



EAFP

EUROPEAN ASSOCIATION OF
FACULTIES OF PHARMACY

University of Ljubljana
Faculty of *Pharmacy*



Personalized medicines

Prof. dr. Irena Mlinarič-Raščan

2014 EAFP Annual Conference
**Science-based pharmacy education:
Towards better medicines and patient care**



Outline of the lecture

Definitions/ understandings

Life cycle of medicine

Facing the challenge

Educational challenges

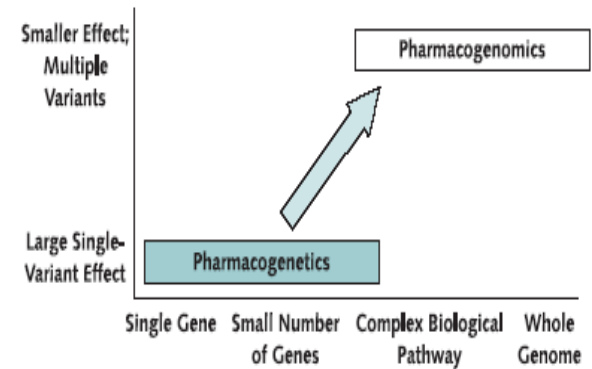


PHARMACO-GENETICS/-GENOMICS

is a process connecting

- ✓ Identification of variation in drug responses
- ✓ Correlation to genetic variation
- ✓ Development of screening tests
- ✓ Implementation of individualized therapy

PERSONALIZED MEDICINES



Roden DM et al. Ann Intern Med 2006; 145:749-57

Promises of PGX

- Focus treatment to likely to respond stratified population
- Predict and reduce adverse events
- Identify potential medicines in the pipeline for certain population
- Better understanding of drug interactions

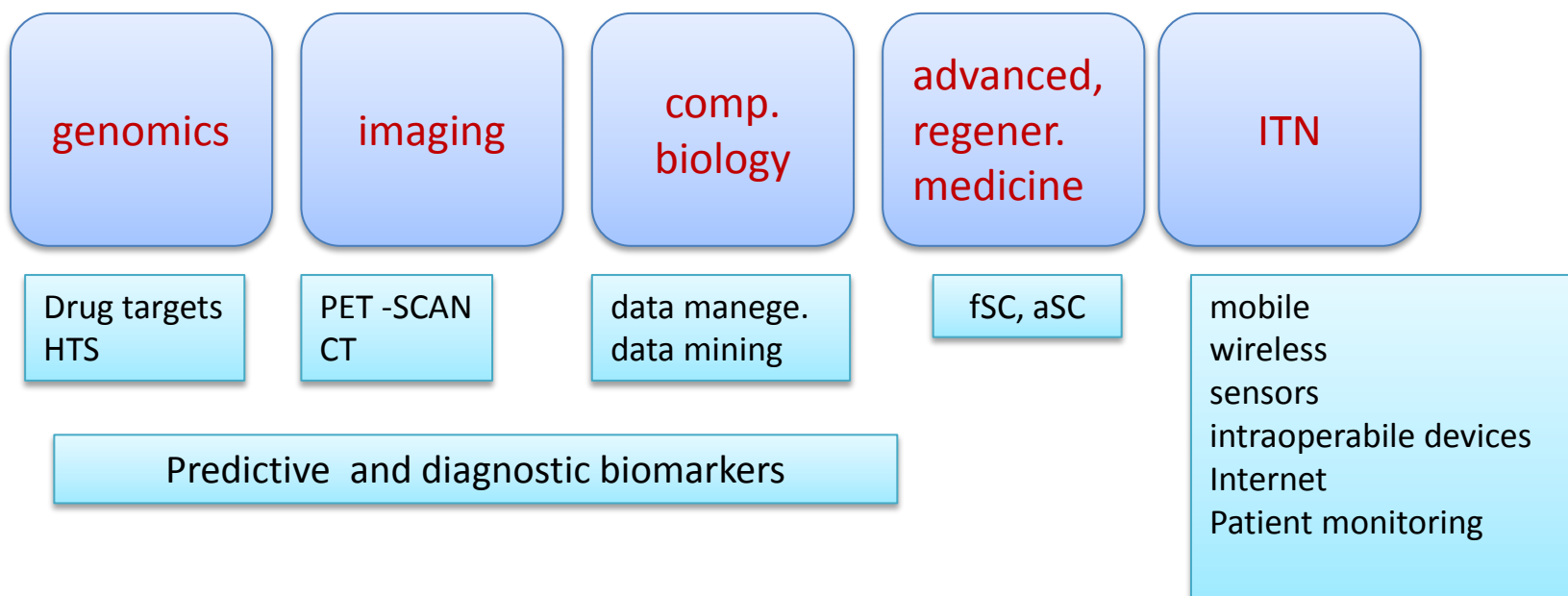


PESONALIZED MEDICINE

The aim: tailoring of treatment to individual characteristics, need and preferences

