PHARMACOGENOMICS
From Research to Clinic

FARMAKOGENOMIKA
iz raziskav v klinično prakso

Workshop for high school and university lecturers
Delavnica za visokošolske učitelje

8. – 10. 6. 2015
Faculty of Medicine, University of Ljubljana
Medicinska fakulteta, Univerza v Ljubljani

Univerza *v Ljubljani*

REPUBLIKA SLOVENIJA
MINISTRSTVO ZA IZOBRAŽEVANJE, ZNANOST IN ŠPORT

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Laboratorij za farmakogenetiko, Inštitut za biokemijo

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Under the auspices of / V sodelovanju z:

Centre for Educational Development, Faculty of Medicine, University of Ljubljana Center za razvoj poučevanja, Medicinska fakultete, Univerza v Ljubljani

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Pharmacogenomics - From Research to Clinic
Farmakogenomika - iz raziskav v klinično prakso

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Delavnica za visokošolske učitelje

Proceedings / Zbornik

Edited by / Uredila
Vita Dolžan

Reviewed by /
Katja Goričar, Barbara Jenko

Design and Prepress /Oblikovanje in prelom
Maja Kolar za Iz principa

Published by/ Izdala
Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
Medicinska fakulteta, Univerza v Ljubljani, Ljubljana, Slovenija

Printed by /Tisk:
Pancopy, d.o.o.

Ljubljana, 2015

Operacijo delno financira Evropska unija iz Evropskega socialnega sklada ter Ministrstvo za izobraževanje, znanost in šport. Operacija se izvaja v okviru Operativnega programa razvoja človeških virov za obdobje 2007-2013, razvojne prioritete 3: Razvoj človeških virov in vseživljenjskega učenja; prednostne usmeritve 3.3: Kakovost, konkurenčnost in odzivnost visokega šolstva.

CIP - Kataložni zapis o publikaciji
Narodna in univerzitetna knjižnica, Ljubljana

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Ljubljana June 8-10 2015
Faculty of Medicine, University of Ljubljana
Medicinska fakulteta, Univerza v Ljubljani

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17.15 – 18.00	***Meet the speakers parallel session:*** Seminar 1: Sabina Passamonti / Samo Ribarič / Vita Dolžan Seminar 2: Nada Božina / Sabina Semiz Seminar 3: Erica Cecchini / Gabriele Stocco/ Magnus Ingelman – Sundberg

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Prof .Dolžan is a Full Professor of Biochemistry and Molecular Biology and the founder and Head of the Pharmacogenetics Laboratory at the Institute of Biochemistry, Faculty of Medicine at the Faculty of Medicine, University of Ljubljana.

She has vast research experience in the field of pharmacogenetics and implementation of novel molecular biology based methods into clinical use. She published over 70 SCI indexed papers that have over 2000 citations. She investigates the influence of genetic variability in drug metabolizing enzymes, transporters and drug targets on drug treatment response in cancer, anticoagulant, antidiabetic, antipsychotic, antidepressant, antirheumatic, and antiepileptic drug treatment. She is particularly interested in development of clinical-pharmacogenetic models that would facilitate the translation of personalized medicine into clinical practice. She also works on the promotion of pharmacogenomics knowledge and awareness among Slovenian medical professionals and general public. In 2013 she received Lapanje award from the Slovenian Biochemical Society as a professional recognition of outstanding contribution to the development of biochemical science in Slovenian and international arena and for the successful transfer of scientific research findings into clinical practice.

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Irina Milisav is a full Professor of Biochemistry and Molecular Biology working on cellular stress responses. She obtained a Ph.D. in Human Molecular Genetics from University of Cambridge, UK (Churchill College) and had a Honorary status Cambridge Overseas Trust Scholar. She worked at BBSRC, Babraham Institute, Babraham, UK and was a Post-Doctoral fellow at Ludwig-Maximilians University Munich working on protein import through the inner mitochondrial membrane. Back in Slovenia she worked on cell death triggering and currently on cell stress responses, aging induced stress & nutrition and the role of antioxidants and ROS in stress responses. She teaches undergraduate and graduate students at the Faculty of Health Sciences and the Faculty of Medicine at University of Ljubljana. She is a Slovenian representative on the European network of researchers on reactive oxygen species, COST BM1203 EU-ROS, and a section editor of the journal Archives of Medical Sciences. From 2012 she is an ECQA certified m-learning manager from 2012 and is listed in Marquis Who'sWho in the World since 2013.

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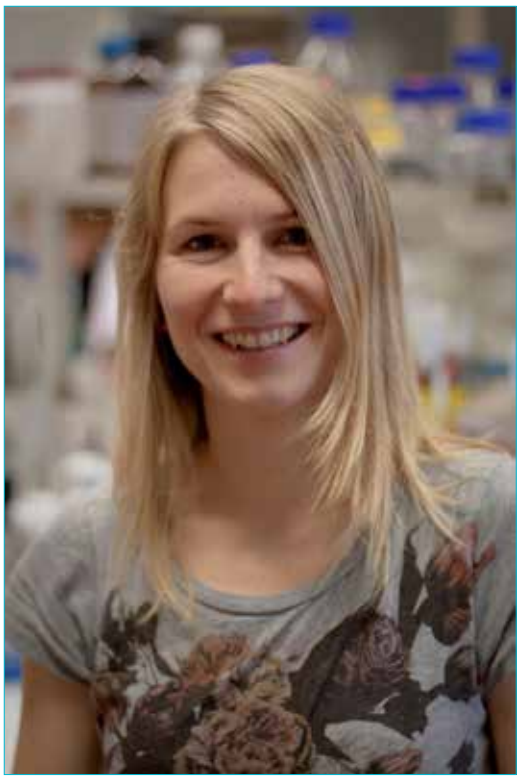

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Lenassi Metka, Ph.D. is an Assist. Prof. of Biochemistry and Molecular biology at the Faculty of Medicine, University of Ljubljana. She started working on extracellular vesicles called exosomes in 2007 as a postdoc in Prof. Dr. Matija B. Peterlin's laboratory at University of California San Francisco. She was the first one to show that HIV infected T cells release exosomes and not only HIV viruses, and that this exosomes have apoptotic effects on the bystander T cells. The importance of the discovery is supported by the fact that her paper: »HIV Nef is Secreted in Exosomes and Triggers Apoptosis in Bystander CD4+ T Cells« was the most cited paper published in Traffic in 2010 and 2011. Together with Prof. Peterlin they were granted a big project by the Slovenian Research Agency (ARRS) to study »HIV, exosomes and neurotoxicity«; starting in October 2013. The mentioned project was graded the best proposal among all (317) submitted research projects by international reviewers. She is currently supervising one research assistant, one PhD student and one postdoctoral student. She was in organising committees of several international conferences, like Halophiles 2004, ISHAM Workshop 2010 and Symposium of Molecular Medicine and Biotechnology in 2012. She is a member of the International Microvesicles and Exosome Society, Slovenian Biochemical Society and Slovenian Microbiology Society.

Selected publication (out of total of 14 publications)

LENASSI, Metka, CAGNEY, Gerard, LIAO, Maofu, VAUPOTIČ, Tomaž, BARTHOLOMEEUSEN, Koen, CHENG, Yifan, KROGAN, Nevan J., PLEMENITAŠ, Ana, PETERLIN, Boris Matija. HIV Nef is secreted in exosomes and triggers apoptosis in bystander CD4+ T cells. Traffic. Print ed., 2010, vol. 11: 110-122

Research support

Project J3-5499: Exosome-associated Nef released from HIV infected cells contributes importantly to the development of neuroAIDS (1.8.2013-31.7.2016); financed by the Slovenian Research Agency

Programmme P1-0170: Molecular mechanisms of regulation of cellular processes related to some human diseases (1.1.2004-31.12.2017); financed by the Slovenian Research Agency

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Professor of Molecular Toxicology since 1996 and research group leader in Pharmacogenetics at the Department of Physiology and Pharmacology, Karolinska Institutet since 2006.

Academic honors, awards and prizes

- More than 420 original papers, 22 000 citations (32 000 in Google Scholar) and an h-factor of 82 (ISI) or 94 (Google Scholar). Member of *The Nobel Assembly at Karolinska Institutet* since 2008 and member of *Faculty of 1000 Biology* since 2006. Member of Editorial Advisory Boards of e.g. *Trends in Pharmacological Sciences, Pharmacogenetics and Genomics, Pharmacogenomics, Drug Metabolism Reviews, Drug Metabolism and Disposition*. Chairman of the Microsomes and Drug Oxidation International Advisory Committee, mdo.ki.se.
- Ranked as the 3rd „highest impact" researcher of 4,000 in the field of drug metabolism (cytochrome.net) and one of the world's most cited authors within the category Pharmacology (http://isihighlycited.com/). Recently categorized by Thomson Reuters as one of the World's Most Influential Scientific Minds (http://sciencewatch.com/sites/sw/files/sw-article/media/worlds-most-influential-scientific-minds-2014.pdf) based on recent (2002-2012) citations.
- Main supervisor to a PhD degree for 29 postgraduate students, postdoctoral training for 25 PhDs. The research group ranked as outstanding in Karolinska Institutet's External Research Assessment (ERA) in 2010.
- Awards include The Svedberg Price, The Swedish Society for Biochemistry and Molecular Biology 1989; Honorary member of The American Society for Biochemistry and Molecular Biology 1990; The Gerhard B Zbinden Lecture Award, EUROTOX 1996; The ISSX European Scientific Achievement Award 2003; The Bengt Danielsson Prize, The Swedish Academy of Pharmaceutical Sciences 2008; The John G Warner Pfizer Lectureship in Pharmaceutical Sciences, University of Michigan, USA 2011.
- Interview with Magnus Ingelman-Sundberg. *Trends Pharmacol Sci.* 2015;36:65-7.

Some publications:

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Sabina Passamonti was born in Trieste on 17.03.1958. She is married with two children (born in 1991 and 1997). She got the Medical Doctor degree from the University of Trieste in 1984. She had research training at the de Duve Institute (formerly International Institute of Cellular and Molecular Pathology in Brussels in 1984-1986, where she studied molecular mechanisms of glycogen and purine metabolism. Back to Trieste, she got her PhD degree in biochemistry in 1991, with a study on the molecular mechanisms of bilirubin transport in the liver. She has continued studying the bilirubin transporter named bilitranslocase (T.C. 2.A.65.1.1), which is found both in animal and in plants. This protein has the property to also transport flavonoids and nucleotides in many epithelial cell lines and in the vascular endothelium. It is currently under study as a drug target and pathology biomarker. Further interest are about the bioavailability and bioactivity of dietary flavonoids.

Publications

Fate of Microbial Metabolites of Dietary Polyphenols in Rats: Is the Brain Their Target Destination? Mattia Gasperotti, Sabina Passamonti, Federica Tramer, Domenicao Masuero, Graziano Guella, Fulvio Mattivi, Urska Vrhovsek. ACS Chem Neurosci. 2015 May 5.

Bioavailability of Flavonoids: The Role of Cell Membrane Transporters. Lovro Ziberna, Stefano Fornasaro, Jovana Čvorović, Federica Tramer, Sabina Passamonti. In Polyphenols in Human Health and Disease (2014) Elsevier, Pages: 489-511.

Direct determination of free bilirubin in serum at sub-nanomolar levels. Mitja Martelanc, Lovro Žiberna, Sabina Passamonti, Mladen Franko. Anal Chim Acta. 2014 Jan 27;809:174-82.

Transport and bioactivity of cyanidin 3-glucoside into the vascular endothelium.

Lovro Ziberna, Federica Tramer, Spela Moze, Urska Vrhovsek, Fulvio Mattivi, Sabina Passamonti. Free Radic Biol Med. 2012 May 1;52(9):1750-9.

Experimental determination and prediction of bilitranslocase transport activity.

Špela Župerl, Stefano Fornasaro, Marjana Novič, Sabina Passamonti. Anal Chim Acta. 2011 Oct 31;705(1-2):322-33.

In the period 2011-2014, she has been the coordinator of the strategic project Trans2Care (www.trans2care.eu) funded by the Cross-border Cooperation Programme Italy-Slovenia 2007-2013.

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Before joining the Faculty of Pharmacy in Sarajevo in 2007, Prof.Dr Semiz completed her PhD thesis at the Faculty of Pharmaceutical Sciences, the University of British Columbia, in Vancouver, B.C., Canada, in 2001, and postdoctoral work at the Program in Molecular Medicine, University of Massachusetts Medical School, in Worcester, MA, USA, between 2001-2005. During this period, Dr. Semiz collaborated with Dr. Craig Mello, Nobel Prize laureate in 2006, in the area of siRNA-induced gene silencing, and Dr. Michael Czech, who have received an award from the American Diabetes Association for his research in the area of Type 2 diabetes. During a period between 2005-2007, she worked as a principal investigator in Cytrx Corporation, Worcester, MA, USA, where she lead the Target Biology group, and in Epic Therapeutics, Inc., a Wholly Owned Subsidiary of Baxter Healthcare Corporation, Norwood, MA, USA, where she worked in development of PROMAXX Microspheres for the in vivo gene therapy.

Prof.Dr. Semiz has led four national research projects within the last four years. Currently, she is leading a project in the area of pharmacogenomics of Type 2 diabetes and actively participates as a member of consortium in three international projects (COST Project of European Commission, MetGen, and PGENI Project). She has established a very constructive collaboration with colleagues from Slovenia, Sweden, Turkey, Holland, and Greece.

She is an Expert in the Evaluation panel for the Horizon 2020 Programme and COST Action in the area of Medical and Health Sciences, an international expert in the field of Medical sciences within the Ministry of education and sport Montenegro, and an expert within the Agency for Development of Higher Education and Quality Assurance in Bosnia and Herzegovina. From December 2014. Prof.Dr. Semiz has been appointed as the Head of the Unit of the UNESCO Chair in Bioethics for Bosnia and Herzegovina. She is an author of 60 scientific publications, published in peer-reviewed journals, as well as more than 100 scientific abstracts presented at the international and national conferences.

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PRESENT TEACHING ACTIVITIES. Since 2008 having courses: Training the trainers, TTT (60 courses until 2015), Teaching professionalism (for professors and students); with 2 colleagues leading courses How to improve teamwork for Ljubljana University EU project, DALACARTE workshops for specific departments with problems. Collaborator of Center for Education Development and Counsellor of Committee for Teachers Tutors of Medical Faculty of Ljubljana University.

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Assist. Prof. Gabriele Stocco, PhD

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Gabriele Stocco is Assistant Professor in Pharmacology at the University of Trieste since 2012.

Gabriele Stocco has a degree in Medicinal Chemistry with honors from the University of Trieste, a PhD in Pharmacology from the University of Trieste and a received doctoral and post-doctoral training from St.Jude Children's Hospital in Memphis, USA, where he attended in 2003 and from 2006 to 2011 the laboratory of prof. William Evans.

His research interest focuses on the translational studies on pharmacogenetics and therapy personalization of antimetabolites and biologics used in chronic and oncologic pediatric diseases, in particular inflammatory bowel disease, acute lymphoblastic leukemia and juvenile idiopathic arthritis.

The scientific effort is witnessed by 46 scientific publications, mostly in international journals and several communications at national and international meetings.

Prof. Stocco is reviewer and member of editorial board for a number of scientific journals, and member of Italian Society of Pharmacology, of the Italian Society of Toxicology and the American Society of Pharmacology and Clinical Therapeutics.

Since 2011, he is assistant member of the Pharmacogenomics laboratory at the Department of Life Sciences of the University of Trieste, coordinated by prof. Giuliana Decorti, performing the translational pharmacogenomic research studies in close collaboration with the Department of Pediatrics of the Institute for Maternal and Child Health IRCCS Burlo Garofolo of Trieste, headed by prof. Alessandro Ventura.

