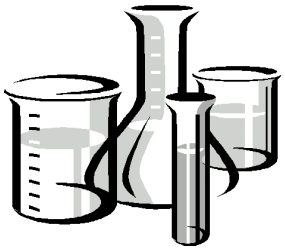
Clinical Pharmacogenomics and Current Medical Paradigm

Kenneth D. Levy PhD, MBA
Adjunct Associate Professor of Medicine
Division of Clinical Pharmacology
Indiana University School of Medicine

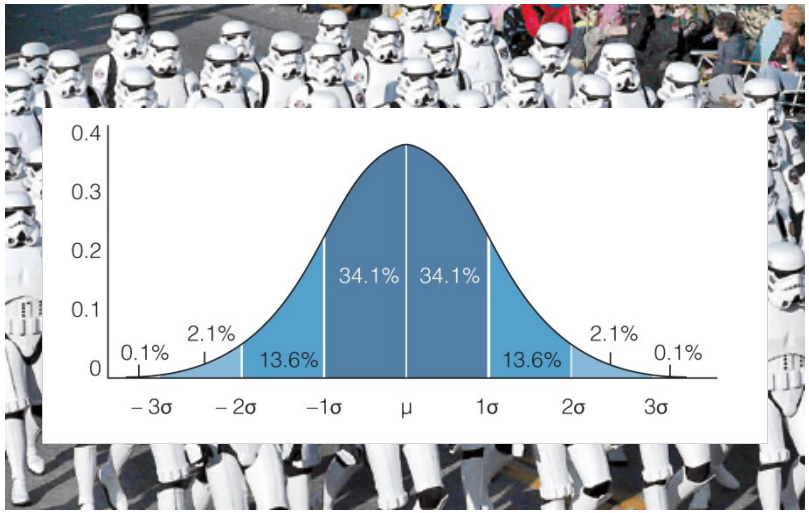
Clinical Pharmacogenomics

Patient Outcome?



Clinical Pharmacogenomics

- **Patient outcome…**
  - **Mitigate or cure disease**
  - **No effect**
  - **Adverse drug event, difficult to predict**
    - **Sometimes serious**



Clinical Pharmacogenomics

- **Pharmacogenomic Medical Paradigm…**

Patient Outcome

-Mitigate or cure

-No serious adverse drug events

"Personalized Medicine"

Clinical Pharmacogenomics

Genetic Test

TAGCTGCTGC

TAACTGCTGC

Identify Phenotypes

Administer drug

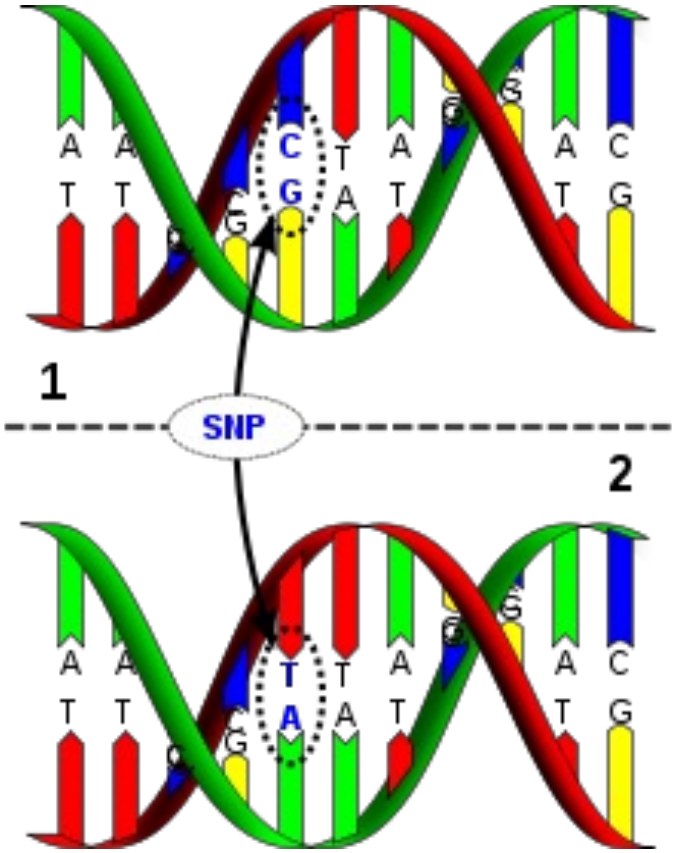
Select alternative drug

Mitigate/Cure

Adverse drug event

Clinical Pharmacogenomics

- **99.5% of the genome between any two individuals is identical**
- **Mutations that occur in genomic DNA give rise to genetic variation**
  - When a **mutation occurs in at least 1% of individuals in a population it is termed a "polymorphism"**
  - Most common polymorphism is the **single nucleotide polymorphism or "SNP"**
    - Occurs when there is a difference in a **single nucleotide**
    - Approximately **90% of all genetic variation is thought to derive from SNPs**
      - 2/3rd of SNPs involve replacement of cytosine for thymine
      - **~10 million SNPs in the human genome, so far…**
  - Much of the research has focused on the characterization of the SNPs in human genes regulating drug disposition
    - **Drug metabolizing enzymes**
    - **Intracellular transport of drugs**



