

Dept. Clinical Pharmacology, University Hospital, Tübingen

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



UNIVERSITÄTS  
KLINIKUM  
TÜBINGEN



***„Pharmacogenomics“ und  
„Precision Medicine“  
leere Worte oder konkrete Realität***

Prof. Matthias Schwab, M.D.

Adjunct Professor of the Yerevan State Medical University, Armenia

***Arzneimittelinformationskongress  
Köln, 02. Februar 2019***

# Meine Pille, deine Pille

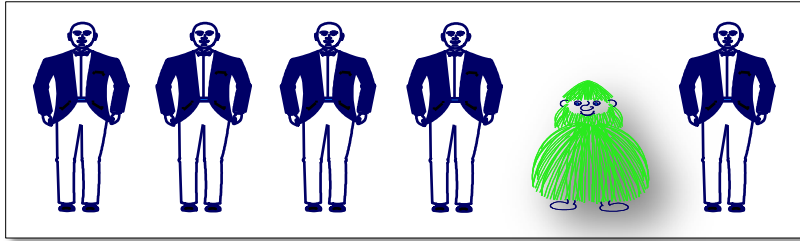
**Personalisierte Medizin** Die Genforschung verheißt perfekt auf den Patienten abgestimmte Therapie. Praxistauglich sind erst wenige.



## Bunte Vielfalt

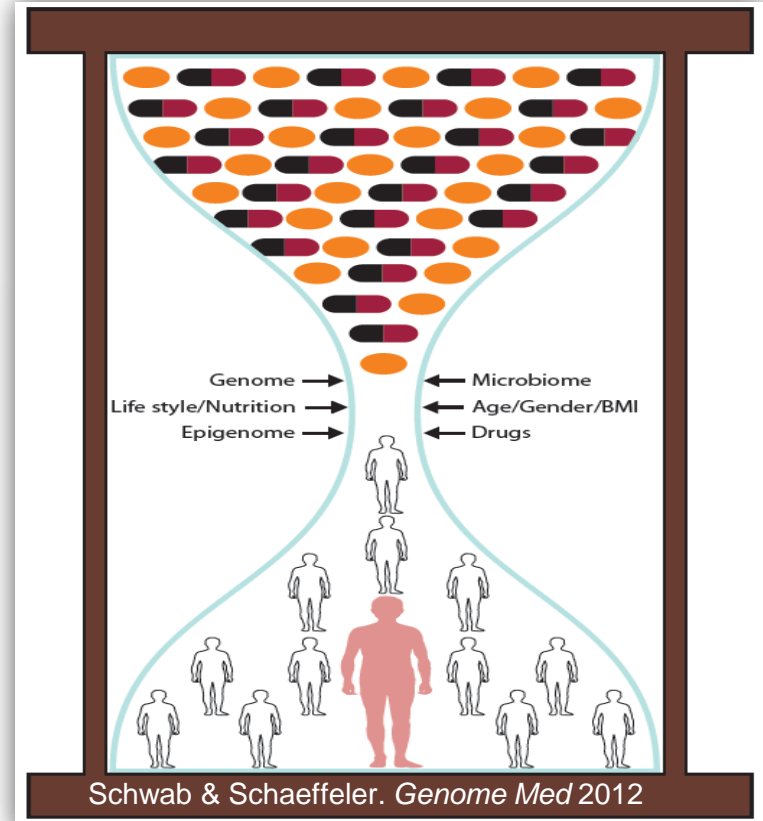
Jeder Mensch ist anders. Was den einen heilt, kann bei anderen versagen. Ziel ist es, mittels Genanalyse die optimale Arznei für jeden zu finden.

# Personalized / Precision Medicine: delicate balance between benefit and risk

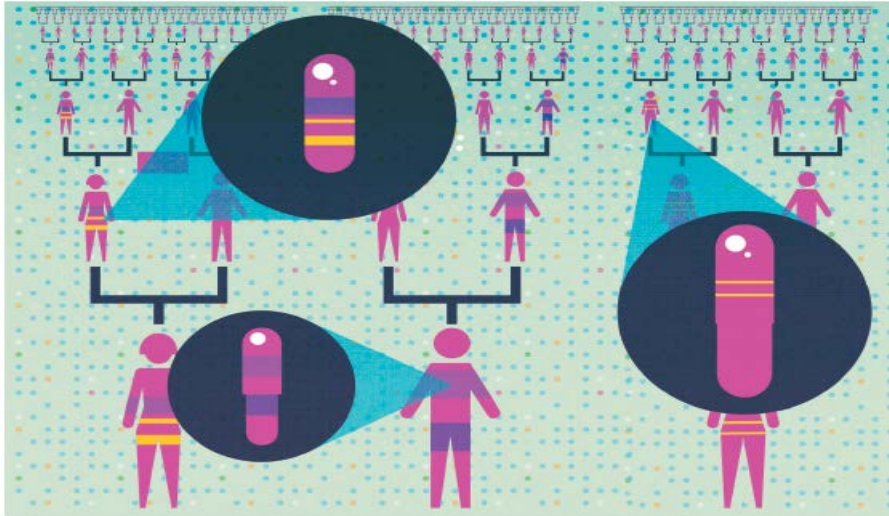


Precision medicine is “*an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment and lifestyle for each person.*”

<https://ghr.nlm.nih.gov/primer/precisionmedicine/definition>



Schwab & Schaeffeler. *Genome Med* 2012



PHARMACOGENETICS

# The right drug for you

*Personalized prescribing is gaining momentum, but is there enough evidence for it to become standard clinical practice?*

News & Analysis

Medical News & Perspectives

## Getting Pharmacogenomics Into the Clinic

Jennifer Abbasi



**“We’ve had 50 years of research showing why it should be done.”**

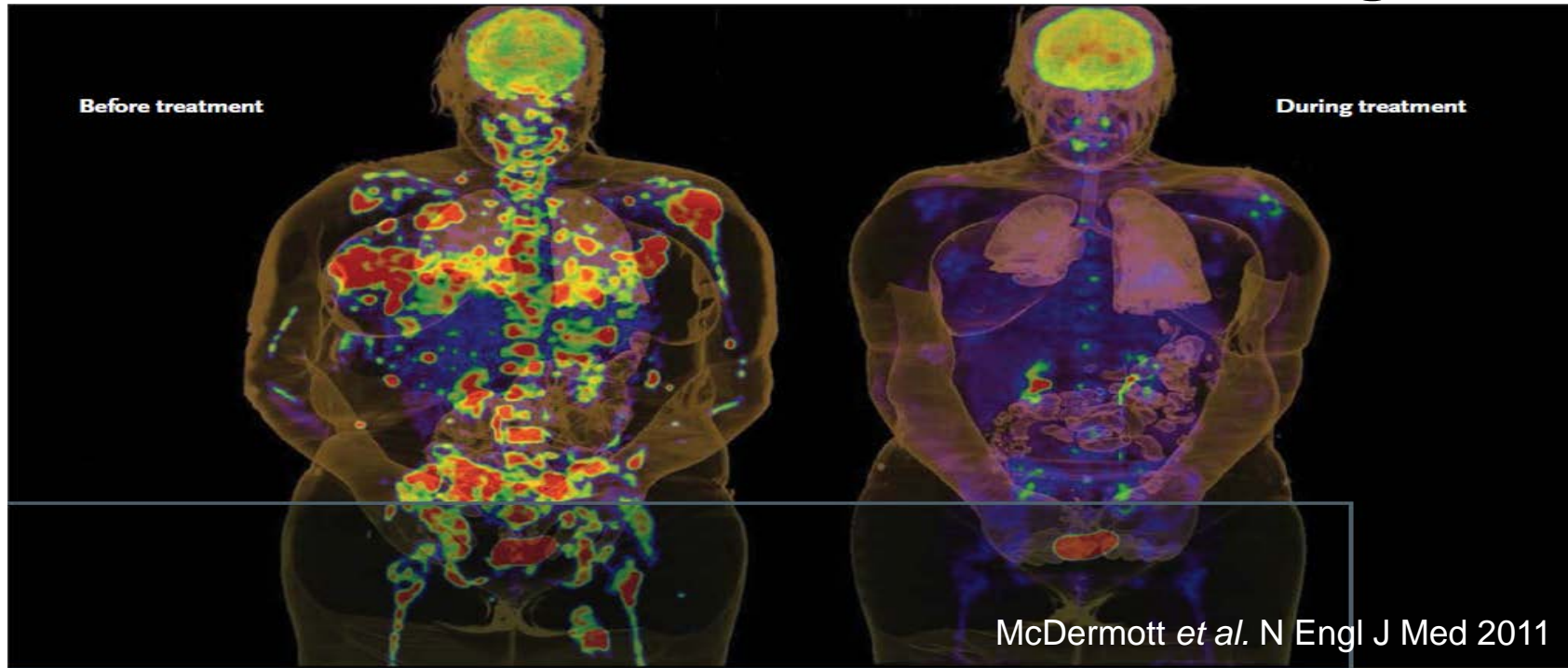
**“Let’s stop arguing about whether to do it and just show how to do it.”**

# Genomic information from tumors provide vital information to guide drug development and treatment decisions



Cohen & Settleman. *Cell* 2014

# Targeting treatment to the activating V600E *BRAF* variant in the melanoma gene

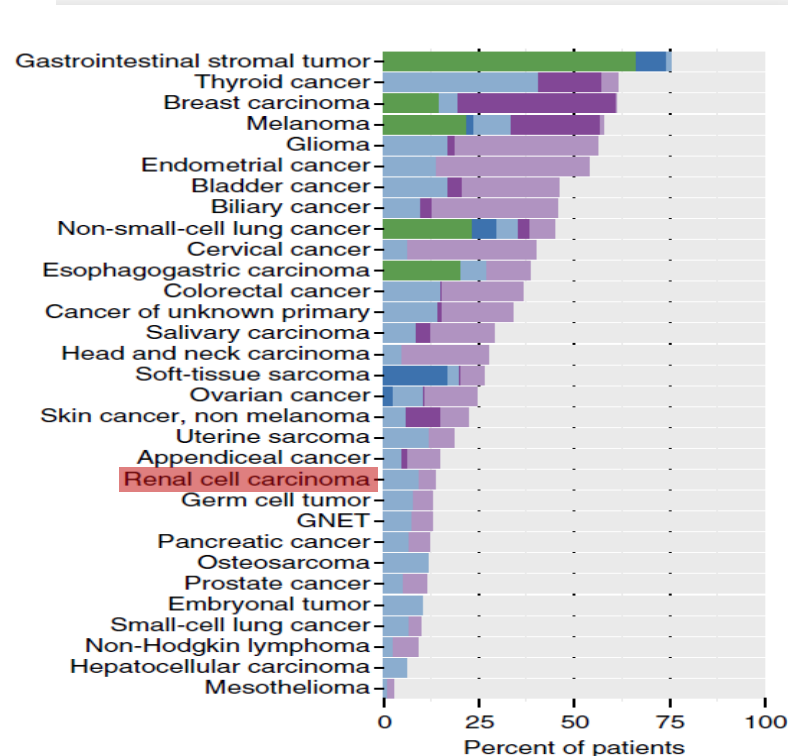
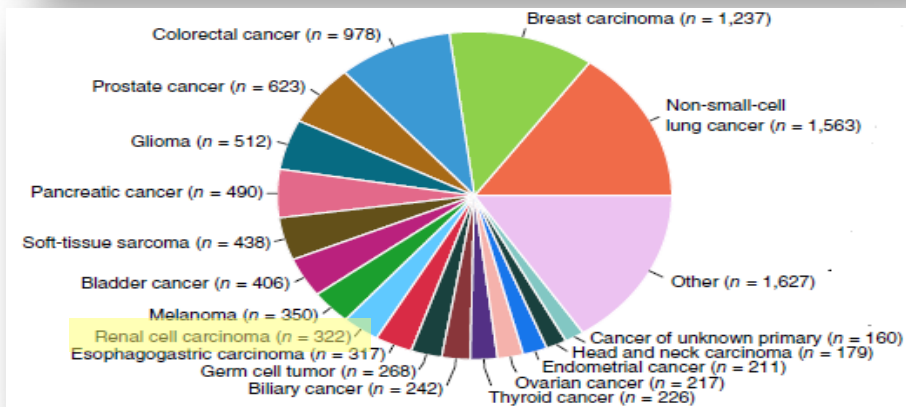