Dr. Erika Cecchin, PharmD, PhD

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Erika Cecchin is a researcher of the Clinical and Experimental Pharmacology Unit, of CRO- Aviano where she works on the pharmacogenetic research for the optimization of the chemotherapeutic treatment in cancer. She is author of several full-length publications in international peer reviewed journals and chapters in international books. In 2010 she has been awarded with the "Guido Berlucchi Foundation" prize for young researchers. She is a member of the scientific board of a recently constituted CRO spin-off (PharmaDIAGEN), with the mission to perform pharmacogenetic research and to integrate it in the clinical practice, by the production of commercial pharmacogenetic/ genomic diagnostic kits. Main focus of her researches is the identification of innovative approaches for tailoring anti-cancer treatments based on the genetic characteristics of the patients. The major objective of her studies is to deeply understand the role of genetic markers (polymorphisms) involved in the pharmacokinetics and pharmacodynamics of anti-cancer drugs and to translate such knowledge into the clinical setting, to improve the pharmacological intervention in cancer treatment.

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3. Toffoli G, Cecchin E, Gasparini G, D'Andrea M, Azzarello G, Basso U, Mini E, Pessa S, De Mattia E, Lo Re G, Buonadonna A, Nobili S, De Paoli P, and Innocenti F: „Genotype-driven phase I study of irinotecan administered in combination with fluorouracil/leucovorin in patients with metastatic colorectal cancer" J Clin Oncol 28:866-71, 2010.
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Lectures presentations / Predstavitve predavanj

Advanced Regional Translation of Excellence into Medical Innovations for Delayed Aging (ARTEMIDA)

H2020 Widespread 2014–1 Teaming

Samo Ribarič,
University of Ljubljana, Faculty of Medicine
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Center odličnosti za translacijsko medicino
SIC PARVIS MAGNA
Center of excellence for translational medicine

artemida.
Advanced Regional Translation of Excellence into Medical Innovation for Delayed Aging

METHODS

- We conducted a prospective study among 210 acute stroke patients who had an indication for anticoagulation and compared the impact of CYP2C9 and VKORC1 genotype-guided warfarin dosing (PhG) with fixed dosing (NPhG) on anticoagulation control and clinical outcome between groups.

artemida.

Mission statement of the planned CETM

Personalised treatment for aging-related neurodegenerative diseases, diabetes and cancer will be provided by developing regional capacities for identification of:

- ❑ disease subtypes
- ❑ predictive and prognostic biomarkers and
- ❑ novel molecular targets linked to oxidative stress.

artemida.

VISION

- ❑ To develop by 2020 a Central and South-East European (C&SE) Centre of Excellence for Translational Medicine (CETM), coordinated by the Faculty of Medicine, University of Ljubljana, that will harness, develop, exploit and market the significant potential for research and innovation of the region.
- ❑ This will be achieved by forming a hub for the ARTEMIDA network, with collaborators from about 100 biomedical and health-related research and innovation institutions from 25 European states and collaborators from the USA and Japan.

artemida.

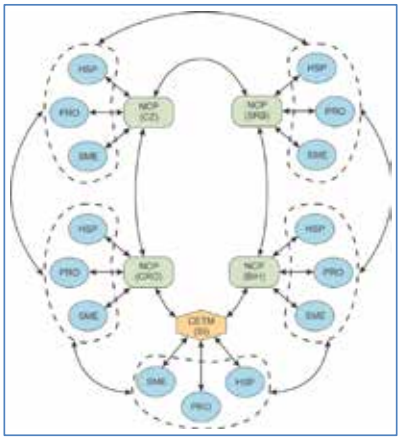
Albania	2.800.138
Bosnia and Hercegovina	3.791.622
Bulgaria	7.284.552
Croatia	4.290.612
Czech Republic	10.562.214
European part of Turkey	14.377.018
Greece	10.816.286
Hungary	9.937.628
Kosovo	1.733.872
Macedonia	2.059.794
Moldova	3.559.541
Montenegro	620.029
North-East Italy	11.447.805
Romania	20.121.641
Serbia	7.120.666
Slovak Republic	5.397.036
Slovenia	2.061.623
	117.982.077

HSP: Health Service Provider

PRO: Public Research Organization

SME: Small & Medium Enterprise

NCP: National Contact Point



ARTEMIDA Slovenian Consortium Members

University of Ljubljana:
- ✓ Faculty of Medicine
- ✓ Faculty of Pharmacy
- ✓ Biotechnical Faculty
- ✓ Faculty of Arts

Kemijski inštitut Ljubljana Slovenija | National Institute of Chemistry Slovenia

NATIONAL INSTITUTE OF BIOLOGY

SMEs: ACIES BIO, MG-soft, MESI, Pristop and Vizera.

Leading Scientific Institutions

Karolinska Institutet, Sweden

EMBL-EBI-Elexir-Hub, United Kingdom (UK)

Karolinska Institutet (KI)

- A Medical University in Solna, Sweden, one of the largest and most prestigious medical universities.
- Research at Karolinska Institute accounts for more than 40% of all academic medical research in Sweden.
- A committee of the Institute appoints the laureates for the Nobel prize in Physiology or Medicine.

Benefit for Karolinska Institutet from ARTEMIDA

Country / Alliance	Population
USA	318.857.056
UK	64.105.654
Canada	35.158.304
Australia	23.135.281
	441.256.295
Sweden	9.555.893
ARTEMIDA	+117.982.077

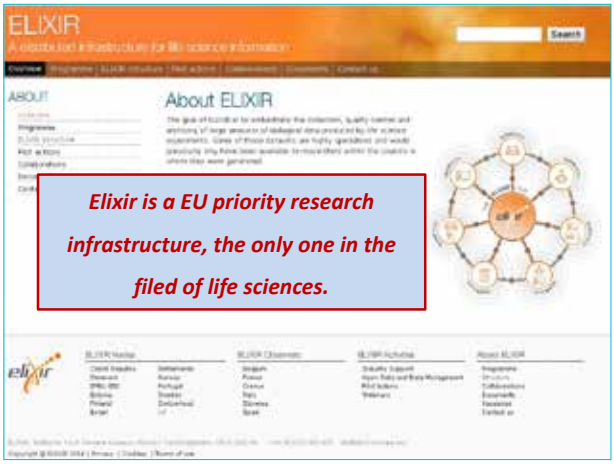
artemida.

The European Bioinformatics Institute

Part of the European Molecular Biology Laboratory

EMBL-EBI's mission

- To provide freely available data and bioinformatics services to all facets of the scientific community.
- To contribute to the advancement of biology through basic investigator-driven research.
- To provide advanced bioinformatics training to scientists at all levels.
- To help disseminate cutting-edge technologies to industry.
- To coordinate biological data provision throughout Europe (via EMBL-EBI-Elixir hub).



Benefits of the proposed CETM for Slovenia

The proposed CETM will overcome challenges of current local policies and practices, small size of national economy and limited national pool of potential subjects available for medical research by:

- providing an innovation friendly environment and culture with a strict quality management system (ISO 9001:2008), service-oriented administration, education and training system (ISO 10015:1999) and meticulous project quality management (ISO 21500:2012).
- upgrading, integrating and exploiting at the national level the research and innovation potential in the field of aging with special reference to neurodegenerative diseases, diabetes and cancer.

artemida.

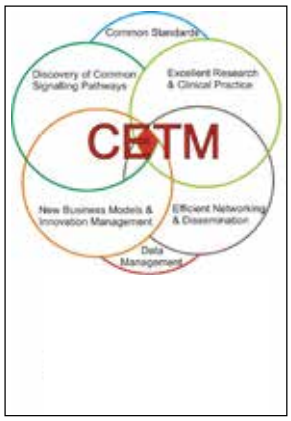
Benefits of the proposed CETM for C&SE Europe

- Addressing the challenge of an ageing European population and an increasing chronic disease burden of neurodegenerative disorders, diabetes and cancer that are jeopardising the sustainability and equity of European health and care systems.
- Facilitating preventive, personalized curative, promotional and rehabilitative health care services to promote active and healthy ageing in Slovenia, the C&SE European region and wider European area.
- Combining the expertise and support of KI and EMBL-EBI-Elixir with the research and innovation potential of the C&SE European region of 117.9 million people.

Benefits of the proposed CETM for Karolinska Institutet (KI) and EMBL-EBI-Elixir

Four streams of benefits will accrue to the Leading Scientific Institutions KI and EMBL-EBI from their association with the CETM:

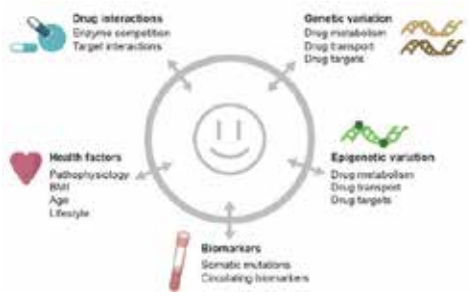
- a new source of potential collaborators, competent researchers from the C&SE European research area, will become available to the leading scientific institutions;
- an access to a C&SE European pool of patient data for clinical studies;
- a fresh flow of new research and innovation approaches from qualified scientists from the C&SE European research area to the leading scientific institutions;
- new partners for international (e.g Horizon 2020) research and innovation funding proposals.



Pharmacogenomics and pharmacoepigenomics; roles for efficient drug therapy

Magnus Ingelman-Sundberg, PhD, BSc.Med
Dept. Physiology and Pharmacology
Karolinska Institutet, Stockholm, Sweden

Personalized medicine



Manners for individualized therapy

- Selection of drugs and dose adjustements in relation to drug pharmacokinetics (CYPs, phase II enzymes and transporters)
- Selection of drugs and doses based on pharmacodynamic properties (cancer, HIV, CV)
- Selection of drugs based on ability to refold and make functional endogenous enzymes/transporters (Cystic fibrosis)

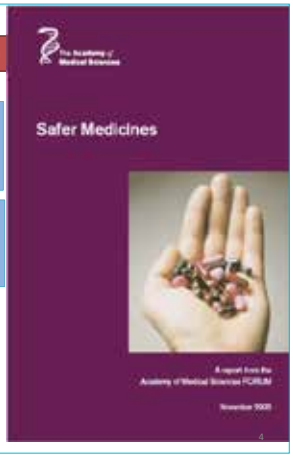
Adverse Drug Reactions (ADRs)

ADRs were between the 4th-6th commonest cause of death in the US in 1994
Lazarou et al, JAMA, 1998

About 3% of the 548 new drugs approved by the FDA between 1975-1999 withdrawn because of safety problems
Lasser et al, JAMA, 2002

20 % of readmissions to the hospital and 30 % of admissions of elderly are caused by ADRs
2 days prolonged hospital visit

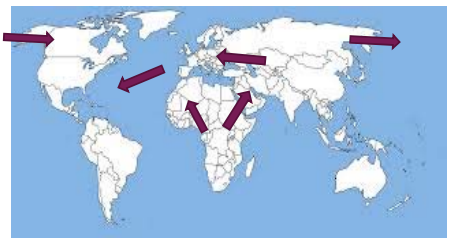
USD 2,500/patient, USD 100 billion in USA /year cf. Sim and Ingeman-Sundberg, 2011



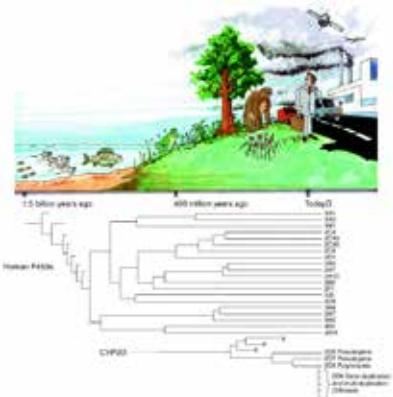
Genetic drift and genetic selection

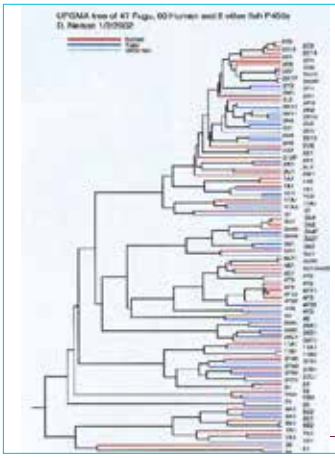
Selection based on environment, e.g.:

- Infections
- Climate
- Diet



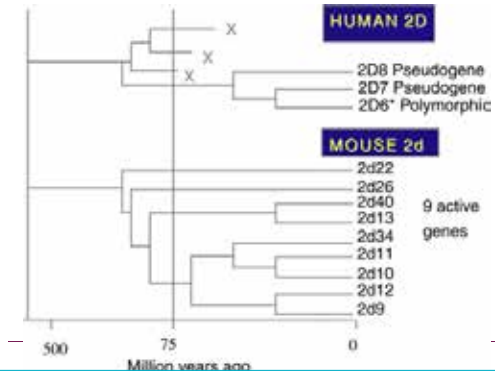
At the beginning.....



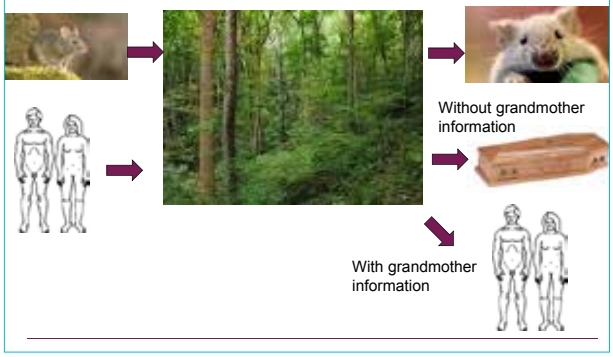


Number of active P450s	
Human	57
Mouse	102
Dog	54
Thale cress	249
Rice	323
Yeast	3

Evolution of CYP2D6 in mice and humans



Forest experiment



Insect selection based on P450 gene inducibility

Honey bees

CYP9Q1, CYP9Q2, and CYP9Q3 metabolize tau-fluvalinate and coumaphos which causes resistance

Honey constituent tau-fluvalinate induced CYP9Q3 expression, whereas the pyrethroid bifenthrin induces CYP9Q1 and CYP9Q2


CYP9Q-mediated detoxification of acaricides in the honey bee (*Apis mellifera*)

Shift of host by insects

Myzus persicae

Tobacco plant

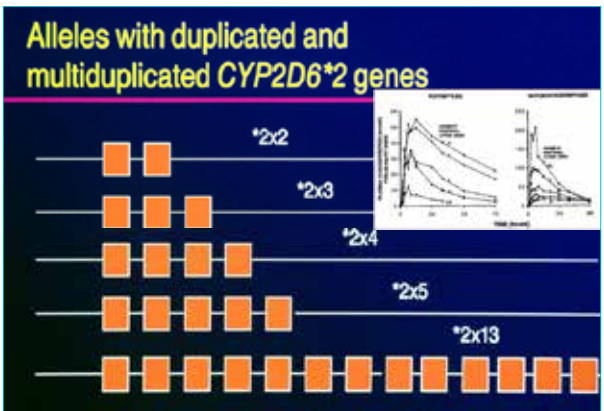
Microsatellite amplification of 100 fold in *CYP6CY3* of the polyphagous aphid adapted to feed on tobacco. The enzyme is active in metabolism of nicotine derivatives

Bass et al., *PNAS* 110, 19460, 2013

The human situation: starting in Ethiopia

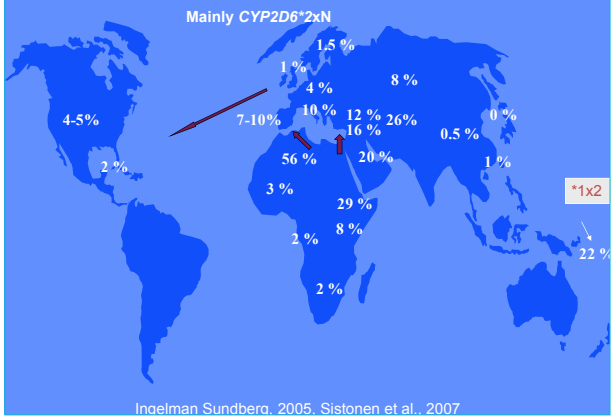
Subject for severe starvation periods killing millions of people in each event in the past

Alleles with duplicated and multiduplicated *CYP2D6*2* genes



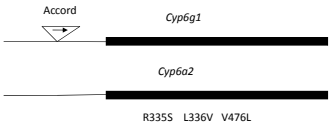
Johansson et al., *PNAS* **90**:1945-51, 1993, Aklillu et al., *JPET* **278**: 441-6, 1996

Global distribution of duplicated *CYP2D6* alleles



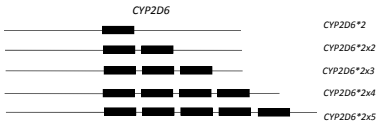
Ingelman Sundberg, 2005, Sistonen et al., 2007

Genetic adaptation to the environment among CYPs



Insecticide resistance in Drosophlila (1930-1960)

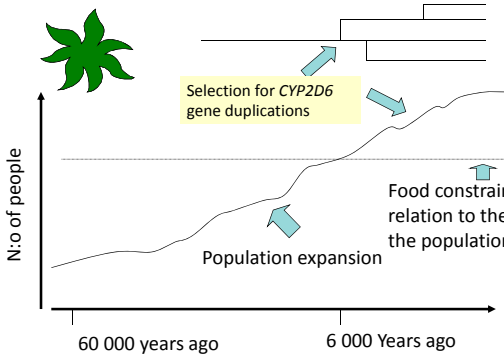
Daborn et al *Science* 2002; **297**:2253Amichot et al *Eur J Biochem*2004; **271**:1250



Alkaloid resistance in CYP2D6 (10000-5000 BC)

Ingelman-Sundberg, *The Pharmacogenomics J,* 2005

Dietary stress induced *CYP2D6* gene duplications in Ethiopia



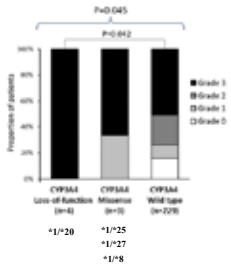
CYP3A4 polymorphism is very rare in general, but...