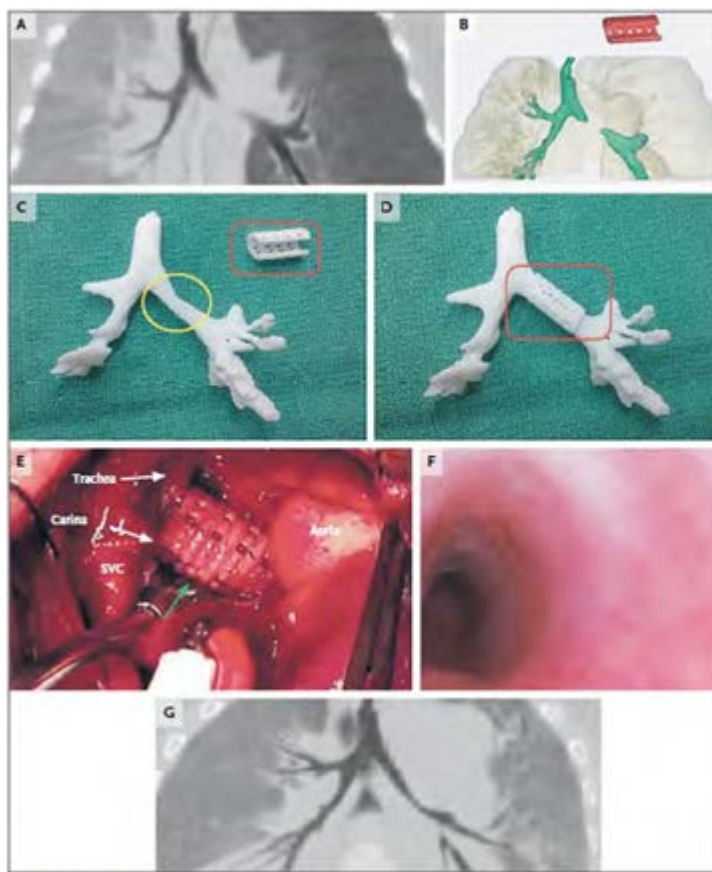
Enabled by parallel advances on multiple scientific fields

- not limited to pharmaceutical therapy*



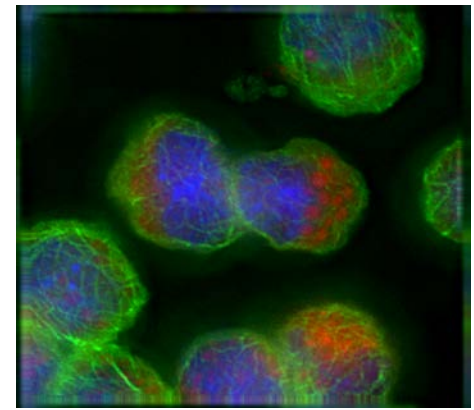
* Paving the way for Personalized Medicine; FDA,10/ 2013

PM- example: Placement of the Printed Airway Splint in the Patient



patient-specific computed tomography-based design of the splint (red).

PERSONALIZED MEDICINES- Advanced therapies



ChondroCelect[®] (2009) tissue-engineered products is a suspension for implantation that contains **cartilage cells**

Glybera[®] (alipogene tiparvovec) the first gene therapy authorised in Europe (2012) approved for the treatment **of lipoprotein lipase deficiency (LPLD)**

MACI[®] (matrix applied characterised autologous cultured chondrocytes) (2013)