BRAF inhibitors  
(V600E, V600K)

**vemurafenib** (Chapmann *et al.* N Engl J Med **2011**)  
**trametinib** (Flaherty *et al.* N Engl J Med **2012**)

# Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients

VOLUME 23 | NUMBER 6 | JUNE 2017 NATURE MEDICINE



Level 1	FDA-recognized biomarker for an FDA-approved drug in the same indication
Level 2A	Standard of care biomarker for an FDA-approved drug in the same indication
Level 2B	Standard of care biomarker for an FDA-approved drug in another indication
Level 3A	Compelling clinical evidence supporting the biomarker as being predictive of drug response in the same indication
Level 3B	Compelling clinical evidence supporting the biomarker as being predictive of drug response in another indication

# Genetic variation in human drug-related genes



Genome Medicine 2017

Charlotta Pauline Irmgard Schärfe<sup>1,2,3</sup>, Roman Tremmel<sup>4</sup>, Matthias Schwab<sup>4,5,6,7</sup>, Oliver Kohlbacher<sup>2,3,8,9,10\*</sup> and Debora Susan Marks<sup>1\*</sup>

ARTICLE

Analysis of protein-coding genetic variation in 60,706 humans

**FOUR in FIVE patients**

**are likely to carry a variant**

**with possibly functional effects**

**in a drug-related gene**

**for commonly prescribed drugs.**



# More than >160 FDA-approved drugs with labeled pharmacogenomic information

U.S. Department of Health and Human Services

**FDA U.S. FOOD & DRUG ADMINISTRATION**

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Home | Food | **Drugs** | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products

## Drugs

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<b>Science &amp; Research (Drugs)</b>
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<a href="#">Research Tools and Resources</a>
<a href="#">Scientific Public Private Partnerships and Consortia</a>
<a href="#">CDER Scientists</a>
<a href="#">Regulatory Science in Action</a>
<a href="#">Videos and Podcasts on Regulatory Science at CDER</a>
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## Table of Pharmacogenomic Biomarkers in Drug Labeling

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Page Last Updated: 02/08/2018

Back to [Pharmacogenomics: Overview of the Genomics and Targeted Therapy Group](#)

Pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose. Drug labeling may contain information on genomic biomarkers and can describe:

- Drug exposure and clinical response variability
- Risk for adverse events
- Genotype-specific dosing
- Mechanisms of drug action
- Polymorphic drug target and disposition genes

### Learn More About Pharmacogenomics at CDER

- [Pharmacogenomics: Overview of the Genomics and Targeted Therapy Group](#)
- [Other FDA Resources Related to Pharmacogenomics](#)

<https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm>

## **Incorporation of Pharmacogenomics into Routine Clinical Practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline Development Process**

Kelly E. Caudle<sup>1\*</sup>, Teri E. Klein<sup>2</sup>, James M. Hoffman<sup>1</sup>, Daniel J. Müller<sup>3,4</sup>, Michelle Whirl-Carrillo<sup>2</sup>, Li Gong<sup>2</sup>, Ellen M. McDonagh<sup>2</sup>, Katrin Sangkuhl<sup>2</sup>, Caroline F. Thorn<sup>2</sup>, **Matthias Schwab**<sup>5,6</sup>, José A.G. Agúndez<sup>7</sup>, Robert R. Freimuth<sup>8</sup>, Vojtech Huser<sup>9</sup>, Ming Ta Michael Lee<sup>10,11,12</sup>, Otito F. Iwuchukwu<sup>13</sup>, Kristine R. Crews<sup>1</sup>, Stuart A. Scott<sup>14</sup>, Mia Wadelius<sup>15</sup>, Jesse J. Swen<sup>16</sup>, Rachel F. Tyndale<sup>3,4</sup>, C. Michael Stein<sup>13,17</sup>, Dan Roden<sup>13,17</sup>, Mary V. Relling<sup>1</sup>, Marc S. Williams<sup>18</sup> and Samuel G. Johnson<sup>19,20</sup>

## **Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing: 2013 Update**

Clin Pharmacol Ther 2013

MV Relling<sup>1</sup>, EE Gardner<sup>2</sup>, WJ Sandborn<sup>3</sup>, K Schmiegelow<sup>4,5</sup>, C-H Pui<sup>6</sup>, SW Yee<sup>7</sup>, CM Stein<sup>8</sup>, M Carrillo<sup>9</sup>, WE Evans<sup>1</sup>, JK Hicks<sup>1</sup>, **M Schwab**<sup>10,11</sup> and TE Klein<sup>9</sup>

## **Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update**

Ursula Amstutz<sup>1</sup>, Linda M. Henricks<sup>2</sup>, Steven M. Offer<sup>3</sup>, Julia Barbarino<sup>4</sup>, Jan H.M. Schellens<sup>2,5</sup>, Jesse J. Swen<sup>6</sup>, Teri E. Klein<sup>4</sup>, Howard L. McLeod<sup>7</sup>, Kelly E. Caudle<sup>8</sup>, Robert B. Diasio<sup>3,9</sup> and **Matthias Schwab**<sup>10,11,12</sup>

Clin Pharmacol Ther 2017

## **Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 Genotype and Use of Ondansetron and Tropisetron**

GC Bell<sup>1</sup>, KE Caudle<sup>2</sup>, M Whirl-Carrillo<sup>3</sup>, RJ Gordon<sup>4</sup>, K Hikino<sup>5</sup>, CA Prows<sup>6</sup>, A Gaedigk<sup>7</sup>, JAG Agundez<sup>8,9</sup>, S Sadhasivam<sup>10,11</sup>, TE Klein<sup>3</sup> and **M Schwab**<sup>12,13,14</sup>

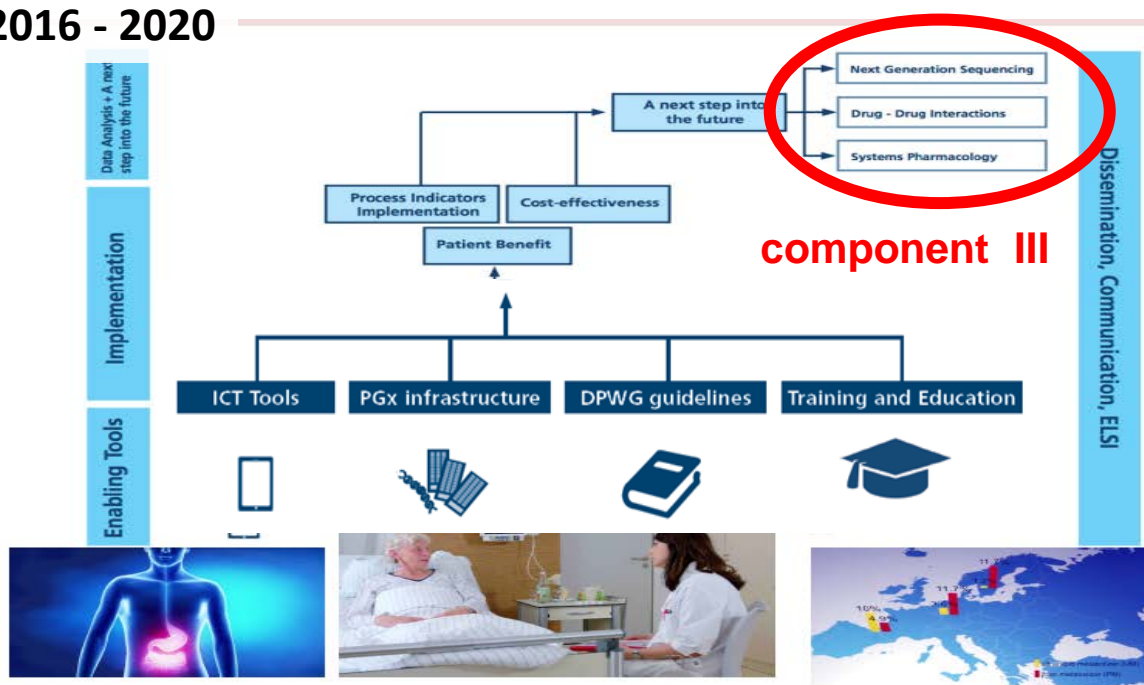
Clin Pharmacol Ther 2017

# Ubiquitous Pharmacogenomics (U-PGx):

Making actionable pharmacogenomic data and effective treatment optimization accessible to Every European citizen

Vice-chair of the consortium / leader of component III: M Schwab

2016 - 2020



component III



H2020-PHC-24-2015

Total budget:

15.000 T€

VIEWPOINT

A brighter future for the implementation of pharmacogenomic testing

Cathelijne H van der Wouden<sup>1</sup>, Jesse J Swen<sup>1</sup>, Matthias Samwald<sup>2</sup>, Christina Mitropoulou<sup>3</sup>, Matthias Schwab<sup>4,5</sup> and Henk-Jan Guchelaar<sup>1</sup> on behalf of the Ubiquitous-Pharmacogenomics Consortium

European Journal of Human Genetics (2016) 24, 1658–1660; doi:10.1038/ejhg.2016.116; published online 31 August 2016

Prospective patient cohort N=8000



Standorte

Disziplinen

Bildung

Forschung

Über uns



20. März 2018 | Dr. Margarete Fischer-Bosch-Institut für Klinische Pharmakologie  
**Robert-Bosch-Krankenhaus Stuttgart und bio.logis GIM integrieren Pharmakogenetik in den klinischen Alltag – ein Meilenstein für personalisierte Medizin**

**Implementierung der IT-Plattform Genetic Information Management Suite (bio.logis) zur automatisierten Befundersterstellung**

#### Pressekontakt

Robert-Bosch-Krankenhaus  
Unternehmenskommunikation  
Auerbachstraße 110  
70376 Stuttgart

