LIVERPOOL HEALTH PARTNERS

Precision Medicine: Its Application in Clinical Investigation and Practice Innovation

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THE WOLFSON CENTRE FOR PERSONALISED MEDICINE

MRC Centre for Drug Safety Science

Definition of Precision Medicine

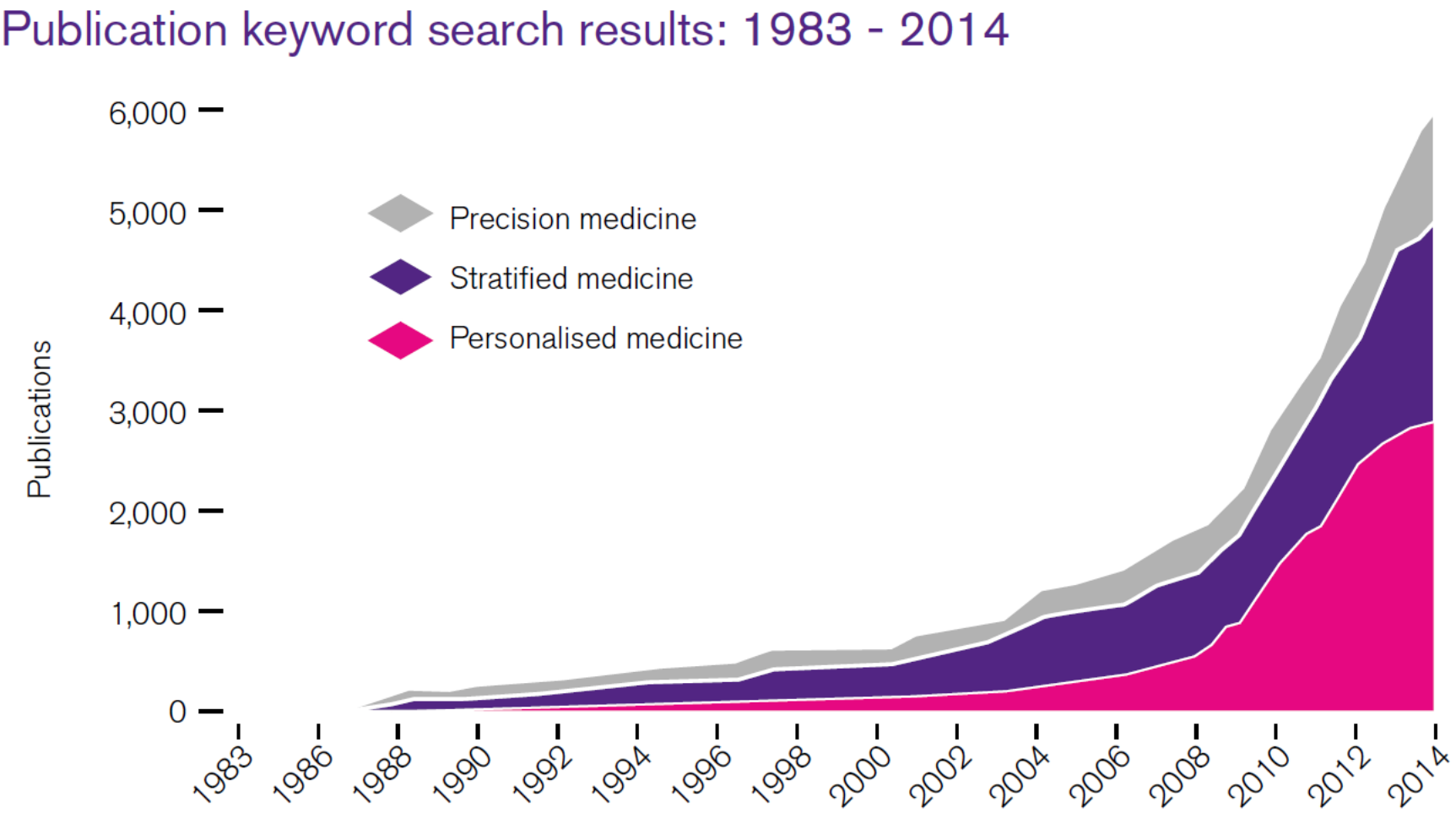
- Precision medicine is an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person

2015

Obama's Precision Medicine Initiative
$215 million

China
$8.2 billion

Terminology



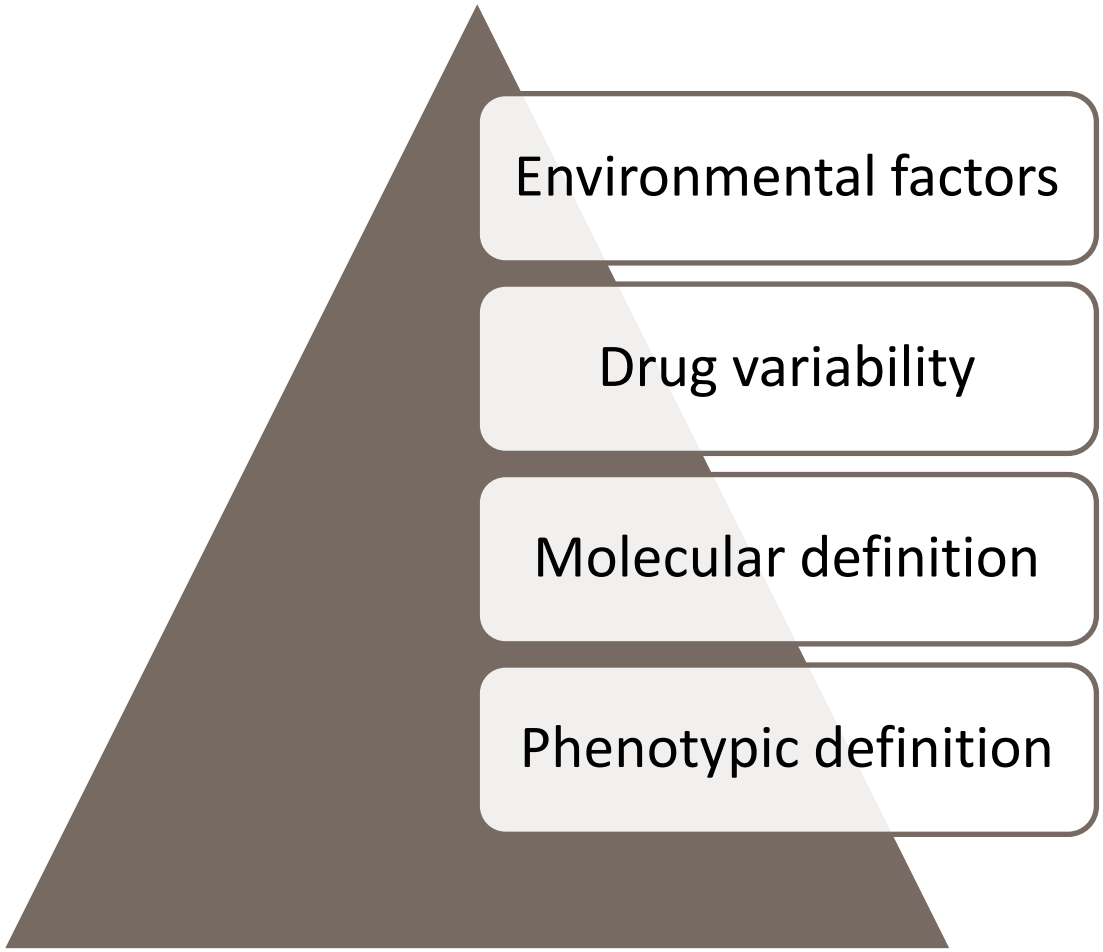
Stratified Medicine in the NHS, ABPI, 2014

Marker of Success

We will have succeeded when this area is simply called:

Medicine

A Concept of Personalised Medicine



Personalised Medicine

Pharmacogenomics

Disease stratification

Current standard

Pirmohamed, Annu. Rev. Genomics Hum. Genet. 2014. 15:15.1–15.22

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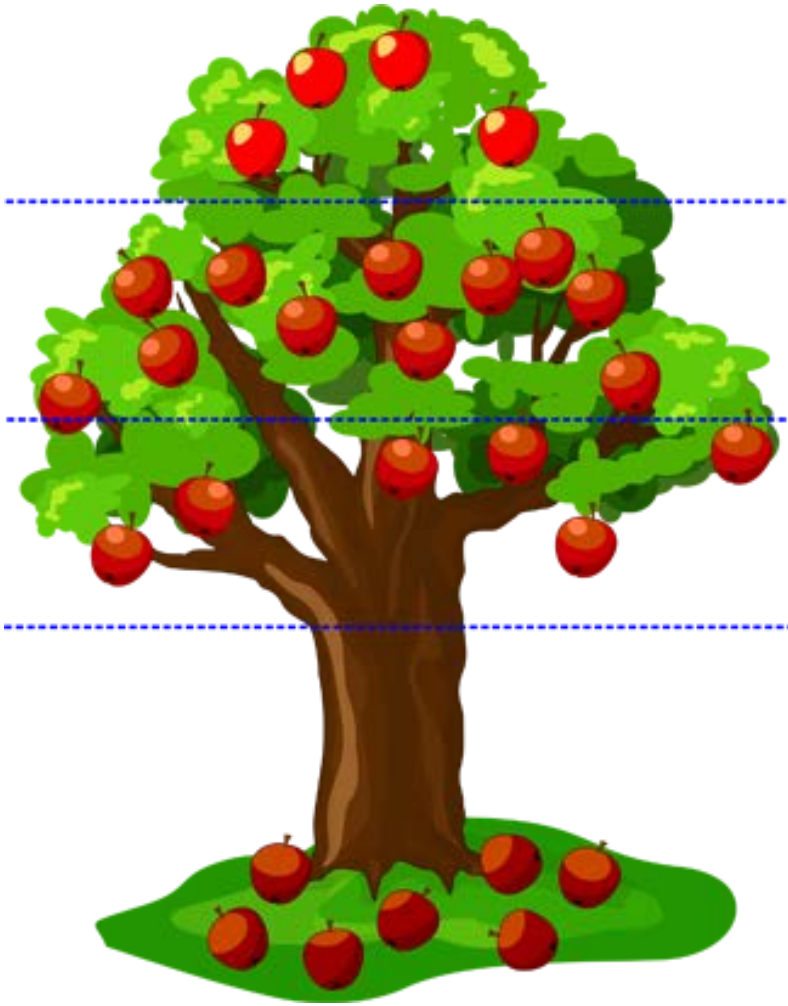


