Using Human Genomic Variation for Individualisation of Drug Treatment

Munir Pirmohamed

David Weatherall Chair of Medicine

Department of Molecular and Clinical Pharmacology

University of Liverpool

UNIVERSITY OF LIVERPOOL

THE WOLFSON CENTRE FOR PERSONALISED MEDICINE

MRC Centre for Drug Safety Science

Current Paradigms

- Physicians “personalise” treatments
- We use the best evidence available to us (usually from RCTs – population based studies) to treat the patient (i.e. individual) consulting us
- From a population perspective, that has proven benefits
- But from an individual perspective, it is less satisfactory and is CRUDE
  - Cannot predict whether the patient will improve
  - Cannot predict whether the patient will develop adverse effects

"One Dose Fits All" – Variability In Improvement

Condition	Efficacy Rate (%)
Alzheimer's	30
Asthma	60
Diabetes	57
HCV	47
Cancer	25
Osteoporosis	48
Rheumatoid arthritis	50
Schizophrenia	60

Source: Physicians Desk Reference

THE INDEPENDENT

No. 5,348 www.independent.co.uk MONDAY 8 DECEMBER 2003 60p

Glaxo chief: Our drugs do not work on most patients

MOST PRESCRIPTION medicines do not work on most people who take them, a senior executive with Britain's biggest drug company has admitted.

Allen Roses, worldwide vice-president of genetics at GlaxoSmithKline (GSK), said fewer than half the patients prescribed some of the most expensive drugs actually derived any benefit from them.

It is an open secret within the drugs industry that most of its products are ineffective in most patients, but this is the first time such a senior drug company employee has gone public. His comments come days after it emerged that the NHS drugs bill has soared by nearly 50 per cent in three years, rising by £2.3bn a year to an annual cost to the taxpayer of £7.2bn. GSK announced last week that it had 20 or more new drugs under development which could each earn the company up to US$1bn (£600m) a year.

Dr Roses, an academic geneticist from Duke University in North Carolina, spoke at a recent scientific meeting in London where he cited figures on how well different classes of drugs work. Drugs for Alzheimer's disease work in fewer than one in three patients, whereas cancer drugs are only effective in a quarter of patients. Drugs for migraines, osteoporosis, and arthritis work in about half the patients, he said. Most drugs work in fewer than one in two

BY STEVE CONNOR
Science Editor

patients, mainly because the recipients carry genes that interfere with the medicine, he said. **"The vast majority of drugs - more than 90 per cent - only work in 30 or 50 per cent of the people,"** Dr Roses said. "I wouldn't say that most drugs don't work … Drugs out there on the market work, but they don't work in everybody."

Some industry analysts said Dr Roses' comments were reminiscent of the 1991 gaffe by Gerald Ratner, the jewellery boss who famously said his high street shops were successful because they sold "total crap". But others believe Dr Roses deserves credit for being honest about a little-publicised fact known to the drugs industry for many years.

"Roses is a smart guy and what he is saying will surprise the public but not his colleagues," one industry scientist said. "He is a pioneer of a new culture within the drugs business based on using genes to test for who can benefit from a particular drug."

Dr Roses has formidable reputation in the field of "pharmacogenomics", the application of human genetics to drug development, and his comments can be seen as an attempt to make the industry realise that its future rests in being able to target drugs on a smaller number of patients with specific genes. The idea is to identify "responders" - people who benefit from the drug - with a simple and cheap genetic test that can eliminate those non-responders who might benefit from another drug.

This goes against a marketing culture within the industry that relies on selling as many drugs as possible to the widest number of patients, a culture that made GSK one of the most profitable pharmaceuticals companies, but whih also means most of its drugs are at best useless, and even possibly dangerous, for many patients.

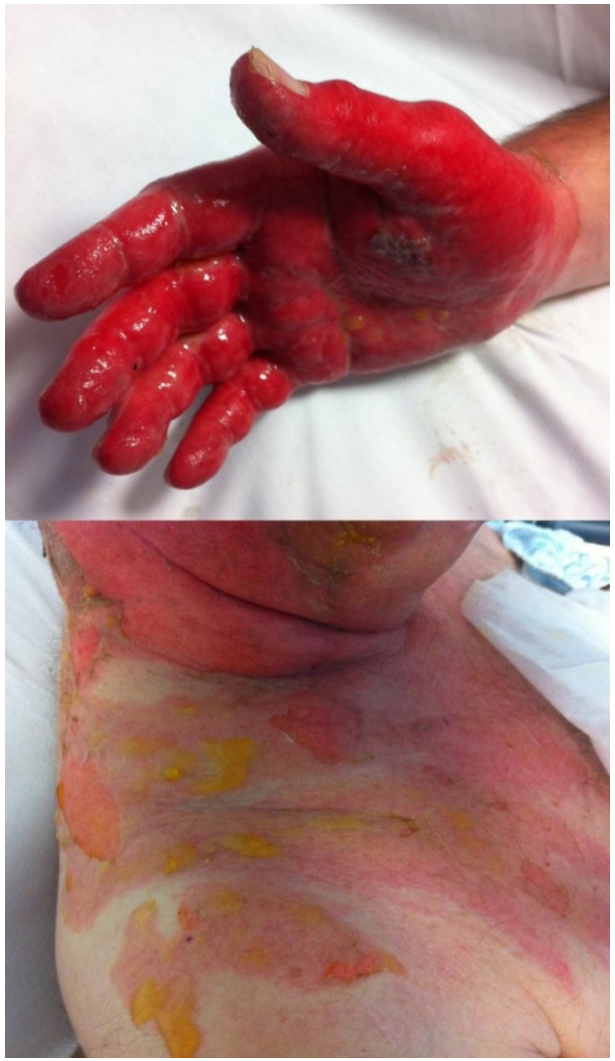
Dr Roses said doctors treating patients routinely applied a trial-and-error approach which says that if one drug does not work there is always another. "I think everyone has it in their experience that multiple drugs have been used for their backache or whatever," he said.

"It's in their experience, but they don't quite understand why. The reason why is because they have different susceptibilities to the effect of that drug and that's genetic. Neither those who pay for medical care nor patients want drugs to be prescribed that do not benefit the recipient. Pharmacogenetics has the promise or removing much of the uncertainty."

Further report, pages 18-19
Leading article, page 30

"The vast majority of drugs - more than 90 per cent – only work in 30 or 50 per cent of the people,"

Adverse Drug Reactions (Side Effects)



Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients

Munir Pirmohamed, Sally James, Shaun Meakin, Chris Green, Andrew K Scott, Thomas J Walley, Keith Farrar, B Kevin Park, Alasdair M Breckenridge

Adverse Drug Reactions in Hospital In-Patients: A Prospective Analysis of 3695 Patient-Episodes

Emma C. Davies[1,2], Christopher F. Green[3], Stephen Taylor[4], Paula R. Williamson[4], David R. Mottram[2], Munir Pirmohamed[5]*

National Surveillance of Emergency Department Visits for Outpatient Adverse Drug Events

PATIENT SAFETY

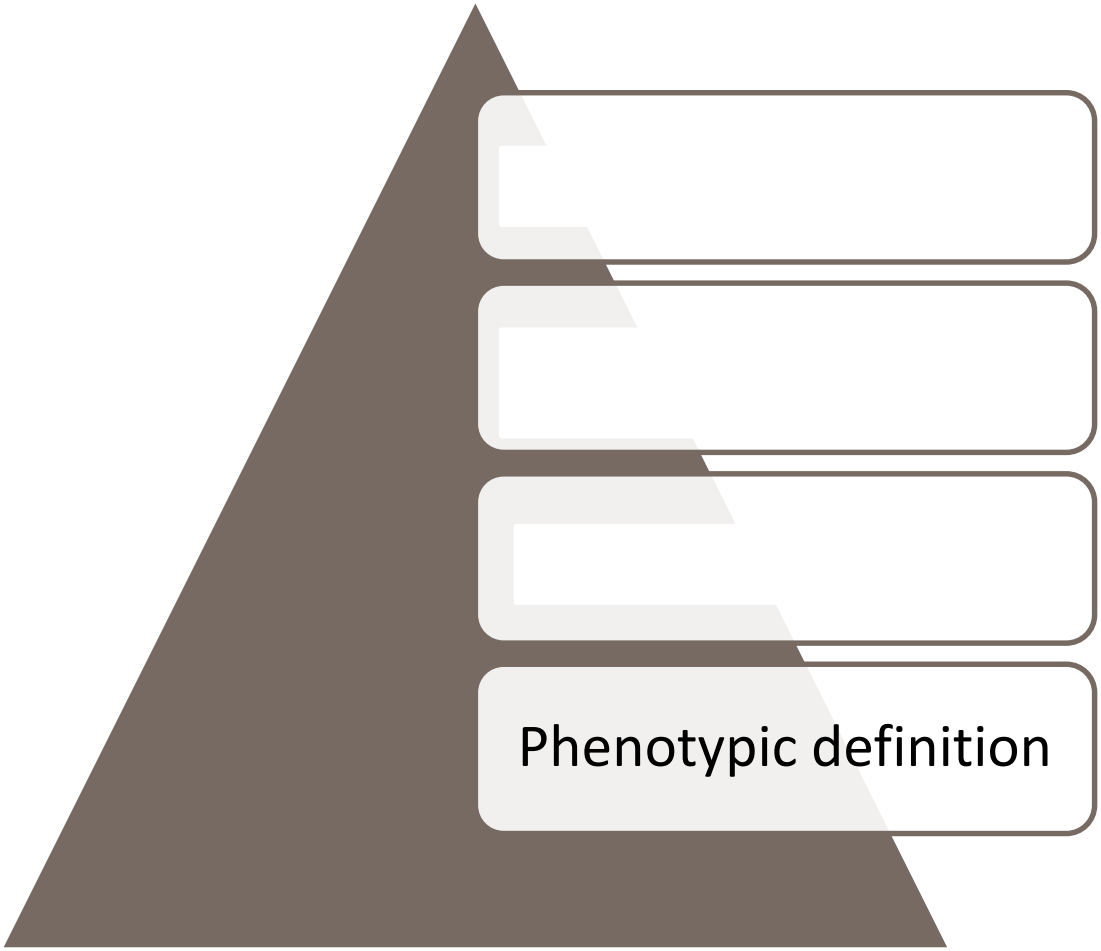
Adverse Drug Events in Ambulatory Care

Tejal K. Gandhi, M.D., M.P.H., Saul N. Weingart, M.D., Ph.D., Joshua Borus, B.A., Andrew C. Seger, R.Ph., Josh Peterson, M.D., Elisabeth Burdick, M.S., Diane L. Seger, R.Ph., Kirstin Shu, B.A., Frank Federico, R.Ph., Lucian L. Leape, M.D., and David W. Bates, M.D.