Telefon 07 11/8101-3047  
Telefax 07 11/8101-3779

März 2018



## Press release

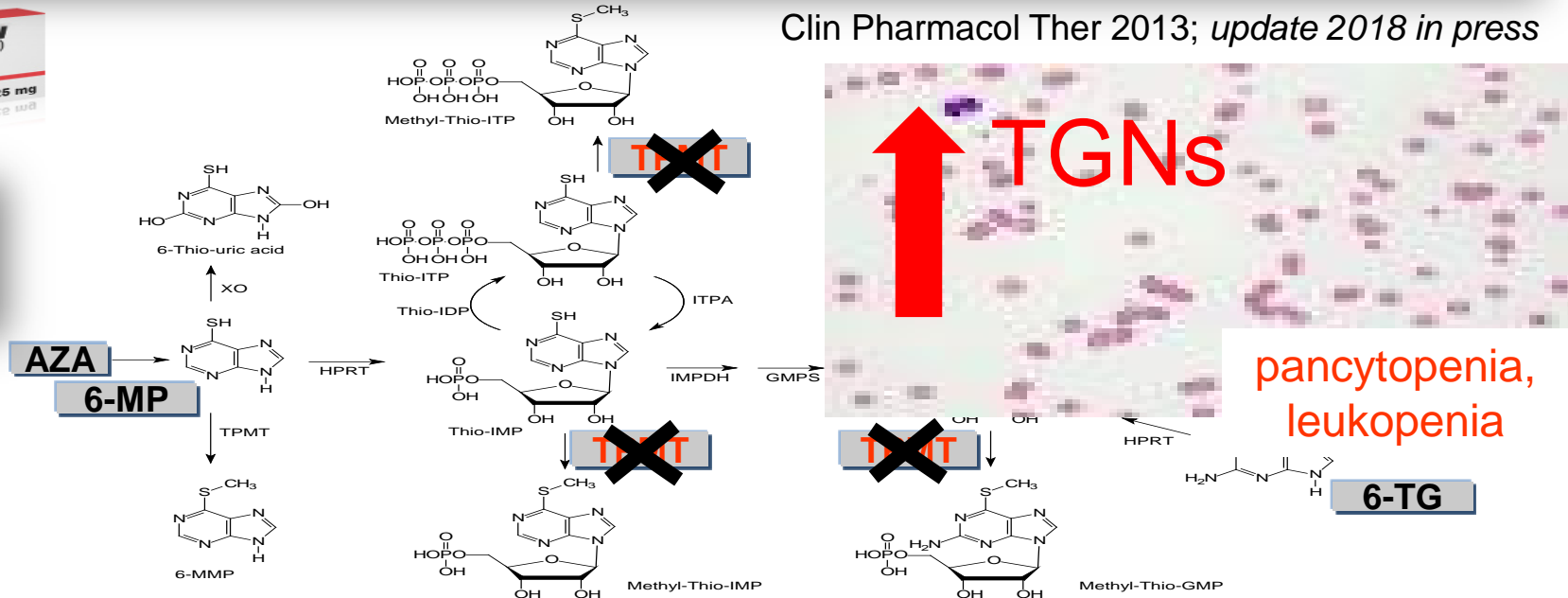
### **German Hospital Integrates New Bio.logis PGx Suite Into Clinical Workflow**

A German hospital is the first to integrate the Bio.logis Genetic Information Management Suite into a clinical genomics program, the company said today.

<https://www.rbk.de/service/presse/pressemeldung/article/robert-bosch-krankenhaus-stuttgart-und-biologis-gim-integrieren-pharmakogenetik-in-den-klinischen-alltag-ein-meilenstein-fuer-personalisierte-medizin.html>

# Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing: 2013 Update

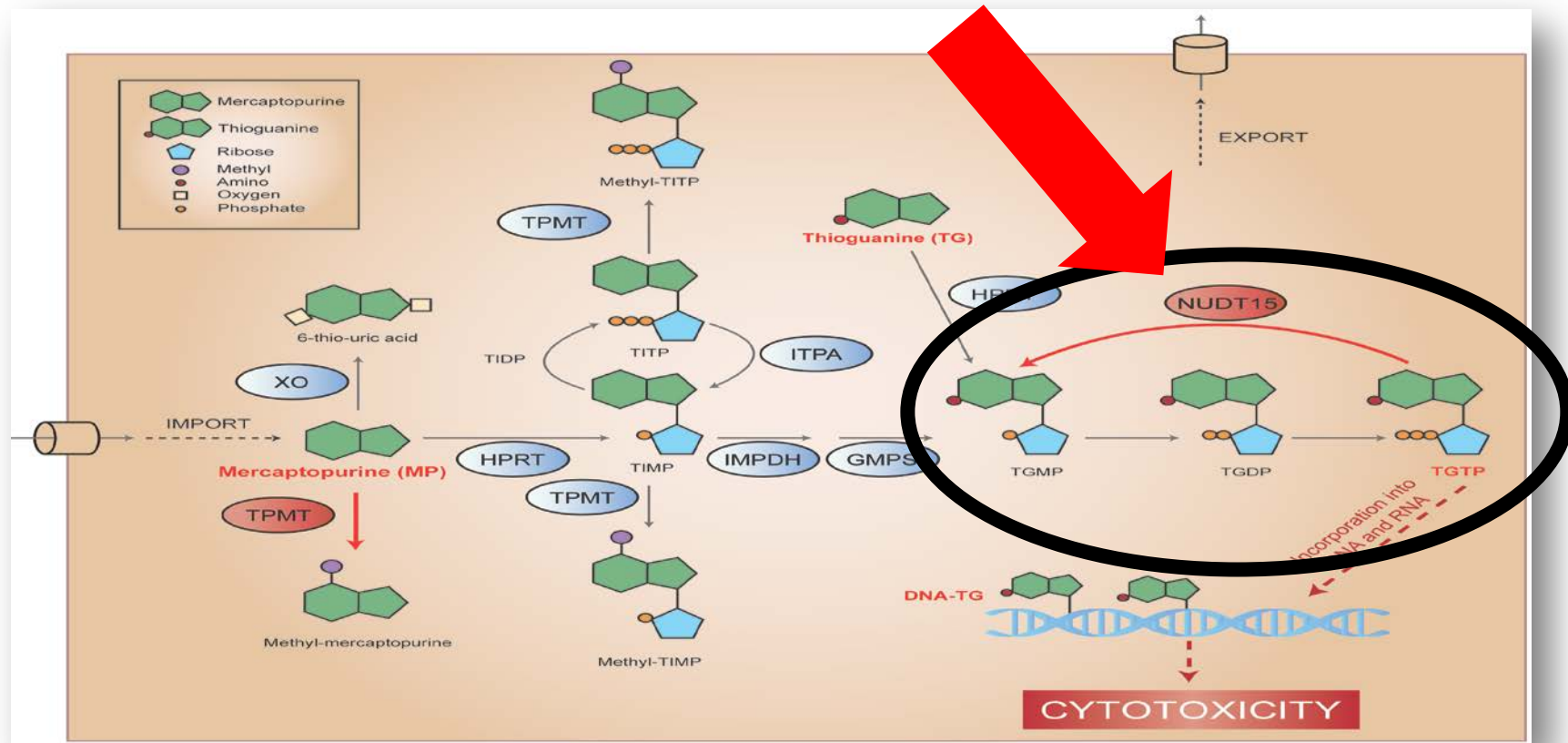
MV Relling<sup>1</sup>, EE Gardner<sup>2</sup>, WJ Sandborn<sup>3</sup>, K Schmiegelow<sup>4,5</sup>, C-H Pui<sup>6</sup>, SW Yee<sup>7</sup>, CM Stein<sup>8</sup>, M Carrillo<sup>9</sup>, WE Evans<sup>1</sup>, JK Hicks<sup>1</sup>, M Schwab<sup>10,11</sup> and TE Klein<sup>9</sup>



Schaeffeler *et al.* 2001, 2003, 2004, 2006, 2008, Schwab *et al.* 2001, 2002, Teml *et al.* 2007, 2009, Stanulla *et al.* 2005, 2009, Appell *et al.* 2013, Relling *et al.* 2013; Tamm *et al.* 2017; Rieger *et al.* 2018

# A new predictor for thiopurine drug toxicity

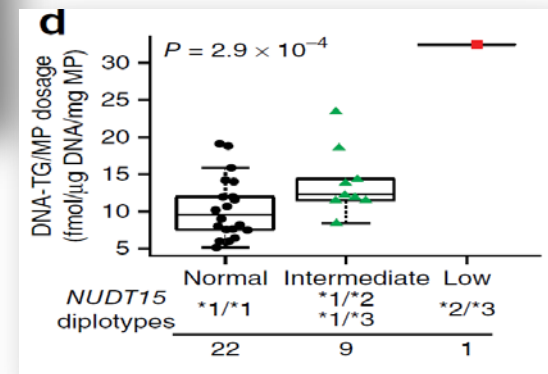
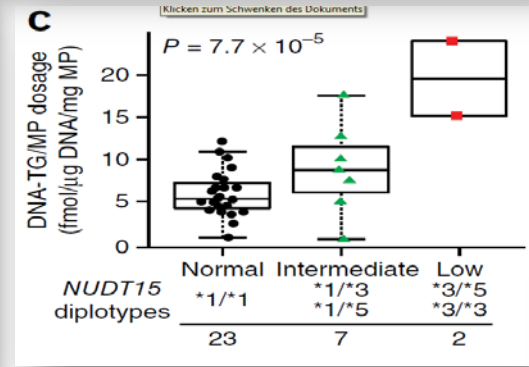
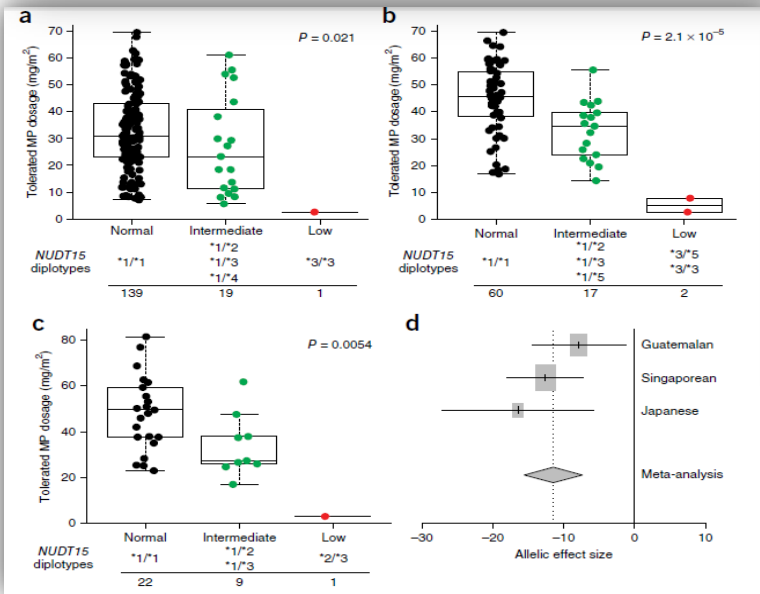
## NUDT15 (Nudix hydrolase 15)



