Integrating Pharmacogenomics into Decision Making

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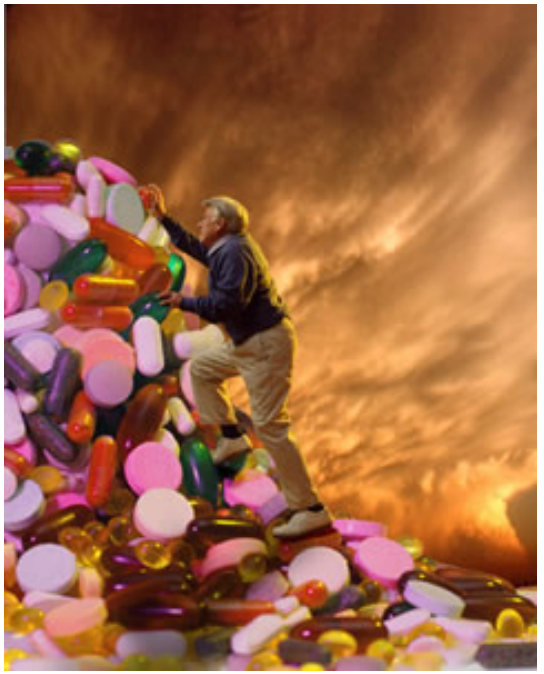
THE WOLFSON CENTRE FOR PERSONALISED MEDICINE

MRC Centre for Drug Safety Science

Definitions

Pharmacogenetics
(after Vogel, 1957)

The study of variations in DNA sequence as related to drug response



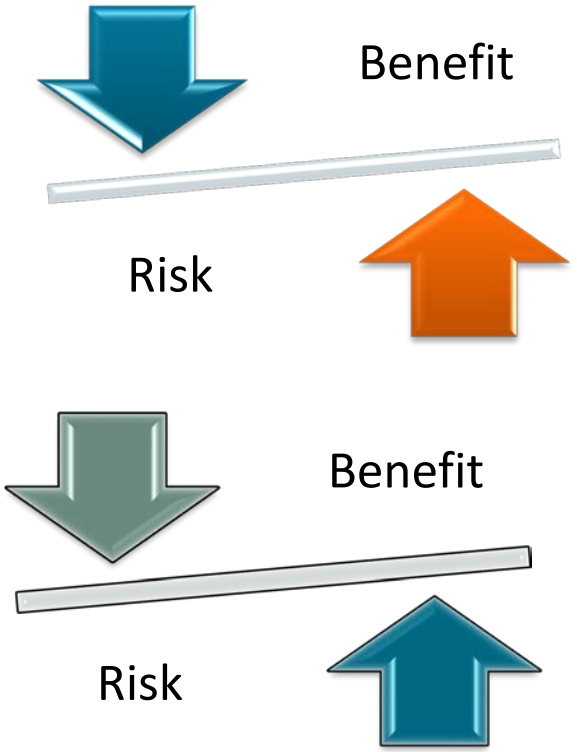
ICH Topic E15, November 2007

Pharmacogenomics
(after Marshall, 1997)

The study of variations of DNA and RNA characteristics as related to drug response

PGx is a part of the drive towards precision medicine

Regulatory Decision Making



Based on population data

Based on individual/small group data

Moving closer to what happens in the clinic

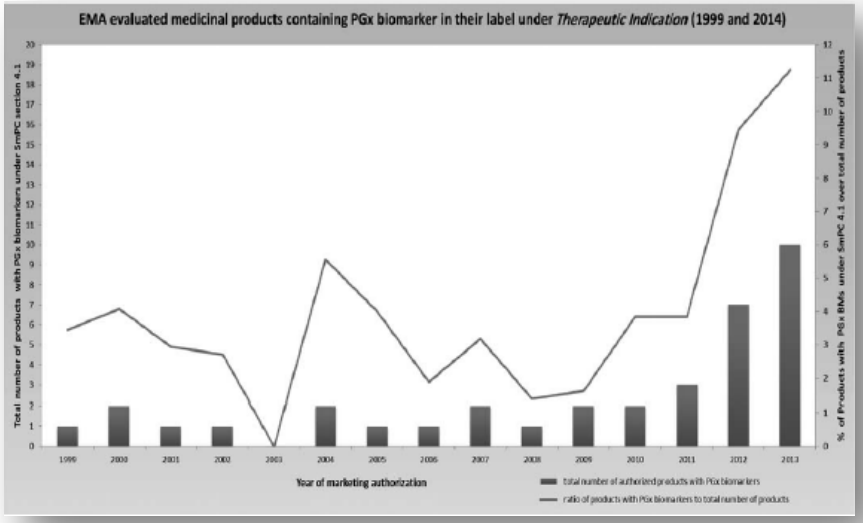
PERSPECTIVE

Pharmacogenomic information in drug labels: European Medicines Agency perspective

