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Impact of Pharmacogenomics on Personalized / Precision Medicine

The Past, the Present and the Future

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ICCP Mangalore, India / August 31, 2023

Pharmacogenetics - Pharmacogenomics

Study and clinical application of the influence of genetic variation on drug response

Pharmacogenetics:
Variability in drug response due to heredity. Vogel,1959
Pharmacogenomics:
Role of the genome in human drug response. After 2001

The two terms are used interchangeably !

Pharmacogenomics
A broader definition

Study of genomic technologies to enable the discovery and development of novel drugs, and the optimization of drug dose and choice in individual patients to maximize efficacy and minimize toxicity

Munir Pirmohamed, Nature Rev Genetics (2023) 24: 350-362.

PHARMACOGENETICS
PHARMACOGENOMICS

Represent an essential component or part of:

Genomic Medicine
Personalized Medicine
Individualized Medicine
Stratified Medicine
Precision Medicine

The Past

PHARMACOGENETICS
PHARMACOGENOMICS

Initial Clinical Observations seven decades ago !

Pharmacogenetics

Landmark discoveries in the 1950s

1952 - 1960

1) Isoniazid: Rx of Tuberculosis

Slow metabolism (acetylation) of isoniazid is an autosomal recessive trait associated with peripheral neuropathy (Bönike & Reif, 1952; Hughes et al, 1953/1954; Evans et al, 1960)

1952 - 1957

2) Succinylcholine: Neuromuscular blocker, adjunct to anaesthesia

Prolonged muscle paralysis (apnoe) is due to altered kinetics by an atypical pseudocholinesterase inherited as an autosomal recessive trait (Evans et al, 1952; Lehmann & Ryan, 1956: Kalow & Staron, 1957)

Pharmacogenetics

Landmark discoveries in the 1950s

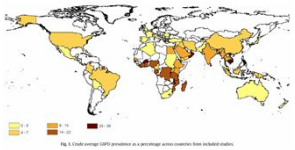
1952 - 1956

3) Primaquine, Rx and Prevention of Malaria

In World War II,10 % of U.S. African-American soldiers developed acute hemolytic crises when given primaquine or other related antimalarial drugs (Clayman et al,1952; Hockwald et al,1952)

*The sensitivity of erythrocytes is caused by a deficiency of glucose-6-phophate dehydrogenase (**G6PD**), which alters erythrocyte metabolism. G6PD deficiency is inherited as X-chromosomal recessive trait (Beutler et al,1955; Carson et al, 1956).*

Glucose-6-Phosphate Dehydrogenase Deficiency



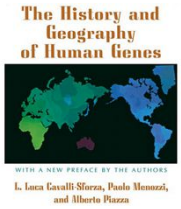
Drugs and chemicals associated with hemolysis

Antimalarials
Sulfonamides
Nitrofurantoin
Co-trimoxazole
Rasburicase
Broad beans
(Favism)
others

High correlation between **prevalence of malaria** and frequency of low activity alleles of G6PD:
Selective advantage of mutation to survive malaria

Most common enzyme deficiency (~ 400 million people)
More than 400 variants of the enzyme
Incidence Italy 0.1 to 23.1 %, Turkey 1.3 to 6.9 %, Syria ~ 3%)
Patients may present with acute hemolysis

Gammal RS et al. *Expanded Clinical Pharmacogenetics Implementation Consortium Guideline for Medication Use in the Context of G6PD Genotype.* Clin Pharmacol Ther (2023) **113** (5): 973-985.