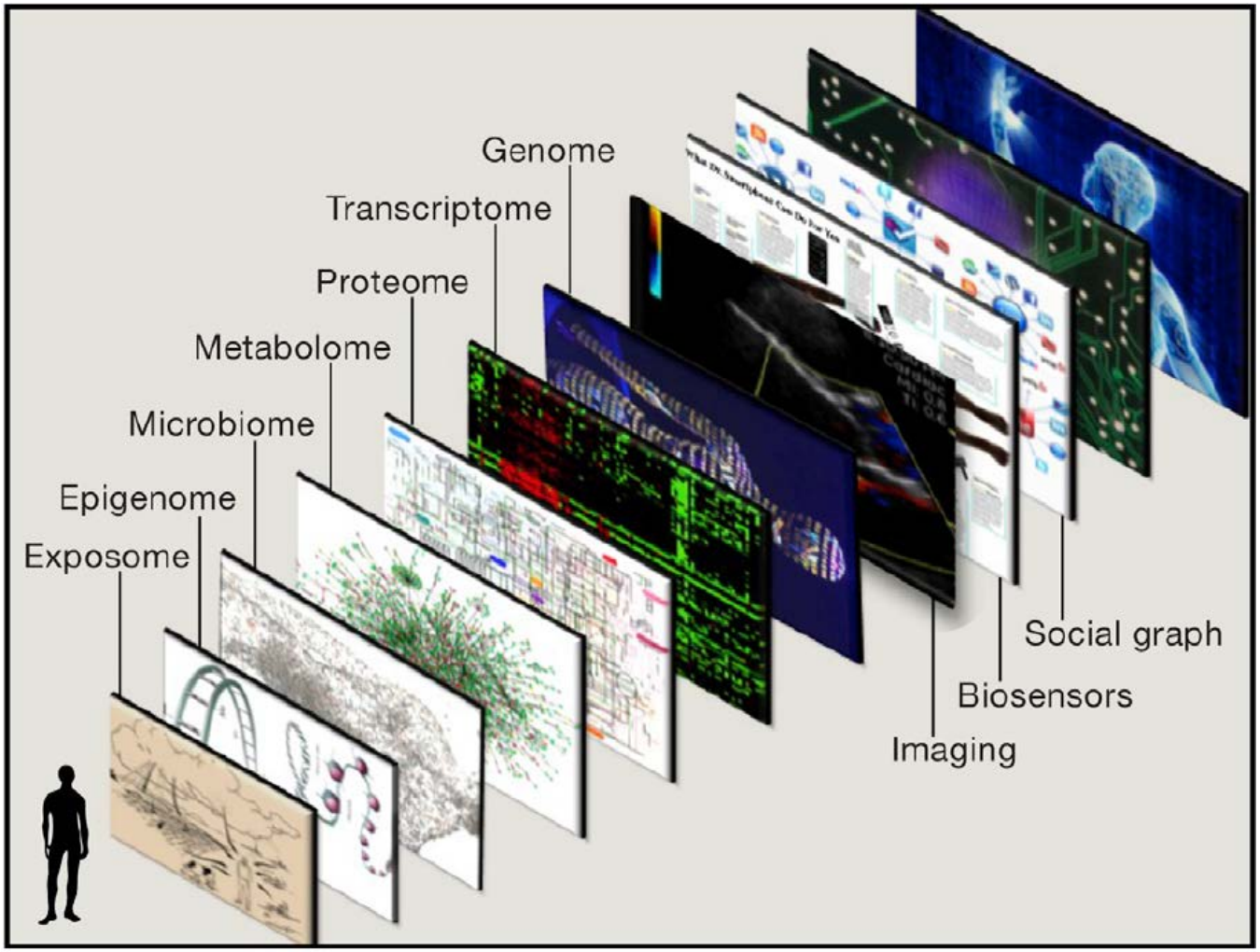
Sweet Fruit

Bulk of Fruit

Low-Hanging Fruit

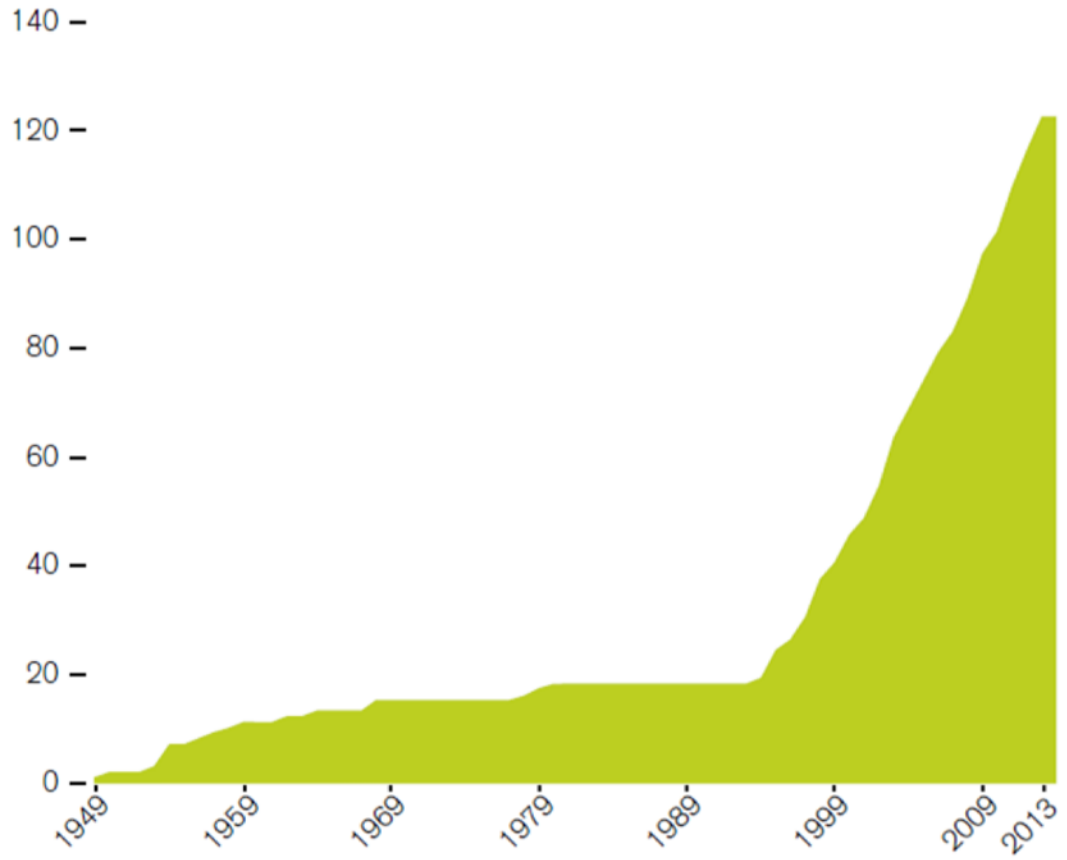
Ground Fruit

Systems Approaches



Topol, Cell, 2014

Regulatory Approvals



The number of Food and Drug Administration (FDA) medicine approvals containing an associated biomarker has increased seven-fold since 1993, an average annual growth rate of

17%

EMA SmPCs With Mandatory Genomic Testing

The Pharmacogenomics Journal (2015), 1–10

Name	INN	Year of approval	PGx biomarker	Indication
SmPC section Therapeutic indications (section 4.1)				
Herceptin	Trastuzumab	2000	HER2	Stomach neoplasms Breast neoplasms
Tyverb	Lapatinib	2008		Breast neoplasms
Afinitor	Everolimus	2009		Carcinoma, renal cell pancreatic neoplasms, breast neoplasms
Kadcyla	Trastuzumab emtansine	2013		Breast neoplasms
Perjeta	Pertuzumab	2013		Breast neoplasms
Ziagen	Abacavir	1999	HLA-B*5701	HIV infections
Trizivir	Abacavir/lamivudine/zidovudine	2000		
Kivexa	Abacavir/lamivudine	2004		
Tarceva	Erlotinib	2005	EGFR	Non-small-cell lung carcinoma pancreatic neoplasms
Iressa	Gefitinib	2009	EGFR	Non-small-cell lung carcinoma
Giotrif	Afatinib	2013	EGFR	Non-small-cell lung carcinoma
Erbitux	Cetuximab	2004	EGFR	Colorectal neoplasms
			RAS	Head and neck neoplasms
Vectibix	Panitumumab	2007	RAS	Colorectal neoplasms
Glivec	Imatinib	2001	BCR-ABL	Chronic myelogenous leukaemia
			Kit *CD117*	Gastrointestinal stromal tumours
			FIP1L1-PDGFR	Myelodysplastic-myeloproliferative diseases Dermatofibrosarcoma Precursor cell lymphoblastic leukaemia-lymphoma Hypereosinophilic syndrome
Sprycel	Dasatinib	2006	BCR-ABL	Chronic myelogenous leukaemia precursor cell lymphoblastic leukaemia-lymphoma
Tasigna	Nilotinib	2007	BCR-ABL	Chronic myelogenous leukaemia
Bosulif	Bosutinib	2013	BCR-ABL	Myelogenous leukaemia
Imatinib (accord, actavis, medac)	Imatinib	2013	BCR-ABL	Chronic myelogenous leukaemia
			Kit CD117	Myelodysplastic-myeloproliferative diseases
			FIP1L1-PDGFR	Dermatofibrosarcoma Precursor cell lymphoblastic leukaemia-lymphoma Hypereosinophilic syndrome
Iclusig	Ponatinib	2013	T315I mutation	Lymphoid leukaemia
			BCR-ABL	Myeloid leukaemia
Zelboraf	Vemurafenib	2012	*BRAF V600*	Melanoma
Tafinlar	Dabrafenib	2013		
Adcetris	Brentuximab vedotin	2012	CD30	Hodgkin disease lymphoma (non-Hodgkin)
Xalkori	Crizotinib	2012	ALK	Non-small-cell lung carcinoma
Kalydeco	Ivacaftor	2012	CFTR *G551D*	Cystic fibrosis
Caprelsa	Vandetanib	2012	*RET* mutation	Thyroid neoplasms
Trisenox	Arsenic trioxide	2002	PML-RAR-α t(15;17)	Acute promyelocytic leukaemia

