

# Personalized drug therapy is here!

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# Objectives

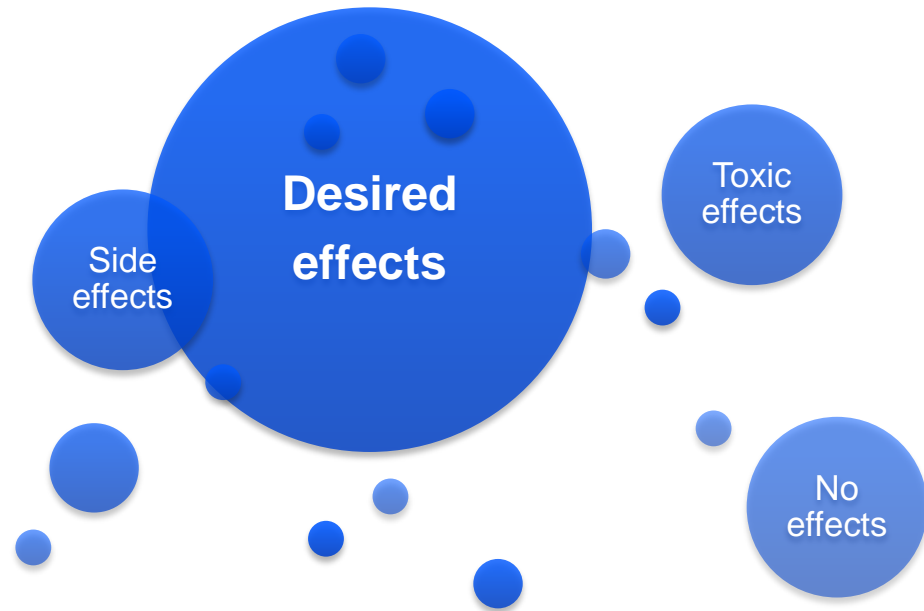


- Describe how genetic testing can predict a drug response phenotype.
- List examples of drug-gene pairs with clinical decision support.
- Discuss limitations of pharmacogenetics testing and implementation of gene-based drug and dose selection.

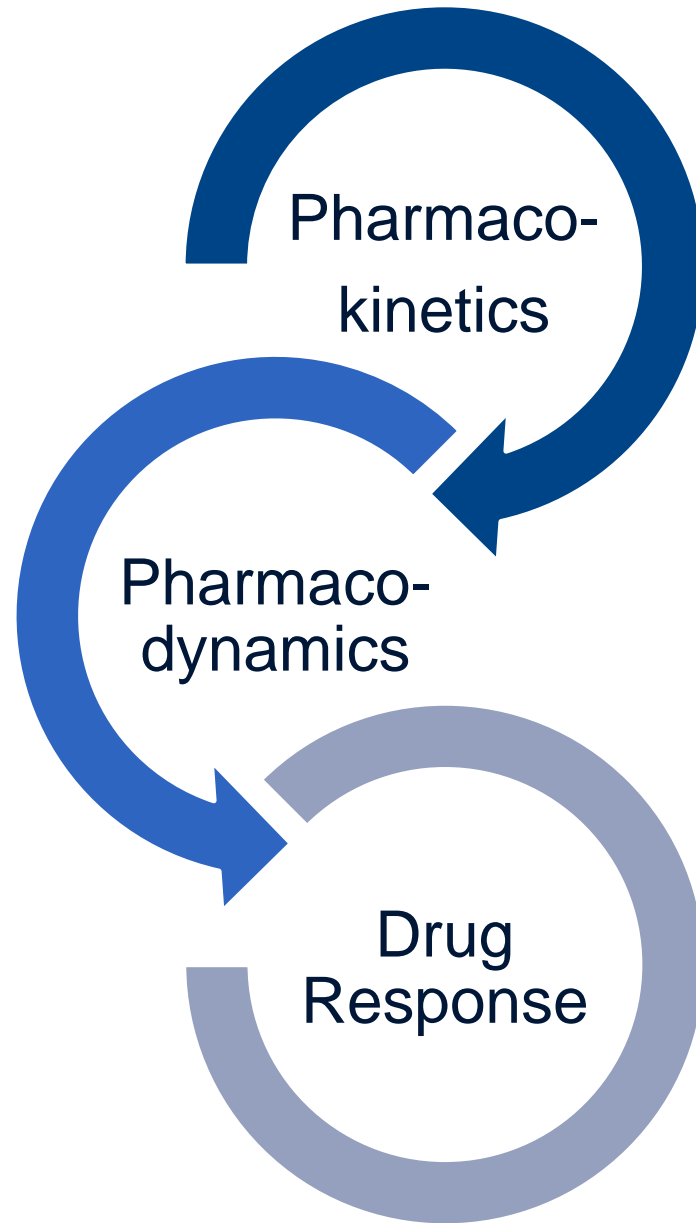
# What is a drug response phenotype?