Geographical distribution of *CYP3A4*20* allele

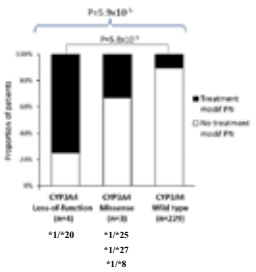
Apellániz-Ruiz M. *et al.*, The Pharmacogenomics J., 04 November 2014

Impact of CYP3A4 variants on neuropathy grade and paclitaxel treatment modification

Neuropathy grade in patients with different CYP3A4 activity

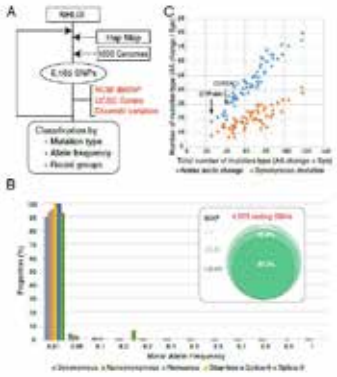


Treatment modification due to neuropathy among patients with different CYP3A4 activity



4 June 2015 19

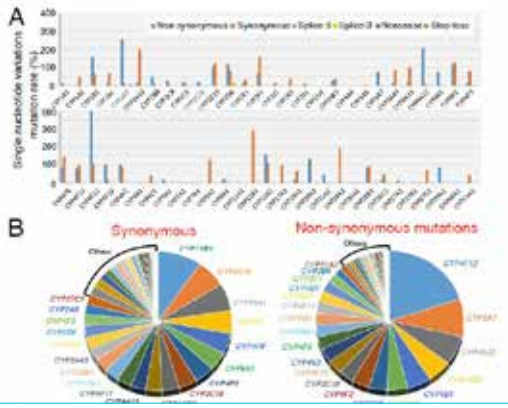
Whole Exome Sequencing (WES) Based analyses of CYP SNPs



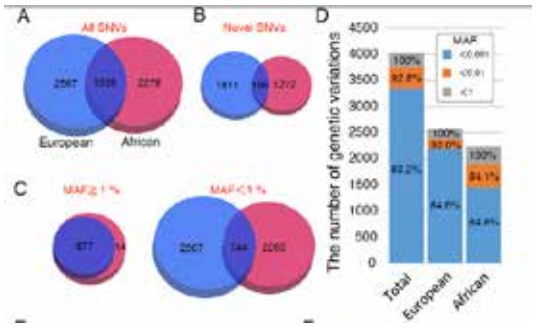
Thousands of rare CYP SNVs

Kohei, Ingelman-Sundberg & Lauschke 2015

CYP gene distribution

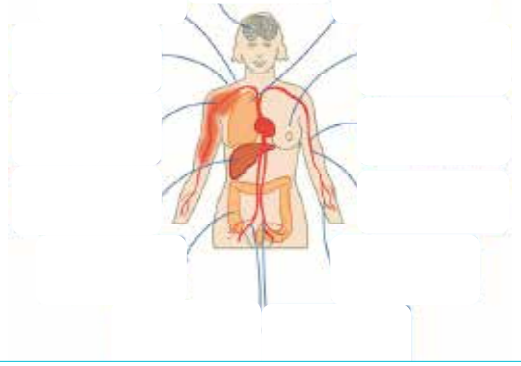


World distribution of CYP SNVs



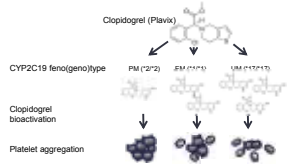
Kohei, Ingelman-Sundberg & Lauschke 2015

Pharmacogenomic biomarkers



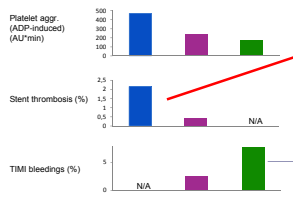
CYP2C19 genotype and clopidogrel treatment

Karolinska Institutet



Clopidogrel (Plavix) - antiplatelet

- Myocardial infarction
- Ischemic stroke
- Coronary stent placement
- Coronary syndromes



FDA - Black Box Warning:

Reduced effectiveness in patients carrying two defective CYP2C19 alleles (poor metabolizers)

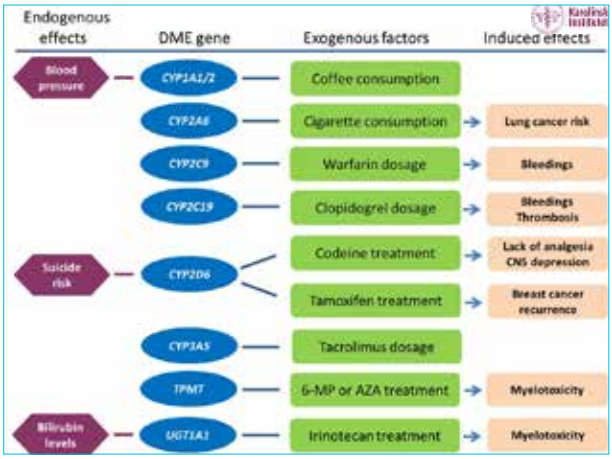
Meta analysis **17* carriers (coronary artery disease, CAD) N=9 428

Bleedings OR=1.25 (95%CI; 1.07-1.47)

MACE OR=0.82 (95%CI; 1.07-1.47)

Li et al 2011

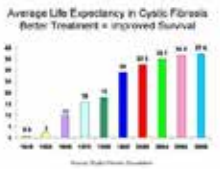
Based on Tiroch *et al.*, 2010, Sibbing *et al.*, 2010, Sibbing *et al.*, 2009



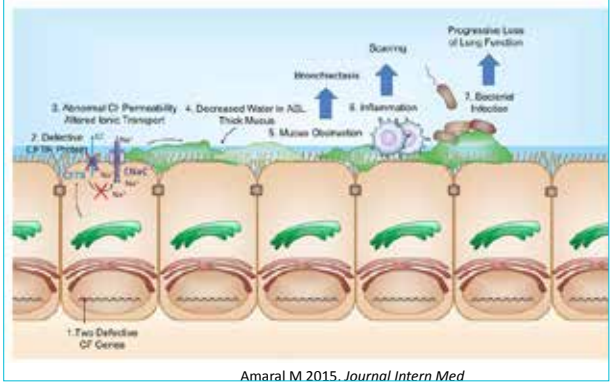
Other pharmacogenomic examples

Karolinska Institutet

- Cystic fibrosis and warfarin treatment



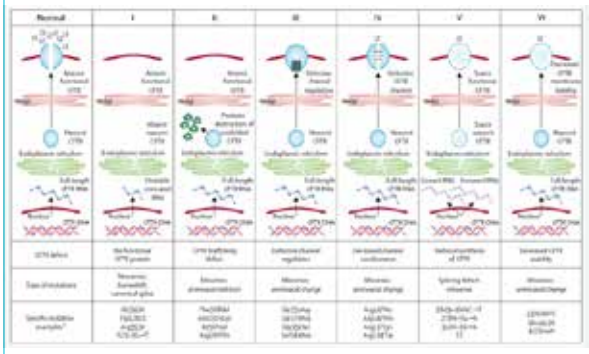
The CF pathogenesis cascade in the lung.



Amaral M 2015. *Journal Intern Med*

Classes of CFTR mutations

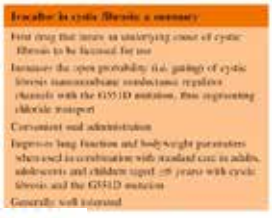
Karolinska Institutet

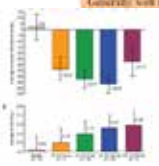


Boyle et al, *Lancet Resp Med* 2013; 1: 158–63

Treatment of cystic fibrosis with drugs affecting chloride channel

Karolinska Institutet





Increase of 10-11 % in FEV

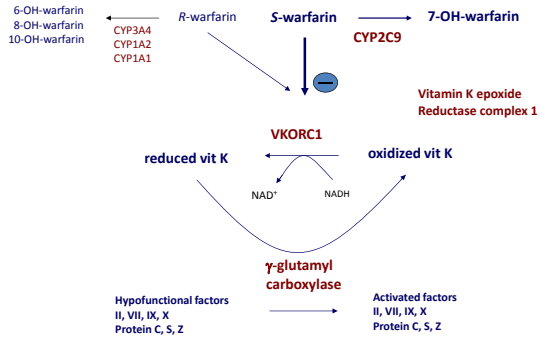
Kalydeco/Ivacaftor originally approved for the G551D mutation in ~4% of CF patients Kalydeco/Ivacaftotor was FDA-approved for another 8 gating (Class III) mutations, which together with G551D, account for ~5% of all CF patients.

Boyle et al, *Lancet Resp Med* 2013; 1: 158–63; Deeks, *Drugs* (2013) 73:1595–1604

Further *CFTR* variants and potential treatment strategy

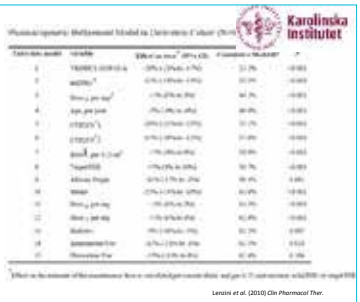
Class	Description	Assoc. CF phenotype	Example variants [b]	Potential treatment strategy
I	Cause splicing defects, frameshift mutations or a premature stop codon resulting in a lack of CFTR expression and impaired biosynthesis.	Severe.	W1282X (c.3846G>A, rs77010898), G542X (c.1624G>T, rs113993959), R553X (c.1657C>T, rs74597325).	A suppressor which prevents premature termination by reading through premature termination codons. This allows for complete translation.
II	Result in an immature protein that is consequently mostly degraded.	Severe.	F508del (c.1521_1523delCTT, rs199826652 or rs113993960;	A corrector, which restores folding and increases trafficking to the membrane and/ or a potentiator which increases CFTR open probability/gating.
III	Result in proteins which are present at the plasma membrane but have disrupted activation or regulation, resulting in defective CFTR channel gating.	Severe.	G551D (c.1652G>A, rs75527207:	A potentiator, which increases CFTR open probability/gating.
IV	Result in CFTR present at the plasma membrane but with reduced conductance of chloride.	Mild.	R347P (c.1040G>C, rs77932196), R334W (c.1000C>T, rs121909011).	A potentiator which increases gating may be able to overcome reduced channel conductance.
V	Result in partly defective processing or synthesis of CFTR.	Mild.	3272-26 A>G (c.3140-26A>G), 3849 +10kb C>T (c.3717+12191C>T, rs75039782).	A potentiator, which increases gating may be able to overcome reduced CFTR availability.
VI	Result in CFTR present at the plasma membrane but with reduced conductance of ions (not including chloride) or reduced membrane stability.	Severe.	1811 + 1.6kb A>G (c.1679+1.6kbA>G), corrected F508del.	Drugs that stabilize CFTR at the plasma membrane.

Warfarin – pharmacokinetics and pharmacodynamics



Warfarin – *ADR + response*

- Anticoagulant (thrombosis, embolism)
- Inhibition of vitamin K-dependent synthesis of active clotting factors
- Narrow therapeutic window: bleedings vs thrombosis
- Vitamin K epoxide reductase complex subunit 1 (VKORC1), CYP2C9

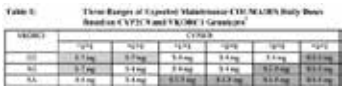


Lenzini et al. (2010) *Clin Pharmacol Ther.*

Regulatory: No genetic test required, but consider dose adjustment if genotype is known (FDA, EMA)

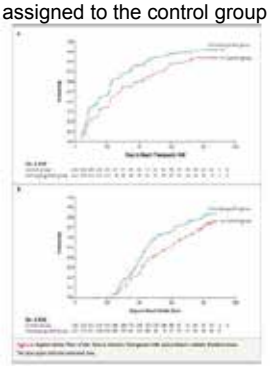
<1/2 dose in 5%
Red dose in 35%

Warfarin drug label (FDA) Standard dose 5-7 mg



Warfarin treatment in genotyped patients

227 randomly assigned to the genotype-guided group and 228 assigned to the control group



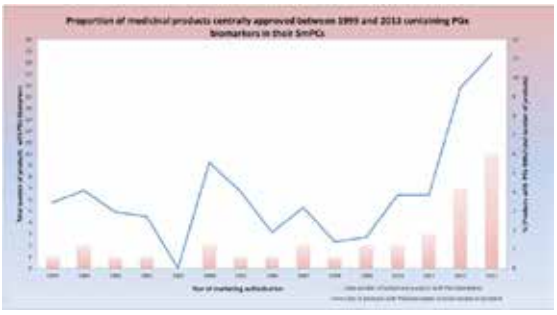
Pirmohamed et al., *N Engl J Med* 369;24, dec 2013

FDA list (part) for cancer pharmacogenomic biomarker

Drug	Appr year	Gene	Type of marker	Type of testing	Referenced Subgroup
Ado-Trastuzumab Emtansine	2013	ERBB2	Efficacy	Required	HER2 protein overexpression or gene amplification positive
Afatinib	2013	EGFR	Efficacy	Required	EGFR exon 19 deletion or exon 21 substitution (L858R) mutation positive
Anastrozole	1995	ESR1, PGR	Efficacy	Informative	Hormone receptor positive
Arsenic Trioxide	2000	PML/RARA	Efficacy	Required	PML/RARα (t(15;17)) gene expression positive
Bosutinib	2012	BCR/ABL1	Efficacy	Required	Philadelphia chromosome (t(9;22)) positive
Brentuximab Vedotin	2011	TNFRSF8	Efficacy	Informative	CD30 positive
Busulfan	1954	BCR/ABL1	Efficacy	Actionable	Ph Chromosome negative
Cetuximab (1)	2004	EGFR	Efficacy	Required	EGFR protein expression positive
Cetuximab (2)	2004	KRAS	Efficacy	Required	KRAS codon 12 and 13 mutation negative
Crizotinib	2011	ALK	Efficacy	Required	ALK gene rearrangement positive
Dabrafenib (1)	2013	BRAF	Efficacy	Required	BRAF V600E mutation positive
Dasatinib	2006	BCR/ABL1	Efficacy	Required	Philadelphia chromosome (t(9;22)) positive; T315I mutation-positive
Denileukin Diftitox	1999	IL2RA	Efficacy	Required	CD25 antigen positive
Erlotinib (1)	2004	EGFR	Efficacy	Required	EGFR protein expression positive
Erlotinib (2)	2004	EGFR	Efficacy	Required	EGFR exon 19 deletion or exon 21 substitution (L858R) positive
Everolimus (1)	2009	ERBB2	Efficacy	Actionable	HER2 protein overexpression negative
Everolimus (2)	2009	ESR1	Efficacy	Actionable	Estrogen receptor positive
Exemestane	1999	ESR1	Efficacy	Informative	Estrogen receptor positive
Fulvestrant	2002	ESR1	Efficacy	Required	Estrogen receptor positive

EMA pharmacogenomic labels in SmPCs

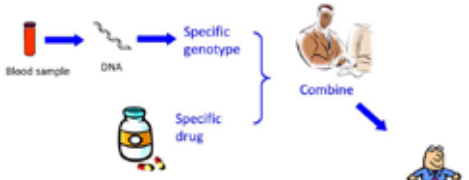
In total 155 pharmacogenomic drug labels



Ehmann et al., *Pharmacogenomics J.* 2015 Feb 24..

