Clinical Adoption of Pharmacogenomics

Implications for Educators and Providers

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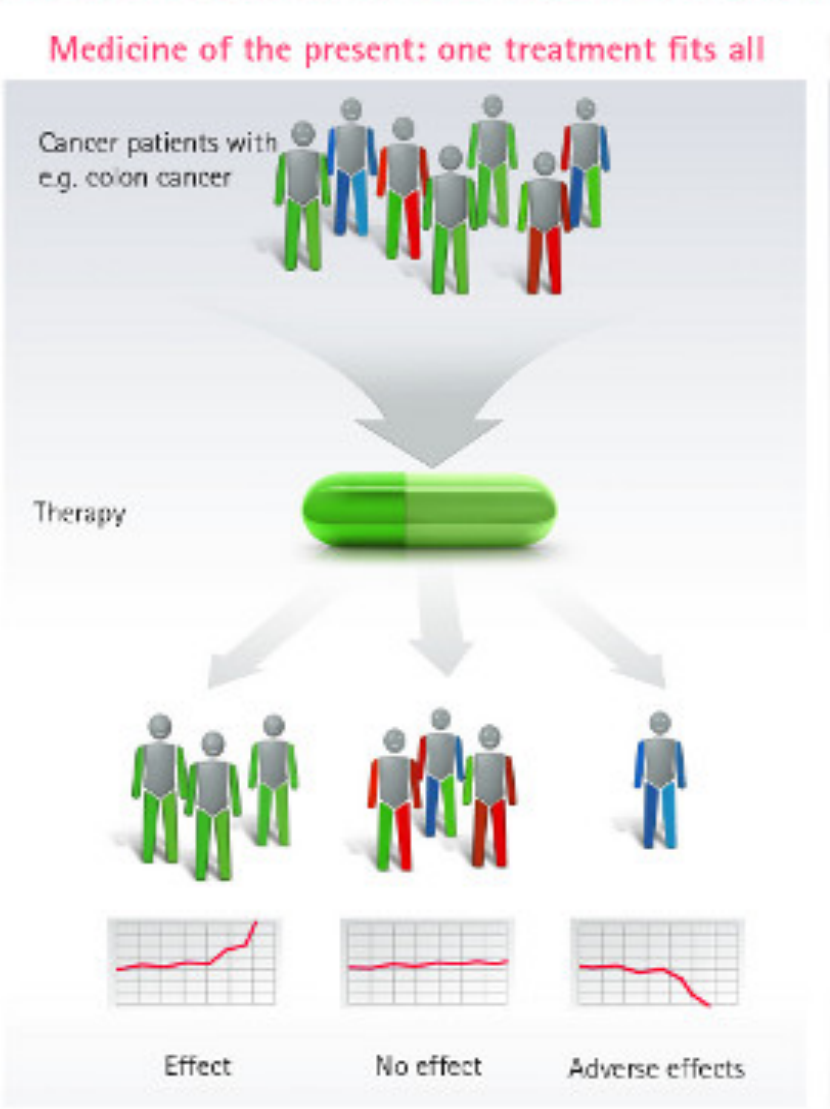
Objectives

- Describe the relevance of genomics to medical education and clinical care by using a patient case example.
- Explore the potential clinical benefits of pharmacogenomics
- Describe the clinical implementation process for pharmacogenomics in a medical institution.
- Discuss resources to facilitate personal and professional genomics education.

Meet Mr. PGx

- 54 year old male presented to the cardiac catheterization laboratory for a left heart cath due to an abnormal stress treadmill study and chest pain
- PMH:
  - Hypercholesterolemia, coronary artery disease
- Intervention:
  - Drug eluting stent in his mid-circumflex coronary artery
- PGx:
  - MD ordered PGx test but sample was not collected
- Patient discharged on clopidogrel 75mg and aspirin 81mg daily

