Pharmacogenomics – Because Every Person in the Population is Unique

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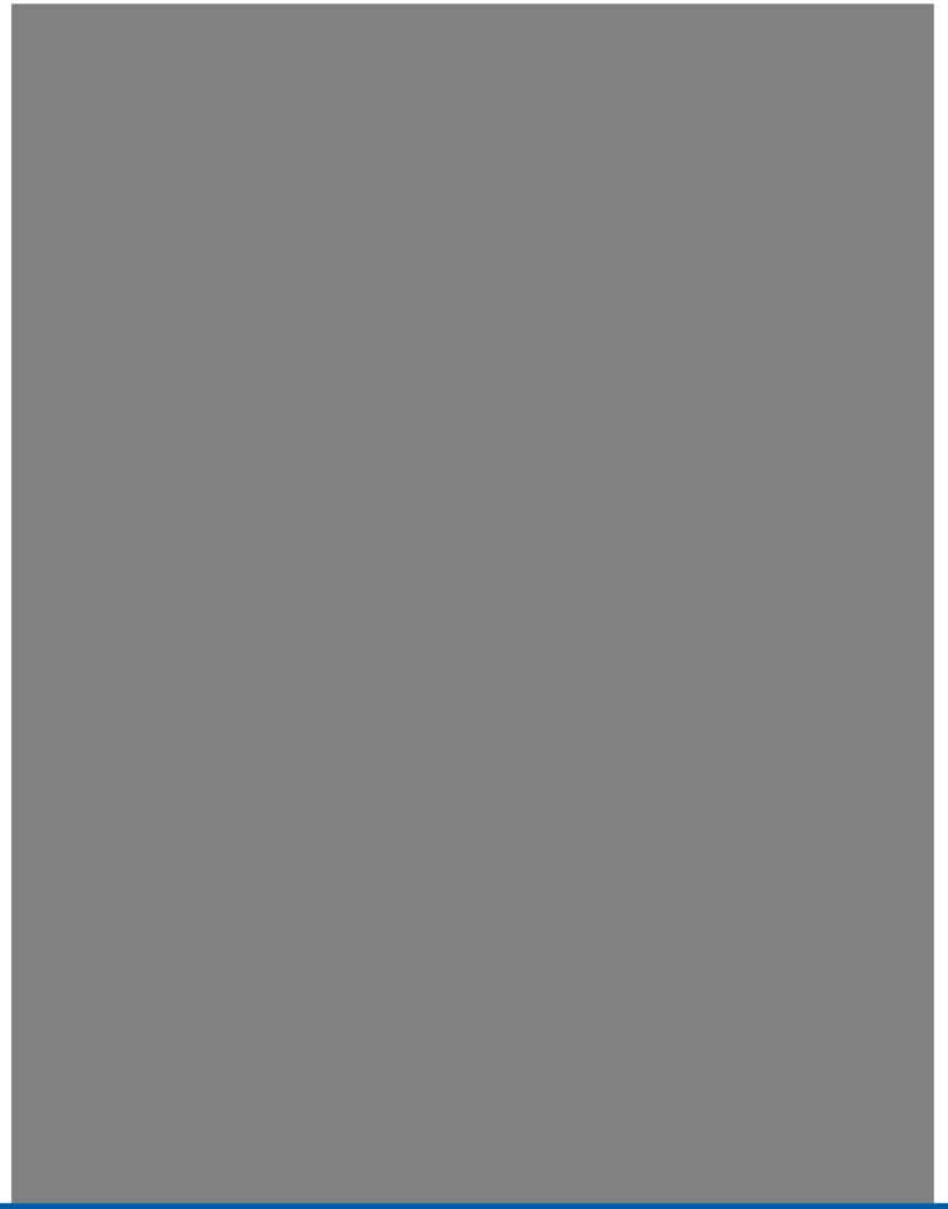
Objectives

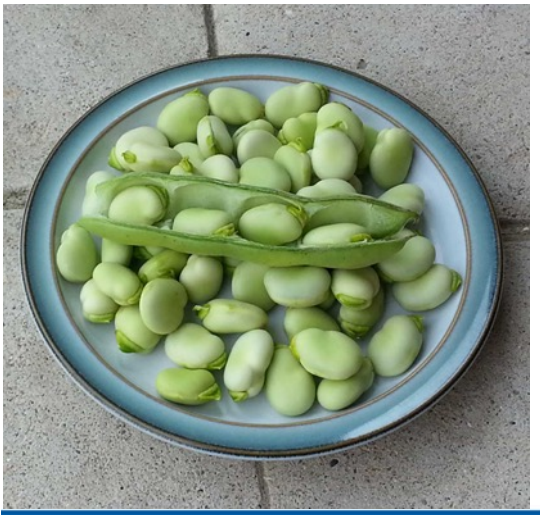
- History of PGx
- Overview of PGx
- Resources for PGx variant interpretation and clinical evidence
- Clinical use of PGx testing & challenges in clinical implementation
- Genetic and genomic technologies used in PGx testing
- Regulatory issues related to PGx in drug labels and testing

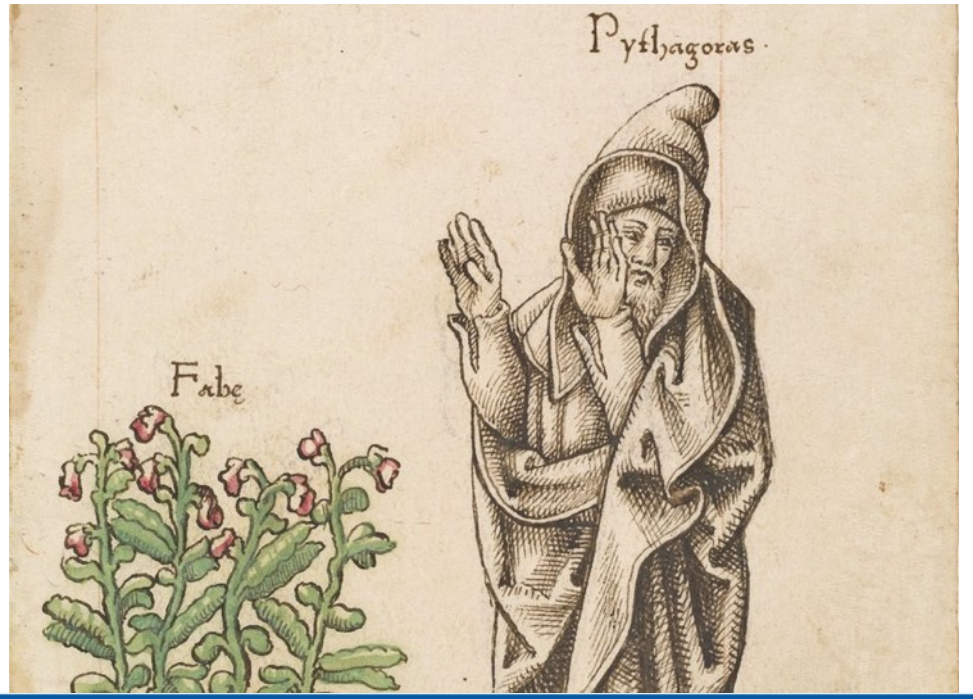
History

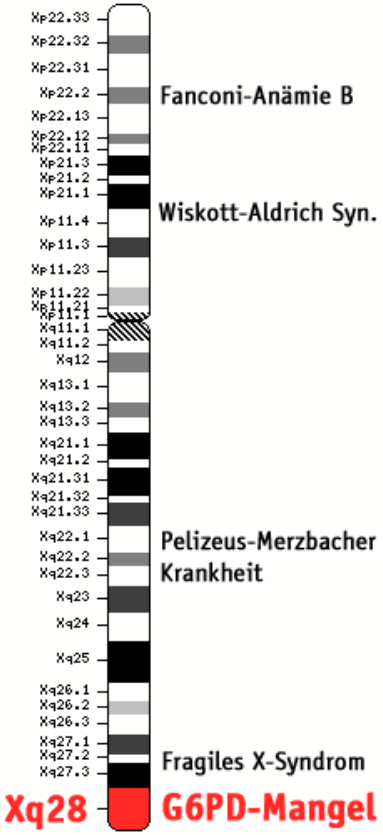


Some History….First Reported Observation

- Historical status of fava beans – emblem of death?
- Pythagoras warned against consumption of fava beans (~510 BC)
- Favism → hemolytic anemia





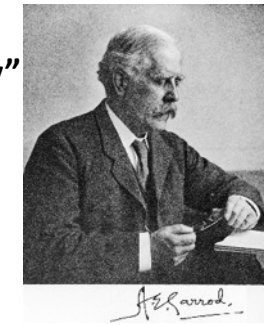


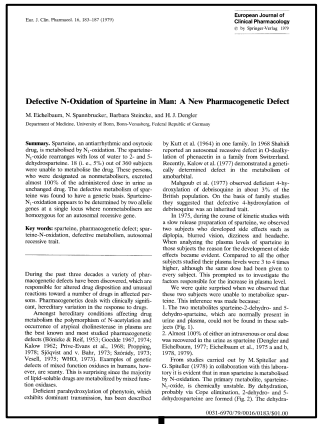
JAMA

"Inheritance might explain many individual differences in the efficacy of drugs and in the occurrence of adverse drug reactions"

Vogel coined term 'pharmacogenetics'

"chemical individuality"





510 BC

1866

1906

1956

1957

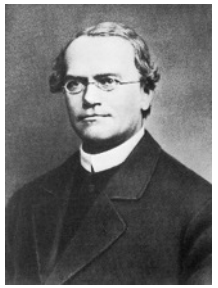
1959

1962

1977

1979

1988



Discovery of G6PD deficiency

Report of malignant hypothermia

Kalow & Genest characterize serum cholinesterase deficiency

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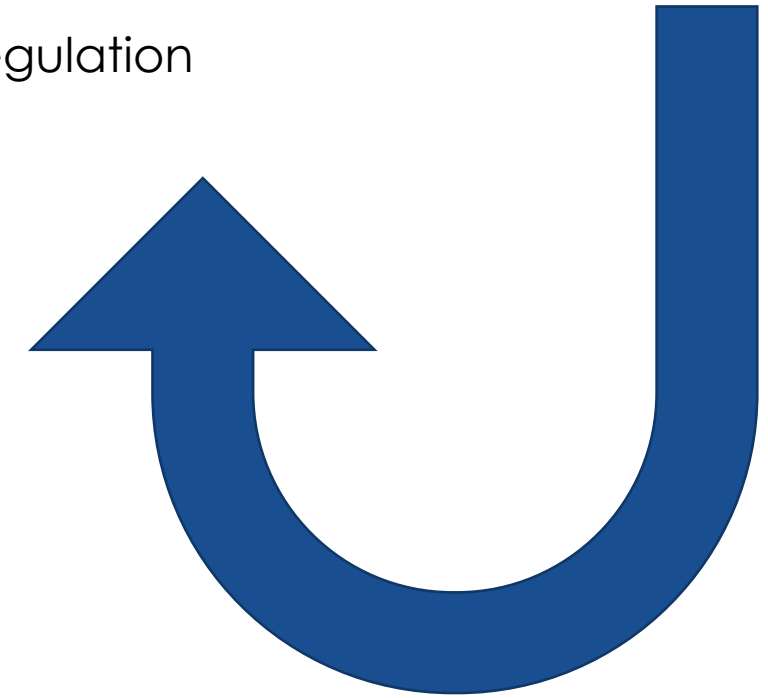
PHARMACOLOGY

