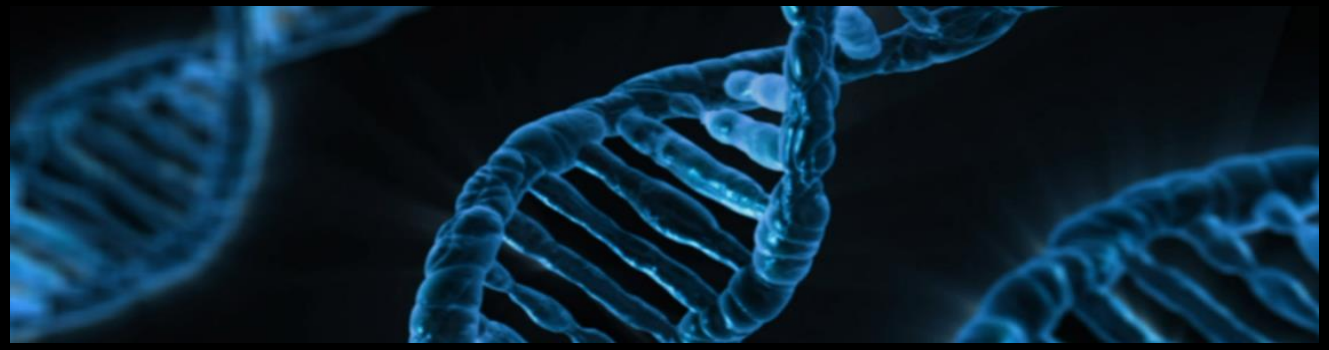
Pharmacogenetics

Steven Curry, M.D.
University of Arizona College of Medicine
Banner – University Medical Center Phoenix



COLLEGE OF MEDICINE PHOENIX
Department of Medicine
Clinical Data Analytics & Decision Support

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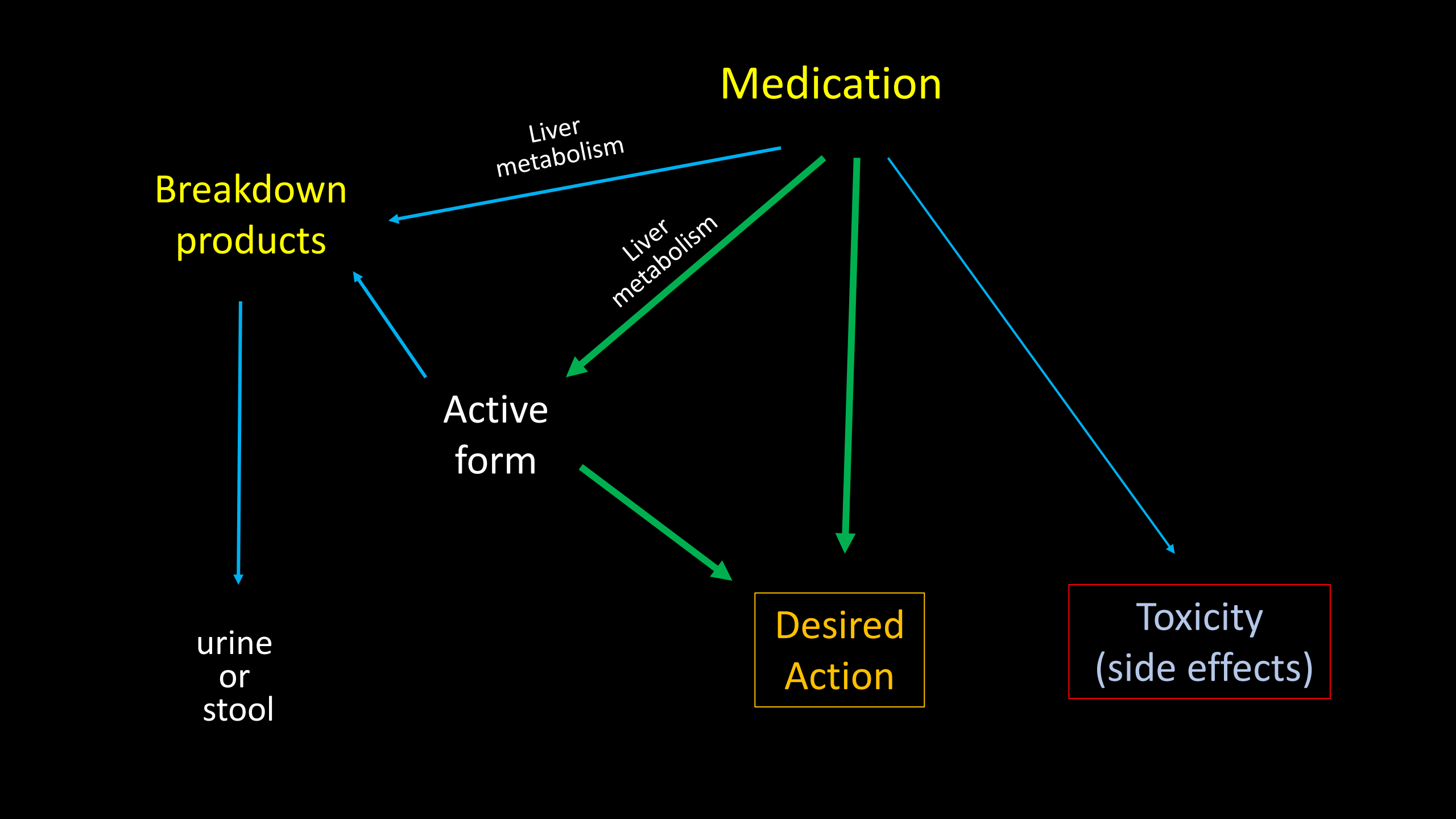
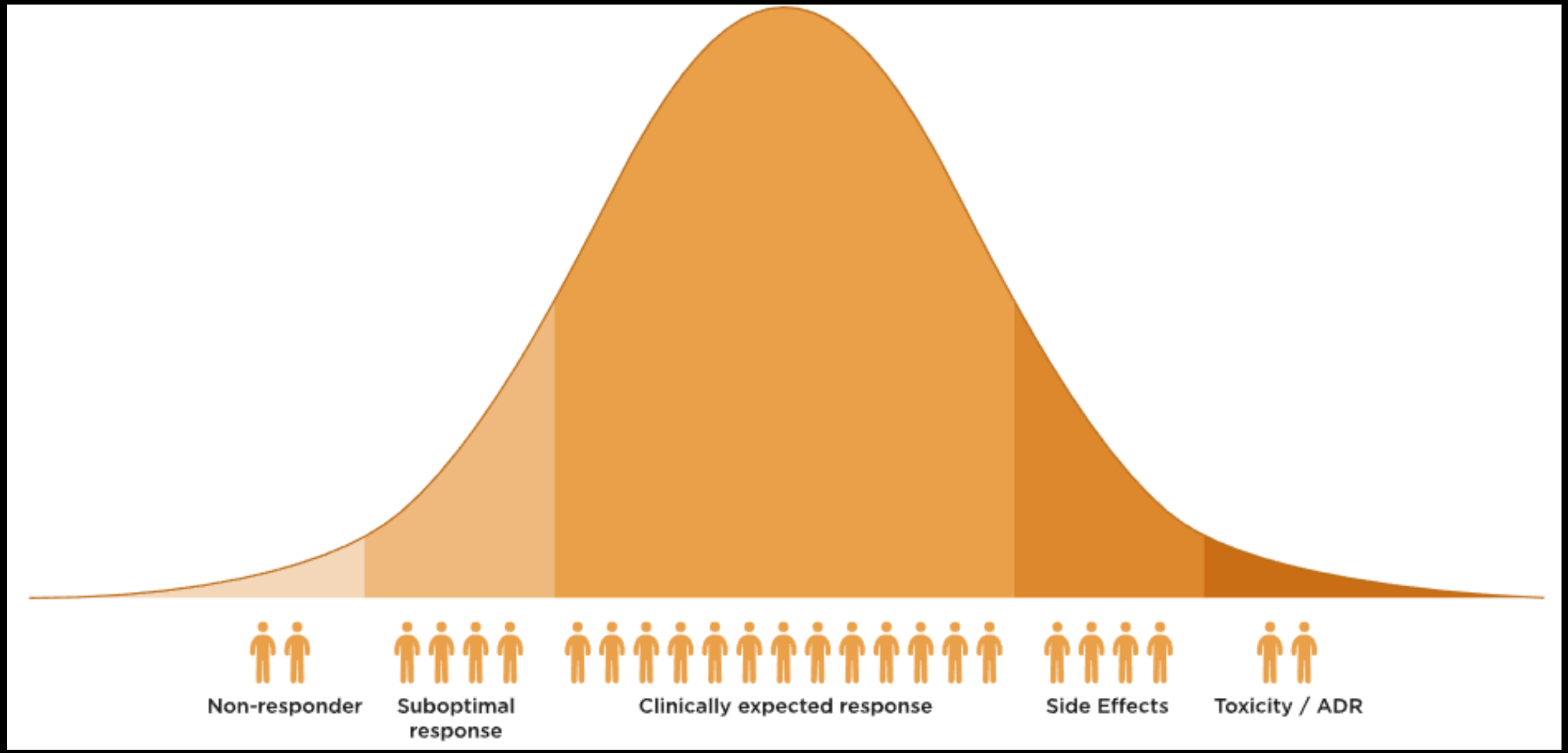
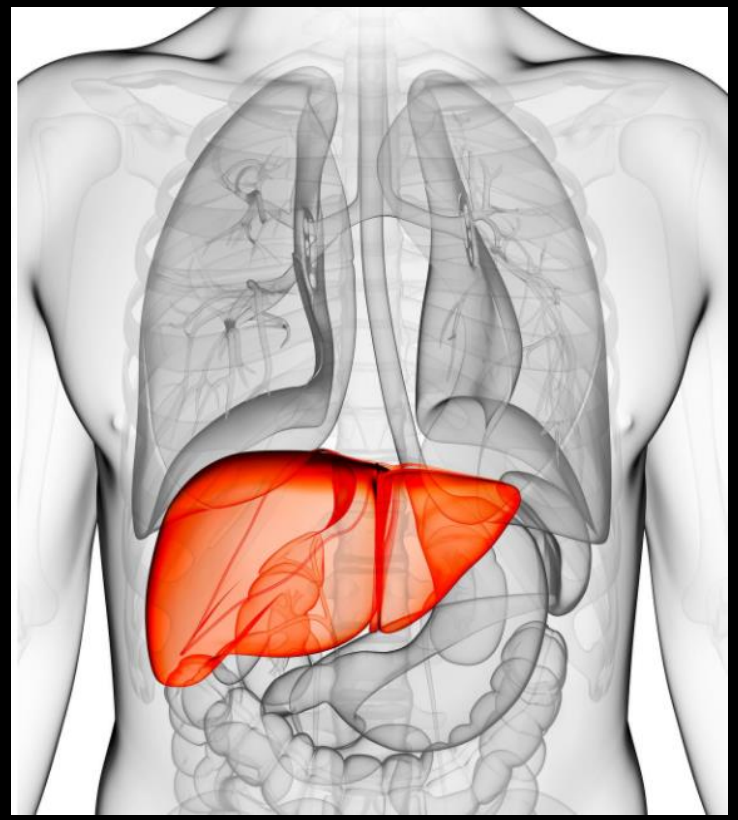
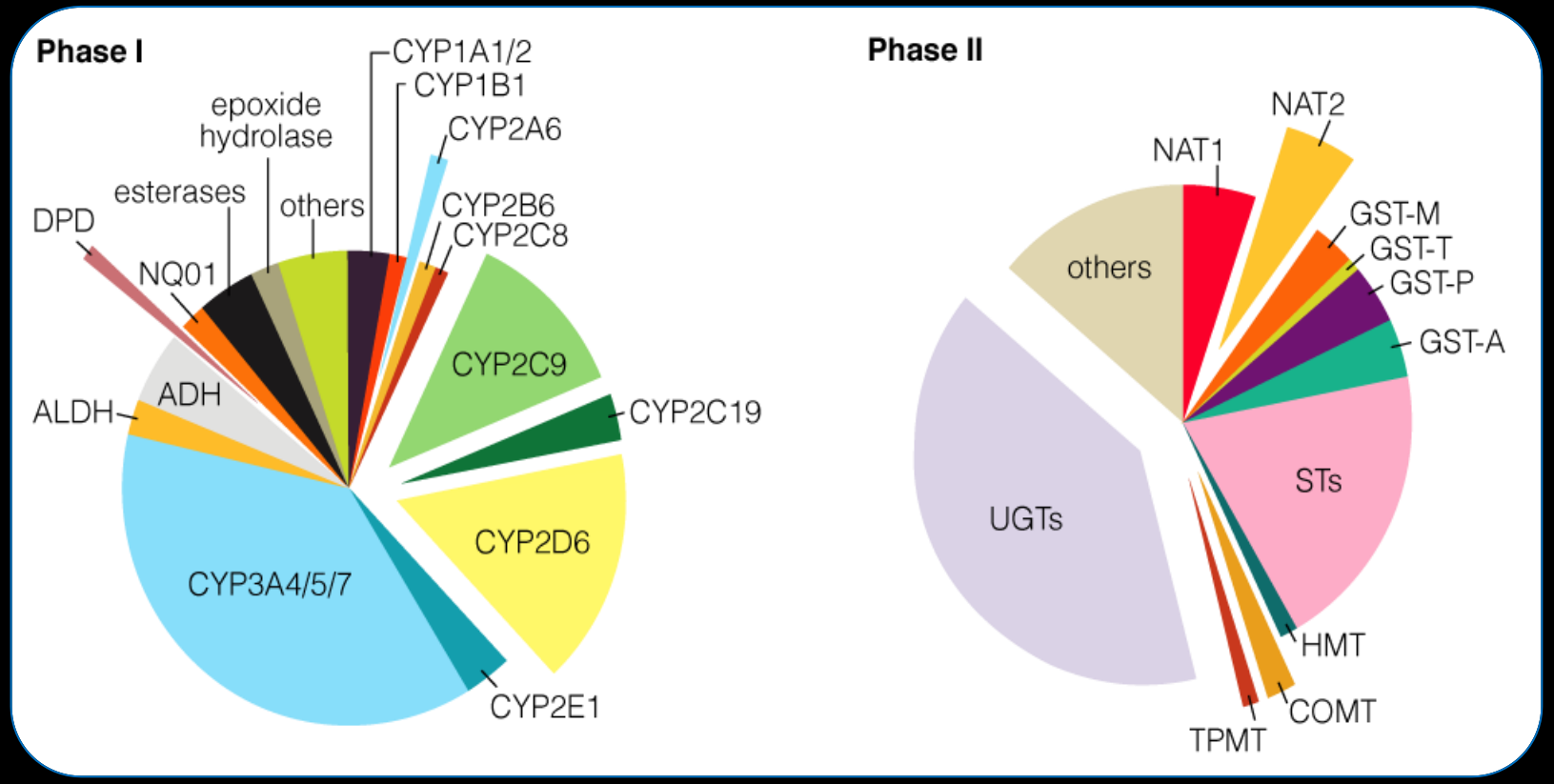