# NUDT15 polymorphisms alter thiopurine metabolism and hematopoietic toxicity

Takaya Moriyama<sup>1,2</sup>, Rina Nishii<sup>1,3,22</sup>, Virginia Perez-Andreu<sup>1,22</sup>, Wenjian Yang<sup>1</sup>, Federico Antillon Klusmann<sup>4,5</sup>, Xujie Zhao<sup>1</sup>, Ting-Nien Lin<sup>1</sup>, Keito Hoshitsuki<sup>1,6</sup>, Jacob Nersting<sup>7</sup>, Kentaro Kihira<sup>2</sup>, Ute Hofmann<sup>8,9</sup>, Yoshihiro Komada<sup>2</sup>, Motohiro Kato<sup>10</sup>, Robert McCorkle<sup>1</sup>, Lie Li<sup>1</sup>, Katsuyoshi Koh<sup>11</sup>, Cesar Rolando Najera<sup>4</sup>, Shirley Kow-Yin Kham<sup>12</sup>, Tomoya Isobe<sup>13</sup>, Zhiwei Chen<sup>12</sup>, Edwynn Kean-Hui Chiew<sup>12</sup>, Deepa Bhojwani<sup>14</sup>, Cynthia Jeffries<sup>15</sup>, Yan Lu<sup>15</sup>, Matthias Schwab<sup>8,9,16,17</sup>, Hiroto Inaba<sup>18</sup>, Ching-Hon Pui<sup>18</sup>, Mary V Relling<sup>1</sup>, Atsushi Manabe<sup>19</sup>, Hiroki Hori<sup>2</sup>, Kjeld Schmiegelow<sup>7,20</sup>, Allen E J Yeoh<sup>12,21</sup>, William E Evans<sup>1</sup> & Jun J Yang<sup>1</sup>

2016

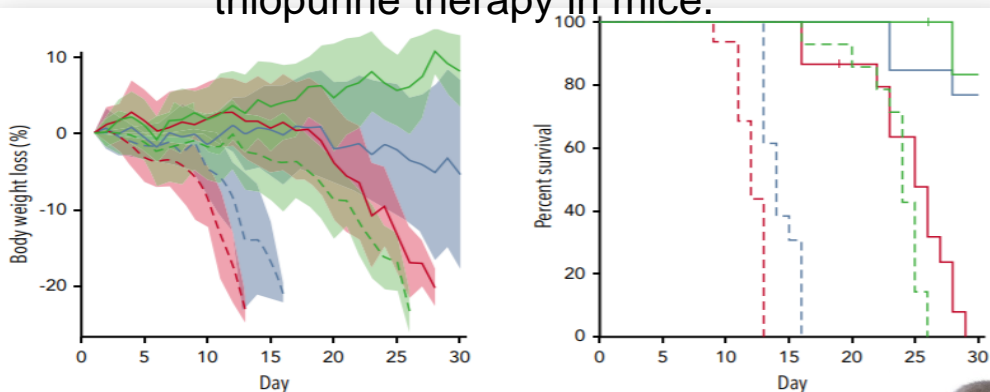


Clinically relevant ONLY for Asians

# Preclinical evaluation of *NUDT15*-guided thiopurine therapy and its effects on toxicity and antileukemic efficacy

Rina Nishii,<sup>1,2,\*</sup> Takaya Moriyama,<sup>1,\*</sup> Laura J. Janke,<sup>3</sup> Wenjian Yang,<sup>1</sup> Chase C. Suiter,<sup>1</sup> Ting-Nien Lin,<sup>1</sup> Lie Li,<sup>1</sup> Kentaro Kihira,<sup>4</sup> Hidemi Toyoda,<sup>4</sup> Ute Hofmann,<sup>5,6</sup> Matthias Schwab,<sup>5-8</sup> Masatoshi Takagi,<sup>2</sup> Tomohiro Morio,<sup>2</sup> Atsushi Manabe,<sup>9</sup> Shirley Kham,<sup>10,11</sup> Nan Jiang,<sup>10,11</sup> Karen R. Rabin,<sup>12</sup> Motohiro Kato,<sup>13</sup> Katsuyoshi Koh,<sup>14</sup> Allen Eng-Juh Yeoh,<sup>10,11,15</sup> Hiroki Hori,<sup>4</sup> and Jun J. Yang<sup>1,16,17</sup>

Nudt15 deficiency: weight loss and early death resulting from toxicity during thiopurine therapy in mice.

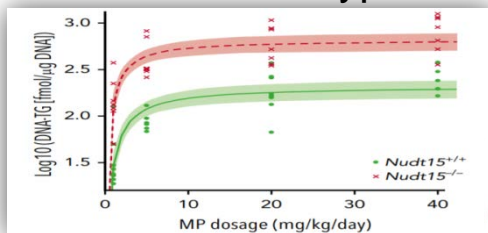


	<i>Nudt15</i> <sup>+/+</sup>			<i>Nudt15</i> <sup>-/-</sup>		
MP dosage (mg/kg/day)	20	5	1	20	5	1
(n =)	(15)	(13)	(10)	(16)	(13)	(14)

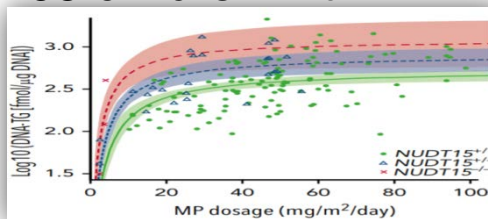


Michaelis Menten kinetics model and DNA-TG levels during MP dosage titration.

*Nudt15*<sup>-/-</sup> and wild-type mice

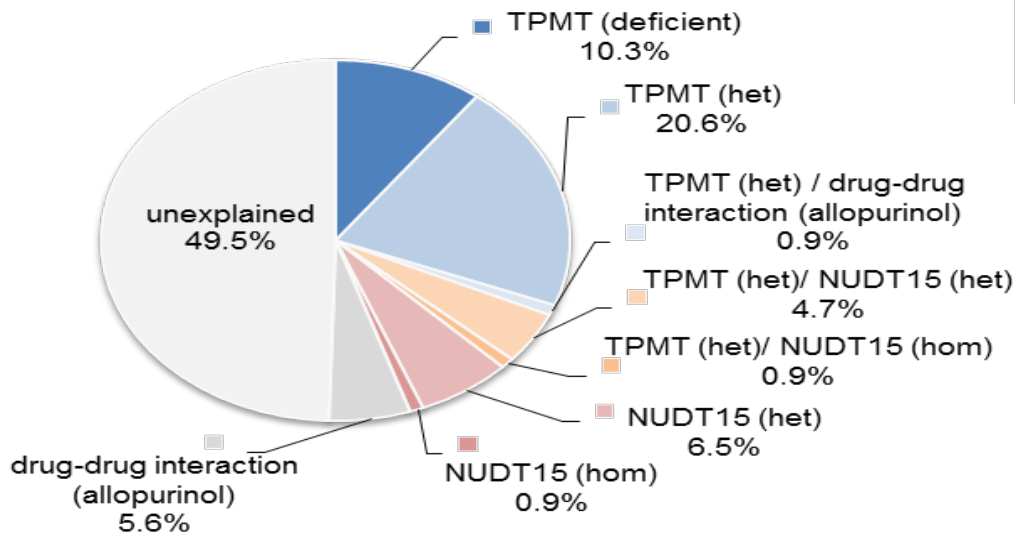


95 children with ALL





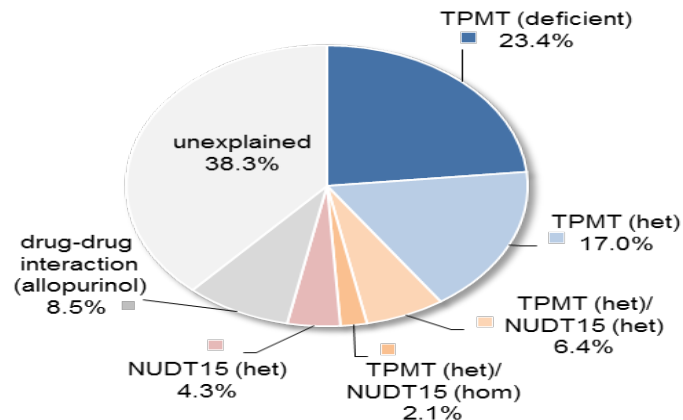
# ***NUDT15* and *TPMT* explain thiopurine related drug toxicity in European patients with severe cytopenia/pancytopenia (n=107)**



Cases (n=47)  
who developed toxicity  
≤ 3 months



IKP diagnostic cohort  
for TPMT (n > 25.000)







# Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing: 2013 Update

Clin Pharmacol Ther 2013

MV Relling<sup>1</sup>, EE Gardner<sup>2</sup>, WJ Sandborn<sup>3</sup>, K Schmiegelow<sup>4,5</sup>, C-H Pui<sup>6</sup>, SW Yee<sup>7</sup>, CM Stein<sup>8</sup>, M Carrillo<sup>9</sup>, WE Evans<sup>1</sup>, JK Hicks<sup>1</sup>, M Schwab<sup>10,11</sup> and TE Klein<sup>9</sup>




# Pharmacogene Variation Consortium Gene Introduction: *NUDT15*

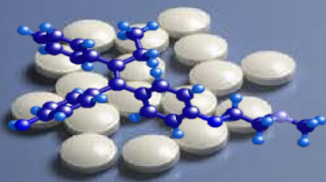
Clin Pharmacol Ther 2018

Jun J. Yang<sup>1</sup>, Michelle Whirl-Carrillo<sup>2</sup>, Stuart A. Scott<sup>3,4</sup> , Amy J. Turner<sup>5,6</sup>, Matthias Schwab<sup>7,8</sup> , Yoichi Tanaka<sup>9</sup>, Guilherme Suarez-Kurtz<sup>10</sup>, Elke Schaeffeler<sup>6,11</sup>, Teri E. Klein<sup>2</sup>, Neil A. Miller<sup>12,13</sup>  and Andrea Gaedigk<sup>13,14</sup> 

# Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on *TPMT* and *NUDT15* Genotypes: 2018 Update

Clin Pharmacol Ther 2018

Mary V. Relling<sup>1</sup>, Matthias Schwab<sup>2,3,4</sup> , Michelle Whirl-Carrillo<sup>5</sup>, Guilherme Suarez-Kurtz<sup>6</sup>, Ching-Hon Pui<sup>7</sup>, Charles M. Stein<sup>8</sup>, Ann M. Moyer<sup>9</sup> , William E. Evans<sup>1</sup>, Teri E. Klein<sup>4</sup>, Federico Guillermo Antillon-Klussmann<sup>10,11</sup>, Kelly E. Caudle<sup>1</sup>, Motohiro Kato<sup>12</sup>, Allen E.J. Yeoh<sup>13,14</sup>, Kjeld Schmiegelow<sup>15,16</sup> and Jun J. Yang<sup>1</sup> 