Lesson

Gene geography*, Ancestry-Ethnicity have a major influence on the prevalence of pharmacogenomic variation

*** population-specific variants**

In the following decades……

Numerous observations of inherited variations in drug response

Next Landmark Discoveries

More examples of Mendelian inheritance of adverse drug reactions

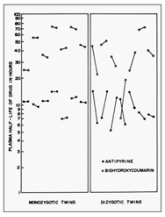
1960 - **Twin studies** suggest (poly)genic influence on pharmacokinetics of numerous drugs

1977 **Debrisoquine/sparteine** polymorphism

1980 Toxicity of **6-mercaptopurine**

1984 **Mephenytoin** polymorphism

1988 **5-Fluorouracil** toxicity



Vesell ES, 1969

Molecular mechanisms of these observations not known

Search for molecular mechanisms

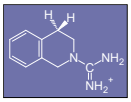
The debrisoquine / sparteine paradigm

Adverse reactions lead to discovery

Robert L.Smith

In 1975, at St. Mary's Hospital Medical School in London, Robert L. Smith, ingested 32 mg of debrisoquine, as did 4 other volunteers.

Robert Smith, but none of the other volunteers, developed severe orthostatic hypotension.



Urine analyis showed inability to hydroxylate debrisoquine. Which led to more extensive studies in medical students and families.
Mahgoub et al, 1977; Smith RL,1986

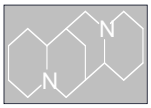
Debrisoquine
adrenergic neuroblocker
lowers blood pressure

The debrisoquine / sparteine paradigm

Adverse reactions lead to discovery

Michel Eichelbaum

Sparteine
antiarrhythmic activity
induction of labour



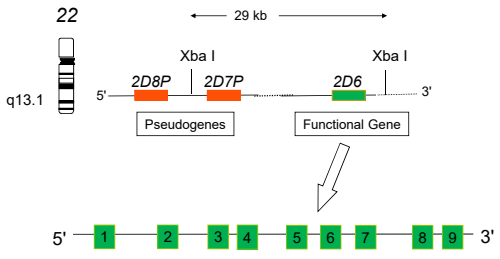
During studies of the pharmacokinetics of sparteine at the University of Bonn, two individuals had unpleasant side effects (nausea, diplopia, headaches) and high plasma levels of sparteine due to inefficient metabolism, triggering family studies. Eichelbaum, 1979

The adverse reactions after debrisoquine and sparteine are the consequence of the same genetic polymorphism.The frequency of this polymorphism is 5-10 % in Caucasians.

Strategy to Elucidate Molecular Mechanisms of Genetic Polymorphisms of Drug Response

- Identify enzyme or drug target responsible
- Identify (clone) gene, its sequence and its variant(s)
- Establish gene (allele) variant - phenotype relationship

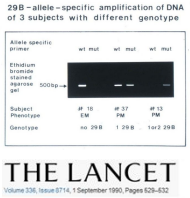
The human *CYP2D* gene cluster responsible for the Debrisoquine-Sparteine Polymorphism



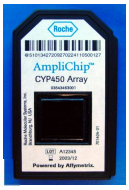
Gonzalez et al. Nature 1988; Skoda et al. PNAS 1988; Heim & Meyer, Genomics1992

1990: A first pharmacogenetic DNA test

Genotyping of poor metabolizers of debrisoquine (*CYP2D6*)

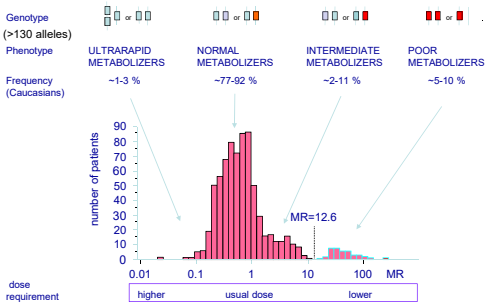


Approval 2004



Genetic Polymorphism of Cytochrome P450 *CYP2D6*

Cause of the "debrisoquine/spartein"polymorphism



Meyer U.A., Nature Reviews / Genetics 2004

The Emergence of Molecular Biology in Pharmacogenomics

1988	**Cloning of the *CYP2D6* gene and its variants** (UA Meyer/ F Gonzalez teams)	***Nature 331, 442-446, 1988***
1991	**Cloning of the *NAT2* gene and its variants** (UA Meyer team)	***PNAS 88, 5237-5241, 1991***
1993	**Cloning of the *TPMT* gene** (R Weinshilboum team)	***Mol Pharmacol 43,878-887,1993***
1994	**Cloning of *CYP2C19*** (J Goldstein and UA Meyer collaboration)	***JBC 269, 15419-15422, 1994***
1996 --	**etc. etc.etc.**	