Current Medical Practice

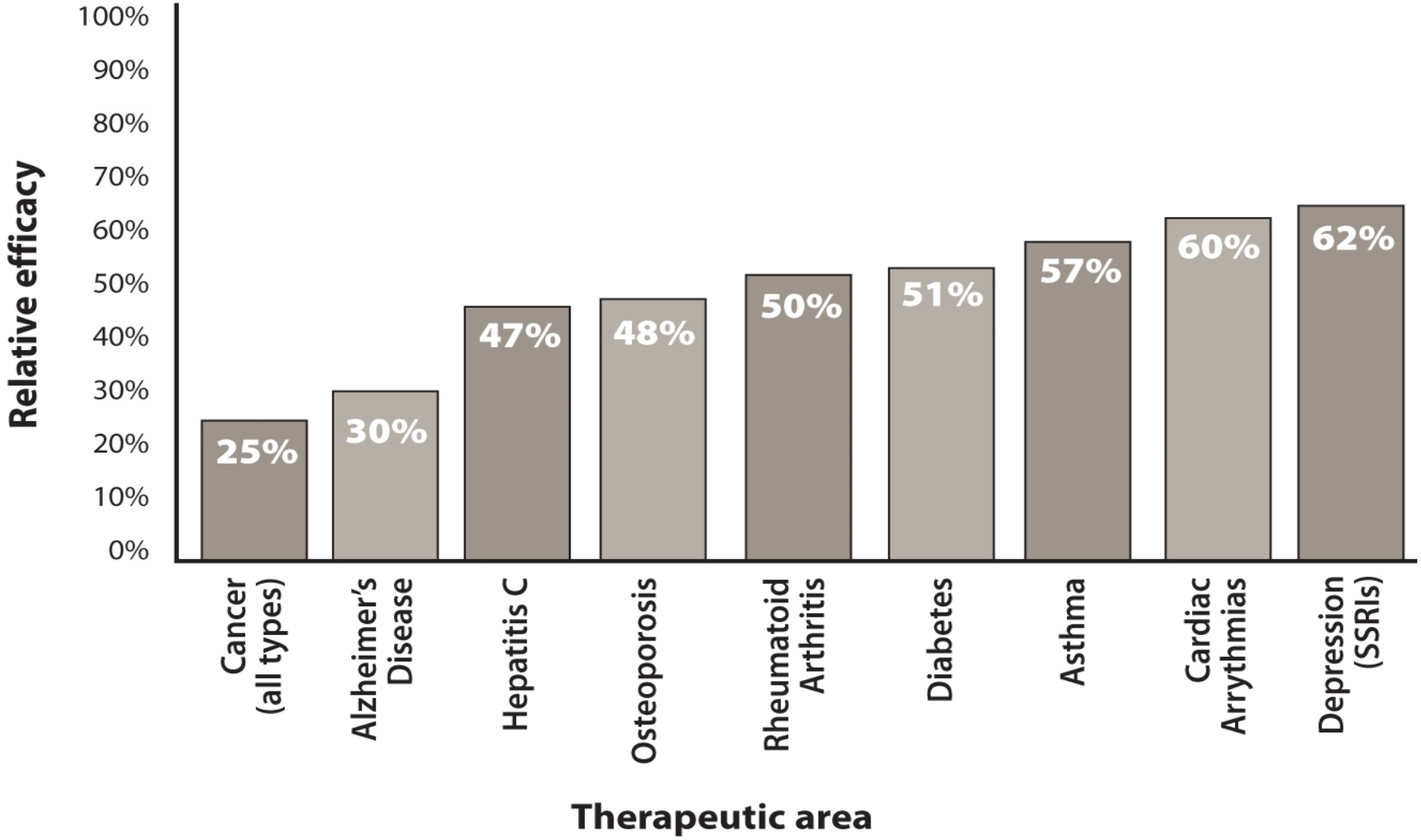


- After diagnosis, patients are prescribed therapy with no reference to the patient's genetic information

- "Trial and error" or
- "One size fits all"

Personalized Medicine. Bayer HealthCare: Science for a better life. 2013. Accessed on April 16, 2013. [Internet]. Available from: http://www.bayerpharma.com/en/research-and-development/research-focus/oncology/personalized-medicine/index.php

One size does not fit all: Relative efficacy of drug and disease, according to Spear et al.



Source: Hua L

Adverse Drug Events

2007 – 2009 : pts ≥ 65 years
99,628 annual hospitalizations
166,174 annual ED visits