PHARMACO-GENOMICS

- Gene Discovery
- Genetic Variation
- Gene Expression & Regulation

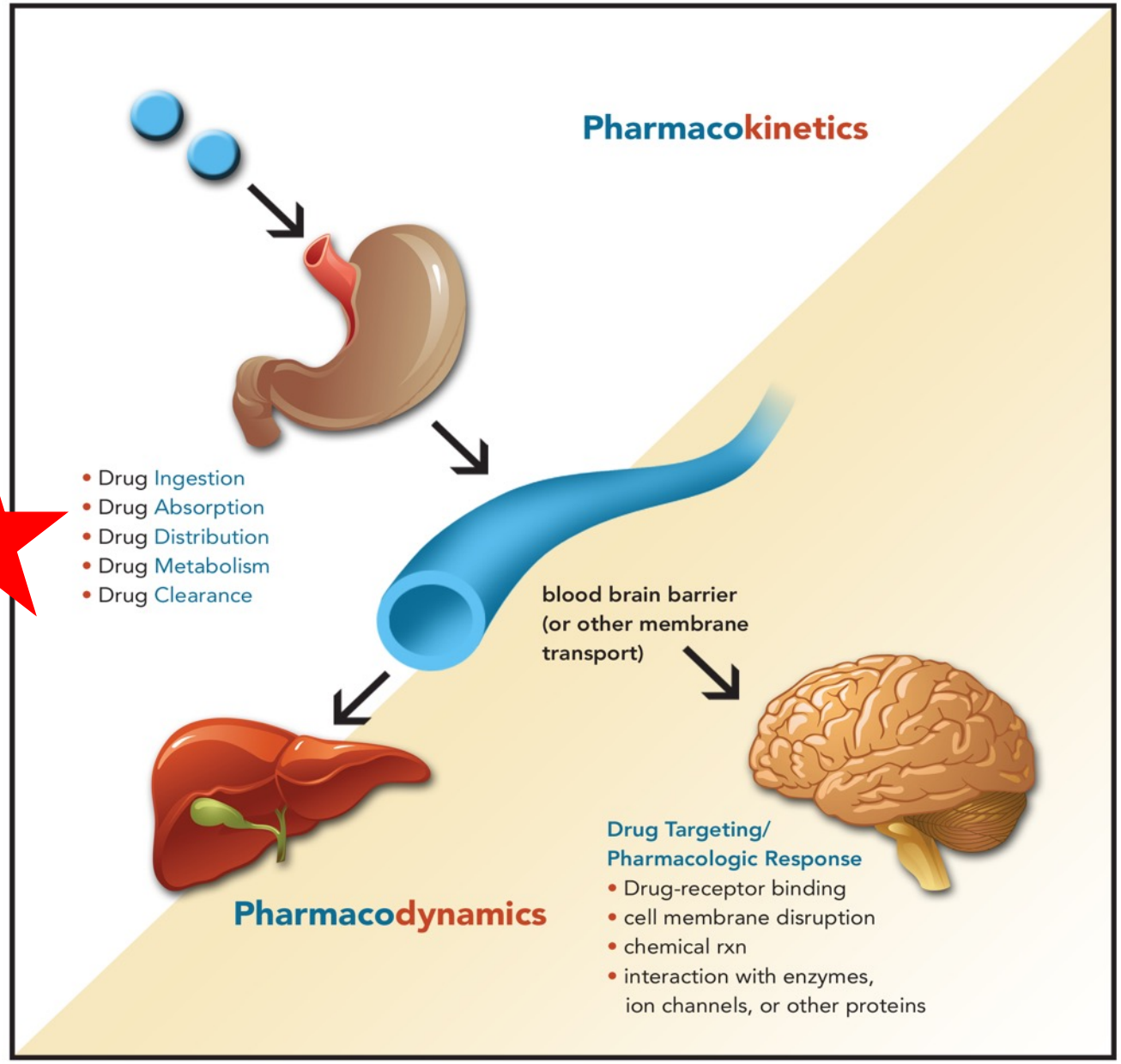
GENOME TECHNOLOGIES



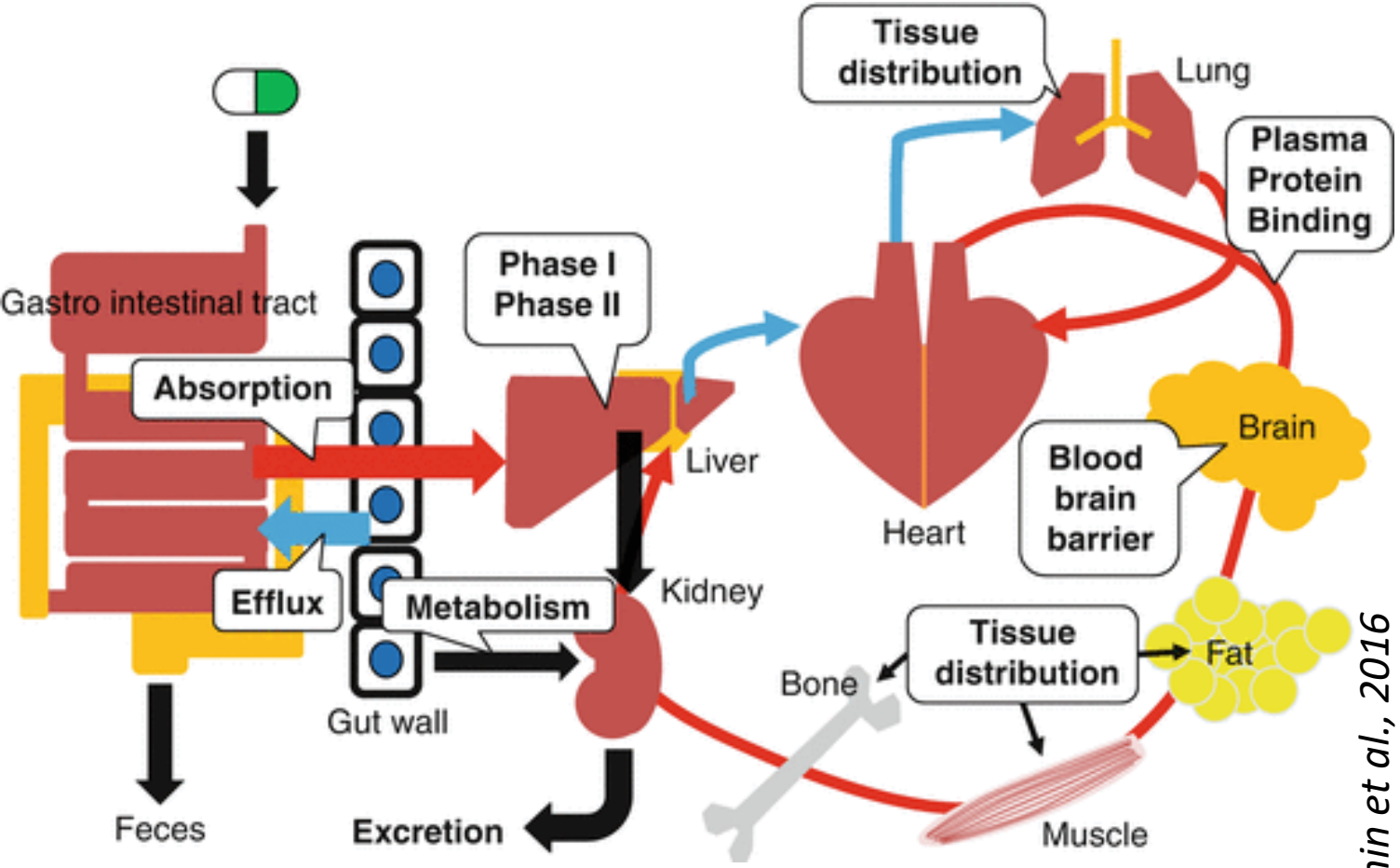
Overview of PGx

Pharmacogenetics

Pharmacokinetics & Pharmacodynamics



ADME (it's complex!)

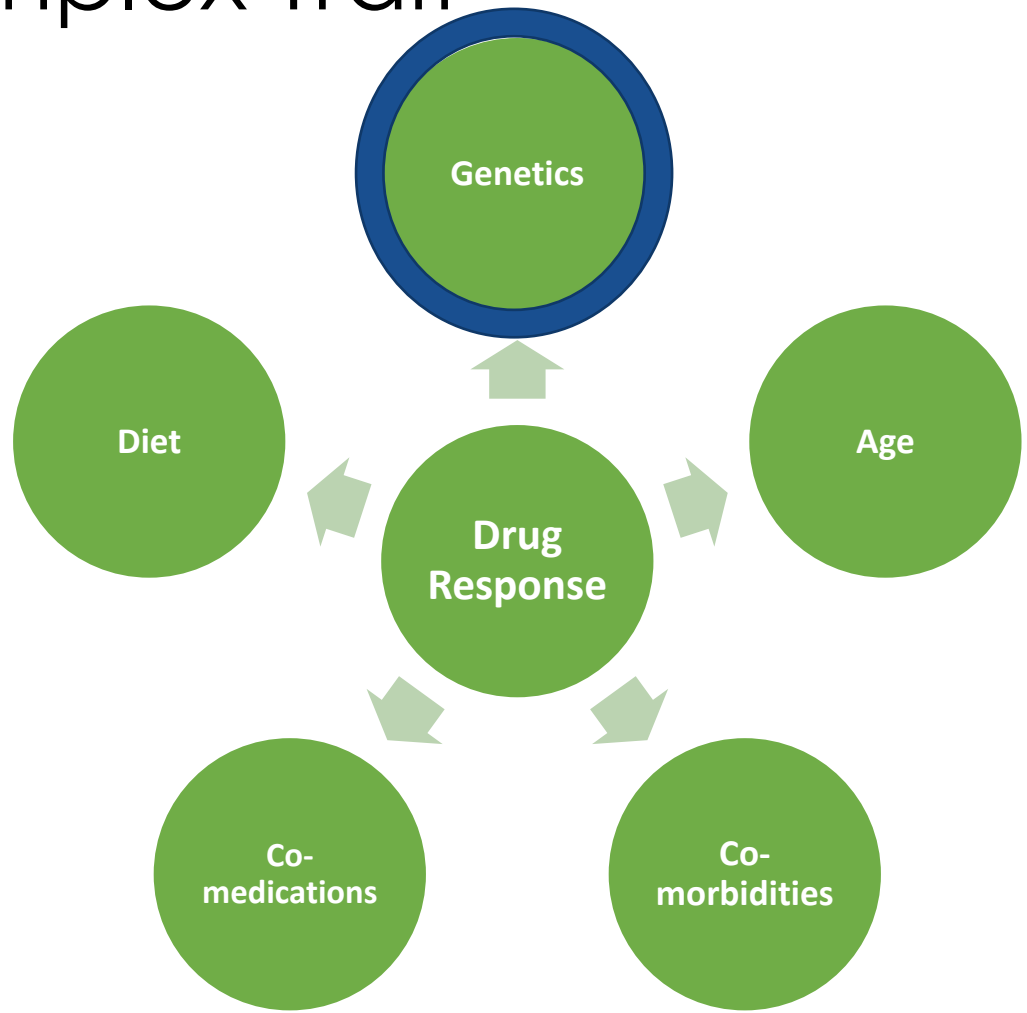


Shin et al., 2016

Common Classes of Pharmacogenes:

- Enzymes
- Transferases
- Receptors
- Transporters

Complex Trait

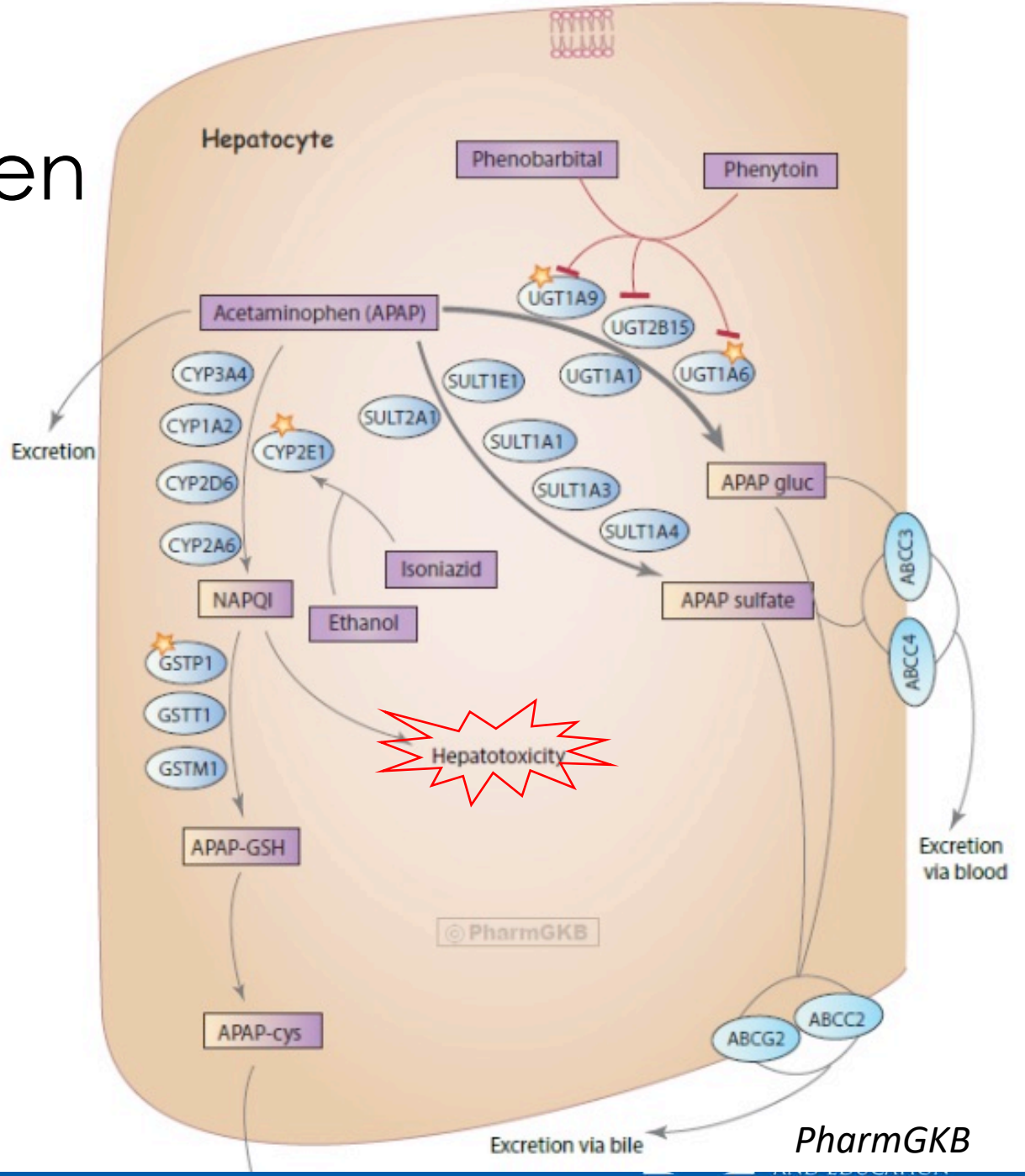


Definitions

A trait that does not follow Mendelian inheritance patterns, is likely derived from multiple genes, and exhibits a large variety of phenotypes (Nature – Scitable)

Example: Acetaminophen

- Metabolism occurs mainly in the liver, and to a lesser extent, the kidney and intestine
- Following oral administration, it is rapidly absorbed from the gastrointestinal tract
- Converted to pharmacologically inactive glucuronide (APAP-gluc) and sulfate (APAP sulfate) conjugates; minor fraction oxidized to a reactive metabolite NAPQI