F Ehmann[1], L Caneva [1], K Prasad[2,3], M Paulmichl[2,4], M Maliepaard[2,5,6], A Llerena[2,7], M Ingelman-Sundberg[8] and M Papaluca-Amati[1]

The Pharmacogenomics Journal (2015) 15, 201–210

- 15% of EMA evaluated medicines containing PGx information
  - Therapeutic indication (3.5%)
  - Posology and method of administration(4.4%)
  - Contraindications (6.4%)



Number of PGx biomarkers increasing

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

Only 3 drugs outside the cancer area

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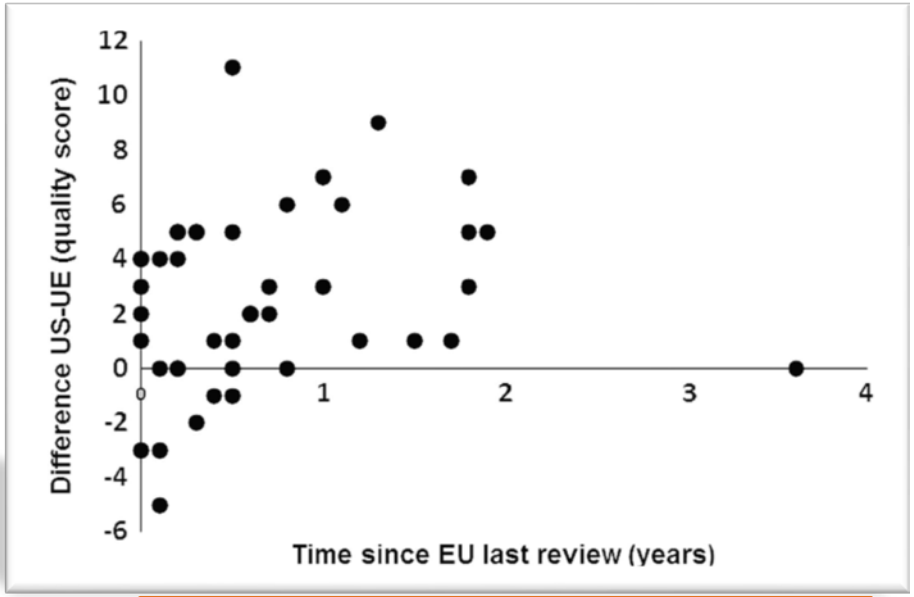
Comparing cytochrome P450 pharmacogenetic information available on United States drug labels and European Union Summaries of Product Characteristics

J Reis-Pardal[1], A Rodrigues[2], E Rodrigues[3] and F Fernandez-Llimos[4]

The Pharmacogenomics Journal (2016), 1–6

US labels:

- Presented more PGx subheadings (51 vs 26%)
- More prevalence and PK data for each phenotype
- More information about dose modification
- Need for more harmonization



75% of US labels scored higher

Original Investigation

Clinical Evidence Supporting Pharmacogenomic Biomarker Testing Provided in US Food and Drug Administration Drug Labels

Bo Wang, PharmD; William J. Canestaro, MSc; Niteesh K. Choudhry, MD, PhD

JAMA Intern Med. 2014;174(12):1938-1944.

- 119 drug-biomarker combinations
- 43 (36.1%) had convincing clinical validity evidence
- 18 (15.1%) evidence of clinical utility
- 61 labels (51.3%) – clinical decisions based on results of biomarker test: 36 (30%) contained convincing clinical utility data

"It may be premature to include biomarker testing recommendations in drug labels when convincing data that link testing to patient outcomes do not exist."

Drug Development and Companion Diagnostics

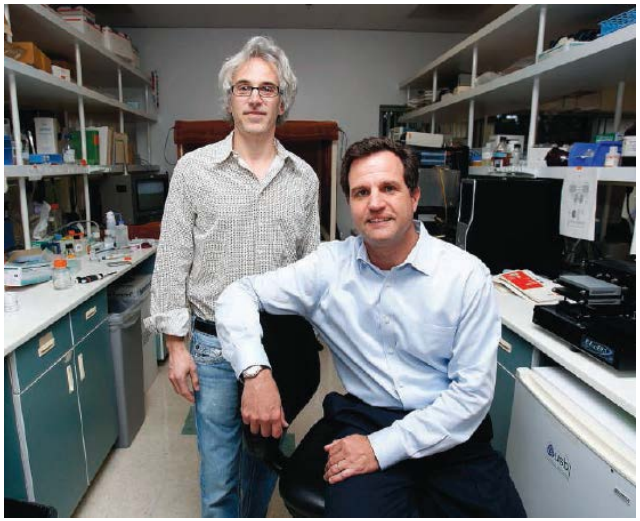
- Co-development of targeted drug with a companion diagnostic
- Usually evidence based on randomised controlled trials and reflected in the label
- Guidance available from EMA and FDA

- **Looking to the future:**
  - With single biomarkers, tests from multiple providers can pose issues in terms of analytic validity
  - We may be moving from single biomarkers to biomarker panels or ultimately to next generation sequencing
  - Regulation of such multiple biomarker panels will be challenging – single provider, multiple providers etc?
  - Debate on how to regulate next generation sequencing.