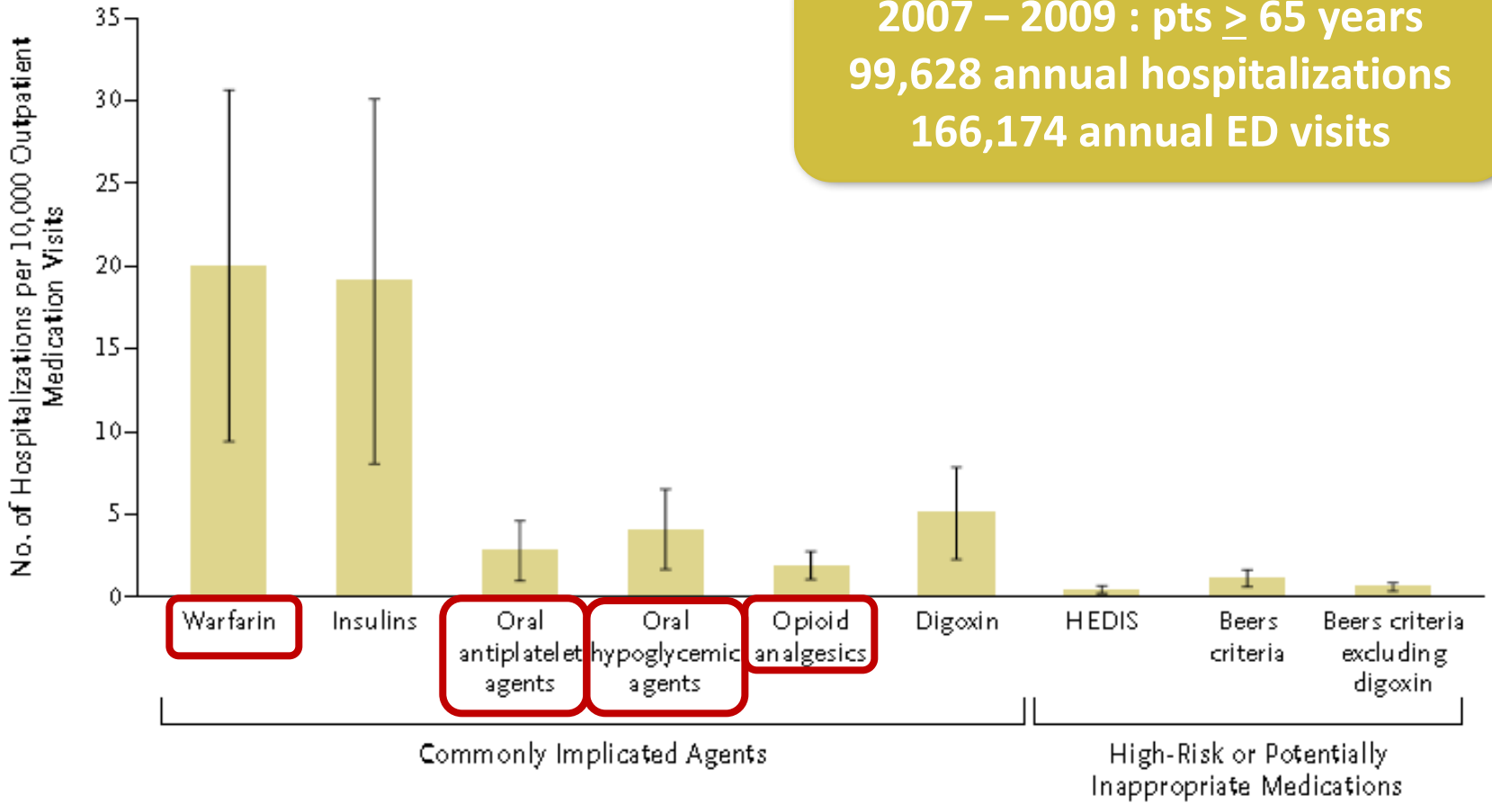


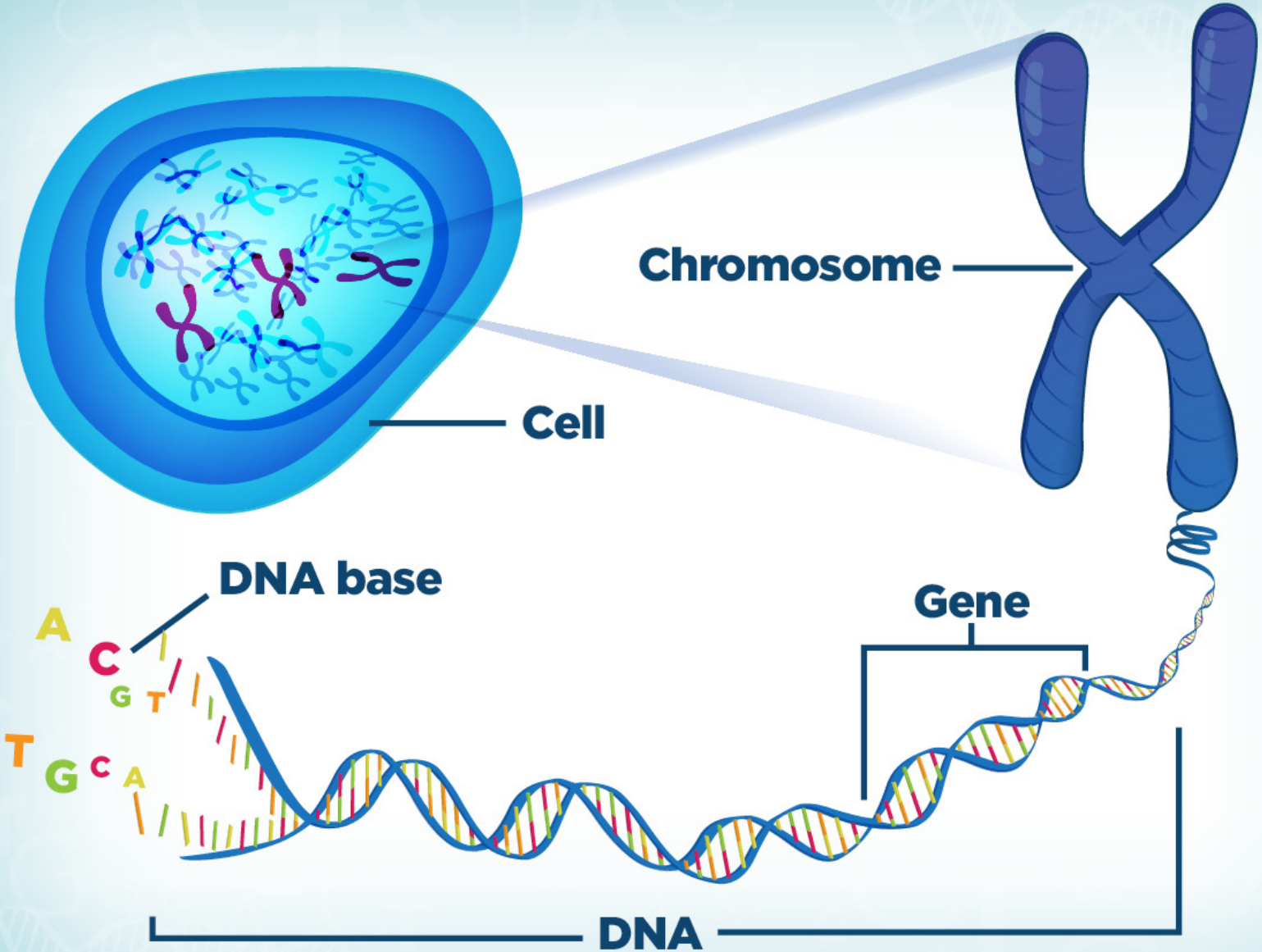
Figure 1. Estimated Rates of Emergency Hospitalizations for Adverse Drug Events in Older U.S. Adults, 2007–2009.

Budnitz DS, Lovegrove MC, Shehab N, et al. NEJM 2011; 365: 2002 - 12

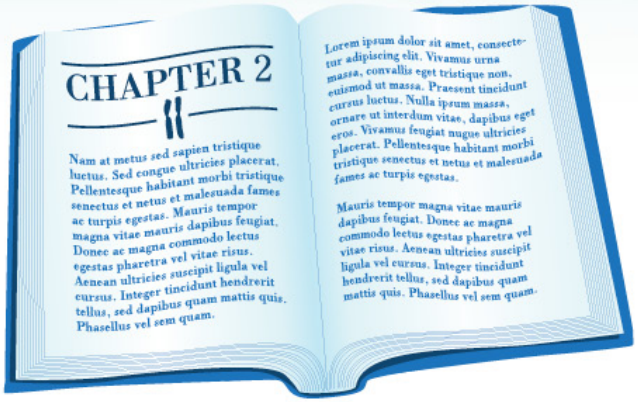
Factors that Influence Medication Response

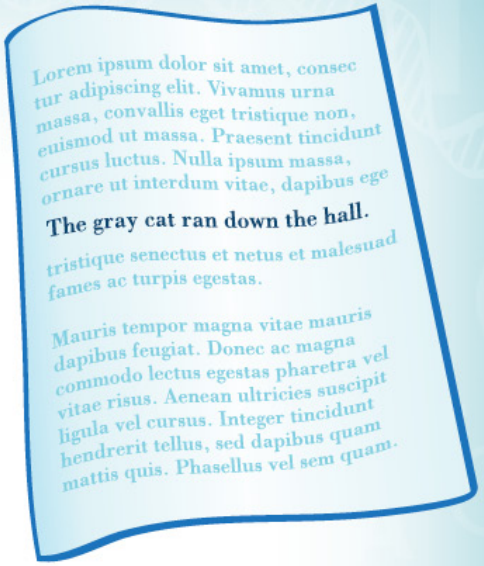
Hussar DA. Overview of Response to Drugs. April 2007. Accessed on July 23, 2015. [Internet] Available from: http://www.merckmanuals.com/home/drugs/factors_affecting_response_to_drugs/overview_of_response_to_drugs.html

