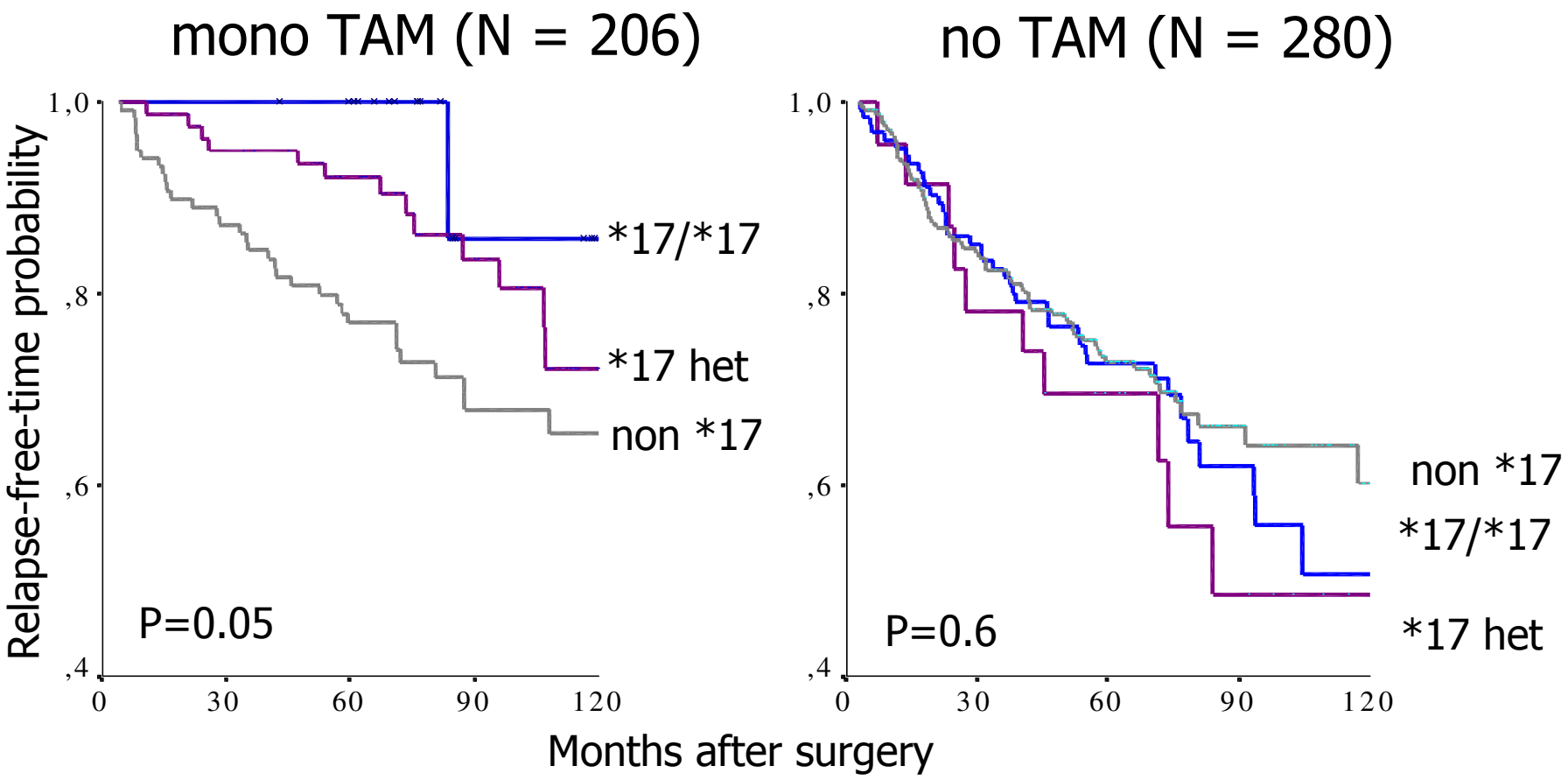
***Schroth et al. JCO 33:5187-5193, 2007***




