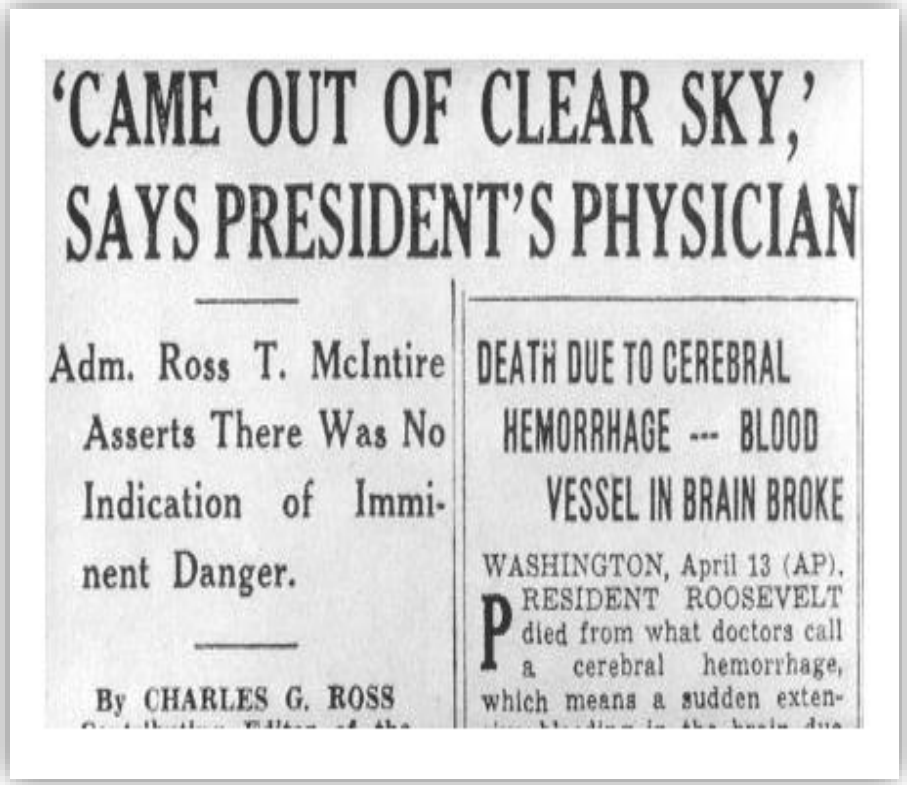
Dept. Clinical Pharmacology, University Hospital, Tübingen
Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart

Pharmacogenomics and Personalized Medicine: Implication for Clinical Practice

Prof. Matthias Schwab
Adjunct Professor of the Yerevan State Medical University, Armenia

ICPerMed Workshop CPerMed Workshop
“Advancing Personalised Medicine Through Technology Development”
November 14, 2023, Siena, Italy

Arterial pressure of Franklin D. Roosevelt from 1935 until his death on April 12, 1945



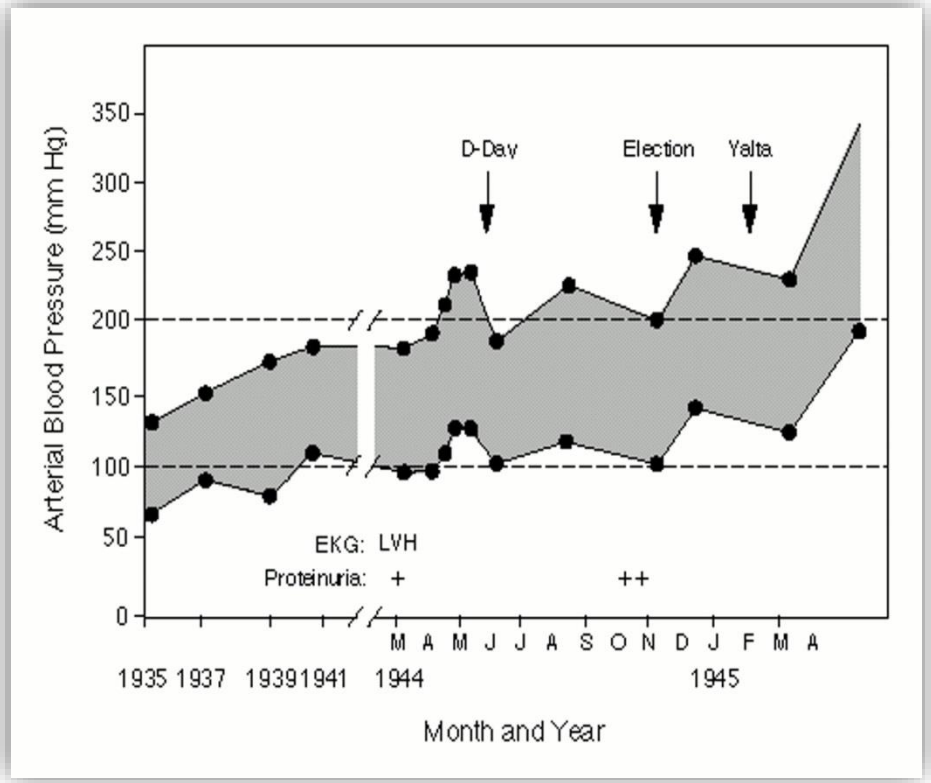
‘CAME OUT OF CLEAR SKY,’ SAYS PRESIDENT’S PHYSICIAN

Adm. Ross T. McIntire Asserts There Was No Indication of Imminent Danger.

By CHARLES G. ROSS

DEATH DUE TO CEREBRAL HEMORRHAGE --- BLOOD VESSEL IN BRAIN BROKE

WASHINGTON, April 13 (AP). PRESIDENT ROOSEVELT died from what doctors call a cerebral hemorrhage, which means a sudden exten-



Messerli FH: This day 50 years ago *N Engl J Med* 1995

Schwab M
IKP Stuttgart

Treatment of hypertension and consequences on mortality

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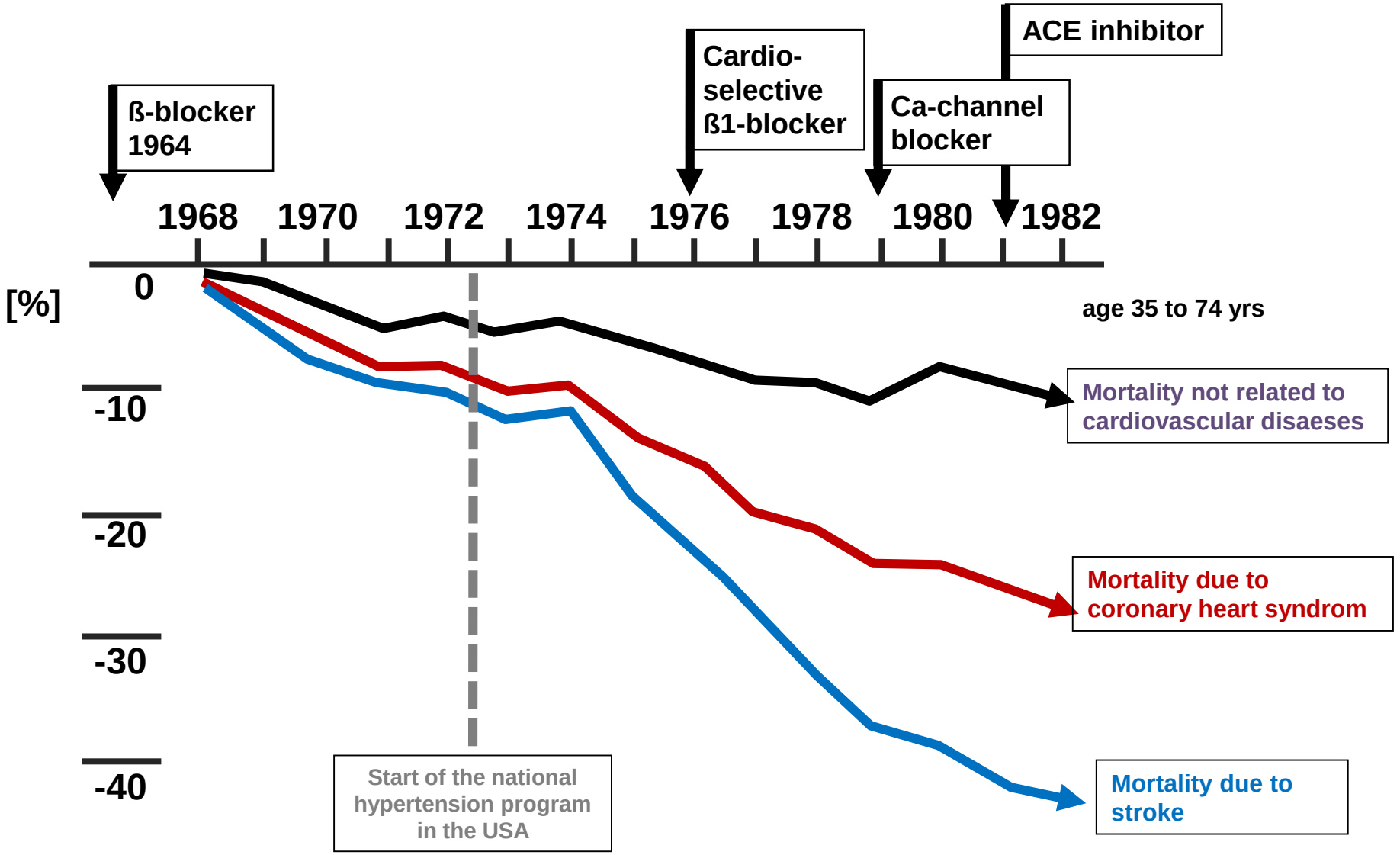
Institut für Klinische Pharmakologie



acc. to Lohmann FW, 1989

A key example for precision medicine and drug development

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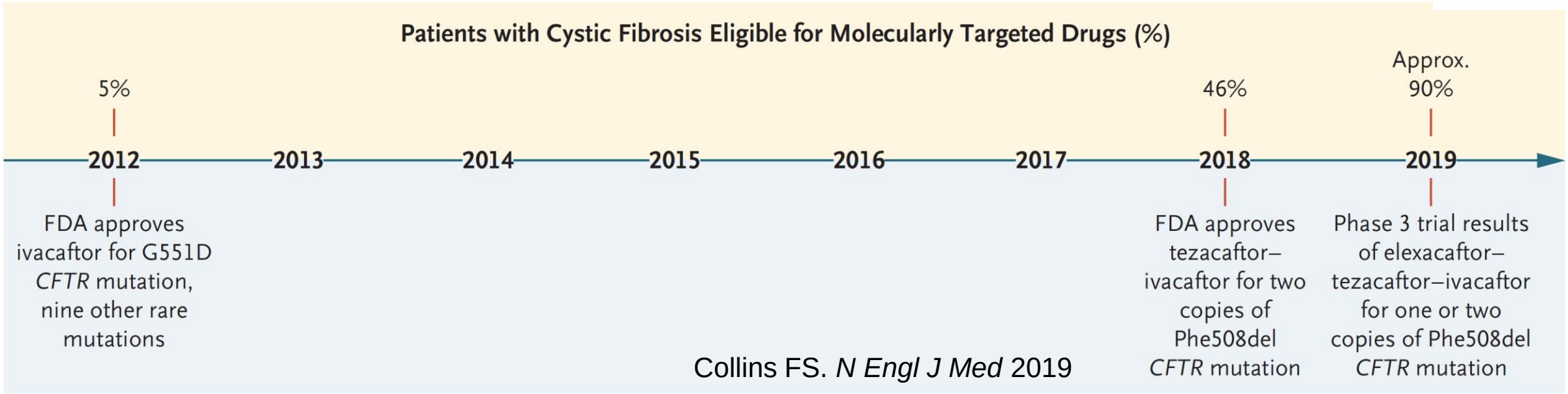
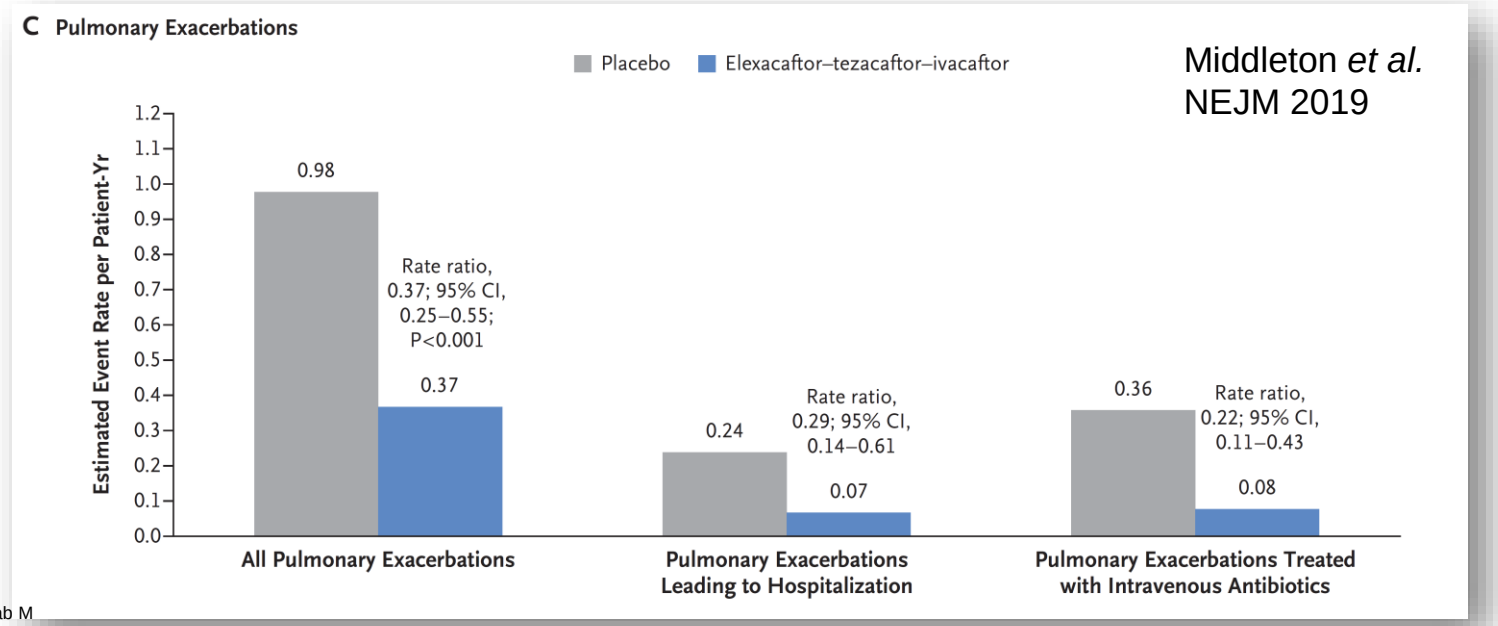
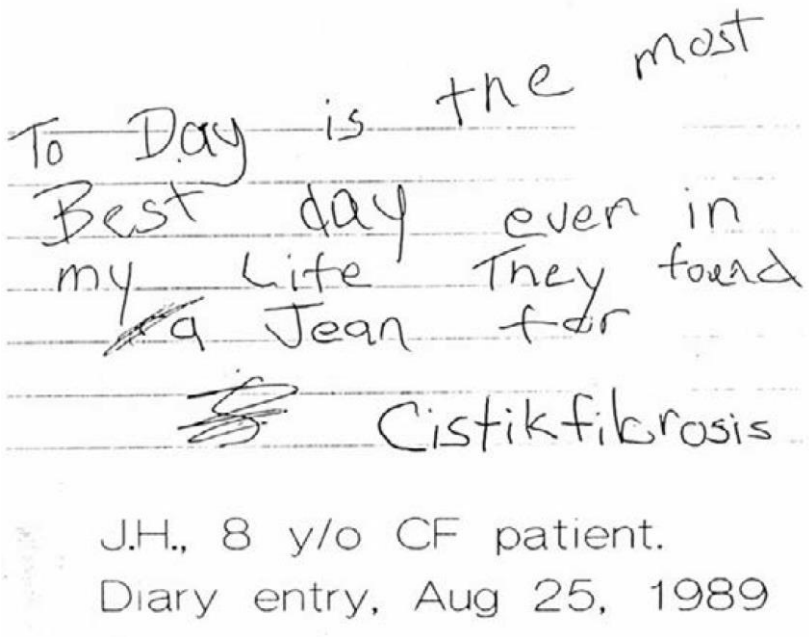
Institut für Klinische Pharmakologie