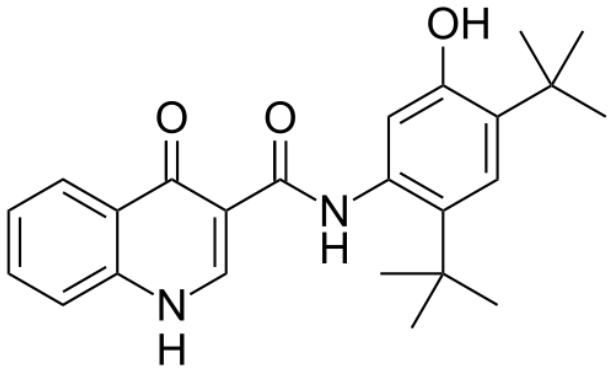
New Cystic Fibrosis Drug Offers Hope, at a Price

SCIENCE VOL 335 10 FEBRUARY 2012

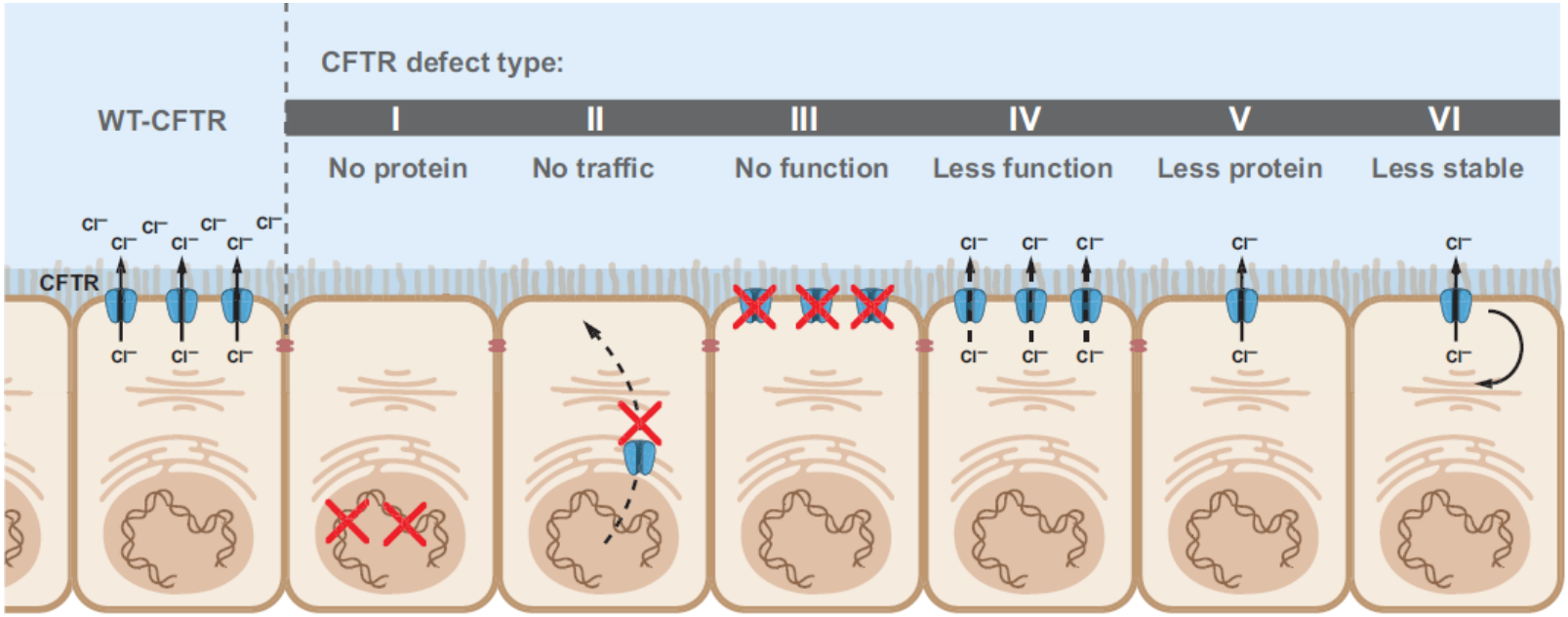
- New CF drug, ivacaftor
- Targets *G551D* mutation in the *CFTR* gene (4% of CF population)
- Fantastic innovation with increases in FEV1 ~10%