Clinical Pharmacogenomics
Primarily focuses on Drug Metabolism

Two basic metabolic reactions

- **Phase 1 metabolism:**
  - Cytochrome P450 (CYP450) system (eg. CYP3A, 2D6, 2C9, 2C19)
  - Mixed-function oxidases produce more polar compounds
- **Phase 2 metabolism:**
  - N-acetyltransferase, UDP-glucoruoronysltransferase (UGT), glutathione S-transferase
  - Conjugation reactions increase the molecular weight, increases bulkiness of compounds

Clinical Pharmacogenomics

And drug transporters

- **Drug transporters are found in liver, kidney, intestines, brain and pancreas**
  - **Two major classes**
    - **Uptake**
      - Facilitate translocation of drugs into cells
        - OAT (organic anion transporter) eg. SLCO1B1
        - OCT (organic cation transporter)
    - **Efflux**
      - Excrete drugs from within cells to extracellular space
      - P-gp (p-glycoprotein), MRP2, MRP3

Clinical Pharmacogenomics

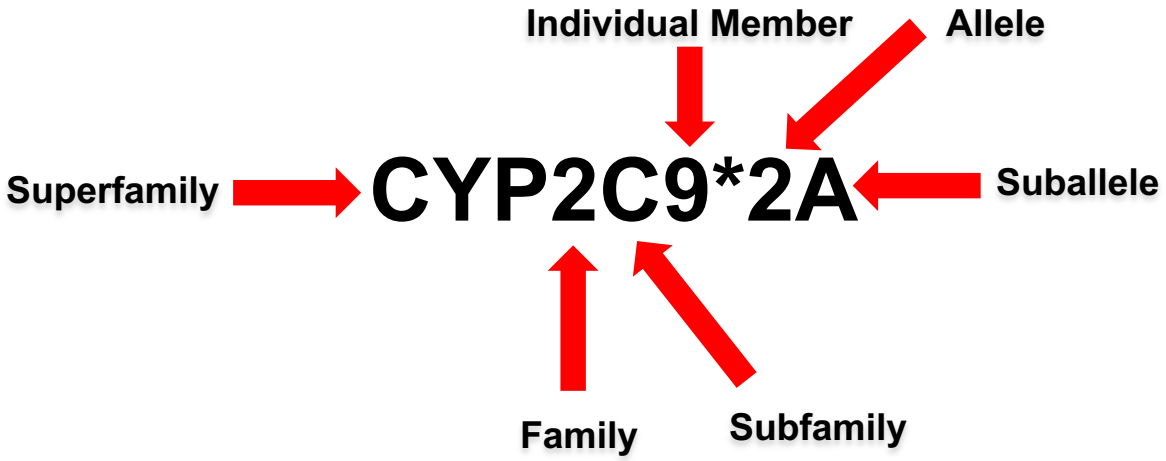
Drug metabolism and transport

- SNPs can change the protein of a CYP450 enzyme or transporter
  - Leads to altered drug metabolism and/or transport
  - Effects on drug disposition leading to unpredictable pharmacodynamics
    - **Drug response?**
    - **Adverse drug event?**

Clinical Pharmacogenomics

Nomenclature of SNPs

- **Phase 1 enzymes:**



- **Alleles are alternate versions of a gene**
- ***1 allele designation (CYP2C9*1) most commonly refers to the "wild type" or "normal" enzyme**
- ***2 or greater denote polymorphic alleles and are typically numbered in order of discovery-validation**
  - Homozygous designation: **CYP2C9*1/*1 (two copies of wild-type allele)**
  - Heterozygous designation: **CYP2C9*1/*2 (one copy of wild-type and one copy of reduced function allele)**