Collins FS. *N Engl J Med* 2019



Middleton *et al.*
NEJM 2019



Poor *or* Non response of drugs: A major problem with clinical consequences

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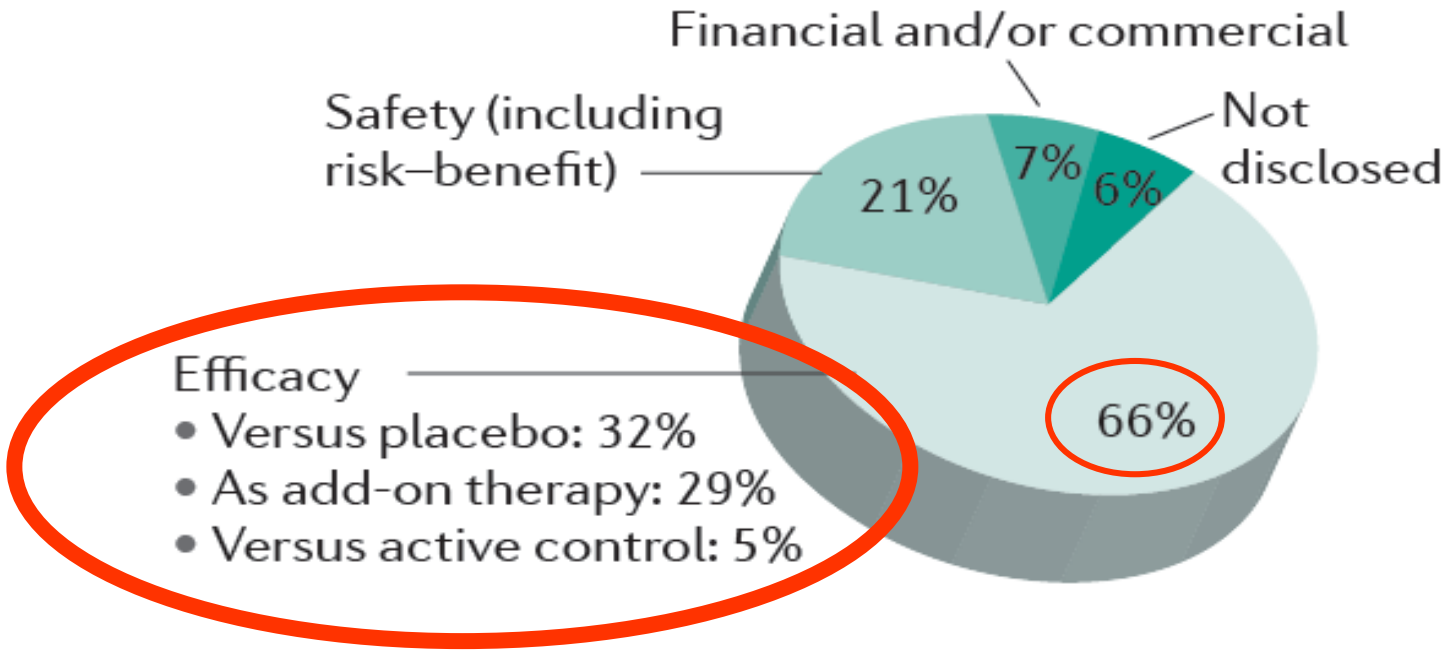
Institut für Klinische Pharmakologie

Phase III and submission failure of 83 drugs from 2007-2010



Arrrowsmith. *Nat Rev Drug Discov* 2011

Various factors explain interindividual variability of expression and function of drug-relevant CYP enzymes

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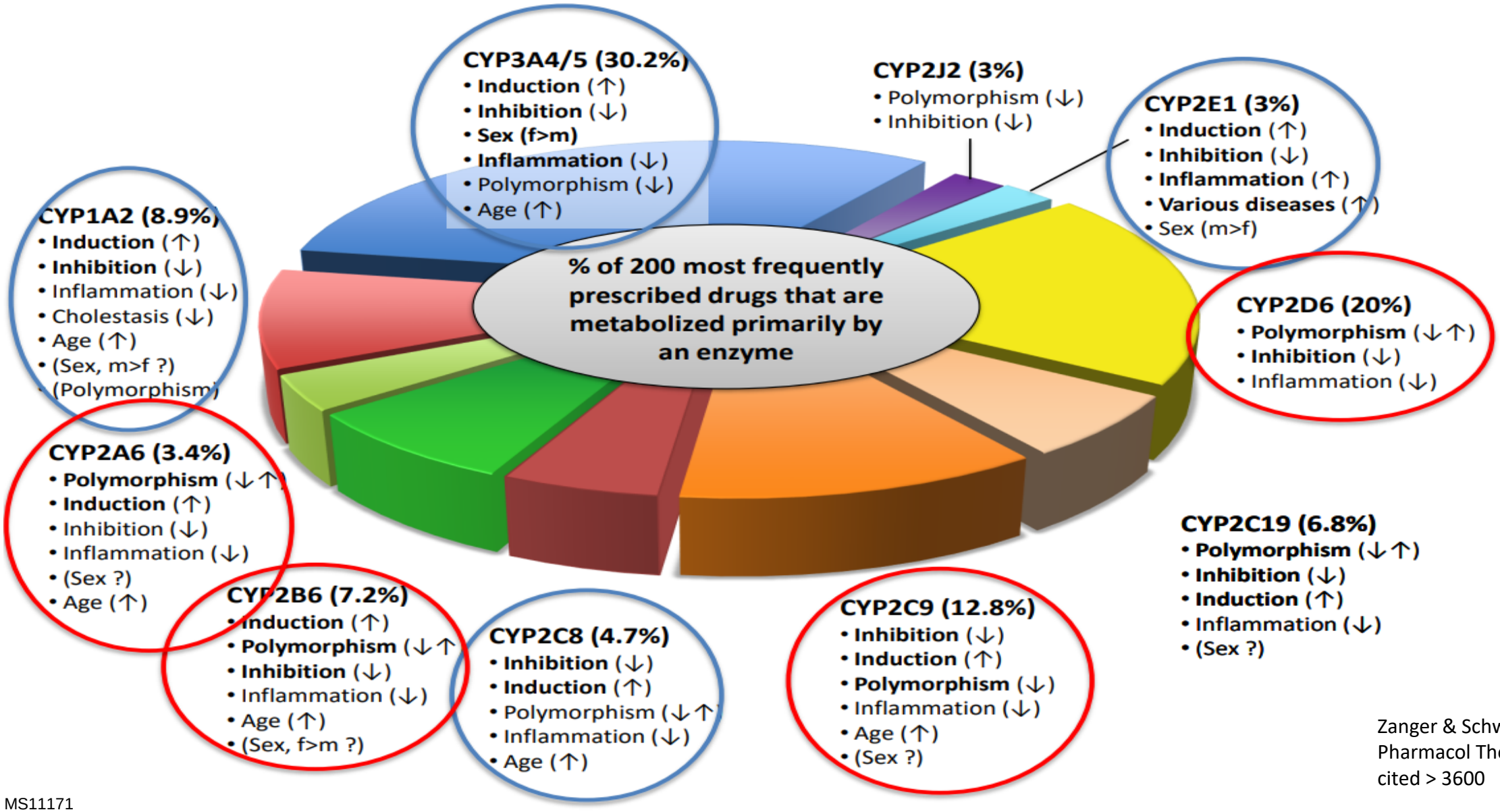
Dr. Margarete Fischer-Bosch
Institut für Klinische Pharmakologie



Zanger & Schwab,
Pharmacol Ther 2013
cited > 3600

Expression variability of human Cytochrom P450 enzymes in the IKP human liver bank (up to 900 fold)

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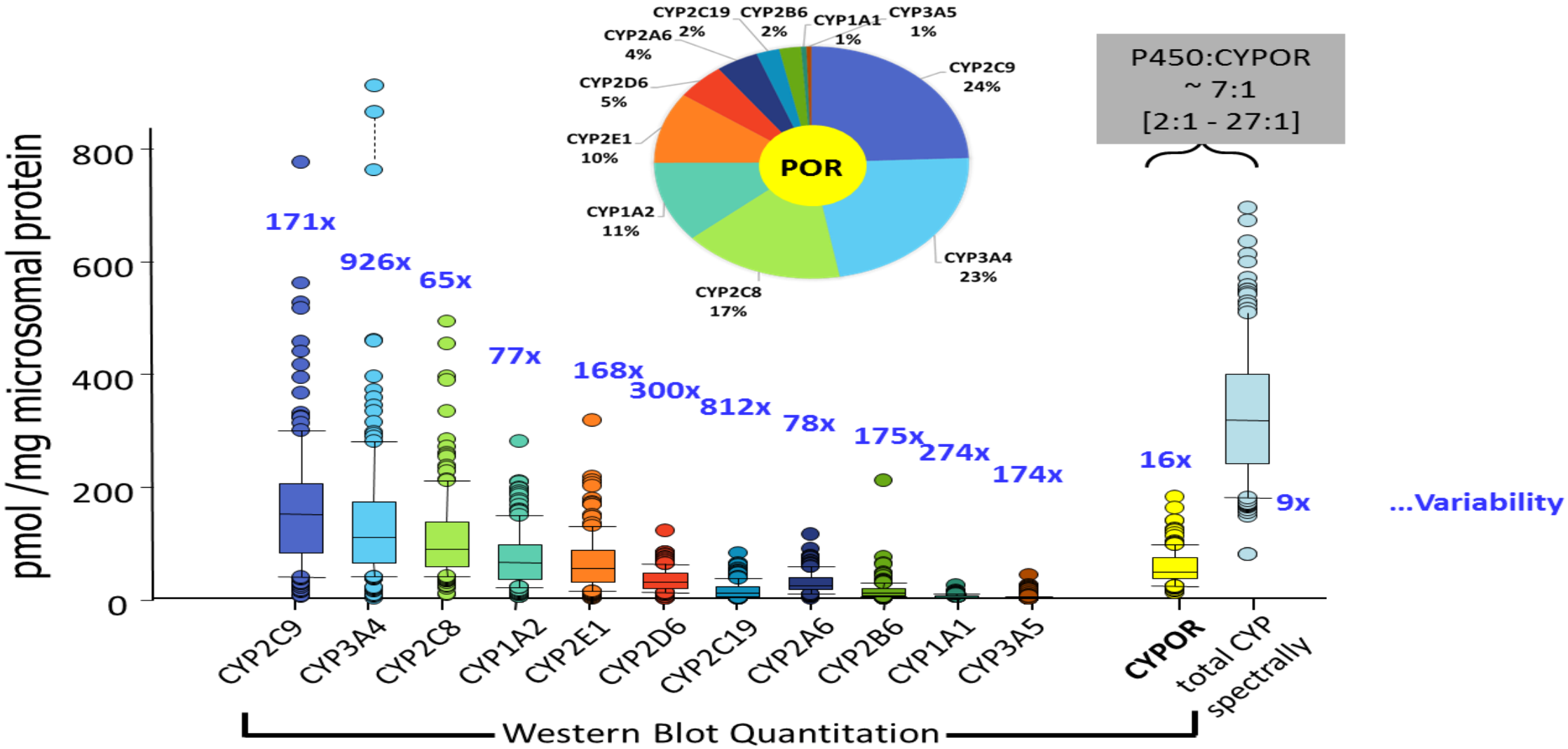

IKP Stuttgart: Unpublished data

n=150

Schwab M
IKP Stuttgart

Sources for Variability in Drug Response

Schwab M
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Precision medicine: from base pairs to bedside

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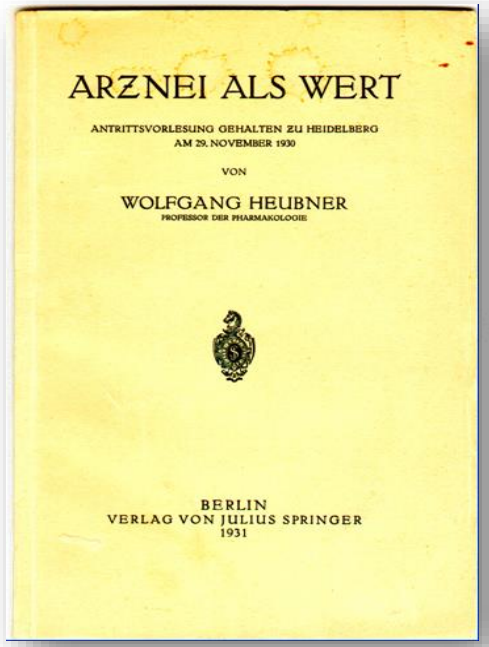
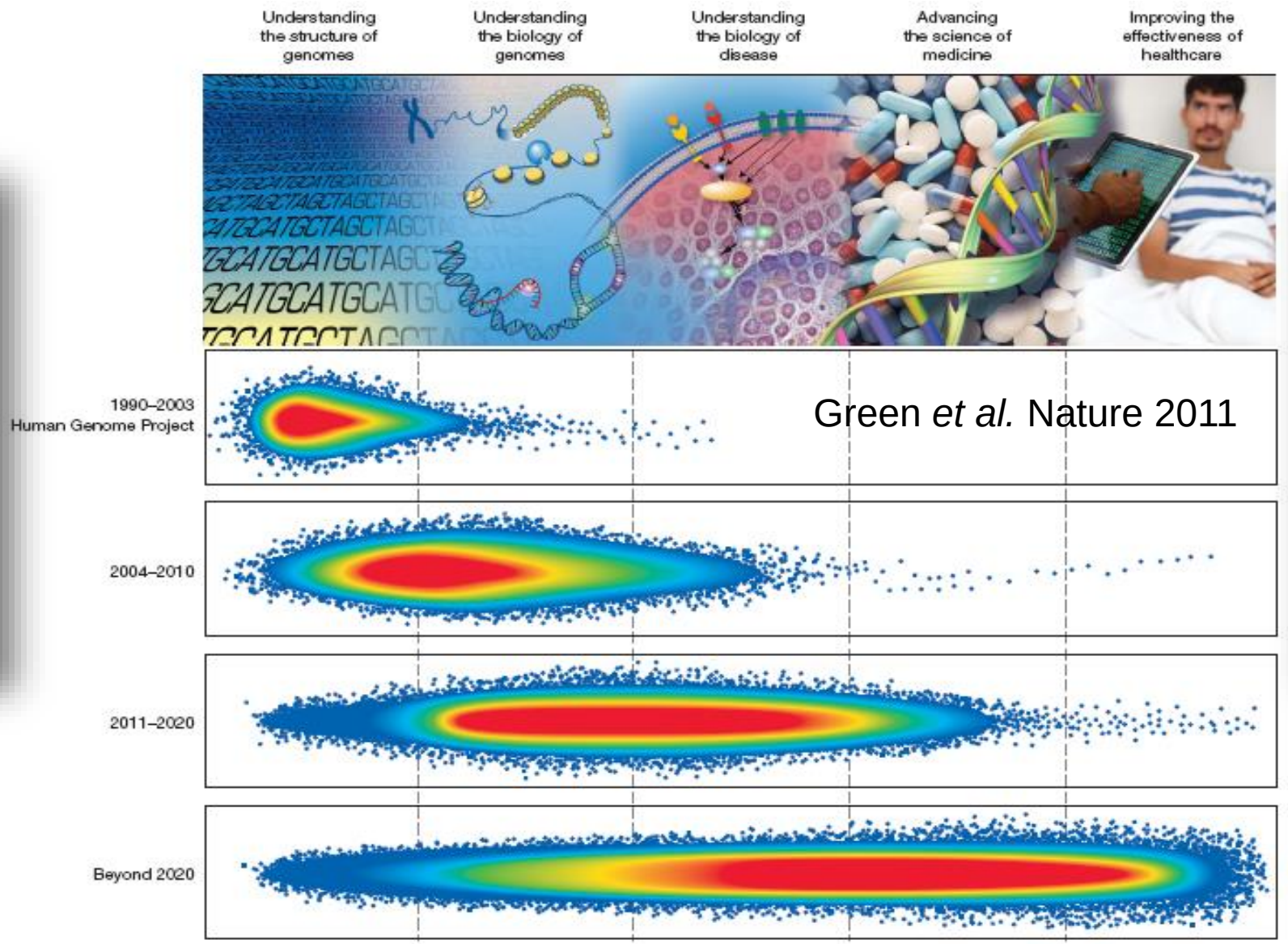