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



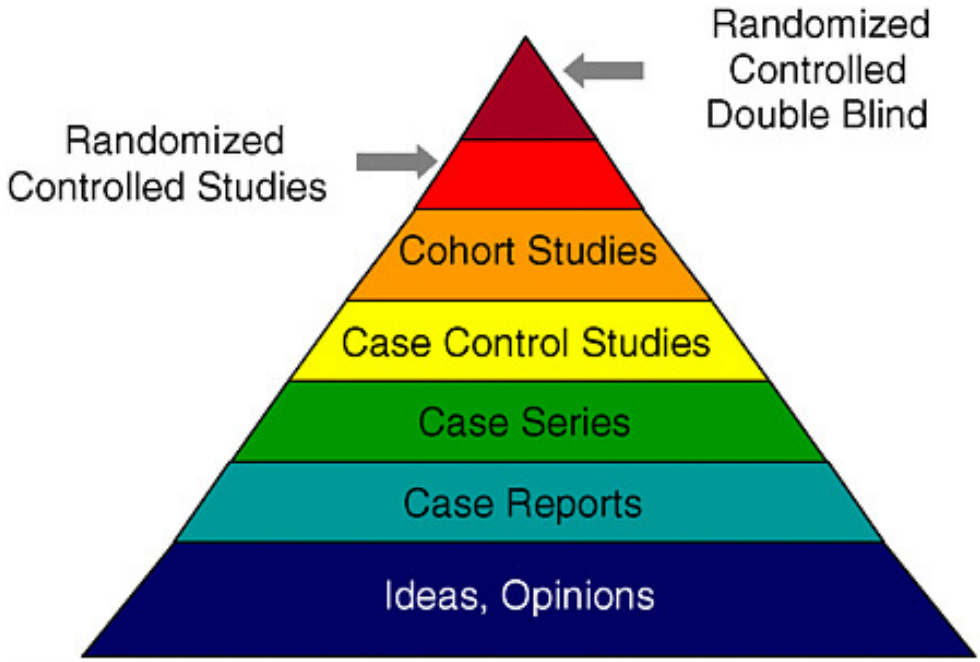
Indication expanded in 2014:
G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, and G1349D



Mutation examples	G542X (a) W1282X (a) 1717-1G (b)	F508del N1303K A561E	G551D S549R G1349D	R117H R334W A455E	A455E 3272-26A>G 3849+10 kb C>T	c.120del23 rF508del
Corrective therapy	Rescue synthesis	Rescue traffic	Restore channel activity	Restore channel activity	Correct splicing	Promote stability
Drug	Read-through compounds	Correctors	Potentiators	Potentiators	AONs Correctors Potentiators	Stabilizers

The Evidence Hierarchy

- RCTs are top of the hierarchy
- Challenges:
  - Smaller populations
  - Multiple mutations
  - Cost
  - Existing drugs

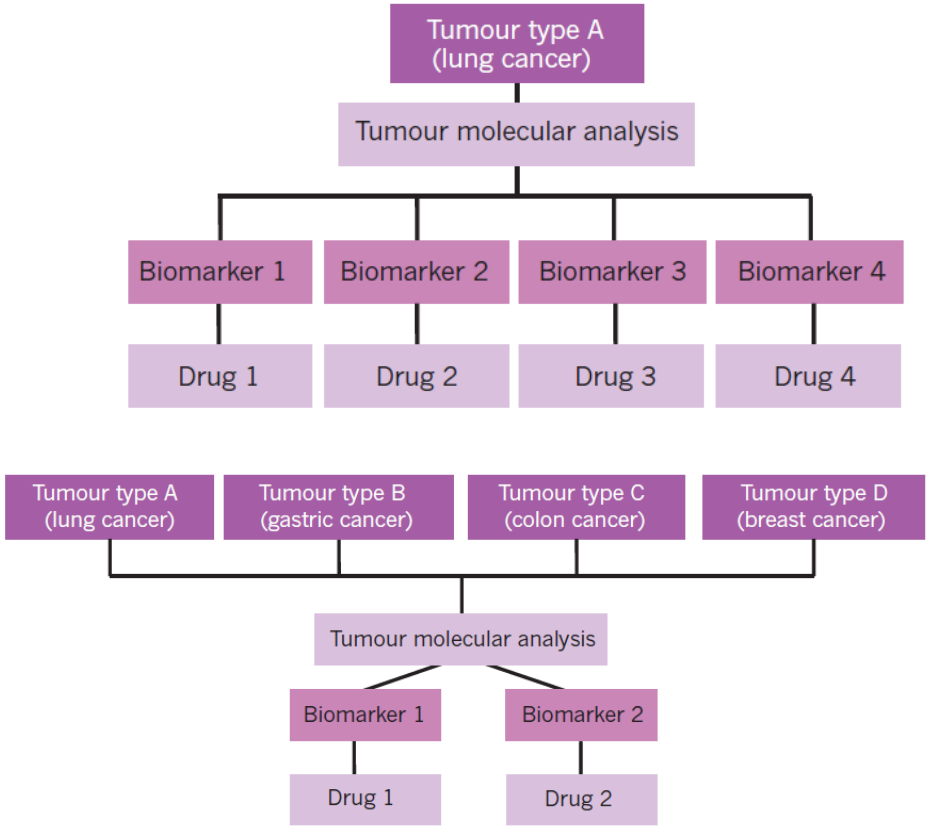


Patient-centric trials for therapeutic development in precision oncology

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



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

Carbamazepine Hypersensitivity

- More complicated than abacavir hypersensitivity
- Different phenotypes
  - Skin (mild → blistering)
  - Liver
  - Systemic (DRESS)
- Predisposition varies with ethnicity and phenotype
  - HLA-B*1502 (Chinese)
  - HLA-A*3101 (Caucasian)

