



Personalised Medicine: Relevance to Pharmacy and Medical Practice

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 : @MPUoL



Terminology

Personalised

Stratified

Precision

Patient quote:

- “..we should stop using the term precision medicine, as the perception that we are practicing imprecisely is frightening to patients”

“an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person”

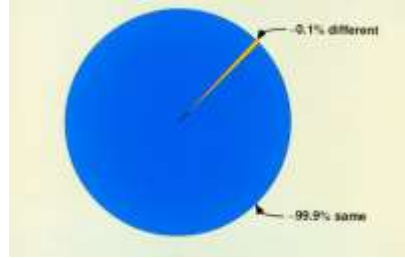


Definitions

Pharmacogenetics

(after Vogel, 1957)

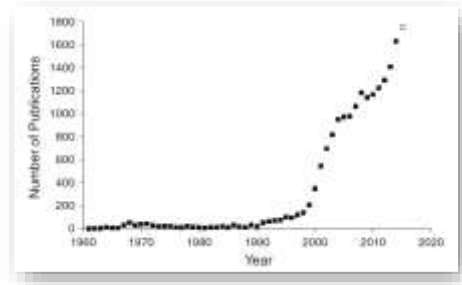
The study of variations in DNA sequence as related to drug response



Pharmacogenomics

(after Marshall, 1997)