GENETICS 101



National Society of Genetic Counselors

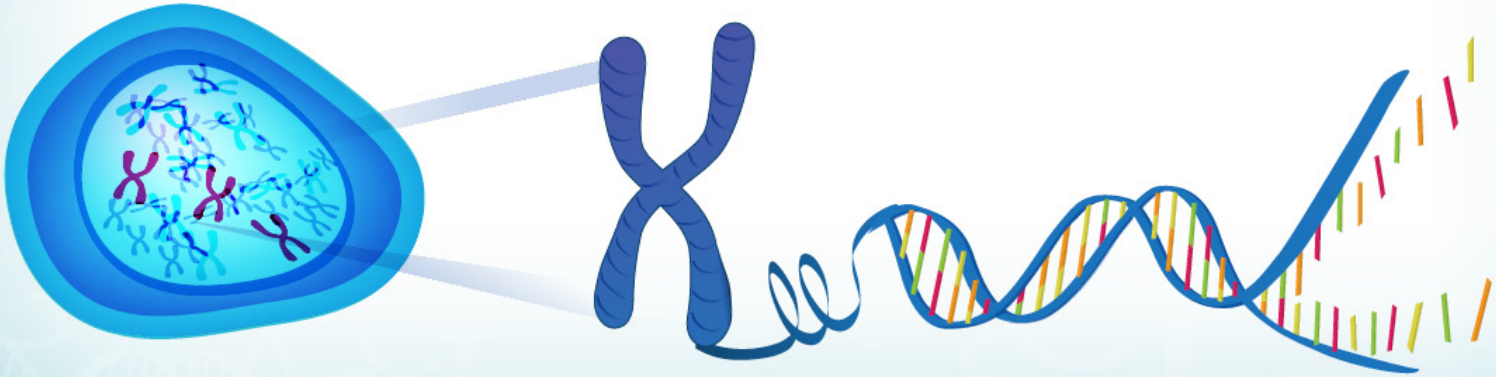




BOOK – GENOME

CHAPTERS – CHROMOSOMES

SENTENCE – GENE



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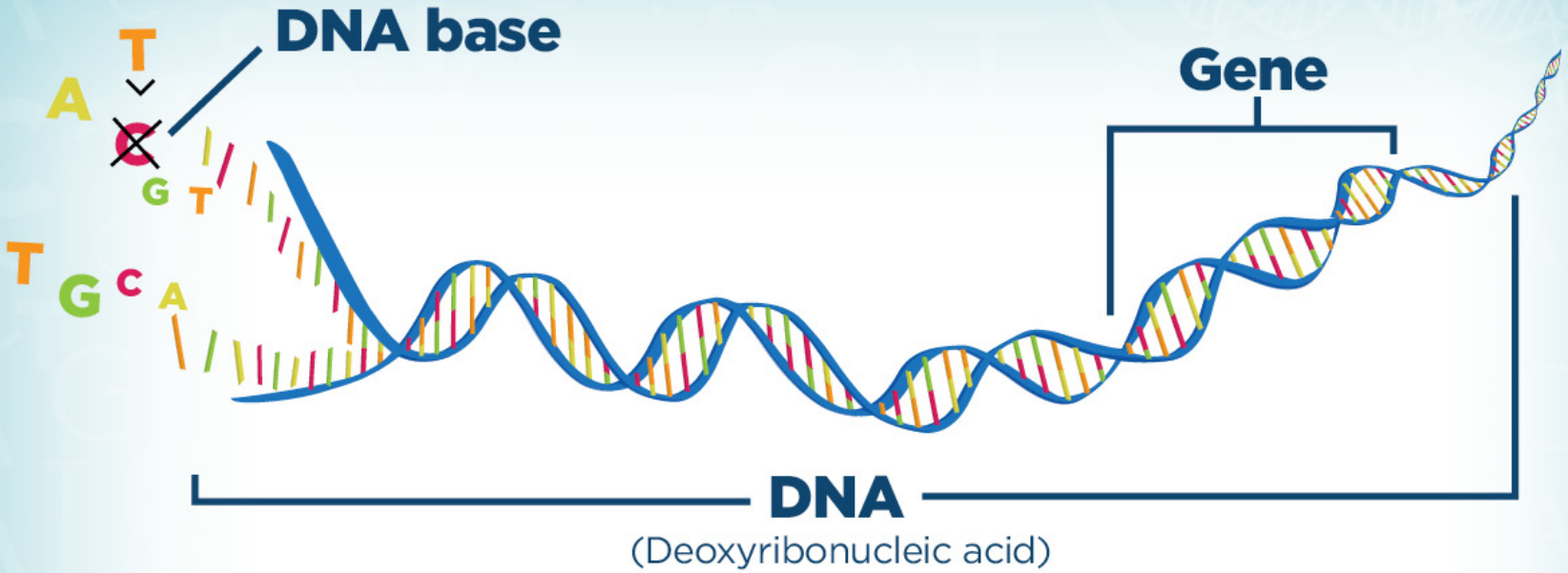


The gray cat ran down the hall.

The gray cat ran down the ball.

Changes in DNA might change the way a gene works.