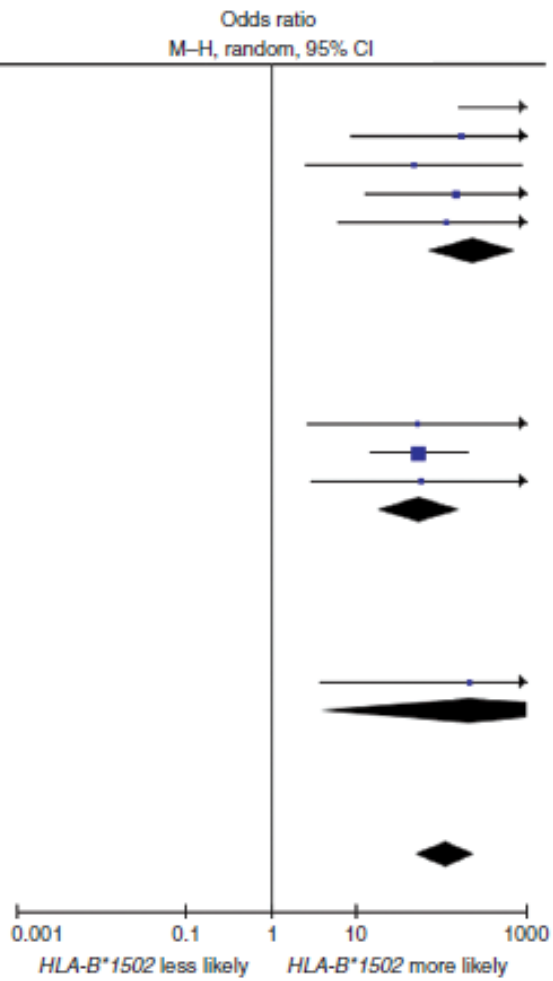
HLA Genotype and Carbamazepine-Induced Cutaneous Adverse Drug Reactions: A Systematic Review

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 ($P = 0.20$); $I^2 = 36.9\%$							



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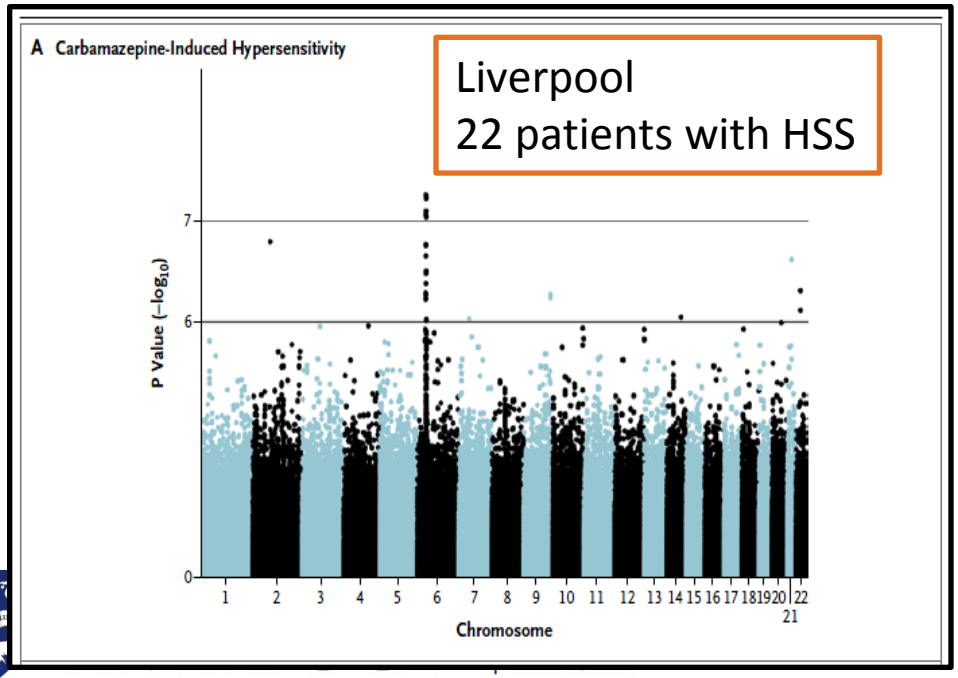
ORIGINAL ARTICLE