- Adverse drug reactions are common
- Vary in severity

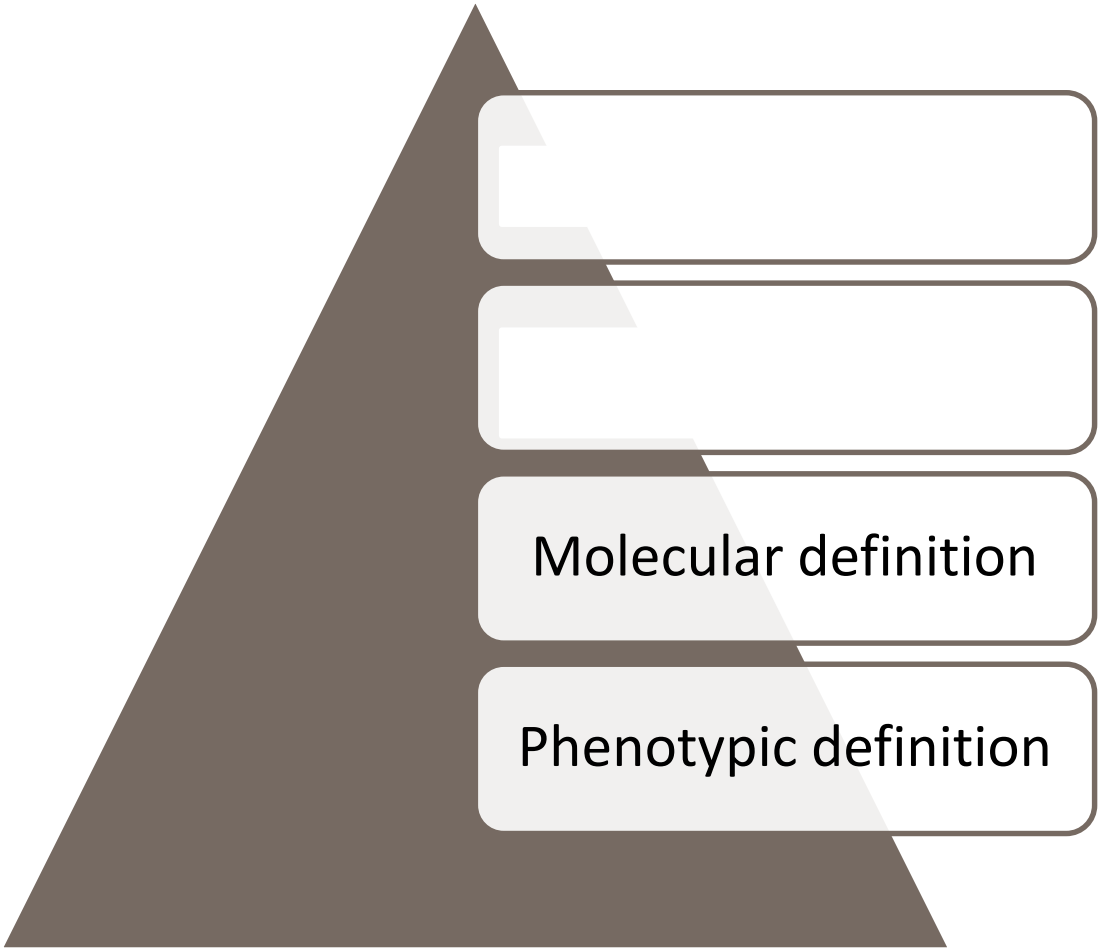
TOXIC EPIDERMAL NECROLYSIS

A Modern Concept of Personalised Medicine



Current standard

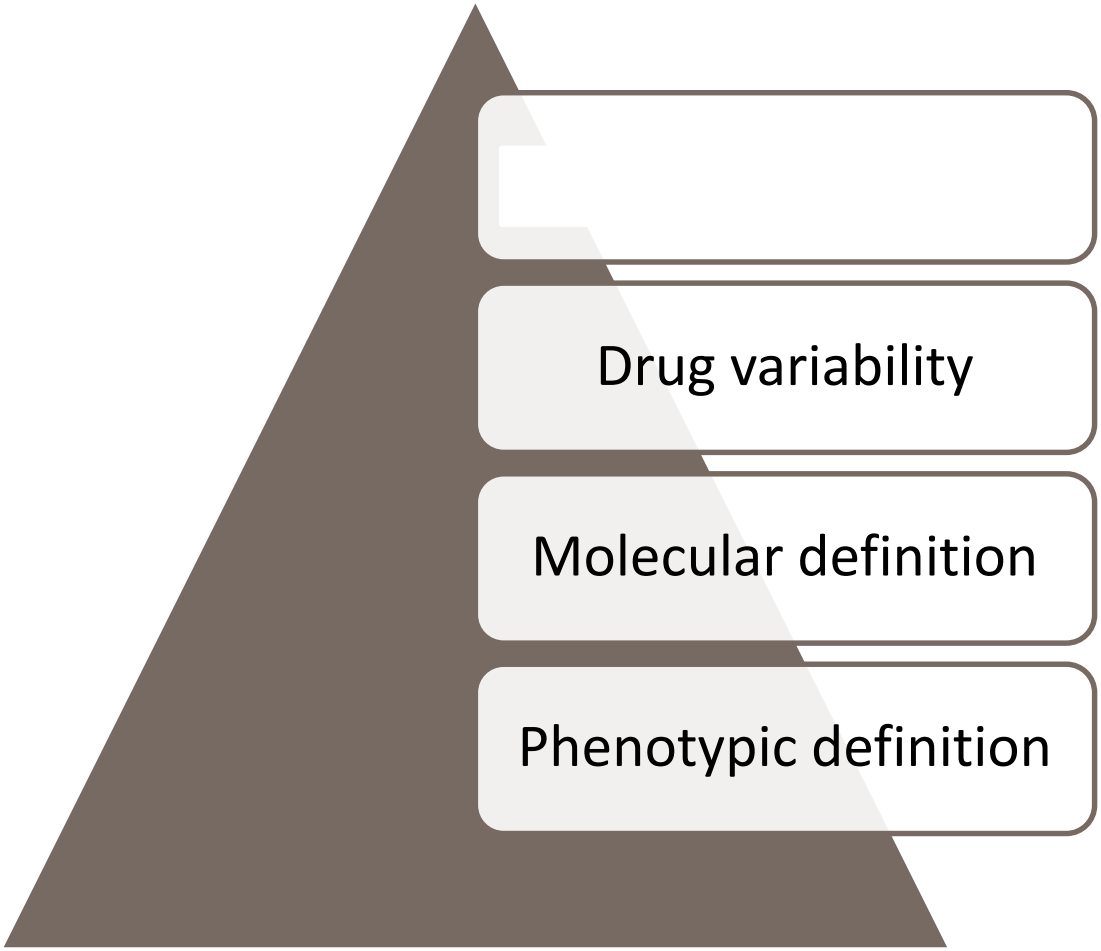
A Modern Concept of Personalised Medicine



Disease stratification

Current standard

A Modern Concept of Personalised Medicine

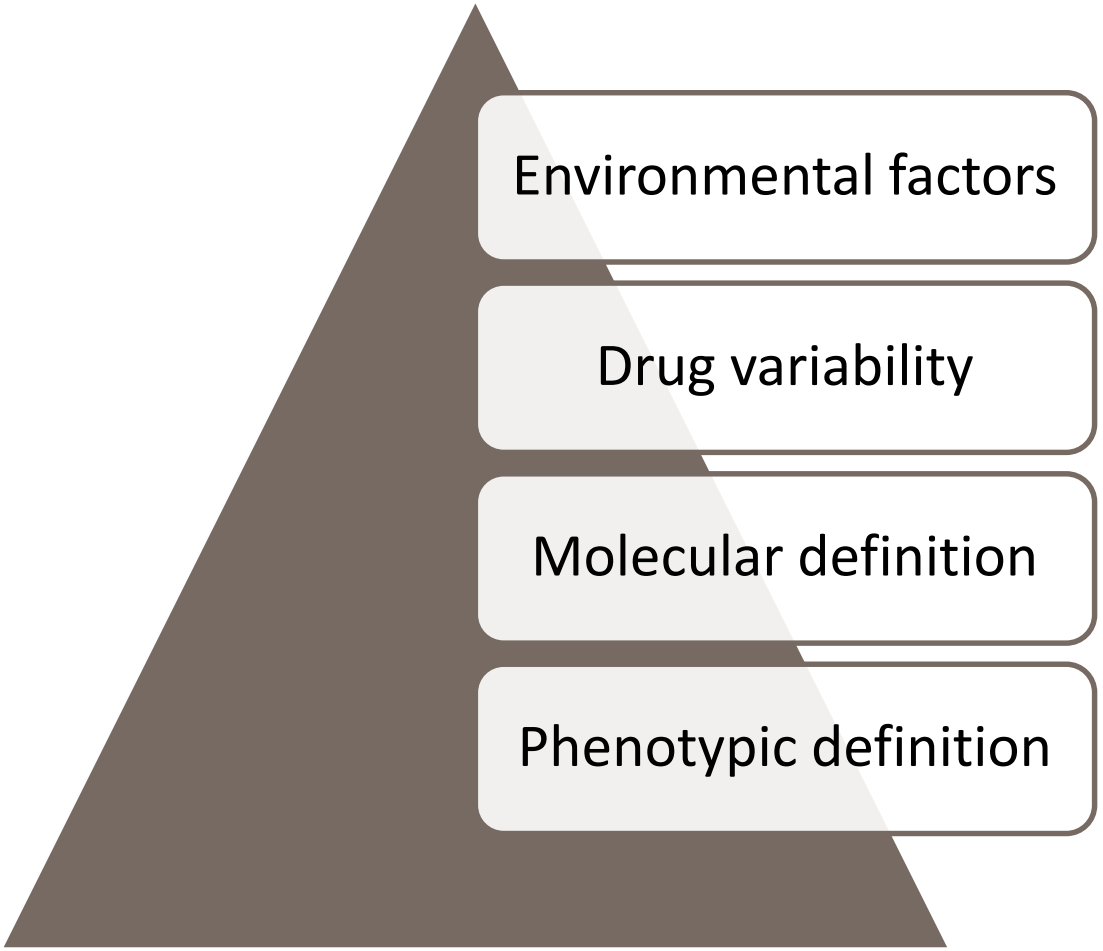


Pharmacogenomics

Disease stratification

Current standard

A Modern Concept of Personalised Medicine



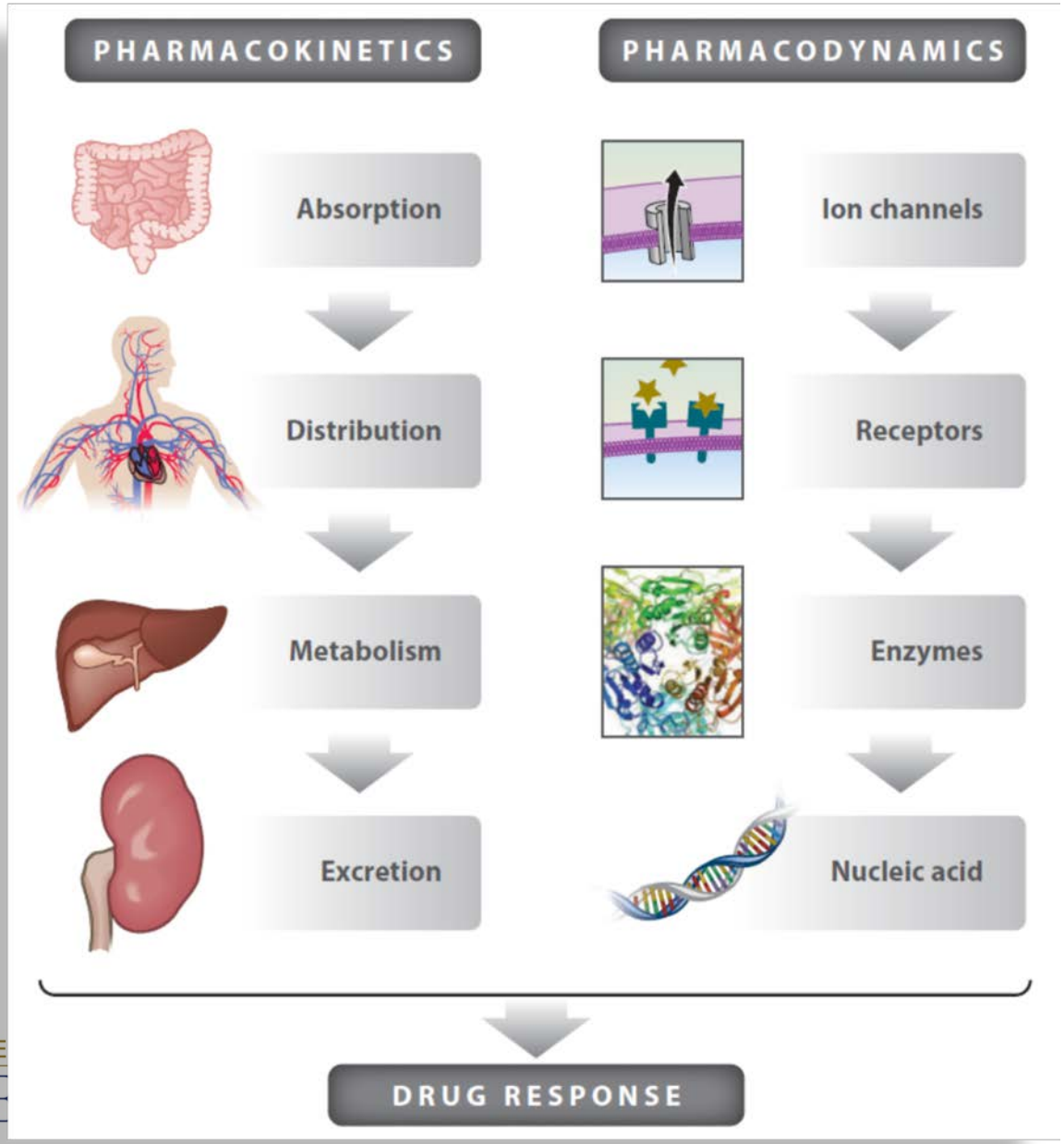
Personalised Medicine

Pharmacogenomics

Disease stratification

Current standard

Pharmacogenomic Variation in Drug Response



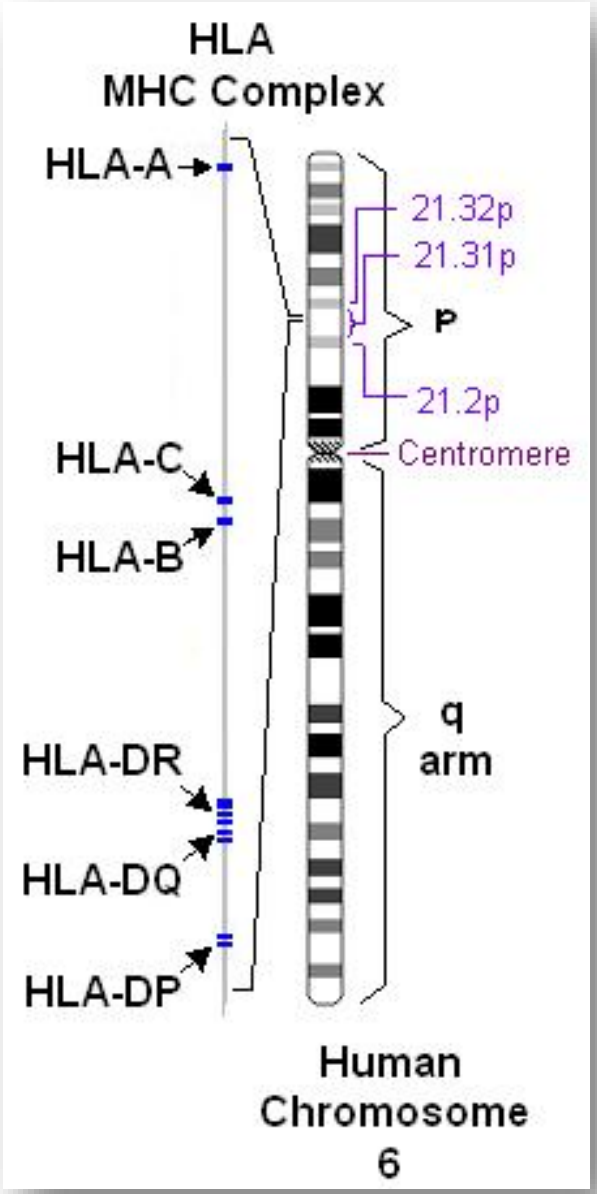
Using Human Genomic Variation for Individualisation of Drug Treatment

When it works……

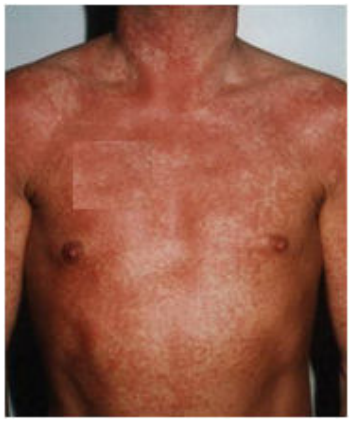
UNIVERSITY OF LIVERPOOL
THE WOLFSON CENTRE FOR PERSONALISED MEDICINE
MRC Centre for Drug Safety Science