Clinical Pharmacogenomics

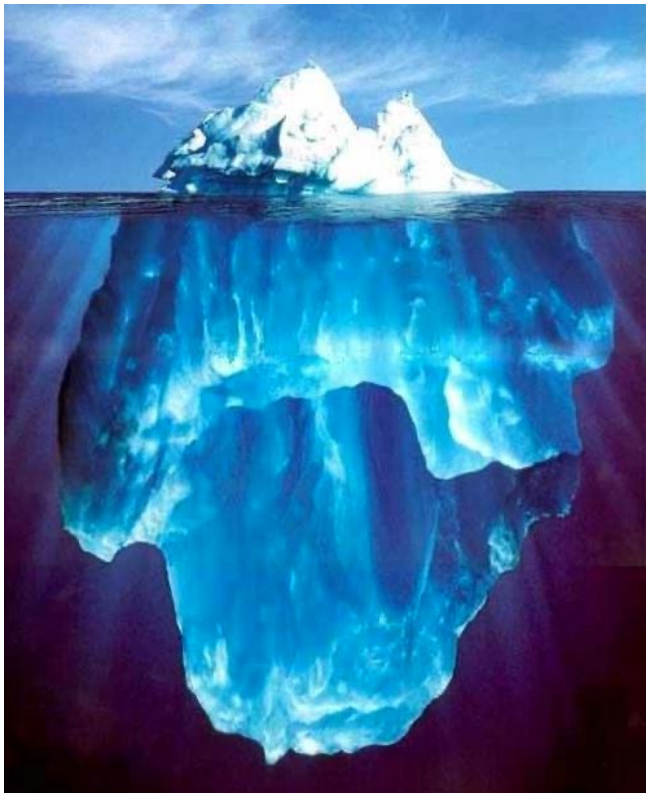
Nomenclature of SNPs

- **Phase 2 enzymes and transporters**
  - **Utilizes similar nomenclature**
    - UGT1A1*1/*1 (homozygous for wild-type)
    - SLCO1B1*1/*5 (heterozygous, contains one functional and one reduced function allele, “C” allele)
- **Still other nomenclatures…**
  - **Named by haplotype**
    - **VKORC1, “haplotype A”, (G1639A)**
      - GG, homozygous, (wild-type), normal levels of VKORC1
      - GA, heterozygous, lower level of VKORC1
      - AA, homozygous, lowest levels of VKORC1
  - **Named by allele**
    - **SLCO1B1*5**
    - “C” high myopathy risk allele, “T” other, low myopathy risk alleles
      - TT, homozygous, (low myopathy risk)
      - CT, heterozygous, (moderate myopathy risk)
      - CC, homozygous, (high myopathy risk)
  - **Human Leukocyte Antigen (HLA)**
    - HLA-B*5701

Clinical Pharmacogenomics

A 2011 list of the top 200 prescribed medications by total prescriptions included 17 with pharmacogenomic information in their FDA package inserts

- Includes the 5th and 7th most commonly prescribed medications
- In 2011, **362 million** prescriptions were filled for these 17 medications
- Numbers are only expected to increase as pharmacogenomics and personalized medicine grows



Interesting, but how do you know which genetic tests have been clinically validated?

And how to utilize this genetic information for the patients in your clinic?

Clinical Application of Pharmacogenomics

- **Clinical Pharmacogenomics Implementation Consortium (CPIC)**
  - Purpose of CPIC is to "translate genetic information into clinical actions and to make recommendations for actionable pharmacogenetic variants"
  - Group of clinical pharmacologists, clinicians and scientists that review all current literature and develop recommendations and algorithms to guide drug dosing based on pharmacogenotypes

- **CPIC prioritizes gene-drug pairs based on community input, sponsored surveys of CPIC members, American Society of Clinical Pharmacology and Therapeutics (ASCPT) and the public**
  - CPIC is a frequent contributor to the FDA and endorsed by the AMA, ASHP

- **CPIC has evaluated 14 drugs so far with more to follow**
  - Abacavir, allopurinol, azathioprine, capecitabine, carbamazepine, clopidogrel, codeine, irinotecan, mercaptopurine, phenytoin, simvastatin, TCAs, thioguanine, warfarin

Case Study

- RF is a 58 year-old female with a PMH of CAD, HTN and hypercholesterolemia who presents to her cardiologist with SOB, and a sensation of a “racing heart”. EKG confirms atrial fibrillation. Included in RF’s treatment plan is oral anticoagulation initiation with warfarin.
- RF agrees to genetic screening for potential variants that could affect her warfarin therapy
- Results reveal that she has the heterozygous **CYP2C9*2/*3** and the **GA VKORC1** genotype

Clinical Pharmacogenomics

CPIC guideline for warfarin:

Recommended daily warfarin doses (mg/day) to achieve a therapeutic INR based on *CYP2C9* and *VKORC1* genotype using the warfarin product insert approved by the US Food and Drug Administration

VKORC1 (1639G>A)	CYP2C9*1/*1 (mg)	CYP2C9*1/*2 (mg)	CYP2C9*1/*3 (mg)	CYP2C9*2/*2 (mg)	CYP2C9*2/*3 (mg)	CYP2C9*3/*3 (mg)
GG	5-7	5-7	3-4	3-4	3-4	0.5-2
GA	5-7	3-4	3-4	3-4	0.5-2	0.5-2
AA	3-4	3-4	0.5-2	0.5-2	0.5-2	0.5-2

Reproduced from updated warfarin (Coumadin) product label.

Clin Pharmacol Ther, 2011, 90: 625-29.

Progress in Clinical Pharmacogenomics

Clinical Tools to Target Drug Therapy for Individual Patients

- History
- Clinical Effect
- Age
- Gender
- Self Described Ethnicity
- Renal Function
- Hepatic Function

Medication History: AVOID Mistakes

Allergies?: Is there any medicine that we should not give you for any reason?

Vitamins and Herbs?