Drug Metabolism: Cytochrome (CYP) P450

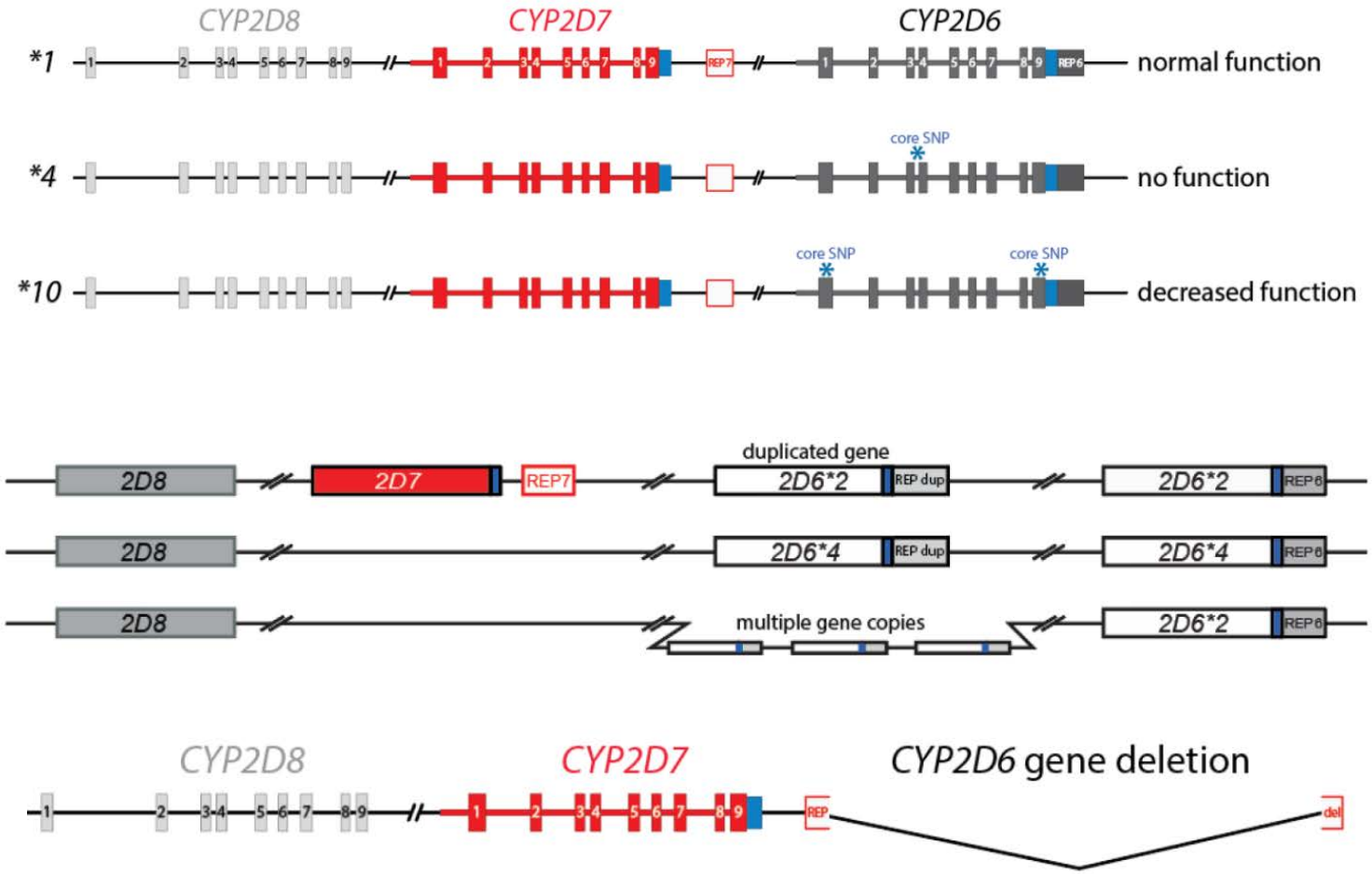
- One of the largest known gene families: 18 gene families, 43 subfamilies
- Metabolize thousands of endogenous/exogenous chemicals as well as play key roles in hormone and cholesterol synthesis
- Present in almost every tissue, but metabolize toxic compounds primarily in liver
- Drug metabolism pathways:
  - Deactivation by CYPs, either directly or by facilitated excretion from the body
  - Bioactivation by CYPs to form active compounds.
- Up to 80% of drugs believed to be metabolized by one of three CYP genes
  - CYP2D6/CYP2C19/CYP2C9

CYP2D6

- Known to metabolize as many as 20% of commonly prescribed drugs
  - Anti-arrhythmic drugs
  - Anti-depressants
  - Beta-blockers
- Highly polymorphic (139 * Alleles)
  - SNPs
  - Gene duplications/deletions
- Classified into major phenotypes:
  - Poor metabolizer (PM) phenotype
  - Intermediate metabolizer (IM) phenotype
  - Extensive metabolizer (EM) phenotype
  - Ultrarapid metabolizer (UM) phenotype

CYP2D6 Genotypes/Enzyme Activity

- Normal Activity (*1, *2)
  - 2850C>T, 4180G>C
  - 2613-2615del AGA
- Increased Activity
  - Gene Duplication
- Decreased Activity
  - 100C>T
  - -1584G>C
- Inactive Enzyme
  - 1707T>del frameshift
  - 1846G>A splice site
- No Enzyme (gene deletion)



Cascorbi, 2003

CYP2D6 Allele Functionality/Diplotype

CYP2D6 *Allele	Activity Value (Optional)	Allele Clinical Function Status (Required)*
*1	1.0	Normal function
*1x2	2.0	Increased function
*1≥3	≥3.0	Increased function
*2	1.0	Normal function
*2x2	2.0	Increased function
*2≥3	≥3.0	Increased function
*3	0	No function
*3x2	0	No function
*4	0	No function
*4≥2	0	No function
*5	0	No function
*6	0	No function

CYP2D6 Diplotype	Activity Score	Coded Diplotype/Phenotype Summary
*1/*1	2	Normal Metabolizer
*1/*1x2	3	Ultrarapid Metabolizer
*1/*1≥3	≥4	Ultrarapid Metabolizer
*1/*2	2	Normal Metabolizer
*1/*2x2	3	Ultrarapid Metabolizer
*1/*2≥3	≥4	Ultrarapid Metabolizer
*1/*3	1	Intermediate Metabolizer
*1/*3x2	1	Intermediate Metabolizer
*1/*4	1	Intermediate Metabolizer
*1/*4≥2	1	Intermediate Metabolizer
*1/*5	1	Intermediate Metabolizer

Source: CPIC

Clinical Examples

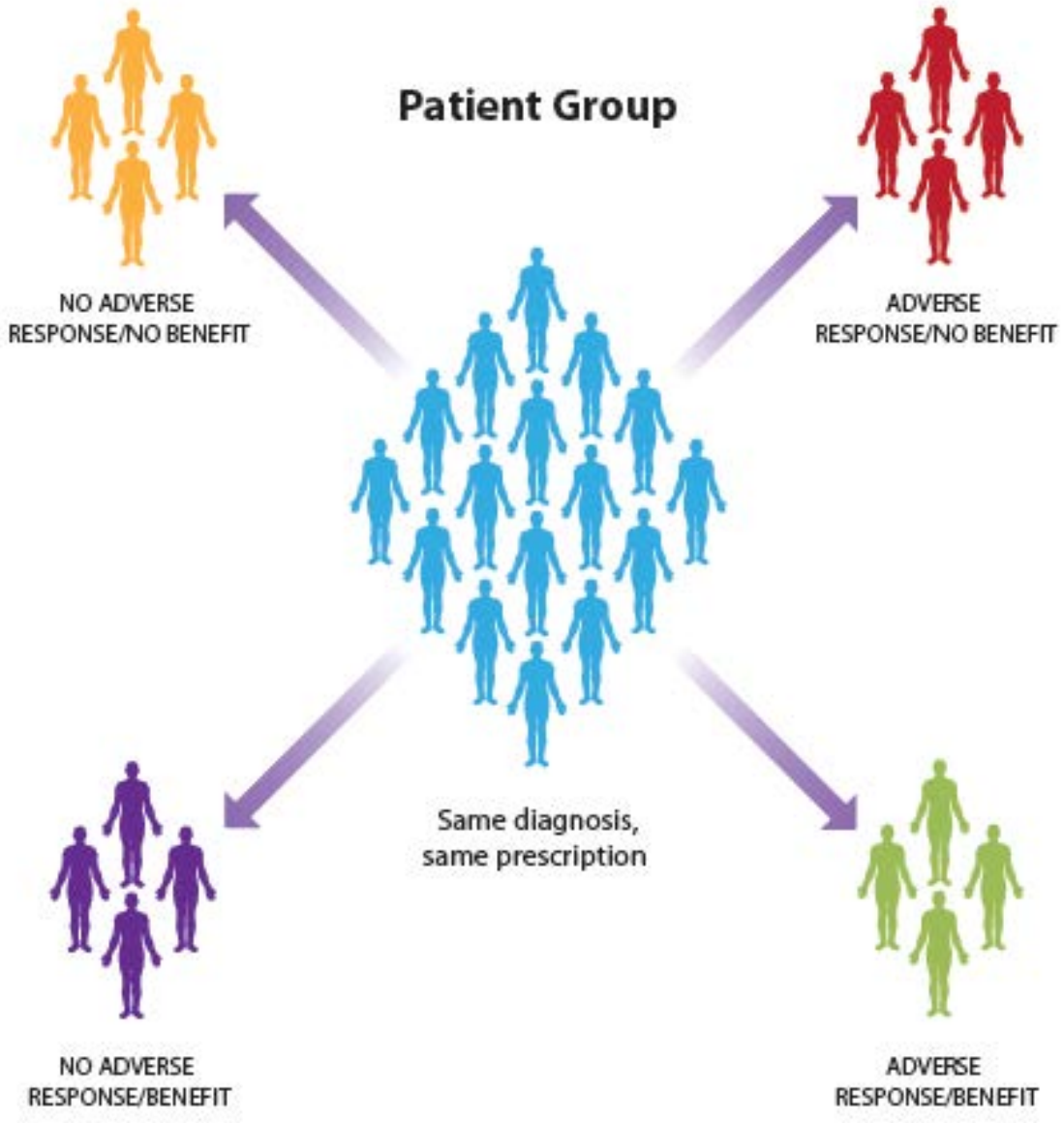
Benefits of PGx Testing

- Reduced risk of side effects and improved efficacy
  - Dose adjustment
    - Higher dose to achieve a therapeutic effect
    - Lower dose to reduce risk of ADR
  - Medication selection
- Possibly higher medication adherence

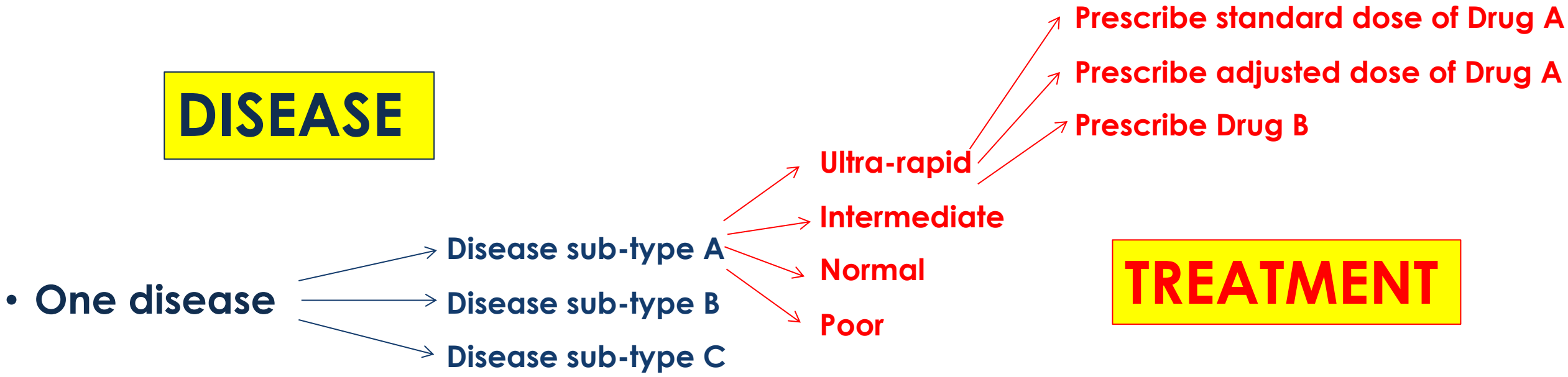
Personalized/Precision Medicine

- **Right medication**
- **Right patient**
- **Right dose**

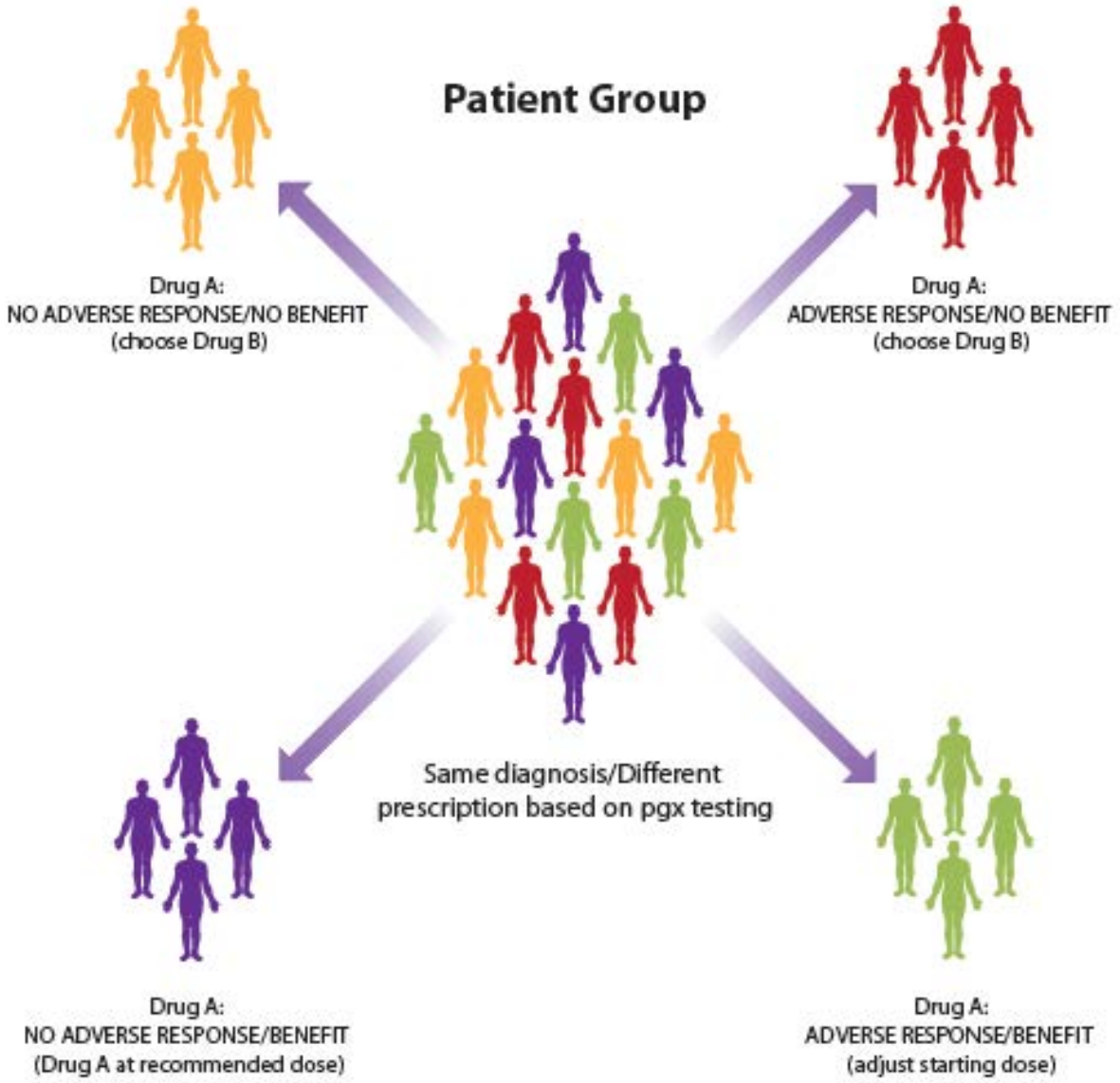
Current Treatment Approach – One Drug for All