Nov 2014: Eliglustat also approved with CYP2D6 genotyping

Only 3 drugs outside the cancer area

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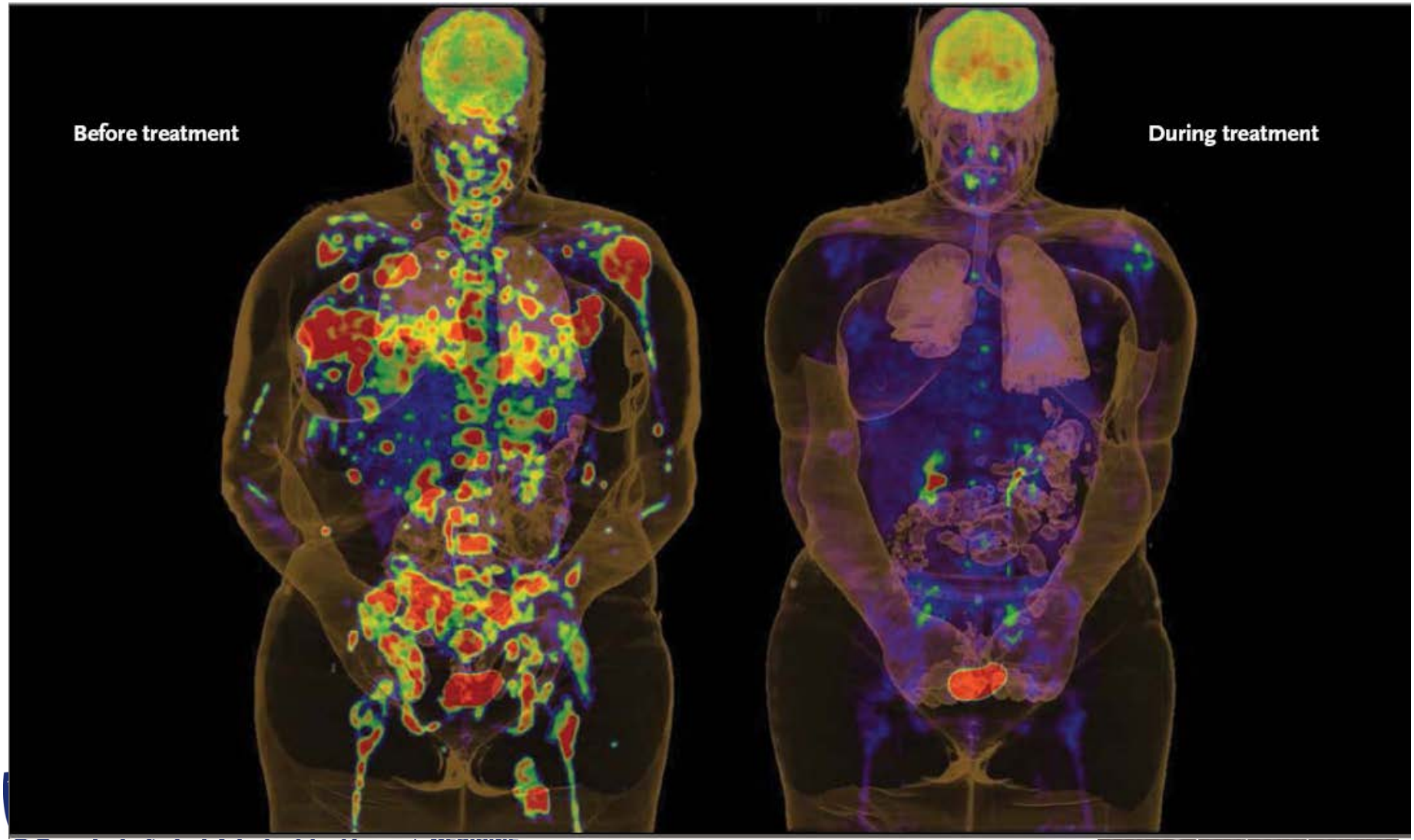
Malignant Melanoma and BRAF Inhibitor: Baseline and 2 Weeks After



Disease area	Drug (Rx) and Companion diagnostic (CDx)		US approval		EU approval	
	Rx	CDx	Rx	CDx	Rx	CDx
Melanoma	**Zelboraf (vemurafenib)** Roche/Plexxikon	**cobas® 4800 BRAF V600 Mutation Test** Roche	Aug 2011	Aug 2011	Feb 2012	Yes
	This drug was selected by Roche for development owing to knowledge of the biomarker: the drug showed effects in melanomas containing a particular mutation, V600E, in a protein called BRAF. The Rx and CDx were developed in parallel, and co-approved in one of the fastest FDA approvals in history (four months). Zelboraf was approved by NICE in November 2012.[20]					
Non small cell lung cancer (NSCLC)	**Xalkori (crizotinib)** Pfizer	**Vysis ALK Break Apart FISH probe kit** Abbott Molecular Diagnostics	Aug 2011	Aug 2011	Jul 2012**	Sep 2011
	A 2007 study linked a subset of NSCLC to the *ALK* fusion gene. This prompted a partnership between Rx and CDx manufacturers, and patient stratification using this CDx resulted in dramatic improvement in response rates. Approval was rapid both in the US and in the EU.					

Source: Academy of Medical Sciences Report

Somatic Gene Variants and Therapies

Genetic abnormality	HGVS nomenclature*	Target†	Medications	Disease
AKT mut (act)	p.Glu17Lys	mTOR	Sirolimus, everolimus	RCC
BCR–ABL (SV)	t(9;22) (q34.1;q11.21)	ABL	Imatinib, dasatinib	CML, Ph^+ ALL
BCR–ABL (SV, mut)	p.Val299Leu	ABL	Bosutinib, nilotinib	Imatinib-resistant CML
BCR–ABL (T135I)	p.Thr135Ile	ABL	Ponatinib	CML, Ph^+ ALL
BCR–ABL (SV)	t(9;22) (q34.1;q11.21)	SRC	Dasatinib	CML, Ph^+ ALL
BRCA1/2 variants	Too numerous to list	PARP	Olaparib	Ovarian cancer
BRAF SNVs (V600E/K)	p.Val600Glu, p.Val600Lys, p.Val600Asp	BRAF	Dabrafenib, vemurafenib	Melanoma
BRAF SNVs (V600)	p.Val600Glu, p.Val600Lys, p.Val600Asp	MEK	Trametinib	Melanoma
EGFR (ex 19 del, SNV L858R)	p.Glu746_Ala750del, p.Leu858Arg	EGFR	Afatinib, erlotinib	NSCLC ($EGFR^+$)
EGFR mut (act, amp)	p.Glu746_Ala750del, p.Leu858Arg	EGFR	Gefitinib	NSCLC ($EGFR^+$)
$EGFR^+$ and WT *KRAS*	N/A	EGFR	Cetuximab, panitumumab	$EGFR^+$ colon cancer (WT KRAS)
EML–ALK (SV)	inv(2)(p21p23)	ALK	Crizotinib	NSCLC
FLT3 CNV (amp)	p.D600_L601insFREYEYD, p.Asp835Tyr	FTL3	Sunitinib, sorafenib	AML
HER2 (amp)	N/A	ERBB2	Lapatinib, trastuzumab	$HER2^+$ breast cancer
KIT mut (act)	p.Trp557_Lys558del, p.Asp579del, p.Val559Asp	KIT	Imatinib, sunitinib	RCC, GIST
PDGFR (mut or SV)	p.Asp842Val	PDGFR	Sunitinib, imatinib	RCC, GIST, pancreatic cancer
PI3K (mut or amp)	PIK3CA p.Glu542Lys, p.Glu545Lys; p.His1047Arg, p.His1047Leu	PI3K	Idelalisib	CLL, NHL
RARA (SV, gene fusion)	t(15;17)(q24;q21)	RARA	Tretinoin, alitretinoin	APL, CTCL, Kaposi sarcoma
RARA (SV, gene fusion)	t(15;17)(q24;q21)	RARA	Arsenic trioxide	APL
SMO mut (act)	p.Trp535Leu, p.Arg199Trp, p.Arg562Gln	Smoothen	Vismodegib	Basal cell carcinoma
VHL (mut)	Too numerous to list	VEGFR	Sorafenib	RCC, hepatic cancer, thyroid cancer
VEGF (mut)	N/A	VEGF	Ziv-aflibercept	Colon cancer

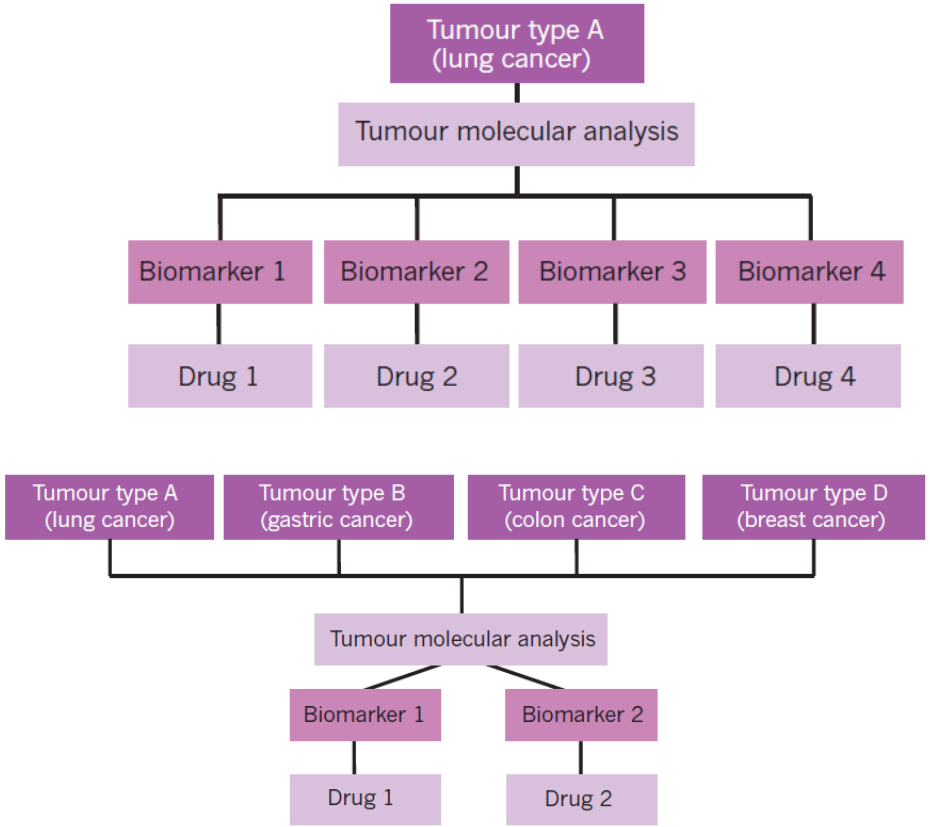
Relling & Evans, Nature 2015

Patient-centric trials for therapeutic development in precision oncology

Andrew V. Biankin[1,2,3,4], Steven Piantadosi[5] & Simon J. Hollingsworth[6]

15 OCTOBER 2015 | VOL 526 | NATURE

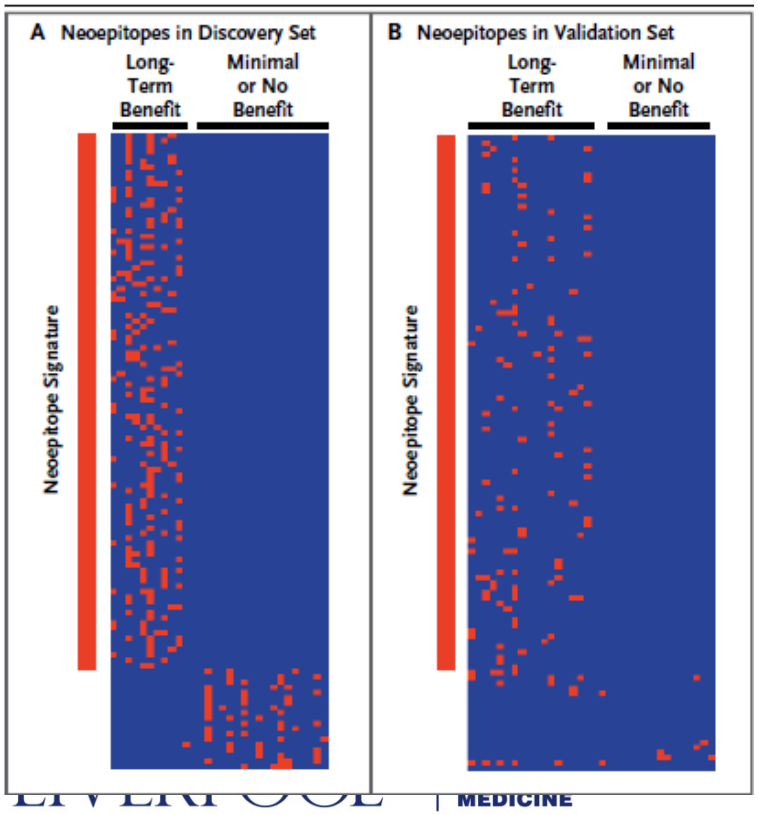
- Novel trial designs – acceptability for registration
- Umbrella trial – investigation of single tumour type but stratification by different mutations linked to specific candidate drugs
- Basket study – in multiple tumour types but with a focus on one or few biomarkers