The present

Ever increasing digital databases

PHARMGKB

Pharmacogenomics Knowledge Base
http://www.pharmgkb.org

Clinical

CLINICAL GUIDELINE ANNOTATIONS	201
DRUG LABEL ANNOTATIONS	993
FDA DRUG LABEL ANNOTATIONS	428
CLINICAL ANNOTATIONS	5,073

Research

PATHWAYS	228
VIPs (Very Important Pharmacogenes)	68
VARIANT ANNOTATIONS	26,499
ANNOTATED DRUGS	764

Accessed August 5, 2023

Which of these many gene-drug interactions can be applied to improve pharmacotherapy ?

Clinical Implementation of Pharmacogenomics

Reminder: Goals of Pharmacogenomics

Identify the conditions in which heritable factors allow pharmacogenomic testing to:

- Predict the «precise» individual dose
- Predict nonresponders & responders to therapy
- Predict which individuals are at risk of drug toxicity
- Select the optimal drug for the individual patient

Table of Pharmacogenetic Associations

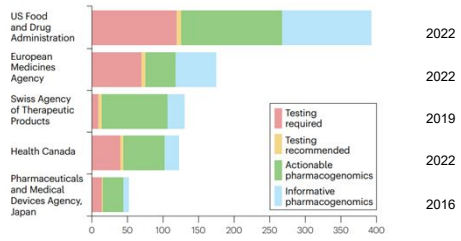
Content current as of October 26, 2022

Drug-gene associations for which data support therapeutic management recommendations	**58**
Pharmacogenetic associations for which the data indicate a potential impact on safety or response	**20**
Pharmacogenetic associations for which the data demonstrate a potential impact on pharmacokinetic properties only	**39**

https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations

FDA: Food and Drug Administration, U.S. Department of Health and Human Services

Guidance provided in drug labels from different drug agencies



Data from PharmGKB (https:www.pharmgkb.org/labelAnnotations)
Adapted by Pirmohamed M. Nature Rev Genetics 24: 350-362 (2023)

Implementation: Data Banks, Consortia and Working groups

PHARMGKB · CPIC · ClinGen · PharmVar · PGRN · Global Core Biodata Resource

Dutch Pharmacogenetics Working Group (**DPWG**)

eMERGE PGx · SPHINX · UK Pharmacogenetics & Stratified Medicine Network

Vanderbilt U

PG4KDS: Clinical Implementation of Pharmacogenetics

U-PGx | Ubiquitous Pharmacogenomics

Implementation: Data Banks, Consortia and Working groups

CPIC Clinical Pharmacogenetics Implementation Consortium — https://cpicpgx.org

CPIC: The **Clinical Pharmacogenetics Implementation Consortium** (open, international non-profit group) creates standardized guidelines on how to use genomic data to inform prescribing.

DPWG: The Dutch Pharmacogenetic Working Group. Dose recommendations for gene-drug interactions, included in PHARMGKB data base.

Many other implementation initiatives and consortia in North America, Europe and Asia

Preemptive Genotyping & Clinical DecisionSupport

Definitions

Actionable: Evidence meets threshold of clinical implementation, i.e. the genotype triggers a change in standard therapy

Preemptive: The test result is available in the medical record as a pre-prescription patient characteristic at the PoC. Screening for multiple genes has already been performed.

Clinical Decision Support (CDS): Computational CDS delivered through the EHR / EMR, provides clinicians, patients, or others with knowledge and person-specific information, intelligently filtered and presented to enhance health and healthcare.