*The composite of all a drug's effects for an individual*

- Degree of desired therapeutic effects, including no effect
- Side effects
- Toxicity
- Dose requirements
- Metabolite profile
- Biomarkers of response
- How long the effect(s) persist



*The right  
concentration,  
at the right time*



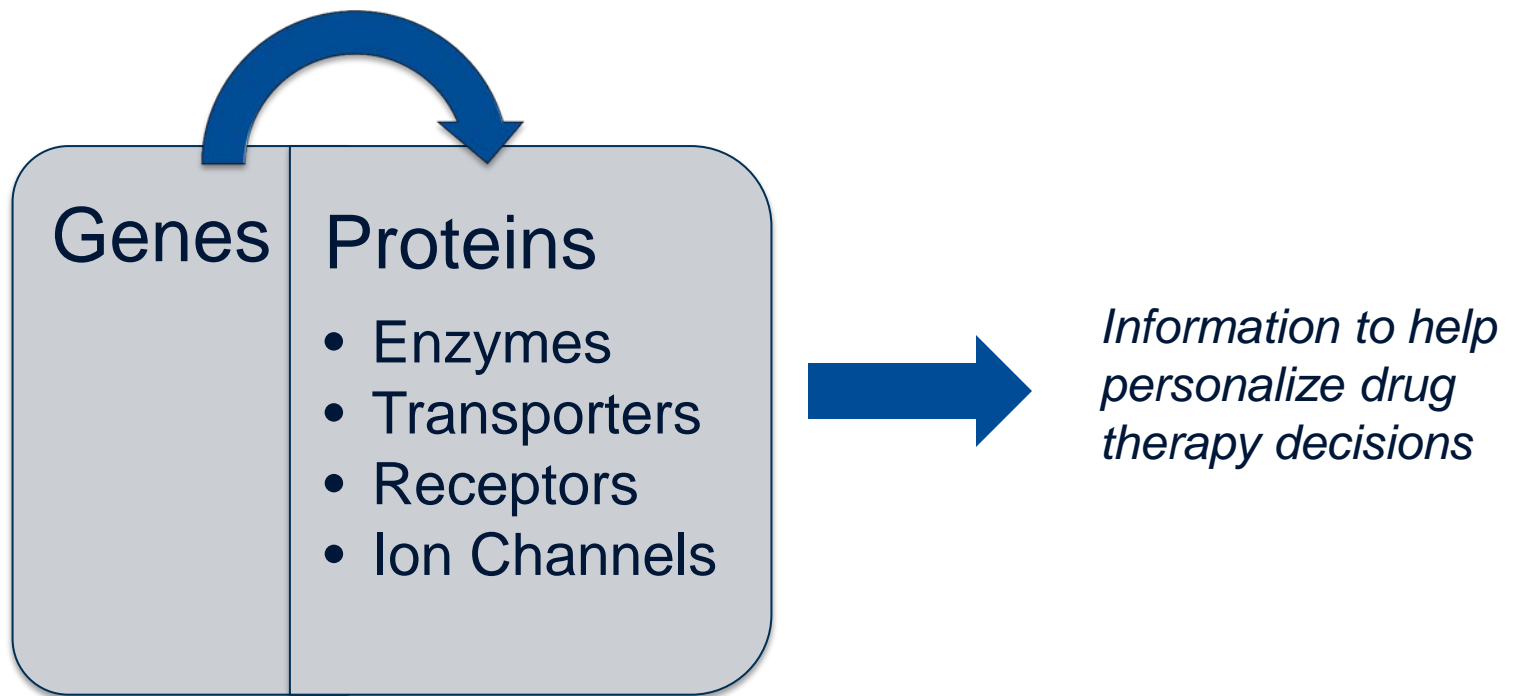
Pharmaco-  
kinetics

Pharmaco-  
dynamics

Drug  
Response

*Physiology to  
support  
mechanism(s)  
of action*

# Germline genetics affect the drug response phenotype = pharmacogenetics



# Pharmacogenetic testing



- Phenotype testing examples
  - Enzyme activity (e.g. TPMT)
  - Therapeutic drug monitoring (e.g. drug and metabolite concentrations in timed blood specimens)
  - Biomarkers of drug response (e.g. INR for warfarin response)
- Genetic testing
  - Targeted variant testing
    - Single genes
    - Gene panels
  - Copy number detection
  - Whole exome / whole genome



# Phenotype vs Genetic testing

## Phenotype



## Genetic

- Reflects current 'state' of the specimen donor
- Specimen requirements strict
- Stability of analyte and drug-drug interactions may affect accuracy of phenotype
- Recent transfusion may be contraindicated

- Detects only what the assay is designed to detect
- Phenotype is inferred
- DNA is generally stable
- Some specimens (e.g. saliva) are not affected by transfusion
- Not affected by drug interactions

# Guidance strategies

- Drug selection/avoidance
  - Identify people at high risk of a serious adverse drug reaction
  - Identify people not likely to respond to a specific drug
  
- Optimize dosing
  - Identify people that are likely require non-standard dosing
  - Estimate optimal dose and dosing frequency





# Guidance may be application specific, or not

got purpose?

- Single gene-drug pair testing, for a specific clinical application
  - Drug labeling (FDA, EMA, PMDA, HCSC)
  - Consensus guidelines
  - Published clinical associations
- Multi-gene testing, for many drugs, many clinical applications
  - Designed for a single clinical indication (e.g. psychotropic drugs)
  - Targets drug metabolizing enzymes, affecting many drug classes
  - Genes for many aspects of both pharmacokinetics and/or pharmacodynamics affecting many drugs