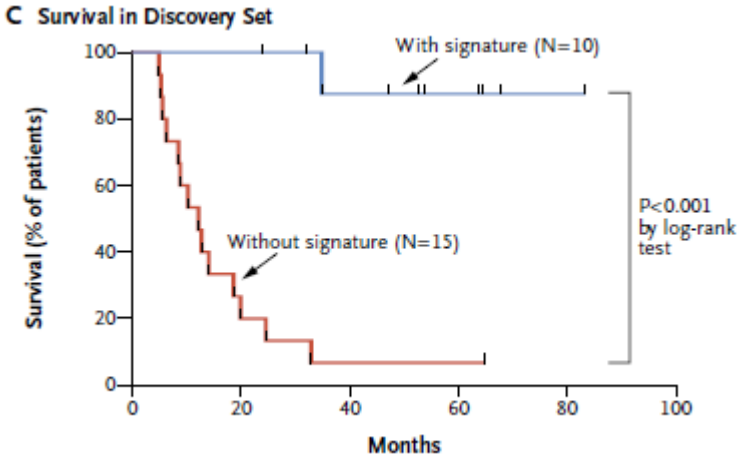


Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma

Alexandra Snyder, M.D., Vladimir Makarov, M.D., Taha Merghoub, Ph.D., Jianda Yuan, M.D., Ph.D., Jesse M. Zaretsky, B.S., Alexis Desrichard, Ph.D., Logan A. Walsh, Ph.D., Michael A. Postow, M.D., Phillip Wong, Ph.D., Teresa S. Ho, B.S., Travis J. Hollmann, M.D., Ph.D., Cameron Bruggeman, M.A., Kasthuri Kannan, Ph.D., Yanyun Li, M.D., Ph.D., Ceyhan Elipenahli, B.S., Cailian Liu, M.D., Christopher T. Harbison, Ph.D., Lisu Wang, M.D., Antoni Ribas, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., and Timothy A. Chan, M.D., Ph.D.

N Engl J Med 2014;371:2189-99.
DOI: 10.1056/NEJMoa1406498





Microbiome and Cancer Immunotherapy

CANCER IMMUNOTHERAPY

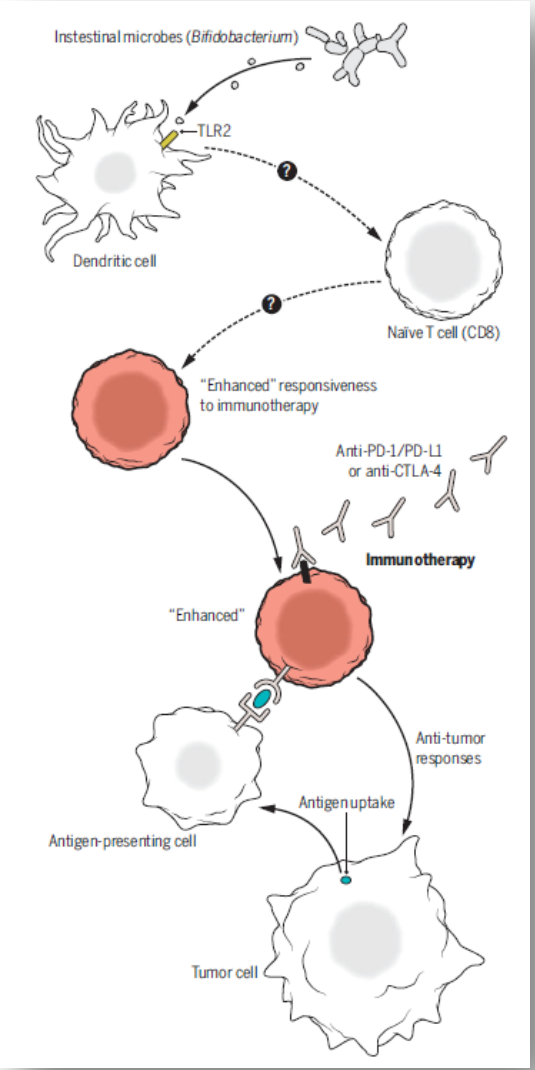
Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota

Marie Vétizou,[1,2,3] Jonathan M. Pitt,[1,2,3] Romain Daillère,[1,2,3] Patricia Lepage,[4] Nadine Waldschmitt,[5] Caroline Flament,[1,2,6] Sylvie Rusakiewicz,[1,2,6] Bertrand Routy,[1,2,3,6] Maria P. Roberti,[1,2,6] Connie P. M. Duong,[1,2,6] Vichnou Poirier-Colame,[1,2,6] Antoine Roux,[1,2,7] Sonia Becharef,[1,2,6] Silvia Formenti,[8] Encouse Golden,[8] Sascha Cording,[9] Gerard Eberl,[9] Andreas Schlitzer,[10] Florent Ginhoux,[10] Sridhar Mani,[11] Takahiro Yamazaki,[1,2,6] Nicolas Jacquelot,[1,2,3] David P. Enot,[1,7,12] Marion Bérard,[13] Jérôme Nigou,[14,15] Paule Opolon,[1] Alexander Eggermont,[1,2,16] Paul-Louis Woerther,[17] Elisabeth Chachaty,[17] Nathalie Chaput,[1,18] Caroline Robert,[1,16,19] Christina Mateus,[1,16] Guido Kroemer,[7,12,20,21,22] Didier Raoult,[23] Ivo Gomperts Boneca,[24,25]* Franck Carbonnel,[3,26]* Mathias Chamaillard,[5]* Laurence Zitvogel[1,2,3,6]†

Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti–PD-L1 efficacy

Ayelet Sivan,[1]* Leticia Corrales,[1]* Nathaniel Hubert,[2] Jason B. Williams,[1] Keston Aquino-Michaels,[3] Zachary M. Earley,[2] Franco W. Benyamin,[1] Yuk Man Lei,[2] Bana Jabri,[2] Maria-Luisa Alegre,[2] Eugene B. Chang,[2] Thomas F. Gajewski[1,2]†

Science, 27 Nov 2015



Snyder et al, Science, Nov 2015

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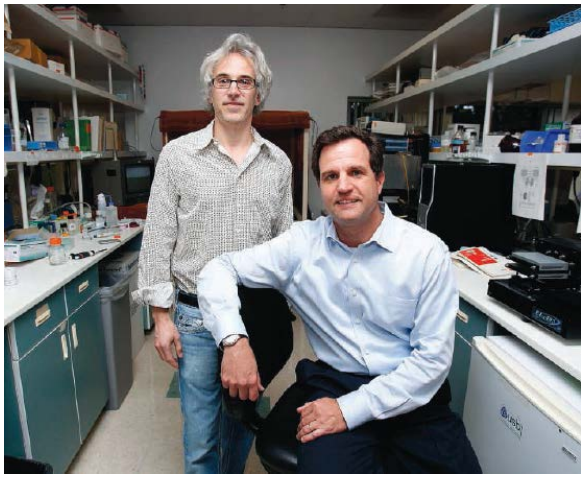
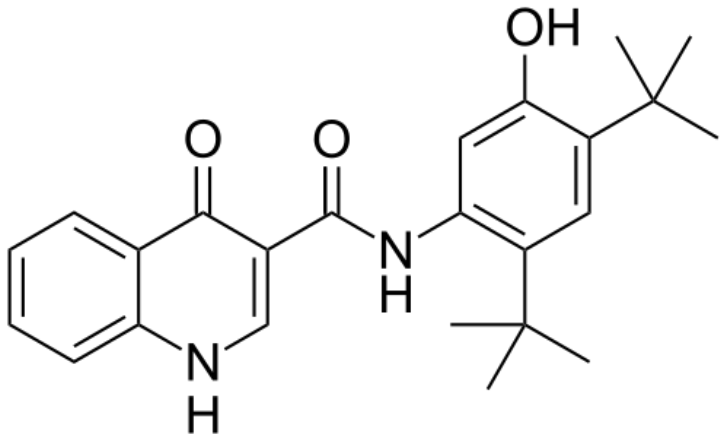
New Cystic Fibrosis Drug Offers Hope, at a Price

SCIENCE VOL 335 10 FEBRUARY 2012

- New CF drug, ivacaftor
- Targets *G551D* mutation in the *CFTR* gene (4% of CF population)
- Fantastic innovation with increases in FEV1 ~10%



- 200 scientists
- 600,000 compounds screened
- *In silico* screening of 2.7 million compounds
- 3 possible candidates



Indication expanded in 2014:
G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, and G1349D

MRC | Centre for Drug Safety Science

New Cardiovascular Targets

PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 (PCSK9)

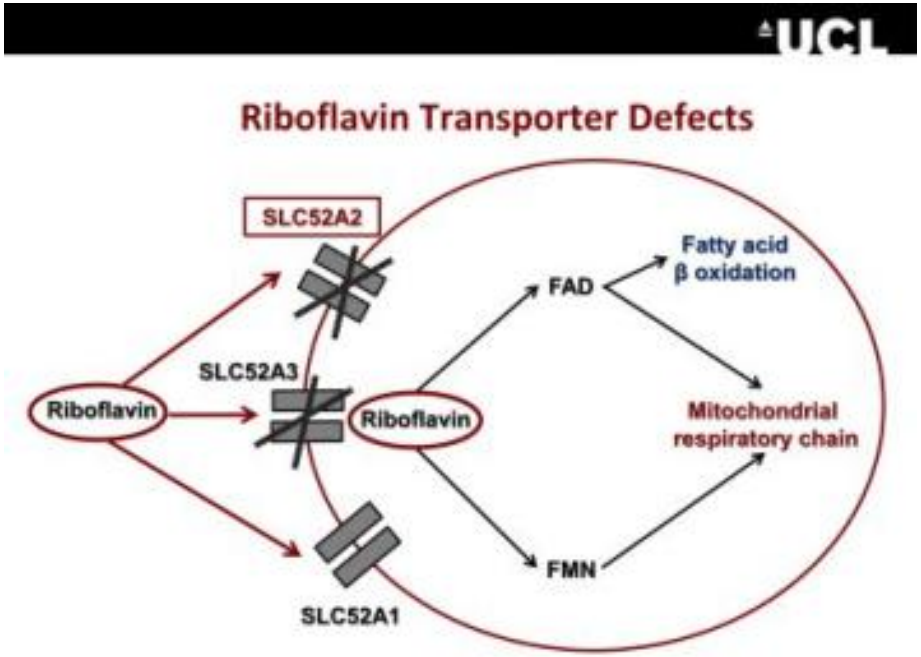
- Gain-of-function-mutations lead to high LDL-C and premature CVD; Loss-of-function mutations – lower plasma levels of LDL-C and lower CVD risk
- Increased PCSK9 attenuates LDL receptor recycling resulting in higher LDL-C levels
- Human monoclonal antibodies now available – lower LDL-C. Effect on mortality not clear yet.