Medication
Liver metabolism
Breakdown products
Liver metabolism
Active form
urine or stool
Desired Action
Toxicity (side effects)

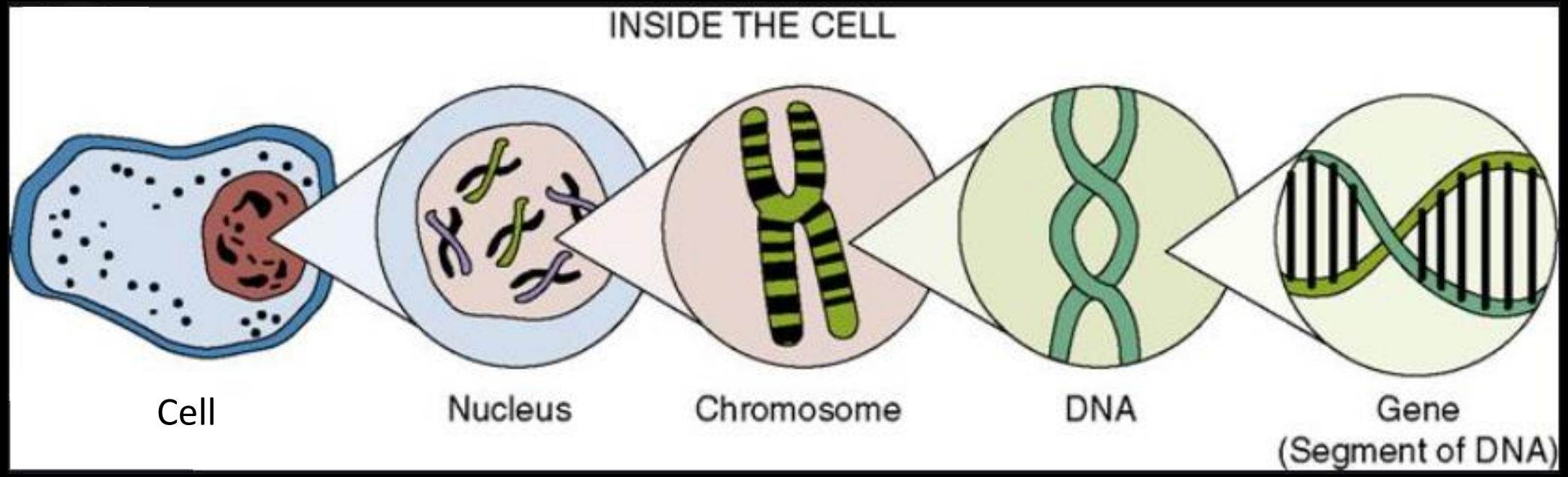

Non-responder
Suboptimal response
Clinically expected response
Side Effects
Toxicity / ADR