ARZNEI ALS WERT

ANTRITTSVORLESUNG GEHALTEN ZU HEIDELBERG
AM 29. NOVEMBER 1930

VON

WOLFGANG HEUBNER
PROFESSOR DER PHARMAKOLOGIE

BERLIN
VERLAG VON JULIUS SPRINGER
1931



Green *et al.* Nature 2011

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

Cohen & Settleman. *Cell* 2014

Schwab M
IKP Stuttgart

A new paradigm for diagnosis and therapy:

Non small lung cancer as prototype for precision medicine

shifting from tumor histology to molecular characterisation

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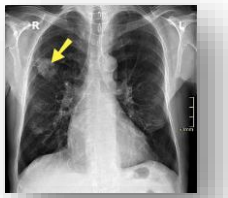
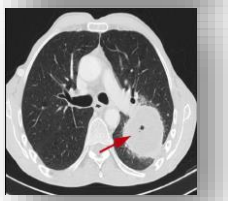
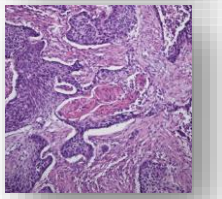
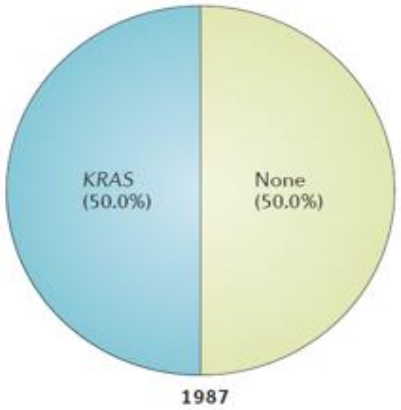
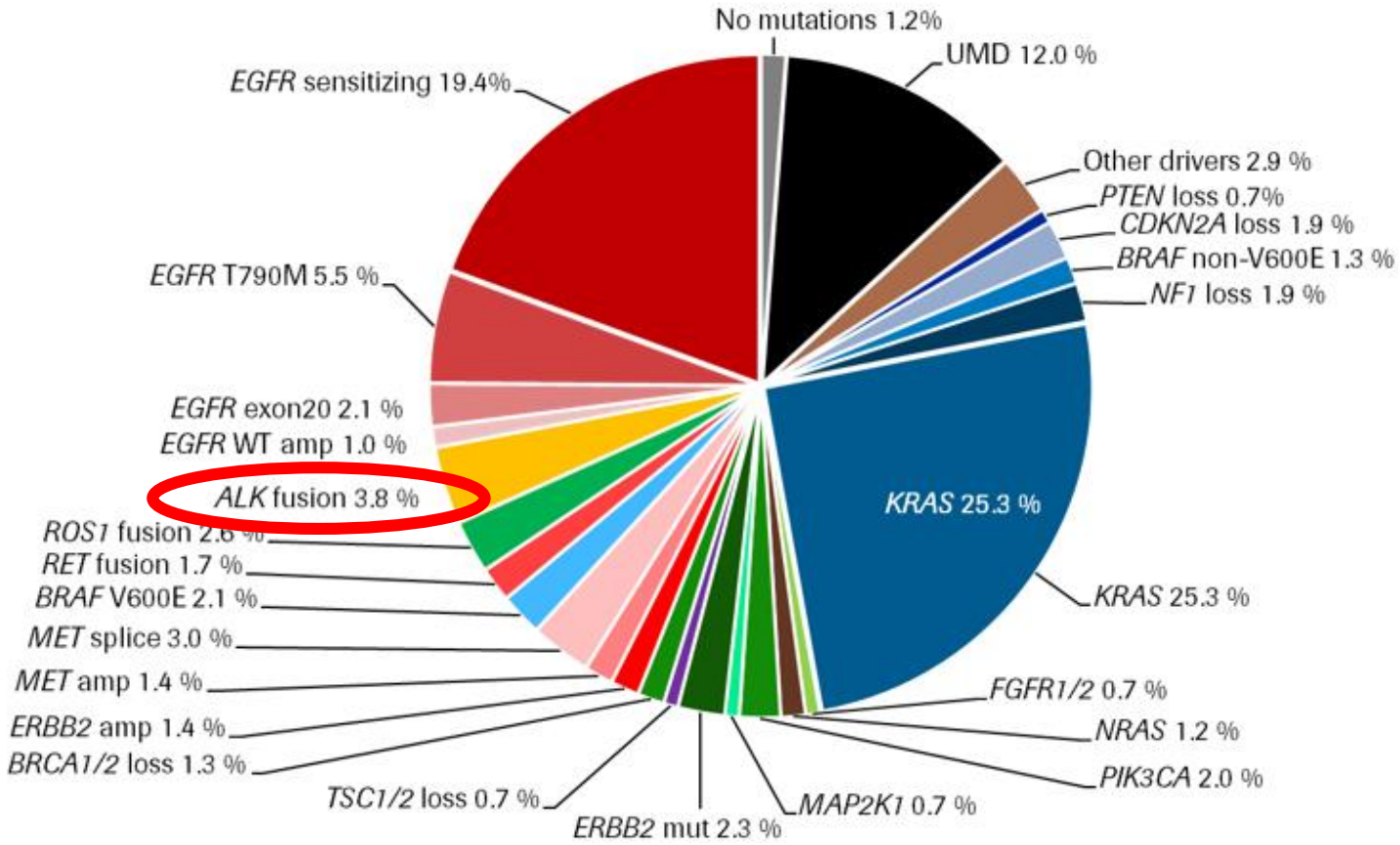
Dr. Margarete Fischer-Bosch
Institut für Klinische Pharmakologie











Blumenthal G (US Food and Drug Administration); Shaw AT (Massachusetts General Hosp. Cancer Ctr.);
Kopetz S. (MD Anderson Cancer Ctr.) – Forum: Precision Therapy: When is better: up front or at relapse? AACR 2018
Jordan et al. Cancer Disov 7: 596-609, 2017.

Predictive biomarkers with relevance for treatment in patients with non-small-cell lung cancer

Biomarker	Method	UICC stage IB	II	III(op)	III(crtx)	IV	Drugs with approval conditional on biomarkers
ALK	IHC, NGS, ISH	+	+	+	–	+	Alectinib, brigatinib, ceritinib, crizotinib, lorlatinib
BRAF	NGS	–	–	–	–	+	Dabrafenib/trametinib
EGFR	NGS	+	+	+	–	+	Afatinib, amivantamab, dacomitinib, erlotinib, gefitinib, mobocertinib*, osimertinib
HER2	NGS	–	–	–	–	+*	Poziotinib*, trastuzumab-deruxtecan*
KRAS	NGS	–	–	–	–	+	Sotorasib, adagrasib*
MET	NGS	–	–	–	–	+	Capmatinib, tepotinib
NTRK1–3	IHC, NGS, ISH	–	–	–	–	+	Entrectinib, larotrectinib
PD-L1	IHC	+	+	+	+	+	Atezolizumab, cemiplimab, durvalumab, pembrolizumab
RET	NGS, ISH	–	–	–	–	+	Pralsetinib, selpercatinib
ROS1	IHC, NGS, ISH	–	–	–	–	+	Crizotinib, entrectinib

ALK, anaplastic lymphoma kinase; *BRAF*, B-rat fibrosarcoma; *EGFR*, epidermal growth factor receptor; *HER2*, human epidermal growth factor receptor 2; IHC, immunhistochemistry; ISH, in situ hybridization; *KRAS*, Kirsten rat sarcoma viral oncogene; *MET*, *MET* proto-oncogene/receptor tyrosine kinase; NGS, deoxyribonucleic acid or ribonucleic acid parallel sequencing ("next-generation sequencing"); *NTRK1–3*, neurotrophic tyrosine kinase 1–3; PD-L1, programmed cell death 1 ligand-1; *RET*, RET proto-oncogene; *ROS1*, ROS proto-oncogene 1; UICC, Union for International Cancer Control; III(op), stage III primary surgery; III(crtx), stage III definitive chemoradiotherapy
+* Not currently approved in Europe for this indication.

Schuler *et al.* Dt Ärzteblatt Int 2023

Genomic information from the tumor and the patient provides vital information to guide drug therapy

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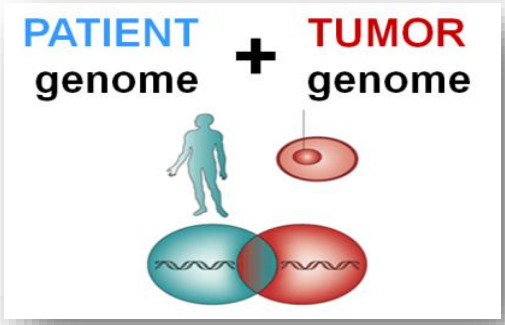
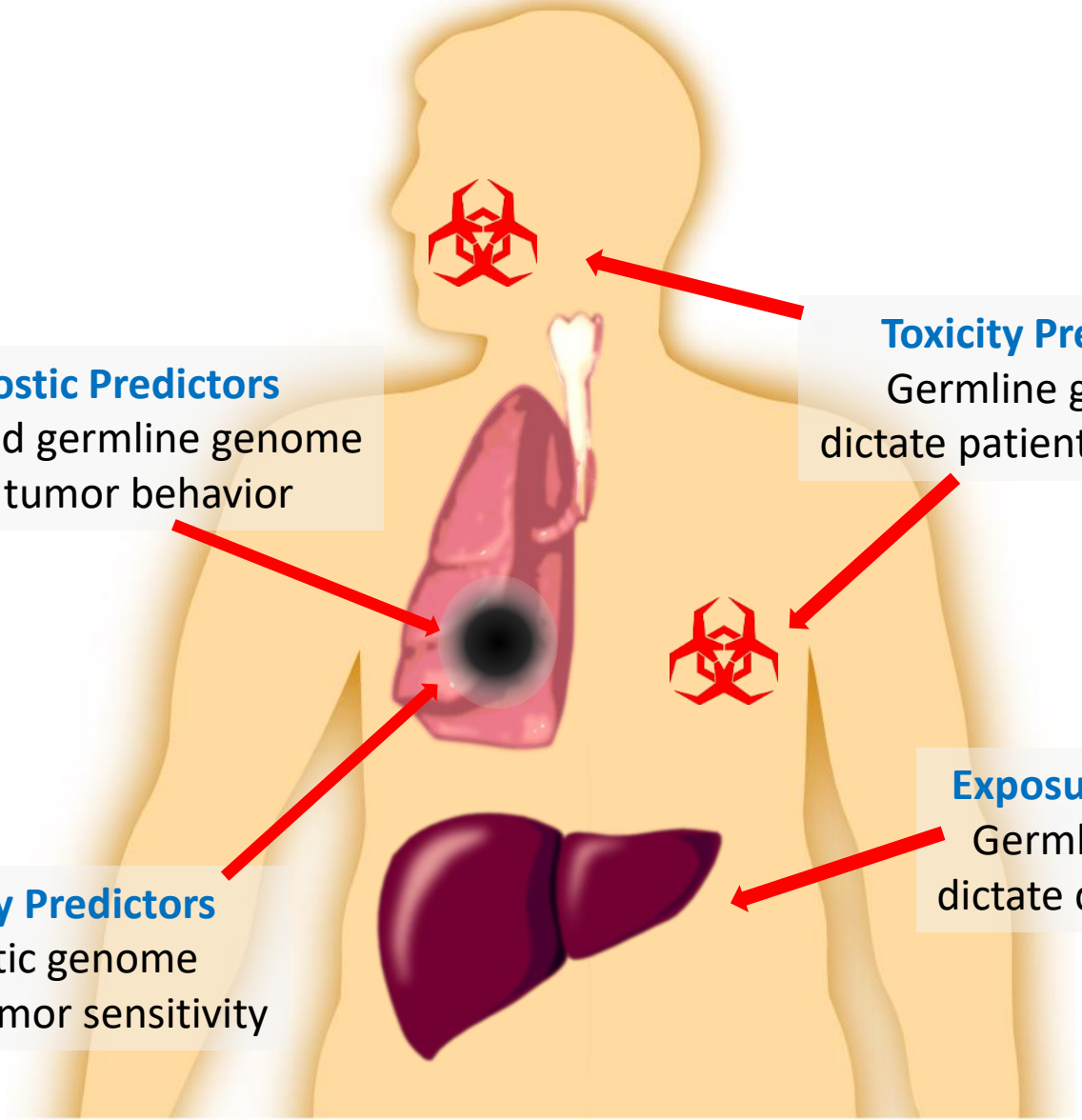
Institut für Klinische Pharmakologie

Cohen & Settleman. *Cell* 2014



Prognostic Predictors
Somatic and germline genome dictate tumor behavior

Toxicity Predictors
Germline genome dictate patient sensitivity



Efficacy Predictors
Somatic genome dictate tumor sensitivity

Exposure Predictors
Germline genome dictate drug exposure

Schwab M
IKP Stuttgart

Personalized / Precision Medicine: delicate balance between benefit and risk

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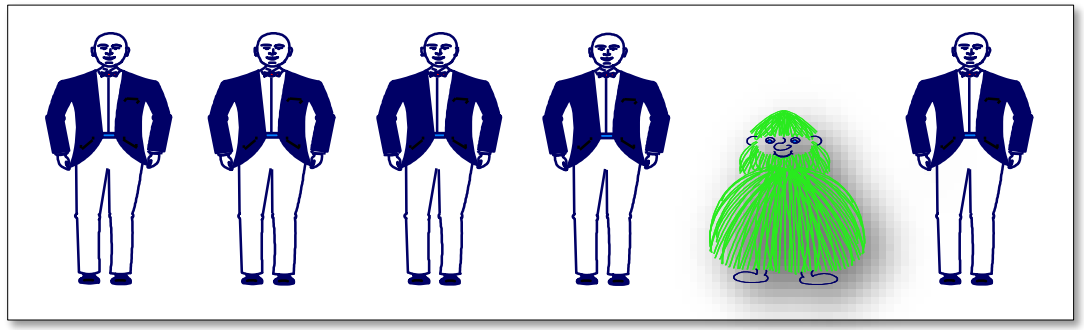
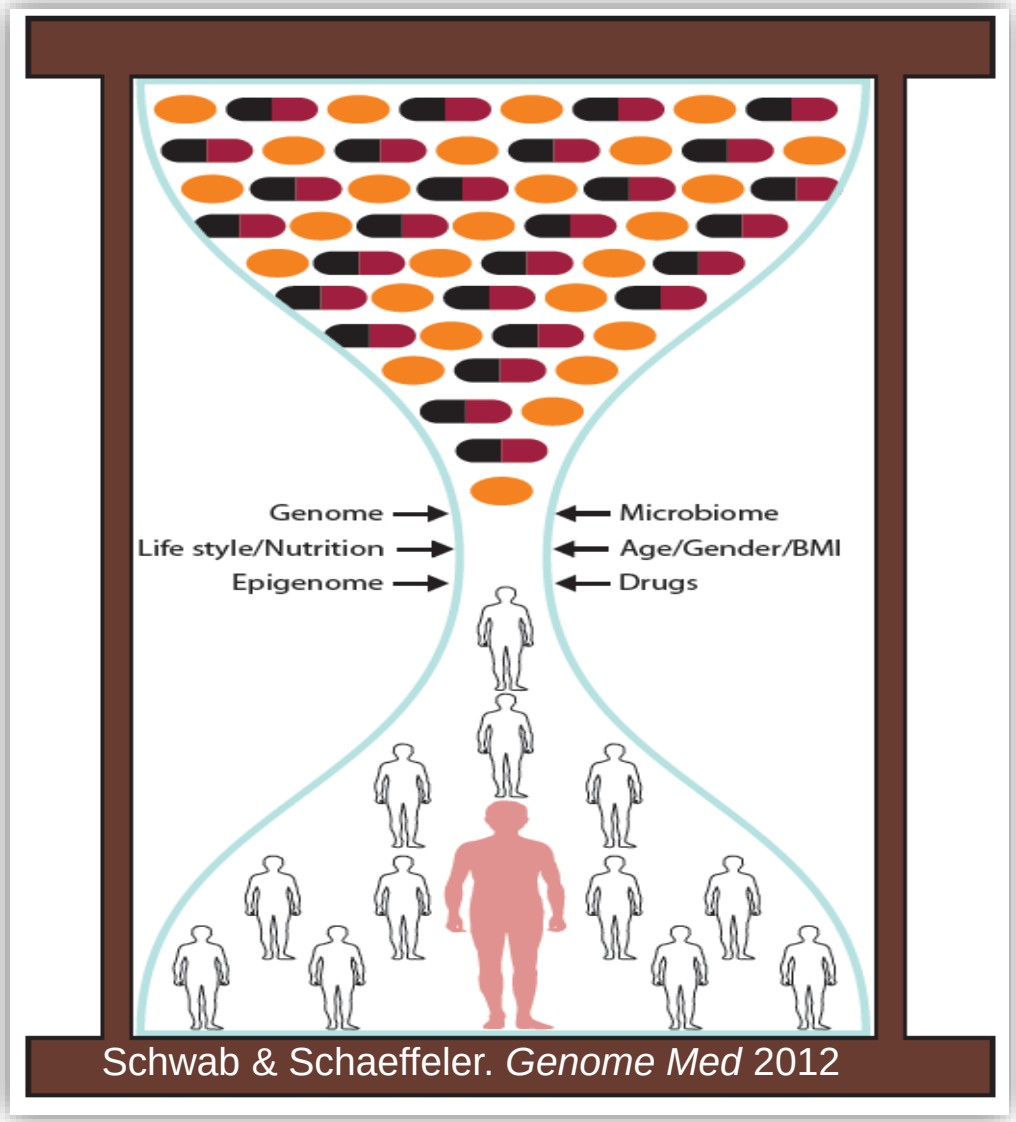
Dr. Margarete Fischer-Bosch
Institut für Klinische Pharmakologie