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

# *CYP2C19* Tamoxifen Metabolizer Phenotypes

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

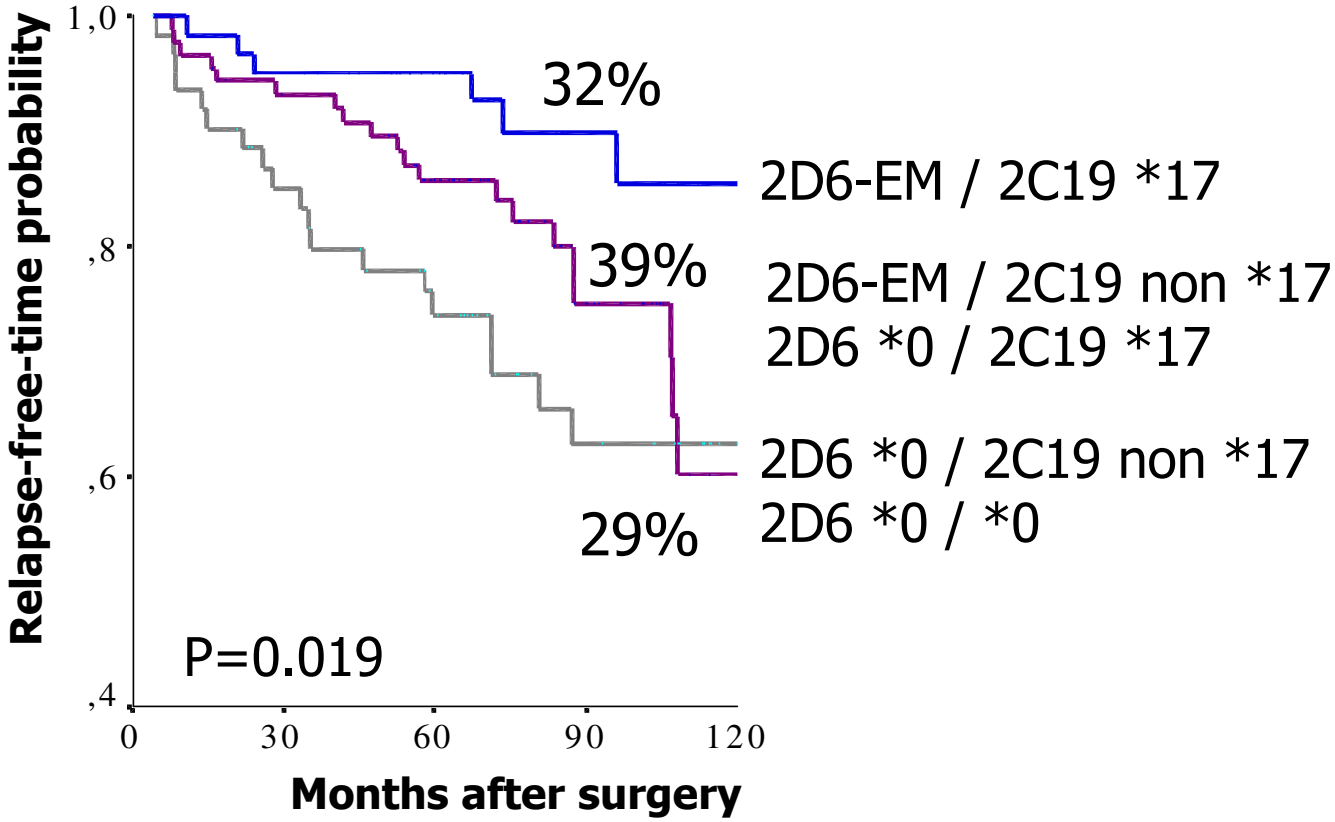



HR 0.45 (95% CI 0.21-0.92; *P* = .03)

# 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 *et al.* J Natl Cancer Inst 2003 | Endoxifen: high ER affinity of and growth suppression, SSRI affect tamoxifen metabolites |
| Desta *et al.* J Pharmacol Exp Ther 2004 | Tam Sequential Biotransformation |
| Jin *et al.* J Natl Cancer Inst 2005 | Endoxifen levels lower in patients with CYP2D6 hom variants |
| Borghes *et al.* Clin Pharmacol Ther 2006 | Quantitative effect of CYP2D6 and inhibitors |
| Lim *et al.* J Pharmacol Exp Ther 2006 | 4-OH Tam and endoxifen: similar changes in global gene expression (MCF7 cells) |
| Goetz *et al.* J Clin Oncol 2005<br>Breast Cancer Res Treat 2007 | Clinical outcome of efficacy and hot flashes<br>Combined effect of genetic variation and inhibition |
| Schroth *et al.* J Clin Oncol 2007 | Clinical outcome, PM and IM, no effect in control group, CYP2C19 potentially relevant |
| Lim *et al.* J Clin Oncol 2007 | Genotypes predictive of tamoxifen pharmacokinetics<br>Clinical Outcome |
| Xu *et al.* Annals of Oncology 2008 | Clinical outcome: genotype and survival |
| Kiyotani *et al.* Cancer Sci 2008 | Clinical outcome: genotype and recurrence |
| Mortimer *et al.* Breast Cancer Res Treat 2008 | WHEL trial: Hot flashes predict breast cancer outcome |
| Punglia *RS et al.* 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 *et al.* Breast Cancer Res Treat 2005 | CYP2D6*4 and decrease in number of recurrences |
| Nowell *et al.* Breast Cancer Res Treat 2005 | No association between CYP2D6 *4 and overall survival |
| Wegman *et al.* 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 Pharmacogenetics Consortium (ITPC)