CPIC Guidelines

Table 1. Genes and associated drugs included in CPIC guidelines as of July 2019

Gene	Drugs	References
CACNA1S	volatile anesthetic agents, succinylcholine	(13)
CFTR	ivacaftor	(14)
CYP2B6	efavirenz	(15)
CYP2C19	clopidogrel, voriconazole, SSRIs, TCAs, PPIs[b]	(16-19)
CYP2C9	phenytoin, warfarin, NSAIDs[b]	(20, 21)
CYP2D6	atomoxetine, codeine, ondansetron, tramadol, tropisetron, tamoxifen, SSRIs, TCAs	(17, 22-25)
CYP3A5	tacrolimus	
CYP4F2	warfarin	
DPYD	capecitabine, fluorouracil	
G6PD	rasburicase	
HLA-A	carbamazepine	
HLA-B	carbamazepine, oxcarbazepine, abacavir, allopurinol	
IFNL3	pegasterferon alfa	
rs8KNR1	aminoglycosides	derway
NUDT15	azathioprine, mercaptopurine, thioguanine	(18)
RYR1	volatile anesthetic agents, succinylcholine	(13)
SLCO1B1	simvastatin	(33)
TPMT	azathioprine, mercaptopurine, thioguanine	(18)
UGT1A1	atazanavir	(34)
VKORC1	warfarin	(21)

SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; PPIs, proton pump inhibitors; NSAIDs, non-steroidal anti-inflammatory drugs

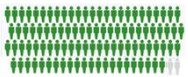
[b]Guideline underway

26 guidelines Covering ~ 90 drugs > 20 genes

https://cpicpgx.org

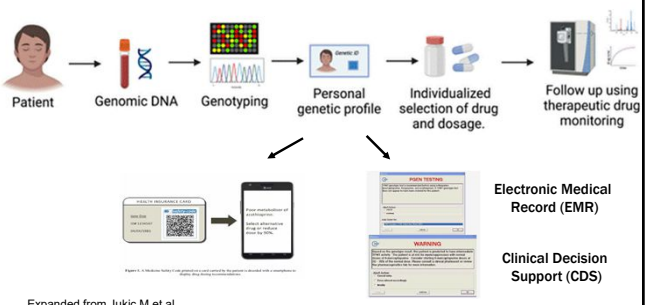
Summary Present Knowledge

- PGx variation is common in the human genome, 92 - 99% of people carry at least one PGx variant with clinically actionable recommendation[1]
- Almost 90 % of patients over the age of 70 were exposed to at least one drug with PGx guidance over the previous 20 years[2]
- Clinically actionable PGx recommendations have been reported by international guideline committees for almost 90 prescribed drugs



1) *Reisberg S et al. Genetics in Medicine 21:1345-1354 (2019)*
2) *Kimpton JE et al. Br J Clin Pharamcol 85:2734-2746*

Individualized Pharmacogenomically Guided Therapy



Expanded from Jukic M et al
Trends in Pharmacol Sciences 2022 doi.org/10.1016/j.tips.2022.09.011

In spite of all this knowledge…….

Reality check Pharmacogenomics

Implementation of pharmacogenomics into clinical practice has been slow, pre-emptive testing not widely adopted to improve patient care

Barriers to implementation include

- A perceived lack of clinical utility for various reasons
- Limited studies demonstrating clinical utility of pharmacogenetic testing
- Limited availability of pharmacogenetic test results at point of care (PoC) and in Electronic Medical Records (EMRs) with clinical decision support (CDS)
- Lack of knowledge on how to interpret pharmacogenomics tests
- Limited studies on cost effectiveness
- Etc etc

Role of Stakeholders in the Implementation of PGx

Stakeholder	Role
Regulatory bodies	Drug labeling, test requirement
Medical Center / hospital administration	Secure funds and infrastructure
Therapeutics committees *(hospital, learned societies)*	Select actionable drug-gene pairs Approve CDS (clinical decision support) in EMR
Laboratory	PoC or preemptive genotyping
Physician/ Clinical Pharmacist	Interpret the test result, therapeutic recommendation,decision
Patient	Provide feedback outcome
Payer / Health insurance	Reimburse test and therapy
Pharma Industry	Diagnostic-therapeutic tandem approach