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

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



Schwab & Schaeffeler. *Genome Med* 2012

nature reviews genetics

https://doi.org/10.1038/s41576-022-00572-8

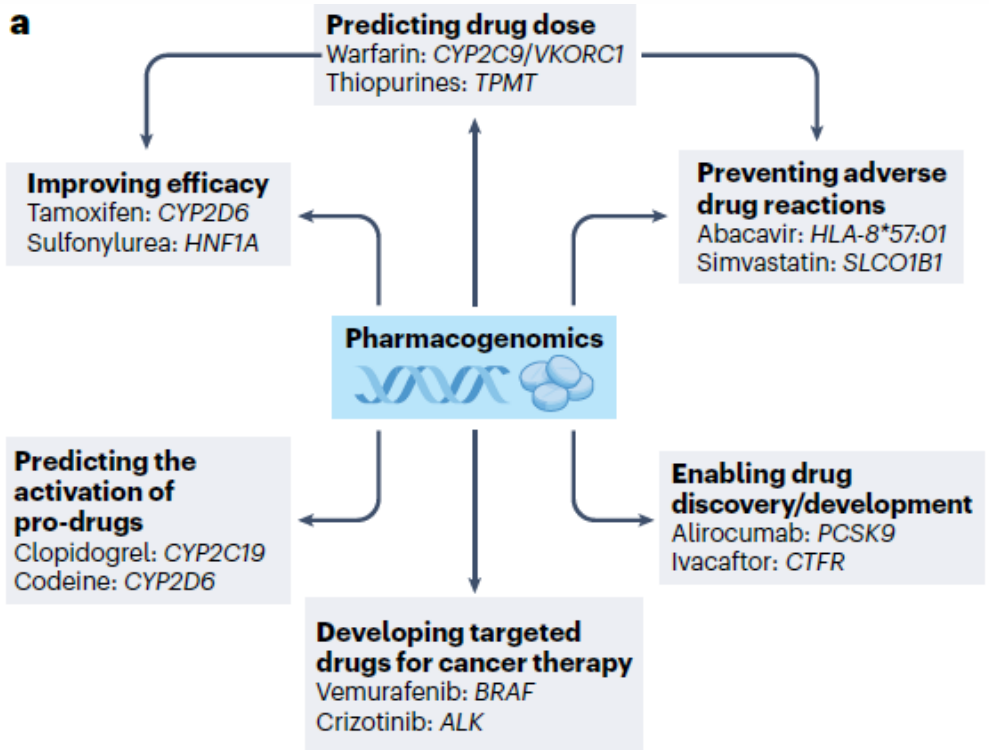
Review article

Check for updates

Pharmacogenomics: current status and future perspectives

Munir Pirmohamed

2023



Country	Number studied	Number of genes evaluated	Proportion carrying at least one actionable genotype or diplotype	Ref.
Australia	5,408	4	95.9%	15
Canada	98	19	96.9%	16
Estonia	42,092	11	99.8%	17
Netherlands	498	11	99.4%	18
Qatar	6045	15	99.5%	19
UK	487,409	14	99.5%	20
UK	713	11	98.7%	21
USA	9,589	6	91.4%	22
USA	1,013	5	99.0%	23

Randomized clinical trials & Pharmacogenomics (PGx)

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Dr. Margarete Fischer-Bosch Institut für Klinische Pharmakologie

Identification of Patients With Variants in *TPMT* and Dose Reduction Reduces Hematologic Events During Thiopurine Treatment of Inflammatory Bowel Disease

Gastroenterology 2015

Mari… Sita… Piet… Hans…

The NEW ENGLAND JOURNAL of MEDICINE

2008

ORIGINAL ARTICLE

HLA-B*5701 Screening for Hypersensitivity to Abacavir

Simon Mallal, M.B., B.S., Elizabeth Phillips, M.D., Giampiero Carosi, M.D., Jean-Michel Molina, M.D., Cassy Workman, M.B., B.S., Janez Tomažič, M.D.,

Reduced-Function *CYP2C19* Genotype and Risk of Adverse Clinical Outc… Among Patients Treated With Clo… Predominantly for PCI

JAMA 2010

A Meta-analysis

JAMA | Original Investigation

Effect of Genotype-Guided Warfarin Dosing on Clinical Events and Anticoagulation Control Among Patients Undergoing Hip or Knee Arthroplasty

…GIFT Randomized Clinical Trial

JAMA. 2017;318(12):1115-1124.

***DPYD* genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis**

Lancet Oncology 2018

Linda M Henricks*, Carin A T C Lunenburg*, Femke M de Man*, Didier Meulendijks, Geert W J Frederix, Emma Kienhuis, Geert-Jan Creemers, Arnold Baars, Vincent O Dezentjé, Alexander L T Imholz, Frank L F Leurissen, Johanna E A Portielje, Rob L H Jansen, Paul Hamberg, Albert I ten Tije, Helga…, Erik v…, Henk-…

The NEW ENGLAND JOURNAL of MEDICINE

2013

ORIGINAL ARTICLE

A Randomized Trial of Genotype-Guided Dosing of Warfarin

…unir Pirmohamed, Ph.D., F.R.C.P., Girvan Burnside, Ph.D., Niclas Eriksson, Ph.D., …drea L. Jorgensen, Ph.D., Cheng Hock Toh, M.D., Toby Nicholson, F.R.C.Path., …rick Kesteve…, Christina S…, Hugo K…, Paula …, …rhad Kama…

Proceedings of The Knee Society 2021

Prospective Randomized Study Using Pharmacogenetics to Customize Postoperative Pain Medication Following Hip and Knee Arthroplasty

J Arthroplasty 2022

William G. Hamilton, MD [a], Jeanine M. Cargiulo, PA-C [a], Thomas R. Reynolds, BS [b]

Prospective *CYP2C19* Genotyping to Guide Antiplatelet Therapy Following Percutaneous Coronary Intervention

A Pragmatic Randomized Clinical Trial

Circ Genom Precis Med 2020

Sony Tuteja, PharmD, MS, Henry Glick, PhD, William Matthai, MD, Irving Nachamkin, DrPH, MPH, Ashwin Nathan, MD, Karen Monono, MS, Craig Carcuffe, BS, Karen Maslowski, BSN

Potential role of *CMPK1*, *SLC29A1*, and *TLE4* polymorphisms in gemcitabine-based chemotherapy in HER2-negative metastatic breast cancer patients: pharmacogenetic study results from the prospective randomized phase II study of eribulin plus gemcitabine versus paclitaxel plus gemcitabine (KCSG-BR-13-11)

ESMO Open 2021

E. H. Cho[1†], J.-Y. Kim[2†], S.-A. Im[3], K. H. Jung[4], J. Sohn[5], K. S. Lee[6], Y. S. Chae[7], K. H. Lee[8], J. H. Kim[9], J.-H. Jang[10], J. H. Ahn[11], M. S. Park[12], S.-Y. Lee[10,13,14*†] & Y. H. Park[2,15*‡]

Clinical utility of combinatorial pharmacogenomic testing in depression: A Canadian patient- and rater-blinded, randomized, controlled trial

Transl Psychiatry 2022

Arun K. Tiwari[1,2,30], Clement C. Zai[1,2,3,4,30], C. Anthony Altar[5], Julie-Anne Tanner[6], Paige E. Davies[6], Paul Traxler[6], James Li[6], Elizabeth S. Cogan[7], Matthew T. Kucera[7], Ana Gugila[6], Nicole Braganza[1,2], Heather Emmerson[1,2], Gwyneth Zai[1,2,3], Daniel J. Müller[1,2,3], Robert Levitan[1,2,3], Stefan Kloiber[2,3,8], Zafiris J. Daskalakis[9], Benicio N. Frey[10,11], James M. Bowen[12,13,14], Jean-Eric Tarride[15,16,17], Richard Tytus[18], Ranjith Chandrasena[19], Nicholas Voudouris[20], Valerie H. Taylor[21], Raymond Tempier[22,23], Verinder Sharma[24], Akshya Vasudev[25,26], Peter Dzongowski[27], Lew Pliamm[28], Todd Greenspoon[29], Bryan M. Dechairo[7] and James L. Kennedy[1,2,3]

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

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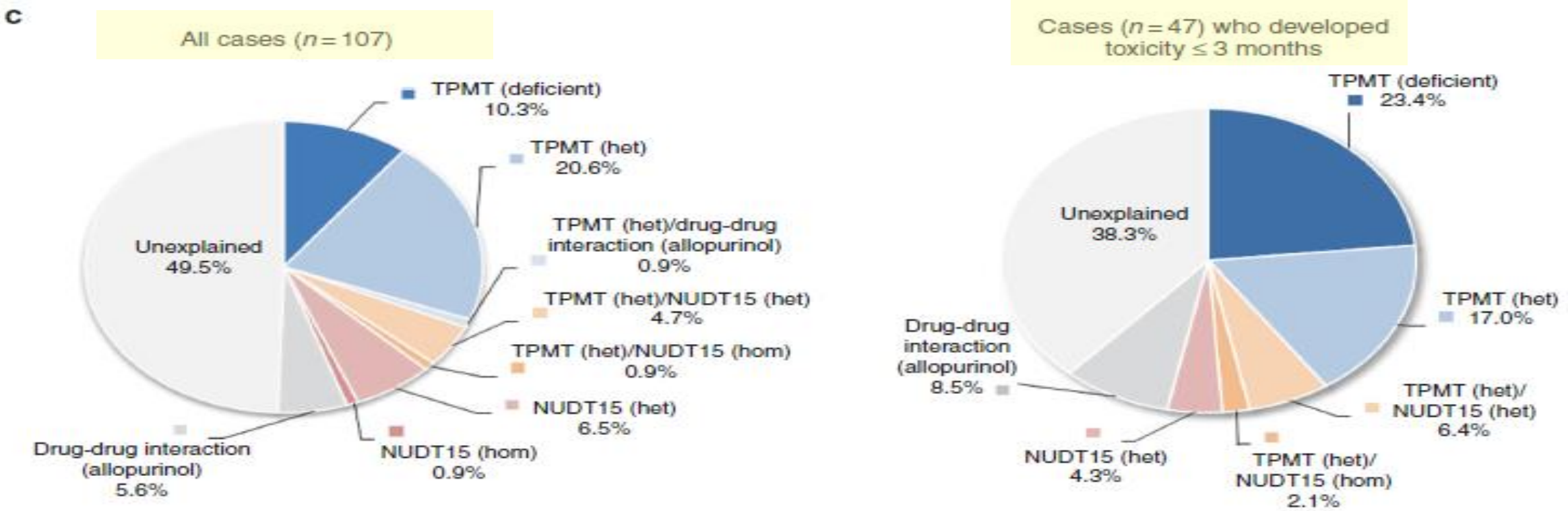
Institut für Klinische Pharmakologie

IKP diagnostic cohort
for TPMT (n > 25.000)



In collaboration with the German ALL study coordination all ALL children *preemptively* tested for TPMT to avoid hematotoxicity

Schaeffeler *et al.* Genet Med 2019

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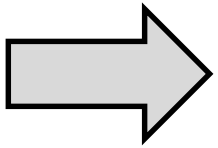
Institut für Klinische Pharmakologie

CPIC
Clinical Pharmacogenetics
Implementation Consortium

TPMT
First description
1980

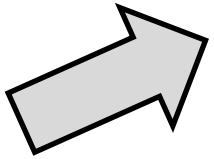


Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing: 2013 Update

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

Clin Pharmacol Ther 2013

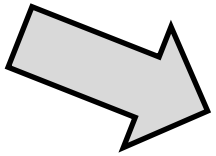
NUDT15
First description
2014



Pharmacogene Variation Consortium Gene Introduction: *NUDT15*

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

Clin Pharmacol Ther 2018



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

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

Clin Pharmacol Ther 2018

CPIC
Clinical Pharmacogenetics
Implementation Consortium

DPYD pharmacogenetic diagnostics is implemented

dihdyropyrimidine-dehydrogenase and 5-fluorouracil-, capecitabine- and tegafur-therapy in patients with colorectal cancer

VOLUME 26 · NUMBER 13 · MAY 1 2008
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

2008

Role of Genetic and Nongenetic Factors for Fluorouracil Treatment-Related Severe Toxicity: A Prospective Clinical Trial by the German 5-FU Toxicity Study Group

Matthias Schwab, Ulrich M. Zanger, Claudia Marx, Elke Schaeffeler, Kathrin Klein, Jürgen Dippon, Reinhold Kerb, Julia Blievernicht, Joachim Fischer, Ute Hofmann, Carsten Bokemeyer, and Michel Eichelbaum

Clinical relevance of *DPYD* variants c.1679T>G, c.1236G>A/HapB3, and c.1601G>A as predictors of severe fluoropyrimidine-associated toxicity: a systematic review and meta-analysis of individual patient data

Lancet Oncol 2015

Didier Meulendijks, Linda M Henricks*, Gabe S Sonke, Maarten J Deenen, Tanja K Froehlich, Ursula Amstutz, Carlo R Largiad…, Barbara A Jennings, Anthony M Marinaki, Jeremy D Sanderson, Zdenek Kleibl, Petra Kleiblova, Matthias Schwab, Ulrich M Zanger, Claire Palles, Ian Tomlinson, Eva Gross, André B P van Kuilenburg, Cornelis J A Punt, Miriam Koopman, Jos H Beijnen, Annemieke Cats, Jan H M Schellens*

CLINICAL PHARMACOLOGY & THERAPEUTICS

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

2018

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

New testing and treatment recommendations for fluorouracil, capecitabine, tegafur and flucytosine

13 March 2020
EMA/125891/2020
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

wichtige Mitteilung

Bundesinstitut für Arzneimittel und Medizinprodukte

04. Juni 2020

5-Fluorouracil- (i.v.), Capecitabin- und Tegafur-haltige Arzneimittel: Tests vor Behandlungsbeginn zur Identifizierung von Patienten mit DPD-Mangel, die ein erhöhtes Risiko für schwere Toxizität haben

DGHO
in Kooperation mit
AIO
gfh
DGVS
MKG
BNHO
ADHOK
QeGHO
SSMO SGOM SSMO

Positionspapier

Dihydropyrimidin-Dehydrogenase (DPD) -Testung vor Einsatz von 5-Fluorouracil, Capecitabin und Tegafur