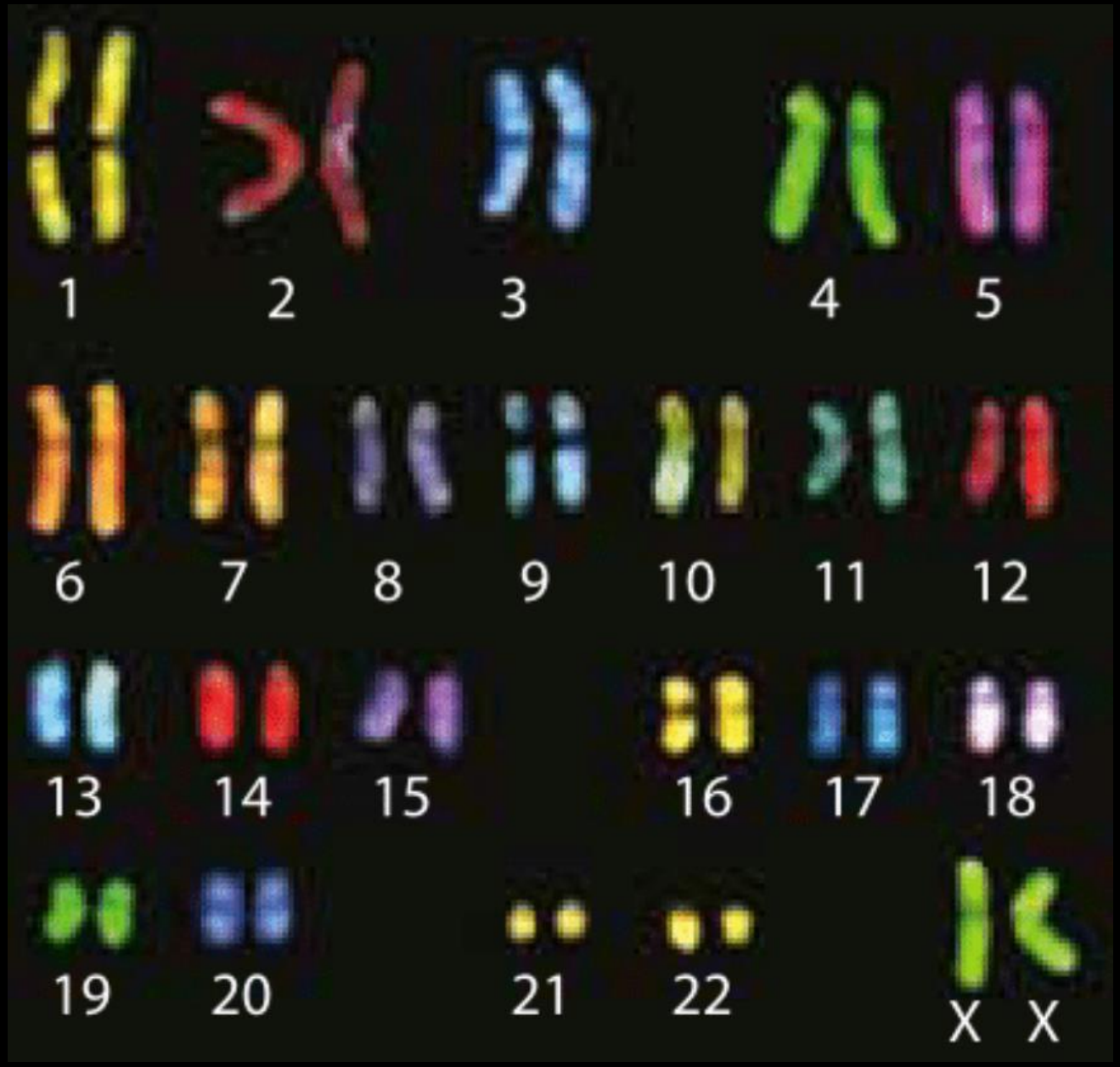


The liver is filled with various enzymes coded for by our DNA that are responsible for influencing drug effects.

Most of these enzymes are responsible for metabolism of drugs.

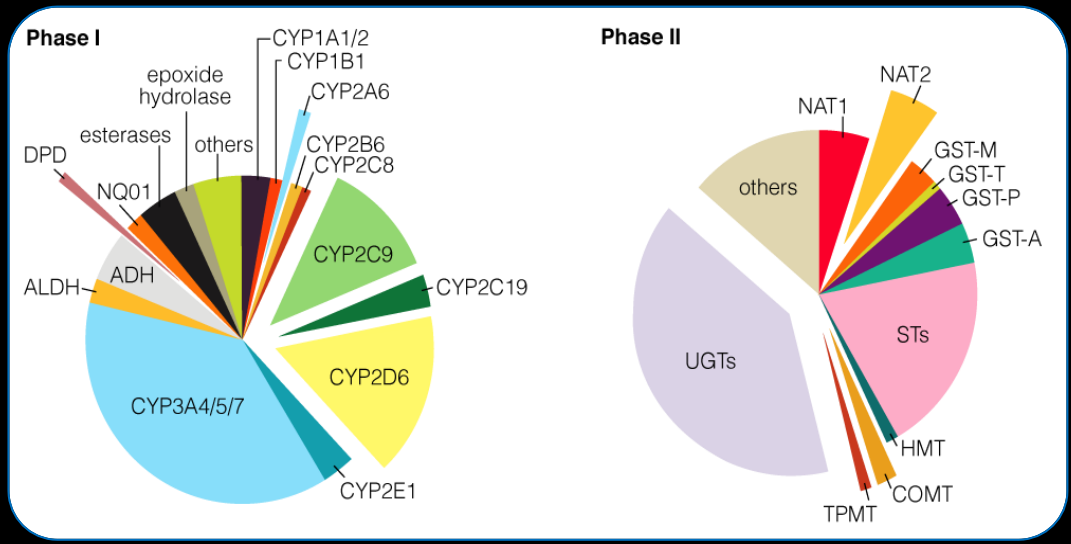


240 billion cells
in adult liver



Each of us has 23 pairs of chromosomes.

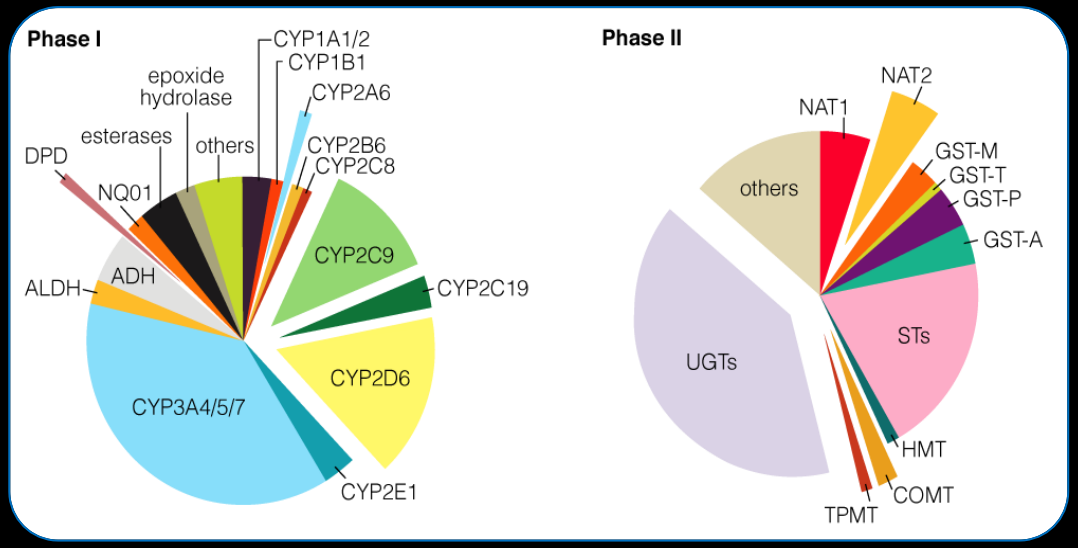
For each pair, we inherit one from our father, and one from mother.



DNA in cells normally is uncoiled when the cell is not dividing.

We have about 30 trillion cells in our body, and each cell contains about 6.5 feet of DNA.

Each person has a total of 93 million miles of DNA in their body, enough to stretch from earth to the sun.



Normal variation in genes in population

Many genes are "polymorphic" - variations are commonly found in a population.

CYP2D6 (example)