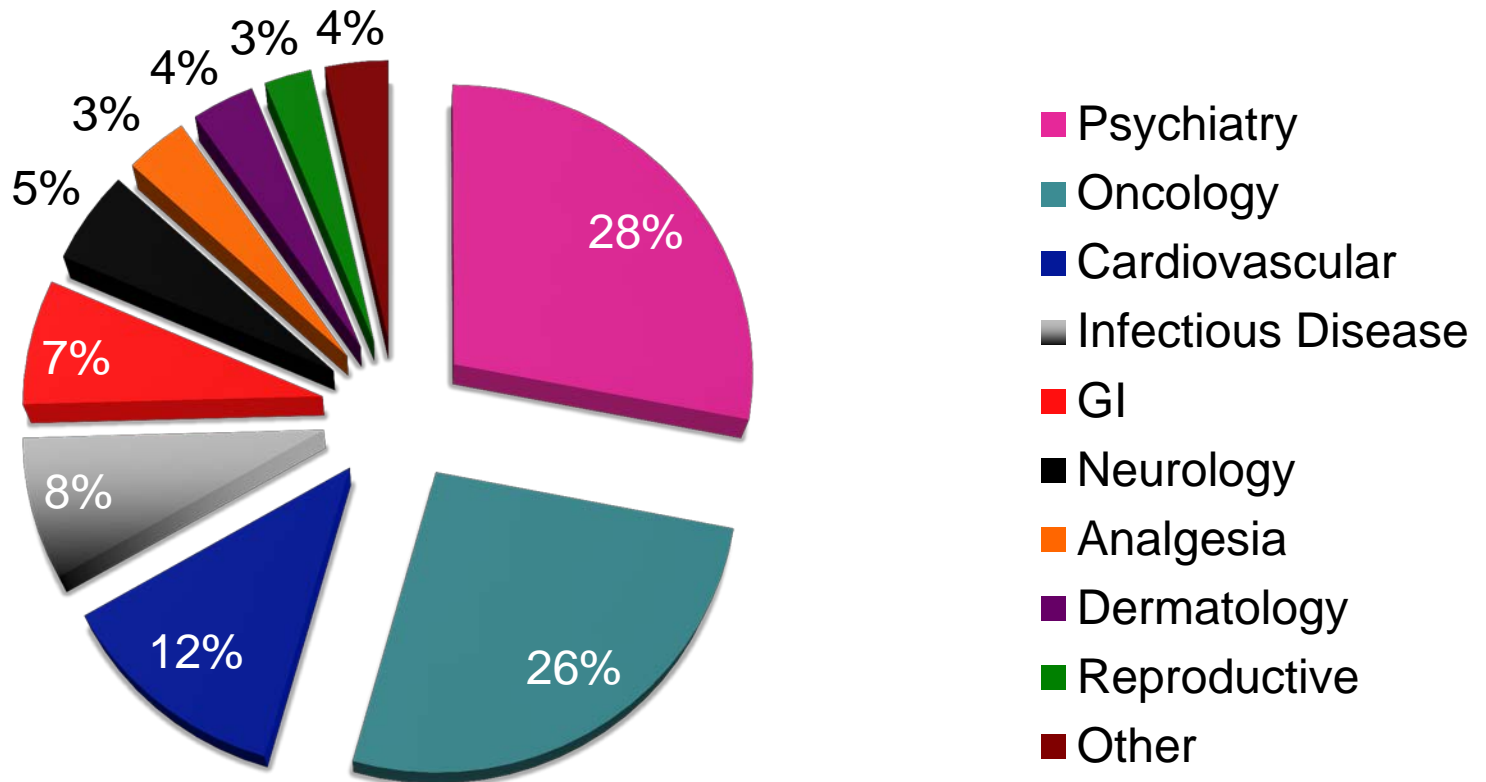
# >160 U.S. Drug Labels (FDA) currently include pharmacogenetic information

## Pharmacogenomic Biomarkers in Drug Labeling

Drug ↕	Therapeutic Area* ↕	Biomarker† ↕	Referenced Subgroup‡ ↕	Labeling Sections ↕
Abacavir	Infectious Diseases	HLA-B	HLA-B*5701 allele carriers	Boxed Warning, Contraindications, Warnings and Precautions

<http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm>  
<https://www.pharmgkb.org/view/drug-labels.do>

# The indications for drug labels containing pharmacogenetic information affect nearly every medical specialty



# Clinical Pharmacogenetics Implementation Consortium (CPIC)

- Formed in 2009, lead by Mary Relling, PharmD
- Shared project between PharmGKB and the Pharmacogenomics Research Network (PGRN)
- Members >50 institutions, several countries
- Rank gene-drug pairs of interest (>200 pairs) with levels of evidence
- Publish guidelines designed to help clinicians understand how to use germline PGx test results to optimize drug therapy in partnership with *Clin Pharmacol Ther*

<https://www.pharmgkb.org/>  
<https://cpicpgx.org/>

# CPIC levels of evidence

## Quality of evidence linking genetics to drug phenotype

1. The evidence includes consistent results from well-designed, well-conducted studies
2. The evidence is sufficient to determine the effects, but strength of evidence is limited by the number, quality, or consistency of the individual studies, by the inability to generalize to routine practice, or by the indirect nature of the evidence
3. The evidence is insufficient...

## Strength of recommendation

A: STRONG

B: Moderate

C: Optional

# Examples of CPIC drug-gene pairs

Drug	Gene	Utility		Comments
		Qualify	Dose	
<b>Abacavir</b>	HLA-B*57:01	X		FDA Requirement for genetic testing
<b>Carbamazepine</b>	HLA-B*15:02	X		FDA Requirement for genetic testing in Asians
<b>Phenytoin</b>	HLA-B*15:02, CYP2C9	X	X	Actionable by FDA
<b>Clopidogrel</b>	CYP2C19	X		FDA Recommendation for genetic testing
<b>Tricyclic antidepressants (TCAs)</b>	CYP2D6, CYP2C19		X	Includes amitriptyline, doxepin, desipramine, imipramine, nortriptyline, trimipramine; value of CYP2D6 and/or CYP2C19 is drug specific.  Actionable by FDA
<b>Selective serotonin reuptake inhibitors (SSRIs)</b>	CYP2D6, CYP2C19		X	Includes citalopram, escitalopram, fluvoxamine, paroxetine; value of CYP2D6 and/or CYP2C19 is drug specific  Actionable by FDA
<b>Opioids</b>	CYP2D6	X	X	Includes codeine, tramadol; evidence for oxycodone also  Actionable by FDA
<b>Tacrolimus</b>	CYP3A5		X	
<b>Thiopurines</b>	TPMT	X	X	FDA Recommendation for genetic testing