Juni 2020

Juni 2020

Cost reimbursement guaranteed by the **statutory health insurances in Germany**

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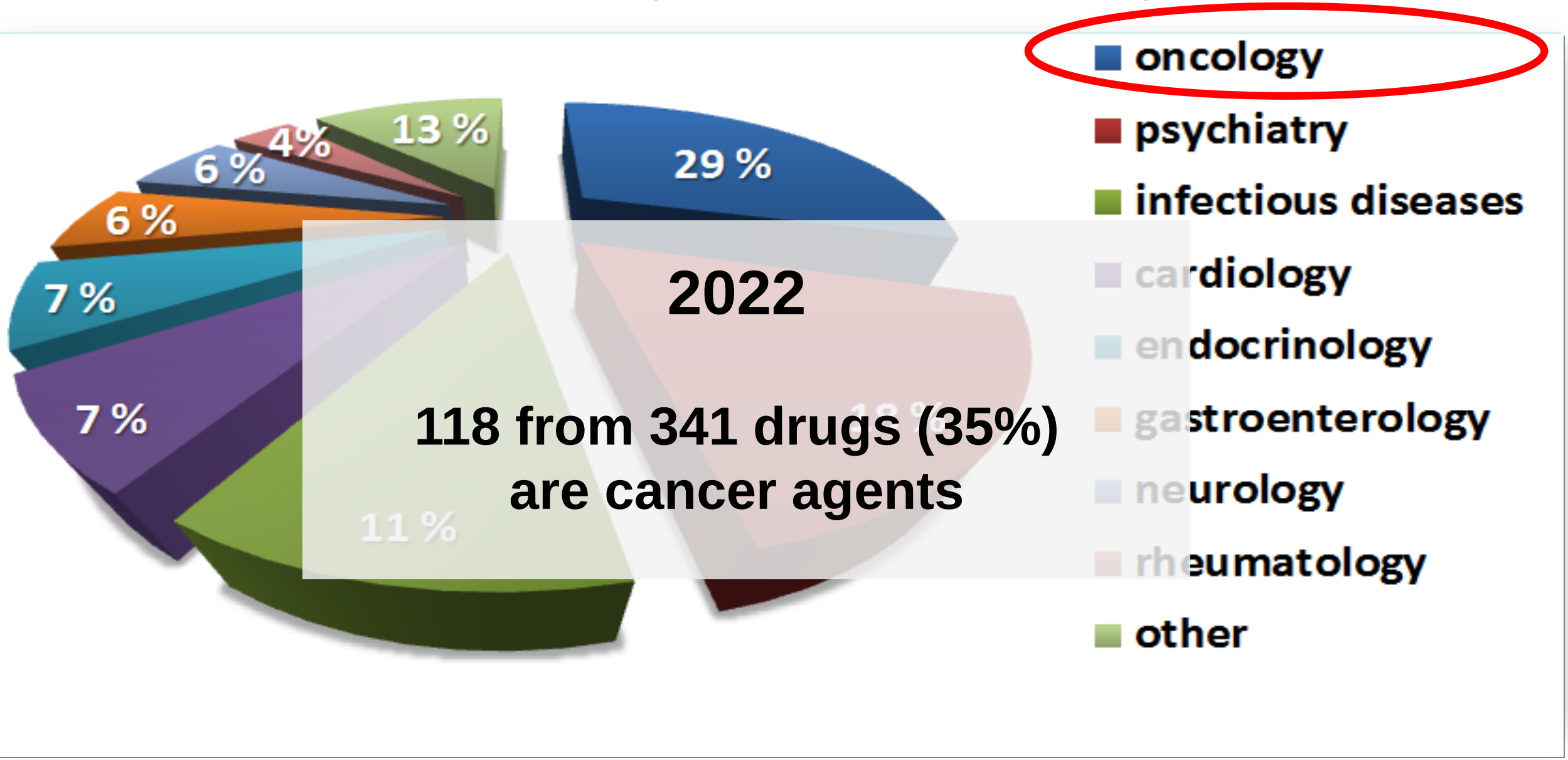
More than 341 FDA-approved drugs with labeled pharmacogenomic information



www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations

Digital-supported PGx information & implementation

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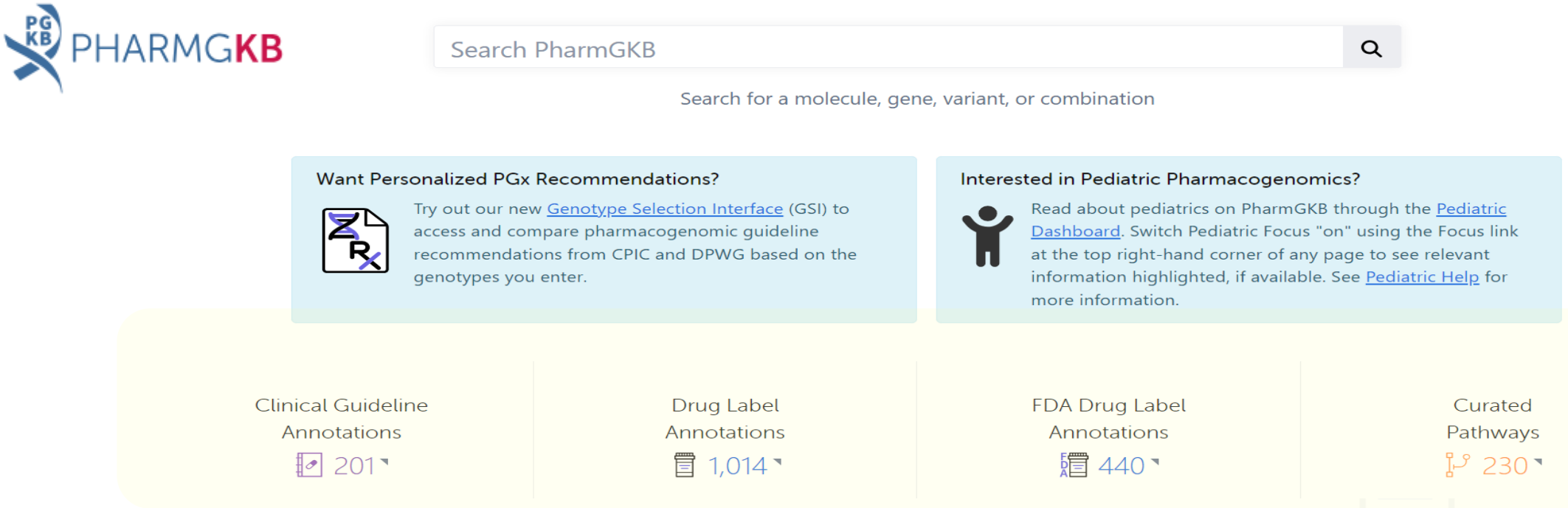

https://www.pharmgkb.org/

PharmGKB
Pharmacogenomics. Knowledge. Implementation.

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CPIC: Clinical Pharmacogenetics Implementation Consortium

CPIC: Implementing PGx
a PharmGKB & PGRN collaboration

11 / 2020:
25 CPIC guidelines covering > 60 drugs

Current Drug Metabolism, 2014, *15*, 209-217 209

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

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

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

GC Bell[1], KE Caudle[2], M Whirl-Carrillo[3], RJ Gordon[4], K Hikino[5], CA Prows[6], A Gaedigk[7], JAG Agundez[8,9], S Sadhasivam[10,11], TE Klein[3] and M Schwab[12,13,14] Clin Pharmacol Ther 2017

Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on *TPMT* and *NUDT15* Genotypes: 2018 Update Clin Pharmacol Ther 2019

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

Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing: 2013 Update Clin Pharmacol Ther 2013

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

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

Ursula Amstutz[1], Linda M. Henricks[2], Steven M. Offer[3], Julia Barbarino[4], Jan H.M. Schellens[2,5], Jesse J. Swen[6], Teri E. Klein[4], Howard L. McLeod[7], Kelly E. Caudle[8], Robert B. Diasio[3,9] and Matthias Schwab[10,11,12] Clin Pharmacol Ther 2017

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6* and Tamoxifen Therapy Clin Pharmacol Ther 2018

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

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2C19* and Proton Pump Inhibitor Dosing Clin Pharmacol Ther 2020

John J. Lima[1,*], Cameron D. Thomas[2], Julia Barbarino[3], Zeruesenay Desta[4], Sara L. Van Driest[5], Nihal El Rouby[2,6], Julie A. Johnson[2], Larisa H. Cavallari[2], Valentina Shakhnovich[7,8,9], David L. Thacker[10,11], Stuart A. Scott[12,13], Matthias Schwab[14,15,16], Chakradhara Rao S. Uppugunduri[17,18], Christine M. Formea[19], James P. Franciosi[20,21], Katrin Sangkuhl[3], Andrea Gaedigk[7], Teri E. Klein[3], Roseann S. Gammal[22,23] and Takahisa Furuta[24]

The Ubiquitous Pharmacogenomics (U-PGx) PREPARE trial

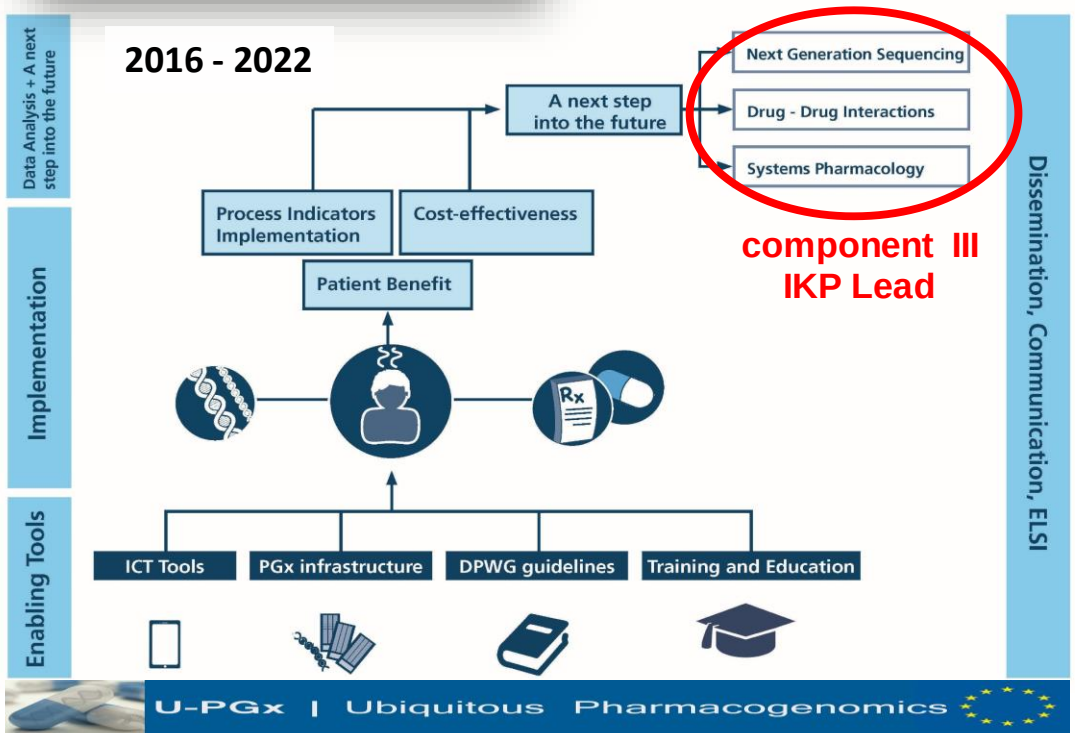
Making actionable pharmacogenomic data and effective treatment optimization accessible to Every European citizen (Lead HJ Guchelaar, NL, Vice Chair M Schwab)

IKP
Dr. Margarete Fischer-Bosch Institut für Klinische Pharmakologie


The right drug for you

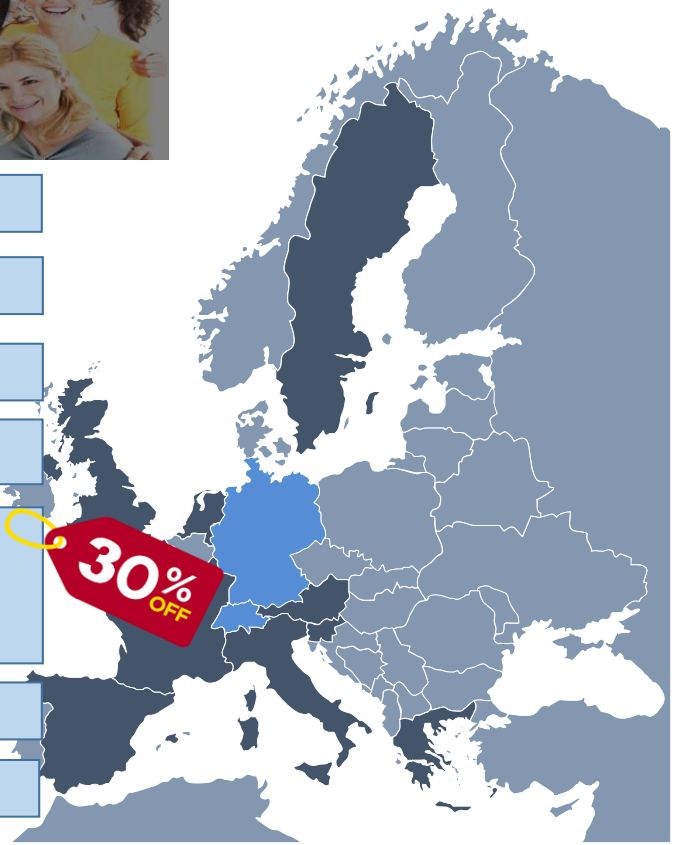
Personalized prescribing is gaining momentum, but is there enough evidence for it become standard clinical practice?

Ubiquitous Pharmacogenomics will spend 3 years studying the clinical outcomes of 8,000 patients in a large randomized controlled trial in 7 hospitals in 7 European countries.



component III
IKP Lead

- 15Mio € Horizon2020 funding
- Framework for implementation
- ~7,000 patients recruited
- 7 European countries
- Pre-emptively PGx testing of a panel of markers can results in reducing ADRs
- Manuscript *in press*
- Extended other research activities



Component III comprises NGS, DDI & pharmacometrics

Schwab M
IKP Stuttgart

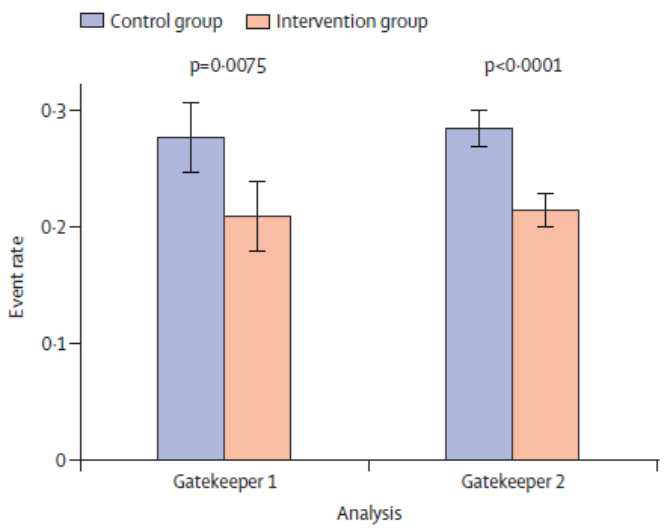
A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study

Jesse J Swen, Cathelijne H van der Wouden, Lisanne EN Manson*, Heshu Abdullah-Koolmees, Kathrin Blagec, Tanja Blagus, Stefan Böhringer, Anne Cambon-Thomsen, Erika Cecchin, Ka-Chun Cheung, Vera HM Deneer, Mathilde Dupui, Magnus Ingelman-Sundberg, Siv Jonsson, Candace Joefield-Roka, Katja S Just, Mats O Karlsson, Lidija Konta, Rudolf Koopmann, Marjolein Kriek, Thorsten Lehr, Christina Mitropoulou, Emmanuelle Rial-Sebbag, Victoria Rollinson, Rossana Roncato, Matthias Samwald, Elke Schaeffeler, Maria Skokou, Matthias Schwab, Daniela Steinberger, Julia C Stingl, Roman Tremmel, Richard M Turner, Mandy H van Rhenen, Cristina L Dávila Fajardo, Vita Dolžan, George P Patrinos, Munir Pirmohamed, Gere Sunder-Plassmann, Giuseppe Toffoli, Henk-Jan Guchelaar, on behalf of the Ubiquitous Pharmacogenomics Consortium†*

THE LANCET

February 2, 2023

Interpretation Genotype-guided treatment using a 12-gene pharmacogenetic panel significantly reduced the incidence of clinically relevant adverse drug reactions and was feasible across diverse European health-care system-organisations and settings. Large-scale implementation could help to make drug therapy increasingly safe.