Pharmacogenomic labels

- Drugs whose actions are dependent on genetic variability are labeled with recommendations regarding altered prescriptions in genetically different parts of the populations



FDA-list of 106 different pharmacogenomic drug labels in total

Effective drug treatment

Department of Life Sciences, University of Trieste, ITALY

Reactive Oxygen Species: biochemistry and their role in health and disease

Sabina Passamonti, MD, PhD

University of Ljubljana, Faculty of Medicine Pharmacogenomics Workshop **8-10 June 2015**

Overeview

1. Principles of
   – oxygen chemistry and reactivity
   – oxidation of biological molecules
2. The main sites of ROS generation
3. The main endogenous defense systems agains ROS and ROS-mediated changes
4. ROS in cell signalling and regulation

Objective

- Enabling to critically reading the literature and critically understanding experimental results
- To feel at ease in a maze of information

WARNING

THIS REVIEW IS NOT COMPREHENSIVE

Free radicals are active participants in diverse processes and they cannot be considered anymore as only damaging agents, but real players in many normal functions of living organisms.

V.I. Lushchak / Chemico-Biological Interactions 224 (2014) 164–175

ROS as bioactive compounds

- 1954 – Discovery of free radicals in biological materials
- 1969 – Discovery of Superoxide Dismutase
- 1973 – Discovery of bactericidal activity of superoxide
- 1987 – Discovery of nitric oxide as vosorelaxant
- 1995 – Discovery of regulation of hydrogen peroxide by insulin

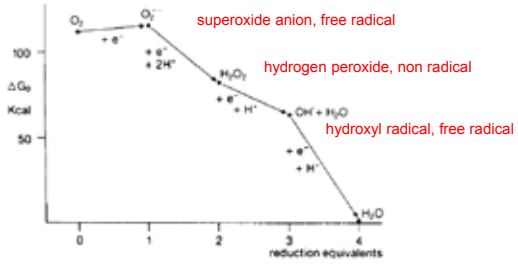
Types of ROS

Reactivity

Interconversion

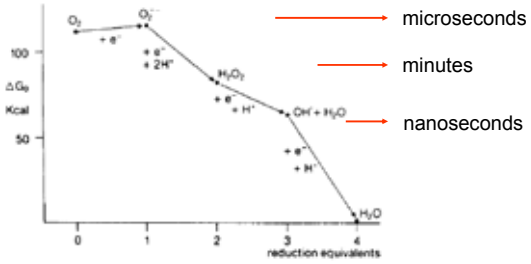
Types of ROS and their free energy

ROS formation is exergonic:
O_2 → ROS



Types of ROS and their half-life

reactivity directly depends of their half-life



ROS in disease

Diabetes mellitus
Neurodegenerative disorders
(*Parkinson's disease, Alzheimer's disease and Multiple sclerosis*),
Cardiovascular diseases
(*atherosclerosis and hypertension*)
Respiratory diseases
(*asthma*)
Cataract development
Rheumatoid arthritis
Various cancers
(*colorectal, prostate, breast, lung, bladder cancers*).

ROS in disease

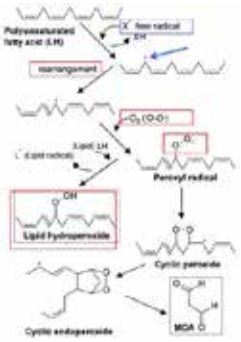
Biochemical mechanisms

ROS attack on biological molecules

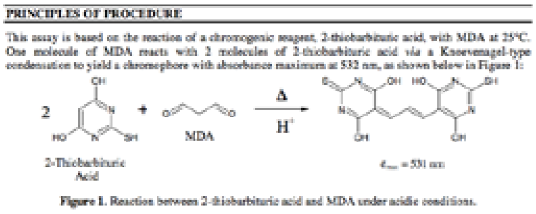
Lipids
Proteins
Nucleic acids

Let's see a few examples

Lipid peroxidation & malodialdehyde formation



Malon dialdehyde assay


PRINCIPLES OF PROCEDURE

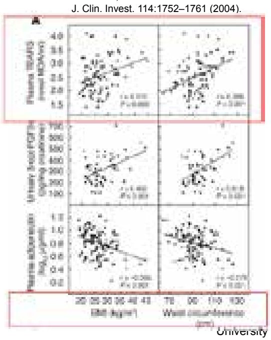
This assay is based on the reaction of a chromogenic reagent, 2-thiobarbituric acid, with MDA at 25°C. One molecule of MDA reacts with 2 molecules of 2-thiobarbituric acid via a Knoevenagel-type condensation to yield a chromophore with absorbance maximum at 532 nm, as shown below in Figure 1:

Figure 1. Reaction between 2-thiobarbituric acid and MDA under acidic conditions.

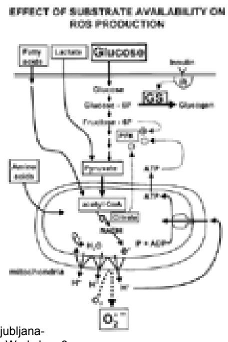
Thiobarbituric acid reacts with malondialdehyde and other lipid peroxides
TBARS *thiobarbituric acid reactive substances*

MALON DIALDHEYDE ASSAY IN CLINICS
Obesity increases ROS

Furukawa, S. et al. J. Clin. Invest. 114:1752–1761 (2004).



Dröge, W. Physiol Rev 82: 47–95, 2002



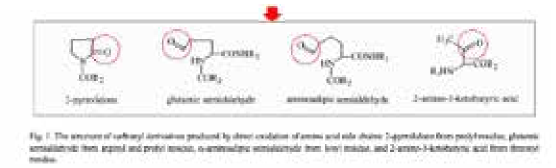
Aminoacids as victims of HO•

General types of protein oxidative modification

- Sulfur oxidation (Cys disulfides, S-thiolation; Met sulfoxide)
- Protein carbonyls (side chain aldehydes, ketones)
- Tyrosine crosslinks, chlorination, nitrosation, hydroxylation
- Tryptophanyl modifications
- Hydro(pero)xy derivatives of aliphatic amino acids
- Chloramines, deamination
- Amino acid interconversions (*e.g.*, His to Asn; Pro to OH-Pro)
- Lipid peroxidation adducts (MDA, HNE, acrolein)
- Amino acid oxidation adducts (*e.g.*, *p*-hydroxyphenylacetaldehyde)
- Glycoxidation adducts (*e.g.*, carboxymethyllysine)
- Cross-links, aggregation, peptide bond cleavage

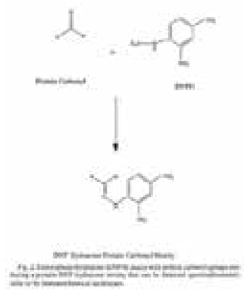
ROS-mediated protein carbonylation

PROLINE | ARGININE, PROLINE | LYSINE | THREONINE



Protein carbonyls can be assayed in biological fluids

Castagna A. et al. Protein Carbonyl Levels— An Assessment of Protein Oxidation
From: Methods in Pharmacology and Toxicology: Methods in Biological Oxidative Stress
Edited by: K. Hensley and R. A. Floyd
© Humana Press Inc., Totowa, NJ
2003



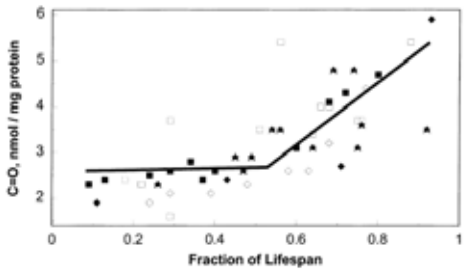
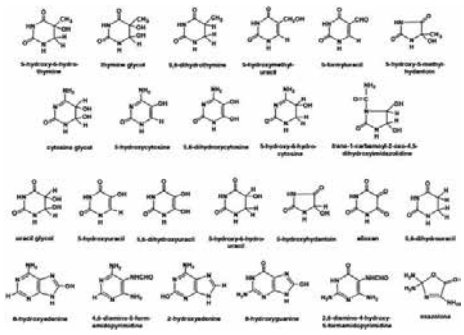


Fig. 1. Carbonyl content of protein from different tissues. One observes a dramatic increase in oxidized protein during the last third of the lifespan. The line is the semi-logarithmic fit to all the data points. The data points were taken from published reports: ■, human dermal fibroblasts in tissue culture (Oliver et al., 1987); ★, human lens (Garland, 1990); □, human brain obtained at autopsy (Smith et al., 1991); ◆, rat liver (Starke-Reed and Oliver, 1989); and ◇, whole fly (Sohal et al., 1993).

D. Harman

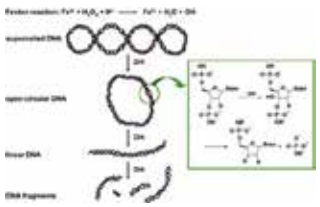
Figure 1. DNA base products of interaction with reactive oxygen and free radical species.



COOKE M S et al. FASEB J 2003;17:1195-1214

The FASEB Journal

Hydroxylation of ribose



ROS ($O_2^{\bullet-}$) generation

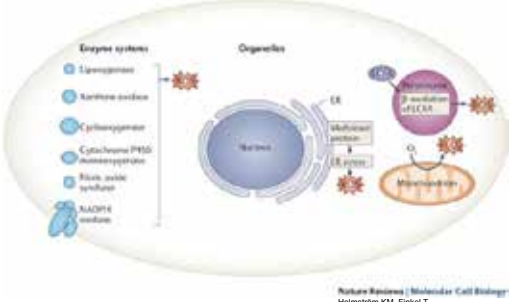
Where in the cell?

At proteins having **redox-active prosthetic groups**

- Heme,
- $FMNH_2$
- $CoQH_2$

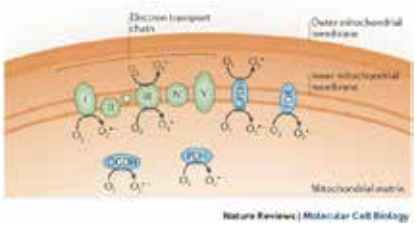
1. ***Mitochondrium*** → *electron transport chain*
2. ***Endoplasmic reticulum*** → *cytochrome P450*
3. ***Plasma membrane*** → *NADPH oxidase*
4. ***Cytosol*** → *nitric oxide synthase, xantine oxidase, etc.*

Intracellular sources of reactive oxygen species



Holmström KM, Finkel T.
Nat Rev Mol Cell Biol. 2014 Jun;15(6):411-21

Superoxide anion $O_2^{\bullet-}$ in mitochondria

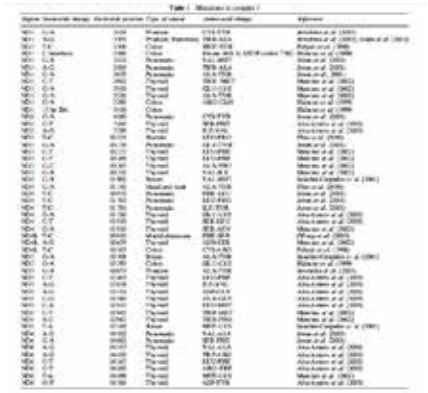


1. Complex I
2. Complex III
3. 2-oxo-glutarate DH
4. Pyruvate DH
5. Glyceraldehyde 3-P DH
6. Electron transfer flavoprotein-ubiquinone oxidoreductase

$O_2^{\bullet-}$ generation at Complex I When?

It happens when **the rate of oxygen consumption is low**, due to **low availability of ADP** (ATP hydrolysis is slow)
„principle of respiratory control"

Scheme from: M. Murphy, Biochem. J. (2009) 417, 1–13



ROS can damage mtDNA coding for Complex I

as found in various cancers

Other mtDNA can be mutated and mitochondrial dysfunction further increases ROS

Shift

From aerobic to anaerobic metabolism

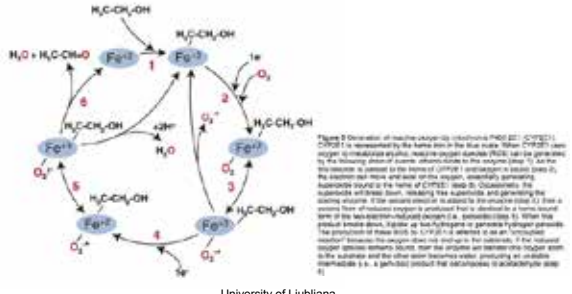
Pasteur effect

Cancer cells consume a huge amount of glucose in spite of normal availability of oxygen

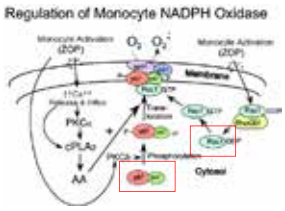
Superoxide anion $O_2^{\bullet-}$ on endoplasmic reticulum

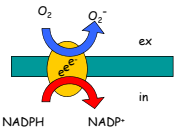
Cytochrome P450

Alcohol Metabolism's Damaging Effects on the Cell
A Focus on Reactive Oxygen Generation by the Enzyme Cytochrome P450 2E1
Dennis R. Koop, Ph.D.
http://pubs.niaaa.nih.gov/publications/arh294/274-280.htm



Superoxide anion $O_2^{\bullet-}$ on the plasma membrane



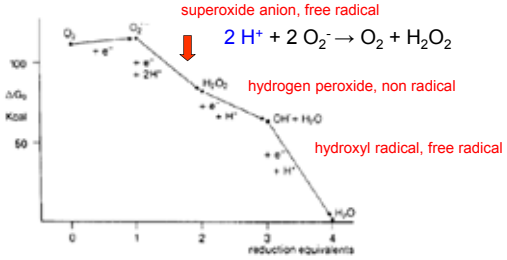


Components of the monocyte/macrophage NADPH oxidase are shown in color-filled circles. The regulatory pathways, controlling NADPH oxidase assembly and activation, are also indicated. Upon monocyte activation by a physiological stimulus, for example opsonized zymosan (ZOP), a serum-coated yeast cell wall, the cytosolic components move to join the membrane components gp91phox and p21phox. The assembly and activation of the NADPH oxidase enzyme complex is regulated by calcium influx, calcium release from intracellular stores, PKC-dependent phosphorylation of cPLA$_2$, and arachidonic acid (AA) production. AA regulates the translocation of p47phox and p67phox to the membrane. These latter 2 components will not translocate unless first phosphorylated. Recent studies indicate that these phosphorylation events are regulated by PKC. Rac1 is the predominant Rac isoform expressed in monocytes, in contrast to Rac2 in neutrophils. Rac1 dissociates from its inhibitor rhoGDI upon monocyte activation and also translocates to the membrane, where it participates in the fully assembled and active NADPH oxidase.