Improved Dx & Predicted Drug Response



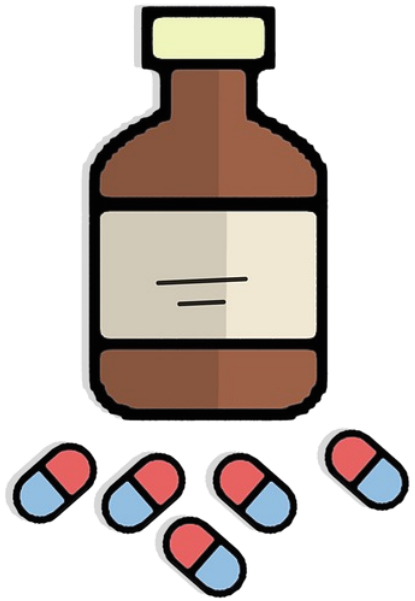
Tailored Approach -- PGx-Guided Treatment Approach



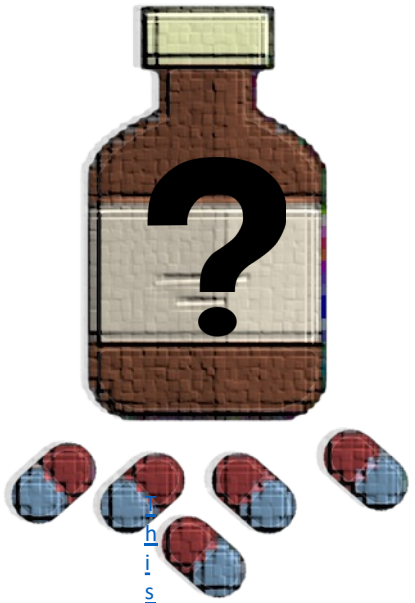
PGx Testing Along Clinical Spectrum

“Pre-emptive” Testing

“Point-of-Care” Testing



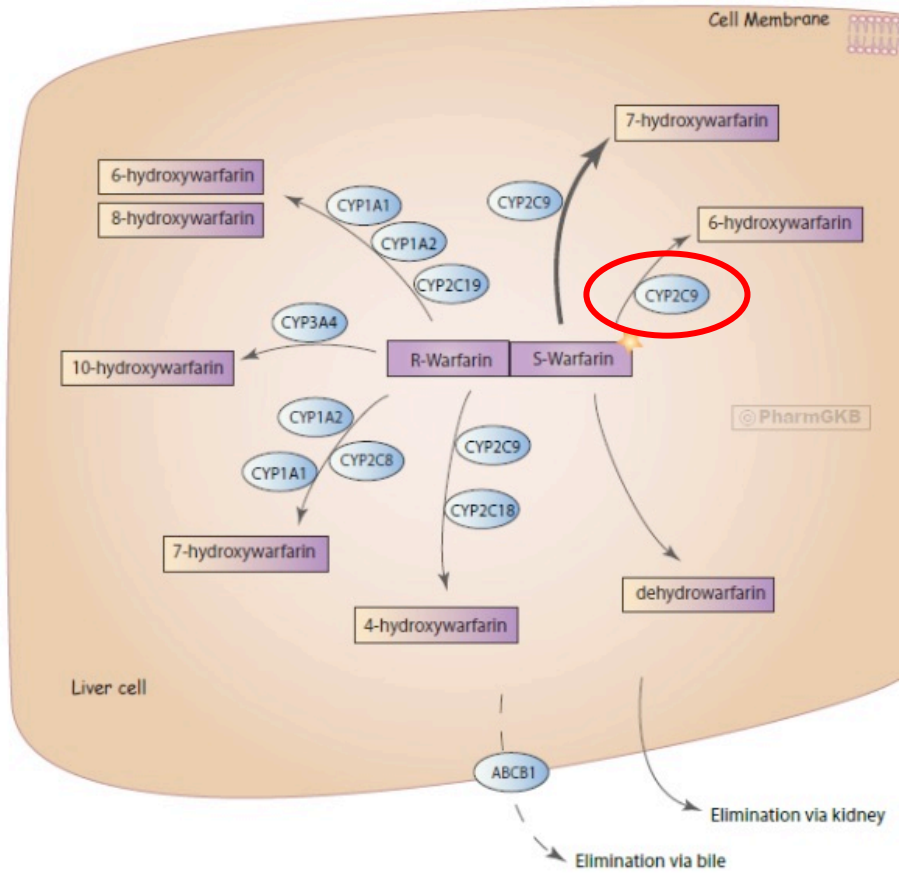
“Diagnostic” Testing



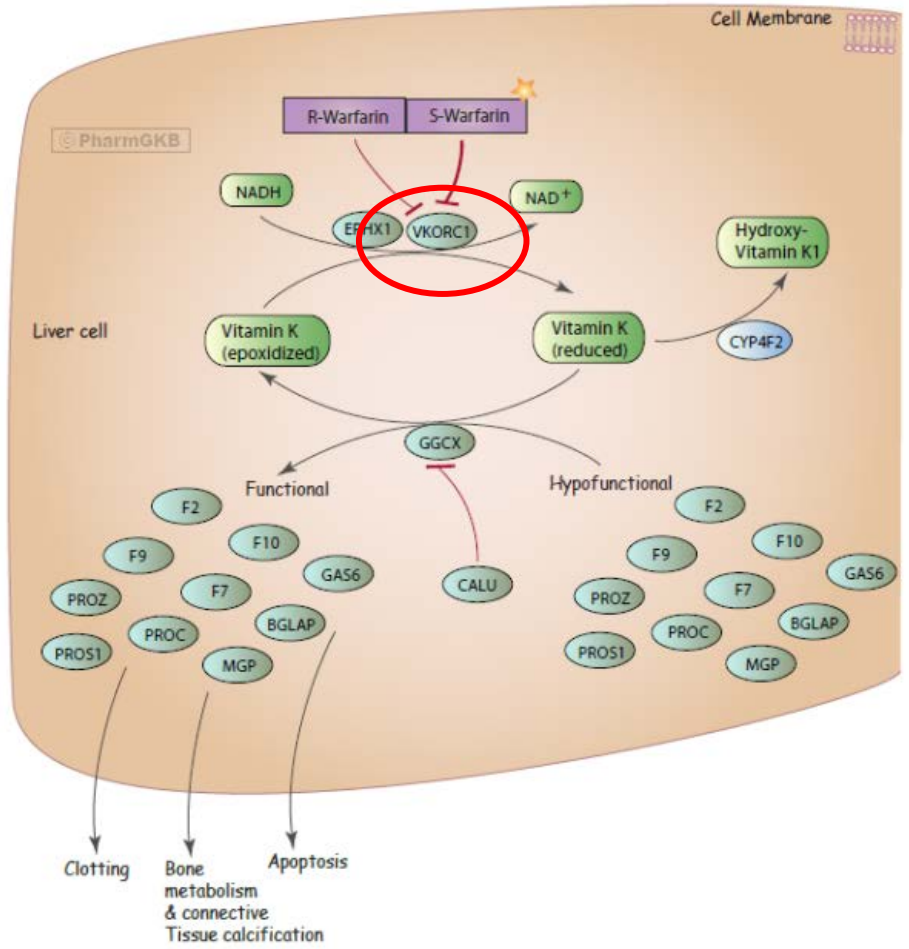
1 Warfarin (CYP2C9/VKORC1)

- Indication: Blood thinner (anti-coagulant)
- Mechanism of Action: Inhibitor of VKORC1
- Challenges to use:
  - Initial dosing
  - Narrow therapeutic window
  - 30x inter-individual variation dose requirements
    - Poor clinical predictors (age, race, body size, co-medications)
- Surveillance: INR monitoring

Warfarin Pharmacokinetics



Warfarin Pharmacodynamics



Clinical Pharmacology & Therapeutics (2012) 92(4): 414-417.

FDA Coumadin label change in 2010

Table 1: Three Ranges of Expected Maintenance COUMADIN Daily Doses Based on CYP2C9 and VKORC1 Genotypes†

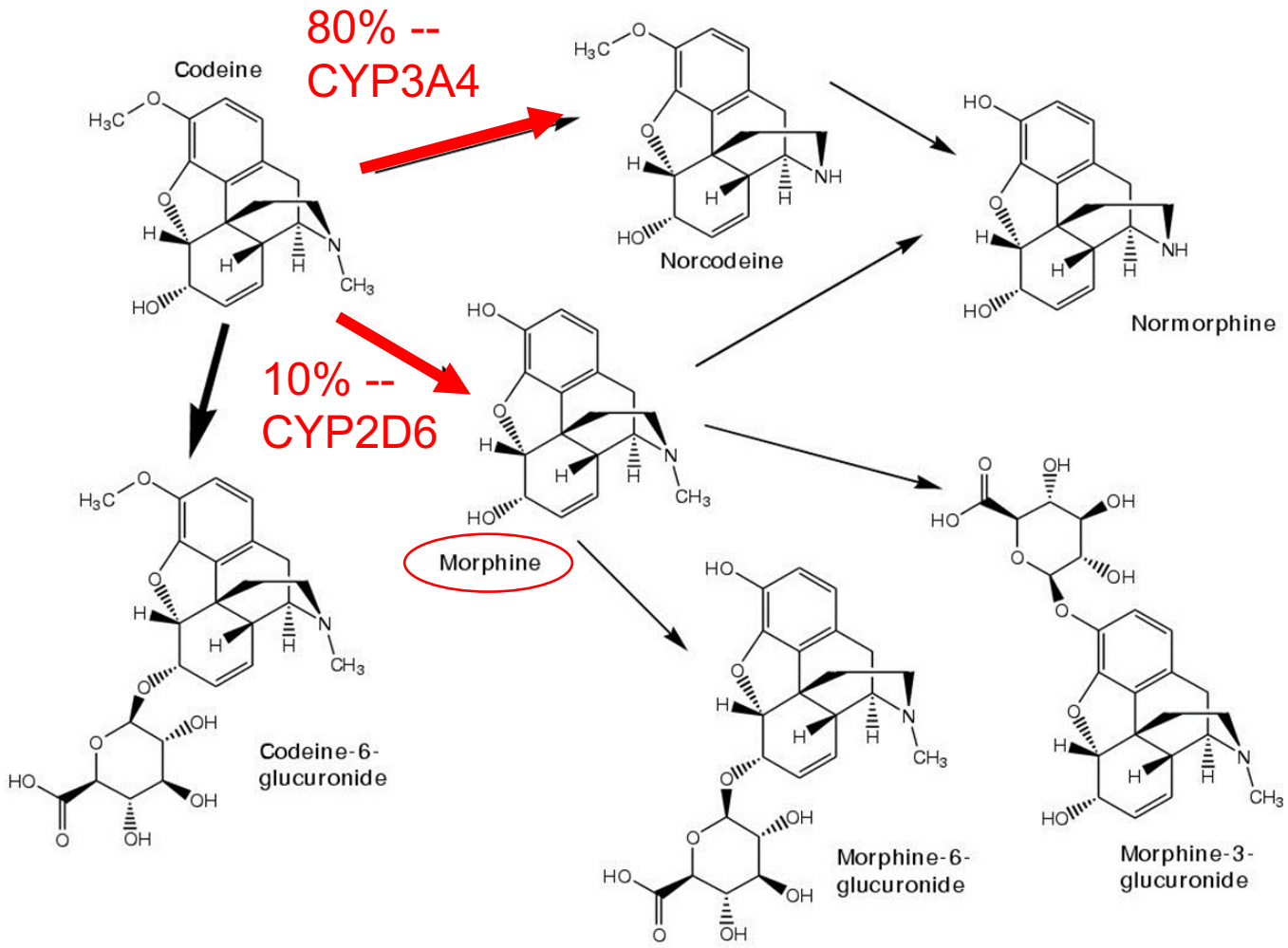
VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

†Ranges are derived from multiple published clinical studies. VKORC1 –1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose.

Coumadin package insert, FDA Center for Drug Evaluation and Research (CDER) – January 2010

2 Codeine

- Indication: Pain
- Drug type: Prodrug
- Highly polymorphic CYP2D6
- Lots of alternative treatments



CYP2D6 – Warnings (4/20/17)

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women

This is an update to the FDA Drug Safety Communications:

- FDA evaluating the potential risks of using codeine cough-and-cold medicines in children issued on July 1, 2015, and
- FDA evaluating the risks of using the pain medicine tramadol in children aged 17 and younger issued on September 21, 2015.