ANGIOPOEITIN-LIKE 4 (ANGPTL4)

- ANGPTL4 inhibits lipoprotein lipase (which reduced lipid levels)
- Mutations in ANGPTL4 decrease triglyceride levels and patients have decreased CV risk
- Monoclonal antibodies against protein in mice lead to reduce TG

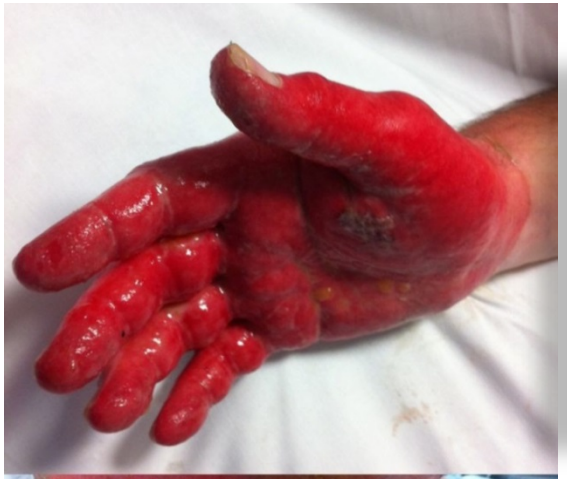
Brown-Vialetto van Laere syndrome

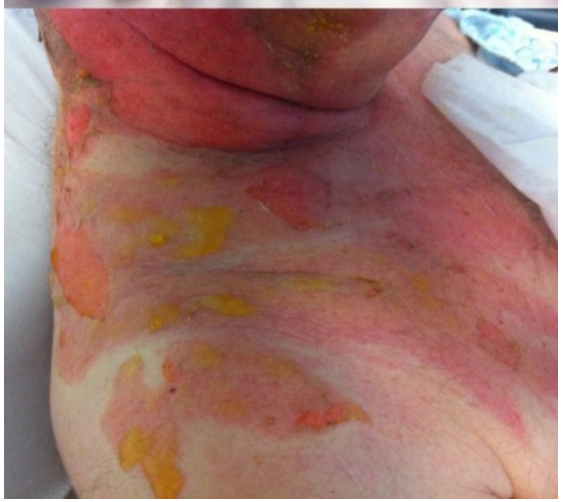
- Childhood motor neurone disease
- Deafness, speech and swallowing problems, face and limb weakness and breathing problems
- Rare, autosomal recessive
- About 60 cases reported
- Exome sequencing



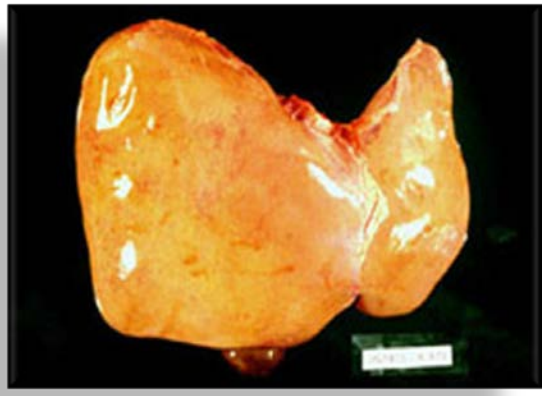
High dose riboflavin (Vitamin B2)

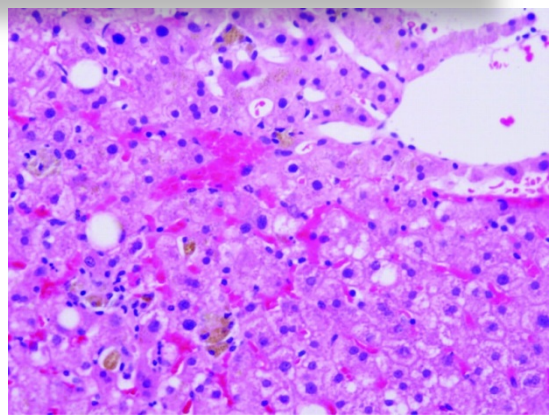
Serious Adverse Drug Reactions





Toxic Epidermal Necrolysis





Hepatocellular hepatitis

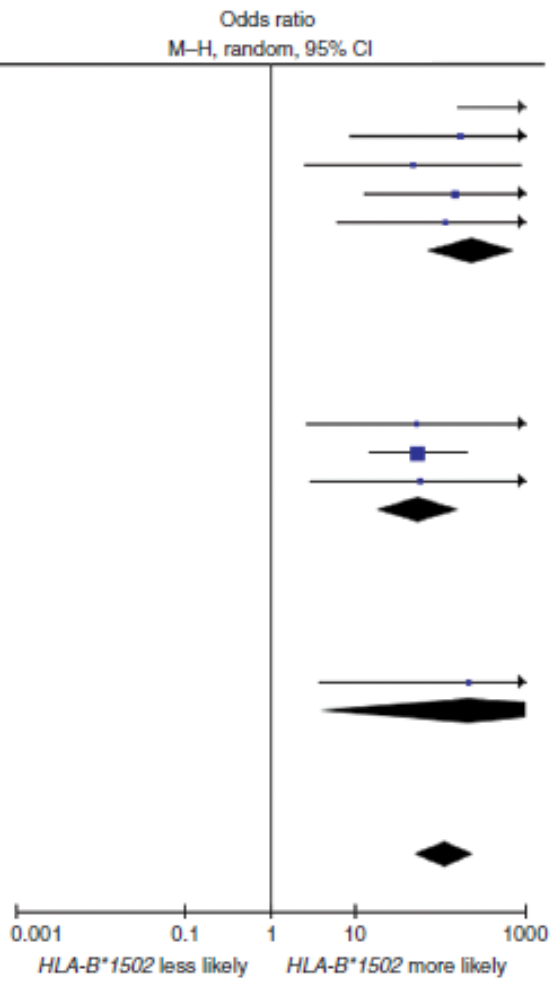
HLA Genotype and Carbamazepine-Induced Cutaneous Adverse Drug Reactions: A Systematic Review

CPT, 2012

VL Yip[1], AG Marson[2], AL Jorgensen[3], M Pirmohamed[1] and A Alfirevic[1]

HLA-B*1502

Study or subgroup	*HLA-B*1502* positive Events	Total	*HLA-B*1502* Negative Events	Total	Weight	Odds ratio M–H, random, 95% CI	Year
1.1.1 Han Chinese							
Hung 2006	59	65	1	139	13.8%	1357.00 [159.84, 11520.40]	2006
Wu 2010	8	12	0	46	7.0%	175.67 [8.64, 3570.35]	2010
Liao 2010	6	22	0	60	7.4%	47.67 [2.55, 890.45]	2010
Zhang 2011	16	18	1	20	10.2%	152.00 [12.59, 1834.92]	2010
Wang 2011	9	20	0	69	7.4%	114.83 [6.25, 2110.92]	2011
Subtotal (95% CI)		137		334	45.7%	236.24 [71.72, 778.11]	
Total events	98		2				
Heterogeneity: $\tau^2 = 0.05$; $\chi^2 = 4.11$, df = 4 ($P = 0.39$); $I^2 = 3\%$							
Test for overall effect: $Z = 8.99$ ($P < 0.00001$)							
1.1.2 Thai							
Locharernkul 2008	6	14	0	34	7.1%	52.76 [2.70, 1031.31]	2008
Tassaneeyakul 2010	37	42	5	42	36.2%	54.76 [14.62, 205.13]	2010
Kulkantrakorn 2012	6	13	0	33	7.1%	58.07 [2.94, 1147.12]	2011
Subtotal (95% CI)		69		109	50.4%	54.92 [17.94, 168.14]	
Total events	49		5				
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.00$, df = 2 ($P = 1.00$); $I^2 = 0\%$							
Test for overall effect: $Z = 7.02$ ($P < 0.00001$)							
1.1.3 Malaysian							
Then 2011	6	6	0	8	3.8%	221.00 [3.85, 12694.65]	2011
Subtotal (95% CI)		6		8	3.8%	221.00 [3.85, 12694.65]	
Total events	6		0				
Heterogeneity: Not applicable							
Test for overall effect: $Z = 2.61$ ($P = 0.009$)							
Total (95% CI)		212		451	100.0%	113.39 [51.24,250.97]	
Total events	153		7				
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 7.43$, df = 8 ($P = 0.49$); $I^2 = 0\%$							
Test for overall effect: $Z = 11.67$ ($P < 0.00001$)							
Test for subgroup differences: $\chi^2 = 3.17$, df = 2 ($P = 0.20$); $I^2 = 36.9\%$							



Effects of a HLA-B*15:02 screening policy on antiepileptic drug use and severe skin reactions

Neurology® 2014;83:2077-2084

Evidence strong and consistent

Serious ADR potentially preventable

Government willing to pay for the test

- Faced with this choice what would you do if a patient needs to be prescribed CBZ?
  A. Ignore screening policy and prescribe CBZ
  B. Screen patient for HLA-B*15:02 and prescribe alternative drug if positive
  C. Avoid CBZ all together and prescribe an alternative

Effects of a HLA-B*15:02 screening policy on antiepileptic drug use and severe skin reactions