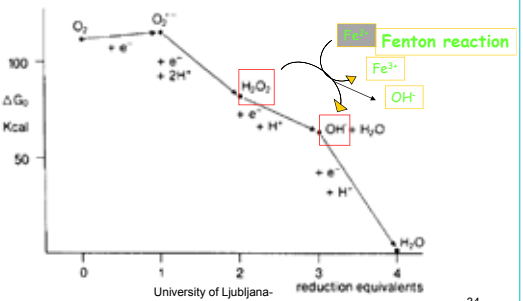
Enzyme-catalysed conversion of ROS to water and oxygen

Enzyme-catalysed **defenses** against ROS

The reaction of superoxide dismutase (EC-Number 1.15.1.1)

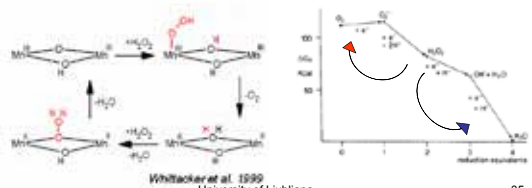


Hydrogen peroxide *Why it's better to get rid of*



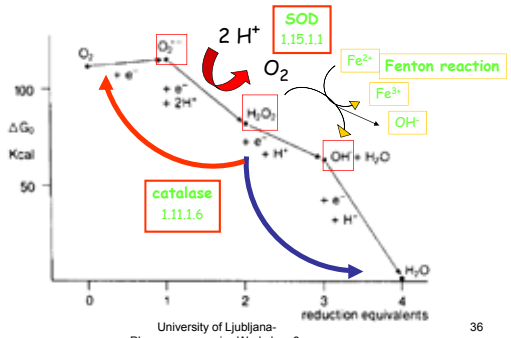
The reaction of catalase (EC-Number 1.11.1.6)

$$2H_2O_2 \xrightarrow{\text{catalase}} O_2 + 2H_2O$$

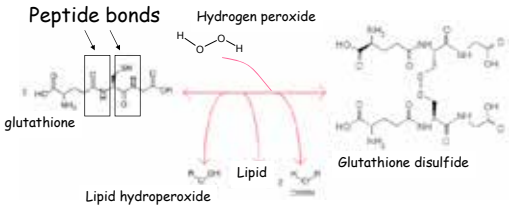


Whittaker et al. 1999

Competition between the catalase and the Fenton reactions

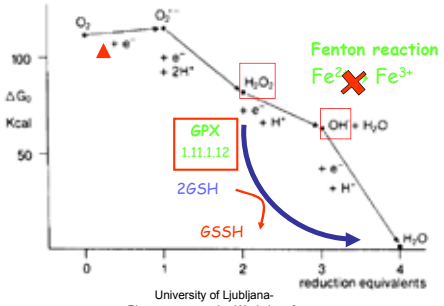


The reaction of glutathione peroxidase (EC-Number 1.11.1.12)

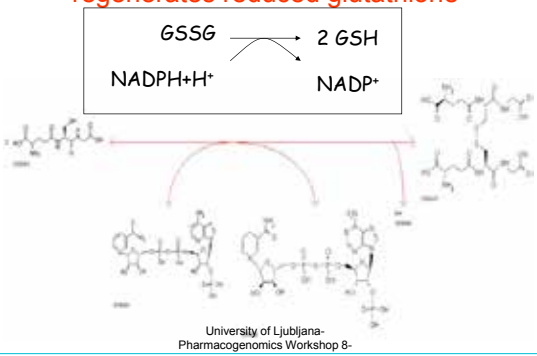


Glutathione is a tripeptide:
γ-glutamylcysteinyl glycine

Competition between the glutathione peroxidase and the Fenton reactions



The reaction of glutathione reductase (EC-Number 1.8.1.7) regenerates reduced glutathione



Endogenous defenses against ROS: non-enzymatic anti-oxidants

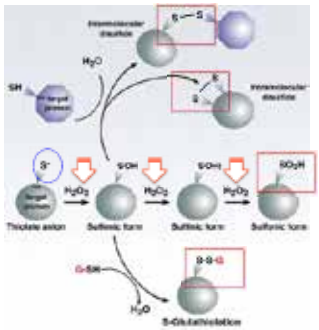
lipoic acid, bilirubin, uric acid, ascorbic acid, flavonoids, carotenoids, … *not discussed here*

…

ROS in PHYSIOLOGY

Biochemical mechanisms

Cysteine biochemistry allows for redox-dependent signaling.



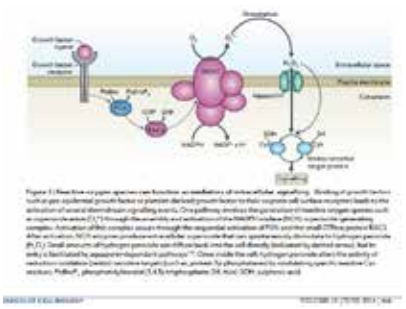
Finkel T J Cell Biol 2011;194:7-15

JCB

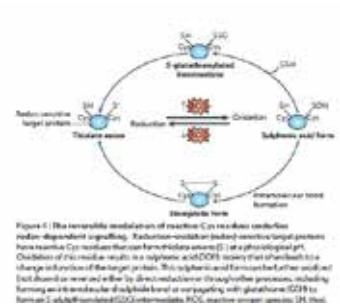
Redox-dependent signalling

CYS chemistry

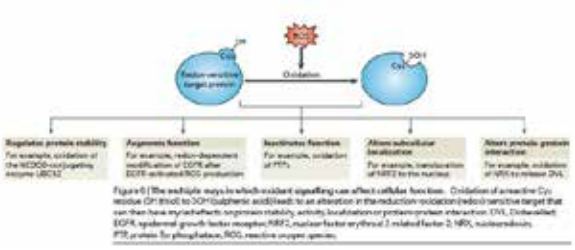
Cellular mechanisms and physiological consequences of redox-dependent signalling. Holmström KM, Finkel T. Nat Rev Mol Cell Biol. 2014 Jun;15(6):411-21.



Reversible cys oxidation



Protein modification can cause either gain or loss of **protein function** and either gain or loss of **cell function**



Physiological protein carbonylation

ANTIOXIDANTS & REDOX SIGNALING
Volume 12, Number 3, 2010
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DOI: 10.1089/ars.2009.2805

FORUM REVIEW ARTICLES

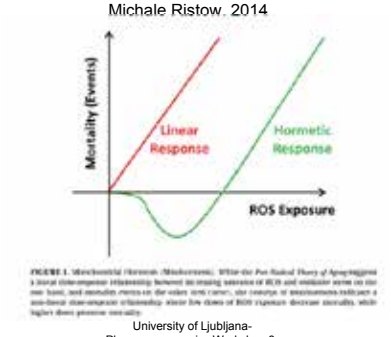
Cell Signaling by Protein Carbonylation and Decarbonylation

Chi Ming Wong,[1] Lucia Marcocci,[2] Lingling Liu,[1] and Yuichiro J. Suzuki[1]

MITOHORMESIS

PROMOTING HEALTH AND LIFESPAN BY INCREASED LEVELS OF REACTIVE OXYGEN SPECIES

Michale Ristow. 2014



It's a very long story …

For today it's enough !

THANK YOU

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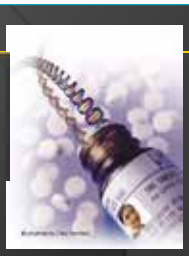
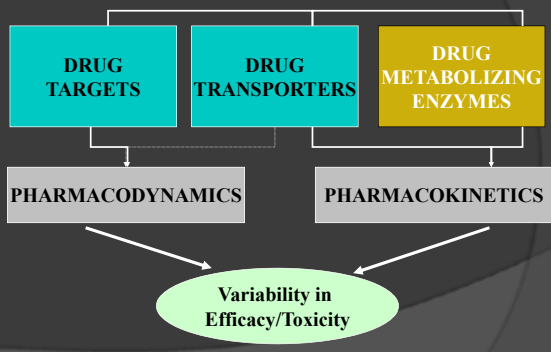
CARDIOVASCULAR PHARMACOGENOMICS



Prof.Dr Sabina Semiz, PhD
Faculty of Engineering and Natural Sciences
International University of Sarajevo

June 8-10, 2015.

Pharmacogenomics



Johnson JA. Trends in Genetics 2003: 660-666

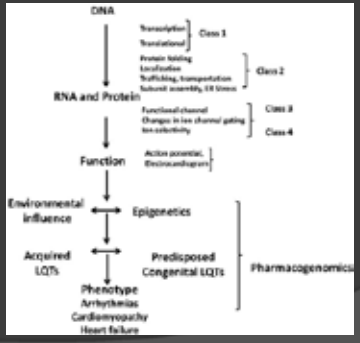
Cardiovascular pharmacogenomics

- Cardiovascular drugs are among the most commonly used in therapy globally.
- Although clinical trials unequivocally demonstrate population benefits with many of these agents, individual patients display striking variability in response;
- Variability in efficacy and serious adverse effects continue to seriously affect therapy.

Cardiovascular pharmacogenomics

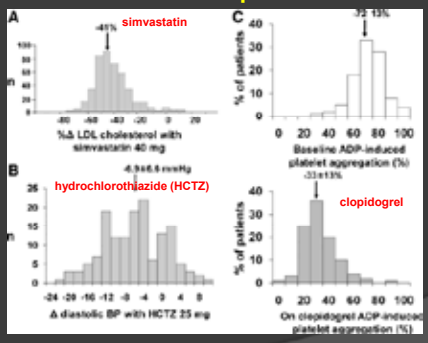
- Patients vary in their responses to drug therapy, and some of that variability is genetically determined.
- Examples from specific therapeutic areas include:
  - Antiplatelet agents (Clopidogrel)
  - Anticoagulans (Warfarin)
  - Cholesterol management (Statins)
  - Hypertension
  - Arrhythmias
  - Heart failure

The pathway depicts the steps leading to pharmacogenomic phenotype for long QT syndromes



Recent Pat Biotechnol. 2014 ; 8(2): 123–135.

Variability in response to common cardiovascular therapies



Dan M. Roden et al. Circulation Research. 2011;109:807-820.

REVIEWS

Genotype-based clinical trials in cardiovascular disease

Naveen L. Pereira, Daniel J. Sargent, Michael E. Farkouh and Dharanjit S. Rihal

Abstract | Consensus practice guidelines and the implementation of clinical therapeutic advances are usually based on the results of large, randomized clinical trials (RCTs). However, RCTs generally inform us on an average treatment effect for a presumably homogeneous population, but therapeutic interventions rarely benefit the entire population targeted. Indeed, multiple RCTs have demonstrated that interindividual variability exists both in drug response and in the development of adverse effects. The field of pharmacogenomics promises to deliver the right drug to the right patient. Substantial progress has been made in this field, with advances in technology, statistical and computational methods, and the use of cell and animal model systems. However, clinical implementation of pharmacogenetic principles has been difficult because RCTs demonstrating benefit are lacking. For patients, the potential benefits of performing such trials include the individualization of therapy to maximize efficacy and minimize adverse effects. These trials would also enable investigators to reduce sample size and hence contain costs for trial sponsors. Multiple ethical, legal, and practical issues need to be considered for the conduct of genotype-based RCTs. Whether pre-emptive genotyping embedded in electronic health records will preclude the need for performing genotype-based RCTs remains to be seen.

Pereira, N. L. et al. Nat. Rev. Cardiol. advance online publication 8 May 2012; doi:10.1038/nrcardio.2012.64

Pharmacogenomics of Clopidogrel

- An antiplatelet drug used in patients with cardiovascular disease to reduce risk for heart attack, stroke, unstable angina, and cardiovascular death.
- The liver's cytochrome P450 (CYP) system converts it to its active metabolite. Several genotypes of the liver enzyme exist in humans: CYP2C19* 2,*3, *4, *5, *6, *7, and *8.
- There are subgroups of patients (2-14% of the population) who are *poor* metabolizers of clopidogrel because of genetic differences (genetic polymorphisms) in this enzyme.
- Racial background is also a factor.
- As a result, these patients do not get the drug's full benefit and have a higher risk for cardiac, cerebrovascular, and peripheral arterial events.

David Holmes, et al, *ACCF/AHA Clinical Alert , 2010*

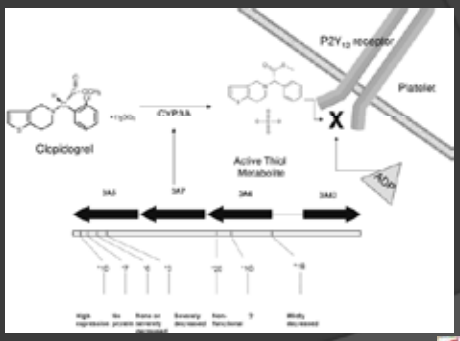
Pharmacogenetics of Clopidogrel

CYP2C19 polymorphisms exist in 3 major forms.

- CYP2C19*1 – normal function
- Loss-of-function alleles are CYP2C19*2 and CYP2C1*3, accounting for 85-99% of the nonfunctioning alleles for Asians and whites
- Other forms exist that could play a role in reduced clinical response.
- The *number* of reduced function alleles is also important.

David Holmes, et al, *ACCF/AHA Clinical Alert , 2010*

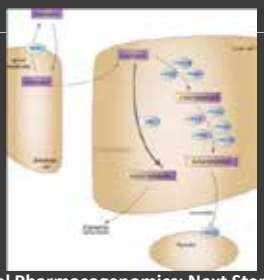
Clopidogrel metabolism and mechanism of action



Amber L. Beitelshees, and Howard L. McLeod Arterioscler Thromb Vasc Biol. 2006;26:1681-1683

JACC Journals

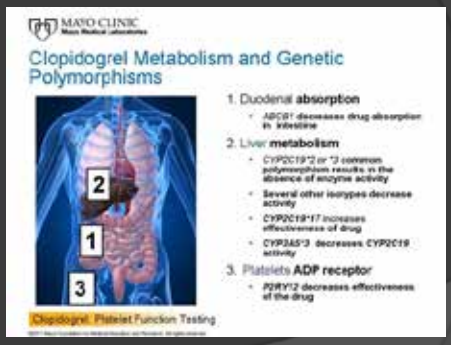
Antiplatelet Drug Clopidogrel Pathway



From: Clopidogrel Pharmacogenomics: Next Steps: A Clinical Algorithm, Gene – Gene Interactions

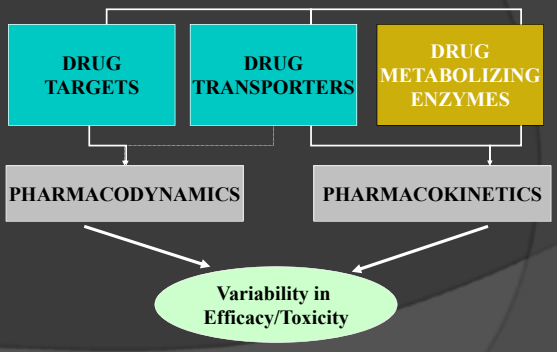
J Am Coll Cardiol Intv. 2010;3(10):995-1000.

Pharmacogenomics of Clopidogrel



The Pharmacogenomics Journal (2013) 13, 105–109

Pharmacogenomics



Johnson JA. Trends in Genetics 2003: 660-666

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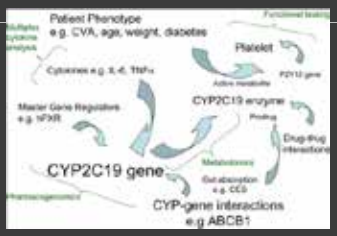
From: Clopidogrel Pharmacogenomics: Next Steps: A Clinical Algorithm, Gene – Gene Interactions



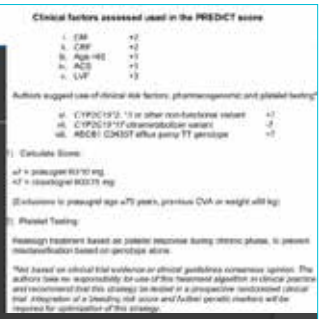
Hypothesized Systems Approach to Clopidogrel Response

Larger font items indicate important components in the system. Green font items indicate other forms of testing which may be valuable in assessing drug response.