HLA-A*3101 and Carbamazepine-Induced Hypersensitivity Reactions in Europeans

Mark McCormack, B.A., Ana Alfirevic, M.D., Ph.D., Stephane Bourgeois, Ph.D., John J. Farrell, M.S., Dalia Kasperavičiūtė, Ph.D., Mary Carrington, Ph.D., Graeme J. Sills, Ph.D., Tony Marson, M.B., Ch.B., M.D., Xiaoming Jia, M.Eng., Paul I.W. de Bakker, Ph.D., Krishna Chinthapalli, M.B., B.S., Mariam Molokhia, M.B., Ch.B., Ph.D., Michael R. Johnson, D.Phil., Gerard D. O'Connor, M.R.C.P.I., Elijah Chaila, M.R.C.P.I., Saud Alhusaini, M.B., Kevin V. Shianna, Ph.D., Rodney A. Radtke, M.D., Erin L. Heinzen, Ph.D., Nicole Walley, B.S., Massimo Pandolfo, M.D., Ph.D., Werner Pichler, M.D., B. Kevin Park, Ph.D., Chantal Depondt, M.D., Ph.D., Sanjay M. Sisodiya, M.D., Ph.D., David B. Goldstein, Ph.D., Panos Deloukas, Ph.D., Norman Delanty, B.M., Gianpiero L. Cavalleri, Ph.D., and Munir Pirmohamed, Ph.D., F.R.C.P.

N Engl J Med 2011; 364:1134-1143 | March 24, 2011

N Engl J Med 2011;364:1134-43.



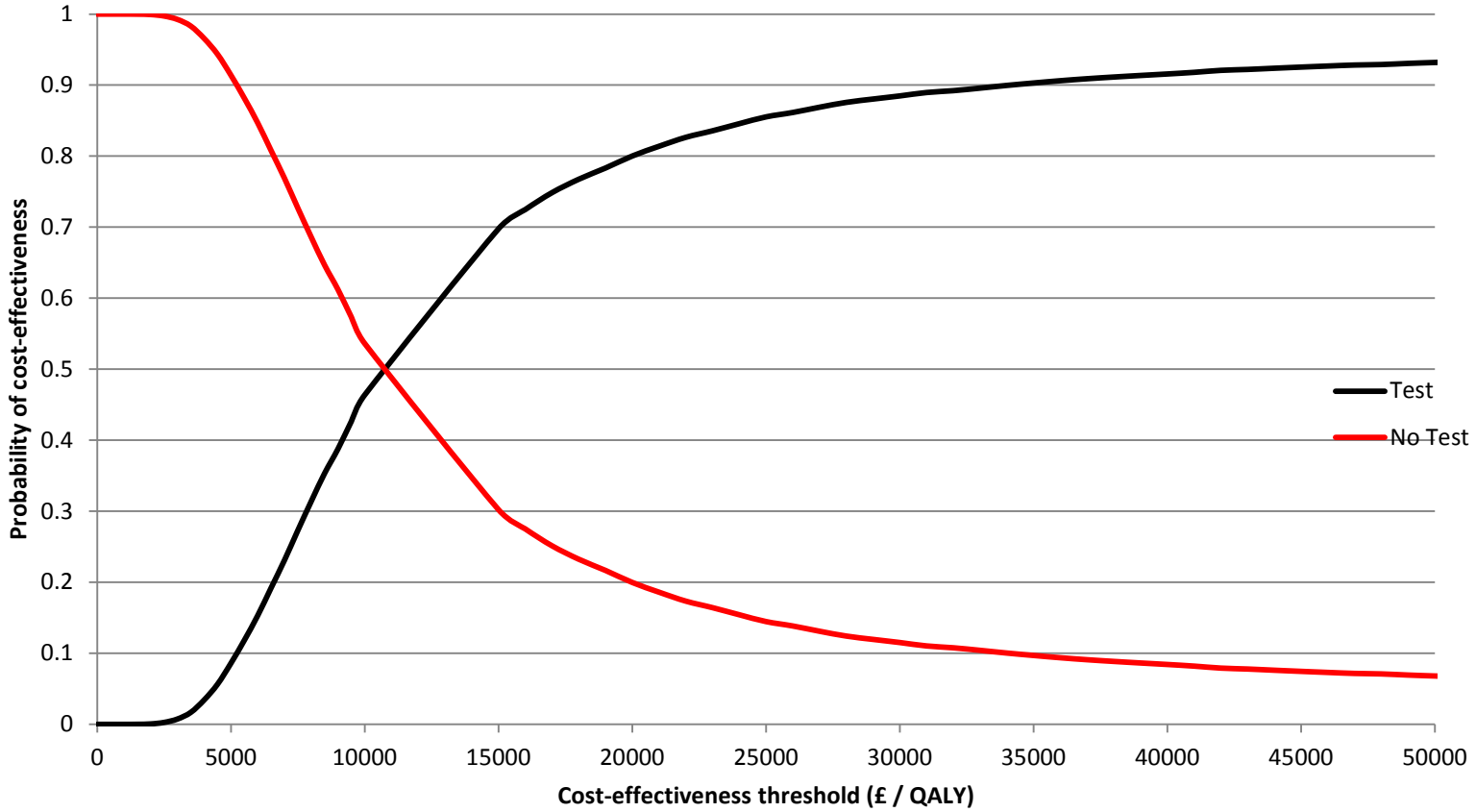
Liverpool
22 patients with HSS

- Replicated in Japanese, Chinese, South Korean, Canadian and EU populations
- NNT = 47
- SmPC/drug label changed (for information). NOT MANDATORY