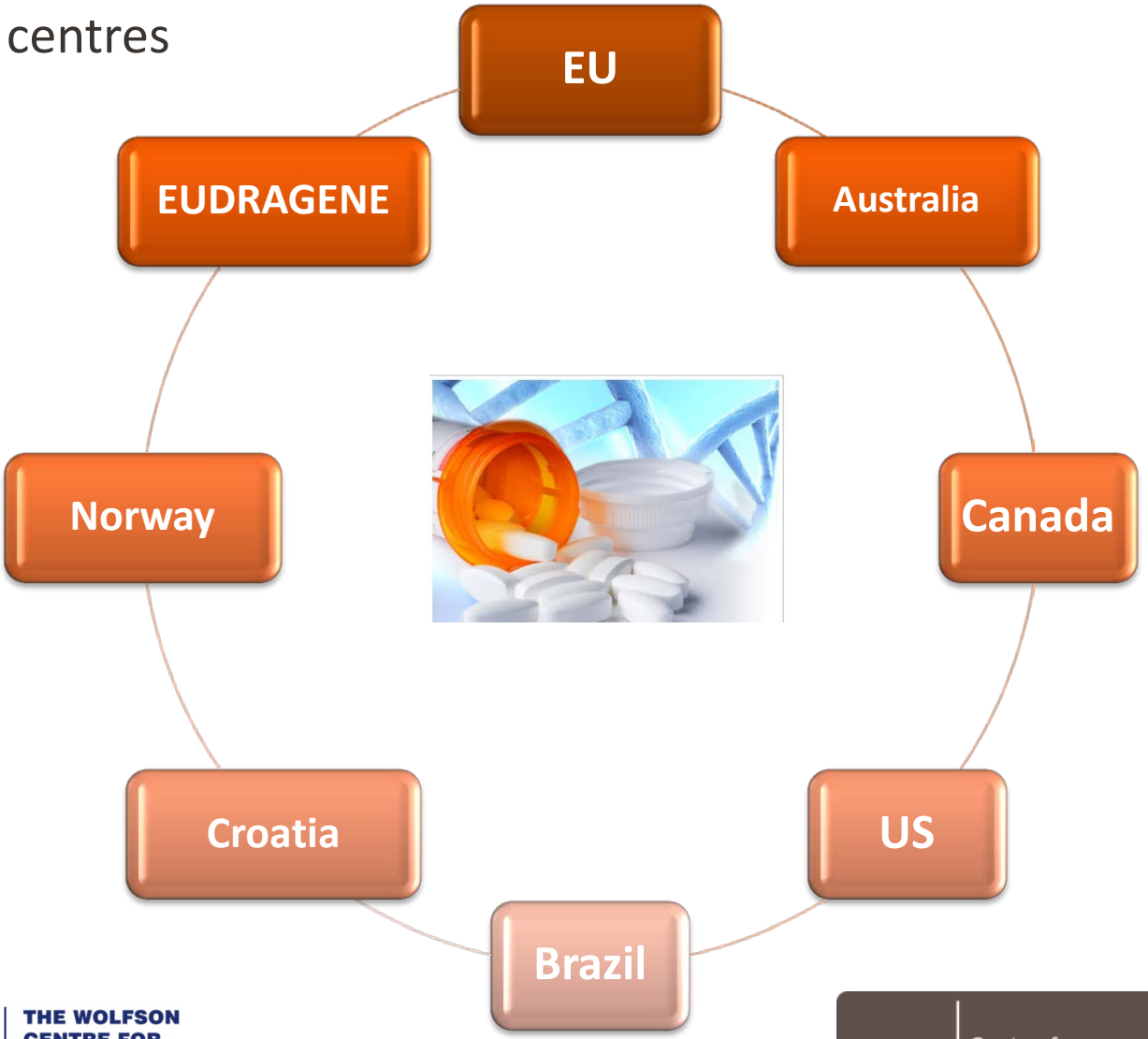
Neurology® 2014;83:2077-2084

- HLA-B*15:02 screening policy introduced in Hong Kong (Sept 16, 2008): Compared 3 years before with 3 years after (111,242 patients)
- CBZ prescriptions declined from 16.2% to 2.6% (other AEDs increased).
- When testing used, it worked: Incidence of SJS/TEN induced by carbamazepine reduced (0.24% to 0%)
- SJS/TEN induced by phenytoin increased
- Overall incidence of AED-induced SJS/TEN remained unchanged (0.09% [42/45,832] vs 0.07% [39/55,326])

Law of Unintended Consequences

InTernational Consortium on Drug Hypersensitivity (ITCH)

- 12 international centres
- 50 UK centres
- 1500 patients



Sponsored by the International Serious Adverse Event Consortium (iSAEC)

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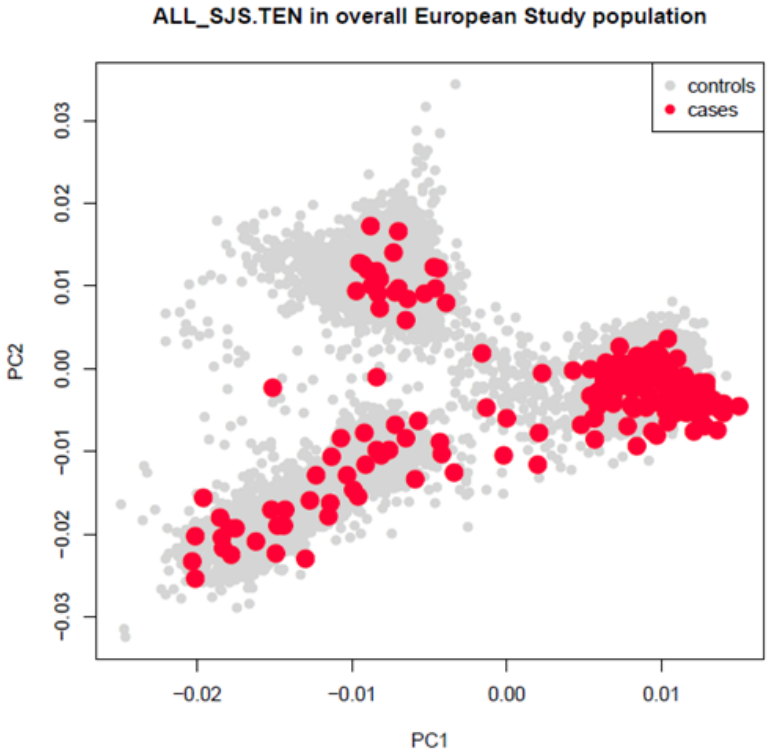
SJS/TEN Patients

DRUGS	SJS/TEN
ALLOPURINOL	10
AMOXICILLIN	16
AMOXICILLIN/CLAVULANIC ACID	5
AMPICILLIN	2
BACAMPICILLIN	1
CARBAMAZEPINE	33
LAMOTRIGINE	18
OTHERS	100
PHENYTOIN	11
SULFASALAZINE	6
TRIMETHOPRIM/SULFAMETHOXAZOLE	26
Total	**227**



177 Caucasians Cases

Associations of Serious Adverse Drug Reactions with HLA Alleles

A*31:01 Carbamazepine	**A*33:03** Ticlopidine	**A*68:01** Lamotrigine	**A*02:06** Cold medicines	**B*13:01** Dapsone Trichlorethylene	**B*15:02** Carbamazepine Phenytoin
B*35:05 Nevirapine	**B*44:03** Cold Medicines	**B*56:02** Phenytoin	**B*57:01** Abacavir Flucloxacillin	**B*58:01** Allopurinol	**C*04:01** Nevirapine
C*08:(01) Nevirapine	**DRB1*07:01** Ximelagatran Lapatinib Asparaginase	**DRB1*11:01** Statins	**DRB1*13:02** Aspirin	**DRB1*15:01** Lumiracoxib Co-amoxiclav	**DQA1*01:02** Lumiracoxib
DQA1*02:01 Lapatinib	**DQB1*02:01** Ximelagatran Clometacin	**DQB1*05:02** Clozapine	**DQB1*06:02** Co-amoxiclav Lumiracoxib	**DQB1*06:04** Ticlopidine	**DQB1*06:09** Aspirin

Problems in Implementing HLA Gene Tests

- Cost varies
- Single HLA tests
- Only available in some immunology laboratories in the NHS
- Turnaround time is variable, and can be about 2 weeks

Multiple HLA Biomarker Panel

Aim

- 24 HLA alleles
- Lower cost than individual alleles
- Turnaround time <48 hours
- Development of a decision support system

Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy

Dose ≠ exposure

Paracelsus, 1493-1541

Variation in Drug Exposure as a Result of Renal Impairment

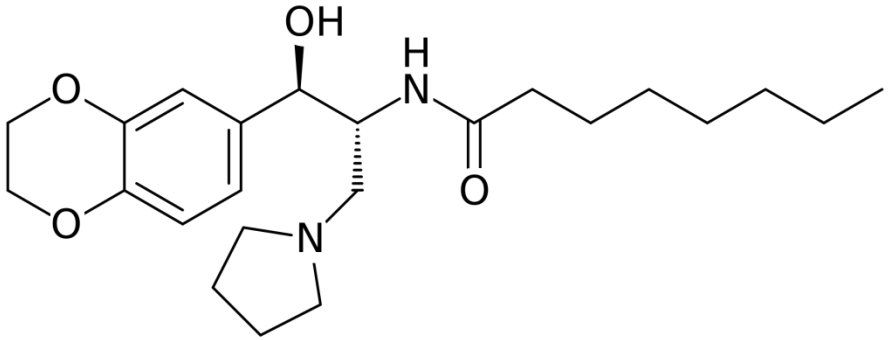
- Example: Aztreonam SmPC
  - "after an initial usual dose, the dosage of aztreonam should be halved in patients with estimated creatinine clearances between 10 and 30 mL/min/1.73 m^2"
- Many different examples in hepatic and renal impairment with dose instructions based on PK studies and occasionally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

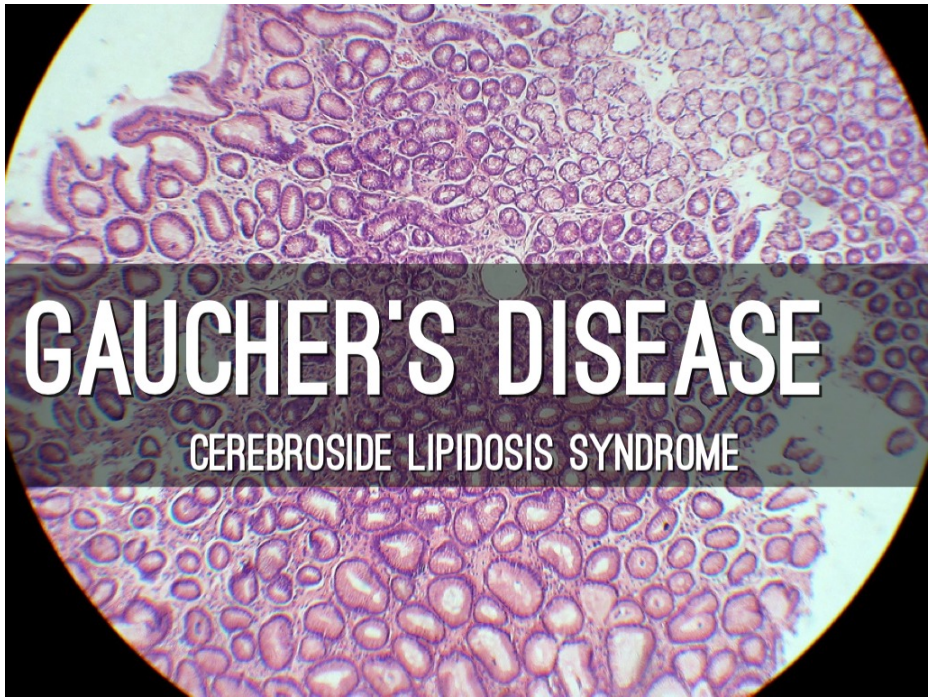
Variation in Drug Exposure as a Result of Genetic Polymorphism

- A genetic polymorphism leading to *same degree of change in drug exposure* as renal impairment is often ignored and/or RCT data are required for implementation
- However, many patients will have genomic data in healthcare records (for example, from 100K genome project)
- Some patients may present with direct to consumer genetic tests
- Should these variants be ignored, and conventional dosing used?
- Or should the same principles as applied to renal/hepatic impairment be used for genetic polymorphisms to enable more precise dosing?