National Society of Genetic Counselors

Types of genetic variants

The gray cat ran down the hall.	**Original**
The gray cat ran down the b**a**ll.	**Missense**
The gray g**r**e**e**n cat ran down the hall.	**Insertion**
The gray ___ ran down the hall.	**Deletion**
The gray c**at c**at ran down the hall.	**Duplication**
The gray**.**	**Nonsense**

The Human Genome Project

- 13 year international project completed in 2003
- Coordinated by US Department of Energy and the NIH
- Project goals:
  - Identify all genes in human DNA
  - Determine the sequences of the 3 billion chemical base pairs
  - Store the information in databases
  - Improve tools for data analysis
  - Transfer related technologies to the private sector
  - Address the ethical, and social issues that may arise

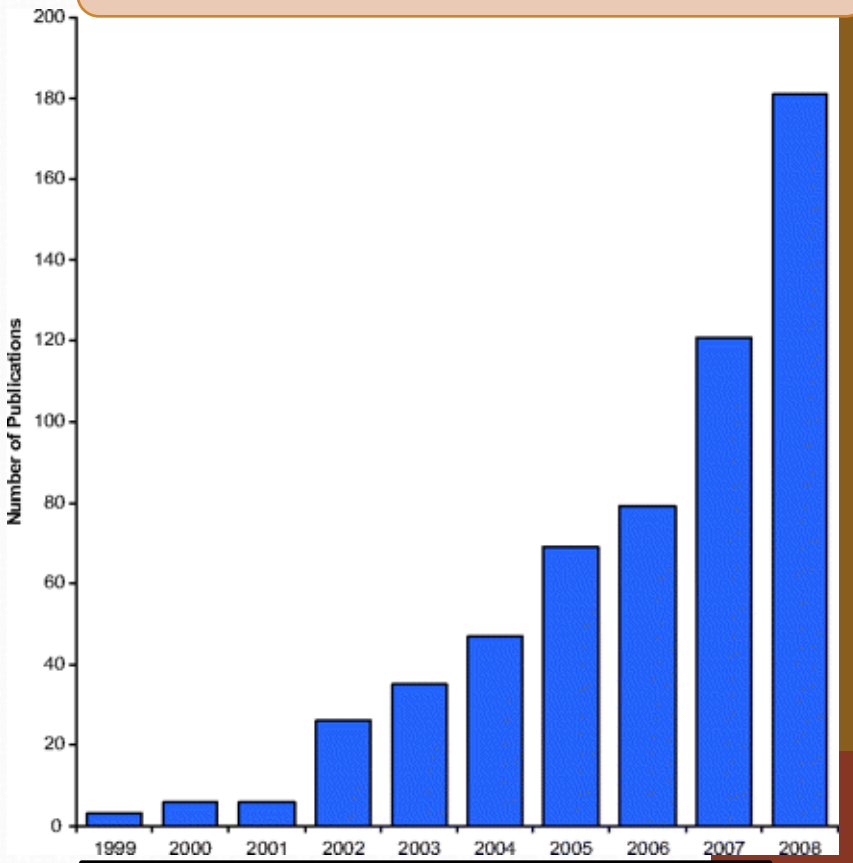
June 26, 2000

Human Genome Project information. Updated on July 31, 2012. Accessed on July 23, 2015. [Internet]. Available from: http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml

The New Era of Medical Practice

- Personalized Medicine
  - "Emerging practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease" - National Human Genome Research Institute
  - First coined in April 1999
    - Robert Langreth and Michael Waldholz in WSJ, later in The Oncologist
  - Also known as:
    - Individualized medicine
    - Precision medicine

Number of articles per year that included the term "personalized medicine"



Jørgensen J T The Oncologist 2009;14:557-558

Personalized Medicine. Genetics Home Reference. Updated on April7, 2013. Accessed on April 16, 2013. [Internet]. Available from: http://ghr.nlm.nih.gov/glossary=personalizedmedicine