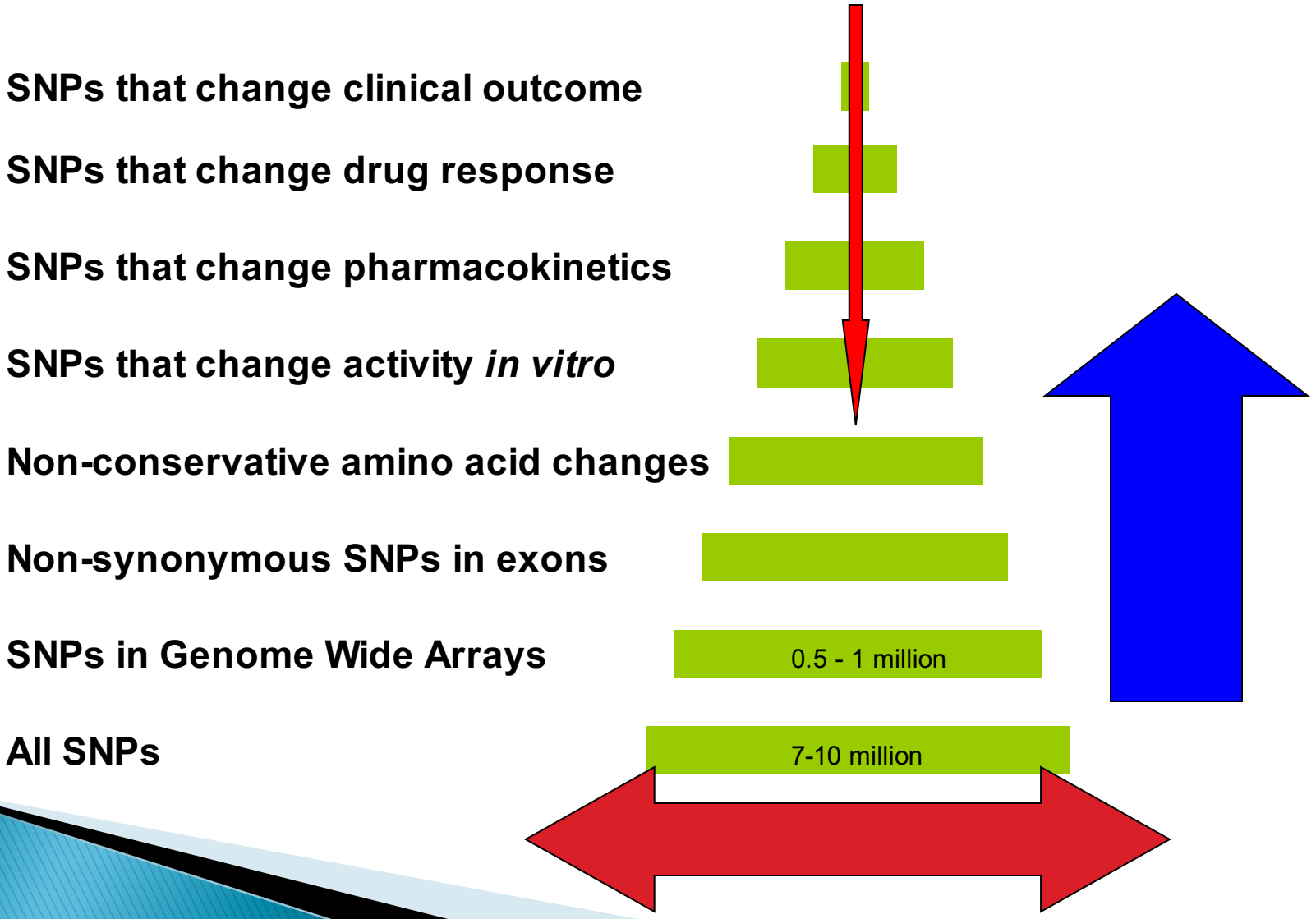
Old drugs? …..as well as current

Interactions?

Dependence?