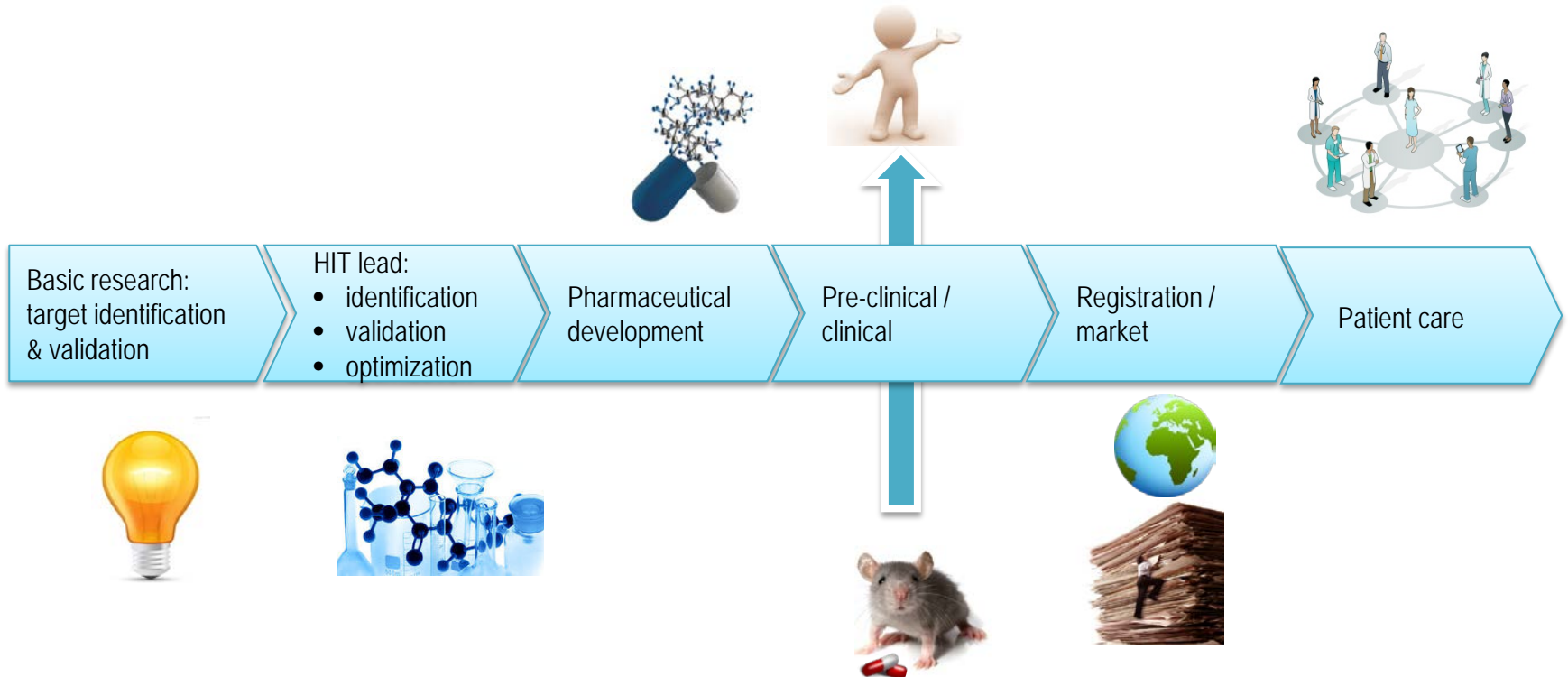
PROVENGE[®] (**sipuleucel-T**) (2013) therapeutic cancer vaccine; an autologous cellular immunotherapy for metastatic prostate cancer



PESONALIZED MEDICINE (s)

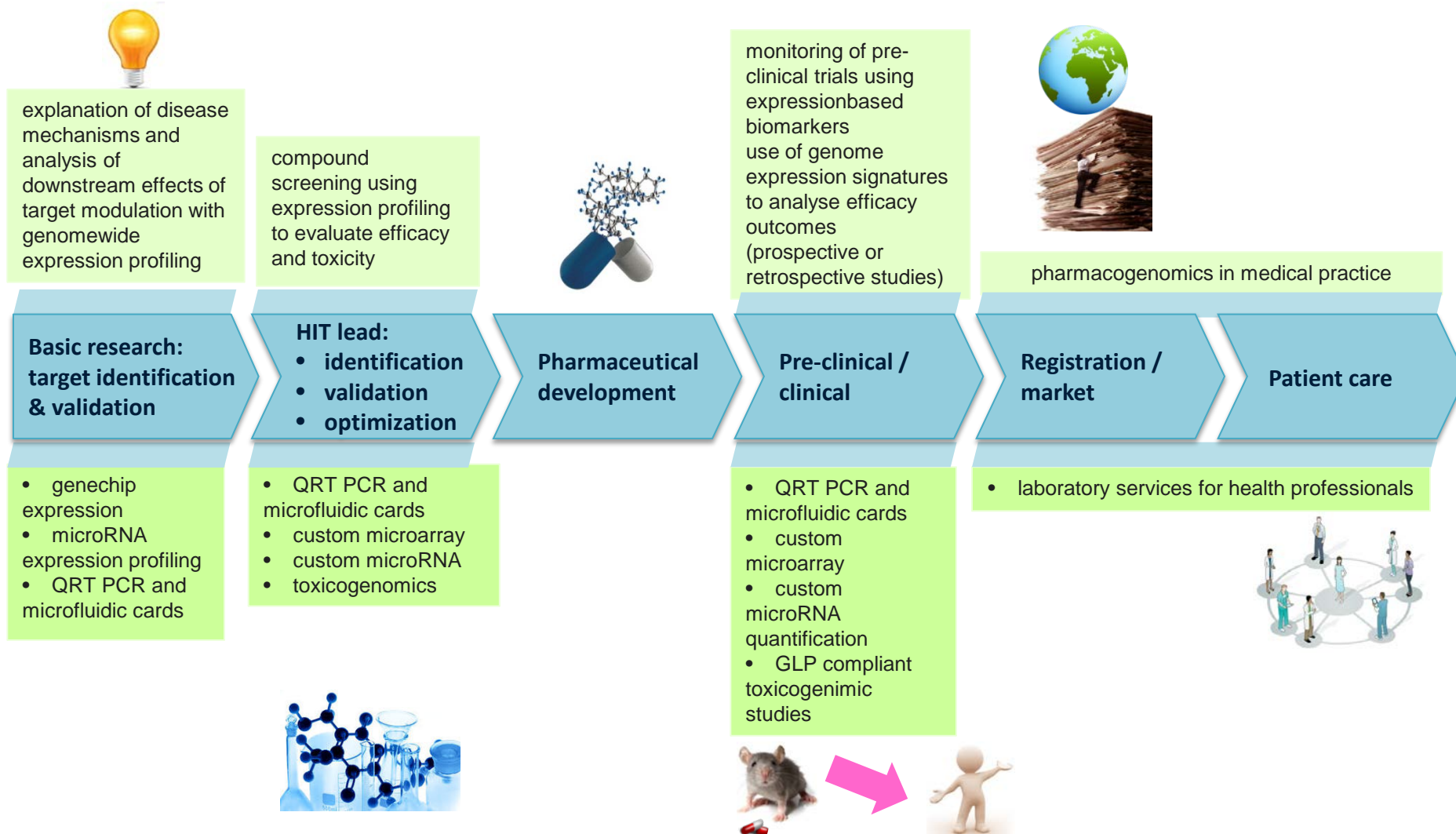
Development of targated therapeutics and diagnostic tools