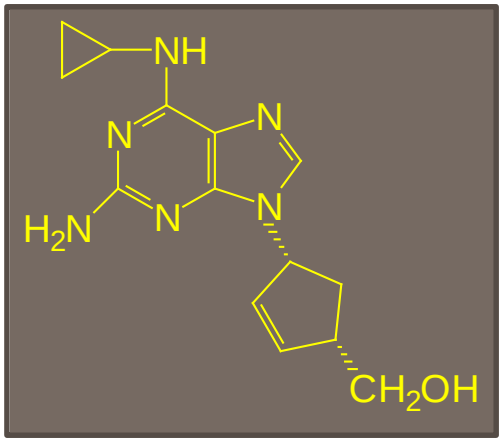
Human Leucocyte Antigens (HLA)

- On short arm of chromosome 6
- Involved in the pathogenesis of immune-mediated adverse drug reactions
- Since 2001, 23 different HLA associations have been reported with ADRs affecting skin and liver

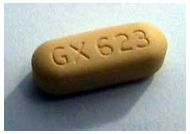


Technology-Based Reduction in the Burden of ADRs: The Case of Abacavir Hypersensitivity

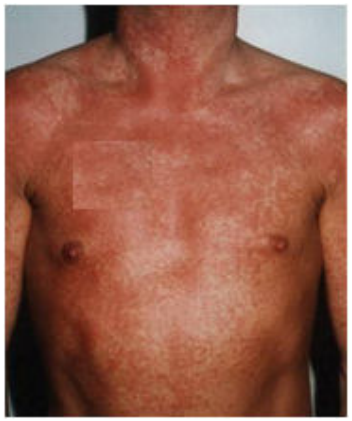


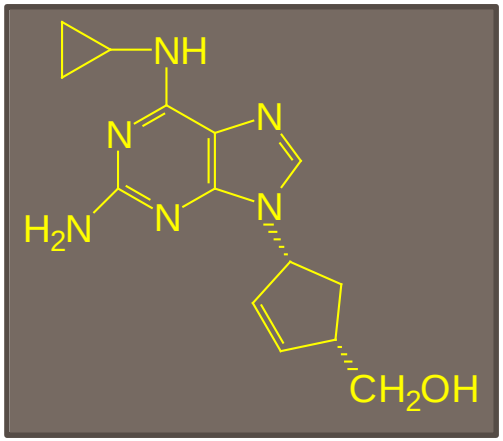


Clinical phenotype



Technology-Based Reduction in the Burden of ADRs: The Case of Abacavir Hypersensitivity

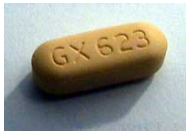




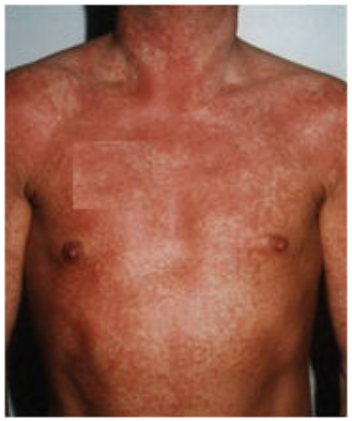
Clinical genotype

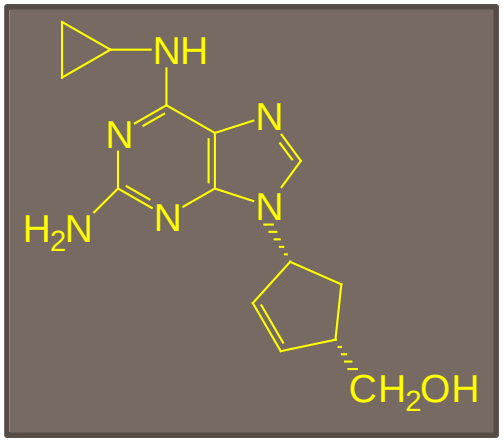
Association with HLA-B*5701

Clinical phenotype



Technology-Based Reduction in the Burden of ADRs: The Case of Abacavir Hypersensitivity

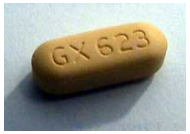




Clinical genotype

Association with HLA-B*5701

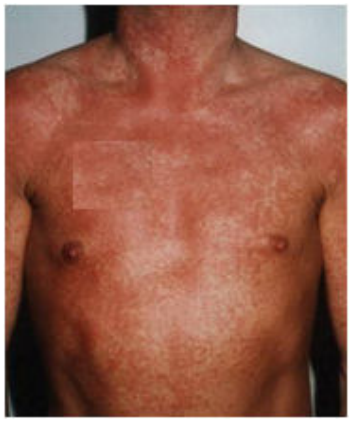
Clinical phenotype

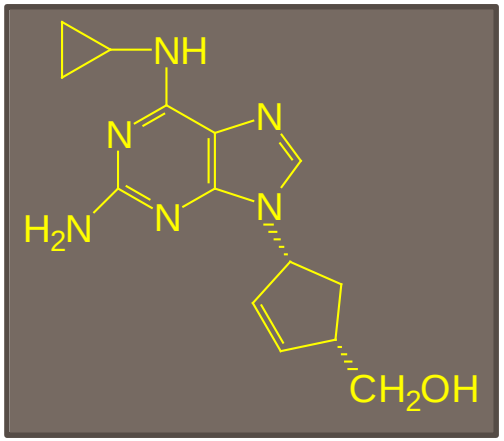


Cost-effectiveness analysis of HLA *B*5701* genotyping in preventing abacavir hypersensitivity

Dyfrig A. Hughes[a], F. Javier Vilar[b], Charlotte C. Ward[a], Ana Alfirevic[a], B. Kevin Park[a] and Munir Pirmohamed[a]

Technology-Based Reduction in the Burden of ADRs: The Case of Abacavir Hypersensitivity





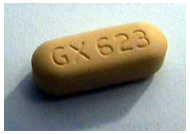
Clinical genotype

Association with HLA-B*5701

Cost-effectiveness analysis of HLA *B*5701* genotyping in preventing abacavir hypersensitivity

Dyfrig A. Hughes[a], F. Javier Vilar[b], Charlotte C. Ward[a], Ana Alfirevic[a], B. Kevin Park[a] and Munir Pirmohamed[a]

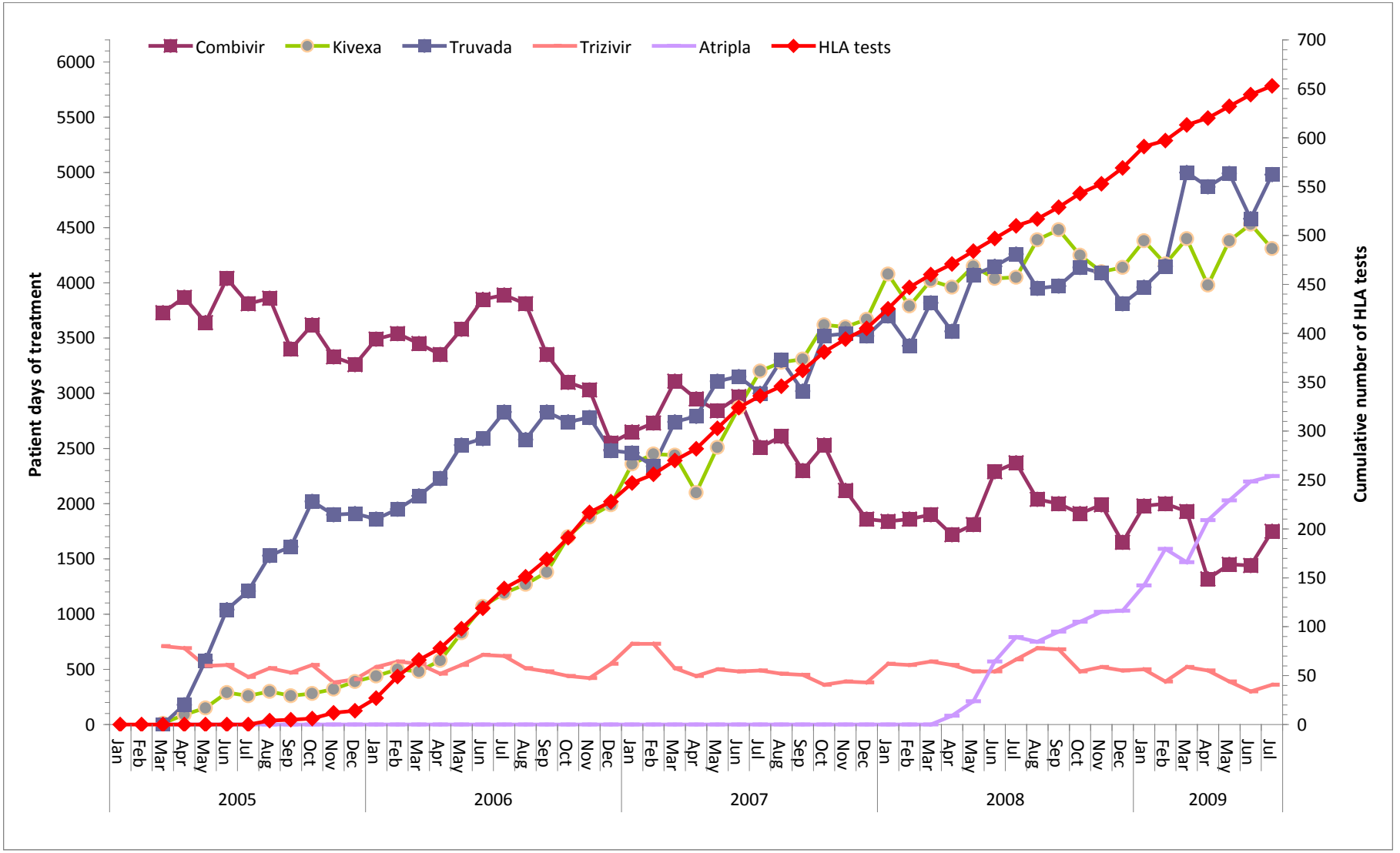
Clinical phenotype



Incidence before and after testing for HLA-B*5701

Country	Pre testing	Post testing	Reference
Australia	7%	<1%	Rauch et al, 2006
France	12%	0%	Zucman et al, 2007
UK (London)	7.8%	2%	Waters et al, 2007

Effect of Pharmacogenetics on Drug Usage



UNIVERSITY OF LIVERPOOL

THE WOLFSON CENTRE FOR PERSONALISED MEDICINE

Data courtesy of Prof Saye Khoo

MRC Centre for Drug Safety Science

Change in Peptide Repertoire

Immune self-reactivity triggered by drug-modified HLA-peptide repertoire

Patricia T. Illing[1,2], Julian P. Vivian[3], Nadine L. Dudek[2], Lyudmila Kostenko[1], Zhenjun Chen[1], Mandvi Bharadwaj[1], John J. Miles[4,5], Lars Kjer-Nielsen[1], Stephanie Gras[3], Nicholas A. Williamson[2], Scott R. Burrows[4], Anthony W. Purcell[2]*, Jamie Rossjohn[3,5]* & James McCluskey[1,6]*

Drug hypersensitivity caused by alteration of the MHC-presented self-peptide repertoire

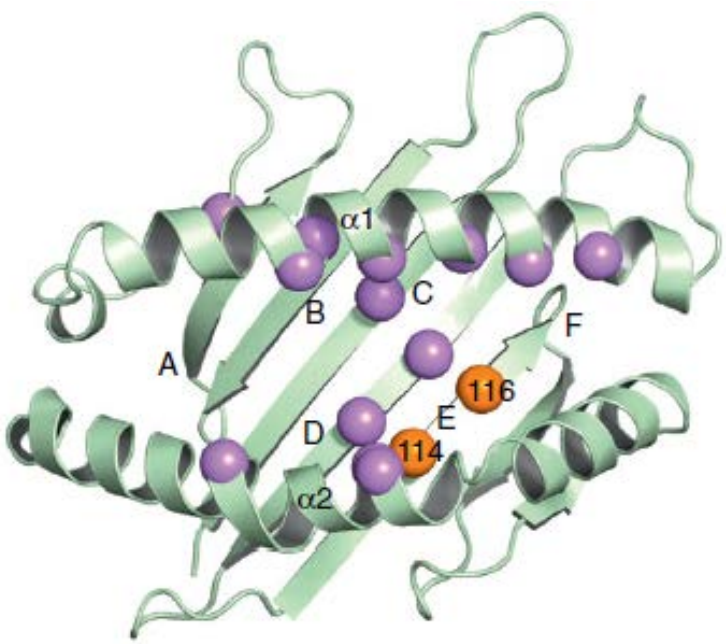
David A. Ostrov[a], Barry J. Grant[b], Yuri A. Pompeu[c], John Sidney[d], Mikkel Harndahl[e], Scott Southwood[d], Carla Oseroff[d], Shun Lu[a], Jean Jakoncic[f], Cesar Augusto F. de Oliveira[g], Lun Yang[h], Hu Mei[h], Leming Shi[h], Jeffrey Shabanowitz[i], A. Michelle English[i], Amanda Wriston[i], Andrew Lucas[j], Elizabeth Phillips[j], Simon Mallal[j], Howard M. Grey[d,1], Alessandro Sette[d], Donald F. Hunt[i], Soren Buus[e], and Bjoern Peters[d,1]

Abacavir induces loading of novel self-peptides into HLA-B*57:01: an autoimmune model for HLA-associated drug hypersensitivity

Michael A. Norcross[a], Shen Luo[a], Li Lu[a], Michael T. Boyne[b], Mary Gomarteli[c], Aaron D. Rennels[c], Janet Woodcock[d], David H. Margulies[e], Curtis McMurtrey[f], Stephen Vernon[f], William H. Hildebrand[f] and Rico Buchli[c]

MRC | Centre for Drug Safety Science

HLA-B*57:01 and Abacavir Hypersensitivity



- Peptides from untreated cells standard peptide profile
- ABC treated cells show novel self-peptides (20-25%) with Ile/Leu occupying C-terminal anchor ptotein
- No change in peptide profile with closely related allotypes

Illing et al, 2013, Curr Opin Immunol

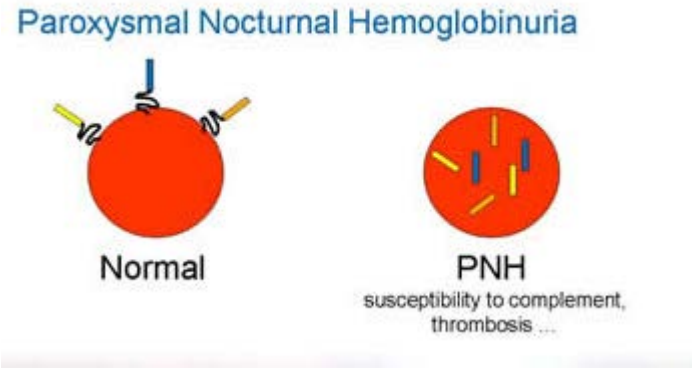
Using Human Genomic Variation for Individualisation of Drug Treatment

When it makes sense….