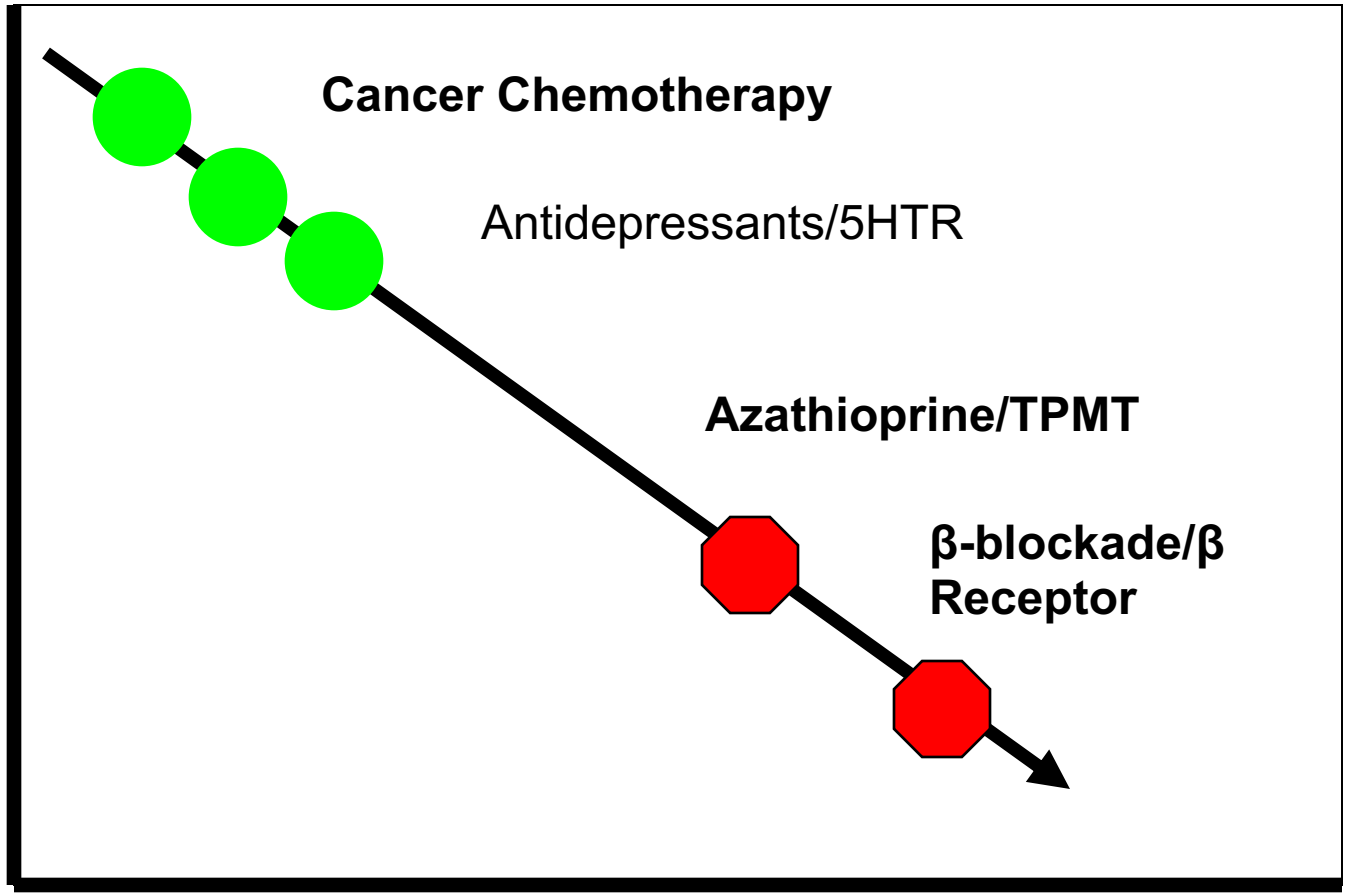
Mendel: Family Hx of benefits or problems with any drugs?

Hierarchy of Pharmacogenomic Information



Which Tests Matter and How to Know?

Value Increases When Current Predictive Ability is Low



Meyer UA and Flockhart DA, 2005

Validity
…as Measured by the Reimbursement Community

- Analytical
- Clinical Validity
- Clinical Utility
- Economic Utility

Analytical Validity

Reproducible Day to Day and between Laboratories

Clinical Validity

The extent to which a test accurately predicts the risk of an outcome, or its ability to separate patients with different outcomes into separate risk classes.

e.g. CYP2D6 and endoxifen concentration in tamoxifen patients

Clinical Pharmacogenomics

Tamoxifen

- Pro-drug metabolized by CYP2D6 to active endoxifen
  - CYP2D6*1, CYP2D6*2 (**normal or "extensive" metabolizers)**
  - **Poor metabolizers** (PM) CYP2D6*3, *4, *5, *6
  - **Intermediate metabolizers** (heterozygotes)
    - One normal and one PM allele (CYP2D6*1/*3)
  - **Ultra-rapid metabolizers**
    - 3 or more copies of normal alleles due to duplication
      - CYP2D6*1/*2/*2

Note: PMs are found in 7-14% of Caucasians, 14.5% of African-Americans

Clinical Utility

Reliable evidence that the genetic variant is consistently associated with a clinical outcome that alters or practice or is associated with improved patient outcomes.

Examples:

- Human Leukocyte Antigen (HLA) and Abacavir
- CYP2D6 and Codeine

Tools for Rational Prescribing

- Pharmacogenetics
- History
- Age
- Ethnicity
- Renal Function
- Hepatic Function

A Future for Precision Prescribing

- Robust, evidence - based and reimbursable tests that save costs
- Tests that combine clinical with genomic scoring algorithms
- **Health Care Professionals trained in using them to improve outcomes, decrease adverse events and reduce the cost of care**