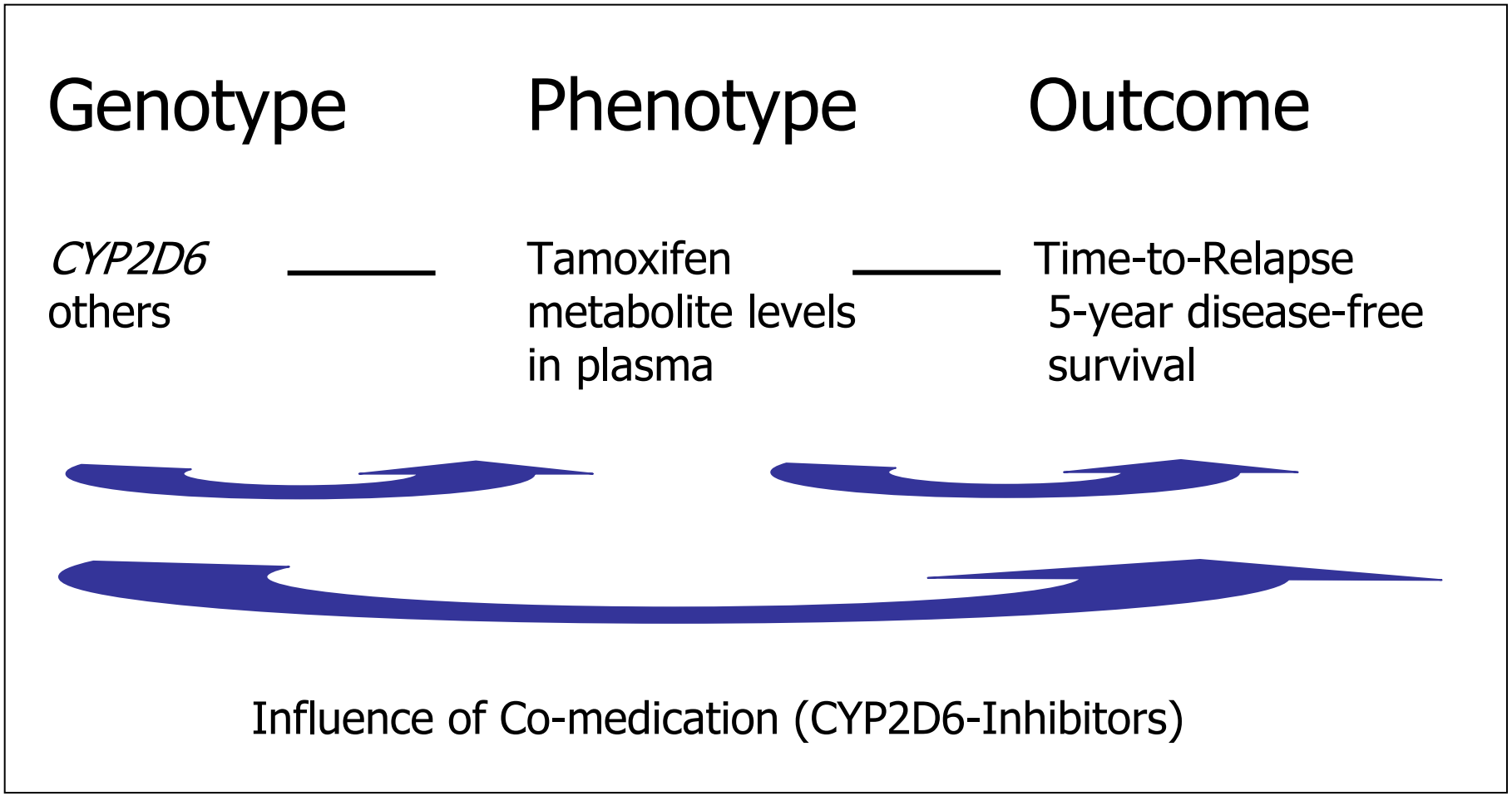
http://www.pharmgkb.org/views/project.jsp?pId=63