Rapid or Ultrarapid metabolizer

Normal (extensive) metabolizer

Intermediate metabolizer

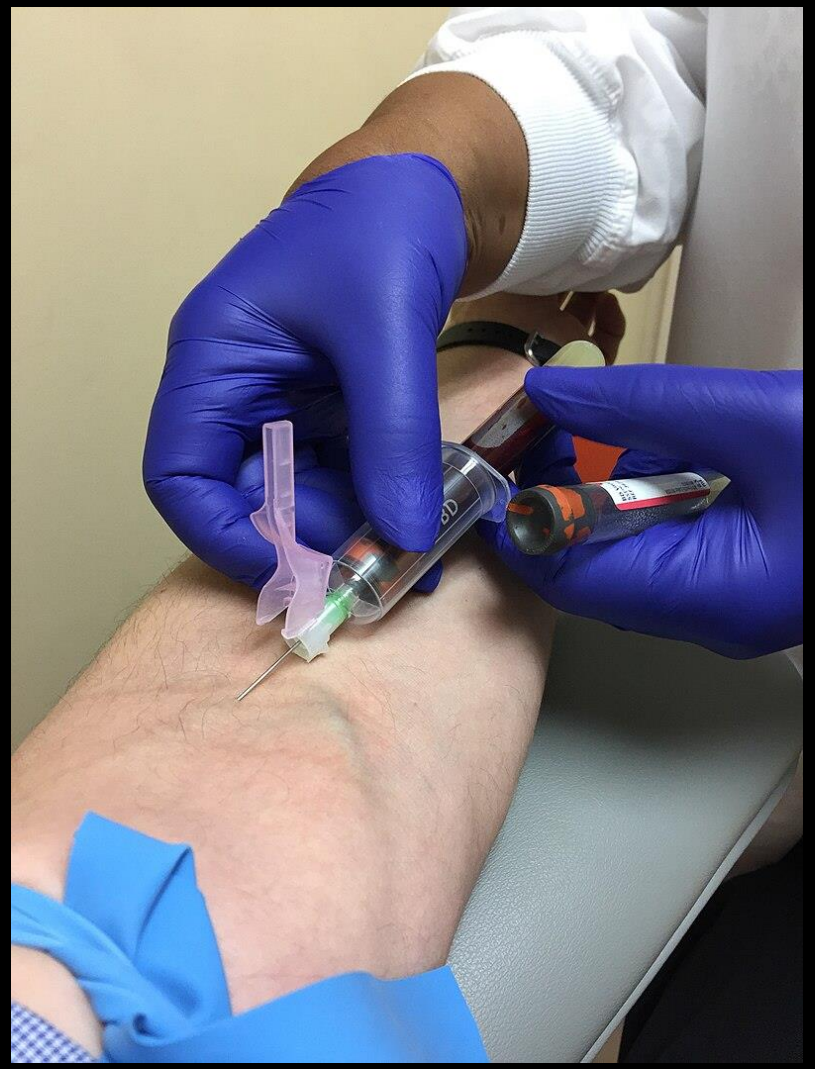
Poor metabolizer

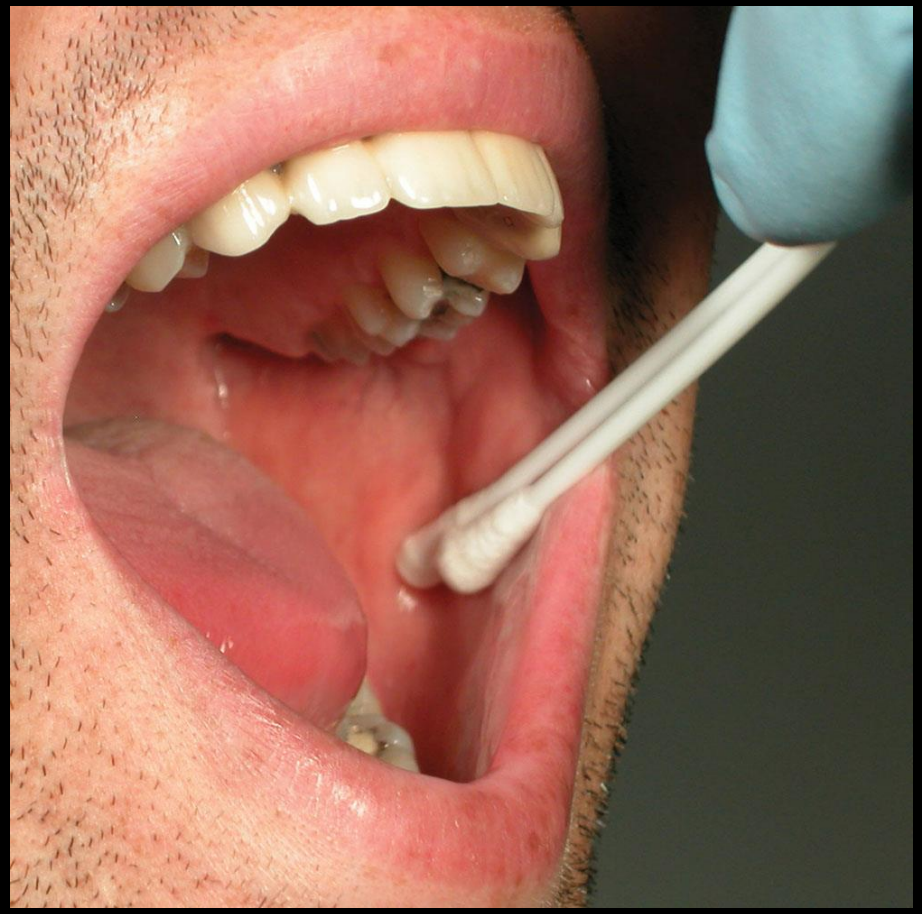
SQL PGx Panel

Sonora Quest Laboratories™
A Subsidiary of Laboratory Sciences of Arizona

- 22 Genes
- >120 genetic mutations/variations

	SQL
ABCB1	3
CYP1A2	10
CYP2B6	10
CYP2C	1
CYP2C9	16
CYP2C19	15
CYP2D6	29
CYP2D6 deletions/CNV	Yes
CYP2D6 Hybrids	Yes
CYP2D6 distal enhancer (WBP2NL)	Yes
CYP3A4	6
CYP3A5	7
CYP4F2	1
DPYD	5
IFNL3	1
NAT2	5
NUDT15	2
RARG	1
SLC28A3	1
SLCO1B1	4
TPMT	5
UGT1A1	3
UGT1A6	1
UGT2B15	1
VKORC1	2


BD

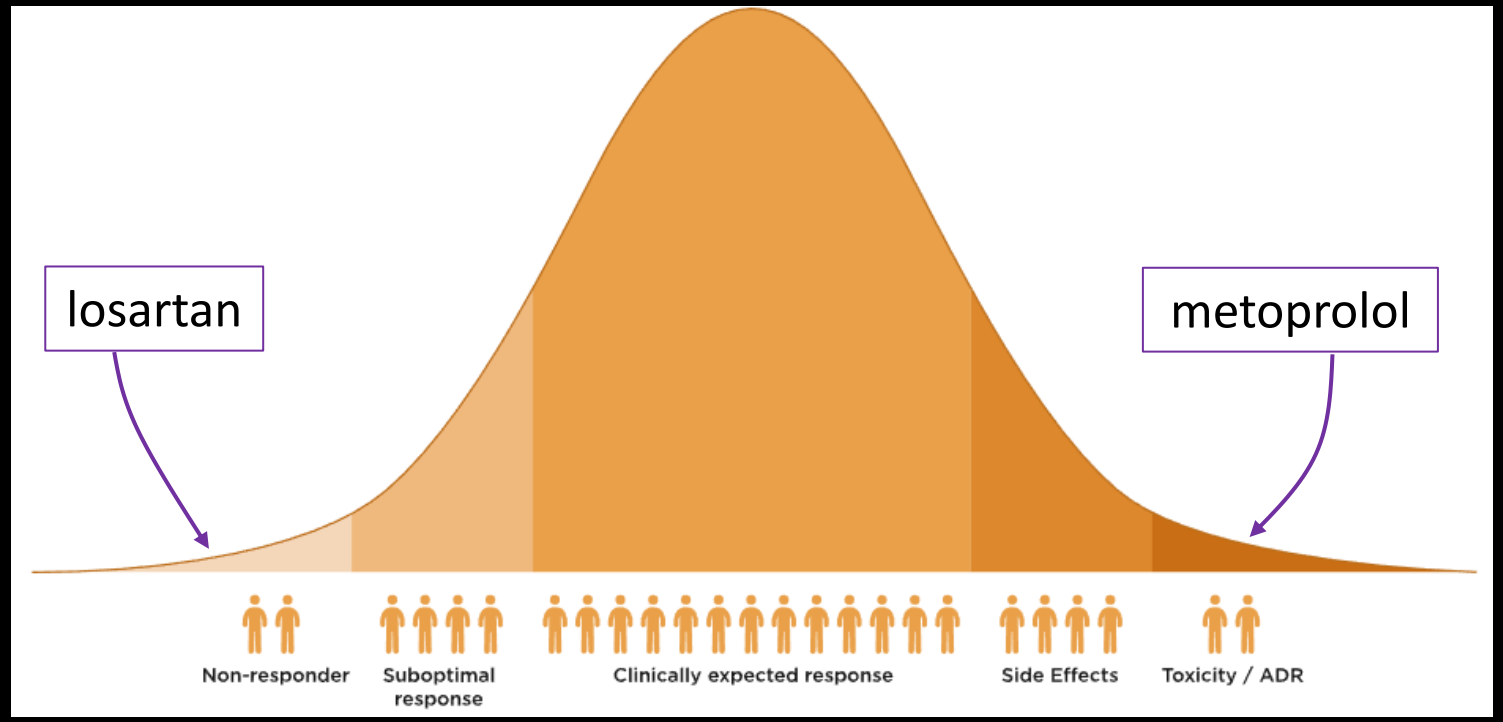


Woman with Hypertension

51-year-old woman with hypertension failed to respond to *losartan*.

She was switched to *metoprolol* and 4 days later presented to the hospital after fainting, low blood pressure and heart rate = 32/min.

Discharged after 4 day of hospitalization.



51-year-old woman with essential hypertension failed to respond to losartan.

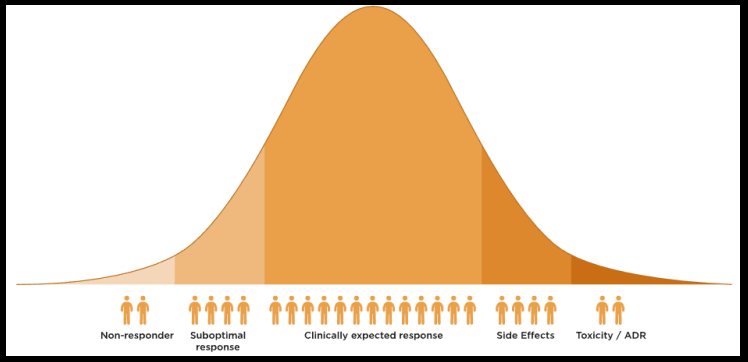
She was switched to metoprolol and 4 days later presented to the hospital with syncope, heart rate = 32/min, systolic BP 80.