UNIVERSITY OF LIVERPOOL
THE WOLFSON CENTRE FOR PERSONALISED MEDICINE
MRC Centre for Drug Safety Science

Genetic Variants in C5 and Poor Response to Eculizumab

N Engl J Med 2014;370:632-9.

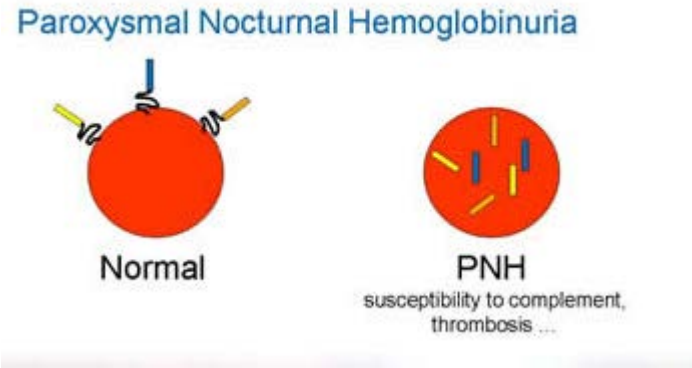


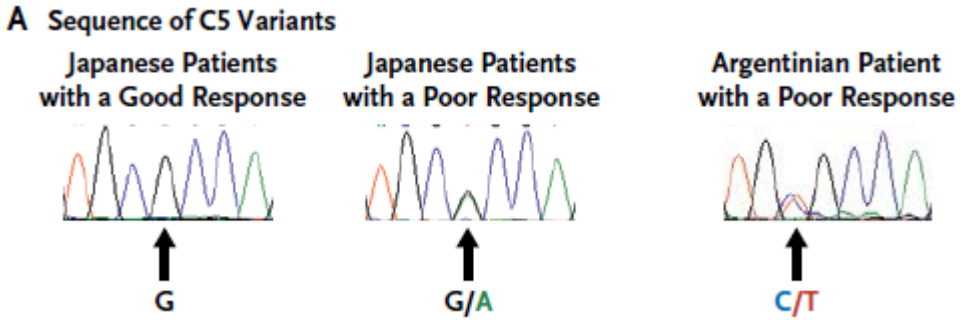
Somatic mutation leads to deficiency of GPI anchored proteins (CD55, CD59)
Susceptible to C5 mediated haemolysis

- Eculizumab – humanised monoclonal antibody binds to C5 inhibiting its activation
- 3% of patients have a poor response
- Missense mutation identified in C5 in these patients
- Eculizumab able to block C5-mediated hemolysis in nonmutant RBCs but not those carrying variant

Genetic Variants in C5 and Poor Response to Eculizumab

N Engl J Med 2014;370:632-9.





- Eculizumab – humanised monoclonal antibody binds to C5 inhibiting its activation
- 3% of patients have a poor response
- Missense mutation identified in C5 in these patients
- Eculizumab able to block C5-mediated hemolysis in nonmutant RBCs but not those carrying variant

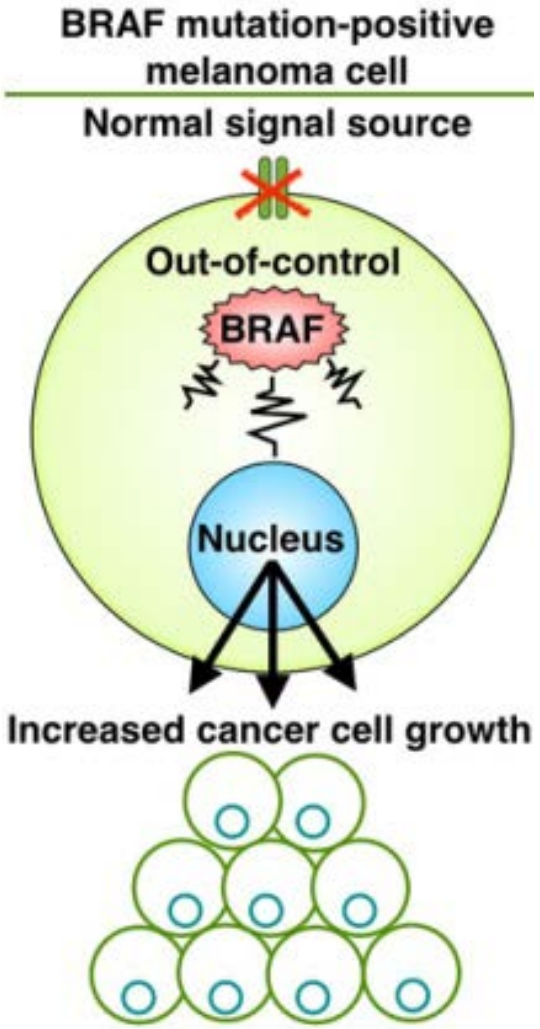
Using Human Genomic Variation for Individualisation of Drug Treatment

More often than not, it is difficult……

UNIVERSITY OF LIVERPOOL
THE WOLFSON CENTRE FOR PERSONALISED MEDICINE
MRC Centre for Drug Safety Science

Sources of Variation

- Increasing number of examples of pharmacodynamic genetic variation which are being used in clinical practice
- Pharmacokinetic variation has been more difficult to implement
  - The most successful has been TPMT and bone marrow suppression with 6MP and azathioprine
- PK and PD factors work together to affect response – accounting for both can improve prediction
  - Warfarin dose prediction



Warfarin

- Number of users UK:

  600,000
- Dose (mg) range per day:

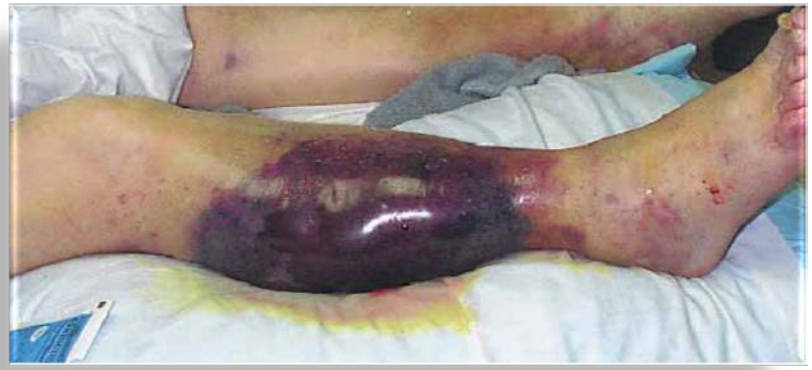
  0.5-20
- Fold variability in dose:

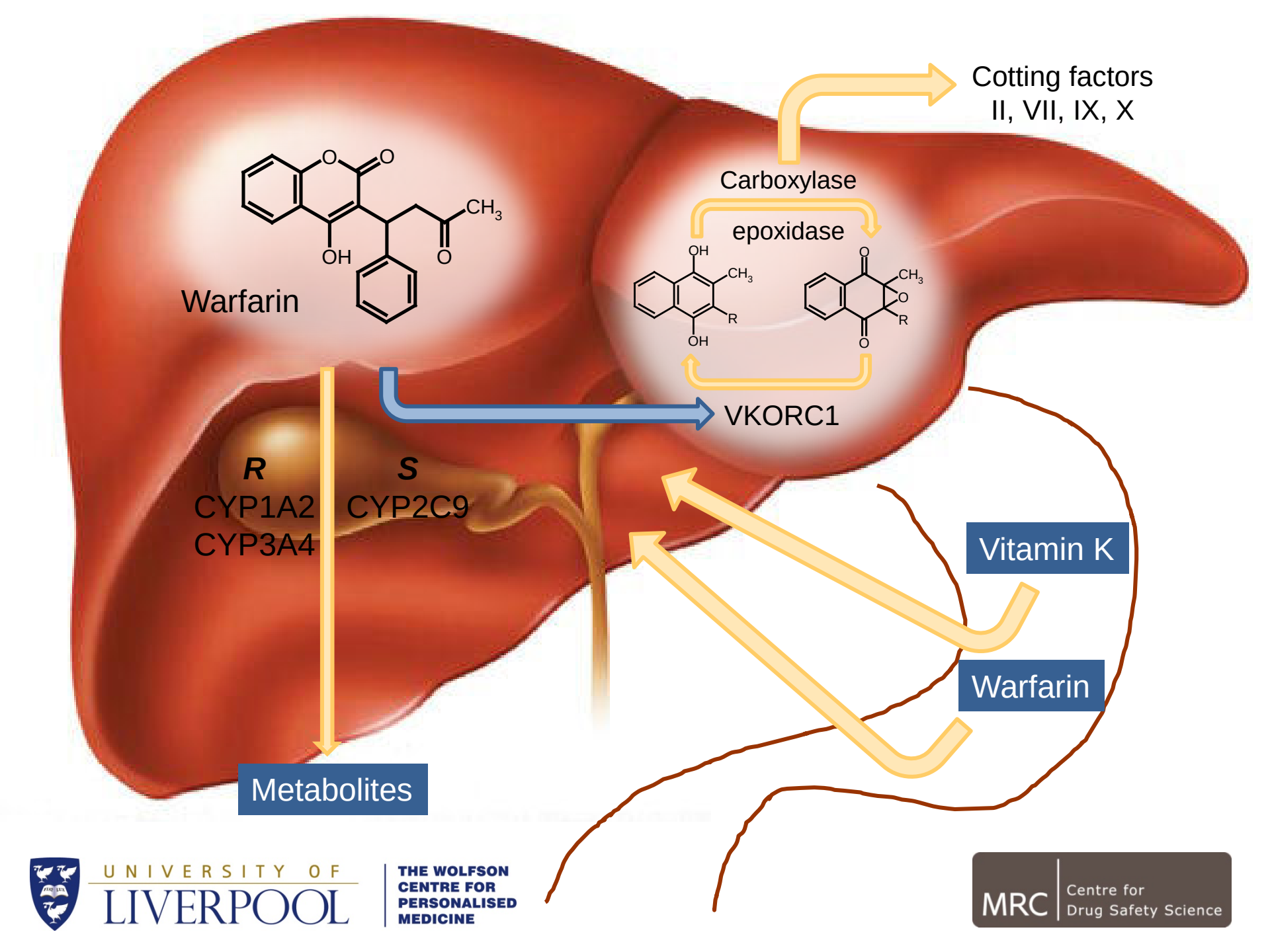
  40
- Major bleeding rate per 100-person years:

  2.6
- Ranking in ADR list:

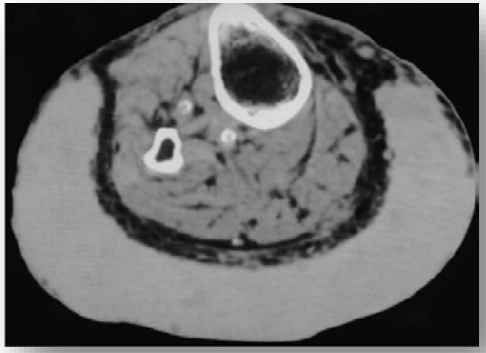
  3

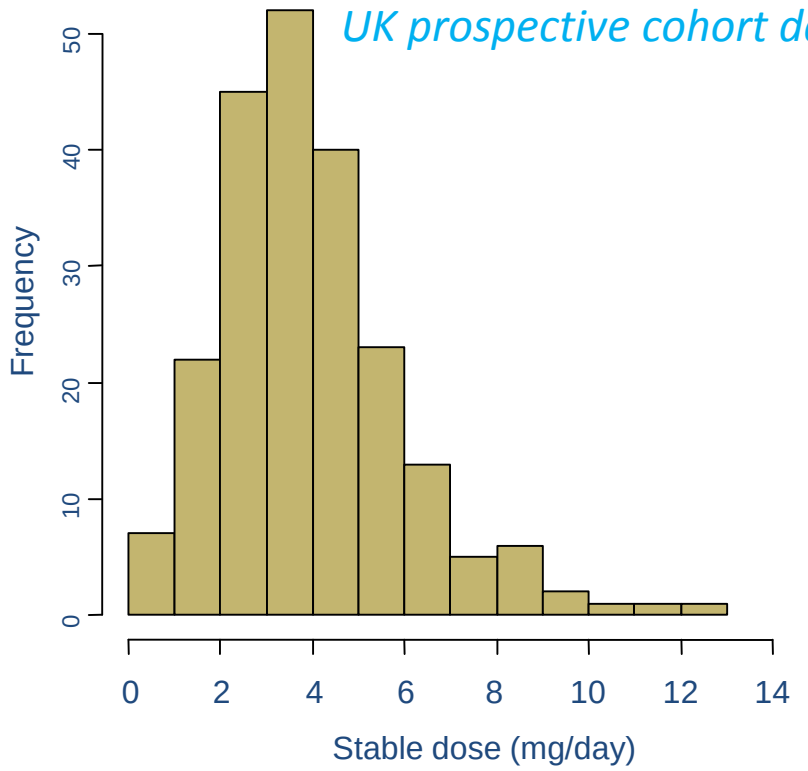
Approved for human use in 1954




Cotting factors
II, VII, IX, X
Carboxylase
epoxidase
Warfarin
VKORC1
R
CYP1A2
CYP3A4
S
CYP2C9
Vitamin K
Warfarin
Metabolites