Pharmacogenomics

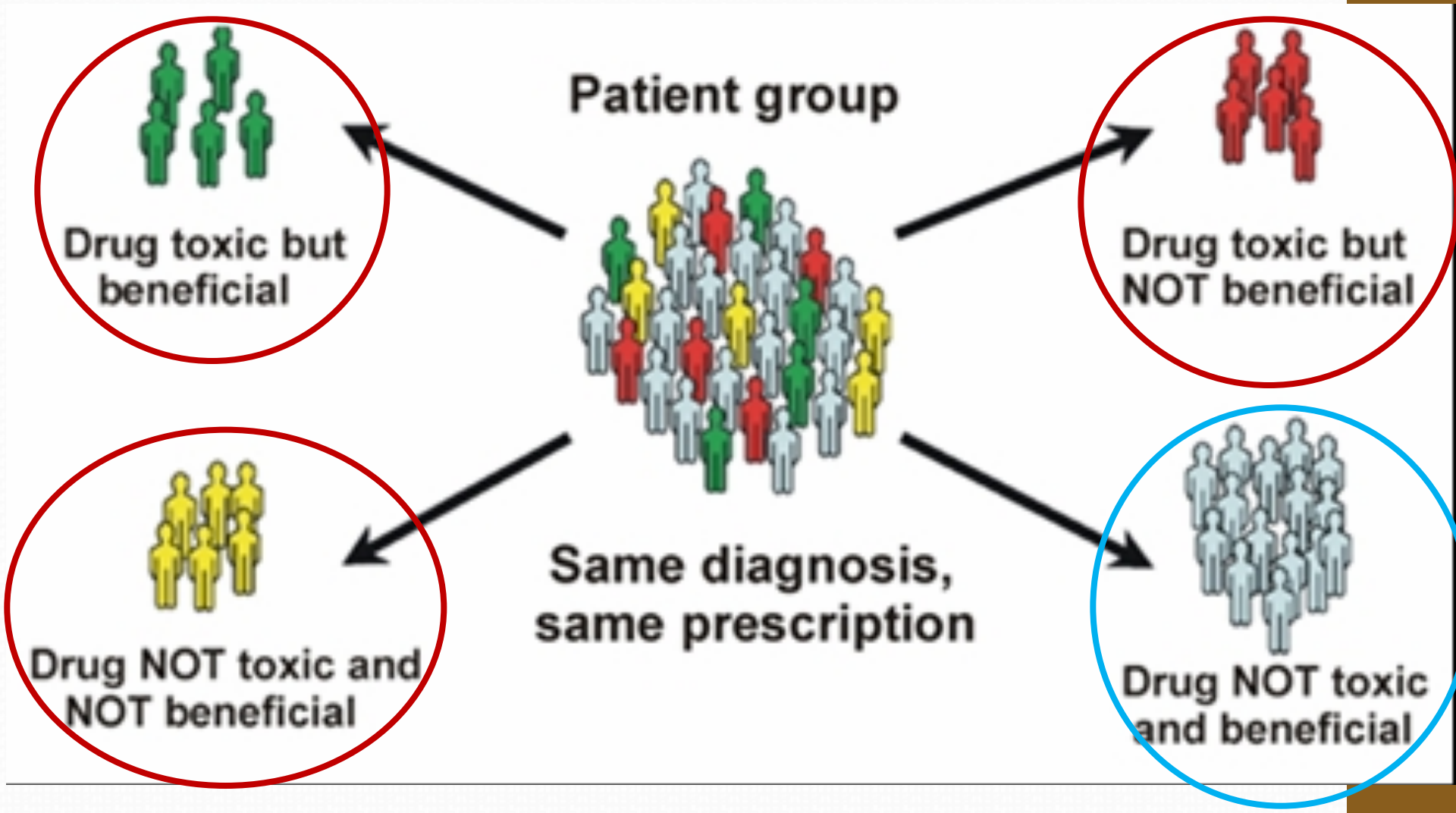
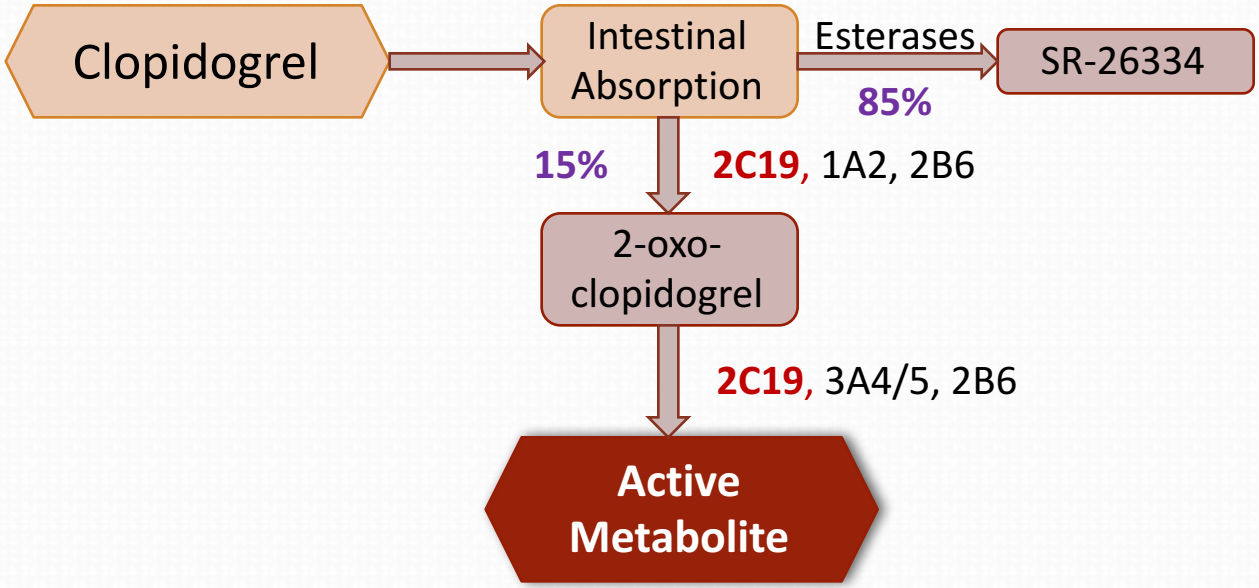


Image accessed from: http://mytorontocanadambastudentexperience.blogspot.com/2012/10/personalized-medicine-or-p4-medicine.html

A PGX EXAMPLE

CYP2C19 & CLOPIDOGREL

CYP2C19 and Clopidogrel



Cytochrome P450 2C19

- CYP2C19 is a hepatic enzyme
- Metabolizes about 5-15% of all prescription drugs
- Variations in genotypic inheritance and hepatic expressions
  - Phenotypic variability in substrate metabolism