In the second analysis, which included all groups, the prevalence of the development of a causal clinically relevant ADR was 21% in the study group and 29% in the control group, **reducing the risk of an ADR by 30% (OR 0.70 [95% CI 0.61–0.79]; p <0.0001)**

COST EFFECTIVENESS of PGx testing based on Clinical PGx Implementation Consortium (CPIC): a systematic review

IKP Dr. Margarete Fischer-Bosch Institut für Klinische Pharmakologie

Table 2 Summary of drug–gene pairs and cost outcomes

Class	Gene	Total articles reviewed	Cost-saving	Cost-effective	Not cost-effective	Uncertain	Drugs
Aminoglycosides[23]	*mt-RNR1*	1	—	—	1	—	Tobramycin
Analgesics[24]	*CYP2D6*	1	—	—	1	—	Codeine
Anticoagulant[25–40]	*CYP2C9 & VKORC1*	15	—	6	5	4	Warfarin
	CYP2C9	1	—	1	—	—	
Antidepressants[41–51]	*CYP2D6*	2	—	—	1	1	Citalopram, escitalopram, fluvoxamine, paroxetine, sertraline, amitriptyline, clomipramine, doxepin, imipramine, nortriptyline, trimipramine, desipramine
	Multigene panel[a]	9	8	1	—	—	
Antiepileptic[52–59]	*HLA-A*31:01*	7	1	2	4	—	Carbamazepine, phenytoin
	*HLA-B*15:02*	1	—	1	—	—	
Antifungal[60–61]	*CYP2C19*	2	2	—	—	—	Voriconazole
Antigout[62–71]	*HLA-B*58:01*	10	1	4	5	—	Allopurinol
Antiplatelet[15,72–93]	*CYP2C19*	22	4	17	1	—	Clopidogrel
	CYPC19 & CYP2D6	1	1	—	—	—	Clopidogrel, tramadol
Antiretroviral[94–104]	*HLA-B*57:01*	8	2	4	1	1	Abacavir
	CYP2B6	2	2	—	—	—	Efavirenz
	UGT1A1	1	—	—	—	1	Atazanavir
Cardiovascular medications[18,105]	*CYP2C9, CYP2C19, SLCO1B1, & VKORC1*	2	—	2	—	—	Clopidogrel, simvastatin, warfarin
Fluoropyrimidines[106–110]	*DPYD*	5	4	1	—	—	Fluorouracil, capecitabine
Multidrug[16]	*CYP2D6, CYP2C19, CYP2C9, CYP3A4, & VKORC1*	1	—	—	—	1	Citalopram, escitalopram, fluvoxamine, paroxetine, sertraline, amitriptyline, clomipramine, doxepin, imipramine, nortriptyline, trimipramine, desipramine celecoxib, hydrocodone, flurbiprofen, ibuprofen, meloxicam, tramadol, piroxicam, phenytoin, clopidogrel, codeine, voriconazole
Pegylated interferon[111–112]	*IFNL3 (IL-28B)*	2	—	2	—	—	Pegylated interferon alpha
Proton Pump Inhibitors[113]	*CYP2C19*	1	1	—	—	—	Omeprazole, lansoprazole
Selective Estrogen Receptor Modulator[114–116]	*CYP2D6*	3	—	2	—	1	Tamoxifen
Thiopurines[117–127]	*TPMT*	11	3	5	2	1	Azathioprine, mercaptopurine
Total	All	108	29	48	21	10	All

[a]Antidepressant studies contain variable multigene panels ranging from 6 to 13 genes. —, none.

Morris *et al.* Clin Pharmacol Ther 2023

CLINICAL Research: Implementation of PGx into clinical practice at Robert-Bosch-Hospital

The use of digital medicine and App-based solutions

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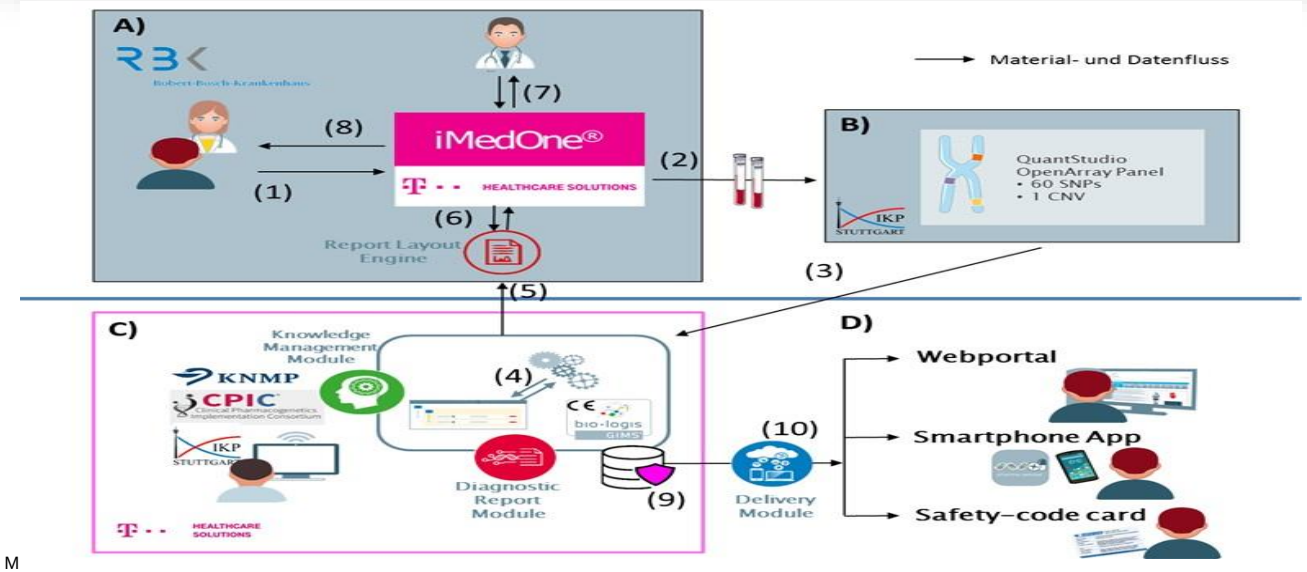
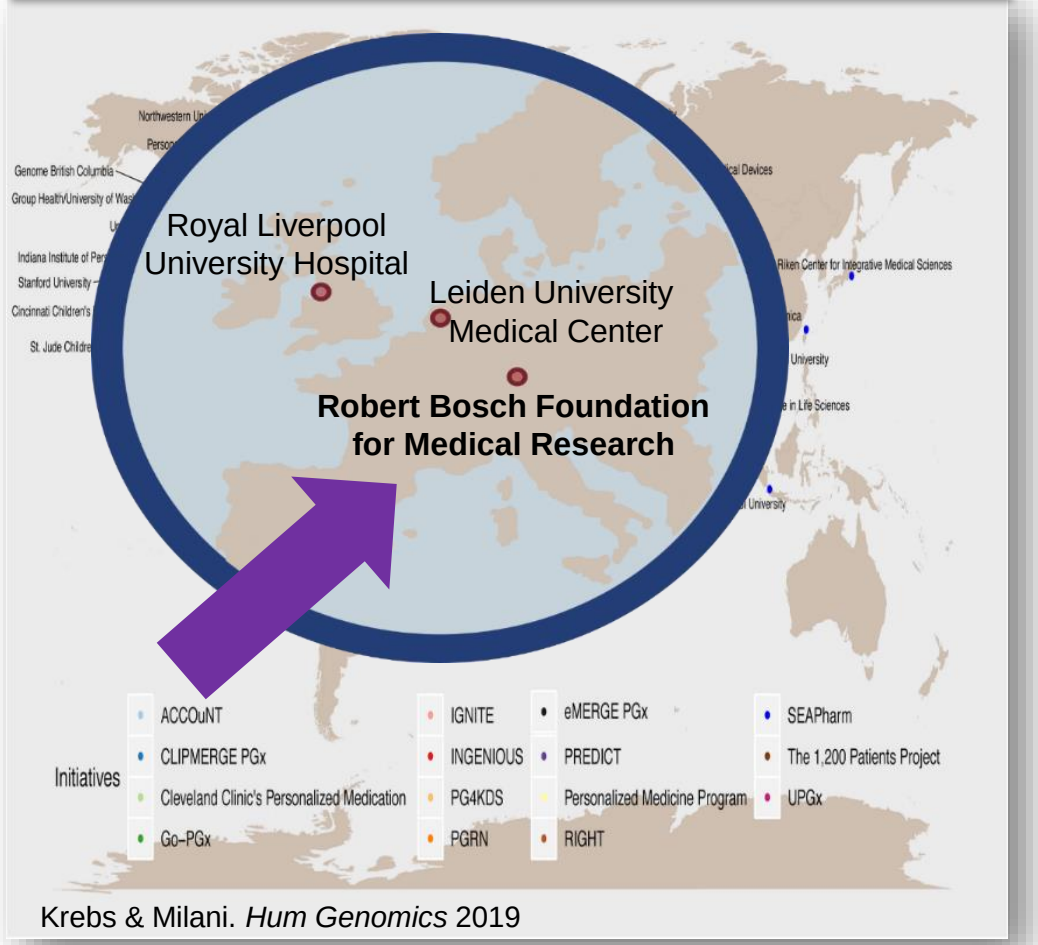


World-wide PGx implementation initiatives



Krebs & Milani. *Hum Genomics* 2019

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Drug Labeling requires up-front PGx diagnostics

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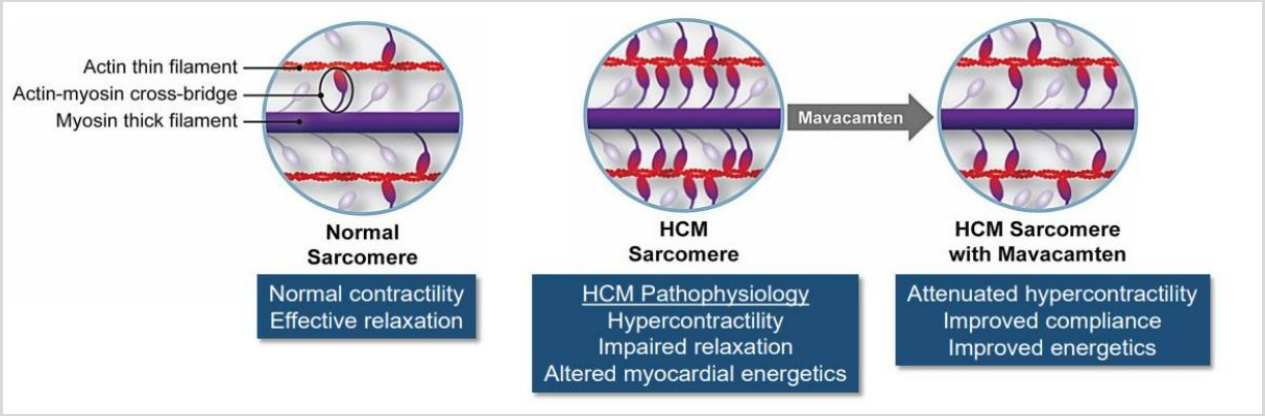
Dug	Kind of Genotyping	Specification acc. to *Summary of product characteristics* (SmPC)	Possible ADRs under standard dosage in variant carriers	Consequence(s)
Cerdelga eliglustat	CYP2D6 genotyping (pretherapeutic) in M. Gaucher type 1	CYP2D6 genotyping is a prerequisite before treatment	PM: significantly increased plasmaconcentation of Eliglustat and increased risk of ADRs (head- and joint aches). UM: Therapy failure	PM: Bisection of the daily dose. UM: Eliglustat should not be applied to CYP2D6-UMs
MAYZENT (siponimod)	CYP2C9 genotyping (pretherapeutic) in secondary progressive MS	CYP2C9 genotyping is a prerequisite before treatment	Significantly increased drug exposure to CYP2C9*3*3/CYP2C9*1*3/CYP 2C19*2*3, thereby increased risk of ADRs such as headache and hypertension	Contraindication for CYP2C9*3*3 genotype. Halving the maintenance dosage for CYP2C9*1*3 or -*2*3 genotype

MAVACAMTEN:
a cardiac myosin inhibitor
to treat obstructive hypertrophic cardiomyopathy

CAMZYOS™ (mavacamten) 2.5, 5, 10, 15mg capsules

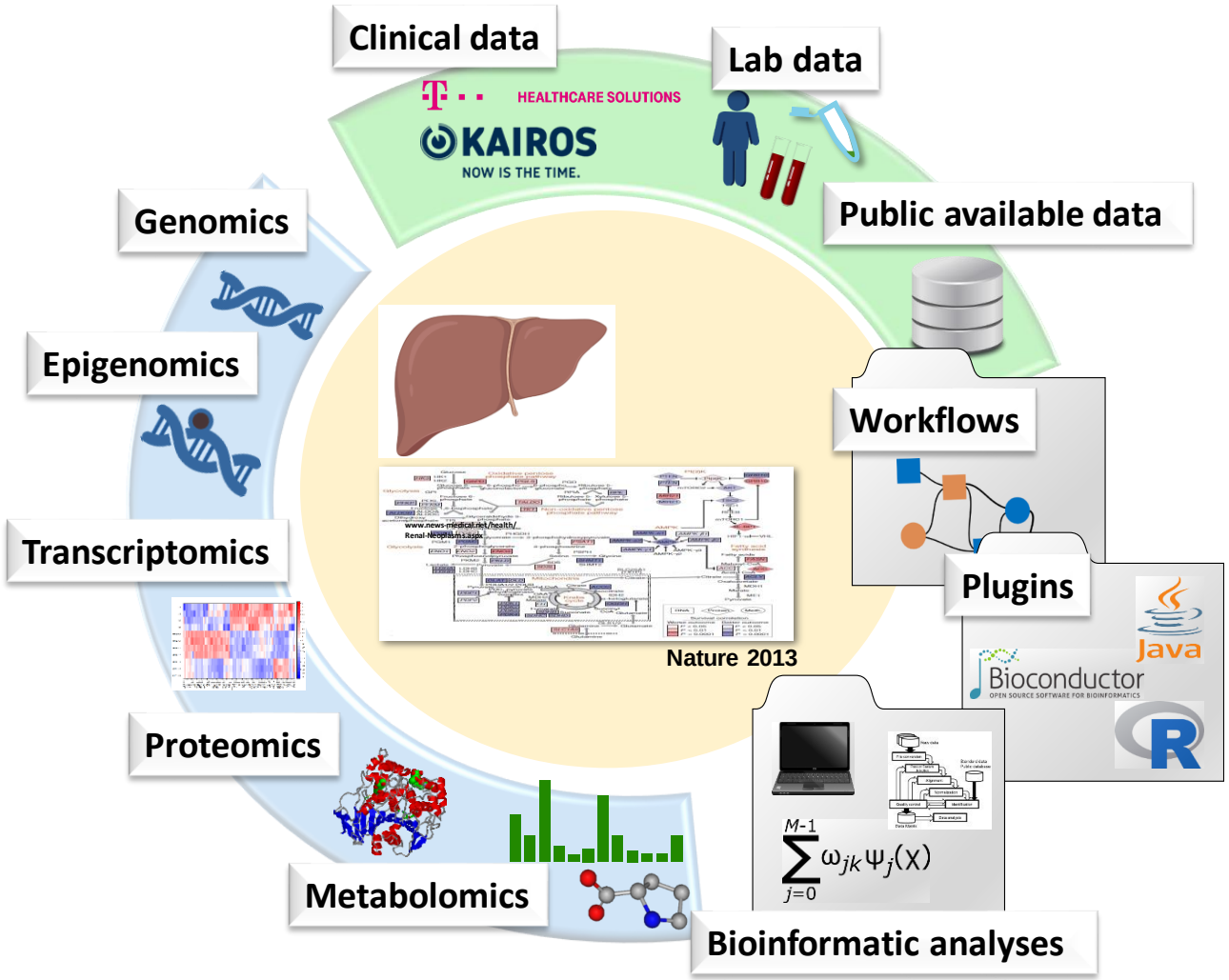


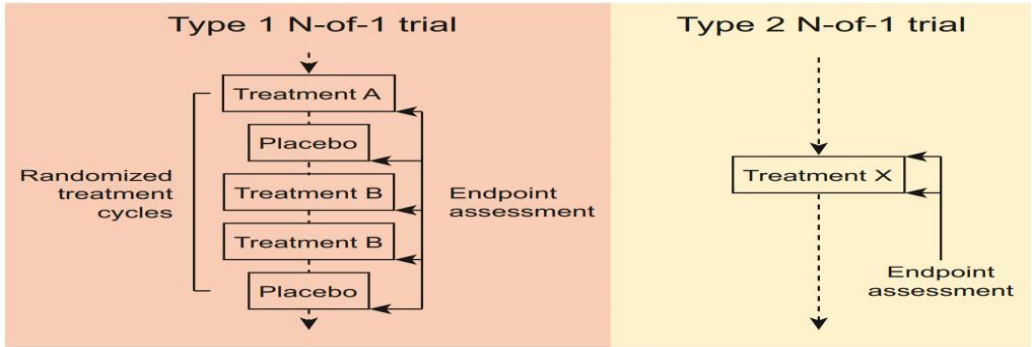
United States
European Union
Australia
Canada
Brazil
Switzerland
Macau
South Korea
Singapore