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

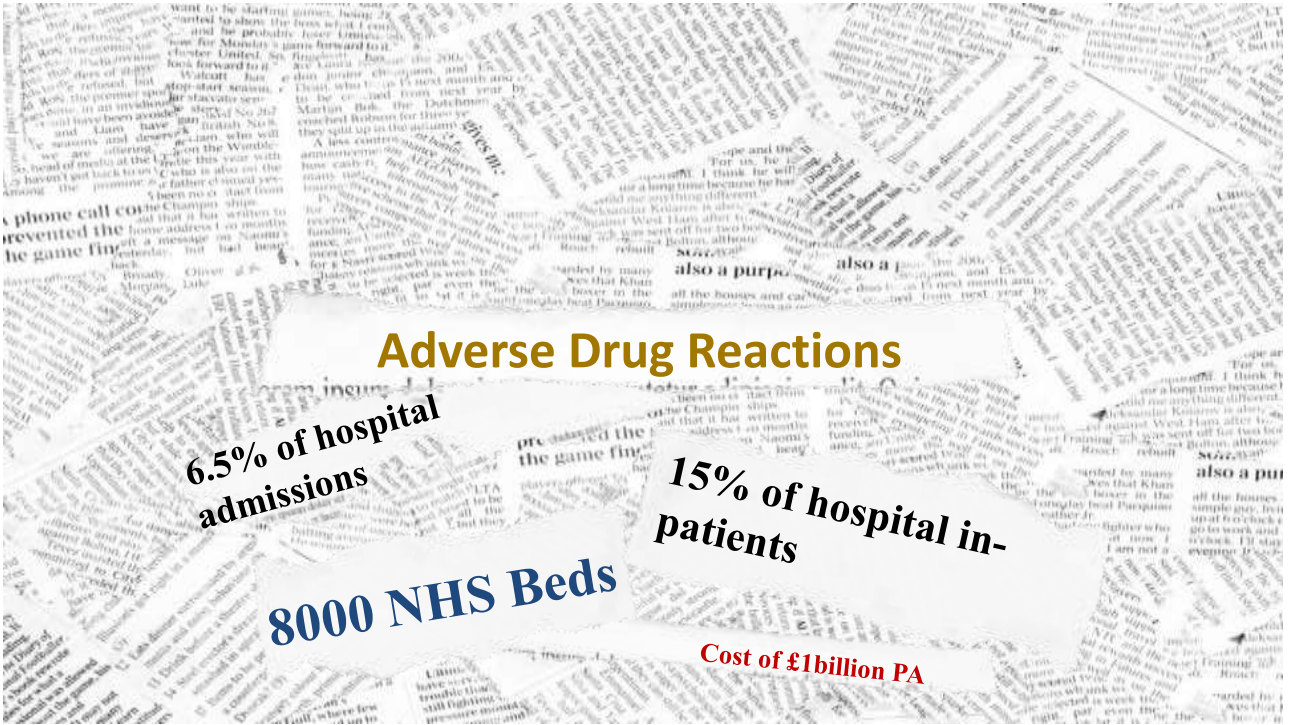


ICH Topic E15, November 2007



Variability in Drug Efficacy

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

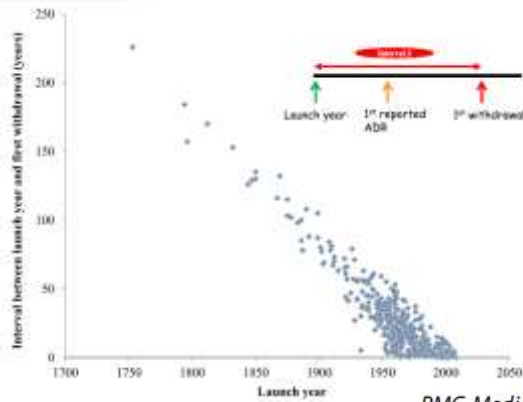


Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature

Igho J. Onakpoya, Carl J. Heneghan and Jeffrey K. Aronson

- 462 withdrawals between 1953 to 2013
- Evidence was anecdotal reports (72% of cases)
- Median interval between first ADR report and withdrawal was 6 years

- ▶ Hepatotoxicity (81 cases; 18%)
- ▶ Immune-related reactions (79 cases; 17%)
- ▶ Cardiotoxicity (63 cases; 14%)



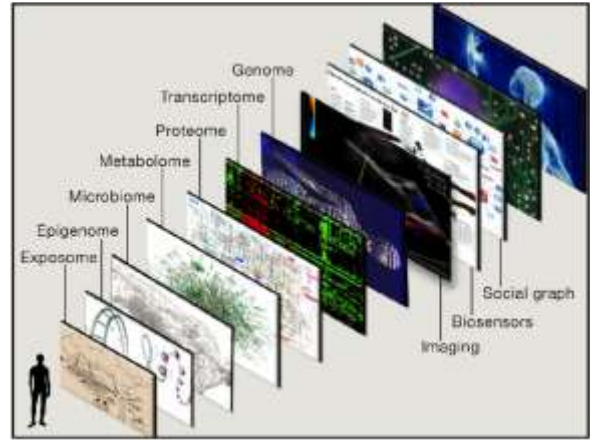
UNIVERSITY OF LIVERPOOL

THE WOLFSON CENTRE FOR PERSONALISED MEDICINE

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BMC Medicine (2016) 14:10

MRC Drug Safety Science

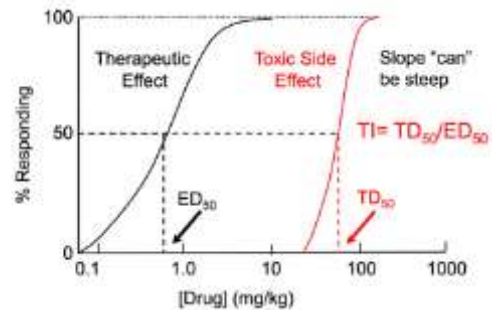


Dose, Genetics and ADRs



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

Paracelsus



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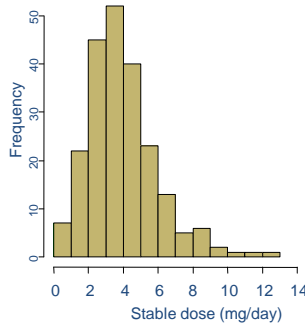