Variation in Dose Requirements



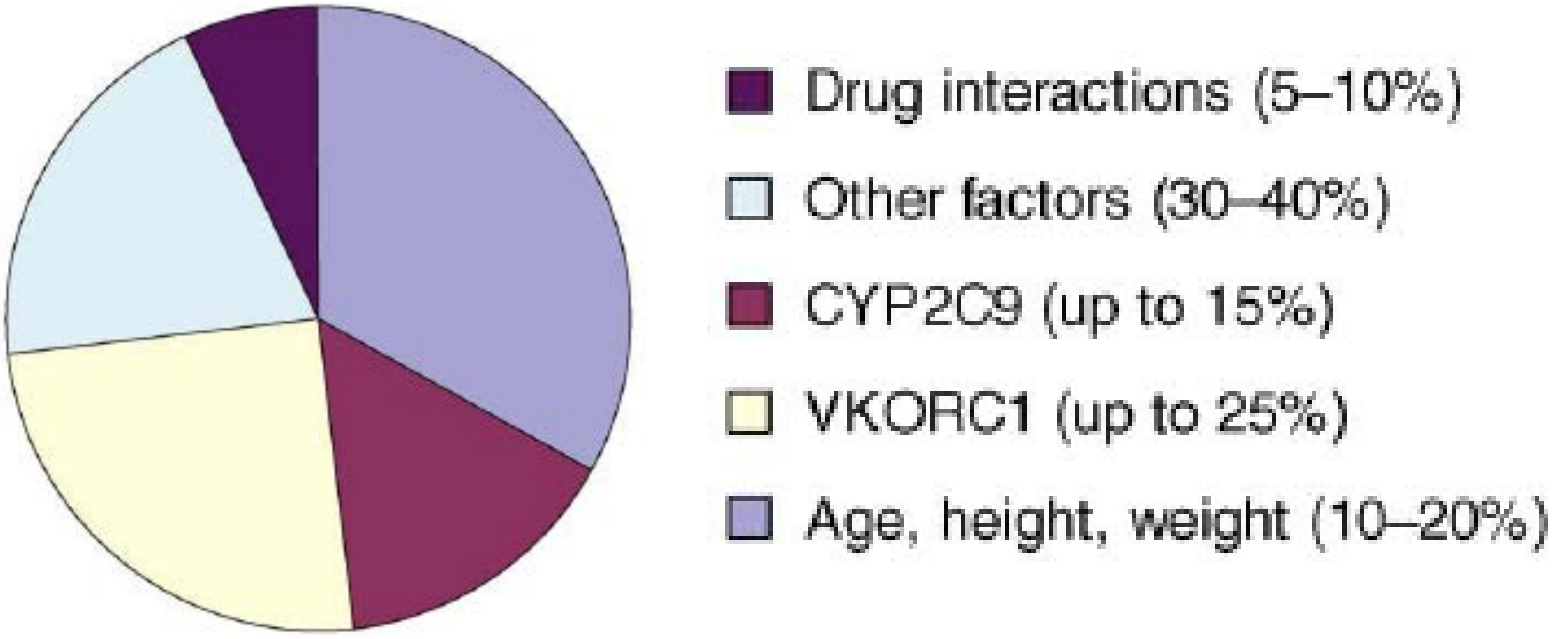


INR	Incidence Rate
<2	4.11
2.1-3.0	3.78
3.1-4.0	15.78
>4.1	99.26

Hylek et al, 2007

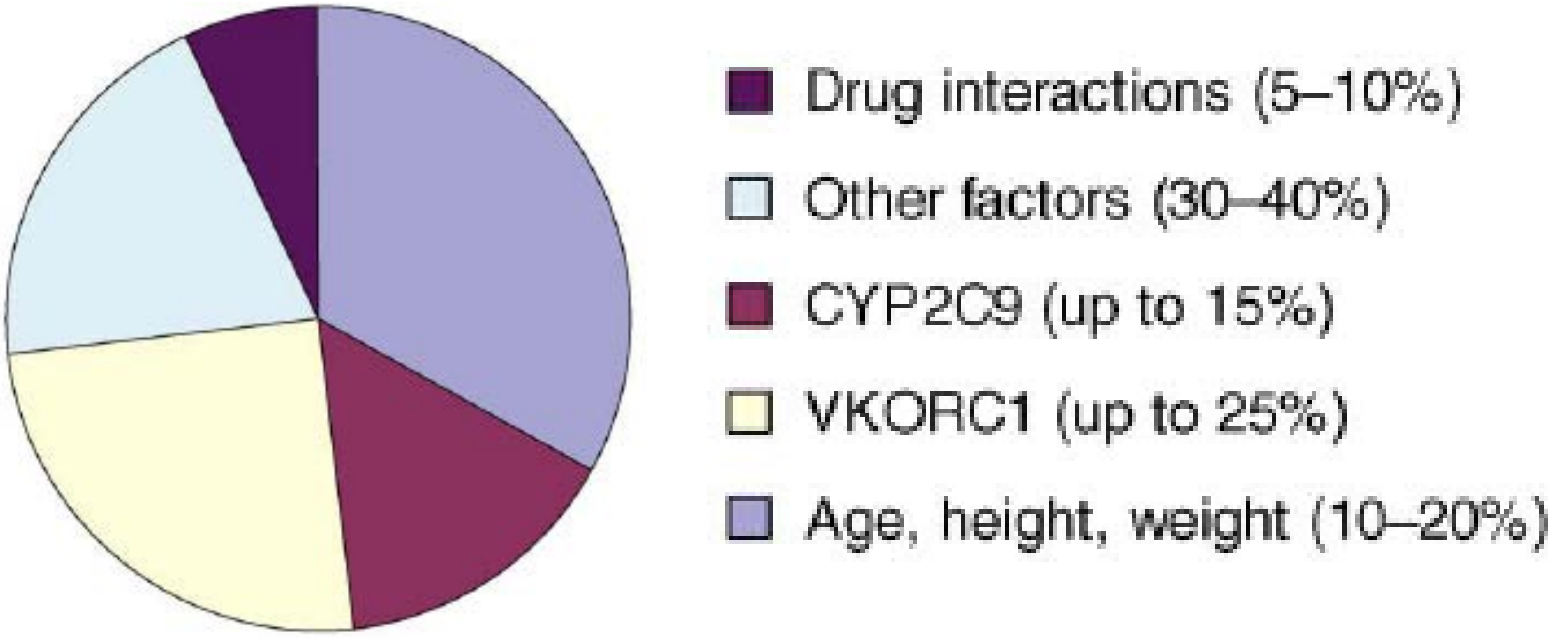
Only 50% of bleeds occur with INR > 2.5;
50% occur at levels below this

Determinants of Anticoagulation Control



McLeod and Jonas, 2009

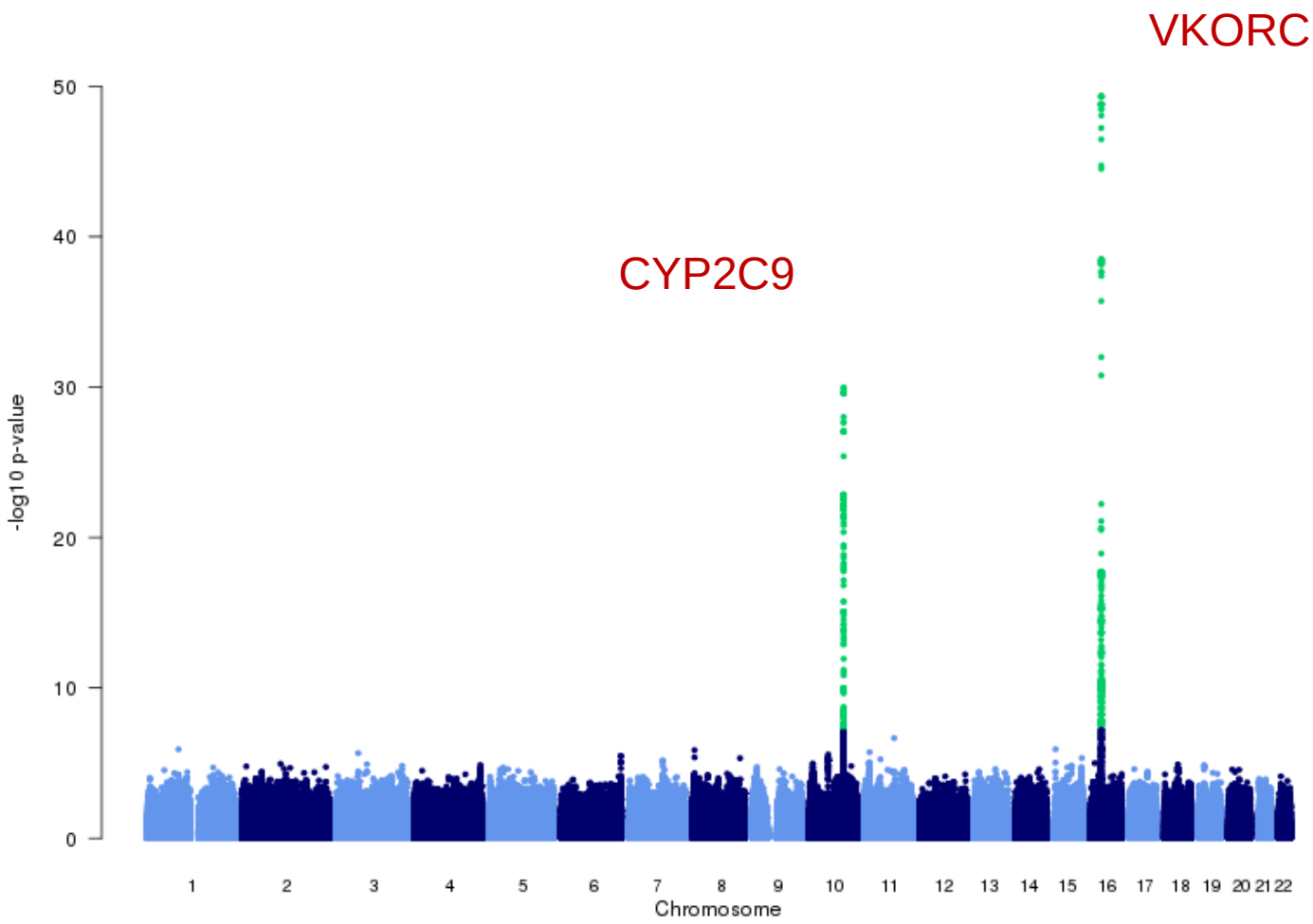
Determinants of Anticoagulation Control



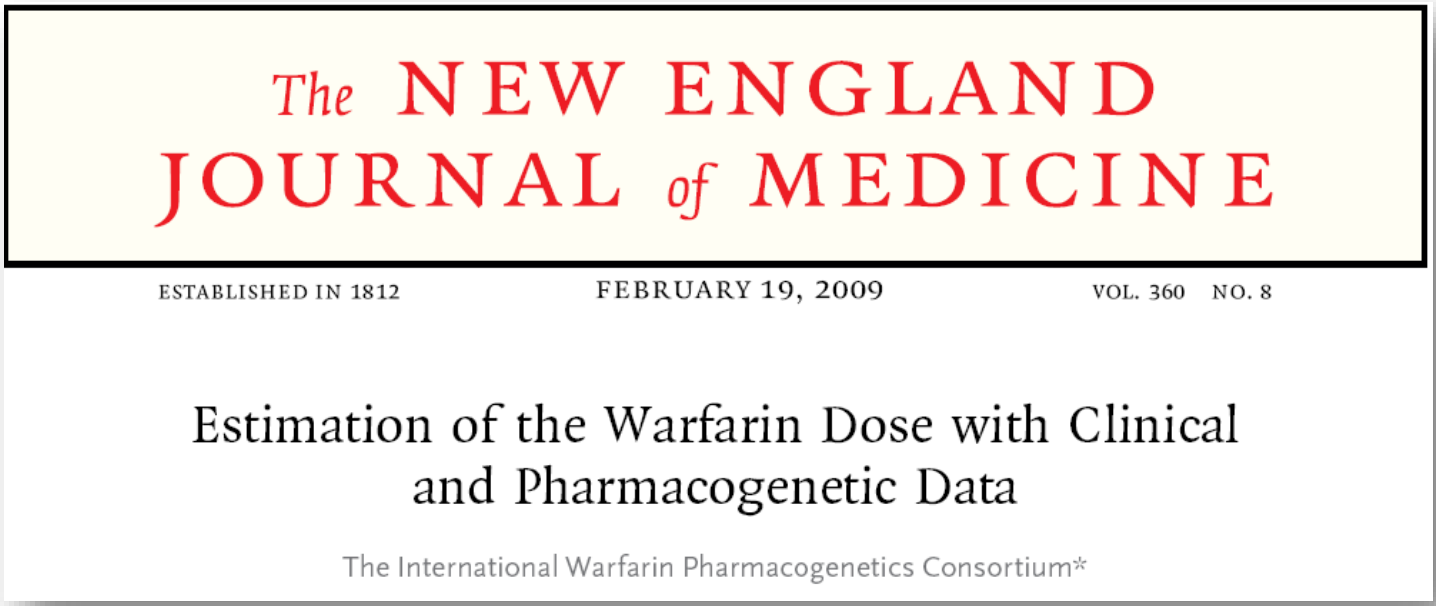
McLeod and Jonas, 2009

One of the most highly replicated genotype-phenotype associations

GWAS Warfarin Mean Weekly Dose (UK Prospective Cohort; n=714)



International Warfarin Pharmacogenetics Consortium (IWPC)



The NEW ENGLAND JOURNAL of MEDICINE

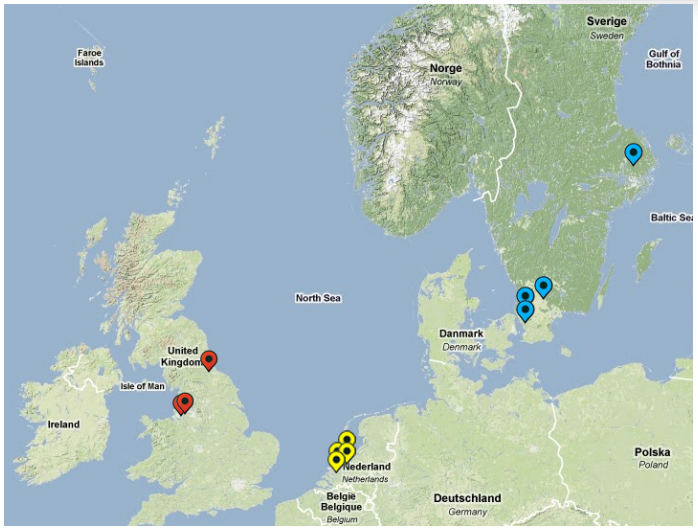
ESTABLISHED IN 1812 FEBRUARY 19, 2009 VOL. 360 NO. 8

Estimation of the Warfarin Dose with Clinical and Pharmacogenetic Data

The International Warfarin Pharmacogenetics Consortium*

Pharmacogenetic-Based Dosing: Warfarin Randomised Controlled Trial

- FP7 sponsored EU trials
- 454 patients
  - 226 in genotype arm
  - 228 in standard care arm
- Point of Care test for genotyping



European Union Pharmacogenetics of AntiCoagulant Therapy

MRC Centre for Drug Safety Science

A Randomized Trial of Genotype-Guided Dosing of Warfarin

Munir Pirmohamed, Ph.D., F.R.C.P., Girvan Burnside, Ph.D., Niclas Eriksson, Ph.D., Andrea L. Jorgensen, Ph.D., Cheng Hock Toh, M.D., Toby Nicholson, F.R.C.Path., Patrick Kesteven, M.D., Christina Christersson, M.D., Ph.D., Bengt Wahlström, M.D., Christina Stafberg, M.D., J. Eunice Zhang, Ph.D., Julian B. Leathart, M.Phil., Hugo Kohnke, M.Sc., Anke H. Maitland-van der Zee, Pharm.D., Ph.D., Paula R. Williamson, Ph.D., Ann K. Daly, Ph.D., Peter Avery, Ph.D., Farhad Kamali, Ph.D., and Mia Wadelius, M.D., Ph.D., for the EU-PACT Group*

EU-PACT

N Engl J Med 2013;369:2294-303.