Another Case-Study

A *Simple Procedure Becomes More Complex*

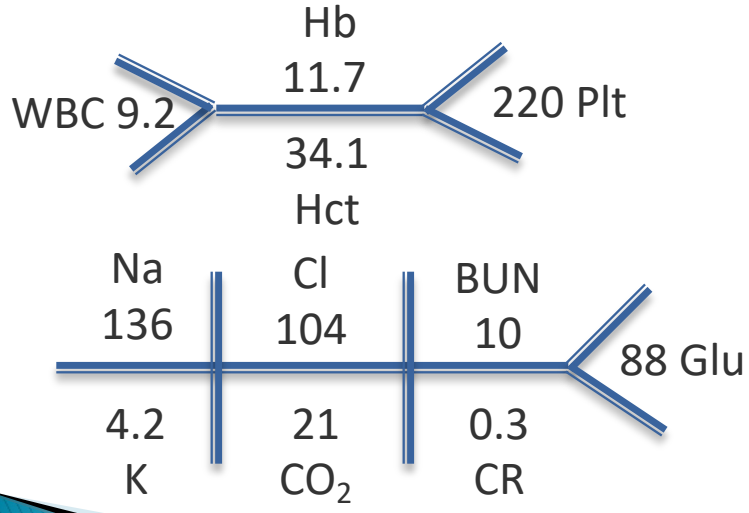
- 2 y.o. previously healthy boy with a history of snoring and sleep study confirmed obstructive sleep apnea undergoes elective adenotonsillectomy.
- The outpatient surgery was uncomplicated and six hours after surgery he received 10 mg of meperidine and 12.5 mg of dimenhydrinate IM.
- He was discharged with instructions to take 12 mg codeine with acetaminophen syrup (5 mL) every 4-6 hours as needed for pain.

Case-Study Continued:

- Child is presented to the ER on post-operative day 2 for evaluation of mental status changes.
- Parents report that he has been extremely sleepy and has not been eating and drinking very well.

Case-Study Continued: ER Findings

- He was afebrile, HR 80, BP 88/45, RR 20, O_2 sat'n 94%
- PE: sleepy but arousable, remarkable for pinpoint pupils
- Labs:



Ca^{2+} 8.5 mg/dL
Mg^{2+} 2.1 mg/dL
Phos 3.9 mg/dL
NH_3 40 mg/dL

Plasma morphine concentration ↑↑ (25 ng/mL)

What additional tests would you order?

1. No additional testing, lower Codeine dosing
2. Drug screen
3. Pharmacogenomic test for CYP2C9
4. Pharmacogenomic test for CYP2D6

The Pharmacogenomic test reports that the child has a genetic variant in CYP2D6 (diplotype *1,*2XN)

Question: How would you classify this patient in terms of Codeine metabolism?

1. He is a CYP2D6 ultra-rapid Metabolizer

Avoid codeine*

2. He is a CYP2D6 Extensive Metabolizer

3. He is a CYP2D6 Intermediate Metabolizer

4. He is a CYP2D6 Poor Metabolizer

* CPIC Dosing Guideline for codeine and CYP2D6

Genetic Variation Critical to Codeine Disposition

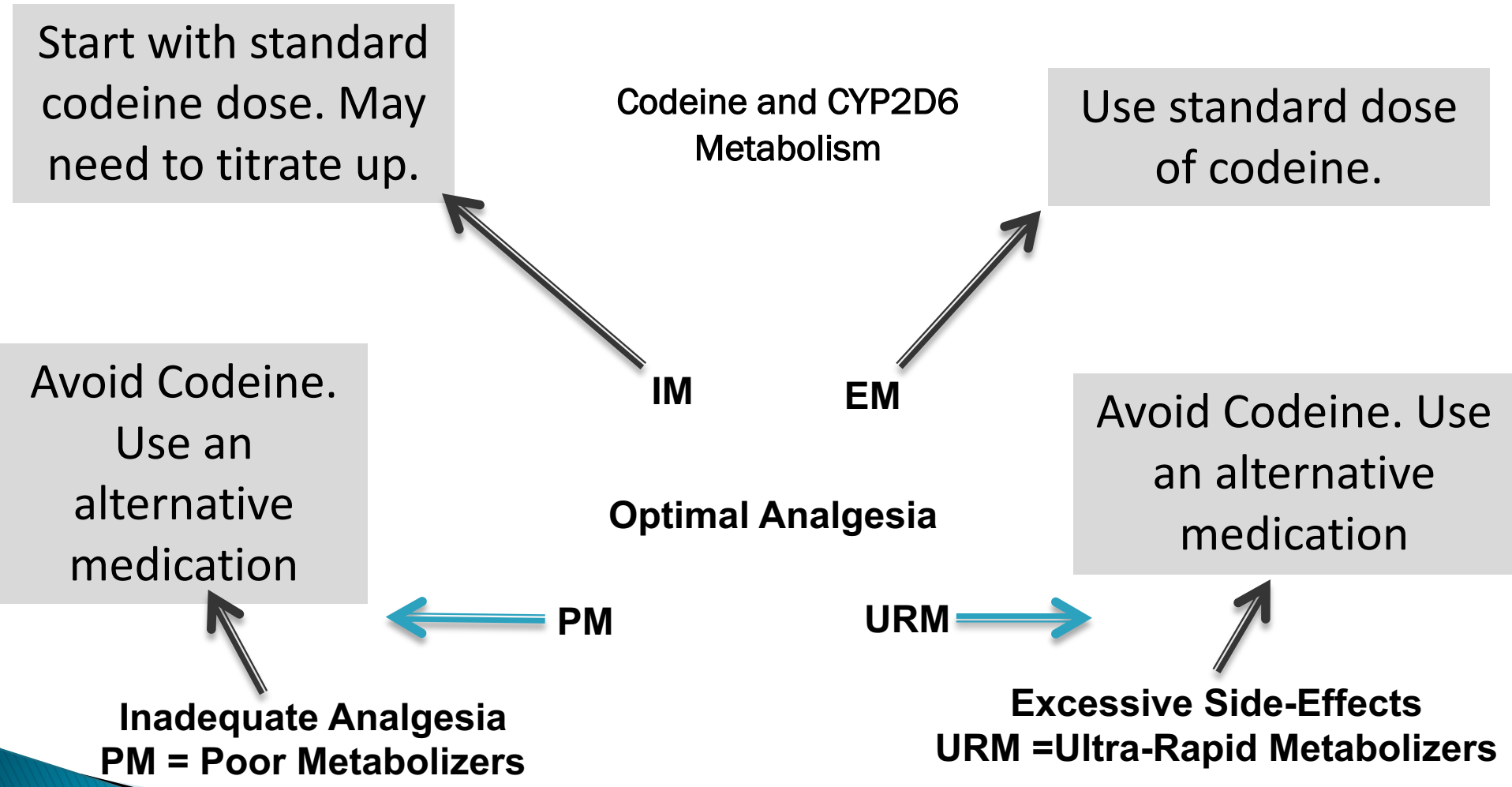
- Child has *CYP2D6* gene duplication
- Rapid conversion of codeine to morphine
- Accumulation of morphine in the CNS of this child resulting in altered mental status
- Multiple reports of respiratory depression and death