Warfarin

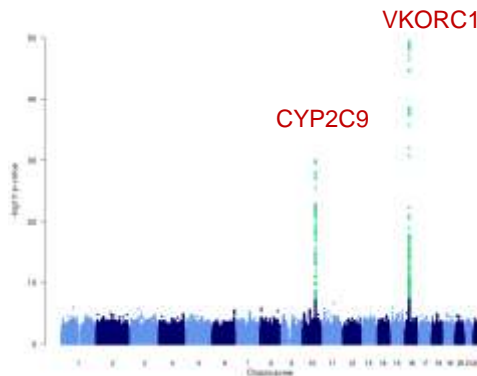
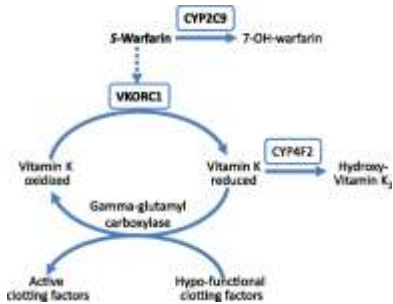
- Number of users UK:
600,000
- Dose (mg) range per day:
0.5-20
- Fold variability in dose:
40
- Major bleeding rate per 100-person years:
2.6
- Ranking in ADR list:
3



Approved for human use in 1954



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



Total = 57.9%

Age: 11.2%

Height 3.56%

Weight: 5.98%

Interacting meds: 0.98%

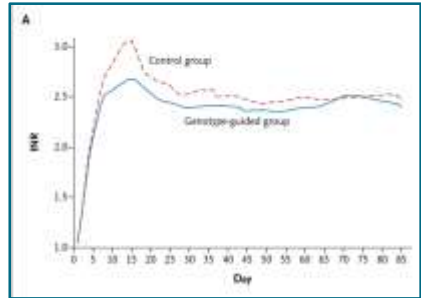
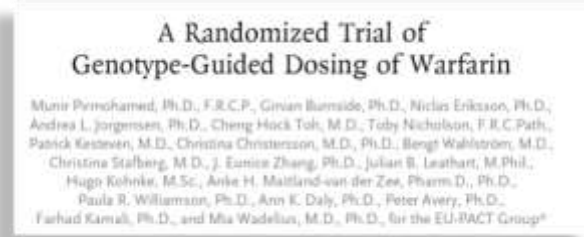
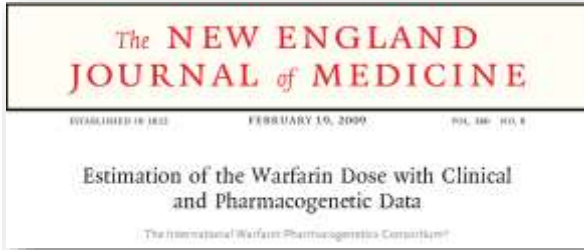
Sum of interacting meds: 2.2%

VKORC1: 25.61%

CYP2C9: 16.65%

CYP4F2: 0.49%

Pharmacogenomics of Warfarin Dosing



Implemented in anticoagulant clinics
Genotype results in 45 min

MRC | Drug Safety Science

Definition of Sensor

- A device which detects or measures a physical property and records, indicates, or otherwise responds to it

Oxford English Dictionary



Nine Sensors

Classification of Sensors

- | | |
|---------------------|------------------------|
| Temperature Sensor. | Proximity Sensors. |
| IR Sensor. | Pressure Sensor. |
| Ultrasonic Sensor. | Level Sensors. |
| Touch Sensor. | Smoke and Gas Sensors. |

Each car has **60-100** sensors on board, but will increase to about **200** in the near future