Gene	Genotype	Phenotype
CYP1A2	*1F/*1V	Normal Metabolizer- Possible Inducibility
CYP2B6	*1/*1	Normal Metabolizer
CYP2C19	*1/*1	Normal Metabolizer
CYP2C9	*1/*3	Intermediate Metabolizer
CYP2D6	*4/*5	Poor Metabolizer
CYP3A4	*1/*1	Normal Metabolizer
CYP3A5	*3/*3	Poor Metabolizer
DPYD	*1/*1	Normal Metabolizer
SLCO1B1	521T>C T/T	Normal Function
UGT2B15	*1/*1	Normal Metabolizer
VKORC1	-1639G>A G/A	Intermediate Warfarin Sensitivity

CYP2C9

losartan (inactive) → active drug (lowers BP)

Use With Caution
Losartan (Cozaar®, Hyzaar®)



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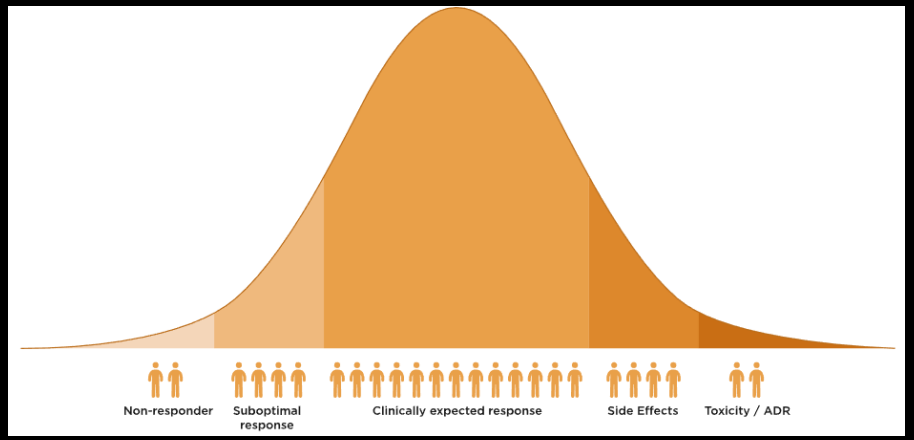
SLCO1B1	521T>C T/T	Normal Function
UGT2B15	*1/*1	Normal Metabolizer
VKORC1	-1639G>A G/A	Intermediate Warfarin Sensitivity

metoprolol → (CYP2D6) → inactive metabolites

Use With Caution	Consider Alternatives
Carvedilol (Coreg®) Timolol (Timoptic®)	Metoprolol (Lopressor®)

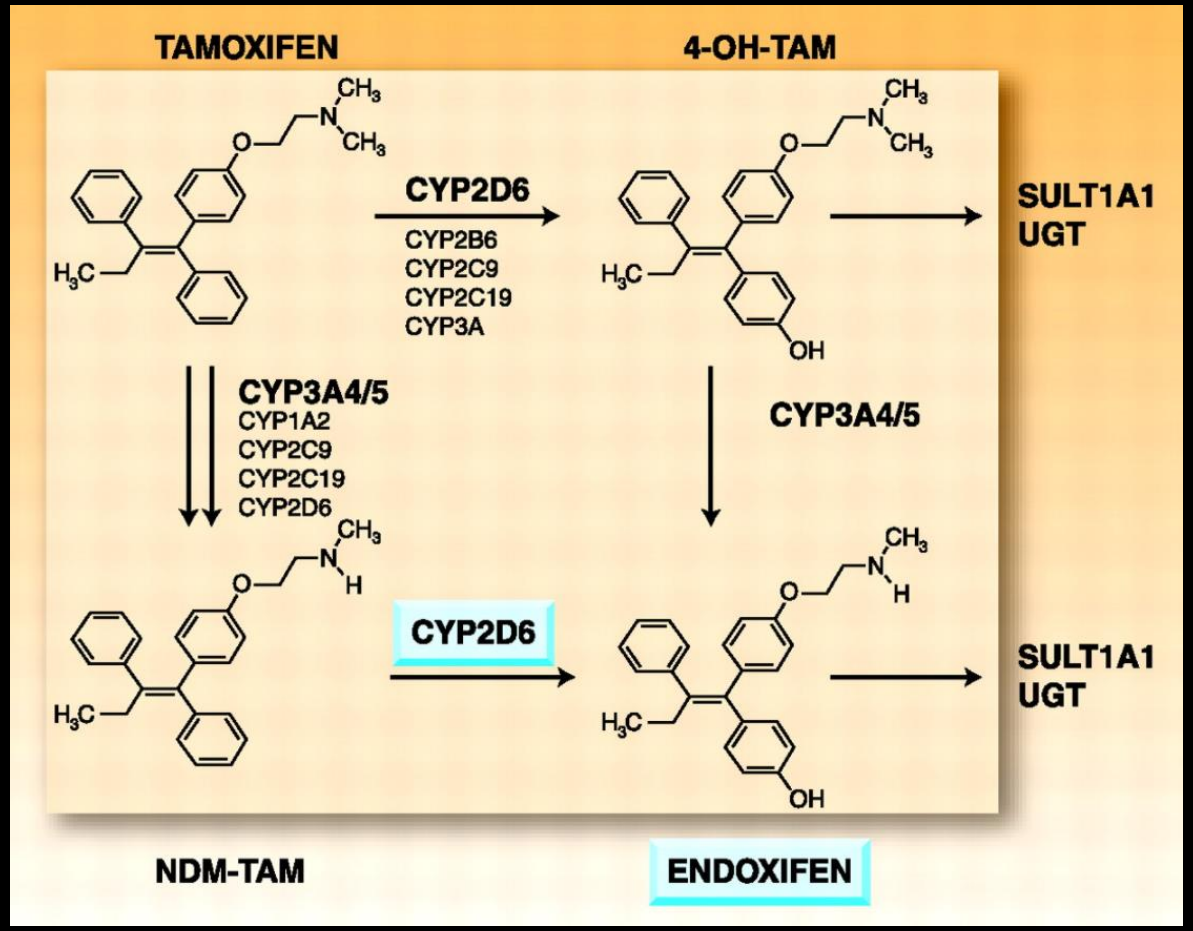


Tamoxifen

estrogen antagonist to prevent and treat breast cancer

Tamoxifen (inactive) —CYP2D6→ Endoxifen (active)

CYP2D6 poor metabolizers have much lower blood endoxifen levels than normal metabolizers.



Comprehensive Pharmacogenetic Report

Test Details

Gene	Genotype	Phenotype	Clinical Consequences
ABCB1	1236T>C T/C	Heterozygous- Variant Allele Present	Consistent with decreased transporter expression.
ABCB1	2677G>T G/T	Heterozygous- Variant Allele Present	Consistent with decreased transporter expression.
ABCB1	3435C>T C/T	Heterozygous- Variant Allele Present	Consistent with decreased transporter expression.
CYP1A2	*1A/*1A	Normal Metabolizer- Possible Inducibility	Consistent with a typical CYP1A2 activity in absence of inducing substances. Rapid metabolism may occur in presence of inducers such as barbiturates, cruciferous vegetables, carbamazepine, rifampin and smoking.
CYP2B6	*1/*1	Normal Metabolizer	Consistent with a typical CYP2B6 activity. This test did not identify risks for side effects or loss of efficacy with drug substrates.
CYP2C	g.96405502G>A G/A	High Sensitivity	
CYP2C19	*2/*17	Intermediate Metabolizer	Consistent with a moderate deficiency in CYP2C19 activity. Potential risk for side effects or loss of efficacy with drug substrates.
CYP2C9	*1/*1	Normal Metabolizer	Consistent with a typical CYP2C9 activity. This test did not identify risks for side effects or loss of efficacy with drug substrates.
CYP2D6	*1/*2	Normal Metabolizer	Consistent with a typical CYP2D6 activity. This test did not identify risks for side effects or loss of efficacy with drug substrates.
CYP3A4	*1/*1	Normal Metabolizer	Consistent with a typical CYP3A4 activity. Caution is advised when prescribing narrow therapeutic index drugs. Alternative drugs or dose adjustment may be required if CYP3A inhibitors or inducers are co-prescribed.
CYP3A5	*3/*3	Poor Metabolizer	Consistent with a poor CYP3A5 activity. This phenotype is the most common in the general population. Caution is advised when prescribing narrow therapeutic index drugs. Alternative drugs or dose adjustment may be required if CYP3A inhibitors or inducers are co-prescribed.
CYP4F2	1347G>A G/G	Homozygous for the G allele (rs2108622)	
DPYD	Activity Score: 2	Normal Metabolizer	Consistent with a typical DPD activity and a typical risk of side effects with conventional doses of fluoropyridines.
IFNL3	rs12979860 C/T	Heterozygous for rs12979860 T allele	Unfavorable Response to Peginterferon alfa-2a and alfa-2b and Ribavirin Based Regimen for Hepatitic C Genotype 1
NAT2	c.191G>A G/G	Homozygous for rs1801279 G allele	
NAT2	c.341T>C T/C	Heterozygous for rs1801280 C allele	
NAT2	c.364G>A G/G	Homozygous for rs4986996 G allele	
NAT2	c.590G>A G/A	Heterozygous for rs1799930 A allele	
NAT2	c.857G>A G/G	Homozygous for rs1799931 G allele	
NUDT15	*1/*1	Normal Metabolizer	Consistent with a typical NUDT15 activity and a typical risk of side effects with conventional doses of thiopurines.
RARG	rs2229774 C/C	Normal Function	Normal receptor function and normal repression of topoisomerase-II beta (TOP2B) expression
SLC28A3	rs7853758 C/C	Normal Function	Normal SLC28A3 influx transporter function
SLCO1B1	521T>C T/T	Normal Function	Consistent with a typical SLCO1B1 transporter function. The patient's risk for statin-induced myopathy is not increased.
TPMT	*1/*3A	Intermediate Metabolizer	Consistent with a moderate deficiency in TPMT activity. Increased risk for serious side effects with conventional doses of thiopurines.
UGT1A1	*1/*80	Intermediate Metabolizer	Consistent with a moderately decreased UGT1A1 glucuronidation function (intermediate activity). Potential risk for side effects with drug substrates.
UGT1A6	rs17863783 G/G	Normal Metabolizer	Consistent with typical UGT1A6 glucuronidation metabolism.
UGT2B15	*2/*2	Poor Metabolizer	Consistent with a decreased UGT2B15 glucuronidation function. Potential risk for side effects with drug substrates.
VKORC1	-1639G>A G/A	Intermediate Warfarin Sensitivity	VKORC1 is the site of action of warfarin. The patient may require a decrease in warfarin dosage.
VKORC1	c.3730G>A G/A	Heterozygous for rs7294 T allele	
WBP2NL	c.63-2604G>A A/G	Heterozygous for rs5758550 G allele	