What are the changes to the DDD landscape in post genome are?





THE IMPACT OF (POST) GENOM ERA ON THE LANDSCAPE OF DDD



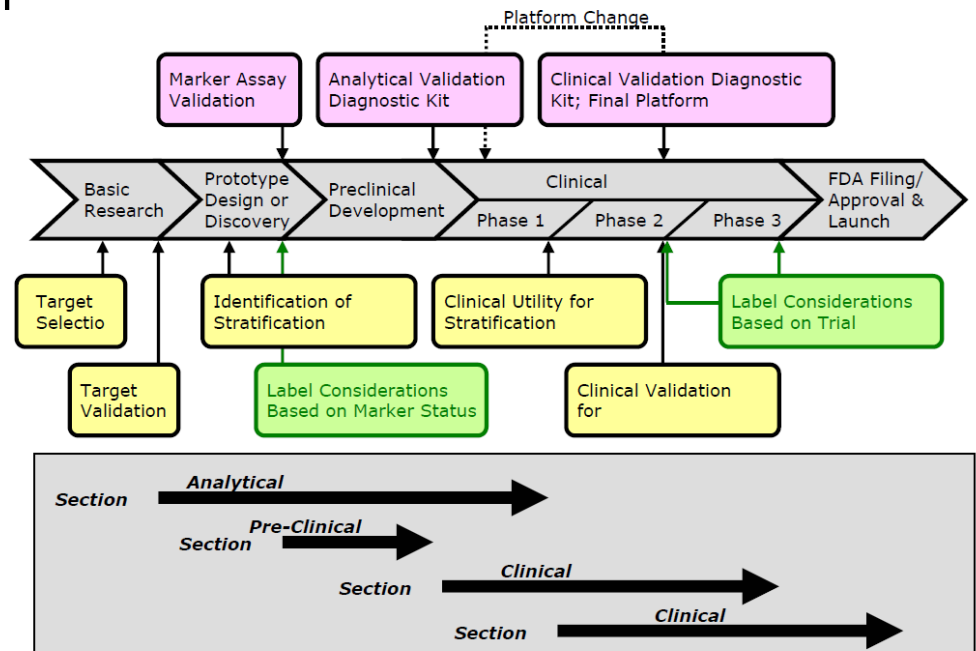


PHARMACOGENOMICS One of the corner stones of PM

CHANGES IN PARADIGM

- diseases delineation
- target identification
- diagnostic markers co-development:
- lead identification and validation
- HTS: toxicogenomics,
- metabolism prediction
- stratification of population