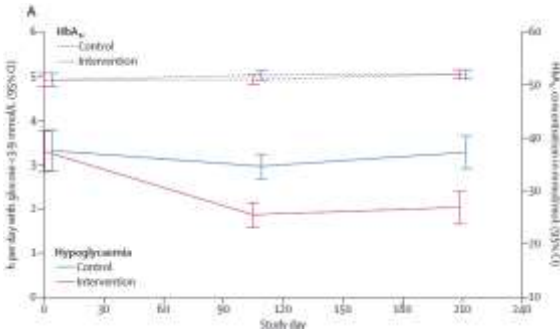


Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial

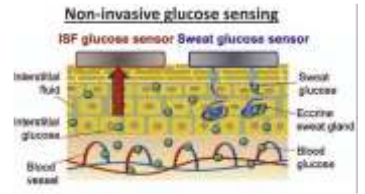
Lancet 2016; 388: 2254-63

Jan Böökler, Ramona Antuna, Petronella Geelhoed-Duyvestijn, Jemi Kröger, Raimund Weitgasser

- RCT to test effect of sensor-based monitoring of glucose vs self-monitoring with capillary strips



- Reduced hypoglycaemic episodes
- No worsening in diabetes control
- Well tolerated
- An example of precision dosing



Adherence Sensor

FDA has just approved formulation of aripiprazole with embedded Proteus' sensor as a drug-device combination product



3D Printing



You could soon be manufacturing your own drugs—thanks to 3D printing

By [Robert Service](#); Science: Jan. 18, 2018 , 2:50 PM

Levetiracetam: the first 3D printed medicine to receive FDA approval (August 2015)



Nucleic acid based therapies: developing frontier for precision medicine

Affordability will be the key challenge

Munir Pirmohamed professor

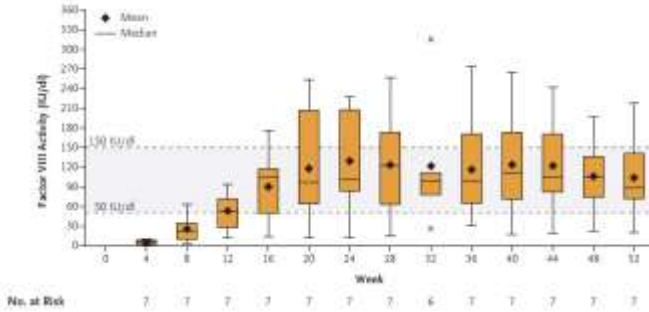
BMJ, published 23 Jan 2018



AAV5–Factor VIII Gene Transfer in Severe Hemophilia A

DOI: 10.1056/NEJMoa1708483

Savita Rangarajan, M.B., B.S., Liron Walsh, M.D., Will Lester, M.B., Ch.B., Ph.D., David Perry, M.D., Ph.D., Bella Madan, M.D., Michael Laffan, D.M., Hua Yu, Ph.D., Christian Vettermann, Ph.D., Glenn F. Pierce, M.D., Ph.D., Wing Y. Wong, M.D., and K. John Pasi, M.B., Ch.B., Ph.D.



- Adenovirus-based gene therapy
- Normalised factor VIII levels in 6 out of 7 at 1 year
- Effect lasted for more than one year
- Bleeding ceased by 22 weeks
- Rescue use of factor VIII declined
- Based on ONE IV INFUSION

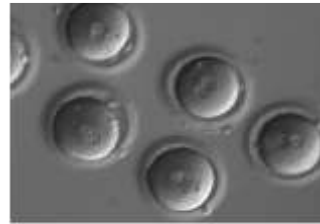


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Genome Editing

- Molecular scissors to alter DNA – remove, insert or replace
- Can be used for the germline genome or for somatic genome
- Ethical issues for human embryo editing and fears of “designer babies”
- Challenge in clinical practice of
 - ▶ Wider availability
 - ▶ Cost of CAR-T cell therapy (\$450,000)



Zygotes

Embryo gene editing: correction of mutation for hypertrophic cardiomyopathy (*MYBPC3*)