# TAMENDOXifen

TAMoxifen

## Genotype and phenotype guided supplementation of TAMoxifen standard therapy with ENDOXifen in breast cancer patients (TAMENDOX)

Principal investigator and LKP: M Schwab  
BMBF „Innovation for Individual Medicine“  
Duration: 4 years (2016-2019)  
Funding: total 4,300,000 €



GEFÖRDEBT VOM

Bundesministerium  
für Bildung  
und Forschung



Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6* and Tamoxifen Therapy

Matthew P. Goetz<sup>1</sup>, Katrin Sangkuhl<sup>2</sup>, Henk-Jan Guchelaar<sup>3</sup>, Matthias Schwab<sup>4,5,6</sup>, Michael Province<sup>7</sup>, Michelle Whirl-Carrillo<sup>2</sup>, W. Fraser Symmans<sup>8</sup>, Howard L. McLeod<sup>9</sup>, Mark J. Ratain<sup>10</sup>, Hitoshi Zembutsu<sup>11</sup>, Andrea Gaedigk<sup>12</sup>, Ron H. van Schaik<sup>13,14</sup>, James N. Ingle<sup>1</sup>, Kelly E. Caudle<sup>15</sup> and Teri E. Klein<sup>2</sup>

Clin Pharmacol Ther 2018

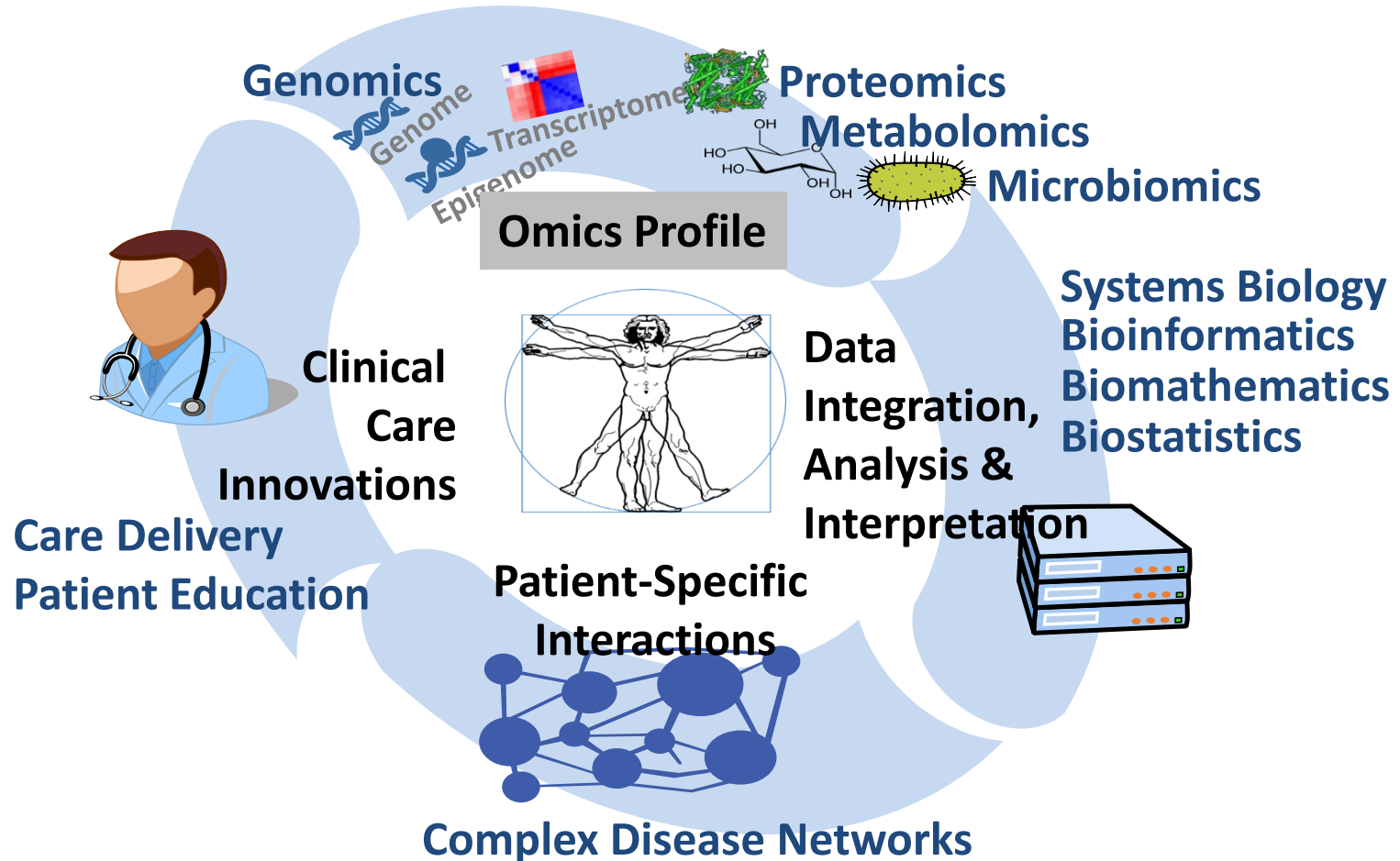
Chemical synthesis  
Pharmaceutical manufacturing  
Pharmaceutical packaging  
Clinical trial phase I/IIa

....  
Drug approval

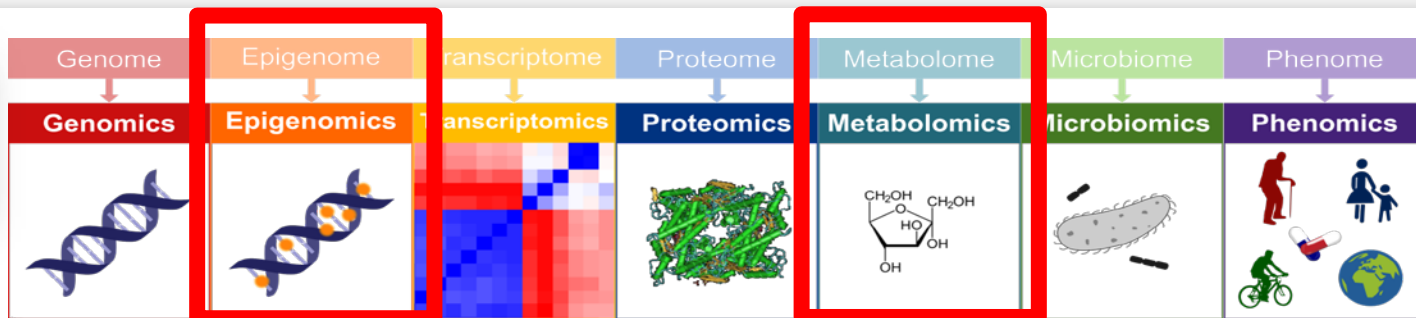


### Personalized Medicine, Pharmacogenomics, and Drug Development

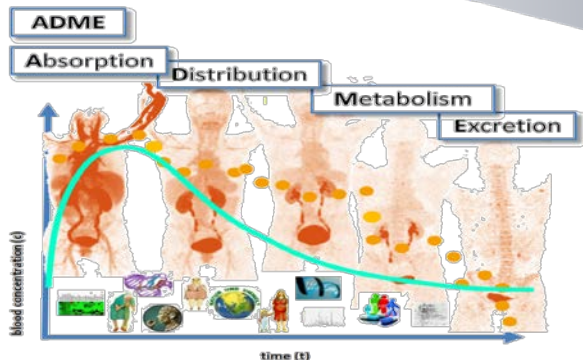
# Personalized Medicine and future direction



# PharmacoOmics to explain individual variability of ADME expression and to identify novel drug targets



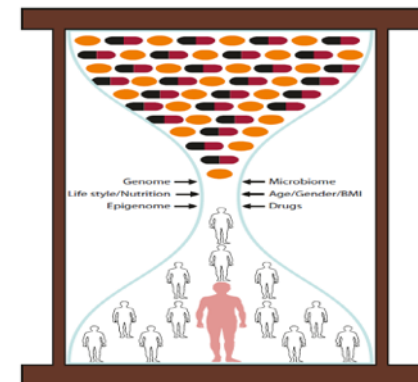
integration of predictive factors explaining interindividual variability in ADME gene expression/function



predicted drug response profile

Electronic health record database  
Therapeutic decision support tools

treatment decision



Schwab & Schaeffeler.  
*Genome Med*, 2012

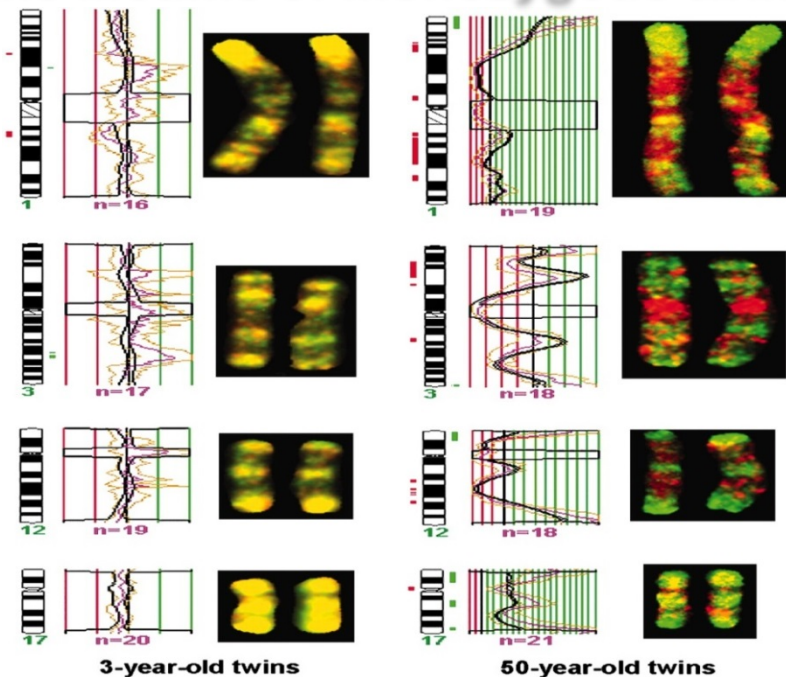
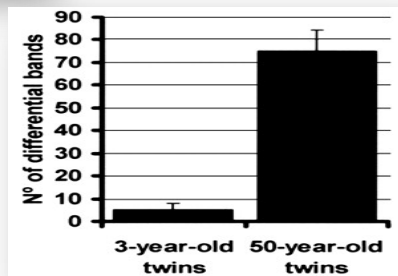
Adapted from:  
Meyer, ...Schwab, *Annu Rev Pharmacol Toxicol*, 2013;  
Emami-Riedmaier ...Schwab, *J Intern Med* 2015;  
Auffray, ... Schwab. *Genome Med* 2016  
Fisel, ...Schwab, *EOMT* 2017