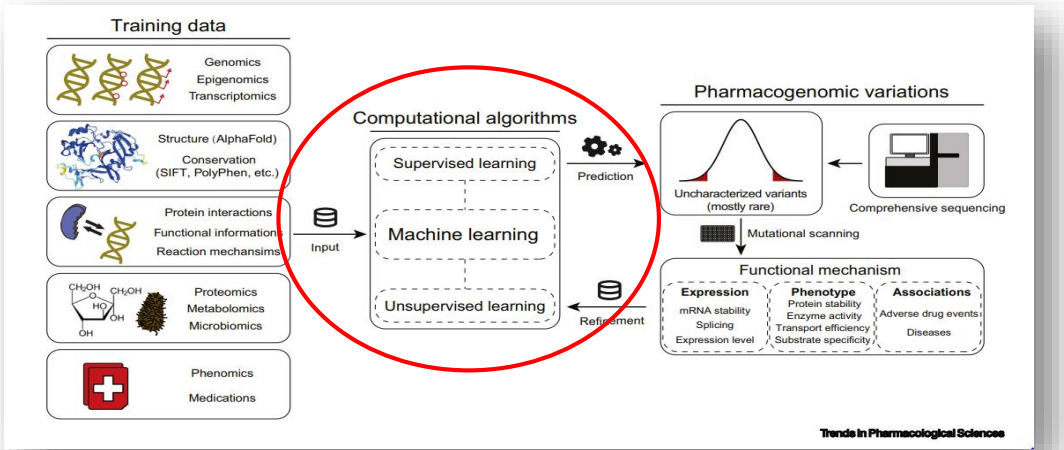
12.5 Pharmacogenomics

Mavacamten AUC_{inf} increased by 241% and C_{max} increased by 47% in CYP2C19 poor metabolizers (PMs) compared to normal metabolizers (NMs) following a single dose of 15 mg mavacamten. Mean half-life is prolonged in CYP2C19 PMs compared to NMs (23 days vs. 6 to 9 days, respectively).

Methodological advances paralleled by innovative trial designs enable individualized targeted therapies







Zhou, Tremmel, Schaeffeler, Schwab, Lauschke. *Trends Pharmacol Sci* 2022
Tremmel, …Schaeffeler, Schwab. *Ann Rev Pharmacol Toxicol* 2023

AI implementation on Pharmacogenomics

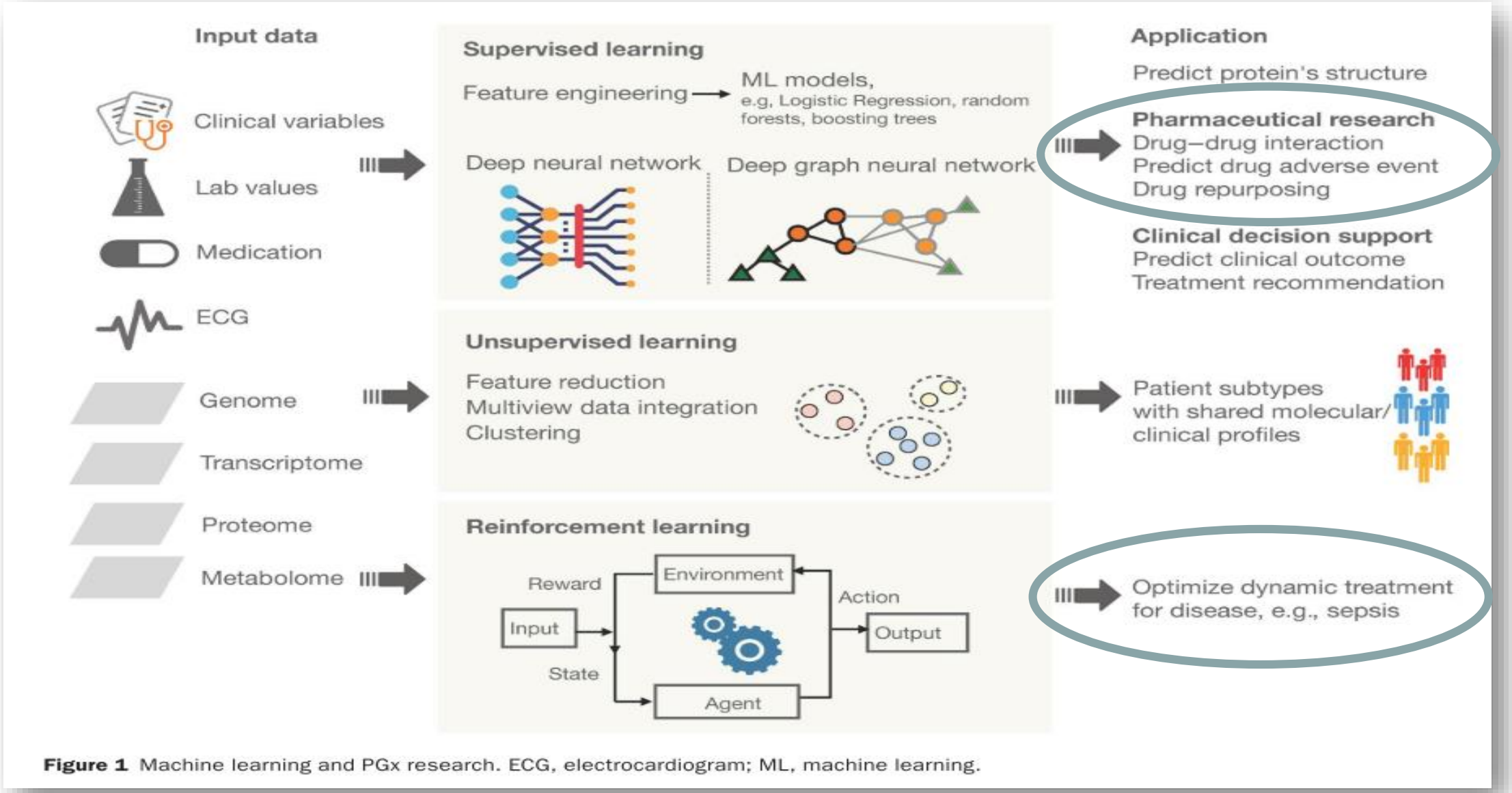
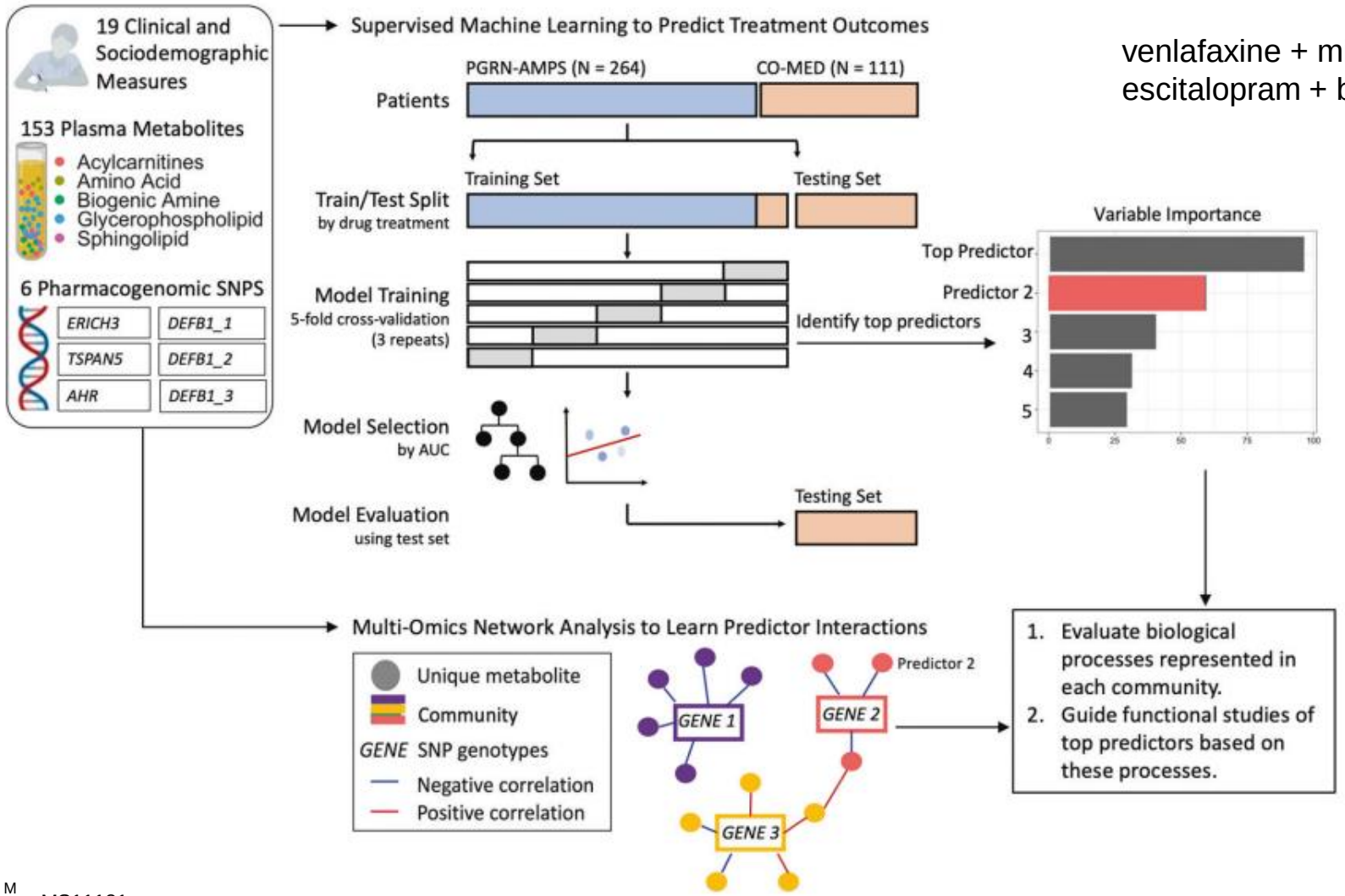


Figure 1 Machine learning and PGx research. ECG, electrocardiogram; ML, machine learning.

Wei *et al.* Clin Pharmacol Ther 2021

Multi-omics driven prediction of response to combination antidepressant therapy: a machine learning approach with cross-trial replication