CAR T-cell therapy



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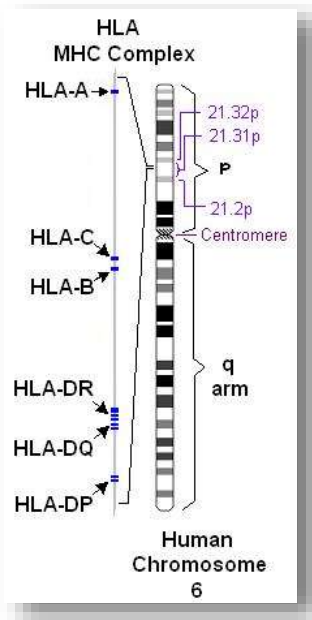


Human Leucocyte Antigens (HLA) and Hypersensitivity Reactions

- On short arm of chromosome 6
- Involved in the pathogenesis of immune-mediated adverse drug reactions



Abacavir hypersensitivity
HLA-B*57:01
 Decrease incidence from 7% to <1%



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



HLA Panel Analytic Validation

- Platform was able to call risk alleles with 100% accuracy at all the loci (n=187 healthy volunteers) using sequence based typing as the standard

Number of Risk Alleles per sample	Number of Samples	% of samples
0	28	15.0
1	39	20.9
2	14	7.5
3	46	24.6
4	34	18.2
5	11	5.9
6	6	3.2
7	8	4.3
8	1	0.5

85% have at least 1 risk allele

Use

- At time needed
- Store data on EHR
- Pre-emptive genotype



Funded by NIHR



Clinical Decision Support

Please select your drug and/or alleles of interest:

Drug				Allele			
Abacavir	Abacavir	Abacavir/Didanosine	Abacavir/Zidovudine Drug	A*31:01	A*32:01	A*40:01	A*41:01
Acyclovir	Carbamazepine	Clonidine	Clonidine	B*15:02	B*15:05	B*40:01	B*50:02
Acyclovir	Clonidine	Clonidine	Clonidine	B*17:01	B*18:01	C*04:01	C*08:01
Acyclovir	MAA1 and MAA2 (Epilim and Epilim-2)	Carbamazepine	Phenytoin	DQ2*19:01	DQ4*03:01	DQ8*13:01	DQ8*19:01
Acyclovir	Carbamazepine	Carbamazepine	Carbamazepine	DQ8*15:02	DQ8*16:04	DQ8*16:05	DQ8*17:01
Acyclovir				DQ8*11:01	DQ8*13:02	DQ8*15:01	



Information updated 01 March 2017



Artificial Intelligence

- Artificial intelligence is a sub-field of computer science. Its goal is to enable the development of computers that are able to do things normally done by people -- in particular, things associated with people acting intelligently.



John McCarthy
Stanford University
1956

OXFORD ENGLISH DICTIONARY

Artificial:

Contrived or fabricated for a particular purpose, esp. for deception; resulting from artifice; feigned, fictitious

Intelligence:

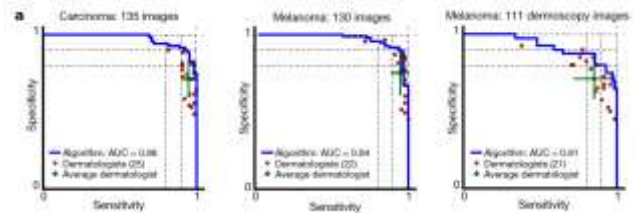
Knowledge concerning events communicated by or obtained from another; information, news



Dermatologist-level classification of skin cancer with deep neural networks

Andre Esteve^{1*}, Brett Kuprel^{1*}, Roberto A. Novoa^{2,3}, Justin Ko², Susan M. Swetter^{2,4}, Helen M. Blau⁵ & Sebastian Thrun⁶

2 FEBRUARY 2017 | VOL 542 | NATURE | 115



Trained the neural network with 129,450 clinical images
2032 different diseases
Tested performance against 21 Dermatologists
6.3 billion smartphones by 2021 – low cost universal diagnostic care