J Am Coll Cardiol Intv. 2010;3(10):995-1000. doi:10.1016/j.jcin.2010.08.012

JACC Journals

Clopidogrel Pharmacogenomics



Pharmacogenomic Algorithm

Based on the PREDICT score: Geisler T, et al. CYP2C19 and nongenetic factors predict poor responsiveness to clopidogrel loading dose after coronary stent implantation. Pharmacogenomics 2008;9:1251–9.

J Am Coll Cardiol Intv. 2010;3(10):995-1000. doi:10.1016/j.jcin.2010.08.012

Ethnic Differences

Approximately

- 50% of Chinese,
- 34% of African Americans,
- 25% of Caucasians and
- 19% of Mexican Americans carry at least 1 copy of the reduced function CYP2C19*2 allele.

David Holmes, et al, *ACCF/AHA Clinical Alert , 2010*

Pharmacogenomics Tests

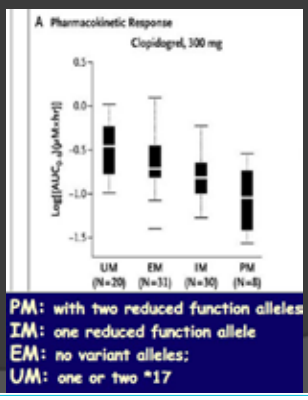
- "Genelex" offers testing for variants of CYP2C19.

Genelex Corporation
Seattle, WA, USA
http://www.healthanddna.com

Roche Chip for Cytochrome P450 Genes: CYPC19 and CYP2D6

Xie and Frueh, Pharmacogenomics steps toward Personalized Medicine, Personalized Medicine 2005, 2, 325-337

Clopidogrel (Plavix) and CYP2C19 Alleles



Boxed Warning

On March 12, 2010 the FDA approved a boxed warning for clopidogrel to:

- Warn about reduced effectiveness in patients who are poor metabolizers of Plavix. Poor metabolizers do not effectively convert Plavix to its active form in the body.
- Inform healthcare professionals that tests are available to identify genetic differences in CYP2C19 function.
- Advise healthcare professionals to consider use of other anti-platelet medications or alternative dosing strategies for Plavix in patients identified as poor metabolizers.

FDA Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug

FDA Drug Safety Communication, March 2010

Recommendations for Practice

- Adherence to existing guidelines for the use of antiplatelet therapy should remain the foundation for therapy.
- Clinicians must be aware that genetic variability in CYP enzymes alter clopidogrel metabolism, which in turn can affect its inhibition of platelet function.
- The specific impact of the individual genetic polymorphisms on clinical outcome remains to be determined.
- Information regarding the predictive value of pharmacogenomic testing is very limited at this time; resolution of this issue is the focus of multiple ongoing studies.

David Holmes, et al, *ACCF/AHA Clinical Alert , 2010*

Recommendations for Practice (*Cont'd*)

- The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time.
- There are several possible therapeutic options for patients who experience an adverse event while taking clopidogrel in the absence of any concern about medication compliance.
- Alternative dosing strategies or newer antiplatelet drugs could improve platelet inhibition and might be considered.

David Holmes, et al, *ACCF/AHA Clinical Alert , 2010*

Clopidogrel
Summary

Because of a lack of evidence-based data, specific recommendations and strategies for routine genetic testing and identification of optimal care strategies cannot be offered at this time.

"The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time. There is no information that routine testing improves outcome in large subgroups of patients. In addition, the clinical course of the majority of patients treated with clopidogrel without either genetic testing or functional testing is excellent. …Careful clinical judgment is required to assess the importance of the variability in response to clopidogrel for an individual patient and its associated risk to the patient."

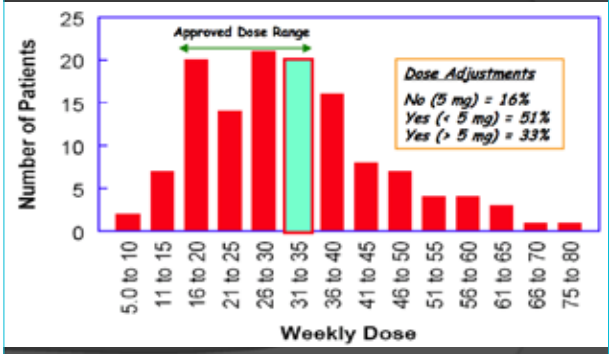
David Holmes, et al, *ACCF/AHA Clinical Alert , 2010*

Pharrmacogenomics of Warfarin

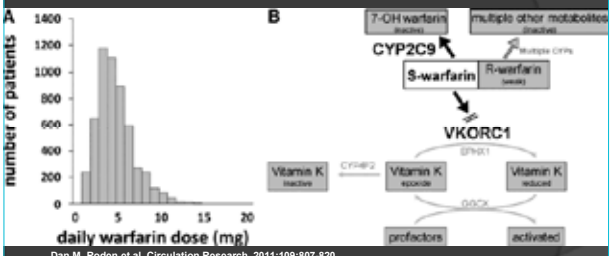
Warfarin: Significant Side-Effects

- Ranks #1 in total mentions of deaths for drugs causing adverse events.
- Ranks among the top drugs associated hospital emergency room visits for bleeding.
- Overall frequency of major bleeding range from 2% to 16% (versus 0.1% for most drugs).
- Minor bleeding event rates in randomized control trials of new anticoagulants has been as high as 29% per year.

Finding Doses to Maintain Therapeutic Anticoagulation is Largely Trial and Error



Multiple genes affecting warfarin dose

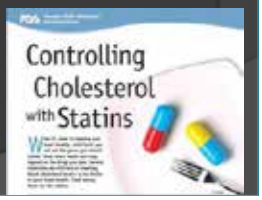


Dan M. Roden et al. Circulation Research. 2011;109:807-820

Genetic Analysis Permits

- More rapid determination of stable therapeutic dose.
- Better prediction of dose than clinical methods alone.
- Applicable to the 70-75% of patients not in controled anticoagulation centers.
- Reduces between 4,500 and 22,000 serious bleeding events annually.
- Genetic testing now required by FDA

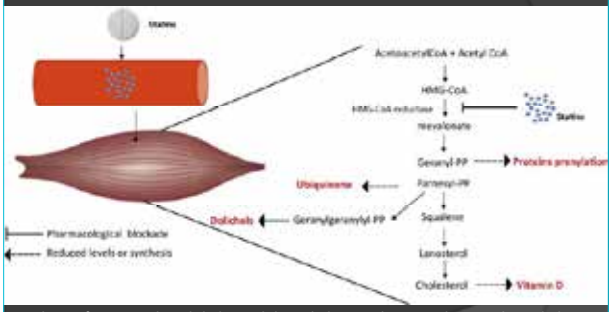
Pharmacogenomics of Statins



Statins

- Statins are widely used to lower LDL cholesterol by inhibiting HMG-CoA reductase in the liver and are generally regarded as safe.
- The most common statin related adverse drug reaction is skeletal muscle toxicity that ranges from mild to severe and is believed to occur in up to 10–15% of exposed subjects in real word practice.
- Clinician often measure creatine kinase (CK) levels as an approximate index for severity but the correlation between CK and symptoms is at best partial, as is our understanding of the causes predisposing to muscle toxicity.

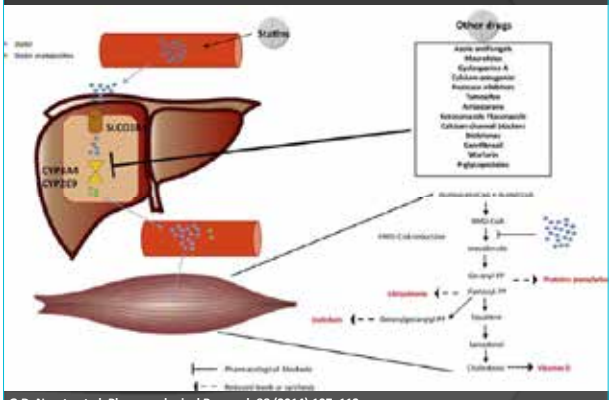
Molecular mechanisms of statin induced toxicity



Synthesis of isoprenoids and cholesterol through the mevalonate pathway and metabolites possibly involved in skeletal muscle toxicity, affected by HMG-CoA reductase inhibitors (statins). HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

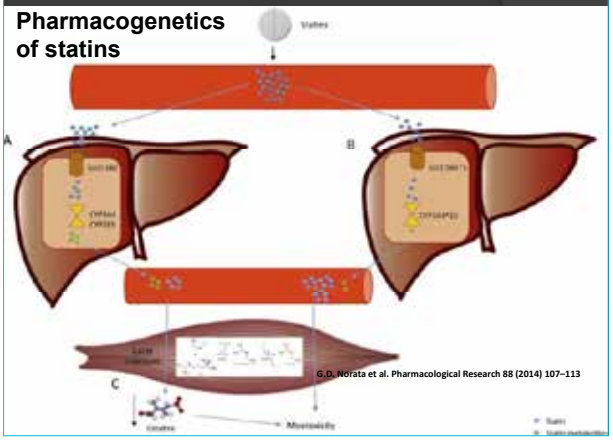
G.D. Norata et al. Pharmacological Research 88 (2014) 107–113

Statins and Skeletal Muscle Toxicity



G.D. Norata et al. Pharmacological Research 88 (2014) 107–113

Pharmacogenetics of statins



G.D. Norata et al. Pharmacological Research 88 (2014) 107–113

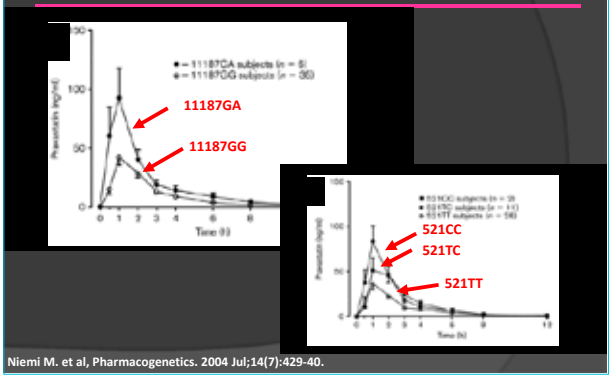
Pharmacogenetics of Statins

- Overall, it is possible to categorize statins genetic related side effects into:
  - those associated with impaired pharmacokinetic in the liver which could result in increased plasma levels of statins, and
  - those related to the alteration in specific genes in the muscles
- Most of the statins are normally bio-transformed via cytochrome p450 3A4 (CYP3A4) with the exception of fluvastatin and rosuvastatin which are mainly metabolized via CYP2E9.
- CYP3A4 it is known to harbor few variants affecting its function compared to the highly polymorphic CYP2D6, recently a relatively frequent SNP in intron 6 termed CYP3A4*22 was shown to affect CYP3A4 expression, resulting in a reduced CYP3A4 activity, and in a better lipid lowering response to simvastatin.

Pharmacogenetics of Statins

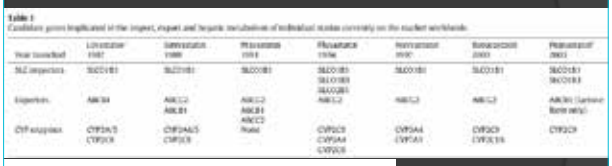
- OATP1B1 facilitates the hepatic uptake of statins.
- Strong evidence that at least one variant on *SLCO1B1*, encoding for the anion transporting polypeptide OATP1B1, alters significantly the risk of simvastatin-induced myopathy.
- Furthermore, the possibility of a strong interaction between CYP3A4 and OATP1B1 on effective statin dose in favoring muscle toxicity should be considered, indeed genetic related low activity of OATP1B1 coupled with poor CYP3A4 metabolizer status could further influence pharmacokinetics parameters and toxicity.
- Six expression quantitative trait loci (eQTLs) interacted with simvastatin exposure, including rs9806699, a cis-eQTL for the gene glycine amidinotransferase (GATM) that encodes the rate-limiting enzyme in creatine synthesis.
  - This locus found to be associated with incidence of statin-induced muscle toxicity in two separate populations.

Individuals with Polymorphisms of OATP1B1 Have Higher Plasma Levels of Pravastatin

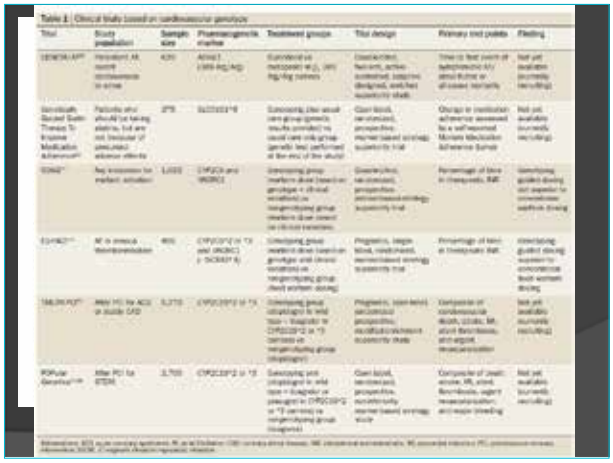


Niemi M. et al, Pharmacogenetics. 2004 Jul;14(7):429-40.

Genetic variants that affect the PK of statins



J.C. Geltsen, A.J. McLachlan / Pharmacological Research 88 (2014) 99–106

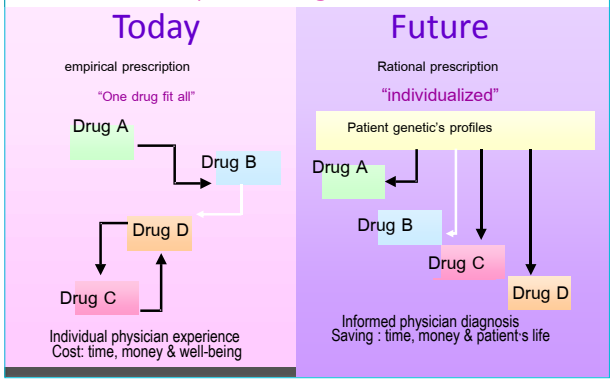


Summary

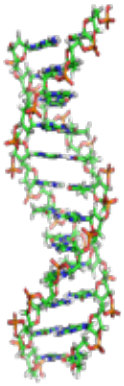
- Substantial progress has been made in the field of pharmacogenomics to study the drug-response phenotype.
- Genetic markers associated with drug toxicity and drug efficacy can be identified by candidate gene, genome-wide association, and next-generation sequencing studies.
- The potential of targeting the right patient with the right drug, and FDA labelling guidance to use pharmacogenetic markers, have provided new impetus to conduct genotype-based randomized clinical trials (RCTs).
- Prospective approaches using a pharmacogenetic-based strategy with enrichment or adaptive designs are being increasingly used in cardiovascular RCTs.
- Clinical adoption of pharmacogenetics in the practice of cardiovascular medicine will become a reality when a transition has been made from conducting genetic association studies to rigorously performed genotype-based RCTs.

Pereira, N. L. et al. Nat. Rev. Cardiol. advance online publication 5 May 2015

Targeted prescription of medicine: applied pharmacogenomics



Nada Božina: Clinical application of genotype-guided dosing of oral anticoagulants - Croatian experiences.



Clinical application of genotype-guided dosing of oral anticoagulants- Croatian experiences

Nada Božina
University Hospital Centre Zagreb
Department of Laboratory Diagnostics
Clinical Unit for Pharmacogenomics and Therapy Individualisation
School of Medicine University of Zagreb

Šupe S, Poljaković Z, Božina T, Ljevak J, Macolić Šarinić V, Božina N. **Clinical Application of Genotype-guided Dosing of Warfarin in Patients with Acute Stroke**. Arch Med Res. 2015 May

BACKGROUND:

Patients with certain types of stroke need urgent anticoagulation and it is extremely important for them to achieve fast and stable anticoagulant effect and receive individualized treatment during the initiation of warfarin therapy.

METHODS

- We conducted a prospective study among 210 acute stroke patients who had an indication for anticoagulation and compared the impact of CYP2C9 and VKORC1 genotype-guided warfarin dosing (PhG) with fixed dosing (NPhG) on anticoagulation control and clinical outcome between groups.