- data pooling and joint analysis

# IKP Studies: Tamoxifen – Pharmacogenomics

*Proof-of-Principle*

## IKP 211 (all in one)



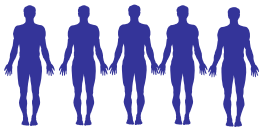
# IKP211 Observational Study

## BMBF Funding Period: 07/05 - 12/10

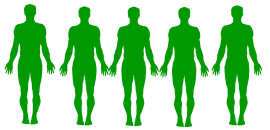
**TRAFO**
**Gütesiegel (05/07)**

## Study population

Newly diagnosed breast cancers
postmenopausal, ER+



600 TAM



600 AI

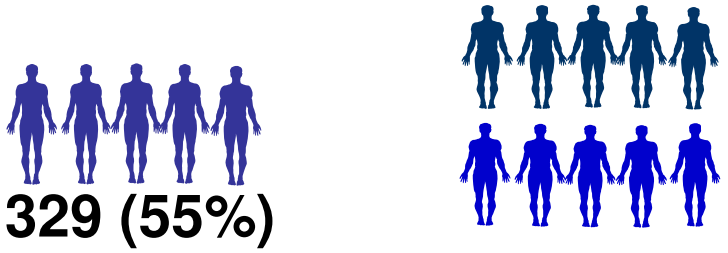
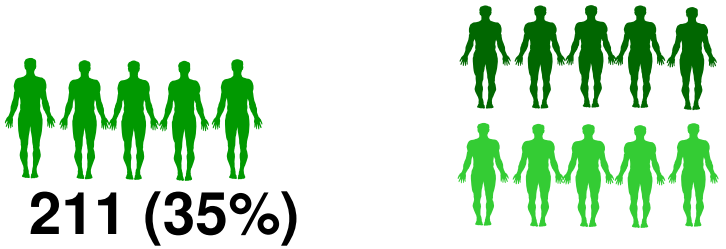
## Participating Centers in Germany

| | |
|---|---|
| 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<br>ER+, postmeno | IKP 211, CYP2D6 genetics<br>(mEH), TAM Metabolite, TGFß2 |
|---|---|
| Tamoxifen<br>600 |  <br>329 (55%) |
| Aromatase Inhibitor<br>600 |  <br>211 (35%) |

Bundesministerium für Bildung und Forschung

# Improvement of Breast Cancer Diagnosis and Treatment Tübingen - Stuttgart

IKP211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Robert Bosch Krankenhaus Stuttgart