MRC | Centre for Drug Safety Science

Cost-effectiveness of screening for *HLA-A*31:01* prior to initiation of carbamazepine in epilepsy

*Catrin O. Plumpton, †Vincent L. M. Yip, †Ana Alfirevic, †Anthony G. Marson, †Munir Pirmohamed, and *Dyfrig A. Hughes



Treating Patients with Renal Impairment

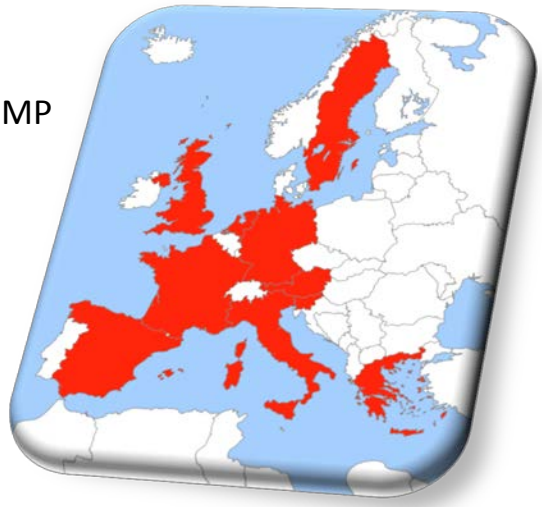
- Degree of dose reduction based on PK (occasionally with PD) modelling
- RCTs not usually done
- Accepted as standard practice by clinicians
- Implementation helped by ready availability of renal function tests

- Genetic polymorphism with the same effect size usually not acted upon
- Lack of availability of tests may be one factor