# Variation in pharmacogenes is common

- 5,639 samples were sequenced for 82 pharmacogenes in a collaboration between the electronic Medical Records and Genomics (eMERGE) network and the PGRN
- Included White (79%), African American (12%), Asian (2%), Pacific Islander, American Indian, and unknown races
- Approximately equal numbers of males and females

**96.19% of all samples had  $\geq 1$  CPIC Level 1A actionable variants, estimated to affect ~75 million prescriptions (2013 data)**



## Single gene-drug case examples



# Case 1

- 50 yr old Han ethnic patient with uncontrolled bipolar disorder
- Prescribed carbamazepine and clozapine
- Within 2 days of medication, the patient developed fever, rash, pruritic blisters and erosions of the mucosal membranes
- Diagnosed with Stevens Johnson Syndrome (SJS)
- Carbamazepine was discontinued and condition resolved

*Chao et al, Psych Clin Neurosci 66:538-9, 2012*

# Acute cutaneous drug reaction

- Symptoms range from mild to severe and include rash, anaphylaxis, and serum sickness
- Diagnosis is clinical
- Treatment is discontinuation of drug, and supportive treatment (eg, with antihistamines)
- An immune-mediated hypersensitivity reaction to a drug that occurs independent of dose



# HLA-B and drug hypersensitivity

- Part of the human major histocompatibility complex located on chromosome 6:

<http://hla.alleles.org/nomenclature/naming.html>

- Variant HLA alleles encode a cell surface protein that binds peptides and some drugs, signaling the immune system to respond, leading to drug hypersensitivity
- Autosomal dominant trait that can be detected by targeted genetic testing
- Allele frequencies vary with ethnicity

# Example carrier frequencies

Allele	European / Caucasian	Asian	African-American
<i>HLA-B*15:02</i> (carbamazepine, phenytoin)	0.01%	4.3%	0%
<i>HLA-B*57:01</i> (abacavir)	6.8%	1.6%	1%
<i>HLA-B*58:01</i> (allopurinol)	0.01%	0.05%	0.04%

<https://www.pharmgkb.org/guideline/PA166105008>  
<https://www.pharmgkb.org/guideline/PA166104997>  
<https://www.pharmgkb.org/guideline/PA166105003>



**Pre-therapeutic pharmacogenetic testing can  
personalized drug selection to prevent  
hypersensitivity reactions**

# Case 2

- 5.5 yr old patient
- Underwent adenotonsillectomy under general anesthesia for obstructive sleep apnea
- Discharged with tramadol prescription for pain relief
- Received first dose of tramadol at 11pm
- Found comatose a few hours later

Orliaguet et al, *Pediatrics* 135(3):e753-5, 2015

## Case 2: continued

- Admitted to the PICU with
  - Pin-point pupils
  - Minimal respirations
  - Low oxygen saturation (48%)
  - Abnormal arterial blood gases
  - All other vitals normal
- Treated with naloxone and ventilation
- Recovered fully within 24 hrs

*Classical opioid  
overdose  
presentation!*

# Two ways that an overdose can occur

- Taking too much drug
- Taking 'standard' dose of a drug, with unexpected pharmacokinetics
  - Absorbed more than expected
  - Elimination slower than expected
  - Variant metabolism, leading to unexpected proportions of active drug





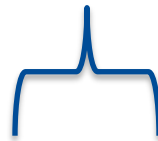
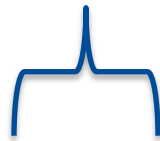
# Drug metabolism

- Metabolism = biochemical modification, usually mediated by specialized enzymes, and classified as Phase I or Phase II
  - **Phase I reactions: oxidation, reduction, hydrolysis (e.g. CYP2D6, DPYD)**
  - **Phase II reactions: conjugation (e.g. UGT1A6, TPMT)**
- Reaction products (metabolites) often have different pharmacological activity or potency than the parent drug, as well as unique pharmacokinetics
- Drug metabolizing enzyme function can vary based on genetics or drug-drug interactions