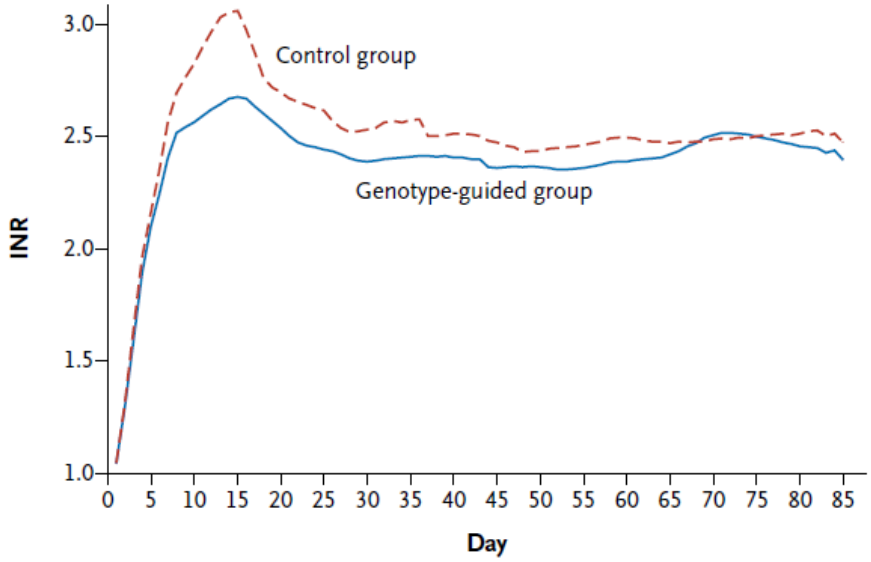
Genotyped arm %TTR	Standard dosing (control) arm %TTR	Adjusted Difference	P value
ITT ANALYSIS (n= 211 vs 216)			
67.4%	60.3%	7%	P<0.001
PER-PROTOCOL (n=166 vs 184)			
68.9%	62.3%	6.6%	P=0.001

PRIMARY OUTCOME MEASURE: Percent time within therapeutic INR range 2.0-3.0 (TTR) during 12 weeks following the initiation of warfarin therapy

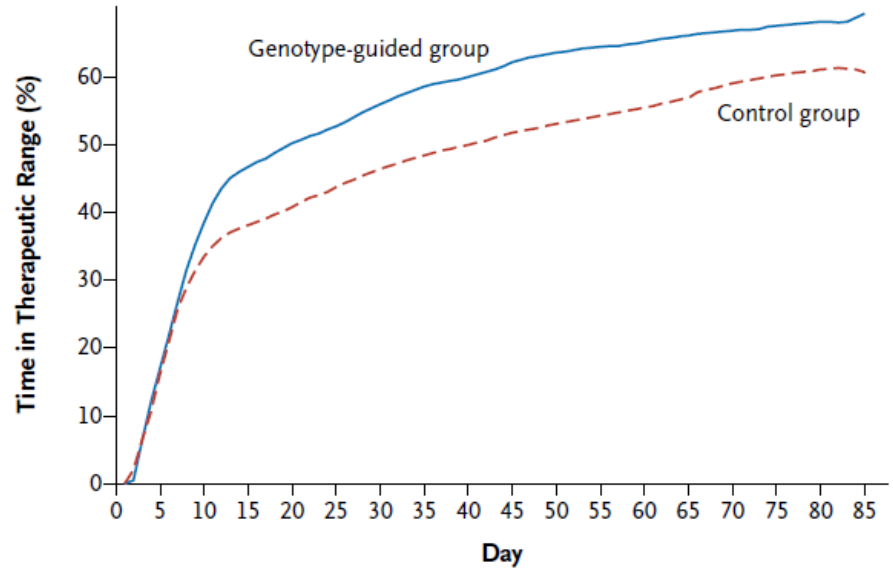
UNIVERSITY OF LIVERPOOL
THE WOLFSON CENTRE FOR PERSONALISED MEDICINE
MRC Centre for Drug Safety Science

Differences Between Genotyped-Guided Group and Control Group

International Normalized Ratio



Time in Therapeutic Range



COAG

A Pharmacogenetic versus a Clinical Algorithm for Warfarin Dosing

Stephen E. Kimmel, M.D., Benjamin French, Ph.D., Scott E. Kasner, M.D., Julie A. Johnson, Pharm.D., Jeffrey L. Anderson, M.D., Brian F. Gage, M.D., Yves D. Rosenberg, M.D., Charles S. Eby, M.D., Ph.D., Rosemary A. Madigan, R.N., M.P.H., Robert B. McBane, M.D., Sherif Z. Abdel-Rahman, Ph.D., Scott M. Stevens, M.D., Steven Yale, M.D., Emile R. Mohler III, M.D., Margaret C. Fang, M.D., Vinay Shah, M.D., Richard B. Horenstein, M.D., Nita A. Limdi, Pharm.D., Ph.D., James A.S. Muldowney III, M.D., Jaspal Gujral, M.B., B.S., Patrice Delafontaine, M.D., Robert J. Desnick, M.D., Ph.D., Thomas L. Ortel, M.D., Ph.D., Henny H. Billett, M.D., Robert C. Pendleton, M.D., Nancy L. Geller, Ph.D., Jonathan L. Halperin, M.D., Samuel Z. Goldhaber, M.D., Michael D. Caldwell, M.D., Ph.D., Robert M. Califf, M.D., and Jonas H. Ellenberg, Ph.D., for the COAG Investigators*

No difference between genotyped and control arms

N Engl J Med 2013;369:2283-93.

genomeweb

Two Conflicting Prospective, RCTs on Warfarin PGx Provide No Definitive Guidance to Physicians

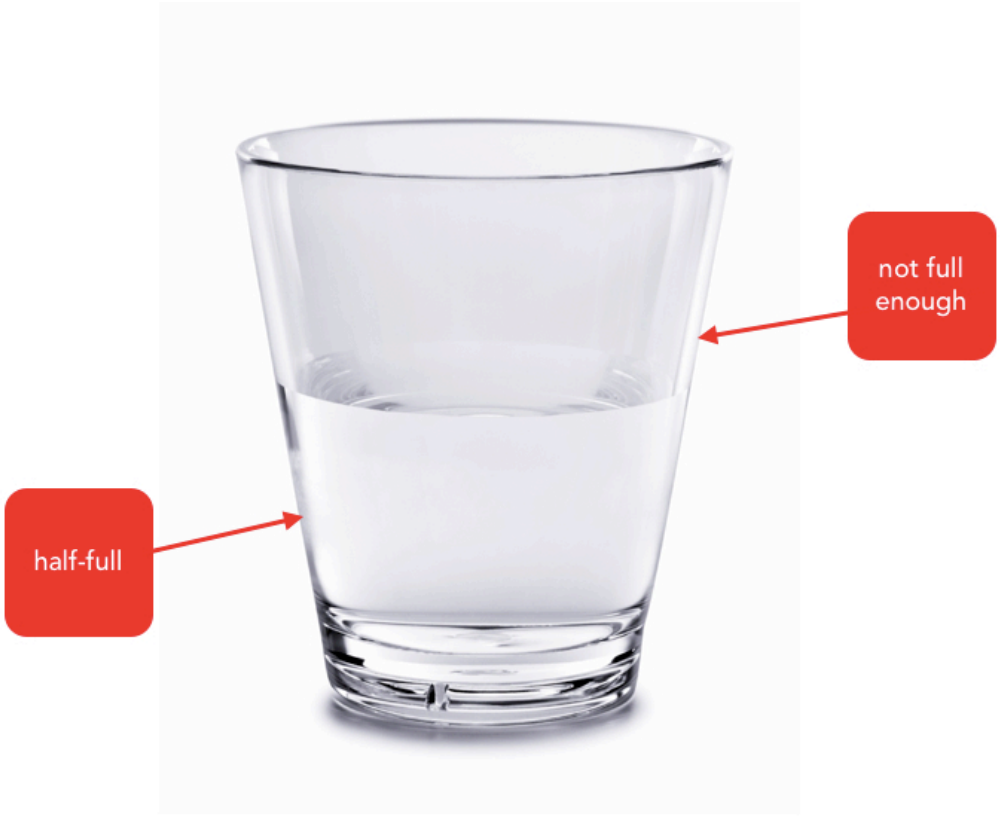
Nov 23, 2013

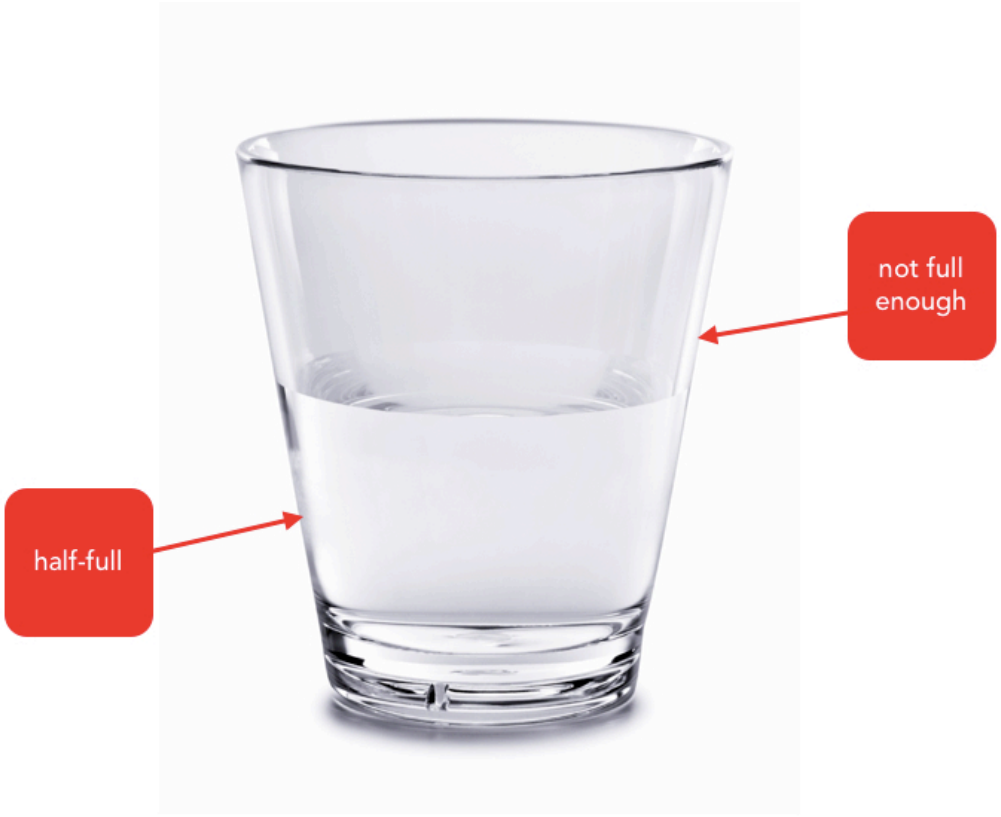
Do Pharmacogenetics Have a Role in the Dosing of Vitamin K Antagonists?

Bruce Furie, M.D.

DOI: 10.1056/NEJMe1313682

"The conclusions of the three studies are similar"


not full enough
half-full



How can we explain the differences?

Dosing Algorithms

EU-PACT

- Day 1-3: Loading dose algorithm
- Day 4/5: Dose revision algorithm
- Up to 3 months: AC clinics (computerised dosing)

COAG

- Day 1-3: Maintenance dose algorithm
- Day 4/5: Dose revision algorithm
- Up to 1 month: Protocol driven

Dosing Algorithms

EU-PACT

- Day 1-3: Loading dose algorithm
- Day 4/5: Dose revision algorithm
- Up to 3 months: AC clinics (computerised dosing)

COAG

- Day 1-3: Maintenance dose algorithm
- Day 4/5: Dose revision algorithm
- Up to 1 month: Protocol driven

- S-warfarin elimination half-life: 18-35 hours
- Time to steady state: 90-175 hours
- Time to steady state shortened by loading dose
- Dose revision algorithm on day 4 dependent on INR
- What proportion of patients will have had a change in INR by day 4?