  - Non functional metabolic activity
    - CYP2C19 *2, *3, *4, *6, *7, *8

  - Decreased metabolic activity
    - CYP2C19 *9 & *10

  - Increased metabolic activity
    - CYP2C19 *17

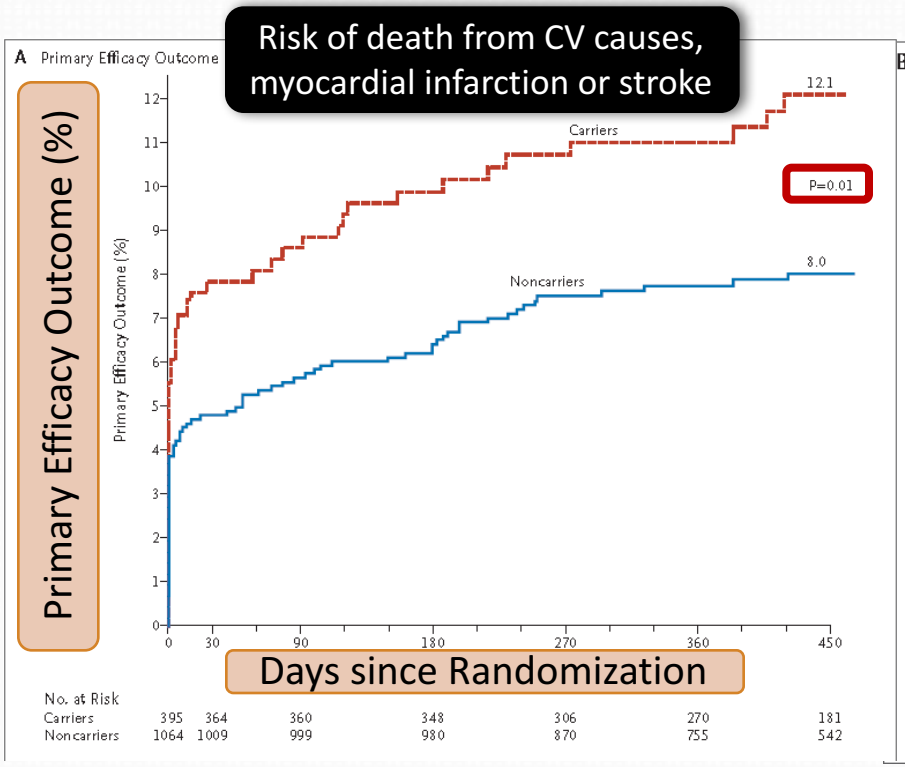
Lima, J. et. al . (2014). Pharmacogenomic testing: the case for CYP2C19 proton pump inhibitor gene-drug pairs. *Pharmacogenomics, 1405-1415*

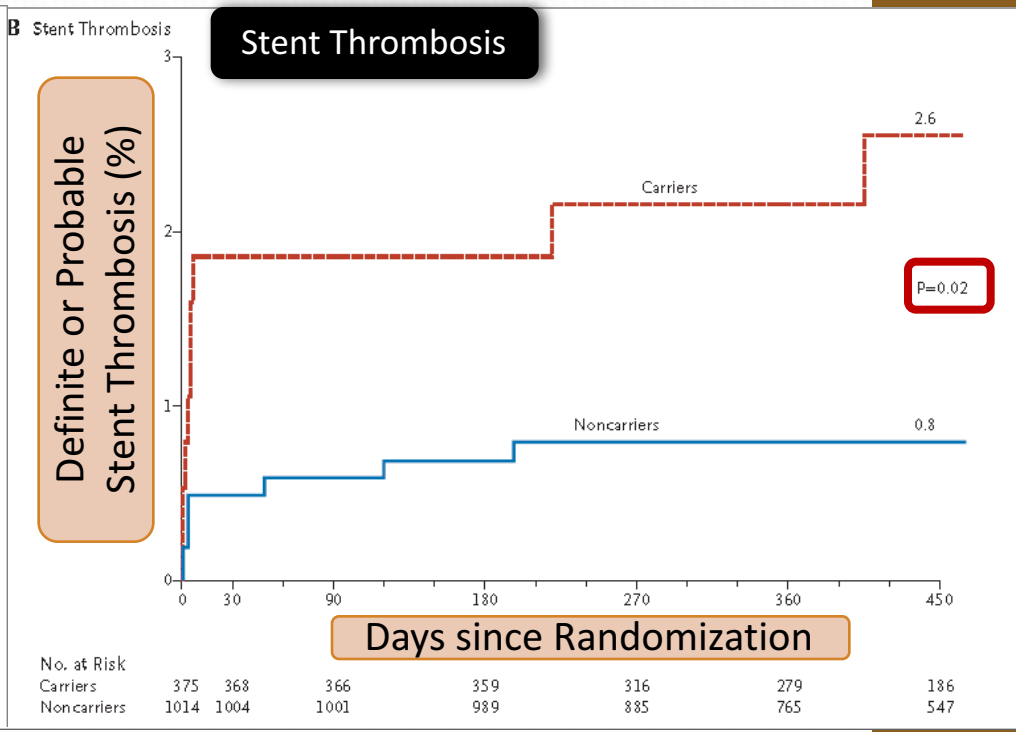
CYP2C19 Genotypes and Phenotypes

Phenotype	Genotype/ Activity	Diplotypes Examples	Population Frequency
Ultra-rapid metabolizer (UM)	Carrier of two increased activity alleles OR one normal plus one increased activity allele	*17/*17; *1/*17	~5 – 30%
Extensive metabolizer (EM)	Wild type (carrier of two normal function alleles)	*1/*1	~ 35 – 50%
Intermediate metabolizer (IM)	Carrier of one functional and one loss of function OR one loss of function and one increased activity allele	*1/*2; *2/*17	~18 – 45%
Poor metabolizer (PM)	Carrier of two loss of function alleles	*2/*2; *3/*3	~ 2 – 15%

Scott SA et al. (2013). Clinical Pharmacogenetics Implementation Consortium Guidelines for *CYP2C19* Genotype and Clopidogrel Therapy: 2013 Update. CPT, 94 (3): 317 - 323

CYP2C19 Polymorphisms and Response to Clopidogrel





Carriers of a reduced-function *CYP2C19* allele have significantly lower levels of the active metabolite of clopidogrel, diminished platelet inhibition, and a higher rate of major adverse cardiovascular events, including stent thrombosis.

Mega JL, et al. NEJM 2009; 360: 354 - 62

PGx Resources

- PharmGKB
  - Pharmacogenomics Knowledge Base
  - Collects, curates and disseminates knowledge about the impact of human genetic variation on drug responses
- CPIC
  - Clinical Pharmacogenetics Implementation Consortium
  - Peer-reviewed guidelines
  - Designed to help clinicians understand **HOW** available genetic test results should be used to optimize drug therapy
  - Freely accessible online
  - Endorsed by ASHP, ASCPT and other external networks