Leiter der Klinischen Studie: Matthias Schwab
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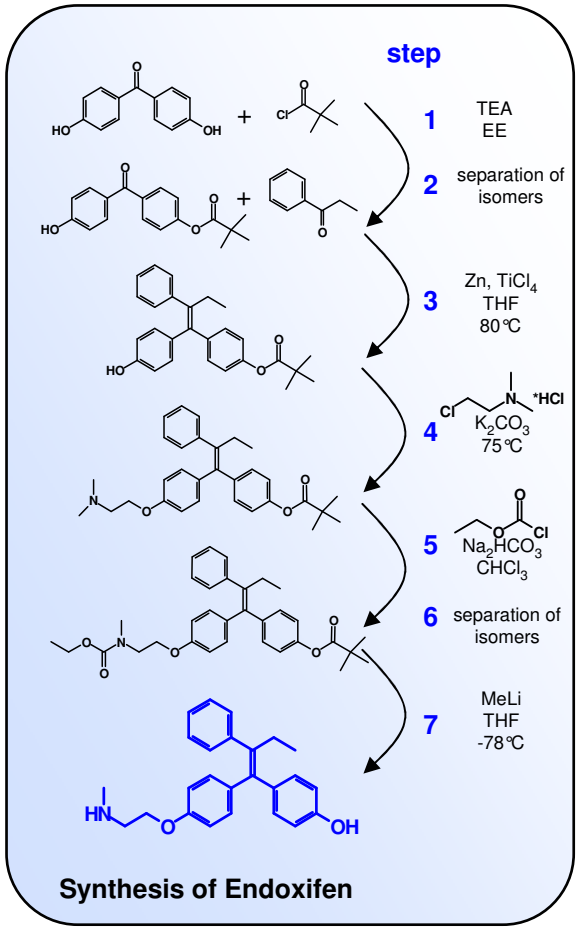
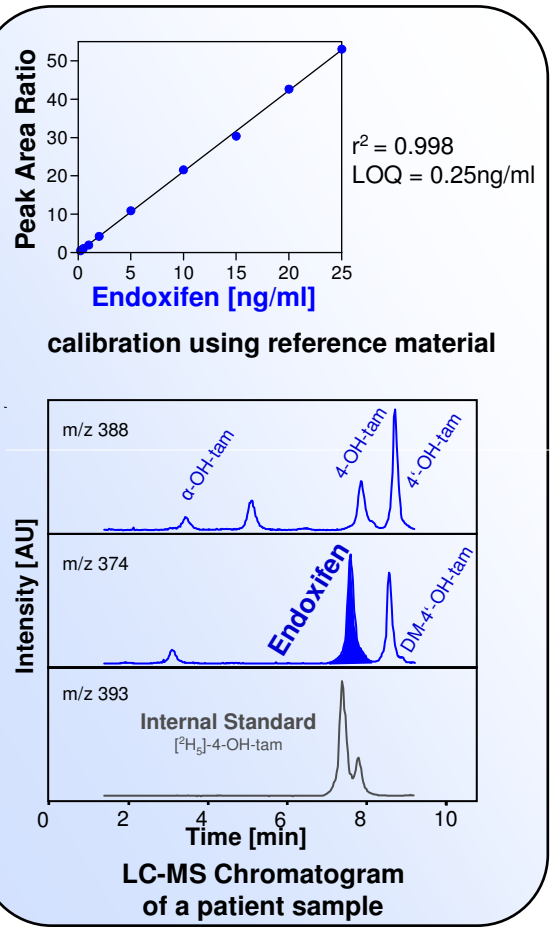
Koordinierungszentrum Klinische Studien am Universitätsklinikum Tübingen