Dosing Algorithm – Day 1

- **COAG** algorithm did not include CYP2C9 on day 1 ("dosing patients with CYP2C9 *2 or *3 variants at lower doses during the first day of therapy may not lead to improvement in AC and could lead to worse anticoagulation"). **BASED ON MAINTENANCE DOSE**.

Dosing Algorithm – Day 1

- **COAG** algorithm did not include CYP2C9 on day 1 ("dosing patients with CYP2C9 *2 or *3 variants at lower doses during the first day of therapy may not lead to improvement in AC and could lead to worse anticoagulation"). **BASED ON MAINTENANCE DOSE**.

Genetic and environmental factors determining clinical outcomes and cost of warfarin therapy: a prospective study

Andrea L. Jorgensen[a], Sameh Al-Zubiedi[a], Jieying Eunice Zhang[a], Andrew Keniry[c], Anita Hanson[a,b], Dyfrig A. Hughes[d], Diane van Eker[a,b], Lisa Stevens[a,b], Karen Hawkins[a,b], Cheng H. Toh[a,b], Farhad Kamali[e], Ann K. Daly[e], David Fitzmaurice[f], Alison Coffey[c], Paula R. Williamson[a], Brian Kevin Park[a], Panos Deloukas[c] and Munir Pirmohamed[a,b]

Pharmacogenetics and Genomics 2009, 19:800–812

SNPs in CYP2C9, but not VKORC1, associated with time to stable warfarin dose, time to therapeutic INR and INR >4 at end of week 1

Ethnic Heterogeneity

- COAG was more heterogeneous (67% white, 27% Black, 6% Hispanic) than EU-PACT (97% Caucasian)
- Blacks did worse in genotype arm than in clinical group (-8% difference)

Allele	Location	Frequency		
		European Caucasians	*US Hispanics*	*African–Americans*
*CYP2C9*2*	Exon 3	0.10	0.07	0.02
*CYP2C9*3*	Exon 7	0.06	0.05	0.01
*CYP2C9*5*	Exon 7	<0.01	<0.01	0.01
*CYP2C9*6*	Exon 5	<0.01	<0.01	0.01
*CYP2C9*8*	Exon 3	<0.01	<0.01	0.06
*CYP2C9*11*	Exon 7	<0.01	<0.01	0.04
CYP2C9 rs7089580	Intronic	0.24	0.11	0.23
VKORC1 -1639A	5-UTR	0.40	0.46	0.11
VKORC1 rs61162043	5-UTR	Unknown	Unknown	0.47

Control Arms in the Two Trials

- EU-PACT: fixed dosing which reflects current clinical care
- COAG: clinical algorithm (includes all factors apart from genetics)
- Interpreted as genetics does not add anything over and above clinical factors – some have advocated use of clinical algorithm
- Clinical algorithm has never been tested in a RCT

Control Arms in the Two Trials

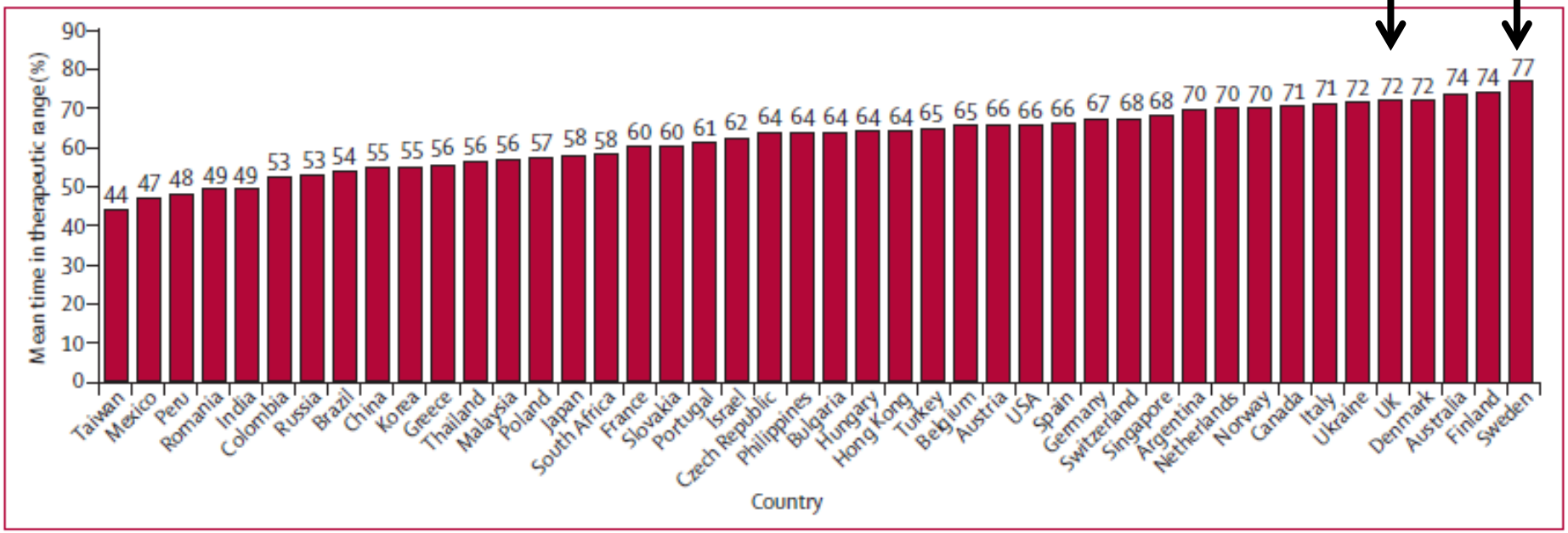
- EU-PACT: fixed dosing which reflects current clinical care
- COAG: clinical algorithm (includes all factors apart from genetics)
- Interpreted as genetics does not add anything over and above clinical factors – some have advocated use of clinical algorithm
- Clinical algorithm has never been tested in a RCT

Trial	Time	Genotyped arm %TTR	Control arm %TTR
COAG	4 weeks	45.2	45.4
EU-PACT	4 weeks	54.6	45.7
COAG	12 weeks	51	
EU-PACT	12 weeks	67.4	60.3

Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial

Lancet 2010; 376: 975–83

Lars Wallentin, Salim Yusuf, Michael D Ezekowitz, Marco Alings, Marcus Flather, Maria Grazia Franzosi, Prem Pais, Antonio Dans, John Eikelboom, Jonas Oldgren, Janice Pogue, Paul A Reilly, Sean Yang, Stuart J Connolly, on behalf of the RE-LY investigators



UNIVERSITY OF LIVERPOOL | THE WOLFSON CENTRE FOR PERSONALISED MEDICINE

MRC Centre for Drug Safety Science

Comparison Between COAG and EU-PACT

	COAG			EUPACT		
Total no of variants	Genotype guided	Clinically guided	Total	Genotyped	Non-genotyped	Total
0	204 (40%)	189 (38%)	**393 (39%)**	63 (28%)	57 (27%)	**120 (27%)**
1	178 (35%)	186 (37%)	**364 (36%)**	113 (50%)	115 (54%)	**228 (52%)**
>1	128 (25%)	125 (25%)	253 (25%)	50 (22%)	40 (19%)	90 (21%)

Higher frequency of allelic variants in EU-PACT compared to COAG, mostly in CYP2C9

EU-PACT: Effect of Number of Variants on % Time in Therapeutic Range (TTR)

Total number of variants	Genotyped arm (n=211) %TTR	Control arm (n=216) %TTR	Adjusted Difference	P value
0	61.83	59.31	2.03	0.588
1	68.56	61.83	7.38	0.005
2 or more	71.95	57.32	11.05	0.009

RELY DATA: a 10% improvement in %TTR leads to a 20% improvement in clinical outcomes

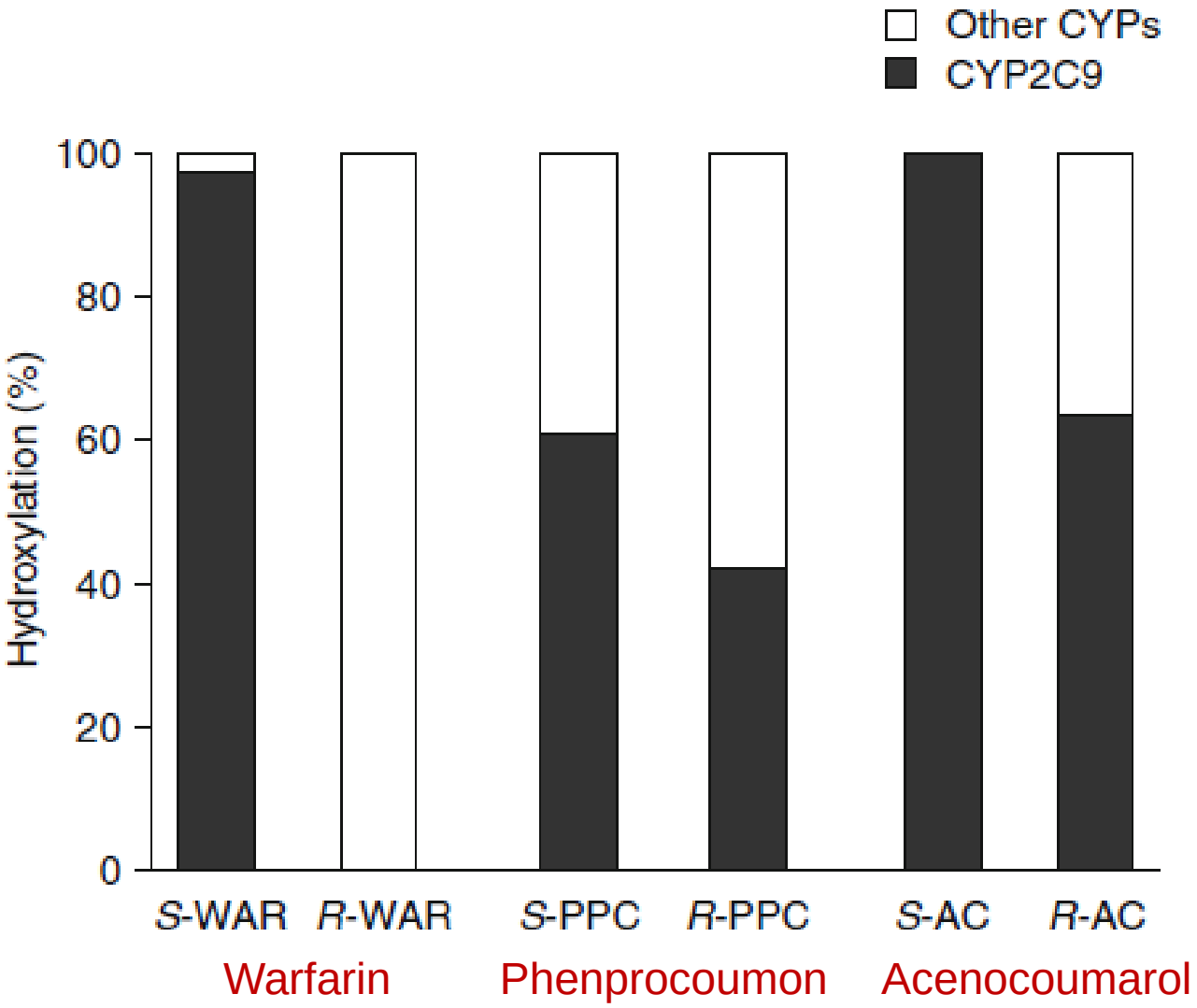
A Randomized Trial of Genotype-Guided Dosing of Acenocoumarol and Phenprocoumon

Talitha I. Verhoef, M.Sc., Georgia Ragia, Ph.D., Anthonius de Boer, M.D., Ph.D., Rita Barallon, Ph.D., Genovefa Kolovou, M.D., Ph.D., Vana Kolovou, M.Sc., Stavros Konstantinides, M.D., Ph.D., Saskia Le Cessie, Ph.D., Efstratios Maltezos, M.D., Ph.D., Felix J.M. van der Meer, M.D., Ph.D., William K. Redekop, Ph.D., Mary Remkes, M.D., Frits R. Rosendaal, M.D., Ph.D., Rianne M.F. van Schie, Ph.D., Anna Tavridou, Ph.D., Dimitrios Tziakas, M.D., Ph.D., Mia Wadelius, M.D., Ph.D., Vangelis G. Manolopoulos, Ph.D., and Anke H. Maitland-van der Zee, Pharm.D., Ph.D., for the EU-PACT Group*

DOI: 10.1056/NEJMoa1311388

- Algorithm incorporating CYP2C9 and VKORC1 genotypes
- No difference at 3 months, but %TTR was higher in genotyped arm in first 4 weeks
- Combined data from acenocoumarol (n=190) and phenprocoumon (n=83) giving total of 273 in genotype group
- Assessed individually, this would be an under-powered trial

Differences in Vitamin K antagonists



Pharmacogenetic tests: the need for a level playing field

Munir Pirmohamed and Dyfrig A. Hughes

NATURE REVIEWS | DRUG DISCOVERY VOLUME 12 | JANUARY 2013 | 3

- Evidence standards differ between non-genetic and genetic tests
- 3 examples given:
  - Drug exposure
  - Prevention of adverse drug reactions
  - Health technology assessment

Drug Exposure: Differential Evidential Standards

- Example: Aztreonam SmPC
  - "after an initial usual dose, the dosage of aztreonam should be halved in patients with estimated creatinine clearances between 10 and 30 mL/min/1.73 m^2"
- Many different examples in hepatic and renal impairment with dose instructions based on PK studies and occasionally PK-PD modelling
- No need for RCTs – in fact, would be impractical

- However, a genetic polymorphism leading to *same degree of change in drug exposure* is often ignored and/or RCT data are required for implementation

Differential Evidence Standards

- Unfamiliarity with genetic tests
- Lack of experience in interpretation
- Perceived cost of genetic testing
- Lack of availability of tests
- Poor turnaround time