Alleles Tested: ABCB1 3435C>T, 1236T>C, 2677G>T; **CYP1A2** *1C, *1D, *1E, *1F, *1J, *1K, *1L, *1V, *1W, *7; **CYP2B6** *4, *5, *6, *7, *8, *9, *11, *13, *16, *18; **CYP2C** g.96405502G>A; **CYP2C19** *2, *3, *4, *4B, *5, *6, *7, *8, *9, *10, *16, *17, *24, *25, *35; **CYP2C9** *2, *3, *4, *5, *6, *7, *8, *9, *11, *12, *13, *15, *16, *25, *31, *36; **CYP2D6** *2, *3, *4, *4M, *6, *7, *8, *9, *10, *11, *12, *14A, *14B, *15, *17, *18, *19, *29, *31, *33, *35, *38, *41, *42, *44, *51, *56A, *56B, *59, *62, *5 (gene deletion), XN (gene duplication); **CYP3A4** *1B, *2, *3, *12, *17, *22; **CYP3A5** *1D, *2, *3, *3C, *6, *7, *8, *9; **CYP4F2** 1347G>A; **DPYD** 1905+1G>A, 1679T>G, 2846A>T, 557A>G, c.1129-5923C>G; **IFNL3** rs12979860; **NAT2** 590G>A, 191G>A, 341T>C, 857G>A, 364G>A, c.590G>A, c.191G>A, c.341T>C, c.857G>A, c.364G>A; **NUDT15** *2, *3, *5; **RARG** rs2229774; **SLC28A3** rs7853758; **SLCO1B1** 521T>C; **TPMT** *2, *3A, *3B, *3C, *4; **UGT1A1** *6, *27, *80; **UGT1A6** rs17863783; **UGT2B15** *2; **VKORC1** 3730G>A, -1639G>A, c.3730G>A; **WBP2NL** 63-2604G>A, c.63-2604G>A

Sonora Quest Laboratories™

Medications by Class

Class	Normal prescribing	Drug genomic effect (see details below)
Analgesics	codeine hydrocodone methadone oliceridine tramadol	
Anesthetics		
Anti-Infective Agents	atazanavir primaquine	efavirenz isoniazid sulfasalazine voriconazole
Cardiovascular (Antihypertensives)	carvedilol metoprolol	hydralazine
Cardiovascular (General)	flecainide mavacamten propafenone	clopidogrel

Categories

Analgesics
Anesthetics
Anti-Infectives
CV - Antihypertensives
CV - Anti-blood clotting
CV - Statins
GI
Neurology
Anticancer
Psychiatry - stimulants
Psychiatry - antidepressants
Psychiatry - antipsychotics
Rheumatology
Transplantation
Miscellaneous

Amitriptyline

Likely decreased efficacy. Suggest considering alternative drug.

Supporting Evidence: Strong **Genotype:** CYP2C19*17 / CYP2C19*17

Atomoxetine

Possible risk of decreased efficacy. Monitor serum blood levels.

Supporting Evidence: Good **Genotype:** CYP2D6*41 / CYP2D6*35

Citalopram

Decreased efficacy. Recommend an alternative drug or consider higher dose.

Supporting Evidence: Strong CYP2C19 ultra-rapid metabolizer **Genotype:** CYP2C19*17 / CYP2C19*17

Amitriptyline

This individual has a variant of the CYP2C19 gene, which may decrease the efficacy of this tricyclic antidepressant. Individuals with this variant are classified as ultra-rapid metabolizers (UM). CYP2C19 is member of the cytochrome P450 enzyme system, which is a pathway of metabolism for amitriptyline. Increased drug metabolism in this individual may result in increased drug clearance and reduced peak plasma levels, which may decrease efficacy. The prevalence of the CYP2C19 ultrarapid metabolizers is 5-30% of patients.

It is suggested to avoid the use of amitriptyline and consider an alternative non-tricyclic drug when using higher doses (>100 mg per day) for the treatment of depression.

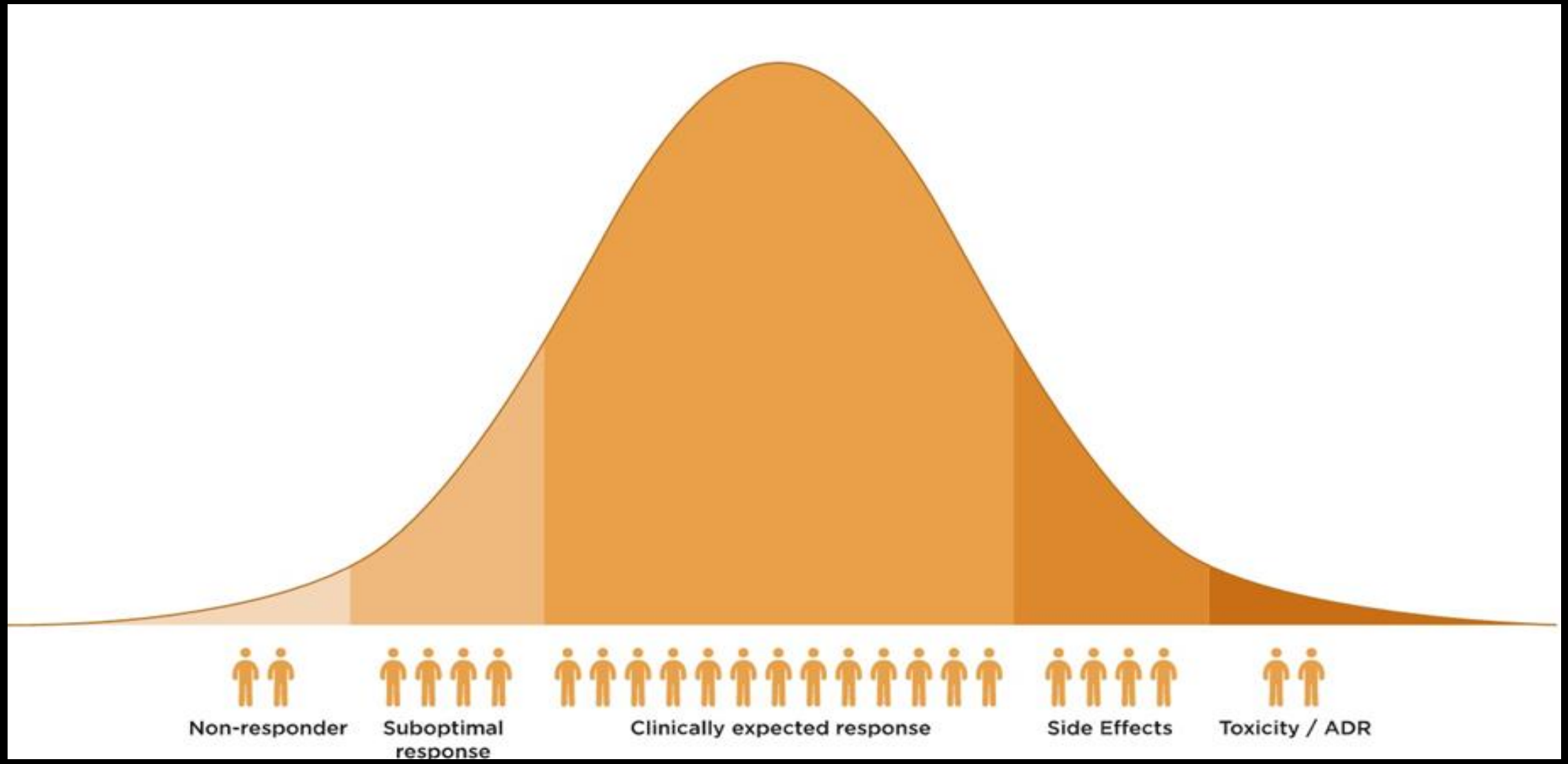
1.Hicks JK, Swen JJ, Thorn CF, et al. Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. Clin Pharmacol Ther 2013; 93(5):4028. http://www.ncbi.nlm.nih.gov/pubmed/23486447