# Cytochrome P450 (CYP) nomenclature

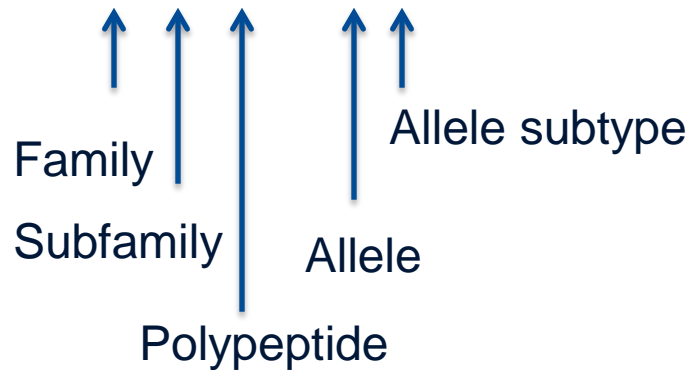
Gene/enzyme  
name

“Star” allele  
name



***CYP2D6\*4E***

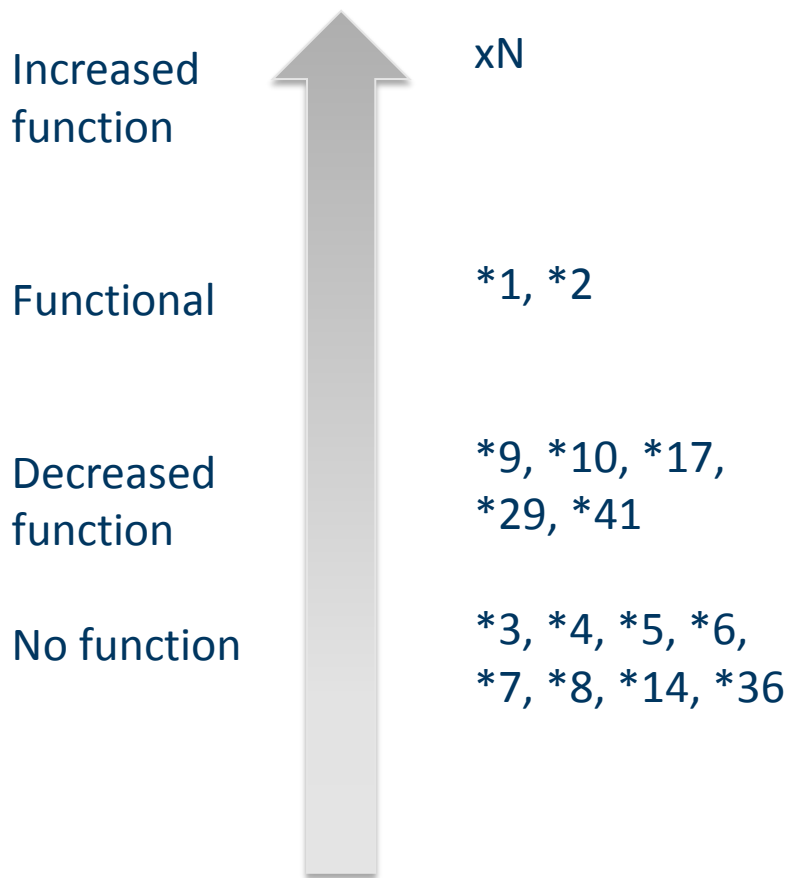
100C>T  
1661G>C  
1846G>A  
4180G>C



*\*1 suggests that no variants were detected*

<http://www.cypalleles.ki.se/>

# CYP2D6 alleles and phenotype assignment



## Phenotype assignment

Ultra-rapid metabolizer: *more than two copies of functional alleles*

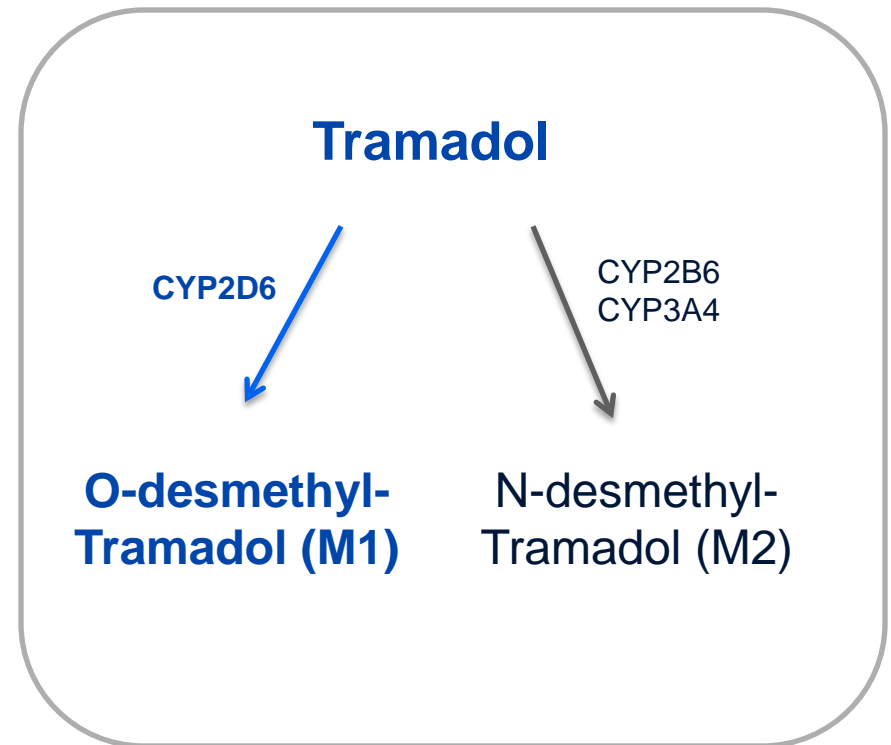
Normal metabolizer: *two copies of functional alleles, combinations of decreased function and functional alleles, or one copy of a no function allele and one copy of a functional allele*

Intermediate metabolizer: *one decreased function and one or more no function alleles*

Poor metabolizer: *two or more copies of no functional alleles*

# Activation of tramadol by metabolism

- ~20% of tramadol is converted to an active metabolite: O-desmethyltramadol, also known as M1
- M1 is 2-4x's more potent than tramadol
- Variation in CYP2D6 phenotype will impact the proportion of M1