Consort diagram
Assesed for eligibility (587 Caucasian patients with acute ischemic stroke) , Grouped by allocation [eliegble patients with an indication for urgent anticoagulation with warfarin that meets inclusion criteria, 36%(N=210) of total], PhG group (patients in pharmacogenetically-guided group, N=106)); NPhG group (patients without pharmacogenotypisation, fixed-dosing group,N=104)

Inclusion and exclusion criteria for the study

Inclusion criteria	1. Previously taking warfarin due to atrial fibrillation, mechanical heart valves, deep vein thrombosis, pulmonary embolism 2. Newly discovered atrial fibrillation confirmed by HOLTER-ECG 3. Acute dissection of intracranial arteries 4. Patent foramen ovale with septal aneurysm 5. Cerebral venous sinus thrombosis
Exclusion criteria	1. Age<18 year 2. Hemorrhage in the brain, detected by CT scan, except in patients with cerebral venous thrombosis 3. Malignancy, pregnancy 4. Hepatic/renal insufficiency

Primary and secondary endpoints results among PhG/NPhG patients

Patients	PhG (N=106) 95% CI	NPhG (N=104) 95%CI
De	3.6-4.2	0
Di	5.8-6.6	6.0
Dm	3.4-4.0	3.6-4.5
T-Dm *	10(9.9-10.7	13.9(13.3-14.7)
Tm*	16.1(15.7-16.4)	14.1(13.5-14.6)
To*	0.0(0.07-0.7)	1.6(1.0-2.3)
T %*	76.6(74.7-78.5)	67.0(64.5-69.5)
T tg*	4.2(4.1-4.6)	5.2(4.7-6.3)

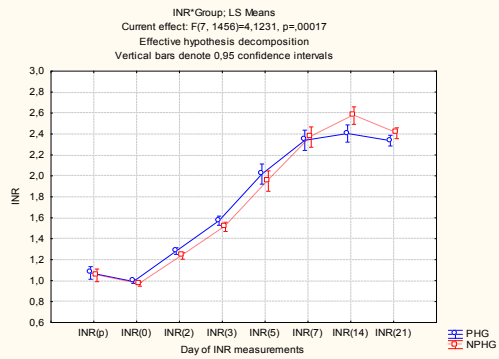
De(estimated dose, mg); Di (dose of introduction, mg); Dm(stable maintenance dose, mg); T-Dm* (time needed to achieve stable maintenance dose, days)
Tm*(time spent within the therapeutic INR range, days); To* (time spent within the INR>3.1, days); T %* (proportion of time within the therapeutic INR range); T tg* (time required to reach target INR values, days)

Demographic and clinical data among PhG and NPhG patients

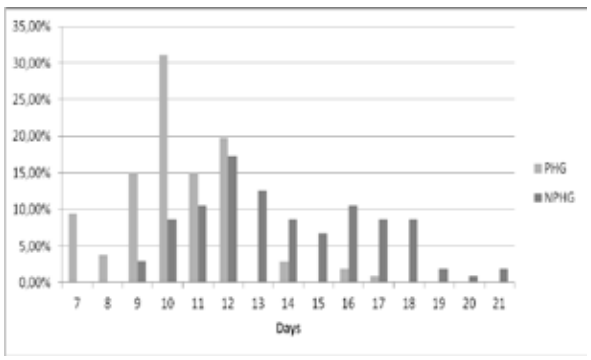
Patients gender	PhG (N=106) Female 60 (56%)	NPhG (N=104) Female 62 (60%)
	Mean (95% CI)	Mean(95%CI)
Age (year)	67.7(65.1-70.3)	69.5(67.1-71.8)
Weight (kg)	75.1(73.1-77.2)	74.3(72.3-76.5)
Height (cm)	174.2(162.5-186.6)	(175.4(163.1-187.2)
De(estimated dose, mg)	3.8(3.6-4.2)	0
Di (dose of introduction, mg)	6.0(5.8-6.6)	6.0
Dm(stable maintenance dose, mg)	3.5(3.4-4.0)	4.1(3.6-4.5)

Day of INR measur.	N(%) PhG < targetINR	N(%) PhG in target INR 2-3	N(%) PhG INR>3,1	N(%) PhG INR>4	N(%) NPhG <target INR	N(%) NPhG in target INR 2-3	N(%) NPhG INR>3,1	N(%) NPhG INR>4
INR(3)	88(83.2)	18(16.98)	0	0	97(93.27)	7(6.73)	0	0
INR(5)	36(33.96)	67(63.21)	0	3(2.83)	56(53.85)	42(40.38)	4(3.85)	2(1.92)
INR(7)	4(3.77)	96(90.57)	5(4.72)	1(0.94)	18(17.31)	70(67.31)	14(13.46)	2(1.92)
INR(14)	0	105(99.06)	0	1(0.94)	4(3.85)	84(80.77)	14(13.46)	2(1.92)
INR(21)	2(1.89)	104(98.11)	0	0	1(0.96)	102(98.08)	1(0.96)	0

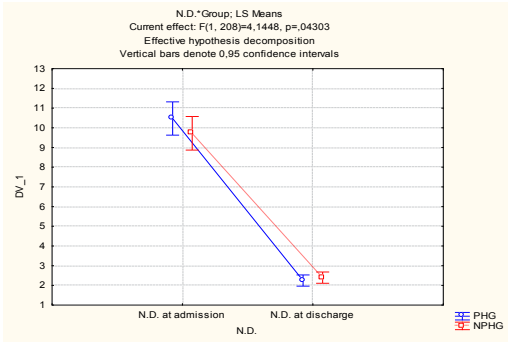
Percentage of PhG and NPhG patients who achieved target INR ≥ 2, therapeutic INR 2-3, supratherapeutic INR >3.1 or INR>4, depending on the day of INR measurement;



Time required to achieve the target International Normalized Ratio (INR) ≥2 and the average INR values depending on the day of INR measurements and monitoring in PhG (pharmacogenetically-guided) and NPhG (fixed dosing) patients (p=0.0017)



Frequencies of patients in pharmacogenetic-dosing group (PHG) and fixed-dosing group (NPHG), depending on the day of achieving stable maintenance dose (p=0.000)



Differences between the neurological deficit at admission (ND at admission, NIHSS) and neurological deficit at the end of the study (ND at discharge, mRS) between PHG and NPHG (p=0.043)

CONCLUSION

We confirmed that warfarin therapy with genotype-guided dosing instead of fixed dosing reduces the time required for stabilization and improves anticoagulant control with better clinical outcome in early stages of warfarin therapy introduction among acute stroke patients, which is essential for clinical practice.

Mitropoulou C, Fragoulakis V, Bozina N, et al. Economic evaluation of pharmacogenomic-guided warfarin treatment for elderly Croatian atrial fibrillation patients with ischemic stroke. Pharmacogenomics 2015;16(2):137-48.

- We developed a pharmaco-economic model to assess whether pharmacogenomic (PGx)-guided warfarin treatment of elderly ischemic stroke patients with atrial fibrillation in Croatia is cost effective compared with non-PGx therapy. The time horizon of the model was set at 1 year.

Our pharmacoeconomic model is a decision tree constructed in a TreeAge Pro Suite 2013 (TreeAge Software, Inc., Williamstown, MA) (**Fig. 1**).

- Our model was populated with cost data from Croatia public tariff lists, in line with current treatment guidelines on patient management, outcomes and economic consequences.
- Differences relate only to the cost of the resources 'consumed' at each corresponding node of the model and the corresponding transition probabilities.

- The structure of the model is identical for both arms and the differences relate only to the cost of the resources expensed and the transition and outcome probabilities in different nodes of the model.
- The model simulates the progression of patients from the moment they start therapy, to various states based on specified probabilities which were collected from our study and from the literature.
- The likelihood of moving between different states is influenced by the effectiveness of each therapy and hence the cost and quality-adjusted years of life.

- The transition probabilities for the first 6 months of the model were based on available data from the study. The transition probabilities concerning the remaining 6 months beyond the duration of our data, was extracted by a study conducted by (De Caterina et all, 2010), while the utility values used in the model was extracted by a similar cost-effectiveness analysis published by Leey, J.A. Am J Geriatr Pharmacother 2009.

As illustrated in figure 1, patients can transition from the initial state to three distinct states including "no event", "major bleeding" and "minor bleeding".

From these states each patients may "survive" or "die" within a one-year time horizon.

Model Diagram

	Pharmacogenomics (PGx)	Non Pharmacogenomics (N-PGx)	P value
Number of patients, n (%)			
All	104 (100%)	102 (100%)	0.555
Male	45 (43.3%)	40 (39.2%)	
Female	59 (56.7%)	62 (60.8%)	
Age, mean ± SD (years)			
All	67.7±13.6	69.6±12.2	0.424
Male	66.5±12.0	67.2±11.3	0.919
Female	68.7±14.7	71.1±12.6	0.449
Weight , mean± SD (kg)			
All	75.2±10.5	74.3±10.5	0.515
Male	83.9±6.5	83.2±7.0	0.557
Female	68.6±7.7	68.6±8.1	0.911
Reason for oral anticoagulant therapy, n (%)			
Chronic Atrial Fibrilation	24 (23.1%)	21 (20.6%)	0.666
Arteficial Aortic Valvule	7 (6.7%)	7 (6.9%)	0.970
Deep venous thrombosis (DVT) or pulmonary embolism (PE)	4 (3.8%)	1 (1.0%)	0.377
Newly diagnosed Chronic Atrial Fibrilation	53 (51.0%)	64 (62.7%)	0.08
Disection	10 (9.6%)	5 (4.9%)	0.301
Thrombosis of venous sinuses	3 (2.9%)	2 (2.0%)	0.667
Foramen Ovale Apertum			0.984

Probabilities, costs and utility values used in the Model

	Mean	SD*	Source
Transition Probabilities			
Minor bleeding (PGx)	0.087	0.028	Study calculations
Major bleeding (PGx)	0.029	0.016	"
Minor bleeding (N-PGx)	0.157	0.036	"
Major bleeding (N-PGx)	0.108	0.031	"
No_ event_to_mortality	0.044	0.003	"
Major_Bleeding_to_Mortality	0.133	0.025	[31]
Minor_bleeding_to_mortality	0.053	0.011	[31]
Values			
Mortality	6 months Alive		Assumption
Survive	12 months Alive		Assumption
Utility Values			
AF without complications	0.98	-	[36]
Major Bleeding	0.8 for one month	-	[36]
	month		
Death	0	-	[36]
Drugs	Costs (€)		
1 mg of warfarin	0.0136		Local Economic Data
Extra costs in case of major bleeding:			"
A. 1 day in hospital 105 euros, for extra 8 days	840		"
B. CT scan x 2 (75.9 x 2)	151.8		"
C. Additional tests for INR 10x 2,1 eur	21		"
D. Frozen plasma and vitamin K for 1 day	350.5		"
E. Colistin (polymyxin E) for 10 days	537.66		"
F. Ciprinol (ciprofloxacin) for 10 days	208.36		"
G. Meronem (meropenem) for 10 days	525.97		"
H. Endoscopic interventions in case of gasstrointestinal bleeding	373.5		"
Cost of Genetic Analysis	140.25		"

Cost Differences between Pharmacogenomics (PGx) and Non-Pharmacogenomics (N-PGx) groups per patient in the primary analysis

	Cost of Bleeding	Cost of INR	Cost of warfarin	Cost of Test	Total Cost
PGx Group					
B-Mean	28.07 €	17.95 €	1.40 €	140.25	187.68 €
B-SD	15.72 €	0.14 €	0.04 €	-	15.74 €
B-95% LCI	2.51 €	17.68 €	1.32 €	-	162.10 €
B-95% UCI	63.82 €	18.23 €	1.49 €	-	223.44 €
B-min	0.00 €	17.46 €	1.26 €	-	159.16 €
B-max	103.39 €	18.51 €	1.58 €	-	262.90 €
N-PGx Group					
B-Mean	147,39 €	23,16 €	1,53 €	-	172,07 €
B-SD	39,04 €	0,19 €	0,02 €	-	39,03 €
B-95% LCI	76,14 €	22,79 €	1,50 €	-	100,67 €
B-95% UCI	228,50 €	23,52 €	1,56 €	-	253,21 €
B-min	24,76 €	22,43 €	1,46 €	-	49,32 €
B-max	310,47 €	23,87 €	1,59 €	-	335,47 €
Cost Differences (N-PGx vs PGx)					
B-Mean	119,32 €	5,20 €	0,12 €	-140.25	-15,60 €
B-SD	40,43 €	0,25 €	0,05 €	-	40,43 €
B-95% LCI	41,95 €	4,72 €	0,03 €	-	-92,89 €
B-95% UCI	202,69 €	5,69 €	0,21 €	-	67,45 €

RESULTS

- Our primary analysis indicates that 97.07% of patients belonging to the PGx-guided group have not had any major complications, compared with the control group (89.12%; $p < 0.05$).
- The total cost per patient was estimated at €538.7 (95% CI: €526.3-551.2) for the PGx-guided group versus €219.7 (95% CI: €137.9-304.2) for the control group.

Results

- In terms of quality-adjusted life-years (QALYs) gained, total QALYs was estimated at 0.954 (95% CI: 0.943-0.964) and 0.944 (95% CI: 0.931-0.956) for the PGx-guided and the control groups, respectively.
- The true difference in QALYs was estimated at 0.01 (95% CI: 0.005-0.015) in favor of the PGx-guided group. The incremental cost-effectiveness ratio of the PGx-guided versus the control groups was estimated at €31,225/QALY.

Results

- The TC (time to achieve targeted INR) in case of the PGx group was estimated at 5.64 days (95%CI: 5.41-5.89), while in the N-PGx arm TC was 7.11 days (95%CI: 6.80-7.43; $p<0.05$)
- Tmd (time to achieve maintenance dose) was 10.35 days (95%CI: 10.05-10.65) in the PGx group compared to 13.87 days (95%CI: 10.05-10.65) in the N-PGx group

Results

- The total cost per patient in the PGx arm was estimated at €187.68 (95%UI: €162.10-€5,901), while in the N-PGx arm the cost was €172.07 (95%UI: €100.67-€253.21), a non significant difference of €-15.60 (95%UI: €-92.69- €67.45) in favor of N-PGx group
- The main item driving total treatment costs was the cost of pharmacogenomic testing in the PGx group, accounting for approximately 75% of the total costs in this arm.

Results

- The mean cost of bleeding was estimated at €28.07 (95%UI: €2.51-€63.52) in the PGx arm, whilst the costs in the N-PGx arm were €147.39 (95%CI: €76.14-€228.50), reaching a statistically significant difference at €119.32 (95%CI: €41.95-€202.69) in favour of the PGx group.
- The difference between the two arms concerning the cost of bleeding, was due to the fact that bleeding was more frequent in control group. The cost of INR testing and warfarin was lower in both arms.

- Deterministic results indicate that PGx arm was associated with higher cost per patient and higher total QALYs gained compared with the N-PGx arm.
- The incremental cost-effectiveness ration was estimated at €31,225/QALY. In terms of QALYs gained, total QALYs was estimated at 0.954 (95%CI: 0.943-0.964) and 0.944 (95%CI: 0.931-0.956) for PGx and N-PGx, respectively.
- The true difference in QALYs was estimated at 0.01 (95%CI: 0.005-0.015) in favor of PGx.

- We have then plotted the cost-effectiveness acceptability curve to demonstrate the probability (on the y-axis) that PGx may be cost-effective compared to the N-PGx for a range (on the x-axis) of maximum monetary values that a decision-maker might be willing to pay per QALY

Barton, G.R., Optimal cost-effectiveness decisions: the role of the cost-effectiveness acceptability curve (CEAC), the cost-effectiveness acceptability frontier (CEAF), and the expected value of perfection information (EVPI). Value Health, 2008.

- .