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ARTICLE OPEN

Scalable and accurate deep learning with electronic health records

Alvin Rajkomar^{1,2*}, Eyal Oren¹, Kai Chen¹, Andrew M. Dai¹, Nissim Hajaj², Michaels Hardt¹, Peter J. Liu¹, Xiaobing Liu¹, Jake Marcus¹, Mimi Sun¹, Patrik Sundberg¹, Hector Yee¹, Kun Zhang¹, Yi Zhang¹, Gerardo Flores¹, Gavin E. Duggan¹, Jamie Irvine¹, Quoc Le¹, Kurt Litsch¹, Alexander Mossin¹, Justin Tansuwan¹, De Wang¹, James Wexler¹, Jimbo Wilson¹, Dana Ludwig², Samuel L. Volchenboum², Katherine Chou¹, Michael Pearson¹, Sriniivasan Madabushi¹, Nigam H. Shah⁴, Atul J. Butte², Michael D. Howell¹, Claire Cui¹, Greg S. Corrado¹ and Jeffrey Dean¹

npj Digital Medicine (2018)1:18; doi:10.1038/s41746-018-0029-1

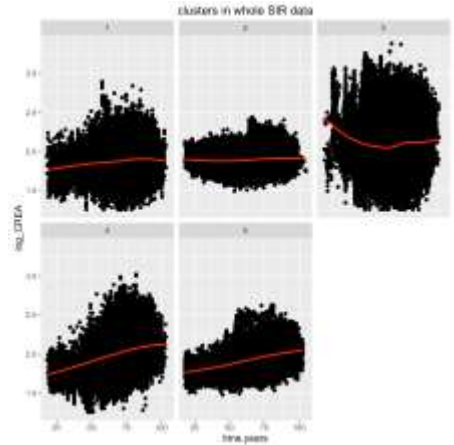
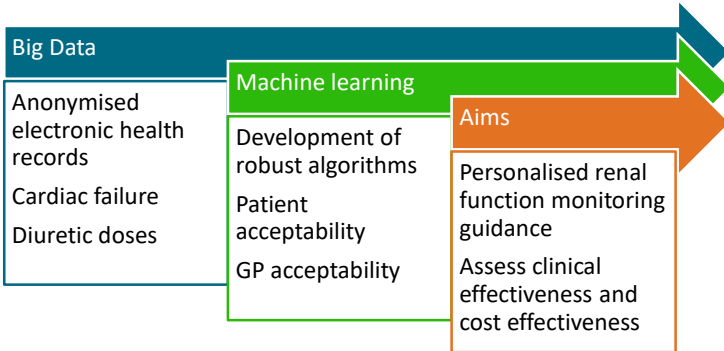
- Predictive models important for personalised medicine
- Statistical models require curated data from EHR where vast majority of data is lost
- What if you can use the entire raw EHR data?
- 2 hospitals: 216,221 records
- Had 46,864,534,945 data points
- Predicting in hospital mortality ((AUROC across sites 0.93-0.94), 30-day unplanned readmission (AUROC 0.75-0.76), prolonged length of stay (AUROC 0.85-0.86), and all of a patient's final diagnoses (frequency-weighted AUROC 0.90).



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Big Data Approach to Personalised Renal Function Monitoring



Direct To Consumer Genetic Testing



- 5 million people have had DTC genetic testing done
- Whole genome sequencing is becoming cheaper



Pharmacogenetic Cards

Gen	Allele	Metabolism	Typ.	Detected
CYP2D6	*10/*1	Normal	80%	72.3
CYP2C19	*17/*1	Normal	80%	72.3, 17
CYP2C9	*1/*1	Slow	10%	72.3, 10, 10, 10, 10, 10, 10
CYP2C10	*1/*1	Normal	80%	72.3, 10, 10, 10, 10, 10, 10

Netherlands

Unknown A

PKA B Gene : PKA-B*15:01/35:03
CYP450 Gene : CYP2C9*17/1

จำนวนยีน : 18 ยีนรวม 2560
รวมยีนหายากทั้งหมด 10 ยีน

ให้บริการโดยเภสัชกรคลินิก Pharmacy Management System
ศูนย์บริการเภสัชกรรม (Pharm-Service) PBM

Thailand

safety-code
The Medication Safety Code initiative

What is it?
The Medication Safety Code on the left represents a patient-specific genetic profile regarding important pharmacogenes.