## Case 2: continued

- Genotype for *CYP2D6*: \*2/\*2xN
- Predicted *CYP2D6* phenotype: ultra-rapid metabolizer
- Urine tramadol concentrations
  - Parent: 38 µg/mL (57%)
  - M1: 24.0 µg/mL (36%)
  - M2: 4.6 µg/mL (7%)

Conclusion:

*Accidental overdose by excessive production of M1 and clinical sensitivity to respiratory depression*

**CPIC guidance for this genotype:  
Avoid tramadol use due to potential for toxicity.**

# Excerpt of CPIC comments regarding tramadol and CYP2D6 phenotype

**Considerations for alternative opioids:** There is substantial evidence for **decreased efficacy of tramadol in poor metabolizers** and **toxicity in ultra-rapid metabolizers**. Use of other analgesics in CYP2D6 poor and ultra-rapid metabolizers may therefore be preferable. Some other opioid analgesics are metabolized by CYP2D6, such as codeine, hydrocodone and oxycodone. To avoid treatment complications, **opioids that are not metabolized by CYP2D6**, including morphine, oxymorphone, buprenorphine, fentanyl, methadone and hydromorphone, along with non-opioid analgesics, may be considered as alternatives for use in CYP2D6 poor and ultra-rapid metabolizers.

<https://www.pharmgkb.org/guideline/PA166104996>



**Pre-therapeutic pharmacogenetic testing can  
personalized drug selection to prevent  
accidental overdose or therapeutic failure**

# Examples of institutions that have implemented single-gene applications

## **PGRN Translational PGx Program**

- University of Maryland
- University of Florida
- St Jude Children's Research Hospital
- Vanderbilt University
- Mayo Clinic
- Ohio State University

<http://www.pgrn.org/>

## **IGNITE Network**

- University of Maryland
- University of Florida
- Mount Sinai Health System
- Vanderbilt University
- Duke University
- Indiana University

<https://ignite-genomics.org/about-ignite/>



# “Ingredients” for successful clinical implementation of single-gene applications

- Recognition that involvement of many parties within the healthcare system is required
- Early, persistent, and collaborative engagement with healthcare providers, faculty and administration
- Clinical decision support (CDS)
- Monitoring uptake



Shuldiner et al., *Clin Pharmacol Ther*, 94(2):207-10, 2013

# Genotype-tailored antiplatelet therapy



Prospective evaluation of antiplatelet prescriptions at Vanderbilt University, in patients that received a coronary stent and were prescribed clopidogrel – triggered alert to genotype *CYP2C19*

- Inpatient CDS was triggered after genotype results were available, often after patient discharge
- Pharmacists-led surveillance reviewed medical records for 93.6% of patients and made recommendations for change in therapy, considering both clinical and genetic risks
  - 64 poor metabolizers; 57.6% received alternate drug
  - 450 intermediate metabolizers; 33.2% received alternate drug
  - 2162 nonactionable *CYP2C19* phenotype; 8.3% received alternate drug

Peterson, et al. *Clin Pharmacol Ther* 100(1):67-74, 2016

# Guidance may be application specific, or not

got purpose?

- Single gene-drug pair testing, for a specific clinical application
  - Drug labeling (FDA, EMA, PMDA, HCSC)
  - Consensus guidelines
  - Published clinical associations
- Multi-gene correlations for many drugs, many clinical applications
  - Designed for a single clinical indication (e.g. psychotropic drugs)
  - Targets drug metabolizing enzymes, affecting many drug classes
  - Genes for many aspects of both pharmacokinetics and/or pharmacodynamics affecting many drugs

# Multi-gene software/algorithmic approach

- Proprietary commercial products are available
  - GeneDose™ – many drug classes
  - YouScript® – many drug classes
  - GeneSight® – psychotropics, ADHD, analgesics
  - CNSDose – antidepressants
- Some integrate genetics with clinical and demographic data and/or offer interactive risk mitigation tools for polypharmacy
- All tools provide decision support tools but few are supported by randomized clinical trials, and no studies directly compare effectiveness of the clinical decision support



# Multi-gene software case example

Medication Summary (more alternatives discoverable at GeneDose™ LIVE)

Therapeutic Class  Standard Precautions   Caution / Info  Consider Alternatives

Anti-ADHD Agents		Atomoxetine	
Antiarrhythmics		Flecainide Propafenone	
Anticoagulants		Acenocoumarol	
Anticonvulsants		Phenytoin	
Antidementia Agents		Donepezil	
Antidepressants	Flupenthixol Mirtazapine	Amitriptyline Clomipramine Desipramine Doxepin Duloxetine Nortriptyline Protriptyline Venlafaxine Vortioxetine	
Antidiabetics	Glibenclamide Gliclazide Glimepiride Tolbutamide		
Antifungals			
Antiplatelet Agents		Clopidogrel	
Antipsychotics	Olanzapine	Aripiprazole Clozapine Haloperidol Risperidone Zuclopenthixol	Thioridazine

Gene	Genotype	Phenotype
<i>CYP2D6</i>	*4/*4	Poor
<i>CYP2C19</i>	*2/*1	Intermediate
<i>CYP2C9</i>	*17/*1	Rapid
<i>CYP3A5</i>	*3/*1	Intermediate

# Detailed information available

## Antidepressants

**Amitriptyline**  
(Elavil)



CYP2D6: Poor metabolizer. Two alleles showing little or no activity.

Individuals with poor metabolizer status have greatly reduced metabolism of amitriptyline to less active compounds; the resultant higher plasma concentrations will increase the probability of side effects. Consider reducing the recommended starting dose by 50% and monitor plasma concentration or select alternative drug (e.g. citalopram, sertraline).