- Always read the label on prescription bottles to find out if a medicine contains codeine or tramadol, or ask your child's health care provider or a pharmacist.
- If patients of any age are known to be CYP2D6 ultra-rapid metabolizers, which means their bodies convert codeine or tramadol into their active forms faster and more completely than usual, they should not use codeine or tramadol.
- If a child has taken codeine or tramadol and you notice any signs of slow or

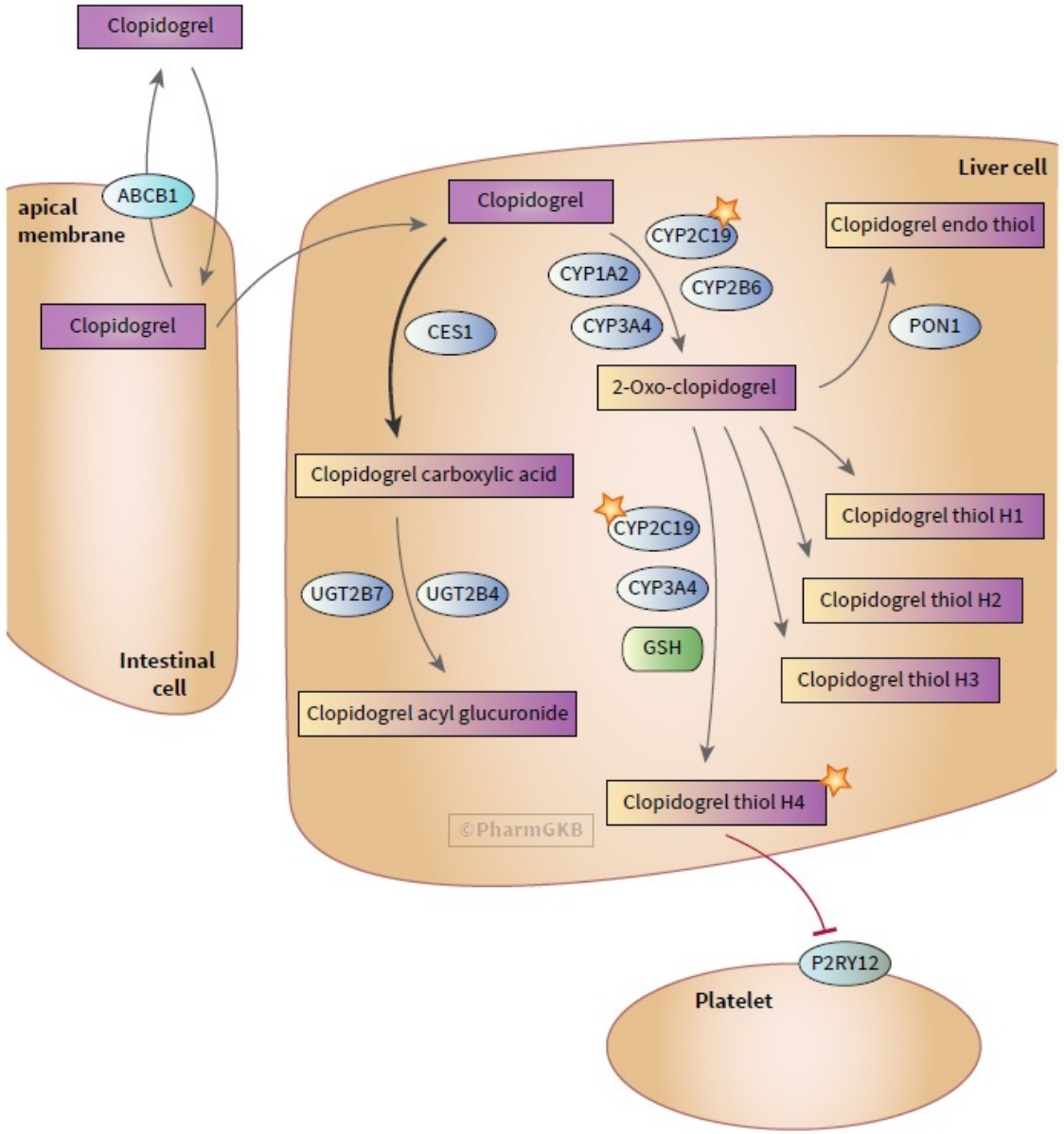
p.5

Ten of the 64 cases mentioned the status of cytochrome P450 isoenzyme 2D6 (CYP2D6) genotype. Seven of these patients were ultra-rapid metabolizers, five of whom died. Ultra-rapid metabolizers of substrates of CYP2D6 convert codeine in their bodies too quickly into potentially dangerously high levels of morphine, the active form of codeine, contributing to life-threatening or fatal respiratory depression. The three other patients were extensive metabolizers, with one death.

p.6

3 Clopidogrel

- Anti-platelet (pro)drug
- Bio-activated by CYPs into active metabolites in two steps:
  1) Formation of intermediate metabolite 2-oxo-clopidogrel by CYP2C19/CYP1A2/ CYP2B6
  2) 2-oxo-clopidogrel hydrolyzed to thiol derivative by CYP2C19/CYP2C9/CYP2B6/ CYP3A5/CYP3A4



PharmaGKB

Clopidogrel Label - Warning

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PLAVIX safely and effectively. See full prescribing information for PLAVIX.

PLAVIX (clopidogrel bisulfate) tablets, for oral use
Initial U.S. Approval: 1997

WARNING: DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE CYP2C19 GENE

See full prescribing information for complete boxed warning.

- **Effectiveness of Plavix depends on conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1, 12.3)**
- **Tests are available to identify patients who are CYP2C19 poor metabolizers. (12.5)**
- **Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers. (5.1)**

----------**RECENT MAJOR CHANGES**----------
Boxed Warning 9/2016

- Initiating Plavix without a loading dose will delay establishment of an antiplatelet effect by several days
- Recent MI, recent stroke, or established peripheral arterial disease: 75 mg once daily orally without a loading dose (2.2)

----------**DOSAGE FORMS AND STRENGTHS**----------
Tablets: 75 mg, 300 mg (3)

----------**CONTRAINDICATIONS**----------
- Active pathological bleeding, such as peptic ulcer or intracranial hemorrhage (4.1)
- Hypersensitivity to clopidogrel or any component of the product (4.2)

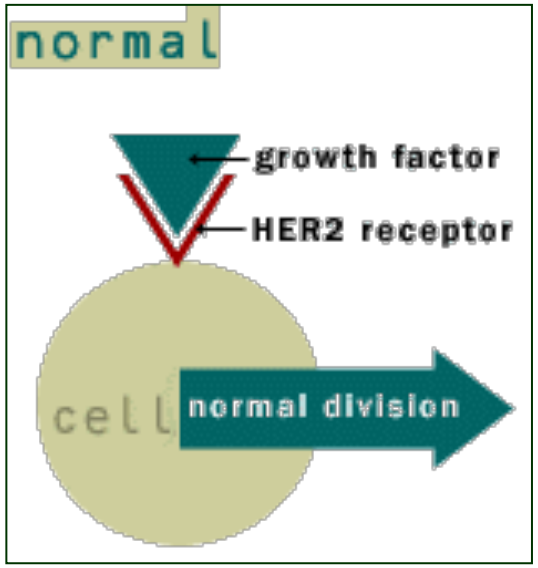
----------**WARNINGS AND PRECAUTIONS**----------
- CYP2C19 inhibitors: Avoid concomitant use of omeprazole or esomeprazole. (5.1)
- Bleeding: Plavix increases risk of bleeding. (5.2)
- Discontinuation: Premature discontinuation increases risk of cardiovascular events. Discontinue 5 days prior to elective surgery that has a major risk of bleeding. (5.3)
- Thrombotic thrombocytopenic purpura (TTP) has been reported. (5.4)
- Cross-reactivity among thienopyridines has been reported. (5.5)

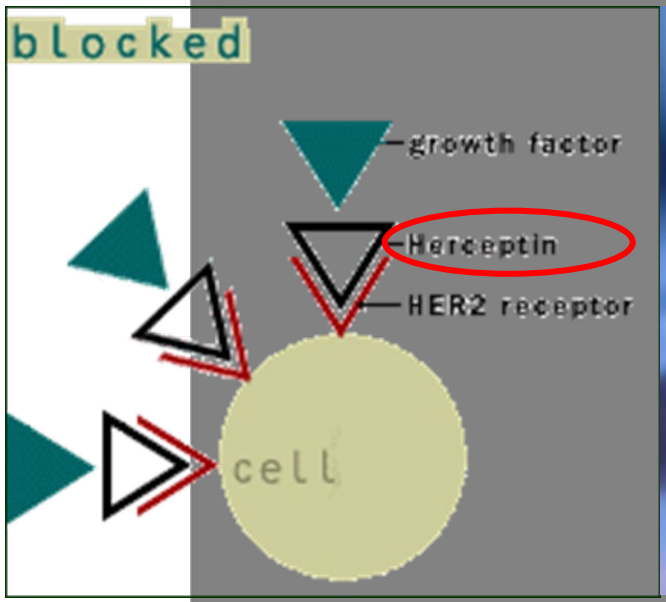
ADVERSE REACTIONS

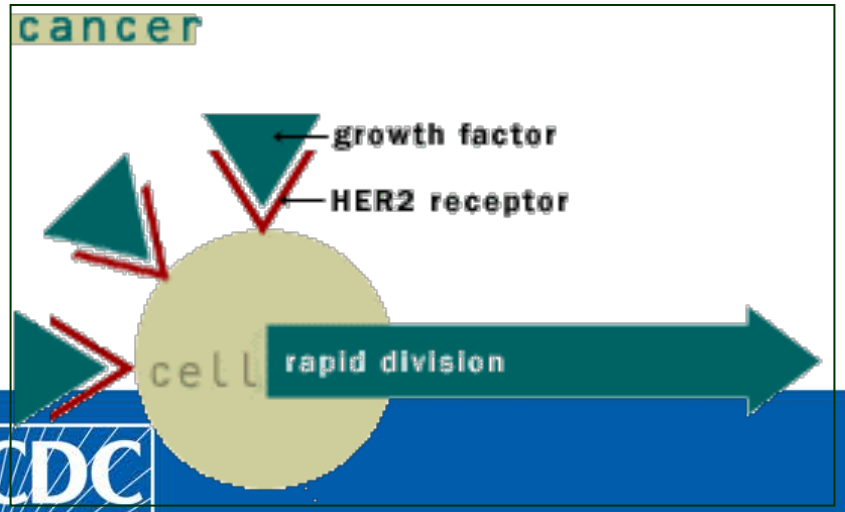
4 Targeted Drugs -- Cancer

- Defined as "treatments for which the label includes reference to specific biological markers, identified with the assistance of a diagnostic test, that guide the use of the medicine or procedure in individual patients
  - Targets changes in cancer cells, often involved in cell growth, repair, and metastasis
    - Small-molecule drugs
    - Monoclonal antibodies
- Testing required to determine drug suitability
  - Companion diagnostic (CDx)

Targeted Drug: Herceptin







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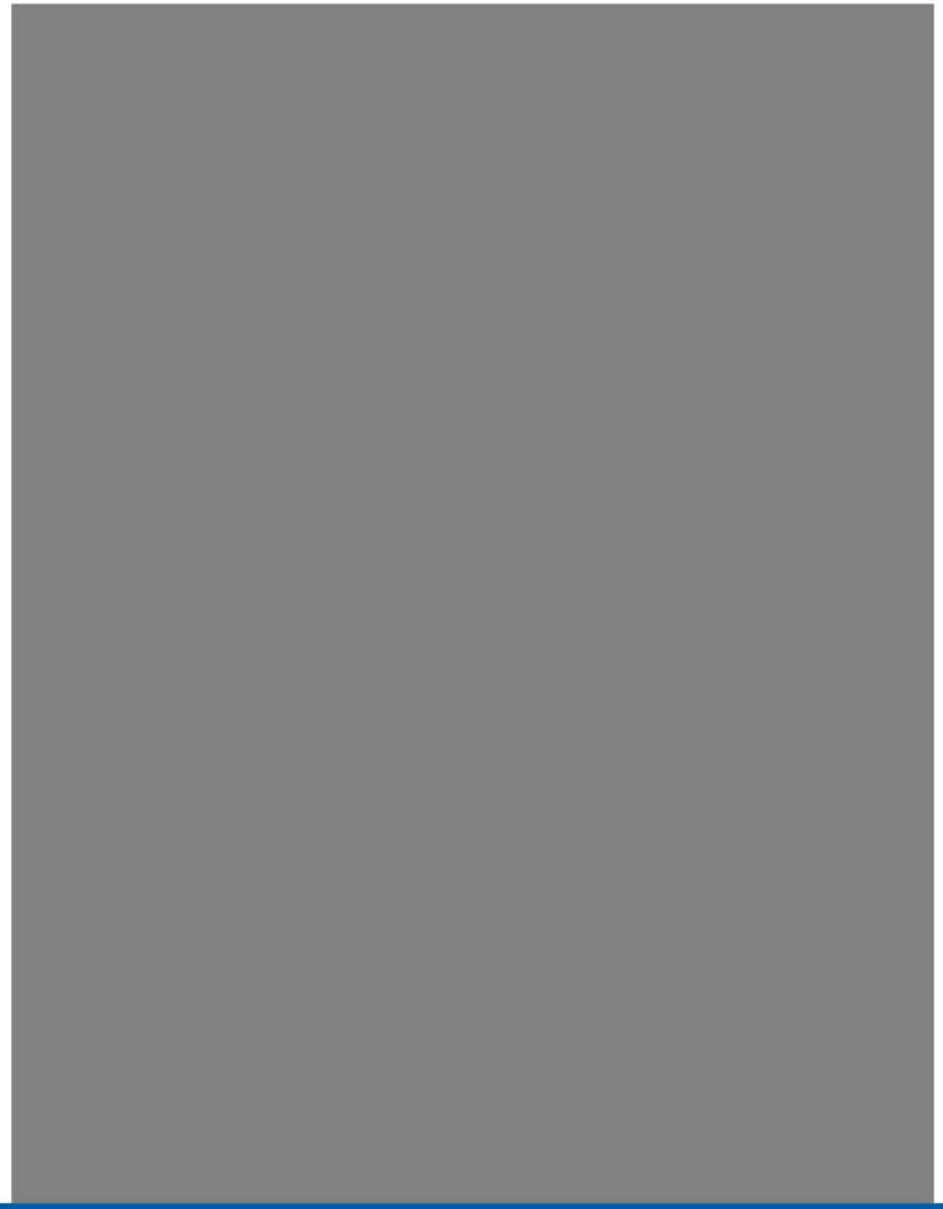
PGx Testing Examples & Methods



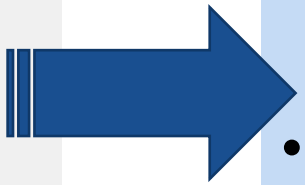
PGx Testing

- Laboratories
  - Bioreference labs: LabCorp, Quest, ARUP
  - Specialty labs
- Analytes
  - Blood, saliva
- Methods
  - DNA-based (genotyping, sequencing)or protein (enzymatic activity)
  - Turn-around time between ~2-10 days
- Single gene vs panel testing

DNA Analysis Methods

What are you looking for?