HER-ceptin, DACO, 1998



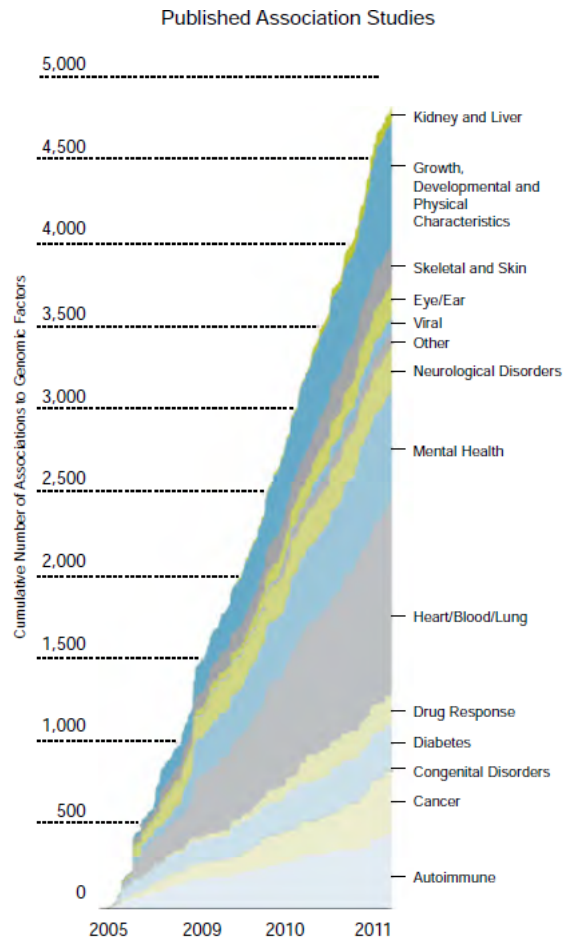


RECENT SUCCESSES WITH CO-DEVELOPMENT

Generic name	US trade name	Indication	Biomarker	Generic name	US trade name	Indication	Biomarker
Arsenic trioxide	Trisenox	APL	PML/RAR α	Lenalidomide	Revlimnid	Multiple myeloma	Chromosome 5q
Cetuximab	Erbitux	Colon cancer	EGFR, KRAS	Maraviroc	Selzentry	HIV	CCR5
Crizotinib	Xalkori	Lung cancer	ALK	Nilotinib	Tasigna	CML/Ph1+ ALL	Ph1/BCR-ABL
Dasatinib	Sprycel	CML/Ph1+ ALL	Ph1/BCR-ABL	Panitumumab	Vectibix	Colon cancer	EGFR, KRAS
Denileukin diftitox	Ontak	Lymphoma	CD25	Pertuzumab	Perjeta	Breast cancer	Her2/neu
Imatinib (1)	Gleevec	CML	Ph1/BCR-ABL	Tositumomab	Bexxar	Lymphoma	CD20 antigen
Imatinib (2)	Gleevec	MDS/MPD	PDGFR	Trastuzumab	Herceptin	Breast cancer	Her2/neu
Ivacaftor	Kalydeco	Cystic fibrosis	CFTR (G551D)	Tretinoin	Vesanoid	APL	PML/RAR α
Lapatinib	Tykerb	Breast cancer	Her2/neu	Vemurafenib	Zelboraf	Melanoma	BRAF



UNDERSTANDING OF DISEASE-MARKER ASSOCIATIONS



Contemporary methods eg GWAs generate knowledge about associations between genomic factors and disease

Source: Raskin, A. Casdin, E. (2011). *The Dawn of Molecular Medicine: The Transformation of Medicine and Its Consequences for Investors*. New York, NY: Alliance Bernstein.)



PGx GUIDELINES

CLINICAL PHARMACOGENETICS IMPLEMENTATION CONSORTIUM (*CPIC*)

TPMT/Thiopurines (Relling et al., Clin Pharmacol Ther. 2011;89:387-91)

CYP2C19/Clopidogrel (Scott et al., Clin Pharmacol Ther. 2011;90:328-32)

CYP2C9-VKORC1/Warfarin (Johnson et al., Clin Pharmacol Ther. 2011;90:625-9)

HLA-B/Abacavir (Martin et al., Clin Pharmacol Ther. 2012; 91:734-8)

CYP2D6/Codeine (Crews et al. Clin Pharmacol Ther. 2012;91:321-6)

SLCO1B1/simvastatin (Wilke et al., Clin Pharmacol Ther. 2012;92:112-7)

HLA-B/allopurinol (Hershfield et al. Clin Pharmacol Ther. 2013;93:153-8)

CYP2D6/TCAs (Hicks et al. Clin Pharmacol Ther. 2013;93:402-8)

HLA-B/carbamazepine (Leckband et al., Clin Pharmacol Ther. 2013;94:324-8)

•Others : DPYD-5FU/capecitabine, HLA-B/phenytoin, G6PD/rasburicase, Septra, UGT1A1/irinotecan, IL28B/pegintron, CTFR/Ivacaftor, CYP2D6/SSRIs



THE STATE of THE ART

- ~ 600 authorized medical products in Europe
- ~ 20% include genomics information
 - imply personalized use of medicines (SNPs- dose, DDI)
- ~ 13 cases with mandatory testing prior to treatment
 - targeted/personalized medicines (safety, efficacy, quality)
 - + information on assays or methods
- rapid increase in understanding disease-marker associations
- affordability of genotyping, the cost of sequencing one or two genes in the past will now produce results for 225 genes



Outline of the lecture

Definitions/ understandings

Life cycle of medicine

Facing the challenge

Societies

Consortia

Regulatory agencies

Educational challenges

The role of pharmacists in PM

UL FFA example



FACING THE CHALLENGE

Pharmacogenetics & Pharmacogenomics Research Network

Network

PharmacoGenetics and PharmacoGenomics Research

European Federation for Pharmaceutical Sciences

Scope and aim

Pharmacogenetics and pharmacogenomics (PGX) are emerging disciplines that focus on genetic determinants of drug response at the levels of single genes or the entire human genome, respectively. The network is the voice of the European science community in pharmacogenetics and pharmacogenomics, with the following objectives. The Network provides a platform for experts for gathering and disseminating knowledge, determining PGX-strategies; for collaboration between academic institutions and industry; for mechanisms of set up and exchange of databases; and for gatherings and promotion of knowledge about pharmacogenetics and genomics in Europe. Objectives also include to serve as a knowledge-bank for EU research programme calls, and to engage in education and training, particularly, PHD students.

Contact Point

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ESPT
European Society of Pharmacogenomics and Theranostics

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Click here for more info!