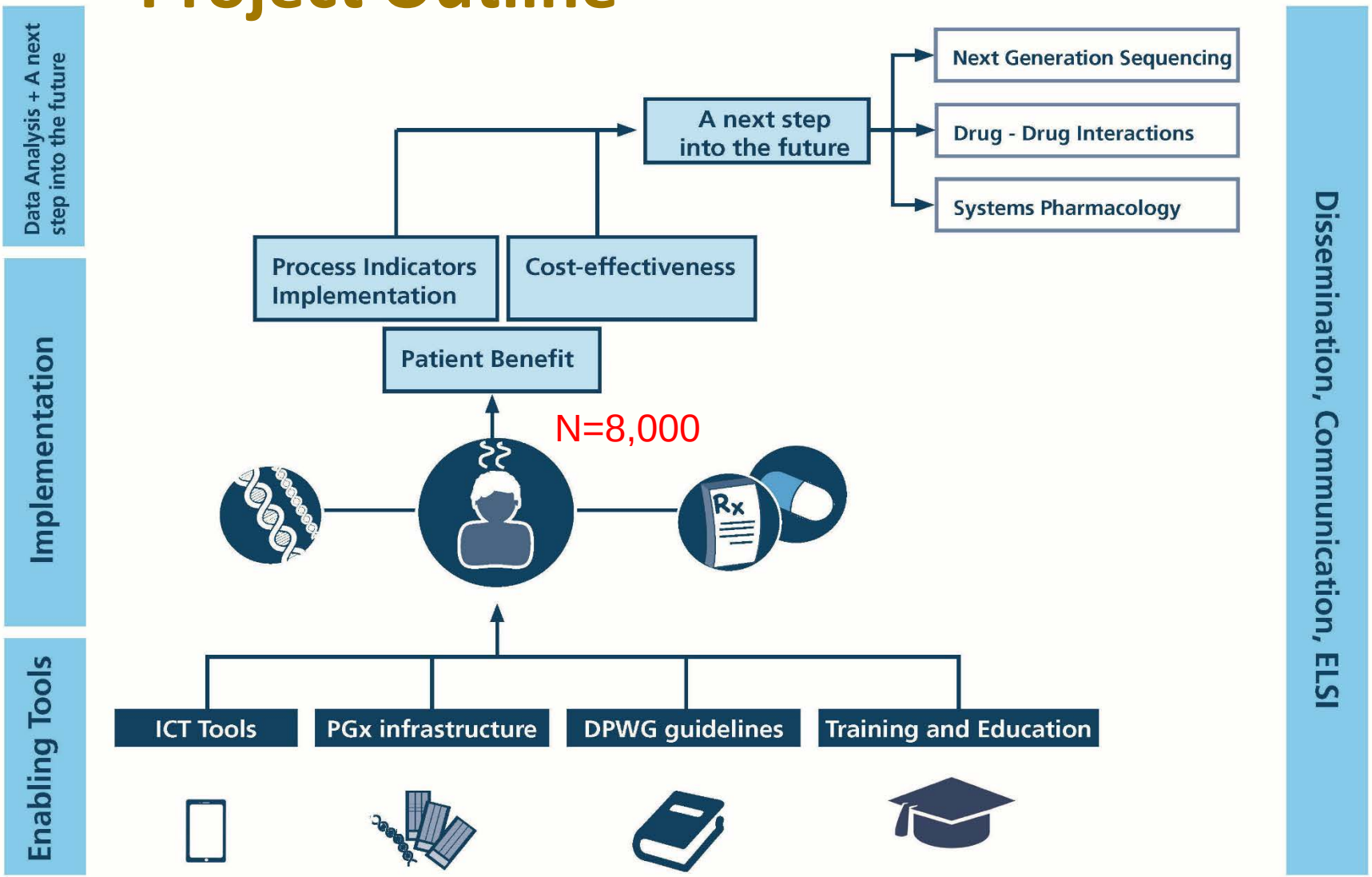
U-PGx | Ubiquitous Pharmacogenomics

- €15 million, H2020, 10 EU countries
- Implement pre-emptive PGx testing in a real world clinical setting across 7 EU sites
- Evaluate **patient outcome** and **cost effectiveness** using solid **scientific methodology**
- Start 1-1-2016, 5 years
- Consortium members:

- **H-J Guchelaar (Coordinator),**
- JJ Swen, M Kriek, LUMC
- M Pirmohamed, R Turner, UOL
- J Stingl, FDMD
- M Ingelman-Sundberg, KI
- M Karlsson, S Jönsson, PBUU
- M Schwab, E Schaeffeler, IKP
- VHM Deneer STZHM
- M Samwald, G Sunder-Plassmann, MUWV
- M van Rhenen, KC Cheung, KNMP
- C Mitropoulou, GHXF
- D Steinberger, BIOL
- CL Davila Fajardo, SAS
- G Patrinos, UPAT
- V Dolžan, ULMF
- A Cambon-Thomsen, UPS
- G Toffoli, E Cecchin, CROA



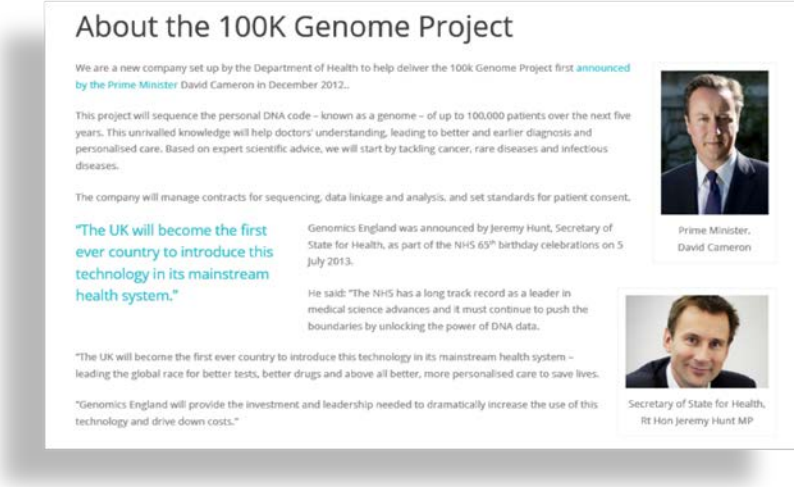
Project Outline



100,000 Genomes Project in England

- A transformational project for the NHS to embed genomic medicine into practice
- 100,000 genomes from 70,000 individuals
- Accompanied by Genomics England Clinical Interpretation Partnerships (to undertake research) - GeCIP
- Pharmacogenomics sub-domain GeCIP to explore issues related to PGx variants

Genomics england



About the 100K Genome Project

We are a new company set up by the Department of Health to help deliver the 100k Genome Project first announced by the Prime Minister David Cameron in December 2012..

This project will sequence the personal DNA code – known as a genome – of up to 100,000 patients over the next five years. This unrivalled knowledge will help doctors' understanding, leading to better and earlier diagnosis and personalised care. Based on expert scientific advice, we will start by tackling cancer, rare diseases and infectious diseases.

The company will manage contracts for sequencing, data linkage and analysis, and set standards for patient consent.

"The UK will become the first ever country to introduce this technology in its mainstream health system."

Genomics England was announced by Jeremy Hunt, Secretary of State for Health, as part of the NHS 65th birthday celebrations on 5 July 2013.

He said: "The NHS has a long track record as a leader in medical science advances and it must continue to push the boundaries by unlocking the power of DNA data.

"The UK will become the first ever country to introduce this technology in its mainstream health system – leading the global race for better tests, better drugs and above all better, more personalised care to save lives.

"Genomics England will provide the investment and leadership needed to dramatically increase the use of this technology and drive down costs."

Prime Minister, David Cameron

Secretary of State for Health, Rt Hon Jeremy Hunt MP

The Only Thing That Is Constant Is Change

Heraclitus (535BC - 475BC)