ADR



## Antiplatelet Agents

**Clopidogrel**  
(Plavix)



CYP2C19: Ultra-rapid metabolizer. One allele showing normal activity and one showing increased activity.

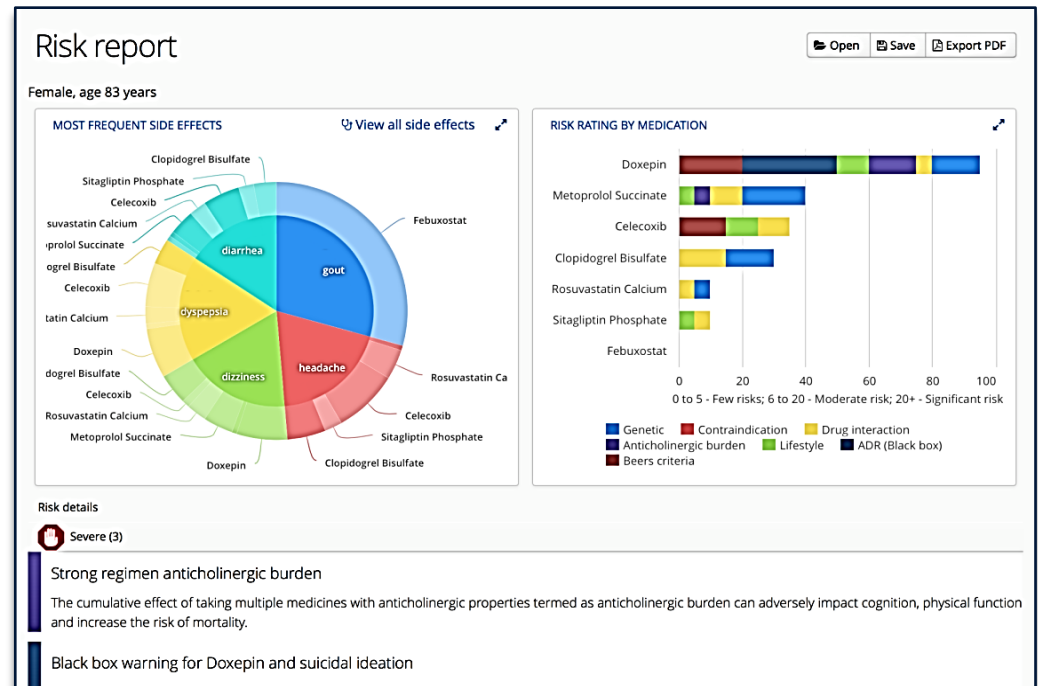
Individuals with ultrarapid metabolizer status may benefit from the elevated plasma concentration of the active compound when taking a standard dose. They may also be at increased risk of bleeding due to elevated plasma concentrations of the active compound. No additional therapeutic recommendations.

Efficacy



# GeneDose LIVE

- Cloud-based software tool
- Incorporates both genetic and nongenetic risk factors, lifestyle factors, drug-drug interactions, Beers criteria, etc.
- Includes >35,000 drug products
- Mitigates risk of adverse drug reactions



# Real time modeling of alternative drug choices

ell GeneDose Live

Alternatives for Doxepin Hydrochloride 150mg Oral capsule

Tricyclic and other cyclic Antidepressants

Alternative drug	Δ drug	Δ regimen ▲	Detail	Risk chart	Est. cost/dose
<input type="checkbox"/> Maprotiline Hydrochloride Oral tablet	-80	-90	⊕		Generic: \$1.18
<input type="checkbox"/> Mirtazapine Oral disintegrating tablet	-50	-60	⊕		Brand: \$4.06 Generic: \$0.94
<input type="checkbox"/> Mirtazapine Oral tablet	-50	-60	⊕		Brand: \$4.89 Generic: \$0.44
<input type="checkbox"/> Amitriptyline Hydrochloride Oral tablet	-40	-50	⊕		Generic: \$0.65
<input type="checkbox"/> Amoxapine Oral tablet	-35	-45	⊕		Generic: \$1.02
<input type="checkbox"/> Protriptyline Hydrochloride Oral tablet	-25	-35	⊕		Brand: \$4.09 Generic: \$1.64
<input type="checkbox"/> Trimipramine Maleate Oral capsule	-20	-30	⊕		Brand: \$5.73 Generic: \$3.05
<input type="checkbox"/> Imipramine Hydrochloride Oral tablet	-18	-28	⊕		Brand: \$7.93 Generic: \$0.13
<input type="checkbox"/> Doxepin Hydrochloride Oral capsule	-10	-10	⊕		Brand: \$19.02

[Update alternatives model](#)

Risk scores represent the cumulative total of warnings from sources such as the Food and Drug Administration, the American Geriatric Society, pharmaceutical labeling, medical publications, and research in genetics. Each risk has been weighted according to the impact severity associated with that risk. These results are intended to complement the complete medical records for this patient and should be used only by a qualified healthcare provider.