Eliglustat

- Glucosylceramide synthetase inhibitor
- Licensed for Gaucher's disease by FDA in 2014
- CYP2D6 and CYP3A4 substrate
- CYP2D6 EMs or IMs: 84mg orally twice daily
- CYP2D6 PMs: 84mg orally once daily





Warfarin

- Number of users UK:

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

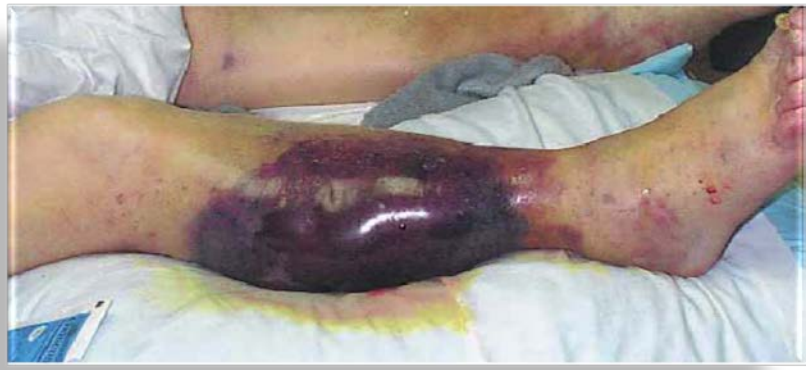
  0.5-20
- Fold variability in dose:

  40
- Major bleeding rate per 100-person years:

  2.6
- Ranking in ADR list:

  3

Approved for human use in 1954



Review

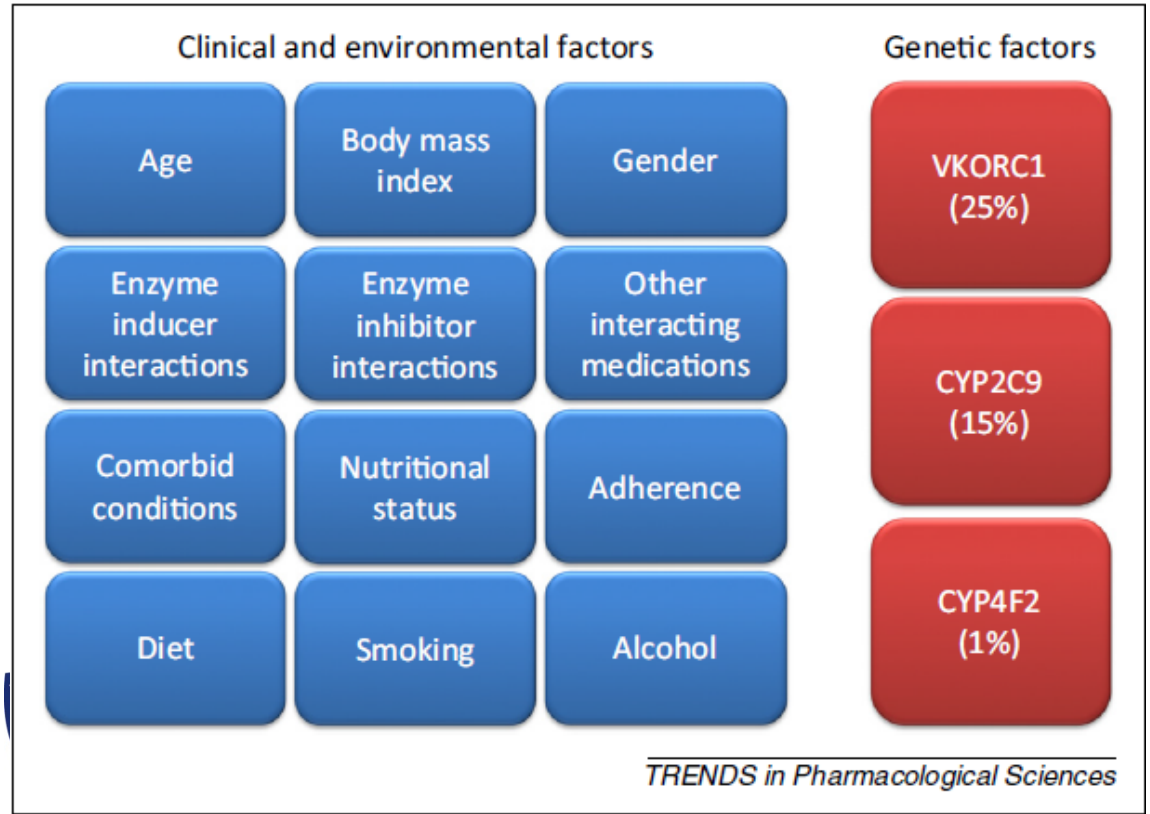
CellPress

Oral anticoagulation: a critique of recent advances and controversies

Munir Pirmohamed[1,2], Farhad Kamali[3], Ann K. Daly[3], and Mia Wadelius[4]

[1] The University of Liverpool, Liverpool L69 3BX, UK
[2] Royal Liverpool and Broadgreen University Hospital National Health Service (NHS) Trust, Prescot Street, Liverpool L7 8XP, UK
[3] Newcastle University, Newcastle upon Tyne NE2 4HH, UK
[4] Uppsala University, 751 85 Uppsala, Sweden

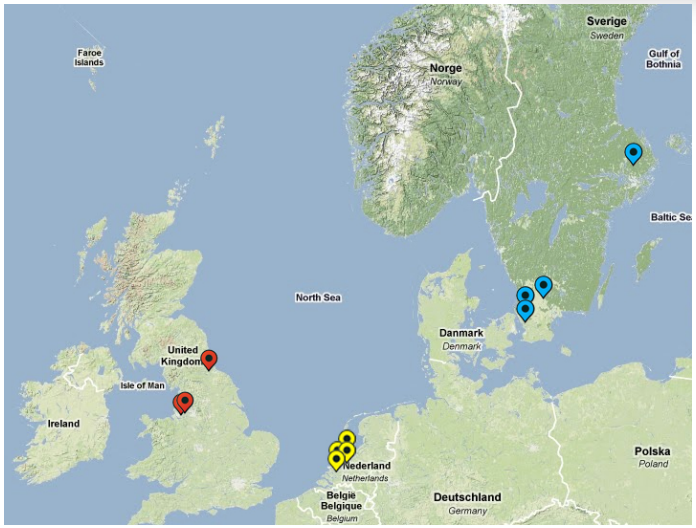
Trends in Pharmacological Sciences, March 2015, Vol. 36, No. 3



MRC Centre for Drug Safety Science

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

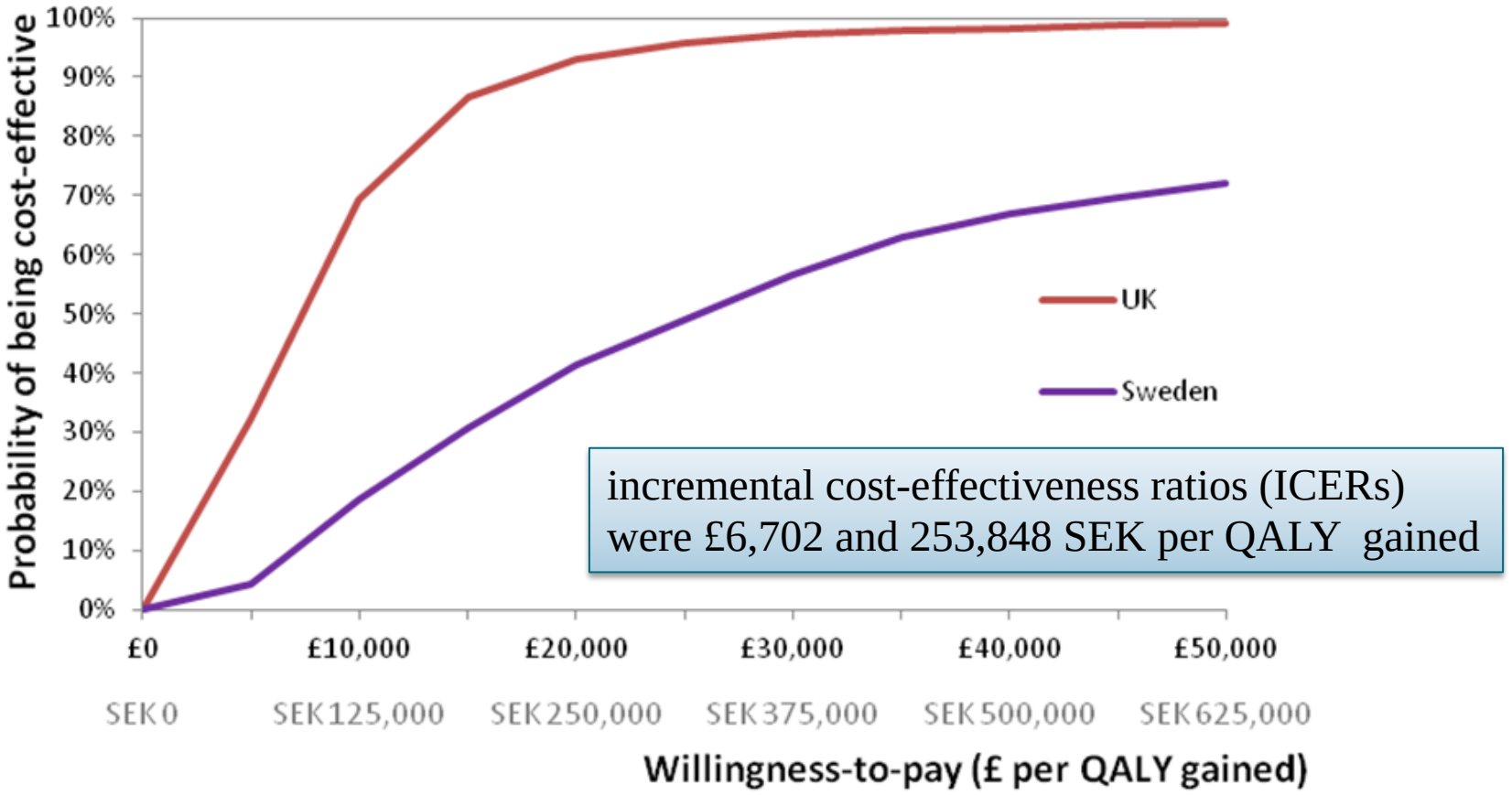
Munir Pirmohamed, Ph.D., F.R.C.P., Girvan Burnside, Ph.D., Niclas Eriksson, Ph.D., Andrea L. Jorgensen, Ph.D., Cheng Hock Toh, M.D., Toby Nicholson, F.R.C.Path., Patrick Kesteven, M.D., Christina Christersson, M.D., Ph.D., Bengt Wahlström, M.D., Christina Stafberg, M.D., J. Eunice Zhang, Ph.D., Julian 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*