- Number of genes/regions: 1 or more?
- Number of variants: 1 or more SNPs (known)?
- Prior knowledge: known or novel?
- Type of variation: SNPs, gene duplications/deletions



What's the best technology to use?

- Targeted analysis to specific SNPs or gene sequence
  - PCR-based assay
  - Microarrays
- Multiple SNPs
  - Microarrays
  - Gene Sequencing

Genotyping

- Analyzes a very specific aspect of the genome (e.g., an allele)

ATTAAAGGTTTATACCTTCCCAGGTAACAAACCAACCAACTTTC
ATTAAAGGTTTATACCTTCCCAGGTAACAAACCAACCAACTTTC

Two alleles inherited for a particular gene

Genotyping

(PCR)-based methods:

1) amplify number of copies of the targeted gene to be analyzed and 2) have a method of detection

- Real-time PCR: amplify target area and use two allele-specific probes to detect SNP alleles in target area
- PCR of targeted region plus sequencing (genotyping by sequencing)

Microarrays

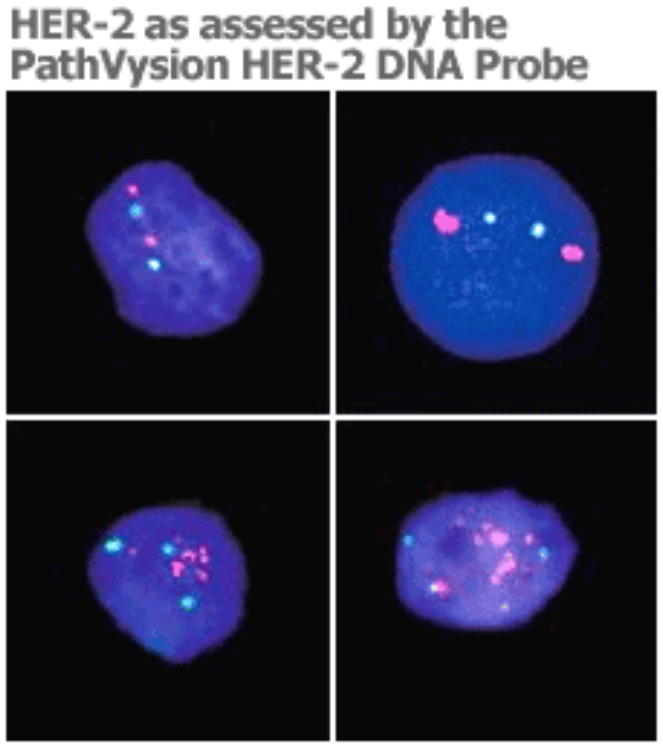
- Analyze many pre-selected SNPs using fluorescent
- Can also capture copy number variations (CNVs)

Roche Amplichip CYP450 Test

- Tests 29 polymorphisms/ mutations for the **CYP2D6** and 2 polymorphisms for the **CYP2C19** to predict phenotype in single assay (PM, IM, EM, UM)

- FDA-approved in 2004

Companion Dx: HER2 Amplification



← GENOMIC TESTING

FOUNDATIONONE®CDx

NGS detection of substitutions, insertion and deletion alterations, and CNVs in **324** genes and select gene rearrangements, as well as genomic signatures including microsatellite instability and tumor mutational burden

The first FDA-approved broad companion diagnostic with Medicare coverage for qualifying patients across all solid tumors, including: NSCLC, Colorectal, Breast, Ovarian, and Melanoma

CANCER TYPE
Solid Tumor

SAMPLE TYPE
FFPE

RESULTS EXPECTED
*<2 weeks**

Jump to a section

Overview | CDx Claims | Real Life Results | Ordering | Patient Resources

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Challenges to Clinical Implementation

Challenges to Clinical Implementation

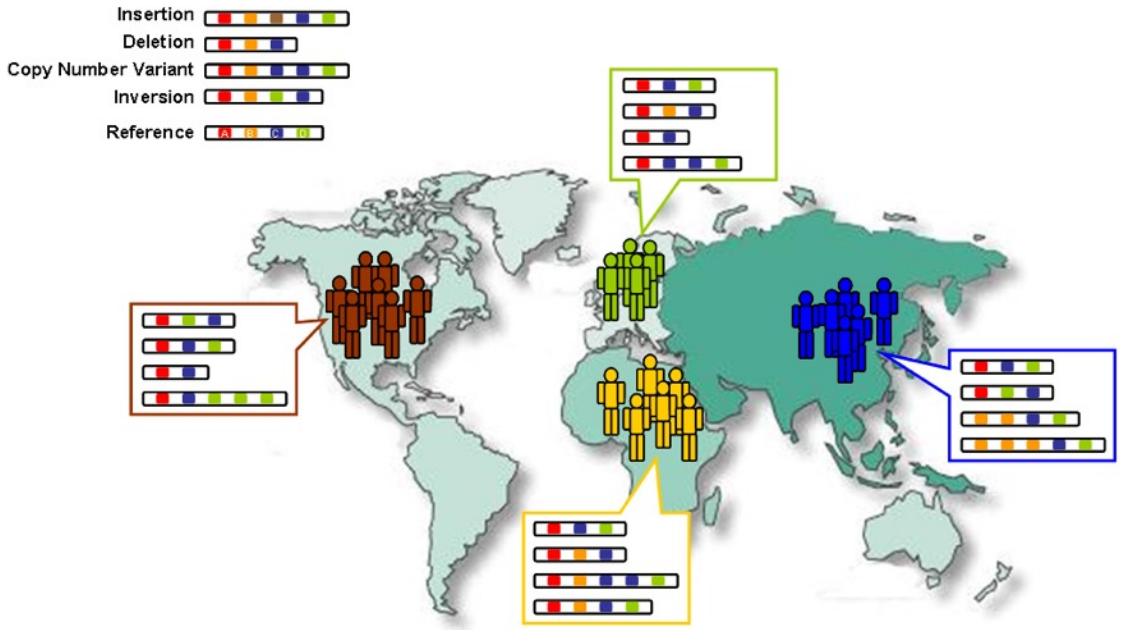
- Provider Knowledge***
- Clinical Decision Support***
- Reimbursement
  - Insurance coverage variable
  - Typically ranges from $300-600 per test

- Clinical Utility for all (allelic diversity)

Limitations for PGx testing

- Vast majority of PGx research is retrospective and has not been tested prospectively
  - Guidelines available
  - Unlikely to have prospective data for all drugs and variants
- Uneven allele prevalence and biased study populations
- Drug response is complex – penetrance of genetic variants not always clear
  - Many patients with a variant will do fine and others without will have poor outcome
- PGx is one additional piece of data to guide treatment decisions
  - Clinical judgment regarding drug selection/dosing paramount

Allelic Diversity



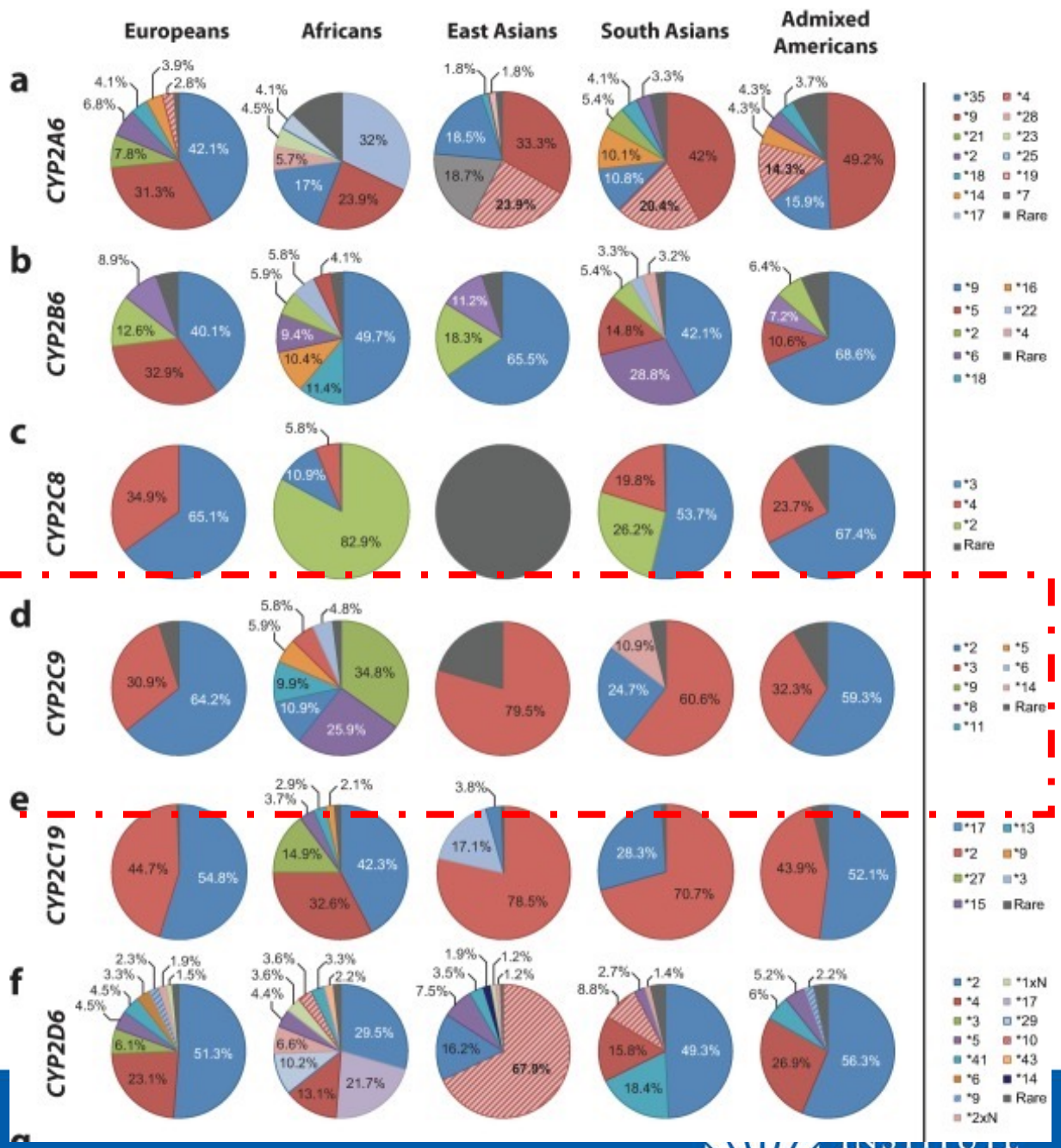
- Differences in allelic prevalence between populations

Early History

- 1952: Clayman & Hockwald reported differences in adverse responses to primaquine between African-American and European ancestry (G6PD)
- 1953: different rates of acetylation of anti-TB drug isoniazid reported
- 1978: Kalow et al. reported two levels of glucuronidation following amobarbital exposure (Chinese – European)
- 1979: Kalow et al. confirmed distribution of amobarbital metabolism status (European – Asian)

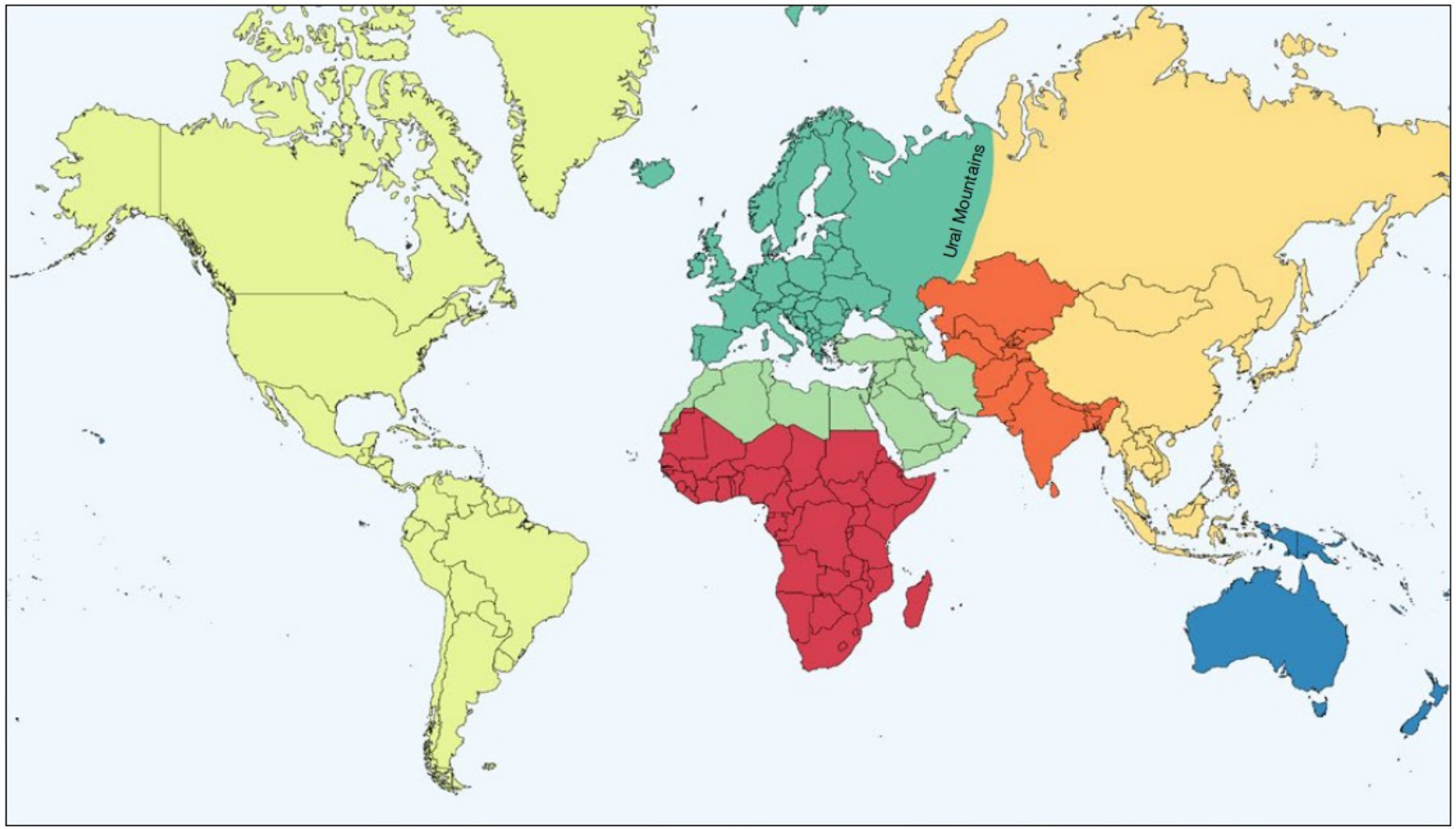
Example - Population Frequency Distribution