# Are more genes better?

- In a review of 22 proprietary algorithms for clinical validity, there were 46 genes represented (Bousman, *Lancet Psychiatry*, 2016)
  - 25 (53%) were associated with supporting evidence graded by the PharmGKB databased as preliminary or low
  - 9 (20%) were associated with high levels of evidence: *CYP2D6*, *CYP2C19* and *HLA-B*
  - All algorithms include *CYP2D6* and *CYP2C19*; most also include *CYP2C9* and *CYP3A4/5*
- 39.1% of patients  $\geq 65$  receive at least one drug metabolized by *CYP2D6*, *CYP2C19* and/or *CYP2C9* (Kuch et al, *Health Informatics*, 2016)

# Examples of positive outcomes from multigene pharmacogenetic testing

- Improved antidepressant efficacy
  - 2.52-fold greater rate of remission of major depressive disorder with testing (Singh, *Clin Psychopharmacology Neuroscience*, 2015)
- Reduced pharmacy costs
  - \$1035.60 savings over 1 yr in total medication costs with testing in cohort of psychiatric patients (Winner et al, *Current Medical Research & Opinion*, 2015)
- Reduced rates of hospitalization
  - 9.8% with testing versus 16.1% without testing in cohort of patients  $\geq 65$  YFS (Brixner et al, *J Medical Economics*, 2015)
- Improved adherence with therapy

# Limitations of pharmacogenetic testing

- What to test?
  - Which genes? Which variants? Copy number?
- When to test?
  - Pre-emptive vs. Reactive (e.g. acute needs, triggers)
  - How to interpret multi-gene panels?
- Guidelines for refining dose and dosing frequency?
- Outcomes data?
- Keeping current with new findings, or changes in phenotype definitions

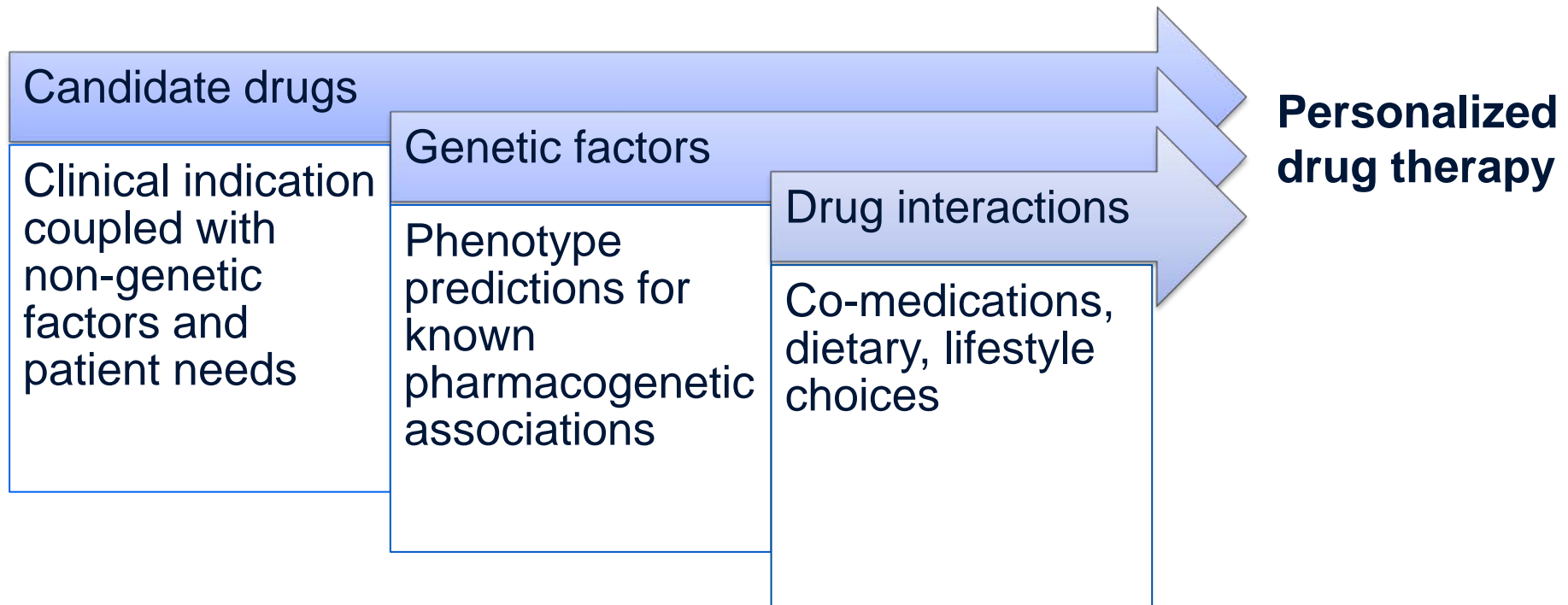


# Disease-drug database concept for pharmacogenomic-based prescribing

- University of Chicago “1200 Patients Project” (clinicaltrials.gov #NCT01280825) based on preemptive pharmacogenomic testing
- Created a Genomic Prescribing System (GPS), a web-based interactive portal with clinical decision support for individual patients,
  - “Traffic light signal” alerts possible medication outcomes to patients
  - Levels of evidence to classify strength of alert
  - Detailed information available
- Prospective evaluation of the tool found “90% of the top ~20 diseases in this population and  $\geq 93\%$  of patients could appropriately be treated with  $\geq 1$  medication with actionable pharmacogenomic information”

<https://cpt.uchicago.edu/page/1200-patients-project>  
Hussain et al, *Clin Pharmacol Ther* 100(2):179-90, 2016

# Considerations for drug and dose selection



# Conclusions

- Dozens of interpretive tools are available to inform therapy decisions for many drugs, based primarily on single drug-gene associations
  - Testing is available
  - Implementation demonstrated successfully in electronic health record
  - Outcomes data and dose refinement tools are lacking
- Multi-gene testing panels and interpretive tools are available to inform therapy decisions for many drugs
  - Outcomes studies are promising
  - Movement towards incorporation of clinical risk factors and disease diagnosis may improve utility
  - Direct comparisons of clinical guidance from the algorithms is lacking

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