2.Steimer W, Zpf K, von Amelunxen S, et al. Amitriptyline or not, that is the question: pharmacogenetic testing of CYP2D6 and CYP2C19 identifies patients with low or high risk for side effects in amitriptyline therapy. Clin Chem 2005; 51(2):37685. http://www.ncbi.nlm.nih.gov/pubmed/15590749

3.Steimer W, Zpf K, von Amelunxen S, et al. Allele-specific change of concentration and functional gene dose for the prediction of steady-state serum concentrations of amitriptyline and nortriptyline in CYP2C19 and CYP2D6 extensive and intermediate metabolizers. Clin Chem 2004; 50(9):162333. http://www.ncbi.nlm.nih.gov/pubmed/15205367

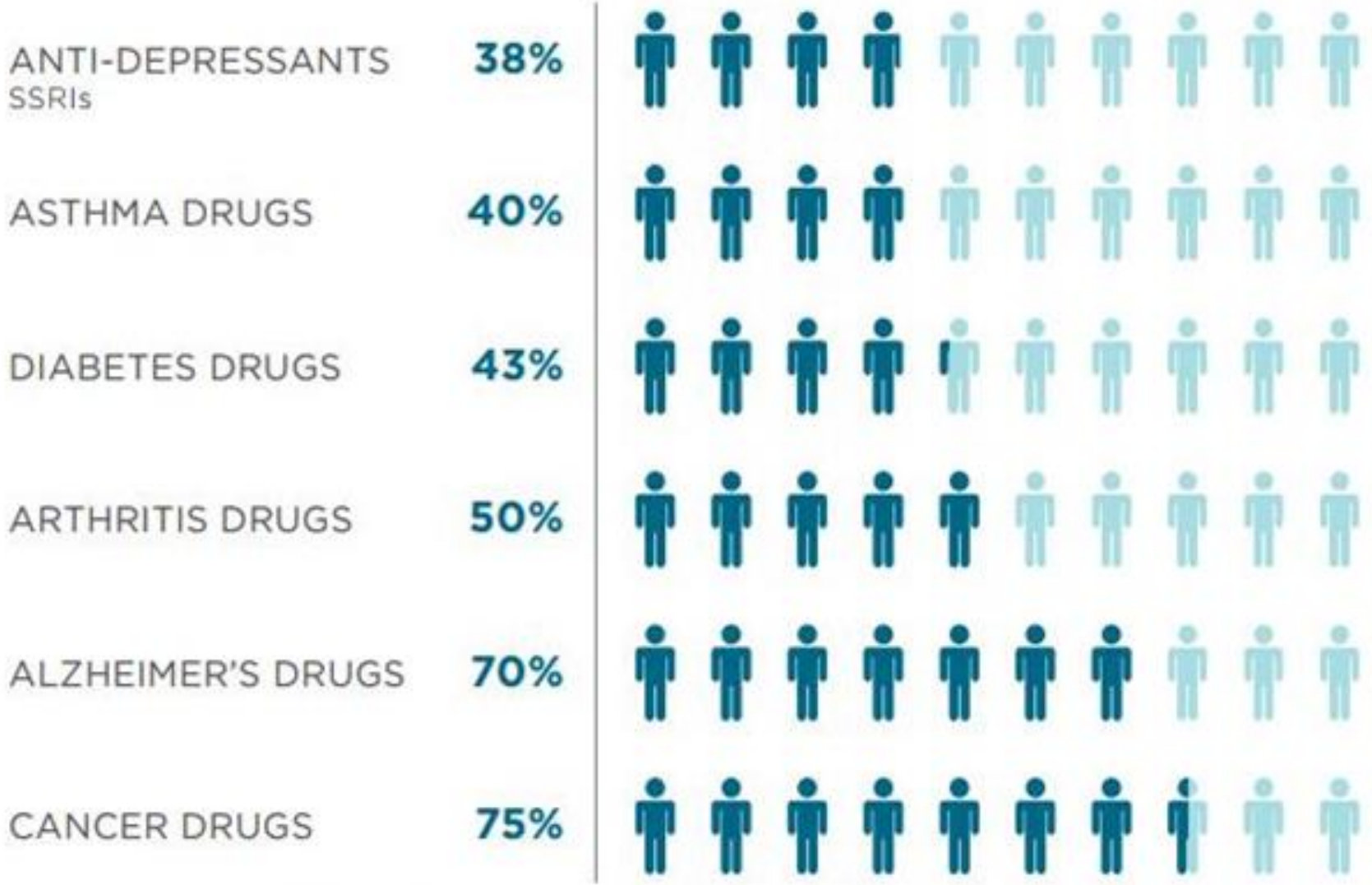
4.Shimoda K, Someya T, Yokono A, et al. The impact of CYP2C19 and CYP2D6 genotypes on metabolism of amitriptyline in Japanese psychiatric patients. J Clin Psychopharmacol 2002; 22(4):3718. http://www.ncbi.nlm.nih.gov/pubmed/12172336

5.Bijl MJ, Visser LE, Hofman A, et al. Influence of the CYP2D6*4 polymorphism on dose, switching and discontinuation of antidepressants. Br J Clin Pharmacol 2008; 65(4):55864. http://www.ncbi.nlm.nih.gov/pubmed/18070221



98% of us carry at least one high risk phenotype

Percentage of the patient population for which a particular drug in a class is ineffective, on average



Source: Brian B. Spear, Margo Heath-Chiozzi, Jeffrey Huff, "Clinical Trends in Molecular Medicine," Volume 7, Issue 5, 1 May 2001, pages 201-204.

PGx Psychiatric Drugs

examples

Antidepressants

amitriptyline
citalopram
doxepin
escitalopram
fluvoxamine
imipramine
sertraline
venlafaxine
vortioxetine

Antipsychotics

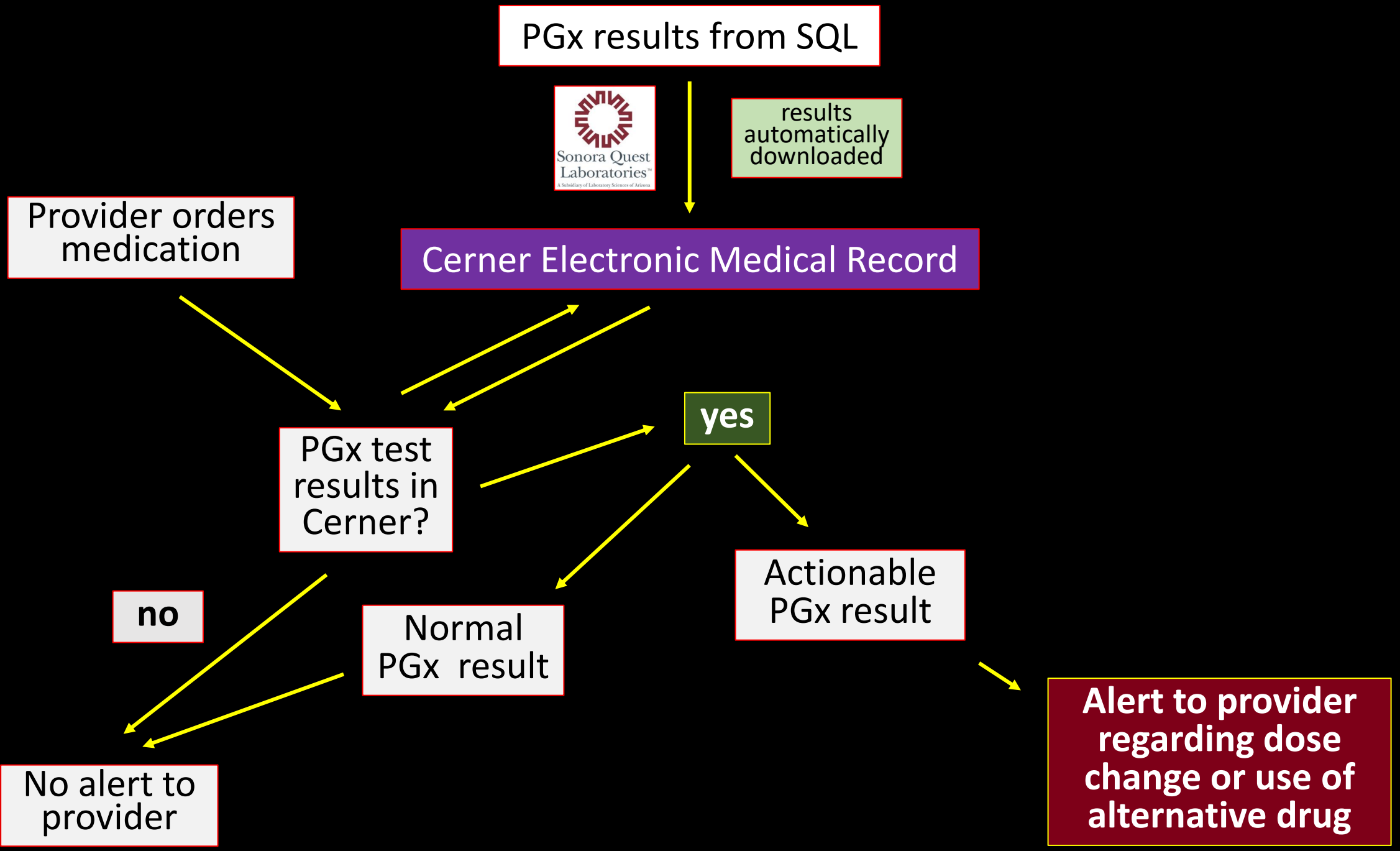
aripiprazole
brexpiprazole
clozapine
haloperidol
quetiapine