- Distribution of relative contributions of major (*CYP*) alleles in five major populations



Zhou et al., 2017

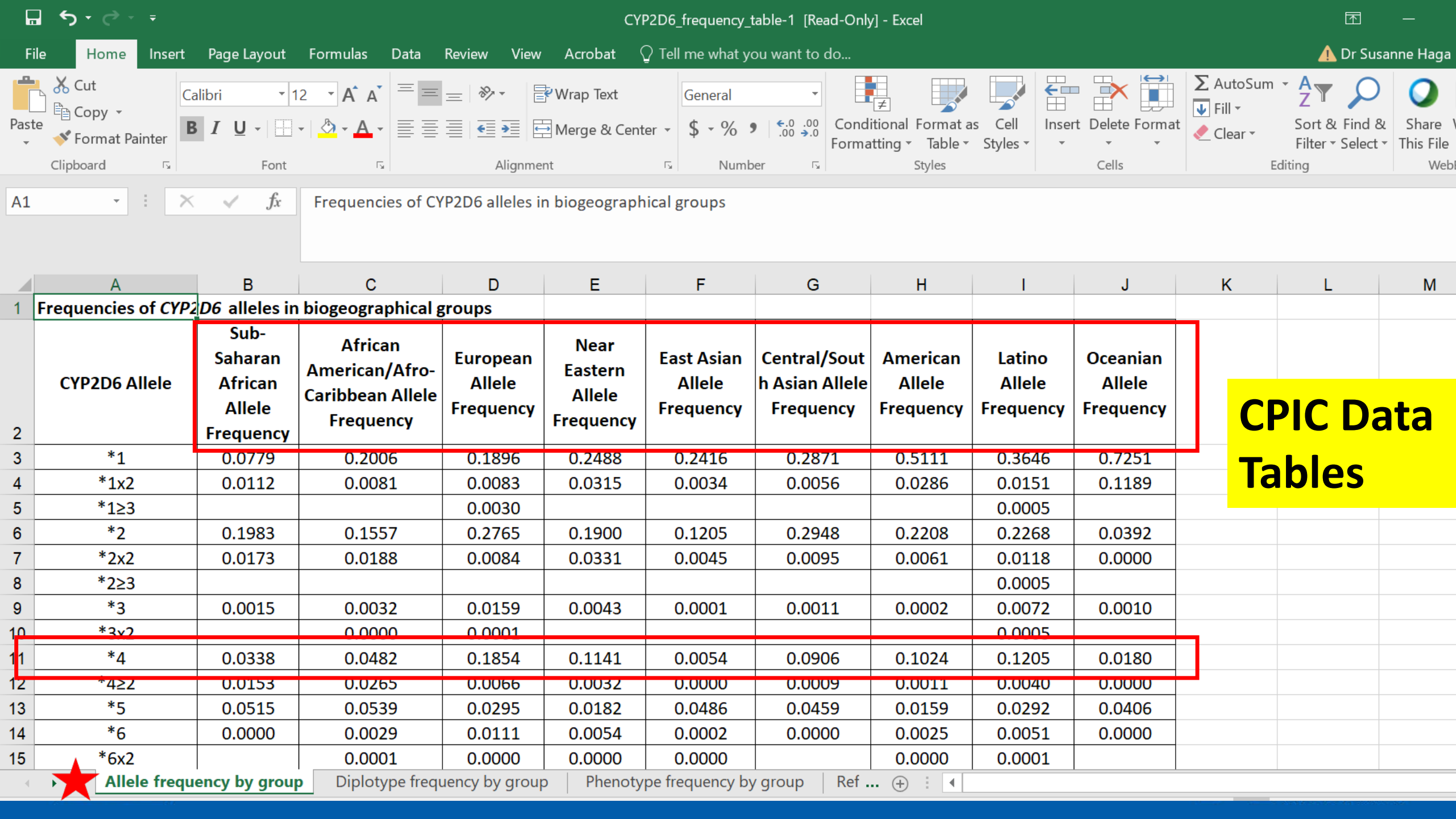
Standardized Biogeographic Grouping System for Annotating Populations in PGx



- American (AME)
- East Asian (EAS)
- European (EUR)
- Central/South Asian (SAS)
- Near Eastern (NEA)
- Oceanian (OCE)
- Sub-Saharan African (SSA)

+ Latino
+ African-American/African-Caribbean

Huddart et al.


CYP2D6_frequency_table-1 [Read-Only] - Excel
File Home Insert Page Layout Formulas Data Review View Acrobat Tell me what you want to do... Dr Susanne Haga
Cut Copy Format Painter Paste
Calibri 12
Wrap Text Merge & Center
General
Conditional Formatting Format as Table Cell Styles
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Sort & Filter Find & Select
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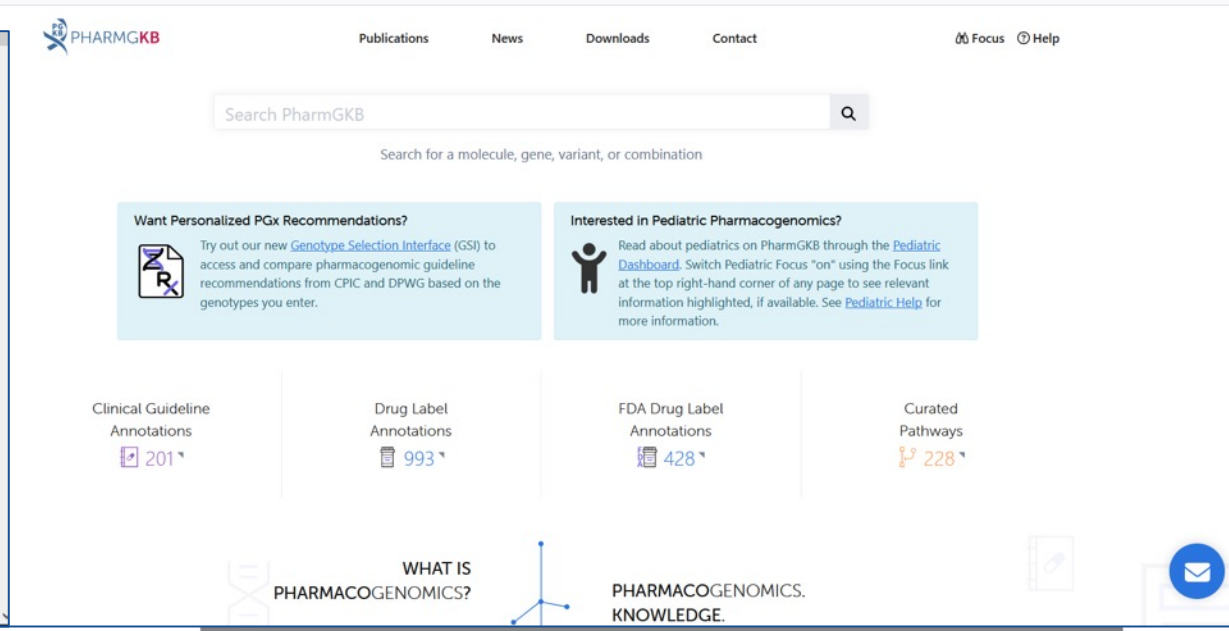
A1
Frequencies of CYP2D6 alleles in biogeographical groups
Frequencies of CYP2D6 alleles in biogeographical groups
CYP2D6 Allele
Sub-Saharan African Allele Frequency
African American/Afro-Caribbean Allele Frequency
European Allele Frequency
Near Eastern Allele Frequency
East Asian Allele Frequency
Central/South Asian Allele Frequency
American Allele Frequency
Latino Allele Frequency
Oceanian Allele Frequency
*1 0.0779 0.2006 0.1896 0.2488 0.2416 0.2871 0.5111 0.3646 0.7251
*1x2 0.0112 0.0081 0.0083 0.0315 0.0034 0.0056 0.0286 0.0151 0.1189
*1≥3 0.0030 0.0005
*2 0.1983 0.1557 0.2765 0.1900 0.1205 0.2948 0.2208 0.2268 0.0392
*2x2 0.0173 0.0188 0.0084 0.0331 0.0045 0.0095 0.0061 0.0118 0.0000
*2≥3 0.0005
*3 0.0015 0.0032 0.0159 0.0043 0.0001 0.0011 0.0002 0.0072 0.0010
*3x2 0.0000 0.0001 0.0005
*4 0.0338 0.0482 0.1854 0.1141 0.0054 0.0906 0.1024 0.1205 0.0180
*4≥2 0.0153 0.0265 0.0066 0.0032 0.0000 0.0009 0.0011 0.0040 0.0000
*5 0.0515 0.0539 0.0295 0.0182 0.0486 0.0459 0.0159 0.0292 0.0406
*6 0.0000 0.0029 0.0111 0.0054 0.0002 0.0000 0.0025 0.0051 0.0000
*6x2 0.0001 0.0000 0.0000 0.0000 0.0000 0.0001
CPIC Data Tables
Allele frequency by group
Diplotype frequency by group
Phenotype frequency by group
Ref ...

Resources



CDC

OAK RIDGE INSTITUTE FOR SCIENCE AND EDUCATION

CPIC®
Clinical Pharmacogenetics Implementation Consortium

What is CPIC?

The Clinical Pharmacogenetics Implementation Consortium (CPIC®) is an international consortium of individual volunteers and a small dedicated staff who are interested in facilitating use of pharmacogenetic tests for patient care.

One barrier to implementation of pharmacogenetic testing in the clinic is the difficulty in translating genetic laboratory test results into actionable prescribing decisions for affected drugs.

CPIC's goal is to address this barrier to clinical implementation of pharmacogenetic tests by creating, curating, and posting freely available, peer-reviewed, evidence-based, updatable, and detailed gene/drug clinical practice guidelines (click here for all CPIC publications). CPIC guidelines follow standardized formats, include systematic grading of evidence and clinical recommendations, use standardized terminology, are peer-reviewed, and are published in a leading journal (in partnership with Clinical Pharmacology and Therapeutics) with simultaneous

Guidelines

CPIC guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy, rather than WHETHER tests should be ordered. A key assumption underlying the CPIC guidelines is that clinical high-throughput and pre-emptive (pre-prescription) genotyping will become more widespread, and that clinicians will be faced with having patients' genotypes available even if they have not explicitly ordered a test with a specific drug in mind. CPIC's guidelines, processes and projects have been endorsed by several professional societies – read more.

Each CPIC guideline adheres to a standard format, and includes a standard system for grading levels of evidence linking genotypes to phenotypes, how to assign phenotypes to clinical genotypes, prescribing recommendations based on genotype/phenotype, and a standard system for assigning strength to each prescribing recommendation. The SOP for guideline creation has been published in Current Drug Metabolism: Incorporation of Pharmacogenomics into Routine Clinical Practice: The Pharmacogenetics Implementation Consortium (CPIC) Guideline Development Process. The CPIC authorship guidelines contain more details on minimizing and managing conflicts of interest.