# Chemical Synthesis, Analytics and Bedside

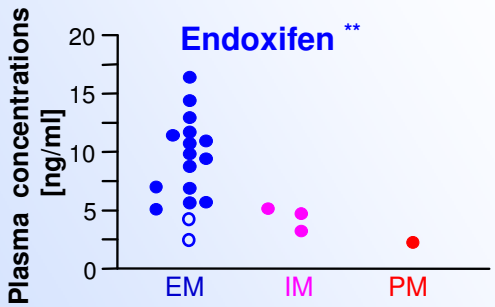
## Synthesis of reference materials




## Development of a sensitive analytical method




## Clinical trial

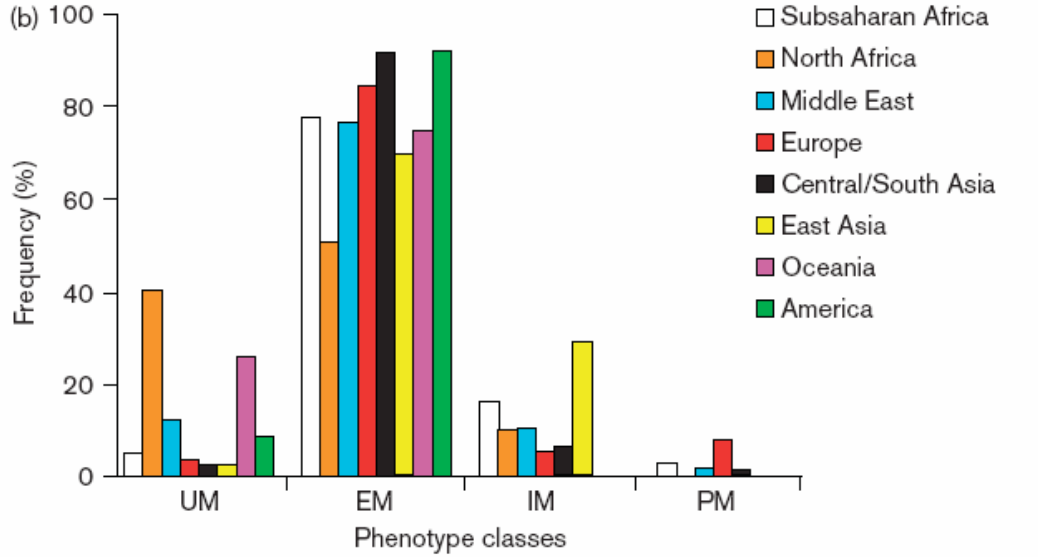



CYP2D6 polymorphisms and metabolism of tamoxifen

Mürdter et al. unpublished

# CYP2D6 Genotype – Phenotypes Correlation

## Global Distribution

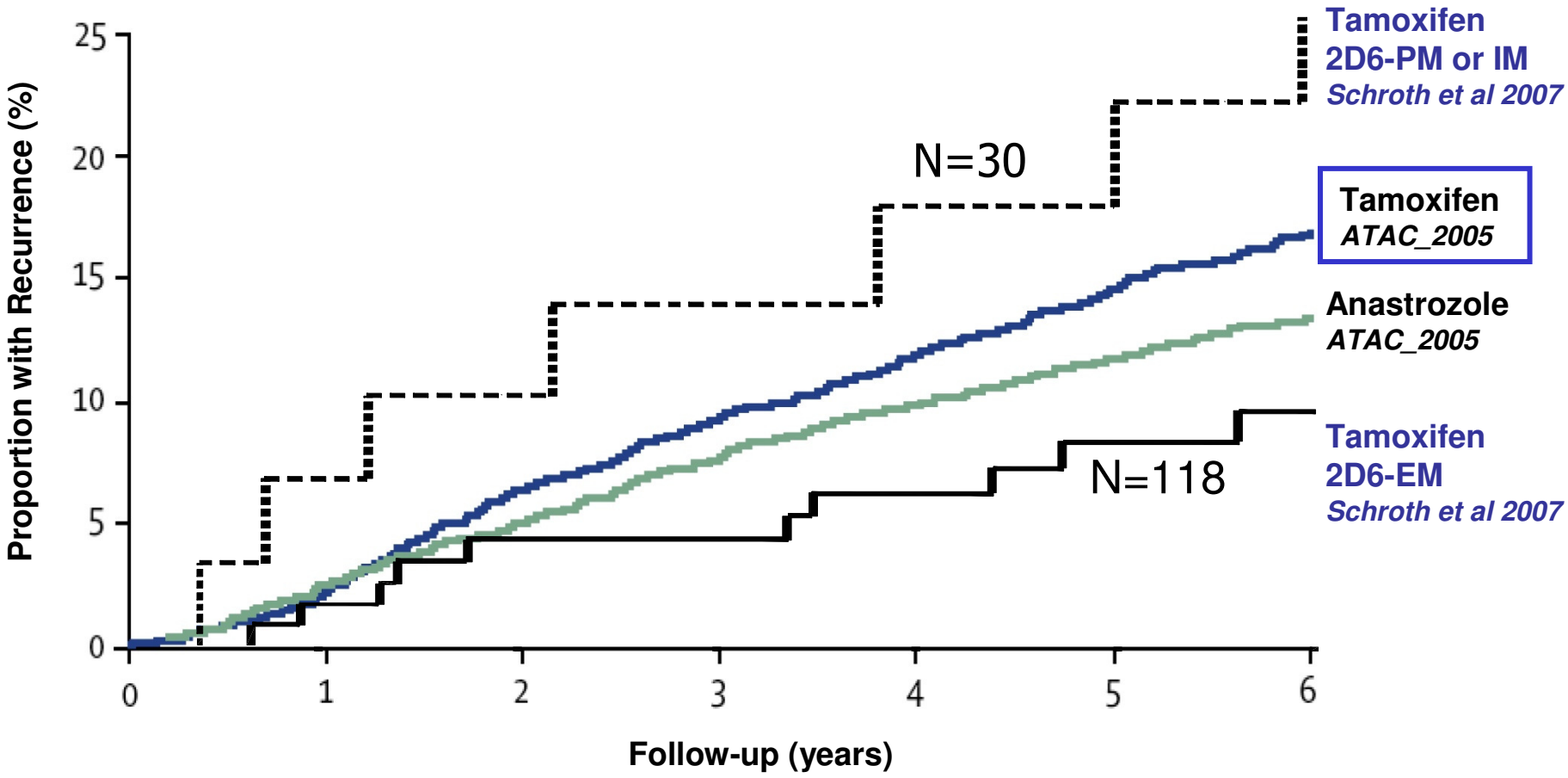



| Metabolizer | Frequency | Alleles |
|---|---|---|
| Poor (PM) | 5-10% | *3, *4, *5, *6, *7, *8 |
| Intermediate (IM) | 10-15% | *9, *10, *41, others |
| Extensive (EM) | 70-85% | *1 (wild type), *2 |
| Ultra rapid (UM) | ~2% | gene duplication |