Modified from Kabbani et al. *Frontiers in Pharmacology. doi 10.3389/fphar.2023.1189976*
18 May 2023. Pharmacogenomics in practice: a review and implementation guide

The Future

The challenge

For acceptance of the clinical utility of pharmacogenomics, it is essential that implementation is supported by evidence demonstrating a clear benefit of the pre-emptive genotyping strategy in **"real-world"** settings

A first study with this purpose has just been reported

U-PGx | Ubiquitous Pharmacogenomics

A consortium (U-PGx) of 7 European centers has performed a prospective study with 6,944 participants (2016-2022)

- To implement pre-emptive PGx testing in a **real world** clinical setting across 7 EU centers, covering 44 variants of 12 genes relevant for 44 drugs
- To evaluate patient outcome and cost effectiveness using solid scientific methodology
- The primary outcome measure was the effect on prevalence of severe adverse reactions (ADRs)

U-PGx | Ubiquitous Pharmacogenomics

Result of the implementation study

Genotype-guided treatment significantly reduced the incidence of clinically relevant adverse drug reactions **by 30 %**

Conclusion

Large scale implementation could help to to make drug therapy increasingly safe

A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study

THE LANCET

Swen JJ et al. (> 50 authors)
Lancet (February 4, 2023) 401: 347-356

Future Perspectives

- More real world studies to establish clinical utility
- Increased ethnic diversity of data sources (GWAS, the PanGenome, etc)
- Use of population biobanks (Estonia, UK, Vanderbilt, etc)
- Be aware of rare (functional) variants, explain missing heritability
- Polygenic risk scores
- Multimodal algorithms and AI to predict drug response
- etc

Summary

- Pharmacogenomics is an essential component of personalized /precision medicine to address the individual nature of drug response
- Pharmacogenomics has evolved from clinical observations of adverse drug reactions and lack of drug effects to predicting drug response from genomic sequence information, including real world settings
- However, clinical implementation of pharmacogenomics has not been widely adopted to improve patient care
- In the future, as genomic information will be increasingly routine, physicians will be faced with having the patient's genotype related to the drug prescribed at the point of care, in the electronic medical record and with decision support
- Ultimately, it will be unethical to ignore patients with clinically important pharmacogenomics variants

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Thank you for your interest, questions and comments

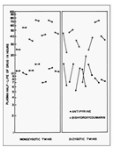
Additional slides

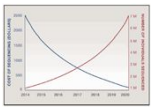
Evolution of pharmacogenomic research

Discovery (1950 -)	Phenotyping (1975 -)	Genotyping (1990 -)	GWAS (2000 -)	Preemptive (2010 -)
Outliers Family studies Twin studies	Probe drugs Metabolic ratios	Candidate genes RFLPs / linkage First PGx DNA test	~100 for PGx SNP arrays Haplotypes	PoC EHR &CDS

Family pedigrees

Twin studies

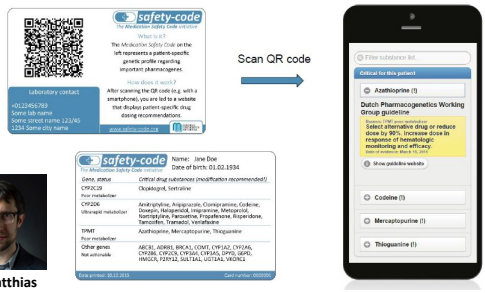




Sequencing (2010 -)

WGS / WES
PGx pannels
Rare variants

Development of powerful and barrier-free CDSS



Dr. Matthias Samwald

http://safety-code.org/

U-PGx | Ubiquitous Pharmacogenomics

A word of caution:

True pharmacogenomic variability is influenced by rare variants and epigenetic effects on transcription

Epigenetics in Drug Response

I Cascorbi[1] and M Schwab[2,3]

Clin Pharmacol Ther 99: 468-470 (2016)

Kozyra M et al Genet Med 19: 20-29 (2017)

Plausible estimates are that up to 30 % of functional variability in pharmacogenes may be attributable to rare variants and epigenetic effects

Rare variants among CYPs