# Epigenomics and DNA methylation

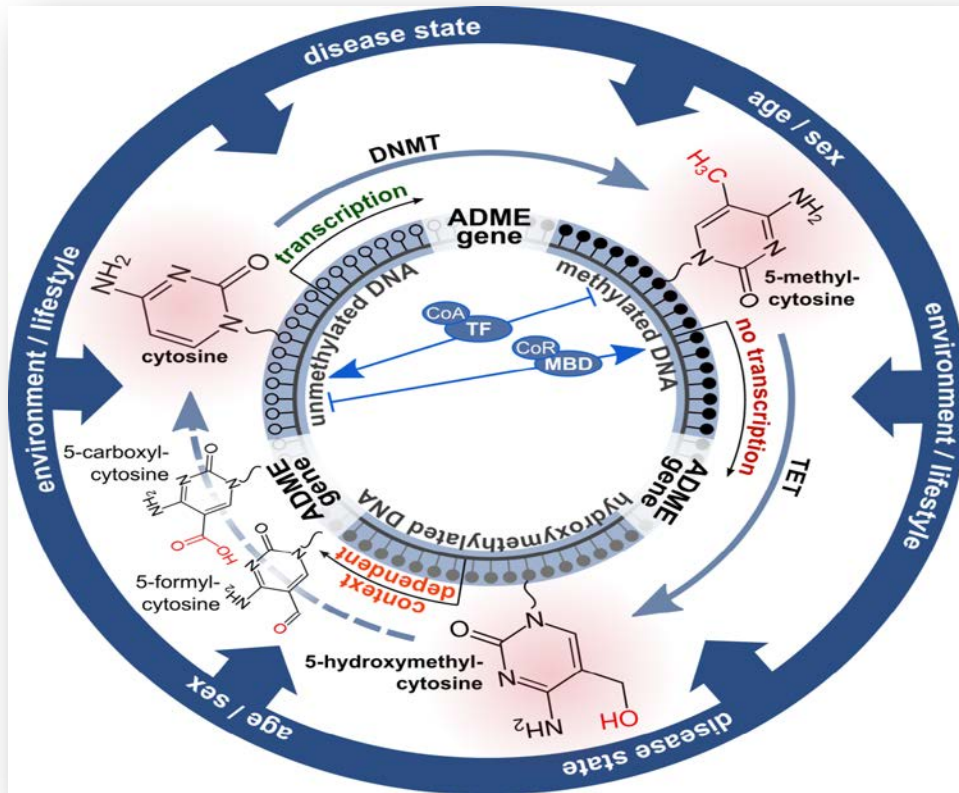
## The same DNA *but* different phenotypes



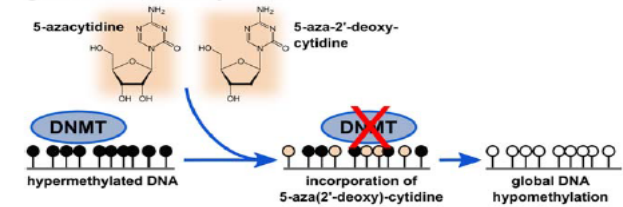
Epigenetic differences arise during the lifetime of monozygotic twins



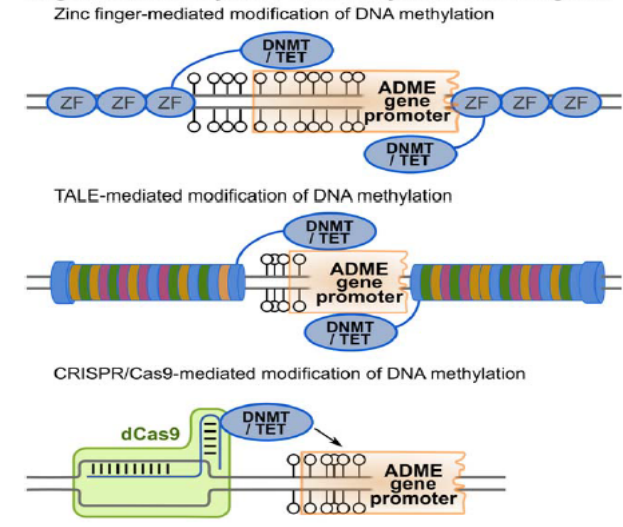
# DNA methylation and its impact on disease pathophysiology and drug therapy



## global DNA demethylation



## targeted DNA methylation or demethylation of ADME genes

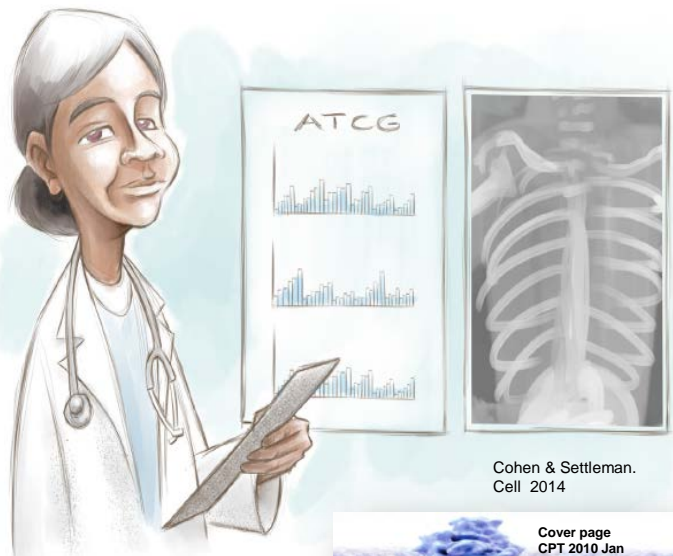


# Feature Review

## Impact of Membrane Drug Transporters on Resistance to Small-Molecule Tyrosine Kinase Inhibitors

Claudia Neul,<sup>1</sup> Elke Schaeffeler,<sup>1</sup> Alex Sparreboom,<sup>2</sup> Stefan Laufer,<sup>3</sup> Matthias Schwab,<sup>1,4,5,\*</sup> and Anne T. Nies<sup>1</sup>

2016

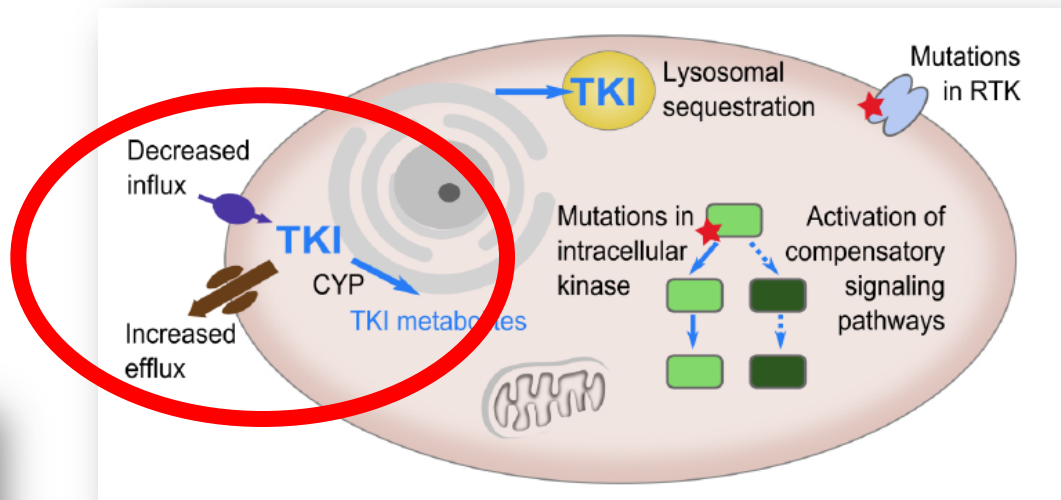


Cohen & Settleman.  
Cell 2014

Cover page  
CPT 2010 Jan

DRUG TRANSPORTERS

# tumor cells



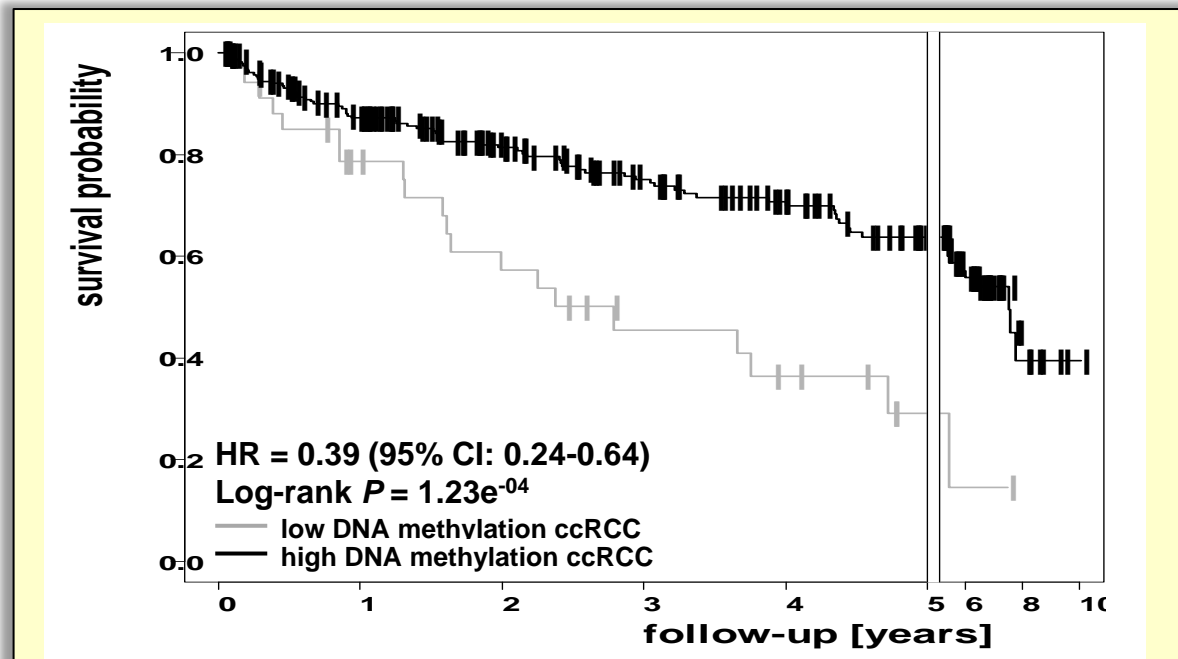
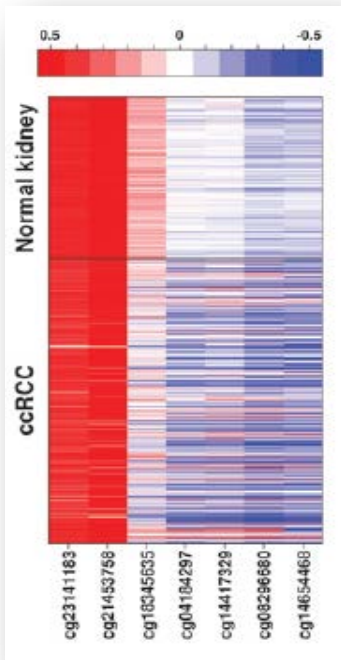
TKI, tyrosine kinase inhibitor



# DNA Methylation of the *SLC16A3* Promoter Regulates Expression of the Human Lactate Transporter MCT4 in Renal Cancer with Consequences for Clinical Outcome