- The results from the Probabilistic Sensitivity Analysis were illustrated by plotting the distribution of differences in costs and effects in the cost-effectiveness plane (**Fig. 2**). All the simulation experiments felt into the North East quadrant indicating that the PGx arm was slightly more expensive but, at the same time, more effective than N-PGx.

Scatter Plot of probabilistic analysis (PGx vs N-PGx)

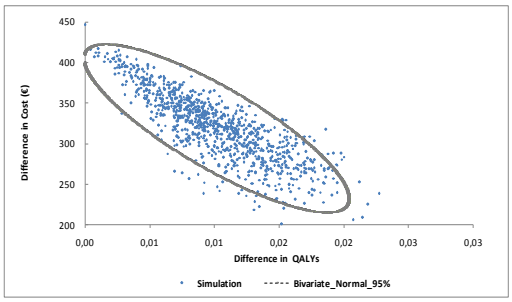
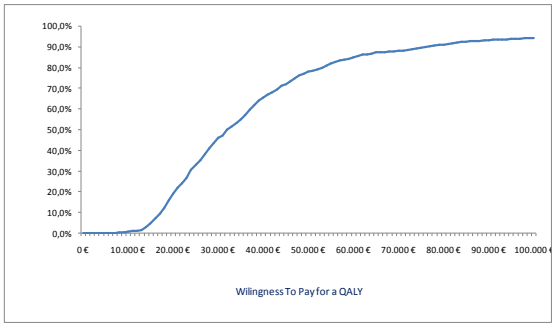


Fig.2 The results from the Probabilistic Sensitivity Analysis were illustrated by plotting the distribution of differences in costs and effects in the cost-effectiveness plane. All the simulation experiments felt into the North East quadrant indicating that the PGx arm was slightly more expensive but, at the same time, more effective than N-PGx.

Cost effectiveness acceptability curve for PGx vs N-PGx



Our data show that the probability of PGx being cost-effective increases significantly at a willingness-to-pay threshold in the range of €40,000 to €50,000 per QALY [35], used in many jurisdictions; notably, at €60,000 per QALY its probability of cost-effectiveness is higher than 80%.

COST EFFECTIVENESS RESULTS (DETERMINISTIC ANALYSIS) FOR PGX VS N-PGX IN THE MODEL

	Cost per patient	Effectiveness (QALYs)	Incremental Cost[!]	Incremental Effectiveness[!]	ICER
PGx	€538.7	0.954	€319.4	0.01023	€31.225/ QALY
N-PGx	€219.2	0.943	-		

Probabilistic Results of the Model

	Statistics	N-PGx	PGx
Cost	Mean	219.7 €	538.7 €
	SD	43.2 €	6.3 €
	Minimum	96.2 €	520.3 €
	2.5%	137.9 €	526.3 €
	10%	163.1 €	530.4 €
	Median	218.0 €	538.6 €
	90%	274.5 €	546.7 €
	97.5%	304.2 €	551.2 €
	Maximum	395.5 €	561.9 €
	Variance	1,869.5 €	39.6 €
QALYs	Mean	0.944	0.954
	SD	0.007	0.005
	Minimum	0.919	0.931
	2.5%	0.931	0.943
	10%	0.935	0.947
	Median	0.944	0.954
	90%	0.953	0.961
	97.5%	0.956	0.964
	Maximum	0.962	0.968

CONCLUSION

- Overall, our data indicate that PGx-guided warfarin treatment may represent a cost-effective therapy option for the management of elderly patients with atrial fibrillation who developed ischemic stroke in Croatia.

Conflicting results

- Kimmel SE, French B, Geller NL; COAG Investigators. Genotype-guided dosing of vitamin K antagonists. N Engl J Med. 2014 May 1;370(18):1763-4.
- Pirmohamed M, Wadelius M, Kamali F; EU-PACT Group. Genotype-guided dosing of vitamin K antagonists. N Engl J Med. 2014 May 1;370(18):1764-5.
- Schwarz UI, Kim RB, Tirona RG. Genotype-guided dosing of vitamin K antagonists. N Engl J Med 2014;370(18):1761-2.

The effects of the CYP2C9, VKORC1 and MDR1 gene polymorphisms on warfarin therapy individualization

Ksenija Makar Ausperger, disertation

Zagreb University School of Medicine, 2015

Achievement of stable anticoagulant effects (INR 2.5-3.5) according to diagnosis (n=106)

	Stable INR achieved					
	yes		no		total		OR_{uv}	95% CI
	n	(%)	n	(%)	n	(%)		
Atrial fibrillation								
no	16	(23,2)	53	(76,8)	69	(100,0)	1	
yes	12	(54,5)	10	(45,5)	22	(100,0)	**4,0**	**(1,45-10,90)**
Deep vein thrombosis								
no	16	(44,4)	20	(55,6)	36	(100,0)	1	
yes	12	(21,8)	43	(78,2)	55	(100,0)	0,4	(0,14-0,87)
Pulmonary embolism								
no	23	(29,9)	54	(70,1)	77	(100,0)	1	
yes	5	(35,7)	9	(64,3)	14	(100,0)	1,3	(0,39-4,32)
NYHA								
no heart failure	10	(18,9)	43	(81,1)	53	(100,0)	1	
heart failure	18	(47,4)	20	(52,6)	38	(100,0)	3,9	(1,52-9,88)

Outcomes after first 5 days of starting therapy with warfarin

	FG(n=106)		NFG(n=99)		P	effects	95% CI
Total sample							
Percentage of time within the INR 2-4	14	(19.2)	16	(19.0)	0.513	MD -2	(-7-4)
Achieved stable dose *, n (%)	22	(20.8)	22	(22.2)	0.798	OR 0.92	(0.45-1.88)
Adverse side effects, n (%)	8	(7.5)	5	(5.1)	0.464	OR 1.54	(0.44-5.63)
Atrial fibrillation							
Percentage of time within the INR 2-4	26	(25.0)	14	(18.6)	**0.04**	MD 12	(0-23)
Achieved stable dose , n (%)	14	(46.7)	7	(21.9)	**0.039**	OR 3.13	(1.42-10.98)
Adverse side effects, n (%)	3	(10.0)	2	(6.3)	0.588	OR 1.67	(0.2-15.67)
Deep vein thrombosis							
Percentage of time within the INR 2-4	11	(16.1)	16	(20.2)	0.083	MD -6	(-12-1)
Achieved stable dose , n (%)	8	(12.9)	14	(23.0)	0.146	OR 0.5	(0.17-1.41)
Adverse side effects, n (%)	4	(6.5)	2	(3.3)	0.414	OR 2.03	(0.3-16.73)
Pulmonary embolism							
Percentage of time within the INR 2-4	18	(25)	21	(19)	0.637	MD -3	(-18-11)
Achieved stable dose , n (%)	4	(25.0)	7	(29.2)	0.772	OR 0.81	(0.15-4.15)
Adverse side effects, n (%)	1	(6.3)	2	(8.3)	0.806	OR 0.73	(0.02-11.96)

Univariate correlation of MDR1 2677G <T/A and CYP2C9 * 2 * 3 genotype to the achievement of the therapeutic range (INR 2-4) in the first 5 days of the introduction of warfarin (n=106)

		INR (2-4)				P
		Achieved		Not achieved	total	
MDR1 2677G>T/A	CYP2C9*2*3					
GT	*1*1	9	(30,0)	21 (70,0)	30 (100,0)	0,003
	*1*2	2	(18,2)	9 (81,8)	11 (100,0)	
	*1*3, *2*2, *2*3	9	(81,8)	2 (18,2)	11 (100,0)	
TT	*1*1	6	(54,5)	5 (45,5)	11 (100,0)	0,434
	*1*2	4	(80,0)	1 (20,0)	5 (100,0)	
	*1*3, *2*2, *2*3	3	(42,9)	4 (57,1)	7 (100,0)	
GG	*1*1	8	(44,4)	10 (55,6)	18 (100,0)	0,762
	*1*2	3	(37,5)	5 (62,5)	8 (100,0)	
	*1*3, *2*2, *2*3	1	(25,0)	3 (75,0)	4 (100,0)	

Contributors

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Training the trainers TTT

European Board and College of Obstetrics and Gynaecology (EBCOG)

Živa Novak Antolič

EBCOG TTT working party

Description of a perfect trainer

- Having inner will to teach
- Having inner power to teach
- Ability to observe and discuss
- Ability to listen, reflect and ask
- Be positive and understanding
- Be patient
- Understands the topic well herself/ himself

Prof Živa Novak Antolič

University Of Ljubljana Medical Faculty, University Medical Centre Ljubljana,

Division for Perinatology

6300 deliveries per year

FEEDBACK

EBCOG TTT

correct and effective feedback is essential for good training

TRAINER'S MAIN TASK

- Trainer's main task is **to give effective feedback regarding** all three domains of learning:
  - Knowledge
  - Skills
  - Attitude

FEEDBACK

Is essential for progress in training

Establishes the culture of positive collaboration of trainer and trainee

Helps trainee to **take responsibility for hers/ his own training**

FEEDBACK

WHY BOTHER?

BECAUSE:
It raises trainee's self-awareness
Reinforces good practice
Motivates trainee
Improves performance

If you want to be heard:

Use **positive words** when giving feedback

- Try to say:
  - "it would be better…"
  - "can we discuss together what you are going to do"
- Instead of: "do not do that!"

Trainees tell about feedback:

That they are unaware they are performing poorly or making mistakes: "*No-one told me my technique was poor*"

That feedback given badly can damage confidence: "*I felt awful*"

That inconsistent feedback does more harm than good: "*Different people tell you different things about the same problem*"

Why do trainers not give feedback:

- We do not know how to do it not to insult the trainee
- Some trainees do not accept our feedback

EFFECTIVE FEEDBACK

Positive

Timed

Based on personal experience

Non-judgmental

EFFECTIVE FEEDBACK

- **Praise in public**
- **Criticize in private**
- **5 : 1**
  positive : negative

EFFECTIVE FEEDBACK

- Be specific ("the use of vacuum extraction in that situation was problematic")
- Encourage self-reflection
- Focus on actions not personality
- Constructive
- Frequent, in small steps
- **Do not appologize**

Encourage self-reflection*

- "tell me about this event"
- "what would you do differently next time"
- ***VERY DIFFICULT IF THE TRAINEE IS IMMUNE TO CRITICISM**

Pendelton's rule

- Let the trainee comment **what s/he did good**
- Let the appraisor comment **what trainee did good**
- Let the trainee comment **what s/he could do better**
- Let the appraisor comment **what trainee could do better**

Exercise: mini talk

- Prepare a short talk
  - Non medical
  - 3 minutes maximum
  - prepare to give feedback (Pendelton's points 1 and 3)
- The audience: prepare to give feedback (points 2 and 4)

APPRAISAL

A part of EBCOG TTT

APPRAISAL

TO SET GOALS FOR THE TRAINEE

APPRAISAL vs ASSESSMENT

- **A PERSONAL PLANNING R A I S A L**
- *A* ***Selection Standard*** *E S S M E N T*

APPRAISAL vs ASSESSMENT

- **Sets goals**
- **Gives support and guidance**
- **For the trainee**
- **In house**
- **Informal**
- Tests competence
- Objective measurement
- For licencing body
- Independent
- Formal

WHY APPRAISAL

- **Appraisal should improve education**
- (Assessment tests knowledge/ skills/ attitude comparing them to minimal standards)

EFFECTIVE APPRAISAL

- **Listen**
  - Support
  - Advise
  - Identify areas for improvement
  - Plan
  - Inform directly
- **Plan next meeting**
- Confidentiality
- Positive feedback
- Pendelton's rules
- **Do not talk too much**
- **Be honest**

APPRAISAL - THE EDUCATIONAL CYCLE

First week → Last week

Induction	Regular review:	Feedback
Appraisal	Support	Future plans
Contract	Feedback	Summative
	Additional guidance	assessment
	(updated plan)	

APPRAISAL: how to do it

☐ Introductory interview 1

- In **the first** week after the start of training!!
- **Take time**
- Get to know the trainee (CV)
- Inform about **time schedules** and describe **hers/ his work**

APPRAISAL: how to do it

☐ Introductory interview 2

- Be specific about **goals**
- Determine **how you two will check the** obtained **goals**
- Set **the date** for next appraisal
- Make a **contract.** Sign. There is a possibility to do that in the LogBook

APPRAISAL: how to do it

Regular review

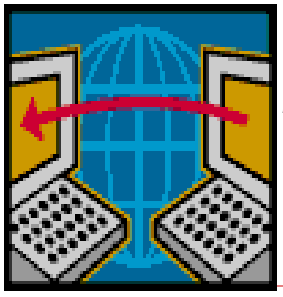
- Check (see PDCA cycle)
- Set new goals
- Take care of additional necessary knowledge/ skills/ attitude

APPRAISAL: how to do it

Be realistic after the first year. Ask this question:

are there goals the trainee will never be able to accomplish and is it perhaps better to re-direct him/ her to another specialization?

COMMUNICATION TRAINER - TRAINEE



Better try to make it in person

Modes of appraisal

- Trainer's opinion
- MSF (multisource feedback, 360 degrees appraisal)
- NOTSS (non technical skills for surgeons)

Multisource Feedback (MSF)

Assesses

- **behaviour**
- **team working**
- **communication skills**

Multisource Feedback (MSF)

- Collection of data on doctor's performance from a range of co-workers
  - Specialists
  - Trainees
  - Midwives
- Trainees give forms to 15 co-workers they choose

Multisource Feedback (MSF)

- Feedback collected by educational supervisor, at least 10 forms and self-evaluation form
- Discussion with trainee
  - Find trainee's strengths
  - Find areas for development

EFFECTIVE FEEDBACK

informal

- After each training session

formal

- Arrange time
- Collect relevant data
- Make notes prior to meeting
- Reinforce good practice
- Identify, analyse and explore possible solutions to deficiencies in practice
- Make a plan to address these

Exercise – role play

- Induction interview
- Interview after 6 months
- Interview before final exam

Exercise – role play

- Induction interview
- Interview after 6 months
- Interview before final exam

DIFFICULT APPRAISAL

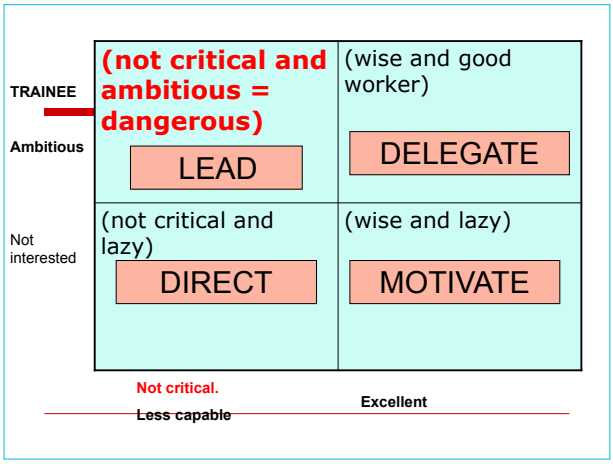
DIFFICULT APPRAISAL: use Pendelton's rule

- Let the trainee comment **what she/ he did good**
- Let the appraisor comment **what trainee did good**
- Let the trainee comment **what she/ he could do better**
- Let the appraisor comment **what trainee could do better**

Wallflower	*Bramble*
Flytrap	**Trainees can be like those**

DIFFICULT APPRAISAL – TRAINEE WITH PROBLEMS

- Prepare for the discussion
  - Have the documents ready
  - Write "minutes" – and put them into his/ her CV
- Focus on **performance**, not on personality
- Be honest, do not judge



HOMEWORK: Difficult appraisal - role play - prepare a scenario

- for »difficult« trainee
  - Who is too courageous,
  - Never asks for help or opinion,
  - Does things s/he does not know enough of,
  - Not critical (no self reflection)
  - For everything bad that happens to her/ him, somebody else is guilty
    - Because they hate him/ her
    - Because s/he is the best

HOMEWORK: Difficult appraisal - role play - prepare a scenario

- How a trainer controls the situation with a difficult trainee
  - Goal: as a trainer you should find a way to **direct properly** a very active and ambitious trainee, who is, however, without appropriate knowledge, skills and attitude