SUMMARY

1. Drug response variability
2. Origins of pharmacogenomics
3. Pharmacogenomics studies and applications
4. Clinical implementation
5. Critical issues
6. Resources and databases
7. Future directions
8. Literature
One-size-fits-all approach:

Different people, same prescription

- 10.1% of hospitalized patients experience adverse drug reactions
- 3.5% of hospital admissions are related to adverse drug reactions
- Adverse drug reactions are the 4th leading cause of death in USA

http://safety-code.org/providers/#
DRUG RESPONSE VARIABILITY

One-size-fits-all approach:

Different people, same prescription

- good efficacy, no adverse reactions
- poor efficacy, adverse reactions

10.1% of hospitalized patients experience adverse drug reactions

3.5% of hospital admissions are related to adverse drug reactions

Adverse drug reactions are the 4th leading cause of death in USA

http://safety-code.org/providers/

Age
Comorbidities
Genetics
Sex
Environmental
Race
Life style
Pharmacogenetics: studies how genetic differences in individual candidate genes contribute to the observed variability in drug response.

Pharmacogenomics: studies how multiple genes (DNA variation + RNA expression) impact drug response.

Fatal hemolytic anemia
Pythagoras, 510 BC

“The influence of inheritance in drug response”
Friedrich Vogel, 1959

First polymorphic human drug metabolizing gene
CYP2D6, 1987
PHARMACOGENOMIC STUDIES

PHARMACODYNAMICS
- Enzymes
- Receptors
- Immune System

PHARMACOKINETICS
- Absorption
- Distribution
- Excretion
- Metabolism

Discovery Approaches
- Candidate gene approach
  - Hypothesis driven
  - Metabolic enzymes
- Genome wide association approach
  - Discovery driven
  - Microarray technologies
- Hybrid approach
  - Custom SNP chips for important variants

ALOX5 – Lipoxygenase inhibitors
CYP2D6 - Codeine
PHARMACOGENOMICS APPLICATIONS

Identification of patients at risk of adverse reactions
- Serious Adverse Drug Reactions: type A and type B

Selection of patients most likely to benefit from treatment
- Agents with narrow therapeutic window
- Severe drug toxicity consequences
- Potentially fatal lack of efficacy consequences

Establish rational safe and effective use of treatment dosing

Inform of clinical trial design and drug development
CLINICAL IMPLEMENTATION

Clinical Utility

- Risks as a result of testing
- Improved health outcomes

Clinical Pharmacogenomics Implementation Consortium

CLINICAL GUIDELINES

https://www.pharmgkb.org/page/clinAnnLevels
CLINICAL IMPLEMENTATION

Clinical Utility

Risks as a result of testing

Improved health outcomes

Clinical Pharmacogenomics Implementation Consortium

CLINICAL GUIDELINES

Level 1a

Level 1b

Level 2a

Level 2b

Level 3

Level 4

variant in PharmGKB VIP

https://www.pharmgkb.org/page/clinAnnLevels

http://safety-code.org/

CLINICAL GUIDELINES

http://safety-code.org/

CLINICAL GUIDELINES

http://safety-code.org/
CRITICAL ISSUES

Pharmacogenomics is unlikely to be useful for improving prescribing for the majority of drugs

- 18,000 human genes
  - Considered actionable for pharmacogenomics

Pharmacogenomic science: involvement of multiple gene products

Translational incentives: research funding, academic centres, pharmaceutic industry, drug regulatory agencies...

Healthcare professional education in clinical genomics science

Patients acceptance: informed patients and realistic expectations
RESOURCES AND DATABASES

Drugs
- 630`

Pathways
- 128`

Dosing Guidelines
- 98`

Drug Labels
- 489`

WHAT IS PHARMACOGENOMICS?
The study of the relationship between genetic variations and how our body responds to medications.

Pretty cool right? Tell me more...

PHARMACOGENOMICS: KNOWLEDGE IMPLEMENTATION.
PharmGKB is a comprehensive resource that curates knowledge about the impact of genetic variation on drug response for clinicians and researchers.

Learn more about PharmGKB

Annotations

Clinical
- DOSING GUIDELINES 98
- DRUG LABELS 489
- CLINICAL ANNOTATIONS 3,454

Research
- PATHWAYS 128
- VIPs (Very Important Pharmacogenes) 64
- VARIANT ANNOTATIONS 18,888
RESOURCES AND DATABASES

OMIM

Online Mendelian Inheritance in Man®
An Online Catalog of Human Genes and Genetic Disorders
Updated December 8, 2017

ClinVar
ClinVar aggregates information about genomic variation and its relationship to human health

ClinGen - A Program
An NIH-funded project building a central resource that defines the clinical relevance of genes and variants. ClinGen is addressing the following critical questions:
- Is the gene associated with disease?
- Is the variant pathogenic?
- Is the variant/gene information actionable?

The ClinGen and ClinVar Partnership
Both provide resources to support genomic interpretation

ClinVar - A Database
Funded by intramural NIH funding
Freely accessible and downloadable public archive of reports of the relationship between variants and conditions
Maintained by the National Center for Biotechnology Information (NCBI)

Find out more online...
ClinGen
https://www.clinicalgenome.org/
ClinVar
RESOURCES AND DATABASES

European Pharmacogenetics Implementation Consortium

Genomic Medicine Alliance

Clinical Pharmacogenetics Implementation Consortium

Welcome to the Hub

Your home for the
Pharmacogenomics Research Network

PGRN

Join the PGRN
FUTURE DIRECTIONS

“Overall steady progress is being made toward pervasive application of pharmacogenomics testing.”

“There is a growing body of evidence that pharmacogenomics will be an expanding component of evidence-based precision medicine.”

“Many challenges remain, including keeping up with the complex regulatory landscape, new sequencing technologies and approved devices, translating research successes to clinical successes and discovering new markers.”

“… pharmacogenomics shows tremendous promise to significantly improve the safety and effectiveness of medications in the future.”


PHARMACOGENOMICS

Cristina Miracle Huguet

11.12.2017