How does it work?
After scanning the QR code (e.g. with a smartphone), you are led to a website that displays patient-specific drug dosing recommendations.

www.safetycode.org

laboratory contact:
+66 228550710
Gene lab name:
GeneLab (GeneLab 133/45-1334)
Specify name:

Ubiquitous PGx Trial



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Education and Training

- Modernisation of curricula
- More skilled workforce
- Intelligent decision support systems
- Education of the public

Education and Knowledge in Pharmacogenomics: Still a Challenge?

Jyothsna Giri¹, Timothy B. Curry², Christine M. Forness³, Wayne T. Nicholson² and Carolyn R. Rohrer Vittek¹

A number of barriers exist for adoption of pharmacogenomics into practice. Physicians, pharmacists, and nurses report limited knowledge about pharmacogenomics and its use in patient care. Lack of pharmacogenomics education curricula as part of professional schools or postgraduate training programs has been reported as a potential cause.¹ Understanding pharmacogenomics is further complicated by a complex and nonstandard lexicon, limited medication guidelines, rapidly changing evidence, and insufficient awareness of test availability and utility.

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Pharmacogenetic Knowledge of Pharmacists

- 66% felt knowledge of genetics was important, but 80% had little knowledge of pharmacogenomics
- 70% had no knowledge of what drugs require genetic testing before prescribing
- Would you like to learn more about PGx? 42% medium learning priority, 13% high learning priority, while 8% said it was essential

- Preliminary data from 112 pharmacist respondents
- Survey undertaken by Vicky Rollinson, Clinical Pharmacist and PhD student
- Looking for more individuals to take part in the survey including undergraduate students
- Please contact Vicky Rollinson: vrollins@liverpool.ac.uk



NHS England Vision for Personalised Medicine

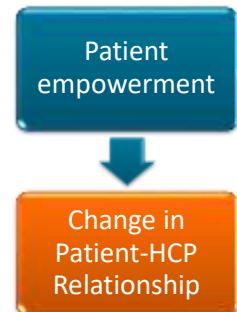


Microbiome analysis	Epigenomics	3D imaging and printing	Consumer m-health apps	Wearables and sensors
Metabolomics	Proteomics	Genome editing /therapy	Implantable biosensors	Point of care testing devices
ctDNA	Single cell 'omics	Stem cell therapy	EPR dependent technologies	Microfluidics
Pathogen Genomics	Transcriptomics	Robotics	Internet of things	Synthetic biology
Genomics	Pharmaco-genomics	Virtual and augmented reality	Machine learning	Nanomedicine

<http://www.phgfoundation.org/report/personalised-medicine-technology-landscape>



50 Years From Now



- At present we can use our phones for GPS (global positioning system)
- In 50 years time, **GPS** will also mean **Genomic Prescribing System**:
 - Whole human genome sequence carried on the phone
 - Linked to your EHR, lab tests, sensors and incorporating AI algorithms
 - Prescribing according to genome variation plus other factors



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- Vicky Rollinson
- Neil French

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- **EU-PACT (Ann Daly, Farhad Kamali, Mia Wadelius)**
- **Funders: Dept of Health (NHS Chair of Pharmacogenetics)**
- **MRC, WT, DH, NIHR, EU-FP7**

Thanks also to **MC Diagnostics** (HLA gene panel) and **LGC** (warfarin genotyping).

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