[DMDI Journal](#)
Click here for more info!

[ESPT Summer Schools](#)
Visit the Summer Schools Site

Mission Statement and Aims

Our mission is to be the leading European organization in the field of pharmacogenomics (PGX) and theranostics (TNX) with worldwide influence.

Aims of ESPT

"Through leadership and innovation in science and education we will strive to enhance the scientific basis for and the quality of diagnosis and therapy for patients throughout the world. We build on the professionalism of our members to provide quality services to patients. We aim to communicate effectively with our members, other healthcare providers, regulators and the public to disseminate and inform them of our excellent scientific and educational achievements. We focus always on maintaining scientific standards, publications, education and communication. We communicate effectively through a variety of conventional and electronic media. We hold outstanding congresses and conferences to bring the efforts of ESPT to the global community"

The specific aims of ESPT are:

- To transcend the boundaries of single nations or single corporations, in developing the field of PGX and TNX.
- To provide a forum for consensus, in the broadest sense, to offer a European view at the highest possible scientific and technical level, aiming to improve quality of care for the patient.
- To disseminate information on "best practice" at various levels of technology, clinical practice and economic development.




CLINICAL PHARMACOGENETICS IMPLEMENTATION CONSORTIUM (**CPIC**)

- **TRANSFER** of pharmacogenetics testing into routine patient care
- gene-drug pairs associated with potential risks of
 - life-threatening toxicity,
 - serious adverse effects,
 - or lack of effectiveness.
- 11 genes have profound effects on 33 drugs.

CPIC: Clinical Pharmacogenetics Implementation Consortium



Host Institution	PharmGKB
Email	cpic@pharmgkb.org
Drug(s)	Azathioprine ; Mercaptopurine ; Thioguanine ; Clopidogrel ; Warfarin ; Codeine ; Capecitabine ; Abacavir ; Carbamazepine ; Phenytoin ; Allopurinol ; Rasburicase ; Irinotecan ; Simvastatin
Related Links	Publications

The [Clinical Pharmacogenetics Implementation Consortium \(CPIC\)](#)  was formed in late 2009, as a shared project between [PharmGKB](#) and the [Pharmacogenomics Research Network](#). CPIC guidelines are peer-reviewed and published in a leading journal (in partnership with [Clinical Pharmacology and Therapeutics](#)) with simultaneous posting to PharmGKB with supplemental information/data and updates. Anyone with clinical interests in pharmacogenetics is eligible for membership. CPIC's goal is to address some of the barriers to implementation of pharmacogenetic tests into clinical practice.

Read an article describing CPIC's guideline development process:

[Incorporation of Pharmacogenomics into Routine Clinical Practice: The Pharmacogenetics Implementation Consortium \(CPIC\) Guideline Development Process](#) .



MEDICINES WITH PHARMACOGENETIC INFORMATION

Search PharmGKB: Search

© PharmGKB

Pharmacogenomics. Knowledge Implementation.

What is the PharmGKB?

Find out how we go from extraction of gene-drug relationships in the literature to implementation of pharmacogenomics in the clinic...

Find out more →

- CPIC G6PD-rasburicase guideline
- SLC22A1 VIP Summary Publication
- CPIC CFTR-ivacaftor guideline
- Uric acid-lowering drug pathways
- PharmGKB Knowledge Pyramid

Clinically-Relevant PGx

- [Well-known PGx associations](#)
- [Clinically relevant PGx summaries](#)
- [PGx drug dosing guidelines](#)
- [Drug labels with PGx info](#)
- [Genetic tests for PGx](#)
- [PGx gene haplotypes](#)

PGx-Based Drug Dosing Guidelines

- [G6PD/rasburicase: article](#) and [supplement](#)
- [CFTR/ivacaftor: article](#) and [supplement](#)
- [See all CPIC guidelines](#)
- [CPIC gene-drug pairs of interest](#)

PGx Research

- **VIP:** [Very Important PGx gene summaries](#)
- [View PharmGKB pathways](#)
 - [Alphabetically](#)
 - [By therapeutic category](#)
- [Annotated SNPs by gene](#)
- [Drugs with genetic information](#)



Pharmacists: Personalized Medicine Experts in Primary Care

- offering the potential for significant advances in optimizing drug therapy outcomes and minimizing adverse drug events
- aiming to equip primary care pharmacists with the knowledge and skills required to take a lead role as personalized medicine experts in the healthcare system and evaluate the impact personalized medicine has on patients' health

Innovation in Personalized Medicine



UNIVERSITY OF TORONTO
LESLIE DAN FACULTY OF PHARMACY



Dr. Lisa McCarthy is the lead for a team that recently received a Canadian Foundation for Pharmacy Innovation Fund grant. "Pharmacists: P Primary Care" is a multi-phase project that will equip primary care pharmacists with the knowledge and skills required to take a lead role as the healthcare system and evaluate the impact personalized medicine has on patients' health outcomes. The interprofessional team working assembly of practicing clinicians, scientists and educators partnered across three institutions - the Leslie Dan Faculty of Pharmacy, the Cent Health, and Women's College Hospital - that includes Dr. Beth Sproule, Dr. Natalie Crown, Dr. Micheline Piquette-Miller, and Maria Bystrin.