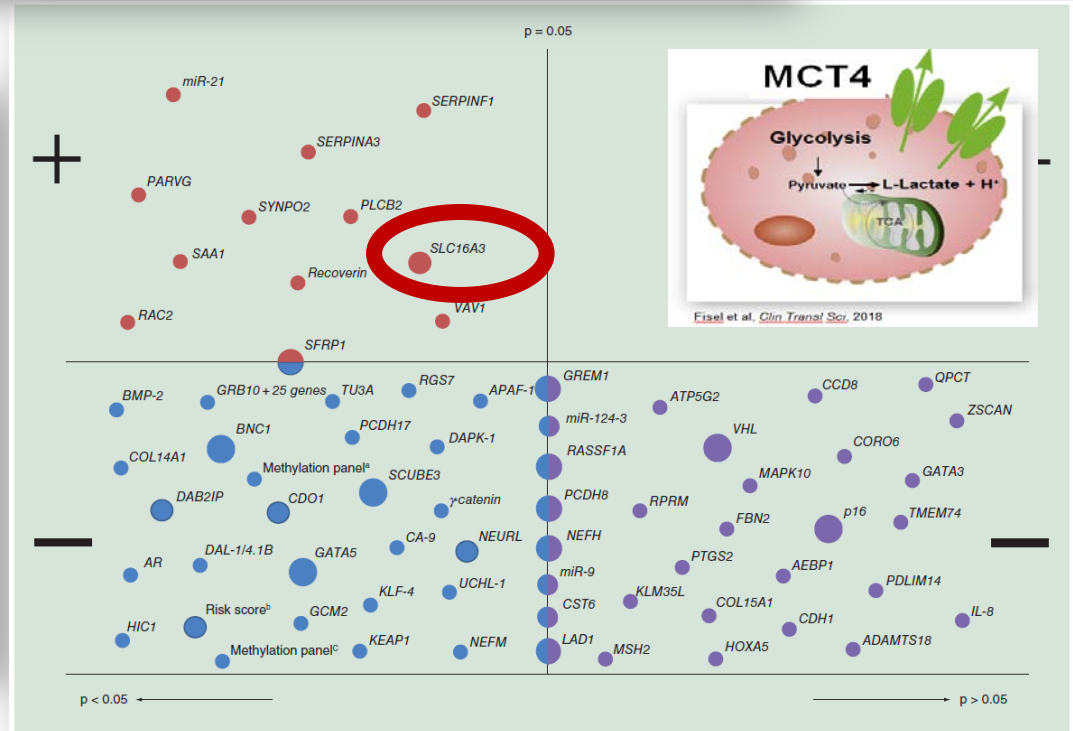
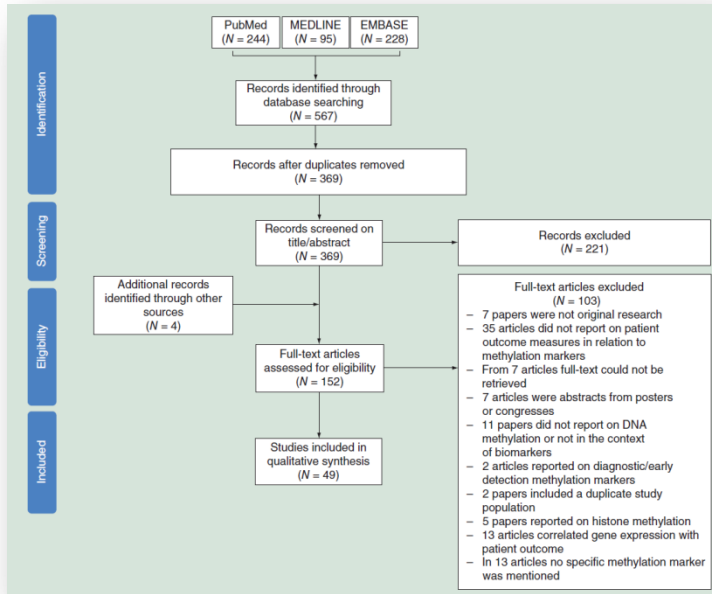
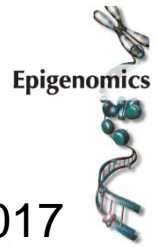
Pascale Fisel<sup>1,2</sup>, Stephan Kruck<sup>3</sup>, Stefan Winter<sup>1,2</sup>, Jens Bedke<sup>3</sup>, Jörg Hennenlotter<sup>3</sup>, Anne T. Nies<sup>1,2</sup>, Marcus Scharpf<sup>1</sup>, Falko Fend<sup>1</sup>, Arnulf Stenzl<sup>3</sup>, Matthias Schwab<sup>1,2,5</sup>, and Elke Schaeffeler<sup>1,2</sup>

## *SLC16A3* DNA methylation predicts survival of ccRCC patients



# Prognostic DNA methylation markers for renal cell carcinoma: a systematic review

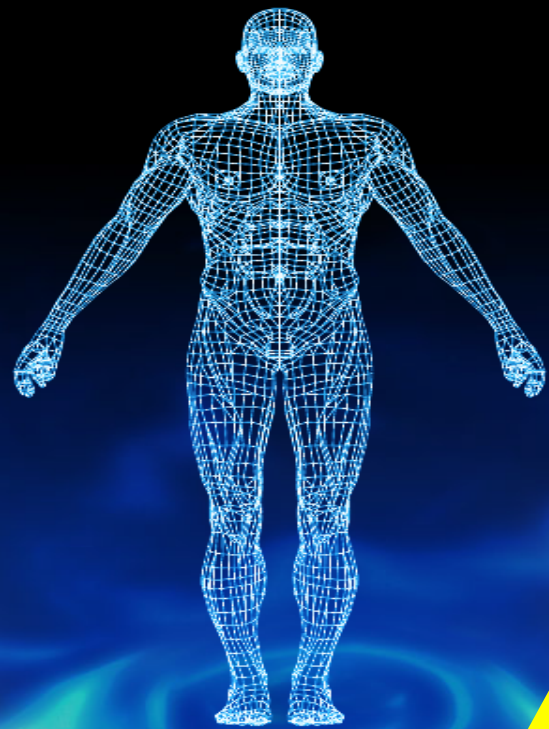
Sophie C Joosten<sup>1</sup>, Ivette AG Deckers<sup>2</sup>, Maureen J Aarts<sup>1</sup>, Ann Hoeben<sup>1</sup>, Joep G van Roermund<sup>3</sup>, Kim M Smits<sup>1,2</sup>, Veerle Melotte<sup>2</sup>, Manon van Engeland<sup>2</sup> & Vivianne C Tjan-Heijnen<sup>\*,1</sup>



**Section editor:**  
Matthias Schwab

# Metabolomics of Disease

**EDITORIAL**  
**Metabolomics: the final frontier?**  
Timothy D Veenstra\*  
**2012, May**



Drug discovery



Food safety



Toxicology



Newborn screening



Markers of disease

## Metabolomics

Metabolites are small molecules produced by living organisms during respiration, digestion and other physiological processes. Measurement of the level of these molecules in the body, an approach known as metabolomics, is already improving the detection and treatment of disease.

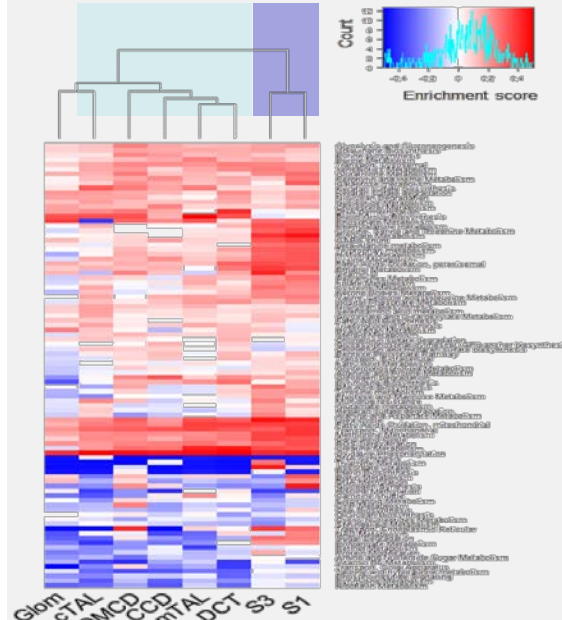
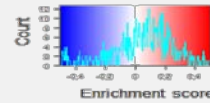
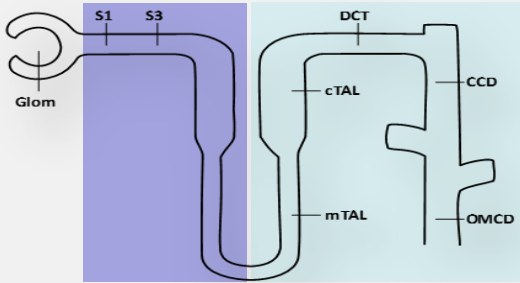


Transplants

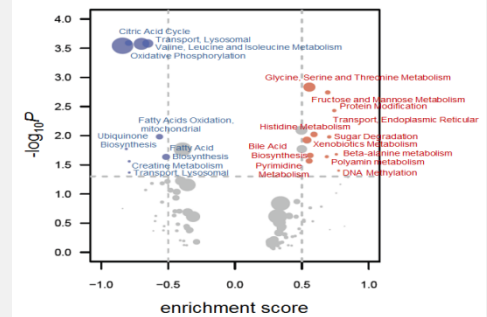


# Metabolic pathways differ between prox. and distal nephron regions and discriminate between RCC subtypes and presumed cells of origin

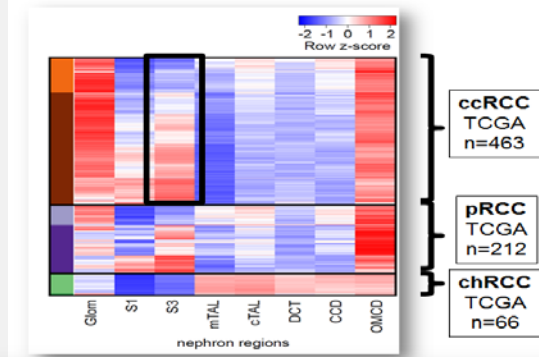
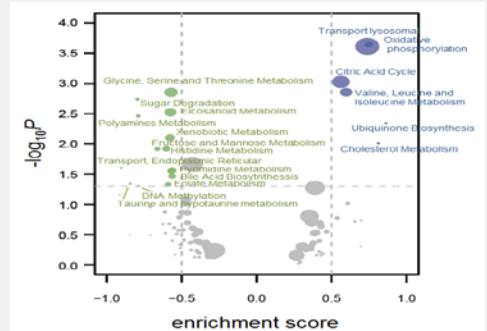
Schwab M  
IKP Stuttgart



## chRCC vs. ccRCC



## papRCC vs. chRCC



Platinum Priority – Kidney Cancer  
Editorial by George M. Yousef on pp. 1021–1022 of this issue