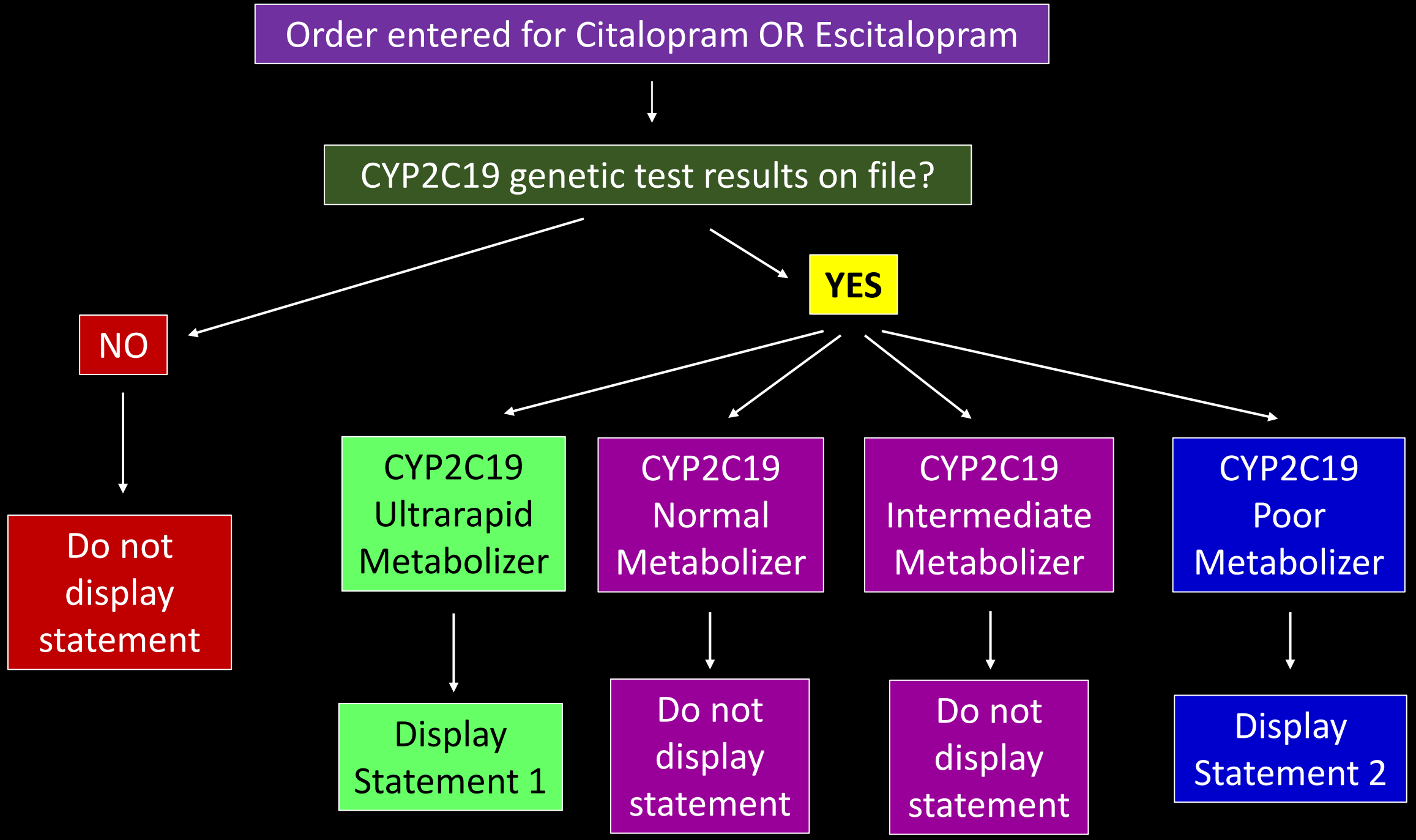
Stimulants

amphetamine
atomoxetine

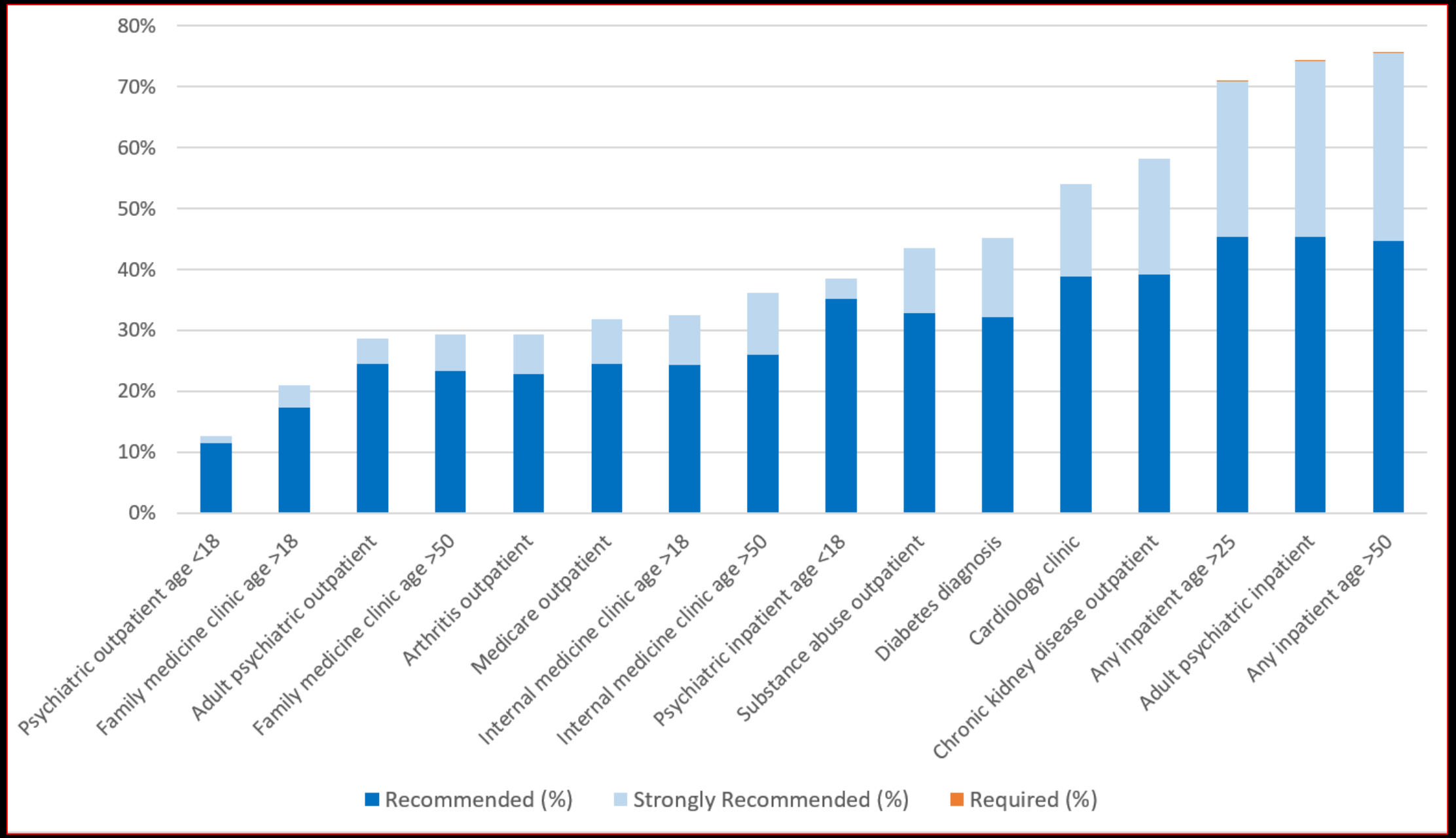
Miscellaneous

tetrabenazine
valbenazine


PGx results from SQL
Sonora Quest Laboratories
A Subsidiary of Laboratory Sciences of Arizona
results automatically downloaded
Provider orders medication
Cerner Electronic Medical Record
PGx test results in Cerner?
yes
no
Normal PGx result
Actionable PGx result
No alert to provider
Alert to provider regarding dose change or use of alternative drug


Order entered for Citalopram OR Escitalopram
CYP2C19 genetic test results on file?
NO
YES
Do not display statement
CYP2C19 Ultrarapid Metabolizer
CYP2C19 Normal Metabolizer
CYP2C19 Intermediate Metabolizer
CYP2C19 Poor Metabolizer
Display Statement 1
Do not display statement
Do not display statement
Display Statement 2

Which Patients Most Likely To Benefit From PGx Testing?



Which Psychiatric Patients Should Be Tested?

- All new psychiatric patients treated with medication?
- Patients failing to respond to drug therapy?
- Patients with unexpected side effects to drug therapy?

Patients receiving PGx-guided antidepressant treatment are 41% more likely to respond favorably compared to patients receiving standard therapy.

Brown et al: Clinical Pharmacology and Therapeutics 2022

Most studies demonstrate PGx testing in psychiatric patients is cost-effective and/or cost-saving strategy (depression).

Morris et al: Clinical Pharmacology and Therapeutics 2022

58% reduction in hospitalizations
40% reduction in ER visit.
13% reduction in clinic visits

PGx Testing

- Joint decision between patient and psychiatrist.
- Patient should never change dose or medication based on results of PGx testing alone, but only with approval of psychiatrist.
- Cost of testing ranges from ~ $150 to $3,000, depending on panel and lab.