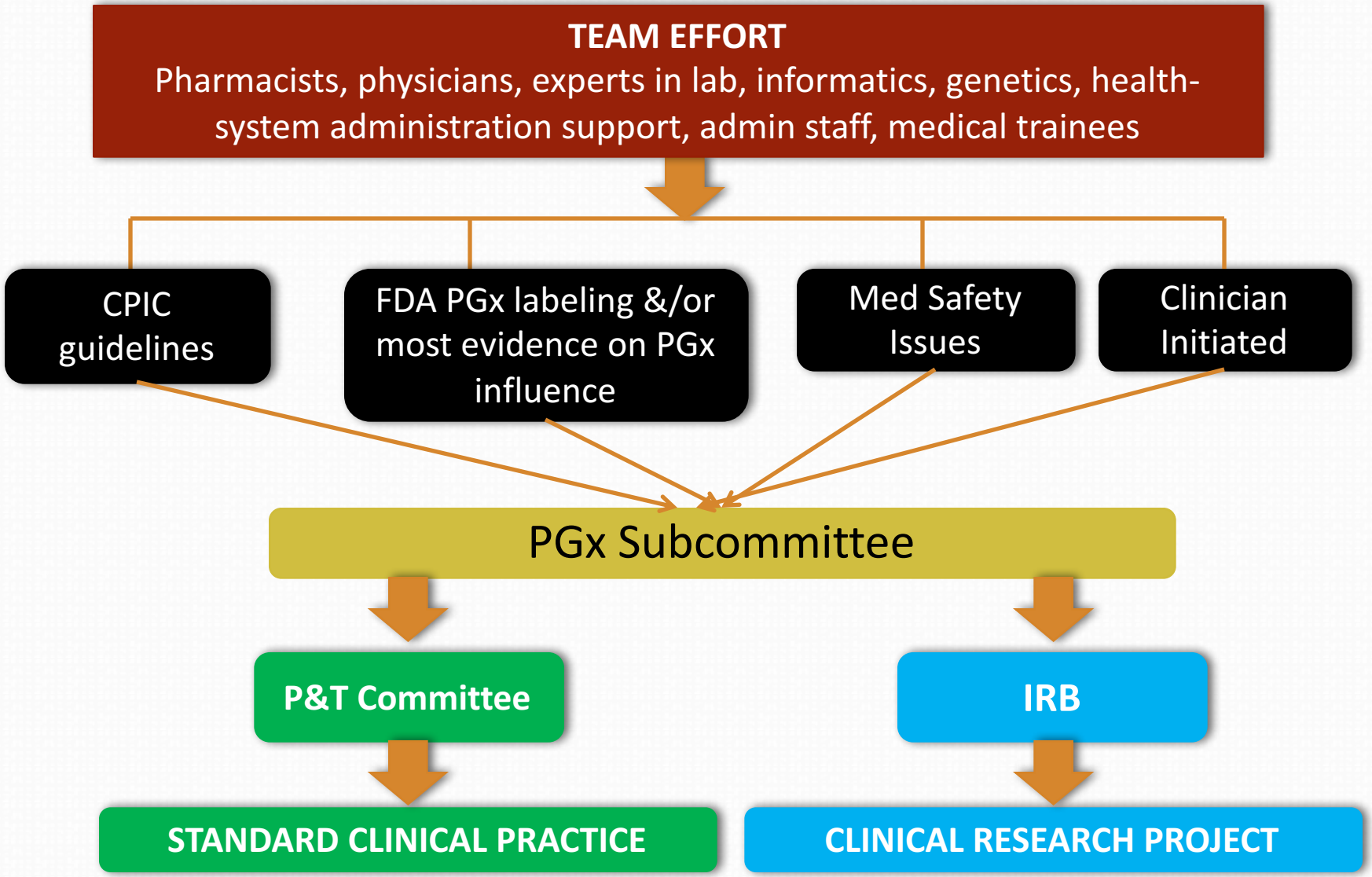
PharmGKB. CPIC: Clinical Pharmacogenetics Implementation Consortium. [Internet]. Available from: https://www.pharmgkb.org/page/cpic

CYP2C19-Guided Antiplatelet Therapy

Phenotype	Clinical Implications on Clopidogrel	Therapeutic Recommendations	Level of Recommendations
Ultra-rapid Metabolizer	Increased platelet inhibition	Use clopidogrel at label recommended doses	Strong
Extensive Metabolizer	Normal platelet inhibition	Use clopidogrel at label recommended doses	Strong
Intermediate Metabolizer	Reduced platelet inhibition, increased risk of adverse CV events	Use alternative antiplatelet therapy (i.e. prasugrel or ticagrelor if not contraindicated)	Moderate
Poor Metabolizer	Significantly reduced platelet inhibition, increased risk of adverse CV events	Use alternative antiplatelet therapy (i.e. prasugrel or ticagrelor if not contraindicated)	Strong

Scott SA, et al. CPT 2013; 94 (3): NEJM 2009; 360: 317-323

PGx Clinical Implementation Process



Mr. PGx continued

- Presented to emergency room 2 days after discharge
  - **CC:** chest pain, substernal chest pressure associated with left arm heaviness and diaphoresis
- Cardiology Intervention:
  - Two overlapping drug eluting stents to right coronary artery
- PGx Team:
  - Followed up with MD the next day to reorder PGx
  - A day later the PGx test was reordered and sample collected
- Discharged on the day 4 on clopidogrel 75mg and ASA 81mg daily awaiting PGx results
  - PGx test resulted as ***2/*2 (poor metabolizer)** on day 5
  - Clopidogrel was changed to prasugrel 10mg daily

Key Roles in Clinical PGx

- Advocates
  - Advocate for the therapeutic applications of pharmacogenomics in practice.
- Translational Researchers
  - To validate and standardize genetic markers and genetic testing for drug therapy
  - To guide and accelerate the application of pharmacogenomics to clinical practice
- Clinical Implementators
  - Inclusion of pharmacogenomic test results in medical and pharmacy records
- Educators
  - Prescribers, nurses, pharmacists and patients
- Students
  - Use of pharmacogenomics and incorporation into professional health care curricula.

What went wrong in Mr. PGx's case?

- How can we improve PGx education for:
  - Physicians assistants?
  - Nurses?
- What are the challenges to PGx education and how can we overcome them?
- What are the roles of faculty and clinicians in the clinical adoption of PGx?

ANY QUESTIONS?

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