ACTIVITIES AT THE EUROPEAN MEDICINES AGENCY

➤ Pharmacogenomics Working Party

a group of European experts in pharmacogenomics that gives recommendations to the CHMP

➤ Specific documents

➤ *Guideline on the use of Pharmacogenetic Methodologies in the Pharmacokinetic Evaluation of Medicinal Products (2009)*

➤ *Key Aspects on the Use of Pharmacogenomic Methodologies in the Pharmacovigilance Evaluation of Medicinal Products (2011)*

➤ *Reflection Paper on Pharmacogenomics in Oncology (2006)*

➤ *Reflection Paper on Co-development of Pharmacogenomic Biomarkers and Assays in the Context of Drug Development (2008).*

➤ *Reflection Paper on Pharmacogenomic Samples, Testing and Data Handling (2006).*

➤ *Reflection Paper for Laboratories that Perform the Analysis or Evaluation of Clinical Trial Samples (2010).*

NEW : EMA has opened public consultations on
“Draft guideline on key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal products”



GUIDELINES ON PHARMACOGENETICS

Issue	Regulatory agency		
	European Medicines Agency	Pharmaceutical and Medical Devices Agency, Japan	US Food and Drug Administration
Development phases covered in guideline or guidance	Preclinical and clinical development (Phases I–IV; focusing on PK)	Clinical development (Phases I–IV)	Early clinical development (Phases I and II)
Banking of DNA samples	Highly recommended	Encouraged*	Strongly encouraged
Genomic testing	Required [‡]	Recommended	Recommended
<i>In vitro</i> cut-off values [§]	>50%	None	None
<i>In vivo</i> cut-off values [§]	>25%	None	None

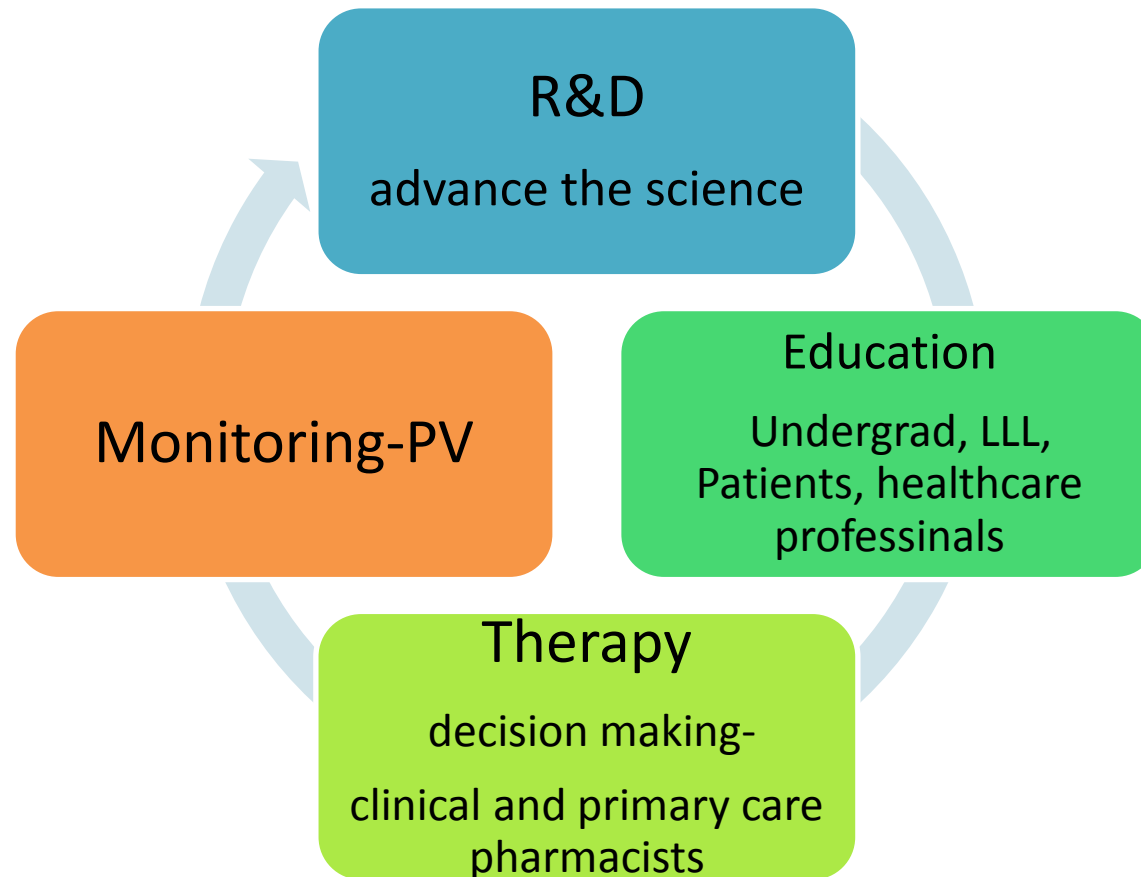
*Does not apply to category A (see main text for more details). [‡]Is a firm requirement only when *in vitro* (>50%) or *in vivo* (>25%) cut-off values are met. [§]For when pharmacogenetics-related testing is required in pharmacokinetics (PK) studies.

www.nature.com/reviews/drugdisc, 2013



EDUCATIONAL CHALLENGES

THE ROLE OF THE PHARMACISTS





EDUCATIONAL CHALLENGES

Opinion

Clinical Pharmacology & Therapeutics (2014); **95** 3, 245–247. doi:10.1038/clpt.2013.184

Is There a Need to Teach Pharmacogenetics?