View CPIC's process for prioritizing CPIC guidelines

Search:

GUIDELINES	DRUGS	GENES
CFTR and Ivacaftor	ivacaftor	CFTR
CYP2B6 and efavirenz	efavirenz	CYP2B6
CYP2C19 and Clopidogrel	clopidogrel	CYP2C19

CPIC® Guideline for Opioids and CYP2D6, OPRM1, and COMT

Most recent guideline publication:

Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6*, *OPRM1*, and *COMT* genotype and select opioid therapy (December 2020)

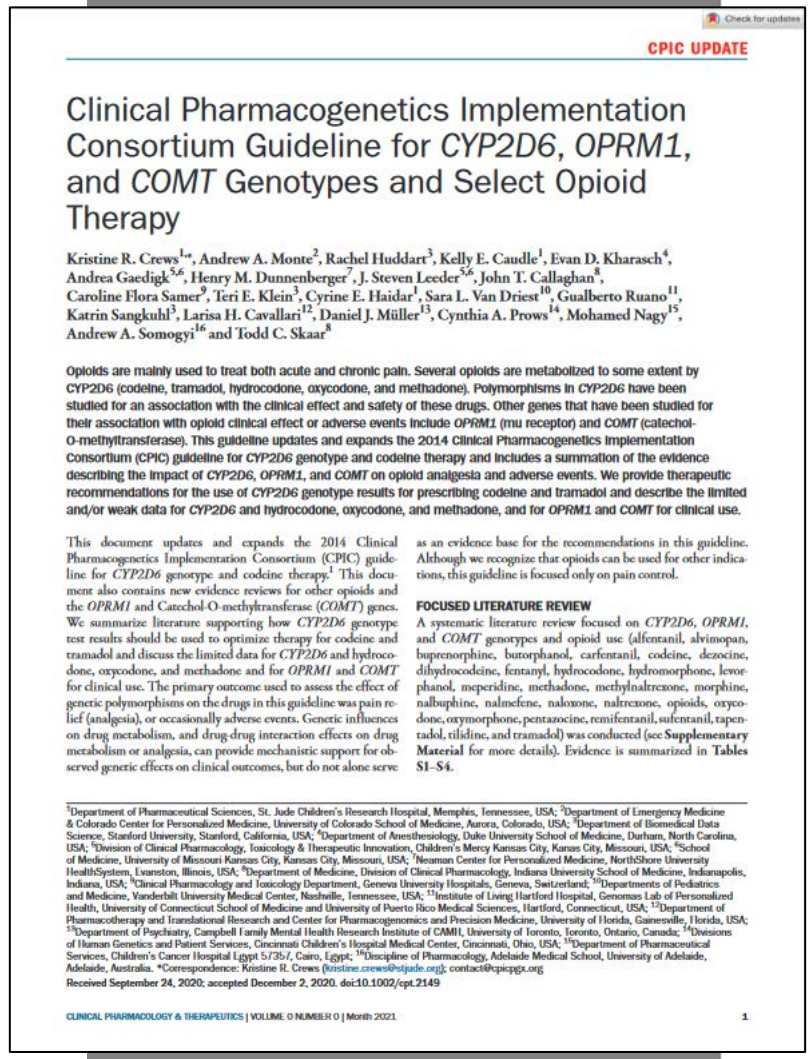
Tables and figure provided in the main manuscript of the guideline:

Table 1. Assignment of predicted CYP2D6 phenotypes based on diplotypes
Table 2. Codeine therapy recommendations based on CYP2D6 phenotype
Table 3. Tramadol therapy recommendations based on CYP2D6 phenotype
Table 4. Hydrocodone therapy recommendations based on CYP2D6 phenotype

Supplement to: Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6, OPRM1, and COMT genotype and select opioid therapy (December 2020)

Tables and figures included in the supplement[a] or referenced in the guideline:

Supplemental Table S1. Evidence linking CYP2D6 phenotype or genotype with opioid metabolism or response
Supplemental Table S2. Evidence linking *OPRM1* genotype with 0pioid response
Supplemental Table S3. Evidence linking *COMT* genotype with opioid response



Check for updates

CPIC UPDATE

Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2D6*, *OPRM1*, and *COMT* Genotypes and Select Opioid Therapy

Kristine R. Crews[1,*], Andrew A. Monte[2], Rachel Huddart[3], Kelly E. Caudle[1], Evan D. Kharasch[4], Andrea Gaedigk[5,6], Henry M. Dunnenberger[7], J. Steven Leeder[5,6], John T. Callaghan[8], Caroline Flora Samer[9], Teri E. Klein[3], Cyrine E. Haidar[1], Sara L. Van Driest[10], Gualberto Ruano[11], Katrin Sangkuhl[3], Larisa H. Cavallari[12], Daniel J. Müller[13], Cynthia A. Prows[14], Mohamed Nagy[15], Andrew A. Somogyi[16] and Todd C. Skaar[8]

Opioids are mainly used to treat both acute and chronic pain. Several opioids are metabolized to some extent by CYP2D6 (codeine, tramadol, hydrocodone, oxycodone, and methadone). Polymorphisms in *CYP2D6* have been studied for an association with the clinical effect and safety of these drugs. Other genes that have been studied for their association with opioid clinical effect or adverse events include *OPRM1* (mu receptor) and *COMT* (catechol-O-methyltransferase). This guideline updates and expands the 2014 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* genotype and codeine therapy and includes a summation of the evidence describing the impact of *CYP2D6*, *OPRM1*, and *COMT* on opioid analgesia and adverse events. We provide therapeutic recommendations for the use of *CYP2D6* genotype results for prescribing codeine and tramadol and describe the limited and/or weak data for *CYP2D6* and hydrocodone, oxycodone, and methadone, and for *OPRM1* and *COMT* for clinical use.

This document updates and expands the 2014 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* genotype and codeine therapy.[1] This document also contains new evidence reviews for other opioids and the *OPRM1* and Catechol-O-methyltransferase (*COMT*) genes. We summarize literature supporting how *CYP2D6* genotype test results should be used to optimize therapy for codeine and tramadol and discuss the limited data for *CYP2D6* and hydrocodone, oxycodone, and methadone and for *OPRM1* and *COMT* for clinical use. The primary outcome used to assess the effect of genetic polymorphisms on the drugs in this guideline was pain relief (analgesia), or occasionally adverse events. Genetic influences on drug metabolism, and drug-drug interaction effects on drug metabolism or analgesia, can provide mechanistic support for observed generic effects on clinical outcomes, but do not alone serve as an evidence base for the recommendations in this guideline. Although we recognize that opioids can be used for other indications, this guideline is focused only on pain control.

FOCUSED LITERATURE REVIEW

A systematic literature review focused on *CYP2D6*, *OPRM1*, and *COMT* genotypes and opioid use (alfentanil, alvimopan, buprenorphine, butorphanol, carfentanil, codeine, dezocine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, methylnaltrexone, morphine, nalbuphine, nalmefene, naloxone, naltrexone, opioids, oxycodone, oxymorphone, pentazocine, remifentanil, sufentanil, tapentadol, tilidine, and tramadol) was conducted (see **Supplementary Material** for more details). Evidence is summarized in **Tables S1–S4.**

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PharmVar

Pharmacogene Variation Consortium

The Pharmacogene Variation (PharmVar) Consortium is a central repository for pharmacogene (PGx) variation that focuses on haplotype structure and allelic variation.

The information in this resource facilitates basic and clinical research as well as the interpretation of pharmacogenetic test results to guide precision medicine.

PharmVar API Services are now available for third party use. For more information, visit the API Service Documentation Page

CYP2D6

Official Symbol	CYP2D6
Official Full Name	cytochrome P450 family 2 subfamily D member 6
Synonyms	CYP2D7BP, CYP2D7P2, CYP2D6, CYP2D7AP, P450C2D, CYP2D, CYP2DL1, CYP2D8P2, CPD6, P450DB1, CYPIID6, P450-DB1, ENSG00000100197
External Resources	EntrezGene:1565 HGNC:2625 PharmGKB:PA128

Download Gene Data

Additional Data Download Information

Read Me for CYP2D6 | Change Log for CYP2D6 | Structural Variation for CYP2D6

LRG_303 | NM_000106.6 | GRCh37 (NC_000022.10) | GRCh38 (NC_000022.11) | M33388

Compare View

Count From: Sequence Start ATG Start

Download Allele Data | Core SNV

Allele Name	Legacy Label	PharmVar ID	Variants (Impact) **variant** = variants with dbSNP rsID	Allele Evidence Level	References
CYP2D6*1		PV00426			CPIC Clinical Function →
CYP2D6*1.001	CYP2D6*1A	PV00126		Def	Kimura et al. 1989
CYP2D6*1.002	CYP2D6*1B	PV00125	3829G>A	Def	deposited by Nofziger Marez et al. 1997 Twist et al. 2016
CYP2D6*1.003	CYP2D6*1C	PV00128	1979C>T	Lim	Marez et al. 1997

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Drug Label Annotations	Clinical Guideline Annotations	Curated Pathways	Annotated Drugs
810	168	183	735

WHAT IS PHARMACOGENOMICS?

PHARMACOGENOMICS. KNOWLEDGE.

codeine

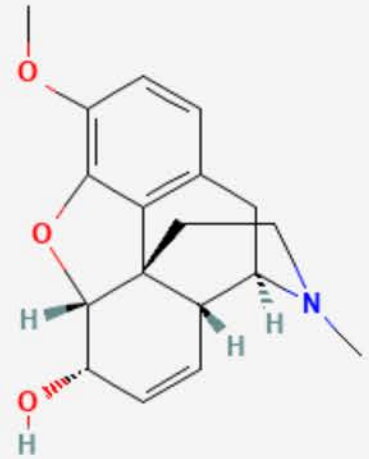
PRESCRIBING INFO 9

DRUG LABEL ANNOTATIONS 4

CLINICAL ANNOTATIONS 11

PATHWAYS 1

Structure



large version

3D version

source: PubChem

Table of Pharmacogenomic Biomarkers in

Pharmacogenomic Biomarkers in Drug Labeling

Search:

Export Excel

Drug	Therapeutic Area*	Biomarker†	Labeling Sections
Abacavir	Infectious Diseases	HLA-B	Boxed Warning, Dosage and Administration, Contraindications, Warnings and Precautions
Abemaciclib (1)	Oncology	ESR (Hormone Receptor)	Indications and Usage, Adverse Reactions, Clinical Studies
Abemaciclib (2)	Oncology	ERBB2 (HER2)	Indications and Usage, Adverse Reactions, Clinical Studies
Ado-Trastuzumab Emtansine	Oncology	ERBB2 (HER2)	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies
Afatinib	Oncology	EGFR	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Studies
Alectinib	Oncology	ALK	Indications and Usage, Dosage and Administration, Adverse Reactions, Clinical Pharmacology, Clinical Studies

Science and Research | Drugs

Regulatory Science at CDER

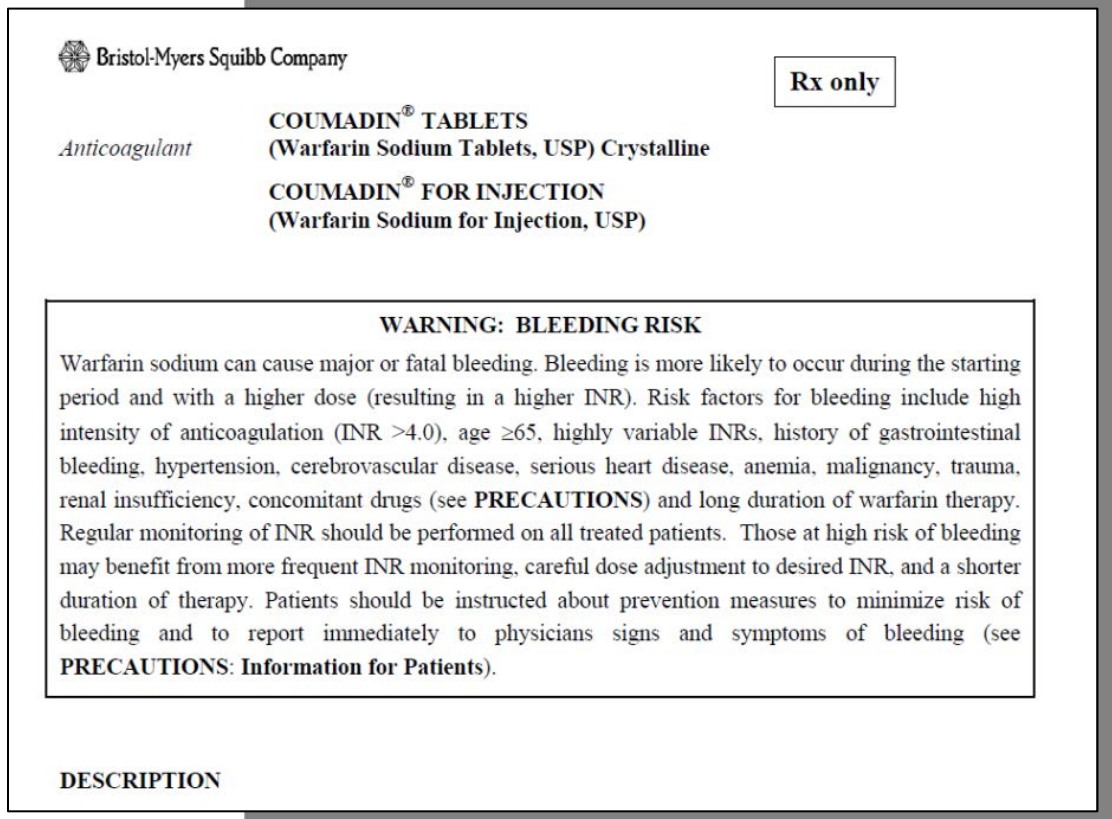
Research Tools and Resources

as of:

ct(s)

Drug Label (Package Inserts)

- Currently, >200 drugs have label information regarding PGx biomarkers
- Est. 25% of outpatients taking medications that contain PGx information in their labels (the majority prescribed by primary care)
  - "Black Box" Warnings
  - Clinical Pharmacology
  - Warnings
  - Precautions – Laboratory Tests
  - Adverse Reactions
  - Dosage and Administration



Bristol-Myers Squibb Company

Rx only

Anticoagulant

COUMADIN® TABLETS
(Warfarin Sodium Tablets, USP) Crystalline

COUMADIN® FOR INJECTION
(Warfarin Sodium for Injection, USP)

WARNING: BLEEDING RISK

Warfarin sodium can cause major or fatal bleeding. Bleeding is more likely to occur during the starting period and with a higher dose (resulting in a higher INR). Risk factors for bleeding include high intensity of anticoagulation (INR >4.0), age ≥65, highly variable INRs, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anemia, malignancy, trauma, renal insufficiency, concomitant drugs (see **PRECAUTIONS**) and long duration of warfarin therapy. Regular monitoring of INR should be performed on all treated patients. Those at high risk of bleeding may benefit from more frequent INR monitoring, careful dose adjustment to desired INR, and a shorter duration of therapy. Patients should be instructed about prevention measures to minimize risk of bleeding and to report immediately to physicians signs and symptoms of bleeding (see **PRECAUTIONS**: **Information for Patients**).

DESCRIPTION

Conclusions

- PGx research boosted with advances in –omics technology and data sciences
- Clinical PGx tests developed and offered by several commercial labs
- Clinical implementation of PGx testing faces multiple challenges
- Clinical evidence limited
- Dedicated PGx resources available