February 2013: FDA puts black box warning on codeine use after Tonsillectomy and Adenoidectomy or Breast Feeding

FDA Drug Safety Communication: Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy

http://www.fda.gov/Drugs/DrugSafety/ucm339112.htm

Codeine is NOT a bad drug - we just need to make informed dosing decisions on its use



Key Medical Value Activities

Establishing the medical evidence

Define

Medical intended use

Establish

Evidence based Medicine

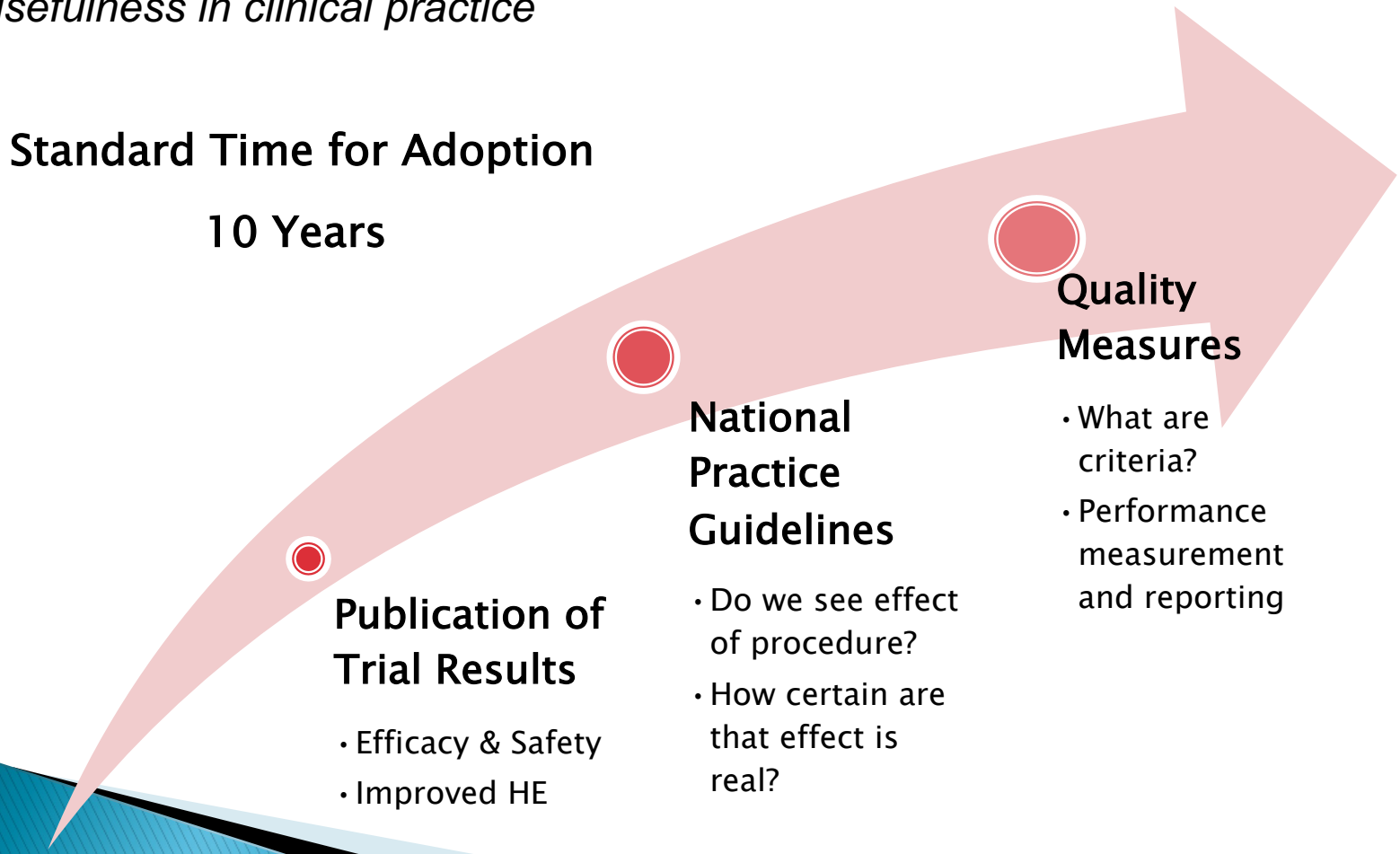
Create

Spreading the message

National Practice Guidelines

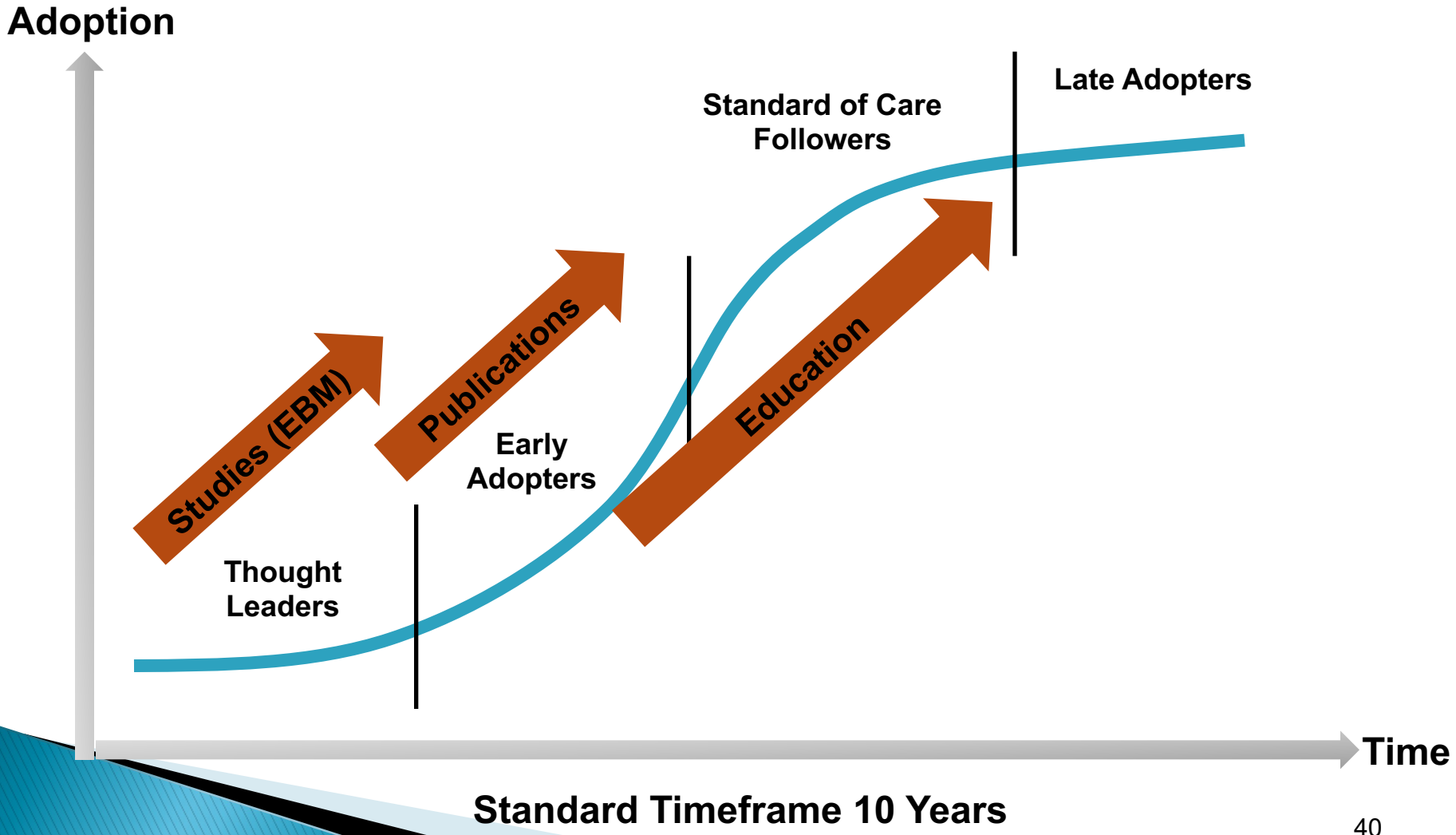
Define Standard of Care

Effectiveness of Pharmacogenomics must be supported by Evidence Based Medicine. Guidelines define requirements and make recommendation for their usefulness in clinical practice



Adoption of New Markers into Standard of Care

Studies providing evidence for improved patient outcomes drive publications and fuel educational programs



Clinical Pharmacogenomics

Conclusions

- Pharmacogenomic medicine is a powerful tool to inform drug selection and clinical decision-making
- Has demonstrated potential to improve efficacy and safety of medications
- As more clinical data emerges and genotyping costs fall, there will be increasing utilization and presence in clinical medicine
- **Changes in standards of care take time**

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