A K Daly¹

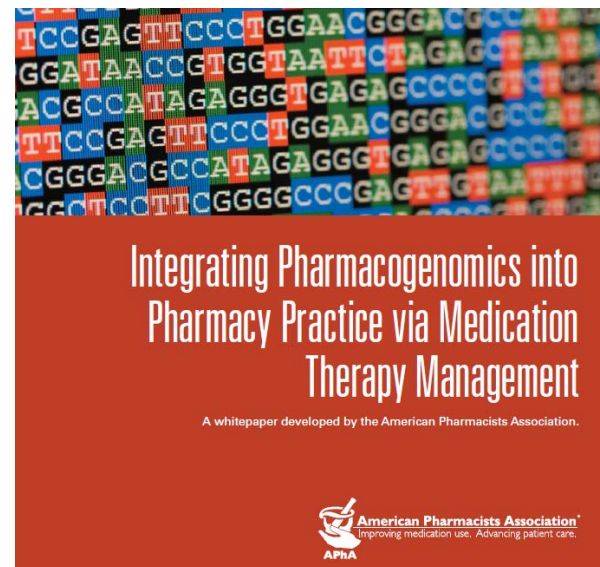
¹Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK

Correspondence: A K Daly, (a.k.daly@ncl.ac.uk)

Abstract

[Top](#)

Pharmacogenetics/pharmacogenomics has been subject to considerable development during the past 10 years and seems likely to advance even more rapidly in the next decade. Several surveys suggest that initial training for health-care professionals—particularly physicians and pharmacists—frequently includes education in this area, but equipping these professions more generally to deal with ongoing development of the field and to make best use of new knowledge remains an important challenge.



Development and Evaluation of a Pharmacogenomics Educational Program for Pharmacists

Design. As part of a continuing education program accredited by the Accreditation Council for Pharmacy Education (ACPE), pharmacists were provided with a fundamental pharmacogenomics education program.

Am J Pharm Educ. Feb 12, 2013; 77(1): 10.



PHARMACOGENOMICS AT THE UL FFA

Since 2003 an **elective subject**

The concept

Incorporated into **other subjects**

Research-based educations

MSc research projects

- Individualized therapy
- Medicines Development

Professional services

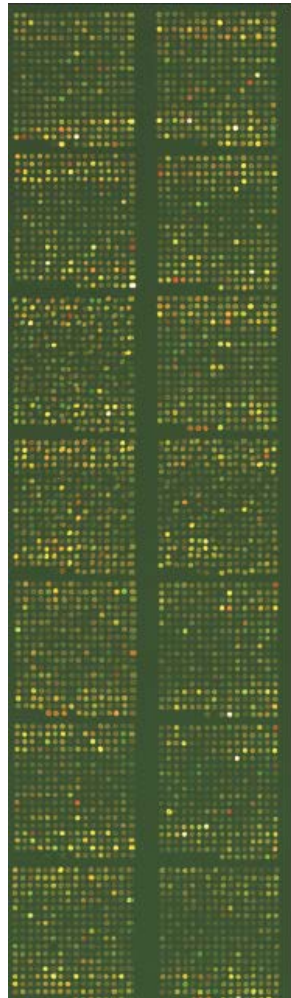
Licenced Mol diagnostics Laboratory

LLL educational program

- +Laboratory Medicine Chamber
- +Pharmacy chamber



PHARMACOGENOMICS AT THE UL FFA



Irena Mlinarič-Raščan
FARMAKOGENOMIKA

Univerza v Ljubljani
Fakulteta za farmacijo
Ljubljana 2010

THE CONCEPT

I. Humane genome

Interindividual variability

II. Metodologies

Highthroughput technologies
microarrays, Sequencing

III. Basic bioinformatic tools

IV. Pharmacogenomics in individualized therapy

V. Pharmacogenomics

incorporated in DDD proces

VI. Etical legal and social aspects



CONCLUSIONS

Genome-era impact on all phases of drug discovery, development and utilization of medicines allowed the emergence and implementation of personalized medicines

Pharmacists as prime drug experts should acquire key competences to both **govern** the concept development as well as **implement** the practice of personalized medicine in terms of tailoring therapeutics to individual patients

The educators shall **provide** access to novelties in the interdisciplinary fields and assure the development of novel skills to be unchallenged drug therapy experts



Thank you!