Differential Evidence Standards

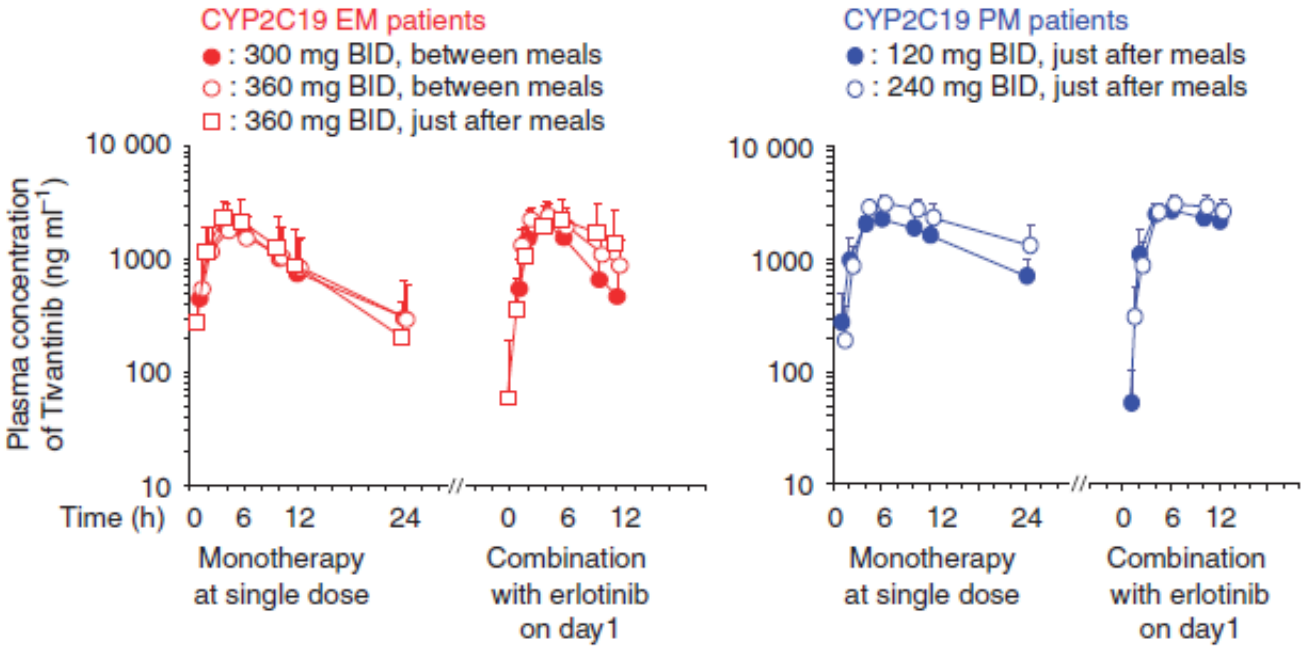
- Unfamiliarity with genetic tests
- Lack of experience in interpretation
- Perceived cost of genetic testing
- Lack of availability of tests
- Poor turnaround time

recommendations on dosing evaluation in patients with polymorphisms in known metabolic pathways

CYP2C19 genotype-based phase I studies of a c-Met inhibitor tivantinib in combination with erlotinib, in advanced/metastatic non-small cell lung cancer

N Yamamoto*,[1], H Murakami[1], H Hayashi[2], Y Fujisaka[2], T Hirashima[3], K Takeda[4], M Satouchi[5], K Miyoshi[6], S Akinaga[6], T Takahashi[1] and K Nakagawa[2]

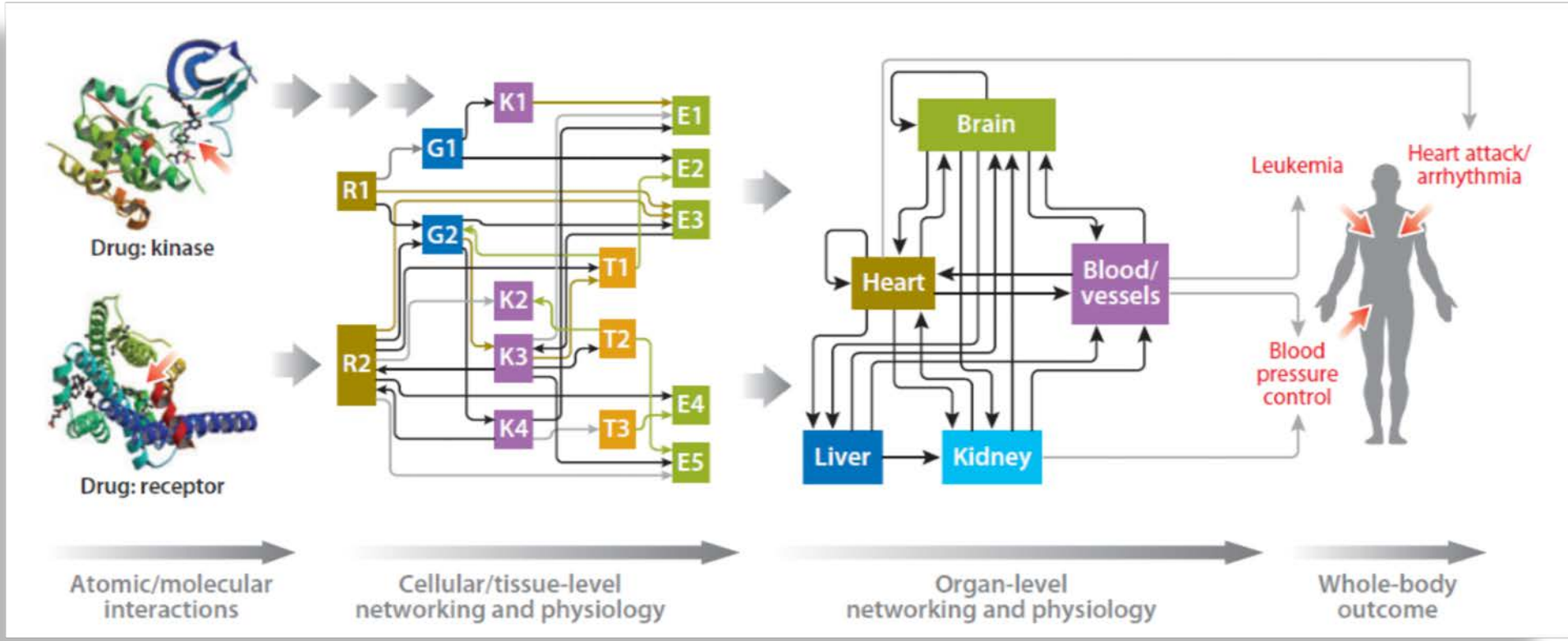
British Journal of Cancer (2013) 109, 2803–2809



Tivantinib: selective, oral, non-ATP competitive, small-molecule inhibitor of c-Met

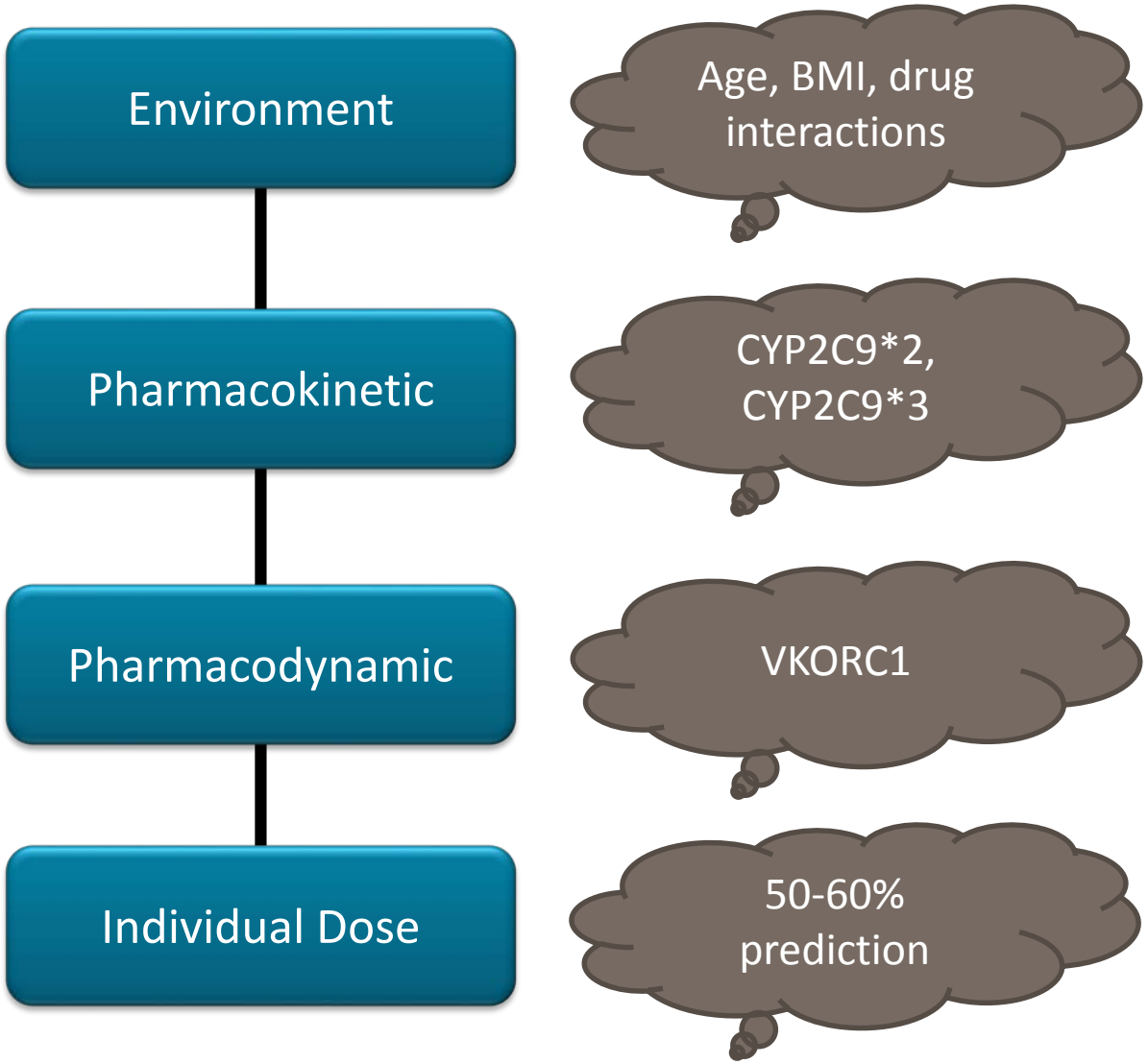
Response to a drug, efficacy or toxicity, is a complex phenotype

Systems Pharmacology Approaches



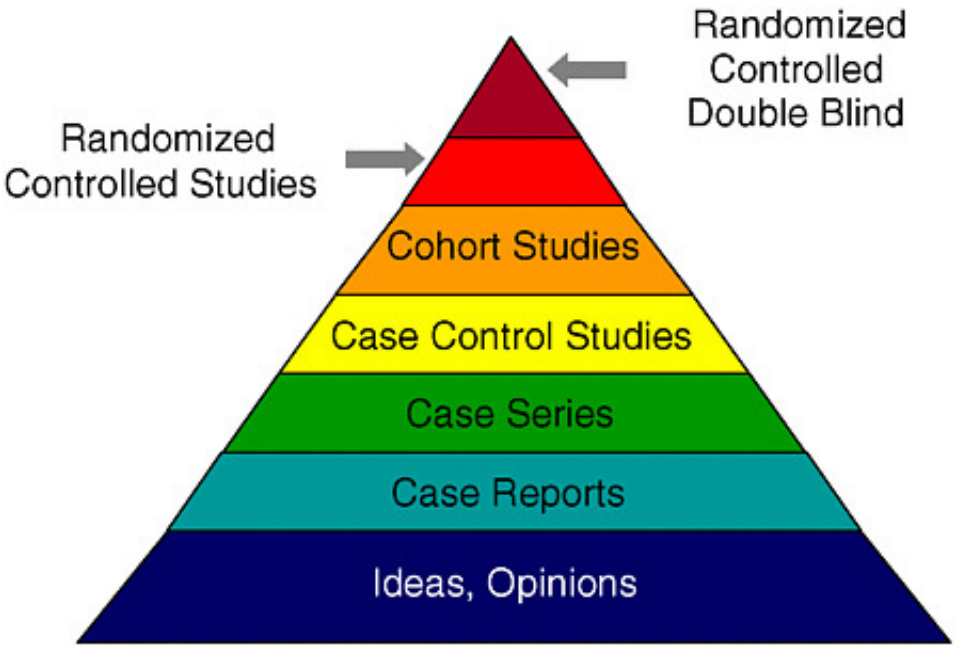
Annu. Rev. Pharmacol. Toxicol. 2012. 52:505–21

Warfarin Dose Prediction



Summary

- Translation into clinical practice is difficult
- Pathway for translation – one size does not fit all
- RCTs are not the ultimate answer to translating biomarkers into clinical practice
- Systems approaches need to be investigated, accompanied by mechanistic analysis



Routine whole-genome sequencing of babies by 2019?

By Daniel MacArthur ✉ February 12, 2009 | 12:15 pm | Categories: Genetic Future

I'm slowly catching up on genomics news from the last week – this story in particular has been getting a lot of press.

The executive summary: Jay Flatley, CEO of genomic technology manufacturer Illumina, predicts that **whole-genome sequencing of newborns will become routine within a decade**.

Flatley has an obvious financial interest in this prediction coming true, since Illumina provides the most commercially successful next-generation sequencing platform currently on the market, the Genome Analyzer, and has recently invested heavily in emerging "third-generation" sequencing technologies (by

http://www.wired.com/wiredscience/2009/02/routine-whole-genome-sequencing-of-babies-by-2019/

Acknowledgements

The University of Liverpool

- B Kevin Park
- Ana Alfirevic
- Andrea Jorgensen
- Girvan Burnside
- Eunice Zhang
- Javier Vilar

- **EU-PACT (Mia Wadelius, Ann Daly, Farhad Kamali, Anke Hilse Maitland, and many others**

Funders:

- **EU-FP7**
- **Dept of Health (NHS Chair of Pharmacogenetics)**
- **MRC Centre for Drug Safety Science**
- **Wolfson Foundation**
- **WT, DH, NIHR**