N Engl J Med 2013;369:2294-303.
DOI: 10.1056/NEJMoa1311386

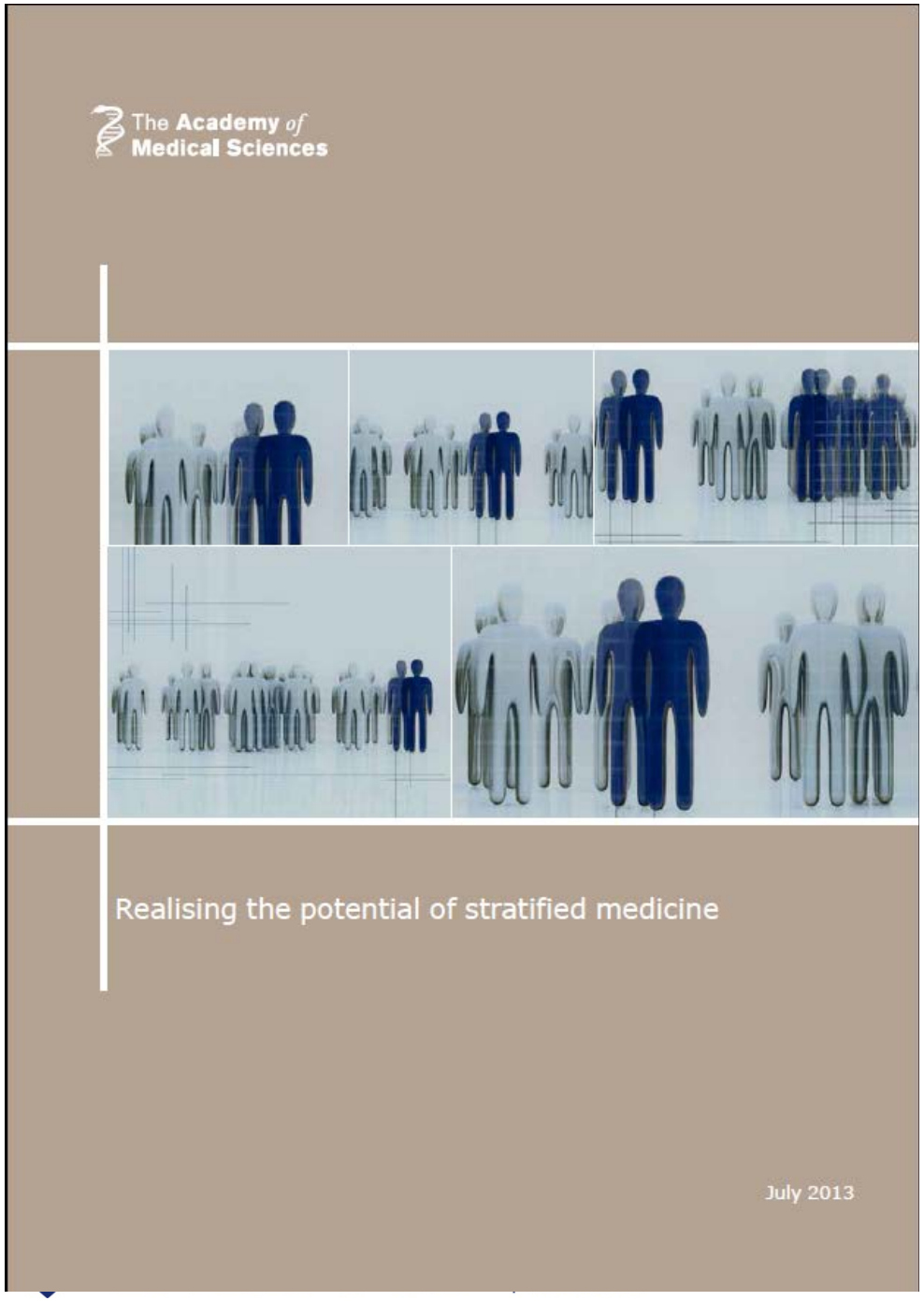
Genotyped arm %TTR	Standard dosing (control) arm %TTR	Adjusted Difference	P value
ITT ANALYSIS (n= 211 vs 216)			
67.4%	60.3%	7%	P<0.001
PER-PROTOCOL (n=166 vs 184)			
68.9%	62.3%	6.6%	P=0.001

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

EU-PACT Cost Effectiveness



incremental cost-effectiveness ratios (ICERs) were £6,702 and 253,848 SEK per QALY gained



- Increase pace of progress which is only possible through involvement of many stakeholders
- Linking of biomedical and health informatics systems
- Incentives to develop stratified medicine products
- Adoption
- Need for collaboration

MRC | Centre for Drug Safety Science

biobank uk

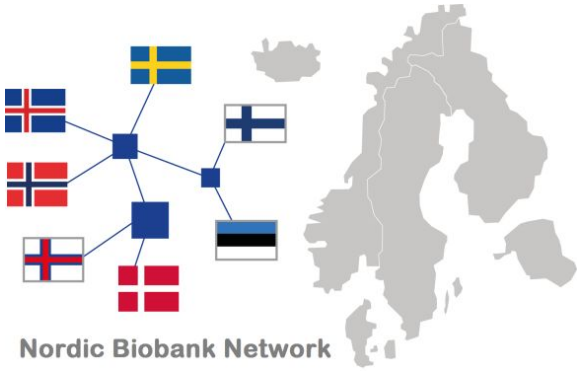
The eMERGE Network
electronic Medical Records & Genomics
A consortium of biorepositories linked to electronic medical records data for conducting genomic studies

CHINA KADOORIE BIOBANK
中国慢性病前瞻性研究

MVP

The Research Program on
Genes, Environment, & Health

قطر بيوبنك
qatarbiobank
for medical research للبحوث الطبية
Member of Qatar Foundation عضو في مؤسسة قطر



Nordic Biobank Network

UNIVERSITY OF TARTU
1632

estonian genome center

deCODE genetics

BIOBANK JAPAN

Deep Phenotyping

- **Deep phenotyping** can be defined as the precise and comprehensive analysis of phenotypic abnormalities in which the individual components of the phenotype are observed and described

DEEP PHENOTYPING

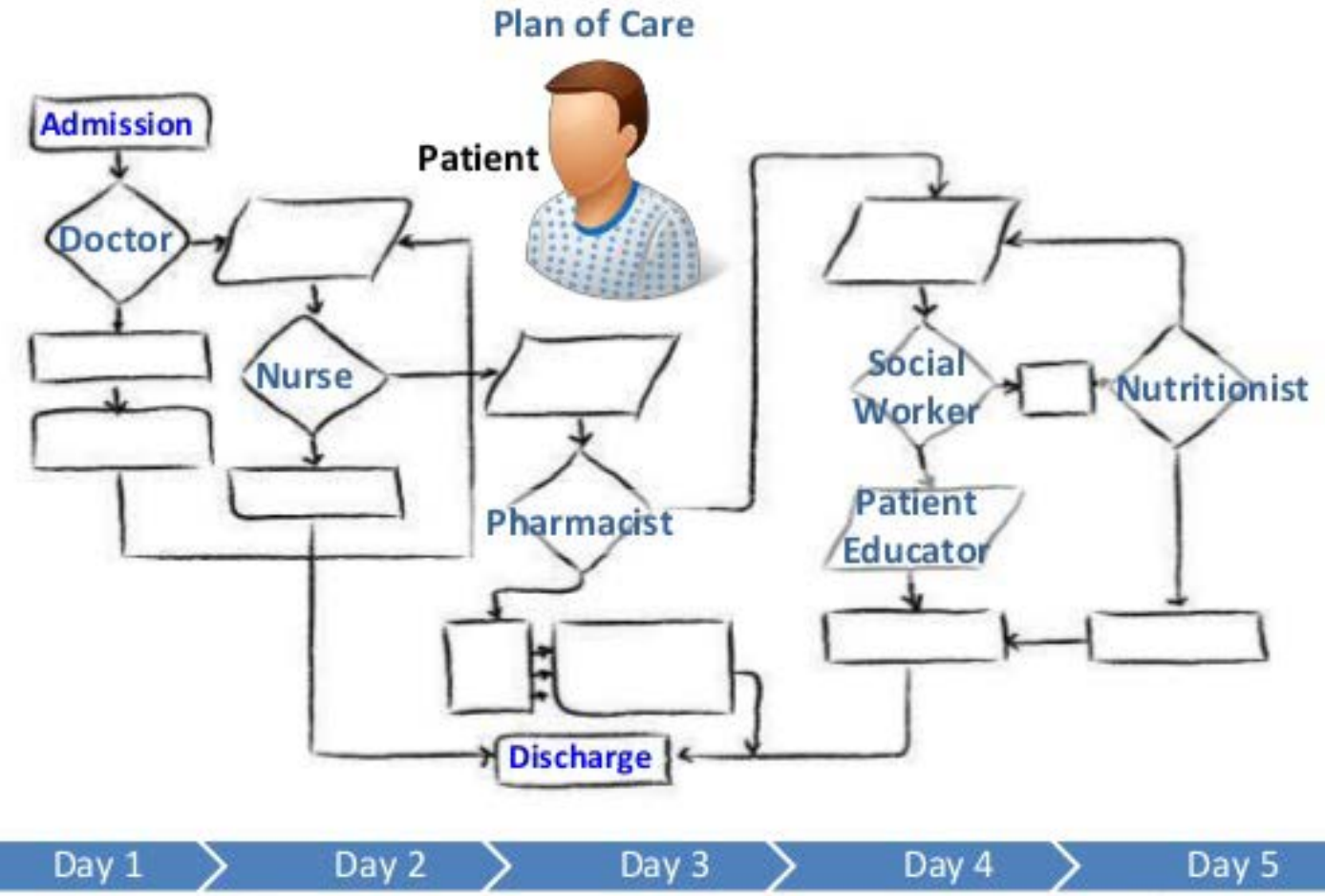
The details of disease

Precision medicine demands precise matching of deep genomic and phenotypic models — and the deeper you go, the more you know.

Delude, Nature, Nov 2015

Are our health records up to the challenge of deep phenotyping?

What is a Clinical Pathway?



http://www.slideshare.net/maryam_kk/kaimrc-2014-arepathwayseffectiveakiakram

Concluding Thoughts

- Landscape is highly positive, but many aspects are at an early stage and thus aspirational. The challenge will be to get them to work
- Electronic health records and connectivity is very important, but key issues will need to be tackled
- The focus is very much on new drugs and partnership with Pharma Industry, which is of course important.
- However, most of the drugs used are off-patent, and the same issues of variability are seen. We could learn a lot, more quickly, by more funding in this area.
- Important not to forget about drug safety and drug dose
- We need buy-in of healthcare systems (re-engineering of pathways and education and training)

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LIVERPOOL HEALTH PARTNERS