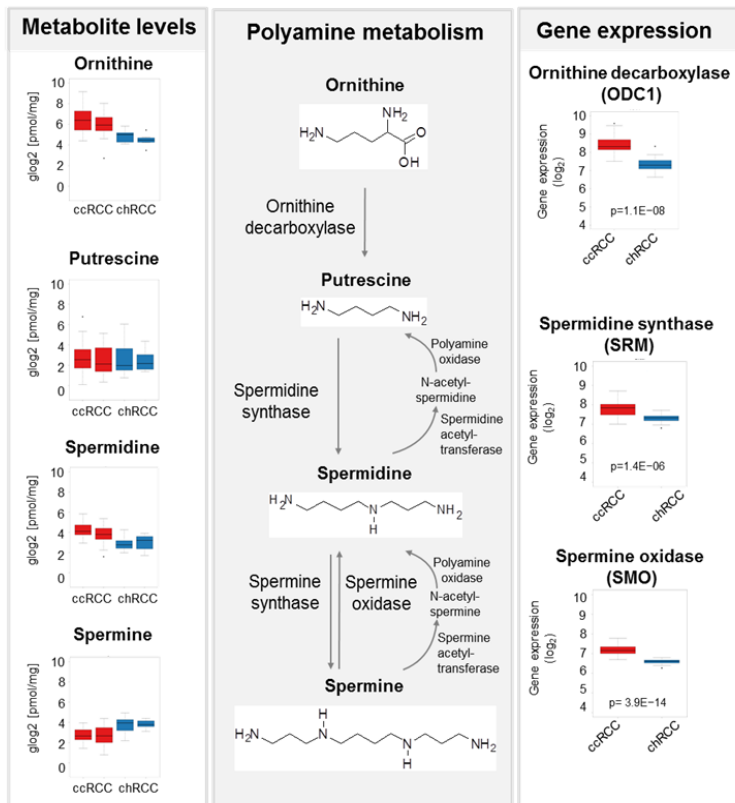
**Survival Prediction of Clear Cell Renal Cell Carcinoma Based on Gene Expression Similarity to the Proximal Tubule of the Nephron**

Florian Büttner<sup>1,2,3,4</sup>, Stefan Winter<sup>1,2,3,4</sup>, Steffen Rausch<sup>1,2</sup>, Anna Reusste<sup>1,2,3,4</sup>, Stephan Kruck<sup>1,2</sup>, Korstin Junker<sup>1,2</sup>, Arnulf Stenzl<sup>1,2</sup>, Abbas Agaimy<sup>1,2</sup>, Arndt Hartmann<sup>1,2</sup>, Jens Bedke<sup>1,2</sup>, Matthias Schwab<sup>1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200</sup>

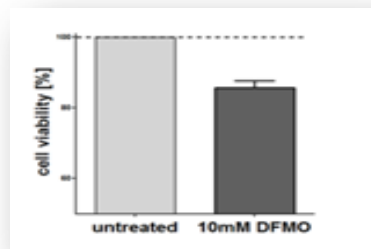
EUROPEAN UROLOGY 68 (2015) 1016–1020

# Identification of novel drug targets for RCC therapy

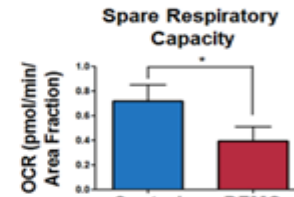
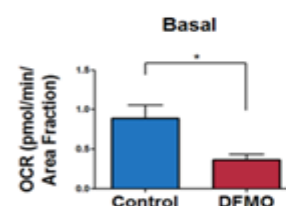
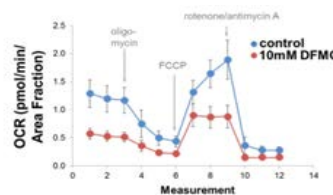
## The example of the polyamine metabolism



## Inhibition of polyamine metabolism (ODC1) using DFMO (2-di fluoromethylornithine)



## Reduced mitochondrial activity in 786-O ccRCC cells measured by Mito stress test (Seahorse-Agilent)



OCR, oxygen consumption rate)

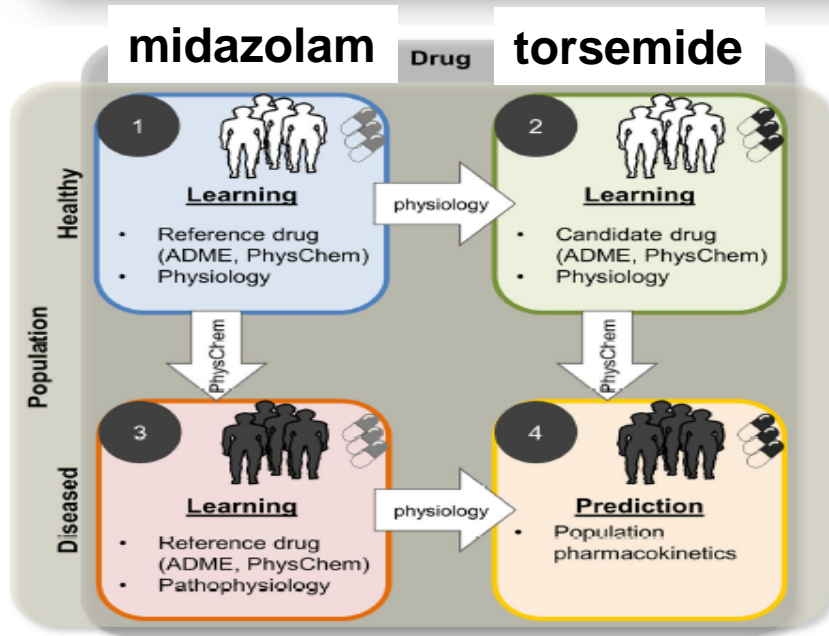


Online published 28 March 2017

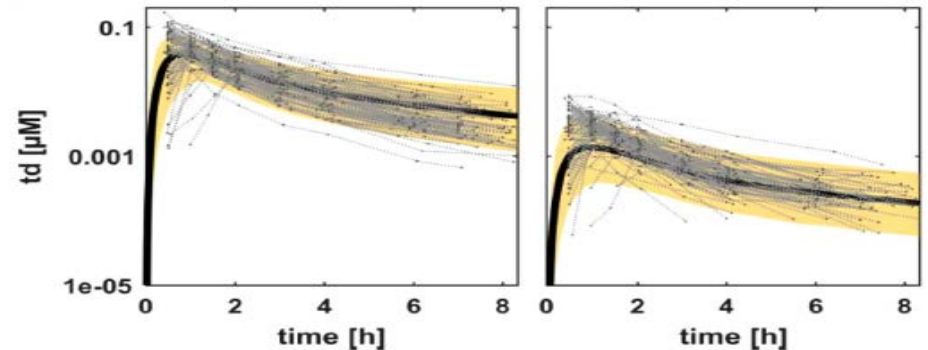
ARTICLE OPEN

# Translational learning from clinical studies predicts drug pharmacokinetics across patient populations

Markus Krauss<sup>1</sup>, Ute Hofmann<sup>2</sup>, Clemens Schafmayer<sup>3</sup>, Svitlana Igel<sup>2</sup>, Jan Schlender<sup>1</sup>, Christian Mueller<sup>4</sup>, Mario Brosch<sup>5</sup>, Witigo von Schoenfels<sup>3</sup>, Wiebke Erhart<sup>3</sup>, Andreas Schuppert<sup>6,7</sup>, Michael Block<sup>1</sup>, Elke Schaeffeler<sup>2</sup>, Gabriele Boehmer<sup>8</sup>, Linus Goerlitz<sup>4</sup>, Jan Hoecker<sup>3</sup>, Joerg Lippert<sup>9</sup>, Reinhold Kerb<sup>2</sup>, Jochen Hampe<sup>5</sup>, Lars Kuepfer<sup>1</sup> and Matthias Schwab<sup>2,8,10</sup>



## Population PK prediction of torse mide venous blood plasma in the diseased population (NAFLD)




95% CI (colored area), mean value curve (black line), experimental data (light gray dashed lines)

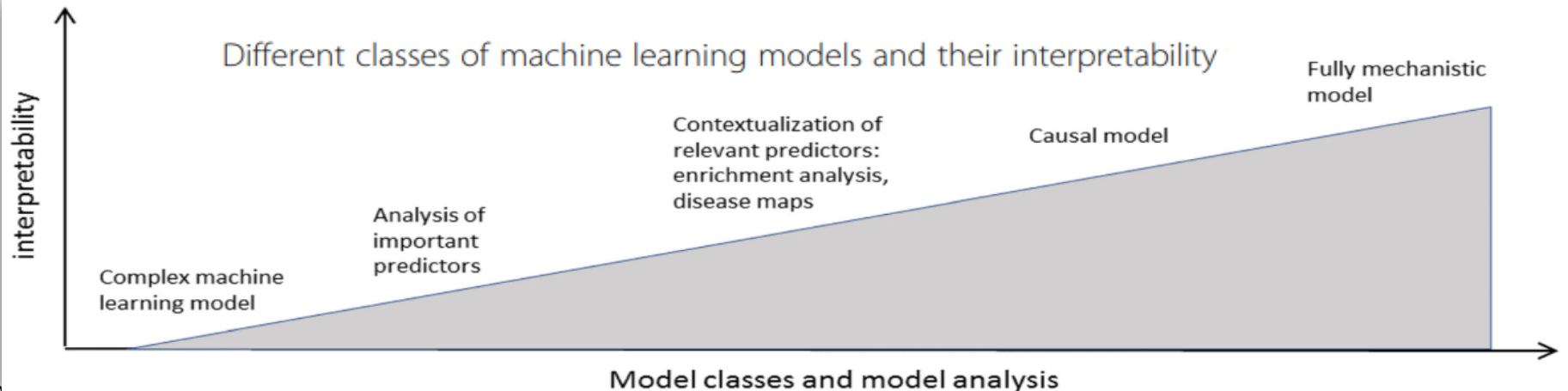
# Pharmacogenomics as major booster for Personalized Medicine

From hype to reality: data science enabling personalized medicine



BMC Medicine 2018

Holger Fröhlich<sup>1,21\*</sup> , Rudi Balling<sup>2</sup>, Niko Beerenwinkel<sup>3</sup>, Oliver Kohlbacher<sup>4,22,23,24</sup>, Santosh Kumar<sup>5</sup>, Thomas Lengauer<sup>6</sup>, Marloes H. Maathuis<sup>7</sup>, Yves Moreau<sup>8</sup>, Susan A. Murphy<sup>9</sup>, Teresa M. Przytycka<sup>10</sup>, Michael Rebhan<sup>11</sup>, Hannes Röst<sup>12</sup>, Andreas Schuppert<sup>13</sup>, Matthias Schwab<sup>14,25</sup>, Rainer Spang<sup>15</sup>, Daniel Stekhoven<sup>16</sup>, Jimeng Sun<sup>17</sup>, Andreas Weber<sup>18</sup>, Daniel Ziemek<sup>19</sup> and Blaz Zupan<sup>20</sup>







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