Conceptual overview of model development and evaluation

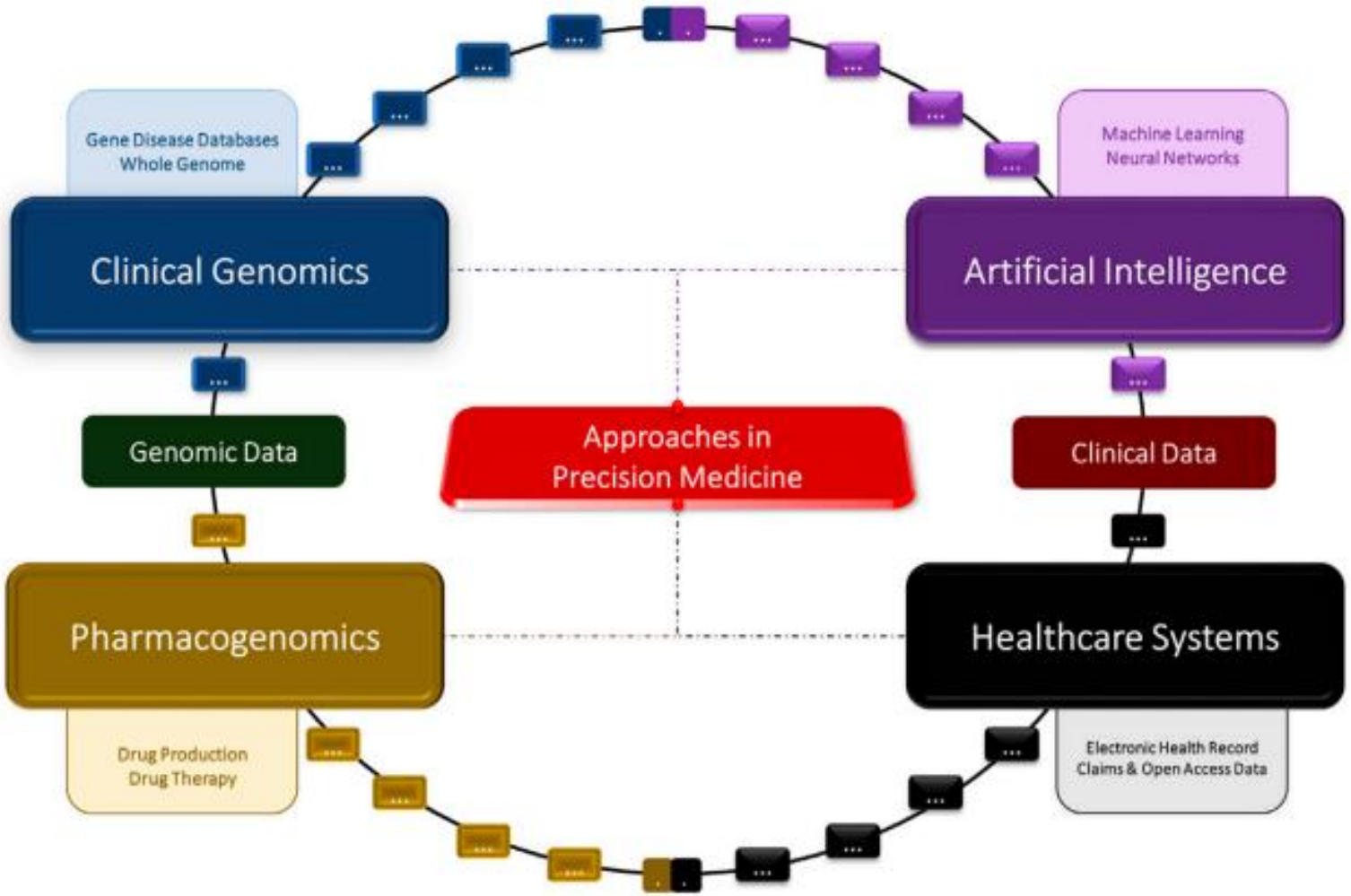


venlafaxine + mirtazapine
escitalopram + bupropion

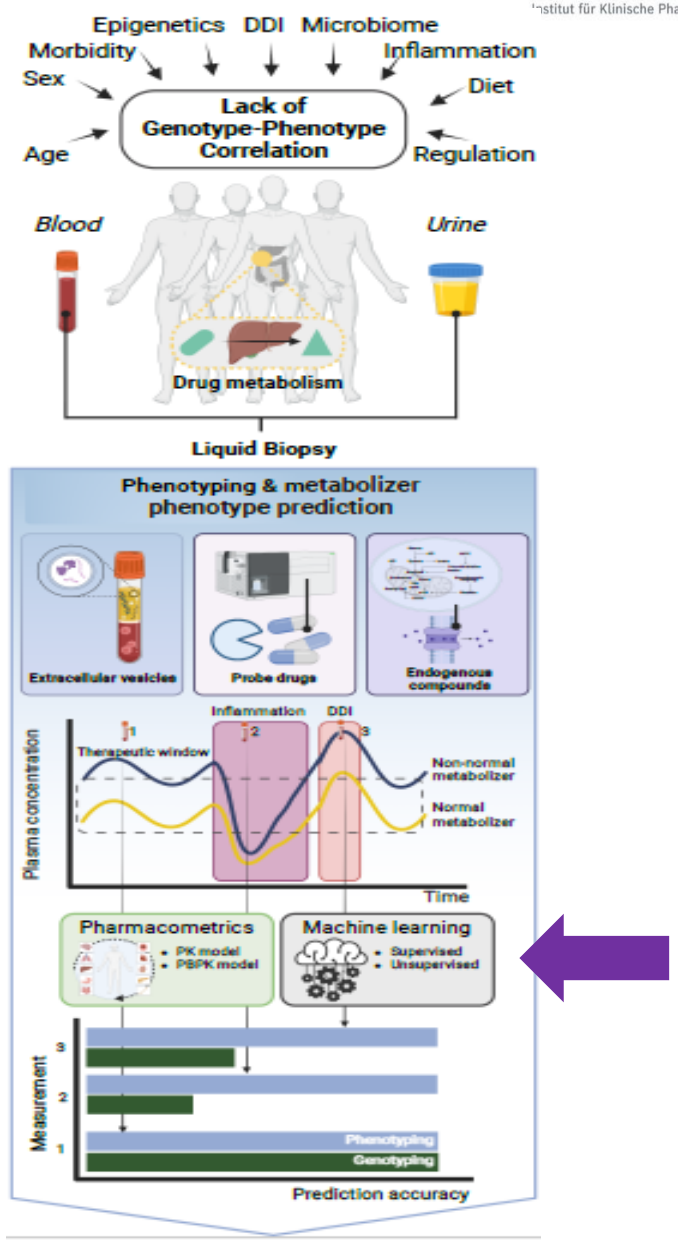
The results suggest that integrating specific metabolites and SNPs achieves accurate predictions of treatment response across classes of antidepressants.

Joyce *et al.* Transl Psychiatry 2021

Concept diagram comprising artificial intelligence, clinical genomics, pharmacogenomics, and big data approaches in precision medicine



Abdelhalim *et al*. Front Genet 2022



Tremmel, …Schwab. Ann Rev Pharmacol Toxicol 2023

The future of Personalized Medicine

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Conventional Big Data

Data derived from advanced analytical technology (eg. Omics, Deep Sequencing, Imaging)

Unused Big Data

Data derived from standard Clinical Care

Private Big Data

Data derived from non-professional, private sources

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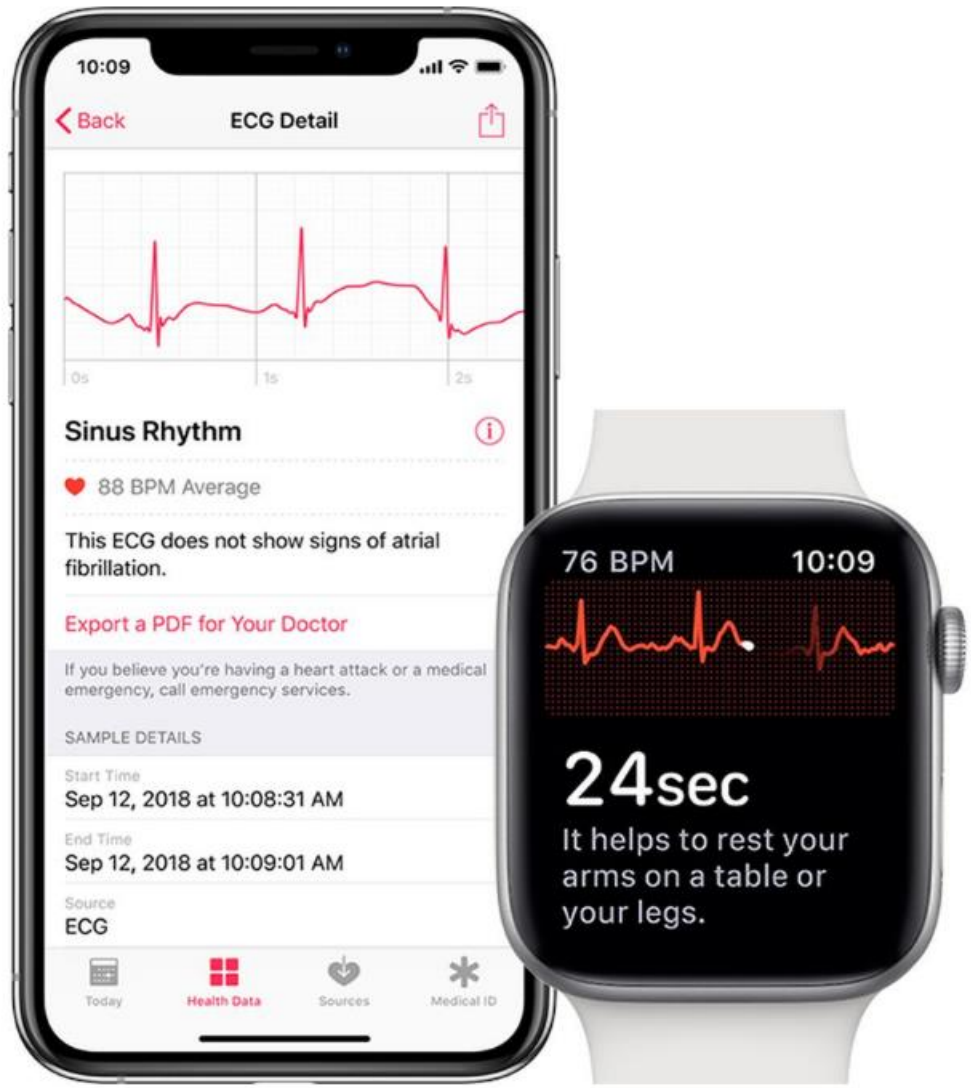
Sensor-based technology combined with AI



www.macrumors.com/2018/11/30/apple-watch-heart-health-45-day-refunds/

Detection of Atrial Fibrillation in a Large Population Using Wearable Devices: The Fitbit Heart Study

Steven A. Lubitz, MD, MPH; Anthony Z. Faranesh, PhD; Caitlin Selvaggi, MS; Steven J. Atlas, MD, MPH; David D. McManus, MD, ScM; Daniel E. Singer, MD; Sherry Pagoto, PhD; Michael V. McConnell, MD, MSEE; Alexandros Pantelopoulos, PhD; Andrea S. Foulkes, PhD

What Are the Clinical Implications?

- The Fitbit wearable-based irregular heart rhythm algorithm may be useful for early detection of undiagnosed atrial fibrillation.
- Individuals with a Fitbit wearable-based irregular heart rhythm detection have a substantial likelihood of having atrial fibrillation confirmed on a subsequent ECG patch monitor and considerable burden of atrial fibrillation.
- Because wearable-based irregular heart rhythm detections using photoplethysmography sensors operate during periods of inactivity, wearing devices at night may maximize the sensitivity.
- Detection of atrial fibrillation during periods of active motion remains a challenge.

Lubitz *et al.* Circulation 2022

Innovative trial designs to foster precision medicine in clinical care: consideration of age groups and molecular markers

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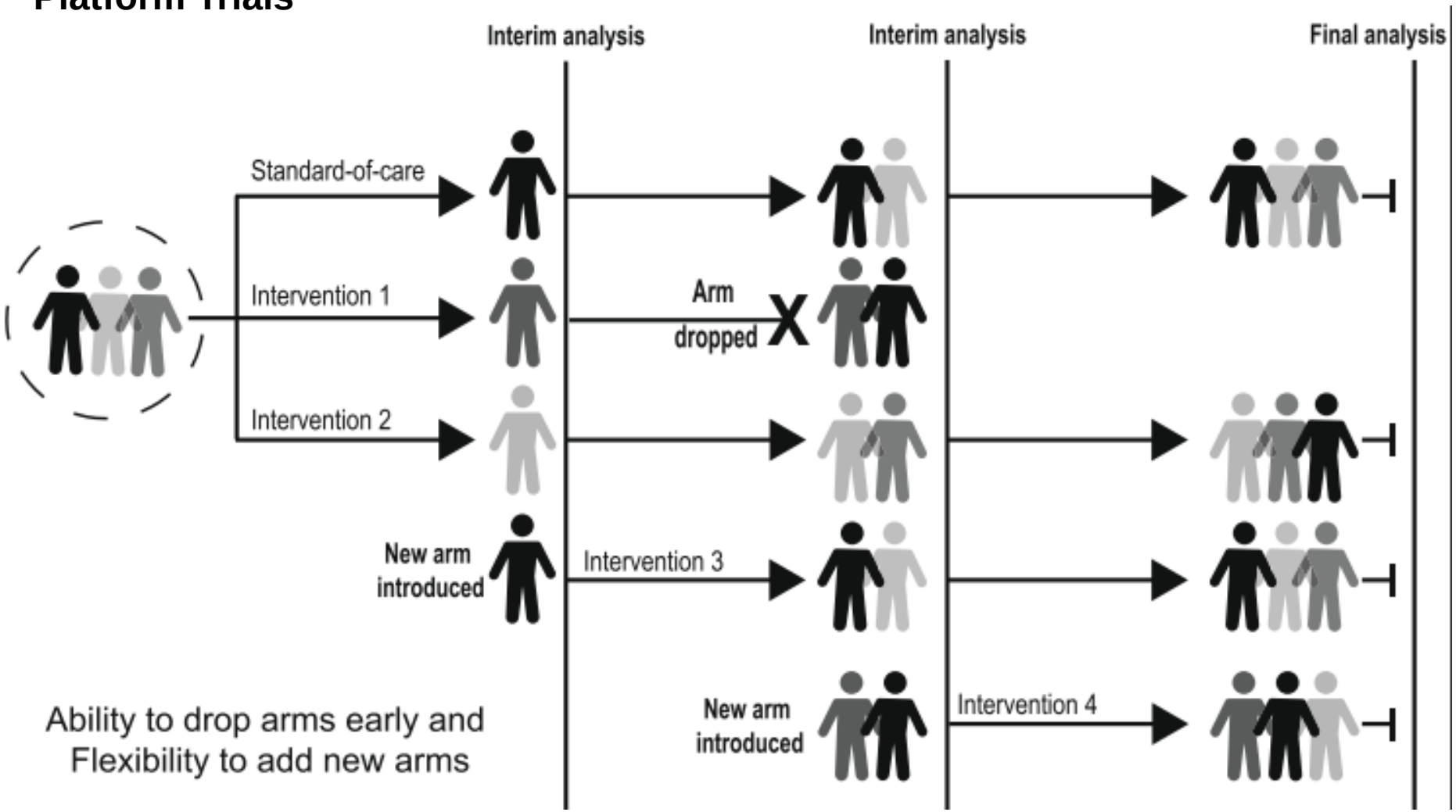
Platform Trials

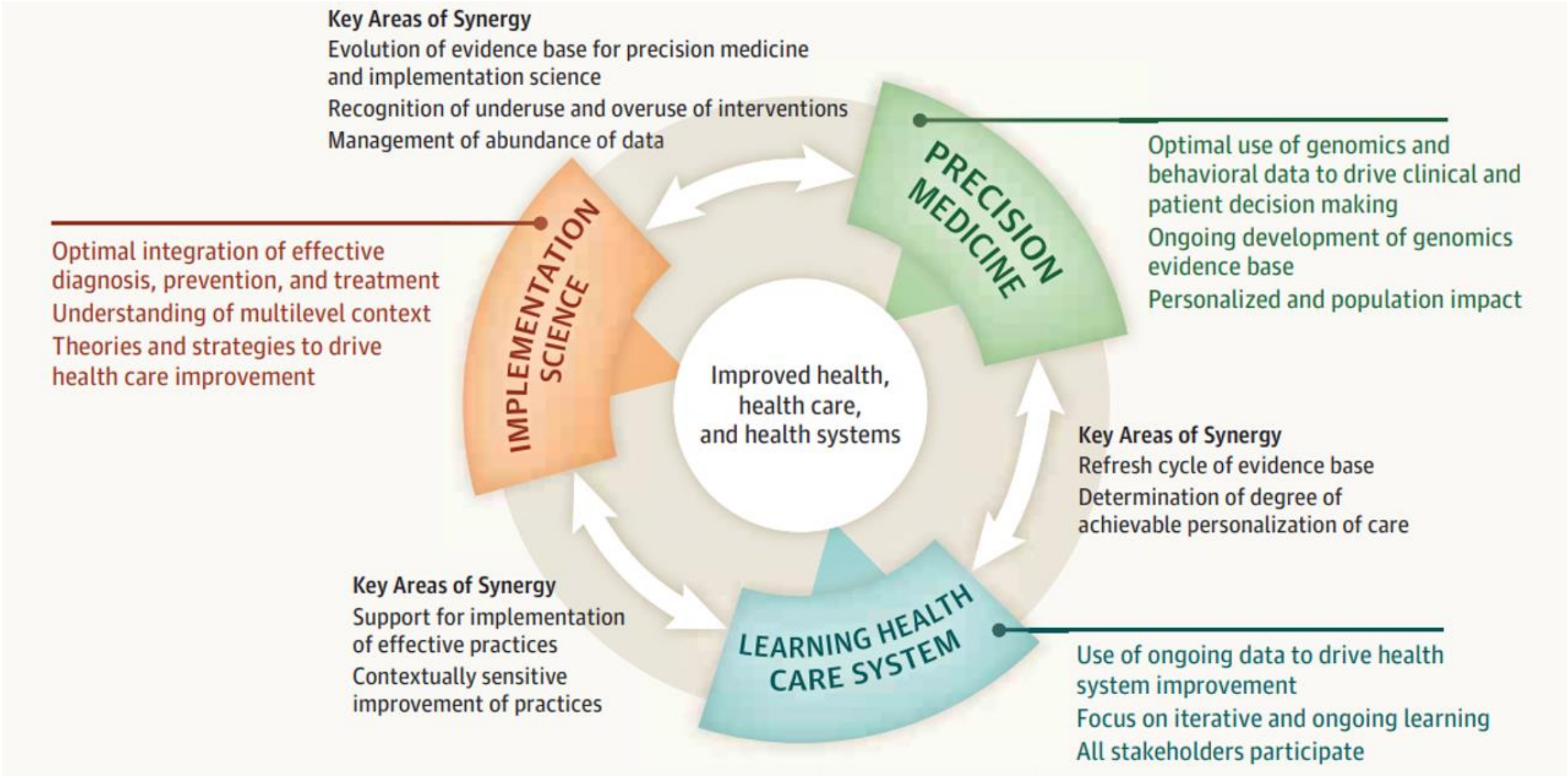


Park *et al.* Trials 2019

Schwab M
IKP Stuttgart

www.recoverytrial.net/news

Contributions of Implementation Science, Learning Health Care system, and Precision Medicine



Chambers DA *et al.* JAMA 2016

Robert Bosch Krankenhaus, Stuttgart

IKP Stuttgart

Bundesministerium für Bildung und Forschung

icepha interfaculty centre for pharma-cogenomics and drug research

IKP Dr. Margarete Fischer-Bosch Institut für Klinische Pharmakologie

RBK Robert-Bosch-Krankenhaus

Eberhard Karls Universität Tübingen

virtual liver network

HORIZON 2020

DFG Deutsche Forschungsgemeinschaft

Bosch Health Campus Behandlung. Forschung. Bildung.

Universitätsklinikum Tübingen

Robert Bosch Stiftung

IKP founded 1973 by Dr. Margarete-Fischer-Bosch

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