*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

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# Breast Cancer Pharmacogenomics

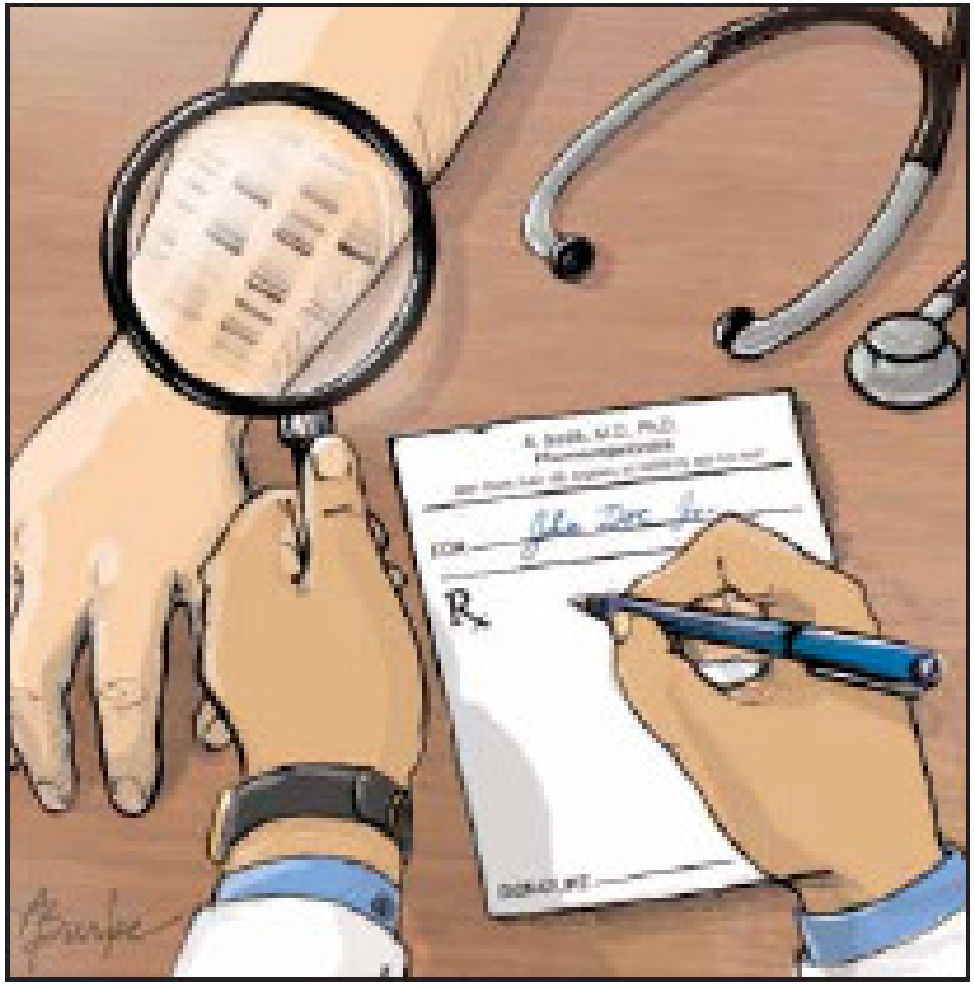
## Individualization of Drug Therapy

The right drug -

to the right patient -

at the right time -

in the right dose



# Acknowledgement


IKP STUTTGART

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Dieter Niederacher
Nadia Harbeck
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IKP STUTTGART

RBK Robert-Bosch-Krankenhaus

Breast Cancer Symposium 2009 Stuttgart

Eberhard-Karls-Universität UKT Universitätsklinikum Tübingen

# 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

IKP STUTTGART

Robert-Bosch-Krankenhaus

Eberhard-Karls-Universität UKT Universitätsklinikum Tübingen

## 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

**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